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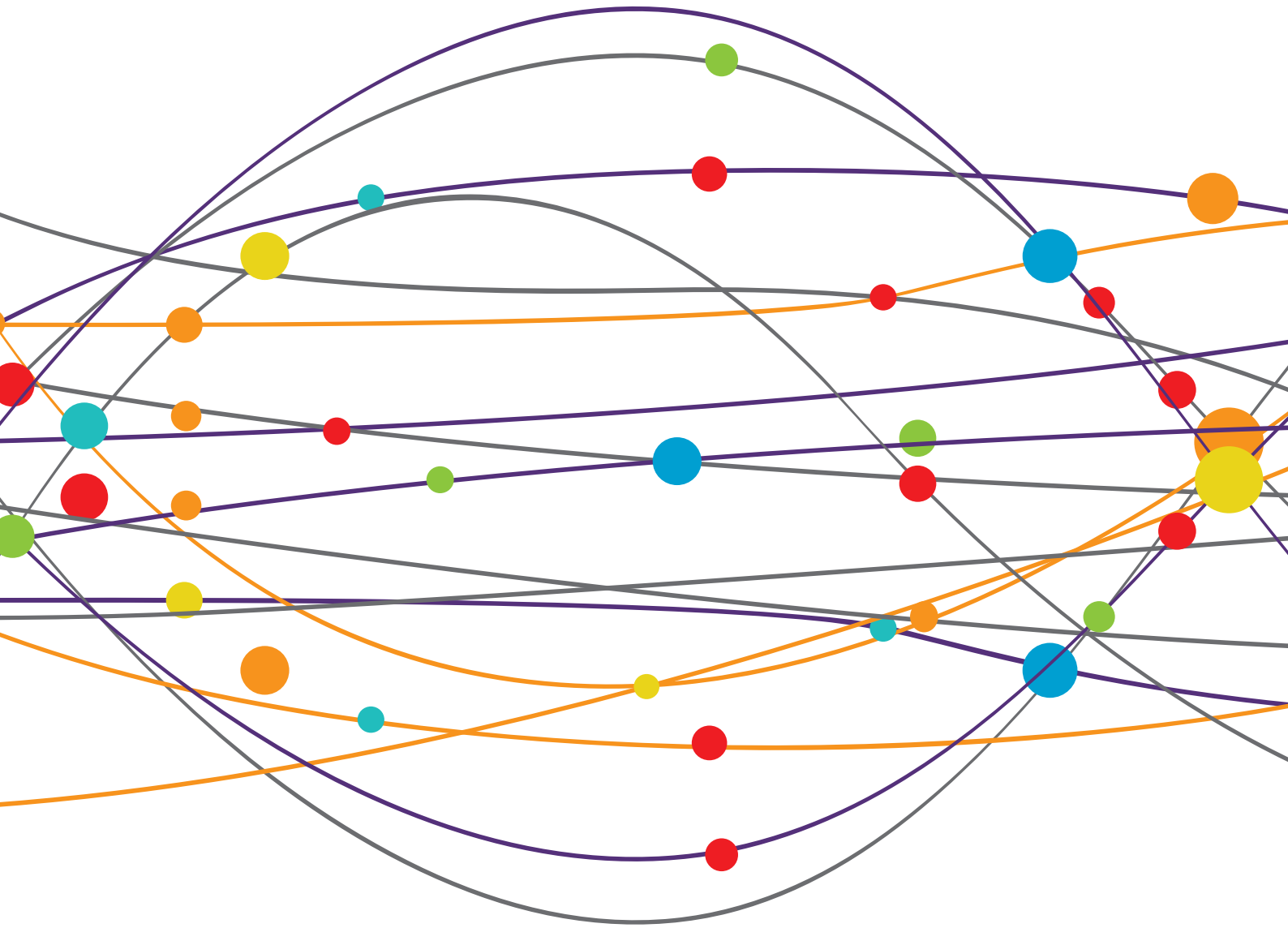

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CONCUSSION REHABILITATION

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Table of Contents

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BRIEF RESEARCH REPORT
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Pre-injury Comorbidities Are Associated With Functional Impairment and Post-concussive Symptoms at 3- and 6-Months After Mild Traumatic Brain Injury: A TRACK-TBI Study

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Introduction: Over 70% of traumatic brain injuries (TBI) are classified as mild (mTBI), which present heterogeneously. Associations between pre-injury comorbidities and outcomes are not well-understood, and understanding their status as risk factors may improve mTBI management and prognostication.

Methods: mTBI subjects (GCS 13–15) from TRACK-TBI Pilot completing 3- and 6-month functional [Glasgow Outcome Scale-Extended (GOSE)] and post-concussive outcomes [Acute Concussion Evaluation (ACE) physical/cognitive/sleep/emotional subdomains] were extracted. Pre-injury comorbidities >10% incidence were included in regressions for functional disability (GOSE $\leq$ 6) and post-concussive symptoms by subdomain. Odds ratios (OR) and mean differences (B) were reported. Significance was assessed at $p < 0.0083$ (Bonferroni correction).

Results: In 260 subjects sustaining blunt mTBI, mean age was 44.0-years and 70.4% were male. Baseline comorbidities >10% incidence included psychiatric-30.0%, cardiac (hypertension)-23.8%, cardiac (structural/valvular/ischemic)-20.4%, gastrointestinal-15.8%, pulmonary-15.0%, and headache/migraine-11.5%. At 3- and 6-months separately, 30.8% had GOSE $\leq$ 6. At 3-months, psychiatric (GOSE $\leq$ 6: OR = 2.75, 95% CI [1.44–5.27]; ACE-physical: B = 1.06 [0.38–1.73]; ACE-cognitive: B = 0.72 [0.26–1.17]; ACE-sleep: B = 0.46 [0.17–0.75]; ACE-emotional: B = 0.64 [0.25–1.03]),

headache/migraine (GOSE ≤ 6: OR = 4.10 [1.67–10.07]; ACE-sleep: B = 0.57 [0.15–1.00]; ACE-emotional: B = 0.92 [0.35–1.49]), and gastrointestinal history (ACE-physical: B = 1.25 [0.41–2.10]) were multivariable predictors of worse outcomes. At 6-months, psychiatric (GOSE ≤ 6: OR = 2.57 [1.38–4.77]; ACE-physical: B = 1.38 [0.68–2.09]; ACE-cognitive: B = 0.74 [0.28–1.20]; ACE-sleep: B = 0.51 [0.20–0.83]; ACE-emotional: B = 0.93 [0.53–1.33]), and headache/migraine history (ACE-physical: B = 1.81 [0.79–2.84]) predicted worse outcomes.

Conclusions: Pre-injury psychiatric and pre-injury headache/migraine symptoms are risk factors for worse functional and post-concussive outcomes at 3- and 6-months post-mTBI. mTBI patients presenting to acute care should be evaluated for psychiatric and headache/migraine history, with lower thresholds for providing TBI education/resources, surveillance, and follow-up/referrals.

Clinical Trial Registration: www.ClinicalTrials.gov, identifier NCT01565551.

Keywords: functional impairment, mild traumatic brain injury, post-concussive symptoms, pre-injury comorbidities, prognosis

INTRODUCTION

Traumatic brain injury (TBI) remains a significant cause of morbidity and mortality worldwide. In 2013 ∼2.8 million TBI cases were recorded annually in the United States (U.S.) (1), which is a 160% increase from 2007 (2). Updated estimates suggest closer to 4 million, due to subpopulations of patients who do not seek care due to either inadequate access or perceived lack of need (2–4). Over 70% of TBI is classified as "mild (mTBI)" defined by Glasgow Coma Scale (GCS) score 13-15 (3, 5), which present heterogeneously with a range of demographic and clinical risk factors. Although a substantial portion of mTBI patients fully recover without intervention, up to 50% suffer long-term functional and/or neuropsychological sequelae, leading to a substantial burden on both patients and the healthcare system (3, 6). This heterogeneity poses a problem in the clinic, as some risk factors are conserved while others differ across different outcome instruments. Whether predictors differ across different outcome time points is also unclear, and hence it remains challenging to risk-stratify patients who will benefit most from additional resources and follow-up in both acute and chronic settings after mTBI (7).

In the orthopedic and geriatric literature, it is recognized that pre-existing conditions impact outcomes after acute illness or injury. However,there is a paucity of research investigating the relationship between pre-injury comorbidities and outcome after mTBI. A number of studies have focused exclusively on psychiatric comorbidities, and PTSD, on mTBI outcome (8–12). Some studies consider the number of rather than types of comorbidities (13), while others focus on mTBI as a risk factor for worsened systemic conditions but not the reverse (14–18). Pre-injury comorbidities are routinely collected during standard clinical interview and documented in the medical record, which underscores their utility as a readily available data source in both acute and ambulatory care settings without increasing time or cost burden. Elucidation of the associations between certain pre-injury conditions and domains of outcome will help clinicians and researchers better understand contributors and modifiers of injury in this heterogeneous group of patients, and may improve early risk stratification of and resource allocation for those at risk for unfavorable recovery.

Systemic medical conditions intrinsically influence physical and cognitive reserve at baseline, and may exert differential effects on recovery in the brain-injured patient. To date, many mTBI studies have understandably excluded patients with pre-injury comorbidities to reduce outcome variability when isolating risk factors (19). Unfortunately, this hinders the clinician's approach to complex patients with pre-injury conditions who suffer mTBI. In the current analysis, we characterize the baseline systemic comorbidities of a prospectively collected multicenter mTBI sample with a high prevalence of pre-injury comorbidities, and investigate the relationships between systemic comorbidities and 3- and 6-month functional and post-concussive outcomes.

METHODS

The prospective Transforming Research and Clinical Knowledge in Traumatic Brain Injury Pilot (TRACK-TBI Pilot) study was conducted at three U.S. Level I trauma centers [Zuckerberg San Francisco General Hospital (California), University of Pittsburgh Medical Center (Pennsylvania), University Medical Center Brackenridge (Austin, Texas)] using the National Institute of Neurological Disorders and Stroke (NINDS) TBI Common Data Elements (CDEs) (20–24). Inclusion criteria for TRACK-TBI Pilot were age ≥16-years, external force head trauma, presentation to enrolling center, and clinically-indicated head computed tomography (CT) scan <24 h of injury. Exclusion criteria were pregnancy, ongoing life-threatening disease (e.g., end-stage malignancy), police custody, involuntary

psychiatric hold, and non-English speakers due to multiple outcome measures administered and/or normed only in English. As the goal of this analysis was to evaluate the associations between baseline comorbidities and outcomes, subjects with emergency department (ED) admission GCS 13–15 who completed the Glasgow Outcome Scale-Extended (GOSE) and Acute Concussion Evaluation (ACE) at 3- and 6-months were included. To minimize confounding of TBI outcomes, subjects with history of central nervous system malignancy, cerebrovascular anomaly/accident, human immunodeficiency virus/acquired immunodeficiency syndrome, and/or developmental delay were excluded.

Eligible subjects were enrolled by convenience sampling from years 2010–2012. Institutional Review Board approval was obtained at each participating site. Informed consent was obtained prior to enrollment. For subjects unable to provide consent due to injury, surrogate consent was obtained. Subjects were re-consented, if cognitively able, during the course of clinical care and/or follow-up timepoints for study participation.

Demographic and Clinical Variables

Subjects underwent a baseline assessment at ED admission. Variables were collected according to NINDS CDE version 1 (21, 23, 24). Twelve CDE pre-injury comorbidity categories (i.e., comorbidities present at baseline prior to the index mTBI of enrollment) were collected by standard checklists through self-report and chart abstraction, including cardiac-hypertension, cardiac-structural/ischemic/valvular, diabetes mellitus, gastrointestinal, hematologic, headache/migraine, hepatic, pulmonary, psychiatric, renal, seizure, and thyroid.

Outcome Measures

Outcome measures were collected through in-person or phone interview at 3- and 6-months. To focus on functional disability and post-concussive symptoms, the following measures were analyzed:

Glasgow Outcome Scale-Extended (GOSE): Structured interview which provides an overall measure of disability based on cognition, independence, employability, and social/community participation, and has been widely used as a standard outcome measure for TBI studies (25). Scores include: 1 = dead, 2 = vegetative state, 3 = lower severe disability, 4 = upper severe disability, 5 = lower moderate disability, 6 = upper moderate disability, 7 = lower good recovery, and 8 = upper good recovery. A score of 8 reflects recovery to baseline without new disability. For the current analysis, the ordinal GOSE was dichotomized into "good recovery (GOSE 7–8)" vs. "moderate disability or worse (GOSE $\leq$ 6)," consistent with prior reports (26, 27).

Acute Concussion Evaluation (ACE): First reported by a consensus sports neuropsychology panel in 1998 and adopted by the U.S. Centers for Disease Control and Prevention (CDC) in 2006 (28, 29). It contains 22 specific post-concussive symptoms classified into 4 domains: physical (10 symptoms), cognitive (4 symptoms), sleep (4 symptoms), and emotional (4 symptoms). Subjects were queried regarding the presence/absence of each symptom and the number of symptoms per domain were totaled for analysis.

Statistical Analysis

Descriptive statistics were assessed using means and standard deviations (SD) for continuous variables and proportions for categorical variables. Three- and six-month functional outcomes were analyzed using logistic regression (GOSE $\leq$ 6 vs. 7–8), and post-concussive outcomes were analyzed by domain using linear regression (number of symptoms). As variables of interest, pre-injury comorbidities with >10% incidence were included in multivariable models for outcome, controlling for age, sex, education (years), ED admission GCS, and presence/absence of intracranial abnormalities on CT. Multivariable odds ratios (OR) and associated 95% confidence intervals (CI) were reported for each predictor. Significance was assessed at $p < 0.0083$ using the Bonferroni correction ($0.05 \div 6$ comorbidities). Analyses were performed using Statistical Package for the Social Sciences (SPSS) version 24 (IBM Corp., Chicago, IL).

RESULTS

Overall, 260 mTBI subjects had a mean age of 44.0 $\pm$ 18.7-years, 70.4% were male, 78.6% were Caucasian, and 42.3% were head CT+. Baseline comorbidities >10% incidence included psychiatric (30.0%), cardiac-hypertension (23.8%), cardiac-structural/valvular/ischemic (20.4%), gastrointestinal (15.8%), pulmonary (15.0%), and headache/migraine (11.5%) **(Table 1)**. At 3- and 6-months, 30.8% had GOSE $\leq$ 6. Additional demographic and clinical variables are shown in **Table 1**.

On multivariable analysis at 3-months, psychiatric history was a predictor for functional disability (GOSE$\leq$6: OR = 2.75, 95% CI [1.44–5.27]) and all domains of post-concussive symptoms (ACE-physical: B = 1.06 [0.38–1.73]; ACE-cognitive: B = 0.72 [0.26–1.17]; ACE-sleep: B = 0.46 [0.17–0.75]; ACE-emotional: B = 0.64 [0.25–1.03]). Headaches/migraine history was a predictor for functional disability (GOSE $\leq$ 6: OR = 4.10 [1.67–10.07]), and sleep and emotional post-concussive symptoms (ACE-sleep: B = 0.57 [0.15–1.00]; ACE-emotional: B = 0.92 [0.35–1.49]). Gastrointestinal history was a predictor for physical post-concussive symptoms (ACE-physical: B = 1.25 [0.41–2.10]) **(Table 2A)**.

On multivariable analysis at 6-months, psychiatric history was a predictor for functional disability (GOSE $\leq$ 6: OR = 2.57 [1.38–4.77]) and all domains of post-concussive symptoms (ACE-physical: B = 1.38 [0.68–2.09]; ACE-cognition: B = 0.74 [0.28–1.20]; ACE-sleep: B = 0.51 [0.20–0.83]; ACE-emotional: B = 0.93 [0.53–1.33]). Headache/migraine history was a predictor for physical post-concussive symptoms (ACE-physical: B = 1.81 [0.79–2.84]) **(Table 2B)**.

DISCUSSION

The heterogeneity of mTBI in risk factors and outcomes leads to clinical challenges in patient-specific triage, treatment and prognosis. In a comprehensive report of pre-injury comorbidities and mTBI, we found psychiatric, cardiac, gastrointestinal,

TABLE 1 | Demographic and clinical characteristics in 260 mTBI subjects.

Variable	*N* (%) or mean ± SD
AGE	
Years (mean, SD)	44.0 ± 18.7
SEX	
Male	183 (70.4%)
Female	77 (29.6%)
EDUCATION	
Years (mean, SD)	14.2 ± 2.9
MECHANISM OF INJURY	
Motor vehicle accident	61 (23.5%)
Pedestrian vs. auto	37 (14.2%)
Fall	117 (45.0%)
Assault	35 (13.5%)
Struck by object	10 (3.9%)
ED ADMISSION GCS	
13	9 (3.5%)
14	53 (20.4%)
15	198 (70.2%)
INTRACRANIAL CT FINDINGS	
No	150 (57.7%)
Yes	110 (42.3%)
ED DISPOSITION	
Discharge home	88 (38.8%)
Hospital ward admit	109 (41.9%)
ICU admit	63 (24.2%)
PRE-INJURY COMORBIDITIES	
Psychiatric history	78 (30.0%)
Cardiac-hypertension history	62 (23.8%)
Cardiac-structural/ischemic/valvular history	53 (20.4%)
Gastrointestinal history	41 (15.8%)
Pulmonary history	39 (15.0%)
Headache/migraine history	30 (11.5%)
Seizure history	22 (8.5%)
Diabetes history	21 (8.1%)
Hepatic history	20 (7.7%)
Renal history	15 (5.8%)
Thyroid history	13 (5.0%)
Hematologic history	12 (4.6%)
3-MONTHS OUTCOMES	
GOSE ≤ 6	80 (30.8%)
ACE physical	2.33 ± 2.56
ACE cognitive	0.94 ± 1.10
ACE sleep	1.38 ± 1.65
ACE emotional	1.05 ± 1.45
6-MONTHS OUTCOMES	
GOSE ≤ 6	80 (30.8%)
ACE physical	2.84 ± 2.74
ACE cognitive	1.22 ± 1.18
ACE sleep	1.70 ± 1.69
ACE emotional	1.42 ± 1.52

ACE, Acute Concussion Evaluation; CT, computed tomography; ED, emergency department; GCS, Glasgow Coma Scale; GOSE, Glasgow Outcome Scale Extended; ICU, intensive care unit; SD, standard deviation.

pulmonary, and headache/migraine comorbidities to be of the highest incidence. In 260 mTBI subjects, psychiatric history was a predictor of functional disability and increased post-concussive at 3- and 6-months controlling for demographic and clinical variables and other pre-injury comorbidities. Additionally, headache/migraine history was a predictor of functional disability, sleep and emotional symptoms at 3-months, and physical symptoms at 6-months. These results constitute a first step to improved understanding of pre-injury risk factors and improved awareness of subsets of patients who may benefit from careful history taking, increased education, and surveillance, including triage to follow-up at early time points.

Psychiatric history is a known predictor of worsened functional and post-concussive outcome after mTBI (30). Over the past decade, studies have shown that baseline psychiatric morbidity is predictive of 2-week and 6-month outcomes separately. The multicenter UPFRONT study in the Netherlands showed that baseline mental health disorders conferred OR 0.31–0.39 for complete functional recovery (GOSE = 8) at 6-months (31). Our study shows that not only is functional recovery more likely to be incomplete in those with psychiatric history, but the effect of OR 2.5–2.8 for moderate functional disability or worse, e.g., unable to return to work, significant social or emotional disruption, is conserved at 3- and 6-months, in addition to the 0.5 to 1.4 more symptoms across post-concussive symptoms domains. Recent studies illustrate that recovery from mTBI is a non-linear process with subgroups of patients failing to rebound from their injury, such that prognostic models using pre-injury risk factors can be constructed to guide post-injury management (32–34). As mTBI patients are increasingly shown to have impairments in cognitive and neuropsychiatric recovery, it becomes ever more important to document and have an accurate understanding of the patient's baseline cognitive, psychiatric, and mental health in order to both monitor post-injury return to baseline, and address deficits from baseline during the process of recovery. Pertinent first steps include documentation of priority pre-injury comorbidities including presence and frequency of *prior* psychiatric and headache symptoms, setting expectations by informing patients with these comorbidities that their symptoms often worsen after mTBI, providing discharge instructions for patients and physicians to monitor whether post-injury symptomatology are new or worse during acute follow-up, and having a lower threshold to refer patients to follow-up with primary or specialist care.

Headache is the most common post-concussive symptom manifestation with 30–90% incidence (35–38). While post-traumatic headache (PTH) is well-documented after mTBI (39, 40), the relationship between pre-injury headaches/migraines with long-term post-injury functional outcomes remains understudied. Improved understanding of this association will help to determine whether a patient's PTH should be considered a new entity vs. a possible exacerbation of baseline headaches after mTBI. We showed that at baseline, 11.5% of patients suffered from headache/migraine, which predicted post-injury functional disability and sleep and

TABLE 2A | Multivariable regression of 3-months outcomes.

Variable	GOSE ≤ 6 (3-months)		ACE physical (3-months)		ACE cognitive (3-months)		ACE sleep (3-months)		ACE emotional (3-months)	
	OR [95% CI]	Sig. (*p*)	OR [95% CI]	Sig. (*p*)	OR [95% CI]	Sig. (*p*)	OR [95% CI]	Sig. (*p*)	OR [95% CI]	Sig. (*p*)
AGE										
Per-year	1.017 [0.997, 1.037]	0.089	0.007 [−0.013, 0.027]	0.478	0.006 [−0.008, 0.019]	0.398	0.001 [−0.008, 0.009]	0.854	0.003 [−0.009, 0.014]	0.629
SEX										
Male	Reference	–	Reference	–	Reference	–	Reference	–	Reference	–
Female	0.94 [0.48, 1.83]	0.855	0.53 [−0.15, 1.20]	0.124	−0.01 [−0.46, 0.44]	0.955	0.10 [−0.20, 0.39]	0.518	0.25 [−0.14, 0.65]	0.201
EDUCATION										
Per–year	0.98 [0.88, 1.09]	0.698	−0.15 [−0.26, −0.05]	0.005	−0.03 [−0.10, 0.04]	0.429	−0.06 [−0.10, −0.01]	0.015	−0.06 [−0.12, 0.00]	0.059
ED GCS										
=15	Reference	–	Reference	–	Reference	–	Reference	–	Reference	–
=13–14	1.17 [0.59, 2.33]	0.653	0.52 [−0.18, 1.22]	0.147	0.33 [−0.14, 0.80]	0.171	0.21 [−0.09, 0.51]	0.175	0.13 [−0.28, 0.53]	0.537
CT INTRACRANIAL LESION										
Absent	Reference	–	Reference	–	Reference	–	Reference	–	Reference	–
Present	3.12 [1.62, 6.02]	0.001	0.35 [−0.30, 1.01]	0.289	0.36 [−0.08, 0.80]	0.104	0.23 [−0.05, 0.52]	0.107	0.09 [−0.29, 0.47]	0.653
CARDIAC-HYPERTENSION HISTORY										
Absent	Reference	–	Reference	–	Reference	–	Reference	–	Reference	–
Present	0.55 [0.23, 1.29]	0.168	0.29 [−0.54, 1.12]	0.493	−0.07 [−0.63, 0.49]	0.813	−0.01 [−0.37, 0.35]	0.949	0.20 [−0.28, 0.68]	0.412
CARDIAC-STRUCTURAL/ISCHEMIC/VALVULAR HISTORY										
Absent	Reference	–	Reference	–	Reference	–	Reference	–	Reference	–
Present	0.68 [0.30, 1.51]	0.338	−0.98 [−1.84, 0.12]	0.026	−0.12 [−0.70, 0.46]	0.685	−0.19 [−0.56, 0.18]	0.317	−0.32 [−0.82, 0.18]	0.206
GASTROINTESTINAL HISTORY										
Absent	Reference	–	Reference	–	Reference	–	Reference	–	Reference	–
Present	1.56 [0.71, 3.43]	0.265	1.25 [0.41, 2.10]	0.004	0.36 [−0.21, 0.92]	0.218	0.44 [0.07, 0.80]	0.019	0.23 [−0.26, 0.72]	0.358
PULMONARY HISTORY										
Absent	Reference	–	Reference	–	Reference	–	Reference	–	Reference	–
Present	0.40 [0.15, 1.07]	0.068	−0.68 [−1.55, 0.20]	0.129	−0.48 [−1.06, 0.11]	0.109	−0.44 [−0.82, −0.06]	0.023	−0.21 [−0.72, 0.30]	0.412
PSYCHIATRIC HISTORY										
Absent	Reference	–	Reference	–	Reference	–	Reference	–	Reference	–
Present	2.75 [1.44, 5.27]	0.002	1.06 [0.38, 1.73]	0.002	0.72 [0.26, 1.17]	0.002	0.46 [0.17, 0.75]	0.002	0.64 [0.25, 1.03]	0.002
HEADACHE/MIGRAINE HISTORY										
Absent	Reference	–	Reference	–	Reference	–	Reference	–	Reference	–
Present	4.10 [1.67, 10.07]	0.002	0.86 [−0.12, 1.84]	0.085	0.76 [0.10, 1.42]	0.023	0.57 [0.15, 1.00]	0.008	0.92 [0.35, 1.49]	0.002

Significance set at $p < 0.0083$. ACE, Acute Concussion Evaluation; CI, confidence interval; CT, computed tomography; ED, emergency department; GCS, Glasgow Coma Scale; GOSE, Glasgow Outcome Scale Extended; OR, odds ratio.

TABLE 2B | Multivariable regression of 6-months outcomes.

Variable	GOSE≤6 (6-months)		ACE physical (6-months)		ACE cognitive (6-months)		ACE sleep (6-months)		ACE emotional (6-months)	
	OR [95% CI]	Sig. (*p*)	OR [95% CI]	Sig. (*p*)	OR [95% CI]	Sig. (*p*)	OR [95% CI]	Sig. (*p*)	OR [95% CI]	Sig. (*p*)
AGE										
Per-year	1.007 [0.988, 1.026]	0.487	0.016 [−0.005, 0.037]	0.127	−0.003 [−0.016, 0.011]	0.670	0.010 [0.000, 0.019]	0.041	−0.007 [−0.019, 0.005]	0.254
SEX										
Male	Reference	–	Reference	–	Reference	–	Reference	–	Reference	–
Female	1.44 [0.76, 2.74]	0.259	0.89 [0.19, 1.60]	0.013	0.08 [−0.38, 0.53]	0.744	0.03 [−0.28, 0.35]	0.838	0.22 [−0.19, 0.62]	0.290
EDUCATION										
Per-year	0.90 [0.81, 0.99]	0.036	−0.08 [−0.19, 0.03]	0.147	−0.04 [−0.11, 0.04]	0.313	−0.05 [−0.10, 0.00]	0.035	−0.02 [−0.09, 0.04]	0.475
ED GCS										
=15	Reference	–	Reference	–	Reference	–	Reference	–	Reference	–
=13–14	2.27 [1.20, 4.35]	0.012	0.73 [−0.01, 1.46]	0.053	0.49 [0.01, 0.96]	0.044	0.32 [−0.01, 0.65]	0.057	0.47 [0.05, 0.89]	0.029
CT INTRACRANIAL LESION										
Absent	Reference	–	Reference	–	Reference	–	Reference	–	Reference	–
Present	1.44 [0.77, 2.70]	0.260	−0.38 [−1.07, 0.30]	0.273	0.32 [−0.12, 0.76]	0.156	−0.37 [−0.67, −0.06]	0.018	−0.17 [−0.57, 0.22]	0.386
CARDIAC–HYPERTENSION HISTORY										
Absent	Reference	–	Reference	–	Reference	–	Reference	–	Reference	–
Present	0.53 [0.22, 1.25]	0.145	0.13 [−0.74, 1.01]	0.762	0.01 [−0.55, 0.57]	0.971	−0.15, [−0.53, 0.24]	0.462	0.00 [−0.50, 0.50]	0.987
CARDIAC-STRUCTURAL/ISCHEMIC/VALVULAR HISTORY										
Absent	Reference	–	Reference	–	Reference	–	Reference	–	Reference	–
Present	0.99 [0.45, 2.15]	0.972	−0.39 [−1.29, 0.51]	0.396	0.12 [−0.46, 0.71]	0.674	−0.16 [−0.56, 0.24]	0.428	0.22 [−0.29, 0.74]	0.396
GASTROINTESTINAL HISTORY										
Absent	Reference	–	Reference	–	Reference	–	Reference	–	Reference	–
Present	1.89 [0.87, 4.11]	0.107	0.61 [−0.27, 1.50]	0.173	0.72 [0.15, 1.29]	0.014	0.37 [−0.02, 0.76]	0.065	0.42 [−0.09, 0.92]	0.106
PULMONARY HISTORY										
Absent	Reference	–	Reference	–	Reference	–	Reference	–	Reference	–
Present	0.87 [0.37, 2.03]	0.740	−0.46 [−1.37, 0.45]	0.323	−0.10 [−0.69, 0.49]	0.743	0.18 [−0.22, 0.59]	0.365	−0.54 [−1.06, −0.02]	0.043
PSYCHIATRIC HISTORY										
Absent	Reference	–	Reference	–	Reference	–	Reference	–	Reference	–
Present	2.57 [1.38, 4.77]	0.003	1.38 [0.68, 2.09]	<0.001	0.74 [0.28, 1.20]	0.001	0.51 [0.20, 0.83]	0.001	0.93 [0.53, 1.33]	<0.001
HEADACHE/MIGRAINE HISTORY										
Absent	Reference	–	Reference	–	Reference	–	Reference	–	Reference	–
Present	1.72 [0.71, 4.13]	0.227	1.81 [0.79, 2.84]	0.001	0.78 [0.12, 1.44]	0.021	0.26 [−0.19, 0.72]	0.259	0.43 [0.16, 1.02]	0.150

Significance set at $p < 0.0083$. ACE, Acute Concussion Evaluation; CI, confidence interval; CT, computed tomography; ED, emergency department; GCS, Glasgow Coma Scale; GOSE, Glasgow Outcome Scale Extended; OR, odds ratio.

emotional post-concussive symptoms at 3-months, as well as physical post-concussive symptoms at 6-months. Our results not only support previous findings regarding the importance of evaluating for premorbid headache/migraine as a risk factor for PTH (40), but also show that headache/migraine history is associated with multiple outcome domains after mTBI. In addition to psychological factors and mental health as predictors of 6-months outcome after mTBI (31), we demonstrate the need to identify risk factors from other categories of pre-injury medical history. In our study, pre-injury headache/migraine was associated with different outcome domains between 3- and 6-months, suggesting that deficits may continue to evolve over time after mTBI. These findings alert both clinicians and researchers to the need for standardized assessment of functional disability and post-concussive symptoms at multiple (and earlier) time points, as early interventions post-injury may decrease maladaptive coping methods, loss of livelihood/productivity, and healthcare costs. Along with psychiatric history and pre-injury headache/migraine being predictors of functional disability and post-concussive symptoms at 3-months, we found that gastrointestinal history also associated with physical post-concussive symptoms. Aside from cognitive and neuropsychiatric impairments, there is emerging interest in understanding systemic effects of autonomic dysfunction after mTBI (41). For the first 3-months post-injury, mTBI can possibly exacerbate the complex and non-specific nature of gastrointestinal symptoms as reflected through physical post-concussive symptoms in the patient.

Limitations

We studied associations between pre-injury comorbidities and outcomes, and in consideration for not overfitting our regression models, we limited to controlling for known predictors of mTBI outcomes rather than all possible predictors available in our dataset. We did not study trajectories of outcomes, nor whether mTBI had effects on the severity of pre-injury comorbidities. Patient recruitment is limited to Level I trauma centers capturing a more urbanized population, and thus our findings cannot be extrapolated to all mTBI patients. Proportions of telephone vs. in-person follow-ups, which have been shown to influence extent of disclosure in cancer and genetics studies (42), were unavailable from our dataset and constitutes another limitation. This is a study of association, hence we are unable to make claims regarding causality or pathophysiology. We limited our multivariable analysis to comorbidities with over 10% incidence in the sample to provide reliable odds ratios, and future studies of larger sample size will enable analyses of the relationship between specific comorbidities within each organ system and outcome. Lastly, we were limited by the variables available and were unable to investigate whether subjects successfully triaged to and/or completed rehabilitation programs. Our goal is to establish a first step in assessing the importance of baseline comorbidities on mTBI outcome, hence our findings remain exploratory and in need of validation by future trials. Integrating the evaluation of pre-injury comorbidities with that of other baseline predictors not routinely collected on admission, such as education level, may be important in the prognostication of outcome after mTBI.

Conclusions

Amongst pre-injury comorbidities, history of psychiatric disorder is a risk factor for decreased functional outcome and increased post-concussive symptoms across multiple domains, at 3- and 6-months post-injury after mTBI. History of headache/migraine may also be a risk factor for decreased functional outcome and increased post-concussive symptoms. mTBI patients presenting to acute and post-discharge care should be evaluated for history of baseline psychiatric and headache/migraine disorders, with lower thresholds for provision of TBI education and resources, surveillance, and follow-up/referrals to primary and specialist care.

ETHICS STATEMENT

This study was carried out in accordance with the recommendations of the University of California San Francisco (UCSF) Institutional Review Board of record, the Committee on Human Research (CHR), with written informed consent from all subjects. All subjects gave written informed consent in accordance with the Declaration of Helsinki. The protocol was approved by the UCSF CHR #10-00011.

AUTHOR CONTRIBUTIONS

JY, MC, DS, AP, RG, EY, PM, AV, DO, HL, and GM: conception or design of work; JY, MC, EW, HD, RP, NC, SS, CR, CS, MV, DS, AP, RG, EY, PM, AV, DO, HL, and GM: acquisition, analysis, or interpretation of data for the work, providing approval for publication of the content, and agree to be held accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved; JY, MC, EW, HD, RP, NC, SS, CR, CS, MV, DS, AP, EY, RG, PM, AV, DO, HL, and GM: drafting the work or revising it critically for important intellectual content.

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Advice to Rest for More Than 2 Days After Mild Traumatic Brain Injury Is Associated With Delayed Return to Productivity: A Case-Control Study

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Objectives: Recent expert agreement statements and evidence-based practice guidelines for mild traumatic brain injury (mTBI) management no longer support advising patients to "rest until asymptomatic," and instead recommend gradual return to activity after 1–2 days of rest. The present study aimed to: (i) document the current state of de-implementation of prolonged rest advice, (ii) identify patient characteristics associated with receiving this advice, and (iii) examine the relationship between exposure to this advice and clinical outcomes.

Methods: In a case-control design, participants were prospectively recruited from two concussion clinics in Canada's public health care system. They completed self-report measures at clinic intake (Rivermead Post-concussion Symptom Questionnaire, Personal Health Questionnaire-9, and Generalized Anxiety Disorder-7) as well as a questionnaire with patient, injury, and recovery characteristics and the question: "Were you advised by at least one health professional to rest for more than 2 days after your injury?"

Results: Of the eligible participants ($N = 146$), 82.9% reported being advised to rest for more than 2 days (exposure group). This advice was not associated with patient characteristics, including gender (95% CI odds ratio = 0.48–2.91), race (0.87–6.28) age (0.93–1.01), a history of prior mTBI(s) (0.21–1.20), or psychiatric problems (0.40–2.30), loss of consciousness (0.23–2.10), or access to financial compensation (0.50–2.92). In generalized linear modeling, exposure to prolonged rest advice predicted return to productivity status at intake ($B = -1.06$, chi-squared(1) = 5.28, $p = 0.02$; 64.5% in the exposure group vs. 40.0% in the control were on leave from work/school at the time of clinic intake, 19.8 vs. 24% had partially returned, and 11.6 vs. 24% had fully returned to work/school). The exposure group had marginally (non-significantly) higher post-concussion, depression, and anxiety symptoms.

Conclusions: mTBI patients continue to be told to rest for longer than expert recommendations and practice guidelines. This study supports growing evidence that

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prolonged rest after mTBI is generally unhelpful, as patients in the exposure group were less likely to have resumed work/school at 1–2 months post-injury. We could not identify patient characteristics associated with getting prolonged rest advice. Further exploration of who gets told to rest and who delivers the advice could inform strategic de-implementation of this clinical practice.

Keywords: brain concussion, craniocerebral trauma, rehabilitation, rest, return to work

INTRODUCTION

In the early twenty-first century, complete rest until symptom resolution was introduced as best practice for mild traumatic brain injury (mTBI) management (1, 2). This practice was widely disseminated (3, 4) and followed (5, 6). Despite a lack of evidence for efficacy or agreement about what constitutes "rest," the majority of observational studies (7–10) and randomized clinical trials (11–13) have found that rest beyond few days after mTBI is not beneficial, and may actually prolong recovery (14). Concerns have also been raised about iatrogenic physiological and psychological effects of prescribed rest. For example, removing individuals from their recreational, occupational, and social settings may increase their risk of developing depression (15–17). Correspondingly, the most recent expert consensus statements and practice guidelines for both sport-related mTBI and mTBI sustained in other settings advise against complete rest for more 1 or 2 days (18–21). In Canada, the setting of the present study, this change came in 2013, with the 2nd edition of the Guidelines for Concussion/Mild Traumatic Brain Injury & Persistent Symptoms (22). However, as with changes to practice guidelines in other health conditions, de-implementation of prescribed rest for mTBI may be slow (23, 24).

The present study had multiple objectives. First, we assessed the degree to which patients with mTBI are still being advised to rest for longer than contemporary guidelines recommend. We hypothesized that most participants would still receive prolonged rest advice, as knowledge regarding mTBI management has evolved rapidly and active knowledge-transfer has likely been insufficient (25). Second, we explored whether certain patient characteristics were associated with receiving guideline non-compliant prolonged rest advice. We hypothesized that demographic (e.g., gender), health history (e.g., prior mTBIs), and injury variables (e.g., presence of loss of consciousness) would make it more likely for clinicians to recommend excessive rest. Knowing which patients are more or less likely to be told to rest can inform de-implementation strategies. Third, we aimed to add to the growing literature on the benefits and harms of excessive rest by comparing patients who were vs. were not exposed to prolonged rest advice. We hypothesized that prolonged rest advice would not be strongly related to symptomatic recovery (11, 13), but would coincide with taking longer to return to work/school and having more depressive or anxiety symptoms. These potential harms of prescribed rest have been previously hypothesized (15, 26) but not empirically evaluated.

MATERIALS AND METHODS

Participants and Procedures

This study was a secondary analysis of a broader clinical trial, which examines the effect of tailored follow-up letters on proactive mTBI symptom management by family physicians (ClinicalTrials.gov Identifier: NCT03221218). The study was approved by the University of British Columbia Clinical Research Ethics Board and Fraser Health Research Ethics Board. Participant recruitment took place from August 2017 to October 2018 in two public sector outpatient mTBI clinics in urban British Columbia, Canada.

At their first clinic appointment, patients were screened for eligibility with the following study criteria: (1) aged 18–60 years; (2) sustained a physician diagnosed MTBI <3 months ago; (3) fluent in English; and (4) had a family physician or could identify a walk-in clinic where they access primary care (for the parent study). After consenting, participants were asked to complete a series of questionnaires and standardized assessments in-person or online (from home) within 3 days. Embedded in a survey about demographics and injury details was the following retrospective question: "Were you advised by at least one health professional to rest for more than 2 days after your injury?" Participants were considered to be exposed to guideline non-compliant prolonged rest advice when they answered this question affirmatively. Of 235 patients who met the eligibility criteria during the recruitment period, 150 agreed to participate, and of those 146 answered the rest advice exposure question, forming the sample for the present study.

Outcome Measures

Participants reported their current productivity status by answering whether they had fully returned or partially returned to work/school, were on leave (e.g., sick or medical leave or short-term disability), or that the question did not apply to them (i.e., they were not working or going to school at the time of their injury).

The Rivermead Post-Concussion Symptom Questionnaire (RPQ) (27) is self-report inventory commonly used for mTBI research (28). It is a 16-item questionnaire that measures the severity of current symptoms (e.g., headache, fatigue, concentration difficulties) on a scale from 0 ("not experienced at all") to 4 ("a severe problem"). A response of one indicates that a symptom is present but "no more of a problem" compared to pre-injury. Item scores of 2–4 are summed to create a total score ranging from 0 to 64.

The Patient Health Questionnaire (PHQ-9) (29, 30) is a brief, reliable, and valid depression screening measure. It queries the

frequency of depression symptoms over the past 2 weeks. Items are summed to create a total score that can range from 0 to 27, where higher scores indicate worse depression symptoms.

The Generalized Anxiety Disorder (GAD-7) (31) screens for anxiety symptoms (e.g., feeling nervous, worrying too much, trouble relaxing) over the past 2 weeks. The total score ranges from 0 to 21, with higher scores reflecting worse anxiety.

Statistical Analysis

Logistic regression was used to examine whether patient characteristics were associated with getting prolonged rest advice. No prior evidence was available to guide predictor selection. We hypothesized that health providers would be more likely to prescribe rest for more than 2 days (what they might view as conservative management) for patients they perceive (intentionally or inadvertently) to be vulnerable, such as women, older adults, and people with more severe injuries (indicated by the presence of loss of consciousness) or a history of prior mTBI(s) or psychiatric problems. Patients with access to financial compensation might be seen as more able to take time off work, so we also included this variable in the logistic regression model. Adjusted odds ratios were derived from the model in which all predictor variables were entered, and therefore reflect the *unique* association between the predictor and outcome, controlling for all other predictors.

We used generalized linear models to evaluate the relationship between advice to rest and clinical outcomes, including productivity status, post-concussion symptoms (RPQ), depression (PHQ-9), and anxiety (GAD-7). Data was missing for <5% of participants for all outcome variables except the RPQ. The total RPQ score was missing for 13% ($n = 19$) of participants. For participants who answered at least 13 of the 16 items ($n = 10$), missing item values were imputed with the participants' average item scores for the items they answered (rounded to a whole number). Participants who did not respond to three or more RPQ items ($n = 9$) and participants who responded "not applicable" to the productivity status question ($n = 8$) were excluded from the generalized linear models involving these outcome variables. We specified a multinomial probability distribution and cumulative logit link function for the ordinal productivity status outcome variable and a Gaussian probability distribution and identity link function for the continuous outcome variables.

Considering that participants who were exposed to prolonged rest advice might systematically differ from those who were not, we used regression-based propensity score adjustment to mitigate this potential bias. Specifically, we re-ran the generalized linear models with an additional covariate. The covariate was the predicted probability of group membership in the logistic regression model described above, where higher scores (closer to 1.0) represent greater likelihood of exposure to prolonged rest advice.

RESULTS

Participant characteristics are summarized in **Table 1**. The majority (82.9%) of participants were exposed to prolonged rest advice. As shown in **Table 2**, exposure to prolonged rest advice was not significantly associated with any of the hypothesized factors, including sex, age, loss of consciousness, or history of prior mTBIs or psychiatric problems.

TABLE 1 | Demographic, injury, and initial assessment characteristics.

	Full sample ($n = 146$)	Exposed to rest ($n = 121$)	Not exposed to rest ($n = 25$)
DEMOGRAPHICS			
Age, M (SD)	40.6 (12.2)	39.8 (11.8)	44.4 (13.5)
Sex, n (%female)	98 (67.1%)	82 (67.8%)	16 (64%)
Ethnicity, *n* (%)			
Caucasian	88 (60.7%)	69 (57.5%)	19 (76%)
Other	57 (39.3%)	51 (42.1%)	6 (24%)
Education Level, *n* (%)			
High school or less	20 (13.7%)	16 (13.2%)	4 (16%)
Some college	24 (16.4%)	20 (16.5%)	4 (16%)
Technical degree/Diploma or associate degree	31 (21.2%)	26 (21.5%)	5 (20%)
Bachelor's degree	47 (32.2%)	38 (31.4%)	9 (36%)
Graduate/Professional degree	24 (16.4%)	21 (17.5%)	3 (12%)
INJURY CHARACTERISTICS			
Loss of Consciousness			
Yes	23 (15.8%)	18 (14.9%)	5 (22.7%)
No	99 (67.8%)	82 (67.8%)	17 (77.3%)
Unclear	7 (4.8%)	7 (5.8%)	0
Missing	17 (11.6%)	14 (11.6%)	0
Mechanism of Injury, *n* (%)			
Motor vehicle accident	68 (47.2%)	58 (48.3%)	10 (41.7%)
Fall	24 (16.7%)	21 (17.5%)	3 (12.5%)
Assault	2 (1.4%)	2 (1.7%)	0
Sports and recreation	24 (16.7%)	18 (15.0%)	6 (25%)
Other	26 (18.1%)	21 (17.5%)	5 (20.8%)
HEALTH HISTORY			
Previous mild traumatic brain injury, *n* (%)	55 (38.2%)	42 (35.3%)	13 (52%)
Pre-injury psychiatric problems, *n* (%)	54 (39.0%)	47 (38.8%)	10 (40%)
INITIAL ASSESSMENT			
Days to initial assessment, M (SD)	41.2 (26.7)	40.34 (26.8)	45.3 (26.6)
PHQ-9 total, M (SD)	13.3 (5.5)	13.6 (5.4)	12.3 (6.0)
GAD-7 total, M (SD)	9.8 (5.5)	9.9 (5.4)	9.2 (5.8)
RPQ total, M (SD)*	36.8 (13.6)	37.6 (13.6)	33.0 (13.8)
Access to Compensation, *n* (%)			
Yes	93 (63.7%)	78 (64.5%)	15 (60%)
No	39 (26.7%)	30 (24.8%)	9 (36%)
Unsure	14 (9.6%)	13 (10.7%)	1 (4%)
Return to Work/School Status, *n* (%)			
Full return	20 (13.3%)	14 (11.6%)	6 (24%)
Partial return	30 (20.5%)	24 (19.8%)	6 (24%)
On leave	88 (60.3%)	78 (64.5%)	10 (40%)
Not applicable	8 (5.5%)	5 (4.1%)	3 (12%)

**Missing n = 9. PHQ-9, personal health questionnaire-9; GAD-7, generalized anxiety disorder-7; RPQ, rivermead post-concussion symptom questionnaire.*

Generalized linear modeling (see **Table 3**) revealed that participants who were exposed to prolonged rest advice had lower productivity at the time of assessment (2–10 weeks post-injury), B = −1.06, chi-squared(1) = 4.88, $p = 0.027$. This finding held after propensity score adjustment, B = −1.02, chi-squared(1) = 4.36, $p = 0.037$. The breakdown was: 64.5% in the exposure group vs. 40.0% in the control were on leave from work/school, 19.8 vs. 24% had partially returned to work/school, and 11.6 vs. 24% had fully returned to work/school. Exposure to prolonged rest advice was not a significant predictor of the post-concussion (RPQ), depression (PHQ-9), or anxiety (GAD-7) symptoms at the time of assessment (see **Table 3**), with trends favoring the non-exposed group on all variables (**Table 1**).

DISCUSSION

Clinical practice guidelines for concussion and mTBI have moved away from "rest until asymptomatic" as the standard of care to promoting early, graded return to activity as tolerated after an initial 1–2 days of rest (19, 21). The present study found little evidence of progress with de-implementation of prolonged rest advice. The vast majority of patients with mTBI in our cohort (83%) reported being told by at least one health professional to rest for more than 2 days after their injury.

Understanding *who* is told to rest could inform knowledge translation efforts to de-implement this practice. If patients with certain characteristics are more likely to receive inappropriate advice, knowledge translation strategies could be tailored accordingly. We hypothesized that, for example, patients with worse injuries (i.e., had an acute loss of consciousness) and a history of prior mTBIs might be perceived to require more conservative management (longer rest time). We did not observe an association between prolonged rest advice and any measured demographic, health history, or injury variable.

Another aim of the present study was to check for empirical evidence consistent with the hypothesis that prolonged rest advice is associated with delayed return to productivity and elevated risk of depression (17). Prescribed rest is likely ineffective, that is, probably does not facilitate recovery (11, 13, 14), but it is unclear whether this clinical intervention has adverse effects. Patients who are (inappropriately) told that prolonged rest is therapeutic may be more cautious in resuming their usual activities. In turn, isolation from socialization and valued activities may precipitate depression (32). We compared the clinical outcomes of patients who reported being advised to rest for a prolonged period (>2 days after their injury) to patients who denied receiving such (guideline non-compliant) advice. Our main finding was that the two groups looked similar (at mean = 41.2 days post-injury) with respect to post-concussion symptoms, anxiety, and depression; however, participants who were exposed to prolonged rest advice were significantly less likely to have returned to their pre-injury work or school status.

The present study has important limitations. It provides a snapshot of de-implementation at one point in time (2017–2018), in one geographic region. It also does not provide any granularity with respect to who delivered the rest advice (which health professionals), where the communication occurred (e.g., in an Emergency Department vs. a primary care office), or the exact content of the communication. Our methodology relied on the patient's recall of what they were told, which may be biased by misunderstanding or misremembering, but is arguably most relevant to their clinical outcomes. Although participants in the exposure group were told to rest for

TABLE 2 | Logistic regression models.

Variable	Odds ratio (95% CI)		Percentage advised to rest (>2 days)
	Unadjusted	Adjusted	
Loss of consciousness	0.69 (0.23–2.10)	0.82 (0.25–2.73)	Present, 78.3%
			Absent, 84.0%
Sex	1.18 (0.48–2.91)	1.32 (0.47–3.69)	Female, 83.7%
			Male, 81.3%
History of mTBI(s)	0.50 (0.21–1.20)	0.50 (0.19–1.35)	one or more, 76.4%
			None, 86.5%
Pre-injury psychiatric problems	0.95 (0.40–2.30)	0.97 (0.35–2.69)	Present, 82.5%
			Absent, 83.1%
Access to compensation	1.21 (0.50–2.92)	1.41 (0.53–3.74)	Yes, 83.9%
			No, 81.1%
Age	0.97 (0.93–1.01)	0.97 (0.94–1.01)	–

TABLE 3 | Generalized linear models.

	Single predictor model (exposure status only)			Two-predictor model (exposure status and propensity score)		
	B	Wald chi-square	Sig.	B	Wald chi-square	Sig.
Productivity status	−1.055	4.875	0.027	−1.02	4.363	0.037
RPQ	−4.224	1.798	0.180	−5.091	2.111	0.146
PHQ-9	−1.102	0.746	0.388	−1.227	0.879	0.348
GAD-7	−0.647	0.248	0.619	−0.402	0.091	0.763

PHQ-9, personal health questionnaire-9; GAD-7, generalized anxiety disorder-7; RPQ, rivermead post-concussion symptom questionnaire.

more than 2 days by "at least one" health professional, it is entirely possible that they were given contradictory advice by other health professionals and/or were exposed to contradictory advice from non-health professionals and written or web-based information sources. Considering this fact, it is somewhat surprising that we detected a significant association between exposure status and productivity outcomes. It is important to emphasis that this was an observational study, not a randomized trial. It may not have been random who was exposed to rest vs. not. No measured patient factors were statistically associated with exposure, which means either that (i) the groups were well-matched, approximating a randomized trial, or that (ii) important confounds went unmeasured. That is, our attempt to control for potential confounds with regression-based propensity matching may have been unnecessary or ineffective. Generalizability of the study findings may be limited by selection bias. Participants were recruited from an outpatient specialty clinic setting and therefore our sample did not include patients who recovered well without seeking care. To the extent prolonged rest advice is associated slow recovery, we may have over-sampled patients with exposure to such advice. Further contributing to selection bias, almost 40% of eligible patients did not enroll in the study.

In summary, we found that prolonged rest advice continues to be dispensed widely and without apparent consideration of individual patient or injury factors. We also found that patients who received prolonged rest advice were less likely to have completely returned to work or school at ∼6 weeks post-injury. De-implementation efforts are warranted, and could be facilitated by research into health provider and environmental factors that influence the practice of advice to rest after mTBI.

ETHICS STATEMENT

This study was carried out in accordance with the recommendations of name of guidelines, name of committee; with written informed consent from all subjects. All subjects gave written informed consent in accordance with the Declaration of Helsinki. The protocol was approved by the University of British Columbia Clinical Research Ethics Board.

AUTHOR CONTRIBUTIONS

NS obtained funding, conceived of the study, oversaw data collection, and co-wrote the first draft of the manuscript. TO refined the research questions, carried out the statistical analyses, and co-wrote the first draft of the manuscript. Both authors reviewed and approved the final version.

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The Predictive Capacity of the Buffalo Concussion Treadmill Test After Sport-Related Concussion in Adolescents

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The Buffalo Concussion Treadmill Test (BCTT) identifies the heart rate threshold (HRt) of exercise tolerance in concussed patients. A previous study found that an absolute HRt of < 135 bpm was associated with prolonged recovery (>30 days) from sport-related concussion (SRC). In this study, we assessed the relationship of ΔHR (difference between resting HR and HRt) and recovery from SRC. Using a retrospective cohort design, we compared acutely (<10 days since injury) concussed adolescents who were prescribed either (1) relative rest (RG, $n = 27$, 15.2 ± 1 years, 33% female, median 17 days to recovery, ΔHR = 69.6 ± 28 bpm), (2) a placebo-stretching program (PG, $n = 51$, 15.4 ± 2 years, 49% female, median 17 days to recovery, ΔHR = 60.9 ± 22 bpm), or (3) sub-threshold aerobic exercise (AG, $n = 52$, 15.3 ± 2 years, 46% female, median 13 days to recovery, ΔHR = 62.4 ± 26 bpm). Linear regression showed that ΔHR significantly correlated with duration of clinical recovery for RG ($p = 0.012$, $R^2 = 0.228$) and PG ($p = 0.011$, $R^2 = 0.126$) but not for AG ($p = 0.084$, $R^2 = 0.059$). ΔHR values were significantly lower in participants with prolonged recovery (>30 days) in RG ($p = 0.01$) and PG ($p = 0.04$). A ΔHR of ≤50 bpm on the BCTT is 73% sensitive and 78% specific for predicting prolonged recovery in concussed adolescents who were prescribed the current standard of care (i.e., cognitive and physical rest).

Keywords: Buffalo Concussion Treadmill Test, sport-related concussion, adolescent, post-concussion syndrome, exercise intolerance

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INTRODUCTION

Sport-related concussion (SRC), a type of mild traumatic brain injury (mTBI), is a significant public health concern (1, 2). Concussion is defined as reversible neurological dysfunction in the absence of gross brain lesions, caused by either by a direct blow to the head, neck, or elsewhere on the body with an impulsive force transmitted to the head (3, 4). SRC presents with a variety of somatic, cognitive, and affective symptoms (5). Symptom-limited exercise intolerance, i.e., the inability to exercise to the level predicted for one's age and fitness because of symptom exacerbation, helps

to define physiological dysfunction after SRC (6). The degree of exercise intolerance within the first week after SRC is a strong indicator of the severity of SRC (7, 8). The cause for exercise intolerance after concussion is not fully understood but may be related to damage to the brainstem that uncouples the autonomic nervous system (ANS) from the cardiovascular system (9, 10). It is theorized that abnormal ANS function alters cerebral blood flow (CBF) regulation during exercise that produces symptoms of headache and dizziness to limit exercise duration (11, 12). Most patients recover from SRC in 7 to 10 days but up to 30% take longer to recover (13, 14). If symptoms persist for more than 2 weeks in adults and for more than 1 month in adolescents, then they are described as having Persistent Post-concussive symptoms (PPCS) (15).

The Buffalo Concussion Treadmill Test (BCTT) (16) is a validated test to measure the amount of aerobic exercise that is safe to perform, even in the acute phase after concussion (17, 18). The heart rate (HR) achieved at symptom exacerbation on the BCTT is called the heart rate threshold (HRt). In a previous randomized controlled trial in acutely concussed adolescents (17), a HRt < 135 bpm was significantly associated with recovery of > 21 days. An absolute HRt cut-off value is, however, not appropriate for everyone due to the large variation in resting HR, which is dependent on multiple factors, including cardiovascular fitness (19). In an attempt to develop a predictor better suited to individual differences in fitness, the purpose of this study was to determine whether the difference between resting HR and HRt (the ΔHR) correlated with duration of clinical recovery. Since the standard of care for SRC is changing to a more active approach (20, 21), we included a prior cohort of 27 adolescents prescribed rest in addition to 2 groups of acutely concussed adolescents who were prescribed either a placebo-stretching program or sub-symptom threshold aerobic exercise. Adolescents were studied because they are predominantly concussed in sport (22) and take the longest to recover (23). We hypothesized that the ΔHR on the BCTT within 10 days of injury would correlate with duration of clinical recovery and that participants who developed PPCS would have significantly lower ΔHR than participants who did not. Our secondary aim was to establish a ΔHR value that differentiated between normal and prolonged recovery.

MATERIALS AND METHODS

Data from two published randomized controlled trials were used for the current study, the first (17) recruited between March 2013 and February 2015 (clinicaltrials.gov: NCT02714192) and the second (24) recruited between September 2015 and June 2018 (clinicaltrials.gov: NCT02710123). The University at Buffalo Institutional Review Board approved both studies.

Study Design

Experienced sports medicine physicians evaluated adolescent athletes seen at the University Concussion Management Clinics within 10 days of injury. If eligible for the study, a research assistant explained the study and obtained consent on the same day. Parental consent was obtained for all minors. Sports medicine physicians diagnosed concussion based on a thorough history (including cognitive evaluation and concussion symptom questionnaire) (25) and a standardized physical examination (26). Participants then performed the BCTT to assess degree of exercise tolerance. All participants reported symptoms online daily on a password-protected website between 7 and 10 p.m. using the Post-Concussion Symptom Scale (PCSS) (27) until they were cleared for return-to-play (RTP) or for up to 4 weeks, whichever came first. For those participants who recovered after 4 weeks, the date of recovery was retrospectively determined by electronic medical records. Recovery was defined as symptom resolution to baseline, confirmed by a physician performed physical examination, and the ability to exercise to exhaustion without exacerbation of symptoms on the BCTT (28).

Intervention

Rest Group

Participants in the Rest Group (RG) were prescribed cognitive and physical rest according to the previous standard of care (29). They were told that rest was recommended to give their concussed brain a chance to heal. Rest was described as not participating in any sports or other forms of exercise, including gym class. They were told to limit activities that could exacerbate symptoms such as watching TV or using their phones. Participants were seen every week and the same advice was given until clinical recovery. Participants were referred for cervical or vestibular therapy as needed if they did not recover by 30 days since injury.

Placebo Group

Participants in the Placebo Group (PG) were prescribed cognitive rest and were instructed to perform a standardized combination of light stretches and breathing exercises that would not elevate HR. They were given a Polar HR monitor (Model #FIT N2965, Kempele, Finland) to monitor their HR while stretching. They were instructed to not participate in sports or other physical activities that would raise their HR. They were also told to limit activities that could exacerbate symptoms such as excessive use of computer screens or using their phones. Participants were seen every week to perform the BCTT and a new set of stretching exercises was given until recovery. Participants were referred for cervical or vestibular therapy as needed if they did not recover by 30 days since injury.

Aerobic Group

Participants in the Aerobic Group (AG) were instructed to perform aerobic exercise (i.e., walking, jogging, or stationary cycling) at 80% of the HRt achieved on the BCTT for 20 min a day. They were given a Polar HR monitor (Model #FIT N2965, Kempele, Finland) to exercise according to their HR prescription. They were instructed to not participate in sports or any forms of physical exercise apart from the prescribed 20-min of aerobic exercise. If the participants felt symptomatic while exercising at home, then they were instructed to stop and rest, and continue the following day. Participants were seen every week to perform the BCTT and a new HR prescription was given until recovery. Participants were referred for cervical or vestibular therapy as needed if they did not recover by 30 days since injury. Further

details on PG and AG exercise prescriptions are provided in a recent study (24).

Participants

Male and female adolescent athletes (aged 13–18 years) presenting within 10 days of SRC were diagnosed with concussion according to international Concussion In Sport Group (CISG) criteria (20). Participants were excluded because of (1) evidence of focal neurological deficit; (2) inability to safely walk on a treadmill due to orthopedic injury or significant vestibular dysfunction; (3) increased cardiac risk according to American College of Sports Medicine criteria (30); (4) history of moderate or severe TBI defined as brain injury with a Glasgow Coma Scale score of 12 or less; (5) current diagnosis of and treatment for ADHD, learning disorder, depression, anxiety, or history of more than 3 prior concussions (because these factors are associated with delayed recovery) (31); (6) sustaining another head injury during the research period before recovery; (7) symptom severity score of <5 on initial visit symptom questionnaire; and (8) limited English proficiency.

BCTT and Calculation of ΔHR

Before beginning the BCTT, the participant rated his/her symptoms on a Visual Analog Scale (VAS, 0–10) (32) and resting HR was measured in a seated position after 2 min of rest by Polar HR monitor (Model #FIT N2965, Kempele, Finland). The participant then walked on a level treadmill at 3.2 mph (3.6 mph in participants 5′10″ and above) at 0 degree incline. The incline was increased by 1 degree after each minute for the first 15 min and then the speed was increased by 0.4 mph every minute thereafter. HR, VAS, and Borg Rating of Perceived Exertion (RPE) (33) were recorded each minute until symptom exacerbation or voluntary exhaustion. This was followed by a 2-min cool down at 2 mph unless the participant opted out of it. Symptom exacerbation was defined as an increase of 3 points or more from the pre-exercise VAS value (a point or more for an increase in symptoms and a point for appearance of a new symptom). Voluntary exhaustion was defined by a report of 17 or more on the RPE scale. Participants were instructed to report symptoms and to not "push through" them. The examiner also observed for visible signs of distress, which could prompt test cessation. If the participant was unable to reach age-appropriate exercise tolerance, the HR at exercise cessation was recorded as the HRt. ΔHR was calculated as the difference between resting HR and HRt.

Statistical Analysis

ANOVA was used to assess for group-wise differences in age, days since injury to initial visit, initial PCSS score, resting HR, HRt, and ΔHR. Non-parametric tests of medians was used to compare the non-normally distributed variable duration of clinical recovery. Chi-squared tests were used to assess group-wise differences in gender, history of concussions, and incidence of PPCS. A nonparametric *t*-test assessed differences in ΔHR between normal recovery and PPCS subjects within each group. Linear regression assessed the association between ΔHR and days to recovery within each group. After analysis, AG's ΔHR did not correlate with duration to recovery and only had 2 participants out of 52 with PPCS so they were not included in subsequent analyses. Subjects in each group were dichotomized into those who had normal recovery (≤30 days recovery) and those who developed PPCS (>30 days recovery) and a Receiver Operating Characteristic (ROC) curve analysis using ΔHR as a predictor was performed using participants from RG and PG only. A $p \leq 0.05$ was considered significant. No power analysis was done. All data analyses were performed using SPSS 24 (Armonk, NY).

TABLE 1 | Participant demographics.

	Rest Group	Placebo Group	Aerobic Group	*p*-value
	(*n* = 27)	(*n* = 51)	(*n* = 52)	
Age (years)	15.2 ± 1.4	15.4 ± 1.7	15.3 ± 1.6	0.81
Sex	33% female	49% female	47% female	0.40
Previous Concussions				0.47
0	18	30	26	
1	8	11	16	
2	1	8	9	
3	0	2	1	
Days since injury	4.2 ± 2	4.8 ± 2	4.9 ± 2	0.31
Weight (kg)	63.3 ± 11.6	66.2 ± 12.8	64.2 ± 13.0	0.590
Height (m)	1.68 ± 0.09	1.67 ± 0.10	1.69 ± 0.11	0.579
Symptom severity (PCSS, max = 132)[a]	35.8 ± 23.0	33.5 ± 19.7	30.8 ± 16.5	0.52

Data are presented as mean ± standard deviations.
[a] *Post-Concussion Symptom Scale.*

RESULTS

A total of 161 eligible adolescents came to the Concussion Clinic within 10 days of concussive head injury. Fifteen participants were either not interested or did not have time to participate. After randomization, 16 participants were lost to follow-up because they did not return to the clinic or did not complete at least 60% of the daily symptom reports. They were excluded because we could not determine their date of recovery. There were no statistically significant differences in age, height, weight, sex, or initial BCTT results between those that were included in the study and those that dropped out. Hence, 27 participants made up RG, 51 participants made up PG and 52 participants made up AG. Demographic data for each group are presented in **Table 1**.

Table 2 shows the results of the BCTT performed at initial clinic visit (<10 days since injury). There were no significant differences in the initial visit BCTT results between the three groups. Linear regression showed that ΔHR was significantly correlated with duration of clinical recovery for RG ($p = 0.012$, $R^2 = 0.228$) and PG ($p = 0.011$, $R^2 = 0.126$) but not for AG ($p = 0.084$, $R^2 = 0.059$).

Table 3 shows mean ΔHR for participants who developed PPCS for each group. Non-parametric *t*-test showed that mean

TABLE 2 | Buffalo concussion treadmill test results.

	Rest Group	Placebo Group	Aerobic Group	*p*-value
	(*n*= 27)	(*n* = 51)	(*n* = 52)	
Resting HR[a] (bpm)	75.4 ± 12.1	74.9 ± 12.4	74.5 ± 12.7	0.96
HRt[b] (bpm)	145.0 ± 24.4	135.8 ± 21.8	136.9 ± 26.2	0.26
ΔHR[c] (bpm)	69.6 ± 28.5	60.9 ± 21.8	62.4 ± 25.6	0.33
Symptom Exacerbation	81.5% (*n* = 22)	96.1% (*n* = 49)	90.4% (*n* = 47)	0.11
Median Duration of Recovery (IQR[d])	17 (9.25–23.25)	17 (13–23)	13 (10–18.75)	0.04
Developed PPCS[e]	14.8% (*n* = 4)	13.7% (*n* = 7)	3.8% (*n* = 2)	0.19

[a]*Heart rate.*
[b]*Heart rate threshold.*
[c]*Heart rate difference.*
[d]*Inter quartile range.*
[e]*Persistent post-concussive symptoms.*

TABLE 3 | Mean heart rate of participants who developed persistent post-concussive symptoms.

	Rest Group (*n* = 27)		*p*-value
	Developed PPCS (*n* = 4)	Normal Recovery (*n* = 23)	
Mean ΔHR[a] (bpm)	35.25 ± 9.5	75.57 ± 26.4	**0.01**
	Placebo Group (*n* = 51)		
	Developed PPCS (*n* = 7)	Normal Recovery (*n* = 44)	
Mean ΔHR (bpm)	43.43 ± 20.5	63.73 ± 20.9	**0.04**

a Heart rate difference, PPCS > 30 days recovery duration, normal recovery ≤ 30 days recovery duration.

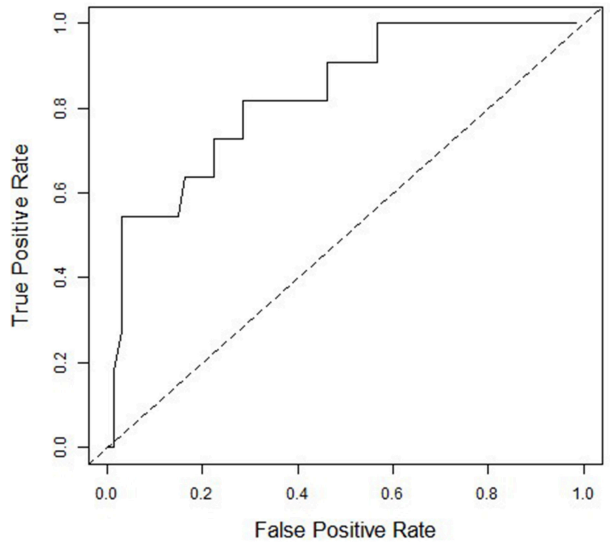

FIGURE 1 | Receiver Operating Characteristics (ROC) curve for ΔHR and Persistent Post-Concussive Symptoms (PPCS) for Rest Group and Placebo Group combined (*n* = 78). An ROC analysis of the placebo and rest group showing the ability of ΔHR to predict PPCS. Area under the curve is 0.81. At the ΔHR of <50 bpm to declare PPCS, sensitivity = 73% and 1-specificity = 22%.

ΔHR for patients who developed PPCS was significantly lower in RG and PG. No analysis between ΔHR and PPCS was performed for AG because there were only 2 participants in the delayed recovery group and ΔHR was not significantly associated with duration of clinical recovery in that group.

Figure 1 presents the ROC curve of ΔHR and PPCS of RG and PG combined (67 normal recovery vs. 11 PPCS). The ΔHR of ≤50 bpm was 73% sensitive (8/11) and 78% specific (52/67) for identifying adolescents who experienced a delayed recovery. AG were not included because ΔHR did not correlate with duration of clinical recovery.

DISCUSSION

We found that the ΔHR correlated with duration of clinical recovery in participants who were prescribed relative rest or a placebo-stretching program but not in participants who were prescribed sub-threshold aerobic exercise. A ΔHR value of ≤50 bpm was 73% sensitive and 78% specific for identifying adolescents who experienced delayed recovery. Other values would have greater specificity but at the cost of reduced sensitivity. Greater sensitivity is more useful to clinicians who are trying to identify those patients who are more likely to have significant difficulty with schoolwork, social relationships and sports team participation after SRC. Normal resting HR values have a wide distribution (between 60 and 100 bpm), which is dependent on modifiable and non-modifiable factors such as age and cardiovascular fitness (34). Our previous study suggested that an absolute cut-off HRt value of more than 135 bpm was associated with normal recovery after SRC vs. those with a HRt < 135 bpm who were much more likely to experience a delayed recovery. We were, however, limited in our ability to accurately predict delayed recovery since only 4 patients (out of 27) developed PPCS. In addition, the previous study used a definition of >21 days to classify delayed recovery. The change in definition of delayed recovery is inform the newer CISG definition (20, 29). On retrospective analysis, using >30 days did not affect the results of the previous study. Furthermore, an absolute cut-off value does not account for differences in resting HR. For example, a patient with a resting HR of 60 bpm who attains a HRt of 140 bpm on the BCTT likely has a better prognosis than one who reaches that level from a resting HR of 90 bpm.

Symptom severity in the acute and sub-acute period, as assessed by concussion-specific symptom checklists, is considered to be the most accurate predictor of recovery duration after SRC (23). One reason for this is that almost all studies define recovery as return to a normal or baseline level of symptoms (28). While symptom reports are essential for the management of SRC, there are issues with clinicians relying on subjective reporting alone to establish recovery from SRC. Athletes, for example, are known to under-report symptoms to avoid missing their sport (35) whereas persons with secondary gain issues have been known to over-report symptoms (36). Symptom

questionnaires may cause reporting bias and encourage the over-endorsement of symptoms, which may not have been reported on free recall (37, 38). For these reasons, researchers are searching for more objective measures of concussion/mTBI severity and predictors of duration of clinical recovery (39). The ΔHR measure on an exercise test performed early after concussion may be a clinically reasonable physiological biomarker of concussion severity because it requires readily available equipment (unlike advanced imaging), is non-invasive (unlike blood tests), is relatively easy to perform, and has been shown to be safe to perform as soon as 2 days after SRC (17).

The ΔHR of the group that performed a placebo-like stretching program was significantly correlated with duration of clinical recovery, which is similar to the group prescribed relative rest in our prior study (17). This was not unexpected because the placebo was designed to mimic relative rest, which is the standard of care (29). RG and PG had almost identical recovery times (17 days) and incidence of PPCS (15 and 14%, respectively) so we are confident that our placebo-like stretching program effectively mimicked rest. Our hypothesis that the ΔHR would be a prognostic indicator of recovery time irrespective of treatment was not confirmed. We suspect that this is because prescribed sub-threshold aerobic exercise treatment reduced recovery time such that a pre-intervention predictor variable of exercise intolerance was no longer valid. There is emerging research to suggest that light to moderate physical activity that does not exacerbate symptoms is beneficial for patients with concussion and reduces recovery time (18, 38, 40–42). In a recent randomized placebo-controlled trial, (24) we showed that sub-threshold aerobic exercise prescribed in the sub-acute phase after SRC safely and significantly reduced recovery time from a median of 17 to 13 days. The mechanism for the beneficial effect of sub-symptom threshold exercise on concussion is not completely understood but may include salutary effects on autonomic nervous system function, control of cerebral blood flow, cognition, mood, sleep, and upon neuroplasticity via increasing levels of brain-derived neurotrophic factor (43–46).

Limitations

There are several limitations to our study. HR varies because it is influenced by fitness level, emotional state, amount and time since food intake, and time of day. We did not control for all of these variables. This, however, increases the external validity of the study. We studied only adolescents so the results cannot be generalized to younger children or adults. As with any clinical test, results of the BCTT are dependent on the clinician performing the test. The BCTT can be performed by anyone who is trained to perform exertion testing. In our setting (a university concussion management clinic), the BCTT is usually performed by physical therapists, athletic trainers, or exercise science students. RG participants completed daily symptom reports whereas PG and AG completed daily symptom reports plus self-reported compliance with the prescribed intervention. Compliance reported by AG and PG was 83 and 86%, respectively, but we cannot be sure if this is accurate, and we cannot be sure if participants adhered to the recommendation to not perform sports or other physical exercise during intervention. Lastly, only two participants in the AG group experienced delayed recovery so we were not able to perform a statistical analysis on participants who had normal recovery vs. those who did not. Therefore, the ROC analysis for ΔHR is applicable only to concussed adolescents who were been prescribed the current standard of care (i.e., physical and cognitive rest) and not to those prescribed sub-threshold aerobic exercise.

CONCLUSION

This study found that the ΔHR (HRt minus resting HR) correlated with duration of clinical recovery in participants who were prescribed relative rest or a placebo-stretching program but not for participants prescribed sub-threshold aerobic exercise. A ΔHR of $\leq$50 bpm on the BCTT was 73% sensitive and 78% specific for predicting delayed recovery in concussed adolescents prescribed the current standard of care (i.e., cognitive and physical rest). This has implications for planning team and school activities in adolescents who sustain SRC.

ETHICS STATEMENT

This study was carried out in accordance with the recommendations of Institutional Review Board, University at Buffalo, SUNY with written informed consent from all subjects. All subjects gave written informed consent in accordance with the Declaration of Helsinki. The protocol was approved by the University at Buffalo, SUNY.

AUTHOR CONTRIBUTIONS

MH, JL, and BW contributed to the inception and design of the paper and writing of the manuscript. KW, CW, IB, and KV contributed to patient recruitment and data collection. JM contributed to the statistical analysis and research design. All authors approved the final version of the manuscript.

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Measuring Change Over Time: A Systematic Review of Evaluative Measures of Cognitive Functioning in Traumatic Brain Injury

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Objectives: The purpose of evaluative instruments is to measure the magnitude of change in a construct of interest over time. The measurement properties of these instruments, as they relate to the instrument's ability to fulfill its purpose, determine the degree of certainty with which the results yielded can be viewed. This work systematically reviews all instruments that have been used to evaluate cognitive functioning in persons with traumatic brain injury (TBI), and critically assesses their evaluative measurement properties: construct validity, test-retest reliability, and responsiveness.

Data Sources: MEDLINE, Central, EMBASE, Scopus, PsycINFO were searched from inception to December 2016 to identify longitudinal studies focused on cognitive evaluation of persons with TBI, from which instruments used for measuring cognitive functioning were abstracted. MEDLINE, instrument manuals, and citations of articles identified in the primary search were then screened for studies on measurement properties of instruments utilized at least twice within the longitudinal studies.

Study Selection: All English-language, peer-reviewed studies of longitudinal design that measured cognition in adults with a TBI diagnosis over any period of time, identified in the primary search, were used to identify instruments. A secondary search was carried out to identify all studies that assessed the evaluative measurement properties of the instruments abstracted in the primary search.

Data Extraction: Data on psychometric properties, cognitive domains covered and clinical utility were extracted for all instruments.

Results: In total, 38 longitudinal studies from the primary search, utilizing 15 instruments, met inclusion and quality criteria. Following review of studies identified in the secondary search, it was determined that none of the instruments utilized had been assessed for all the relevant measurement properties in the TBI population. The most frequently assessed property was construct validity.

Conclusions: There is insufficient evidence for the validity and reliability of instruments measuring cognitive functioning, longitudinally, in persons with TBI. Several instruments with well-defined construct validity in TBI samples warrant further assessment for test-retest reliability and responsiveness.

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Keywords: measurements, neuropsychological tests, psychometrics, clinimetrics, systematic review

INTRODUCTION

Cognitive impairments are among the most important concerns for persons with traumatic brain injury (TBI). These impairments include a wide range of deficits in attention, memory, executive function, and behavioral and emotional difficulties, such as limited flexibility, impulsivity, reduced behavioral control, and inhibition, as well as other affective changes (1). Cognitive impairments directly impact their ability to maintain employment (2), personal and community independence (3), to participate in social activities (4), and their response to rehabilitation interventions (5). These are also among the main concerns of clinicians developing systems of care for TBI patients (6), and patients' family members and/or caregivers, who interact with and aid the injured persons on a daily basis (7). Cognition is a multi-dimensional construct, encompassing learning and memory, language, complex attention, executive functioning, perceptual-motor ability, and social cognition (8). Research to date has used numerous measures of cognitive functioning in persons with TBI longitudinally, to investigate its natural history (i.e., course over time) and the effectiveness of interventions aimed at improving cognition in clinical trials (9). The results were inconsistent, even when accounting for differences in time since injury and injury severity, with reports of improvement, decline, and no change over time (9). To elucidate the source of these inconsistencies, an important consideration involves investigation of the measures of cognitive functioning that have been utilized in the TBI population to date, to assess their suitability to perform the function for which they are intended. This route is one that has received relatively little attention in the discussion of generalization and interpretation of results of studies and this is a tremendous limitation, as selection of a measure affects the validity of the results reported (10). It has been argued that the usefulness of an outcome study or a clinical trial, in terms of the contribution made to the understanding of an issue and the potential to inform how the issue is viewed and treated in a clinical setting, hinges on the appropriateness of the measure used, and cannot be made up for even with otherwise superior design and execution (10). Measures used to study change in a construct over time are termed "evaluative," and their most relevant psychometric properties, according to criteria developed by Feinstein (11) and Kirshner and Guyatt (12), are (i) construct validity, (ii) test-retest reliability, and (iii) responsiveness (11–13).

Construct validity refers to an instrument's ability to measure the construct it is intended to measure in the population of interest (e.g., cognitive functioning in the TBI population) (11). Developing a tool for measuring cognitive functioning that has construct validity is challenging because there is no generally accepted reference or gold standard instrument that is known to accurately define and measure the multidimensional construct, against which all new instruments could be compared (*convergent validity*). *Divergent validity* is another subcategory of construct validity, and it involves assessment of the relatedness of constructs thought to be unrelated and thus expected to yield scores on their respective measures that are not positively correlated (11). Finally, within construct validity there is also *known-groups validity*, which refers to the application of an instrument to two groups known or hypothesized to differ in the construct measured (11, 12). For an instrument to have construct validity, at least two of the construct validity subcategories must be assessed—convergent or divergent validity, and known-groups validity (11, 12).

Test-retest reliability concerns the extent to which application of the same instrument yields the same results in repeated trials under the same conditions (11, 13). This psychometric property is important for quantifying the degree of variance attributed to true differences in the construct under study over time, rather than systematic changes that occur when a procedure is learned (13).

Responsiveness refers to an instrument's ability to detect small, clinically significant differences in a construct of interest over time (12). This property is emphasized for instruments used in clinical trials, where the responsiveness of an instrument is directly related to the observed magnitude of the change in person's score, which may or may not constitute a clinically important difference (12). Responsiveness is inversely

Abbreviations: ANAM, Automated Neuropsychological Assessment Metrics; CNS, Central Nervous System; COWAT, Controlled Oral Word Association Test; CVLT, California Verbal Learning Test; DSM-5, Diagnostic and Statistical Manual of Mental Disorders-Fifth Edition; FIM-Cog, Functional Independence Measure-Cognitive Subscale; GCS, Glasgow Coma Scale; HVLT, Hopkins Verbal Learning Test; ImPACT, Immediate Post-concussion Assessment and Cognitive Test; MMSE, Mini-mental State Examination; PASAT, Paced Auditory Serial Addition Test; PROSPERO, International Prospective Register of Systematic Reviews; QUIPS, Quality in Prognosis Studies; RAVLT, Rey Auditory Verbal Learning Test; ROCF, Rey-Osterrieth Complex Figure Test; SDMT, Symbol Digit Modalities Test; SIGN, Scottish Intercollegiate Guidelines Network; TBI, Traumatic Brain Injury; TMT, Trail Making Test; WAIS, Wechsler Adult Intelligence Scale; WMS, Wechsler Memory Scale.

proportional to between-person variability in individual changes in score over time (12). In the TBI population, as the baseline variability increases, a larger treatment effect is needed to demonstrate intervention efficacy.

Finally, it is important to consider the specifics of the TBI population in the development and use of an instrument for cognitive functioning. Traumatic brain injury can impact not only cognition, but also behavioral and emotional functioning, and concentration, and this is expected to reflect in the ease of comprehension, extent of completion and overall burden on both the test taker and the administrator (in explaining the procedure and assisting with comprehension and completion) associated with administration of an instrument.

To identify the most appropriate instrument(s) for measuring cognitive functioning in the TBI population, we undertook a systematic review of all instruments used for this purpose. The objectives were to: (i) describe each evaluative instrument's key measurement properties (i.e., construct validity, test-retest reliability, and responsiveness); (ii) classify instruments according to the cognitive domains they assess; and (iii) summarize information relevant to their clinical and research applications. The present work intends to inform researchers and clinicians on each instrument's utility as an evaluative measure of cognitive functioning in the TBI population, while identifying pitfalls and future directions for their utility.

METHODS

This systematic review is part of a larger study that focuses on central nervous system (CNS) trauma [TBI and spinal cord injury (SCI)] as a risk factor of cognitive decline over time. For more information, the reader is referred to the published protocol (14) and registry with the International Prospective Register of Systematic Reviews (PROSPERO) (registration number CRD42017055309) (15).

Primary Search: Studies of Cognitive Functioning in TBI

A comprehensive search strategy was developed in collaboration with a medical information specialist (JB) at a large rehabilitation teaching hospital. All English language peer-reviewed studies published from onset to December 2016 with prospective or retrospective data collection and a longitudinal design, identified in six electronic databases (i.e., MEDLINE, Central, EMBASE, Scopus, PsycINFO, and supplemental PubMed), were considered eligible. The following medical subject headings in MEDLINE were used to identify publications of interest (i) TBI terms: exp "brain injuries" or "craniocerebral trauma" or exp "head Injuries, closed" or exp "skull fractures" or "mTBI*2.tw." or "tbi*2.tw" or "concuss*.tw." AND (ii) cognition terms: exp "cognition" or exp "cognition disorders" or "neurocognit*.tw,kw." Or "executive function" or exp "arousal" or "attention*.tw,kw." or "vigilan*.tw,kw." or exp "dementia" AND (iii) evaluation terms: exp "cohort studies" or "longitudinal studies" or "follow-up studies" or "prospective studies" or "retrospective studies" or "controlled before-after studies/or interrupted time series analysis" or exp "clinical trials" or exp "clinical trials as topic." The search terms were adapted for use in other bibliographic databases. The reader is referred to the published protocol (14) and the PROSPERO registry (15) for the full search strategy. Additional studies were identified through review of reference lists of included articles.

Inclusion and Exclusion Criteria

Studies were included if they met the following criteria: (i) focused on longitudinal change in cognitive functioning in adults (i.e., $\geq$16 years) with an established clinical diagnosis of TBI based on accepted definitions [e.g., Glasgow Coma Scale (GCS) score, duration of loss of consciousness, and post traumatic amnesia, etc.], excluding self-report; (ii) reported cognitive functioning outcome data at baseline assessment and follow-up as a score on a standardized measurement instrument; and (iii) the work was published in English in a peer-reviewed journal. Studies were excluded if they: (i) evaluated cognitive functioning in children/adolescents; (ii) studied persons with minor head injury (cases before 1993) without providing assessment criteria; or (iii) reported results in letters to the editor, reviews without data, case/public reports, conference abstracts, articles with no primary data, or theses.

Selection and Quality Assessment of Studies

In the first stage of screening, two reviewers (NP and AD, or SM and AD) assessed study titles and abstracts for potential agreement with the inclusion criteria. In the second stage, each reviewer individually assessed the full texts of studies selected in the first stage to determine whether they met the inclusion criteria. Discrepancies in article inclusion/exclusion were resolved by discussion with TM.

Previously developed standardized forms were used to assess study quality (16) and to synthesize results (17). Study quality was assessed using the Quality in Prognosis Studies (QUIPS) guidelines (18). Assessments were based on the presence of six potential sources of bias (i.e., participation, attrition, prognostic factors, outcome measures, consideration of and accounting for confounders, and data analyses). Each study was assigned an overall "risk of bias," and those with the greatest risk were excluded. Studies of a retrospective nature were automatically excluded from a "low risk" rating, as recommended by the Scottish Intercollegiate Guidelines Network (SIGN) (19). Any discrepancies between the two reviewers in quality assessment were resolved in discussion among the research team followed by independent review by the research supervisor (TM).

Secondary Search: Studies of Measurement Properties of Abstracted Instruments

Instruments used to evaluate cognitive functioning in studies that met inclusion and quality criteria were abstracted. In collaboration with a medical information specialist (JB), proposed MEDLINE search filters were used to identify studies reviewing the abstracted instruments' measurement properties in TBI samples. **Supplementary File 1** provides the terms and outputs from searches for each measure. The reference lists

of eligible articles, instrument manuals and Google Scholar were reviewed for other relevant publications. Studies where the primary objective was not the evaluation of measurement properties were excluded.

Evidence-Based Assessment of Instruments Evaluating Cognitive Functioning

Criteria for evidence-based assessment proposed by Holmbeck et al. (20) were utilized, previously applied in a systematic review of measurement properties of sleep-related instruments in the TBI population (17). Instruments used in at least two of the studies identified in the primary search were given ratings of "well-established," "approaching well-established," or "promising," based on the following criteria: (i) use in peer-reviewed studies by different research teams; (ii) availability of sufficient information for critical appraisal and replication; and (iii) demonstration of validity and reliability in the TBI population (20).

Descriptive Aspects of Instruments of Cognitive Functioning

To assess research and clinical feasibility, in-depth descriptions were completed following a previously developed format for instruments in medical research (17). The following descriptors were abstracted from data sources and reported: (i) general: purpose, content, response options, recall period (ii) application: how to obtain, method of administration, scoring and interpretation, administrator and respondent burden, currently available translations; and (iii) critical appraisal as reported by the researchers who utilized the instrument in TBI and other samples: strengths, considerations, clinical, and research applicability (17).

Categorization of Instruments of Cognitive Functioning by Content

Content validity refers to the degree to which an instrument's items adequately reflect the construct of interest. For a measure to be sensitive to certain or all aspect(s) of cognitive functioning in a person with TBI, it needs to feature representative items or tasks that are part of the construct of cognition, as understood by the instrument's developer. As such, each instrument was categorized according to the cognitive domain(s) it assesses, focusing on those listed in the Diagnostic and Statistical Manual of Mental Disorders-Fifth Edition (DSM-5) (8): (i) complex attention, (ii) executive functioning, (iii) learning and memory, (iv) language, (v) perceptual-motor ability, and (vi) social cognition (8). An additional domain, information processing and reaction time, was included, given its relevance to the TBI population (21, 22). Instruments were then classified, based on the number of domains they assess, as either "global" (all domains), "multi-domain" (two or more domains), or "domain-specific" (one domain).

RESULTS

Literature Search and Quality Assessment

Of 29,566 studies identified in the primary search of articles assessing cognitive functioning longitudinally in the TBI population, 39 met inclusion and quality criteria (**Figure 1**): 14 studies involved patients from acute care (23–36), seven from the rehabilitation setting (37–43), ten involved college-age athletes (44–53), four were clinical trials (54–57), two involved samples from community care settings (58, 59), and another two involved military and veteran participants (60, 61). Sample sizes ranged from 10 (35, 55) to 509 (57), and consisted of mostly males (mean 76.6%, range 38-100%) with participant age ranging from 18 (57) to >60 years (57) (**Table 1**).

All 39 studies were assessed as having "Partly" or "No" on all bias criteria. Twenty-nine studies were of fair quality (23, 26, 29–32, 34, 37–45, 48–54, 54–61), ten were of good quality (24, 25, 27, 28, 33, 35, 36, 46, 47, 53) and none were of high quality. Studies were most frequently penalized by the SIGN criteria for unknown reliability and validity of the utilized instruments, incomplete statistical analysis, and selection bias due to study attrition (**Supplementary File 2**).

Instruments Measuring Cognitive Functioning

Within the 39 studies, 15 instruments were used more than once. The Mini Mental State Examination (MMSE) (54, 55), Hopkins Verbal Learning Test (HVLT) (47, 49), Paced Auditory Serial Addition Test (PASAT) (27, 48), and Rey-Osterrieth Complex Figure Test (ROCF) (36, 58) were each used twice; the California Verbal Learning Test (CVLT) (57, 58, 61) and Wechsler Memory Scale (WMS) (37, 38, 42) were used three times; the Automated Neuropsychological Assessment Metrics (ANAM) (33, 50, 51, 53) and FIM-Cog (Functional Independence Measure-Cognitive Subscale) (34, 40, 43, 56, 58) were used four and five times, respectively; the Rey Auditory Verbal Learning Test (RAVLT) (28, 37, 39, 41, 42, 59), Stroop Color Word Test (SCWT) (27, 28, 37, 49, 57, 58), and Symbol Digit Modalities Test (SDMT) (26, 39, 41, 42, 48, 49) were each used six times; the Immediate Post-concussion Assessment and Cognitive Test (ImPACT) (31, 35, 44–46, 52, 60) and Controlled Oral Word Association Test (COWAT) (24, 25, 39, 41, 42, 49, 57, 58) were used seven and eight times, respectively. The most frequently used instruments were the Trail Making Test (TMT) (23, 24, 28, 32, 37–39, 41, 42, 48, 49, 57, 59) and the Wechsler Adult Intelligence Scale (WAIS) (23–26, 28–30, 32, 36–39, 41, 42, 55, 57, 58), used 13 and 17 times, respectively.

Assessment of TBI

Diagnostic criteria and definitions of TBI varied considerably between studies included in this review (**Table 1**). Nineteen studies used a combinatorial approach to confirm and assess TBI. This included the use of such tools as the Glasgow coma scale (GCS), duration of posttraumatic amnesia (PTA) and/or loss of consciousness, neuroimaging results [i.e., magnetic resonance imaging (MRI), computed tomography (CT)], and

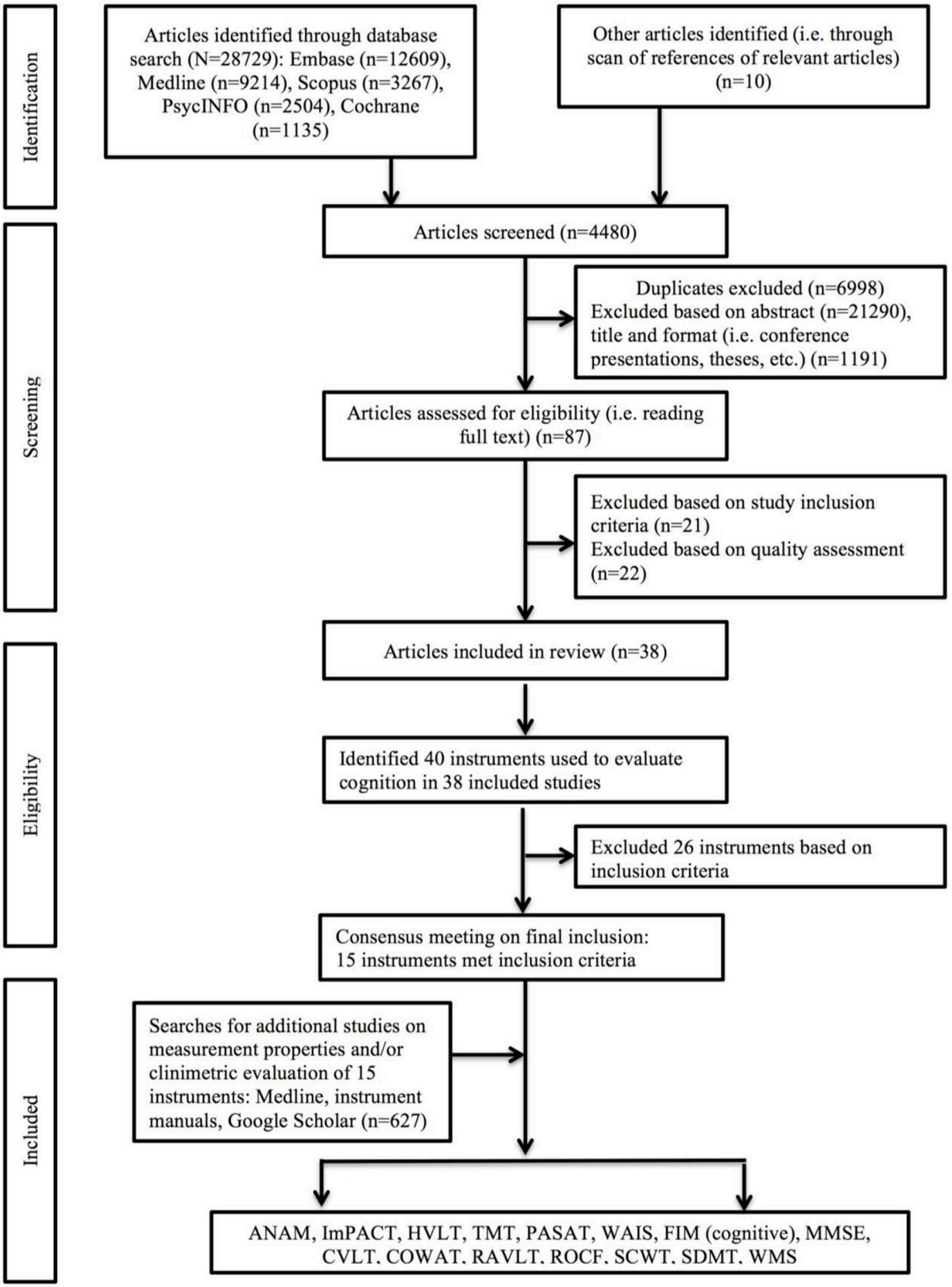

FIGURE 1 | Flow chart documenting review procedure.

TABLE 1 | Summary of study characteristics, including details on study sample, purpose, and instruments used to evaluate cognition.

Authors	TBI sample size	TBI study setting	Injury severity (% of total), time since injury (at initial assessment)	Mean age/ Mean age ± SD/ Mean age (range)/ Age group (%)	Sex (%M)	Study purpose	Instrument (s) used
Bleiberg et al. (53), USA	64	Rehabilitation Institute/University Health Network	AAN: Grade I–9 (14.1); Grade II–49 (76.6); UKN–6 (9.4) TSI: 0–23 h	18.8 ± 0.7	100	To track cog impairment following sport con	**ANAM (CPT, MTS, MTH, Spatial Processing, SRT, Sternberg)**
Christensen et al. (37), Canada	75	Rehabilitation Institute	GCS: 6.97 ± 3.59 TSI: 1.5–2.5 m	37.37 ± 15.49	80	To examine patterns of cog rec in y following TBI	GPT; **RAVLT**; **Stroop; TMT A & B;** VF; **WAIS-III; WMS-III**
Covassin et al. (44), USA	79	College Sports Programs	AAN: GI–49 (62); GII-27 (34); GIII–3 (4) TSI: ≤3 d	NR	63.3	To identify any sex differences in post-con symps and cog function	**ImPACT**
Covassin et al. (45), USA	57	College Sports Programs	AAN (con–): GI-29 (80.6); GII-4 (11.1); GIII-3 (8.33)/(con+): GI-15 (71.4); GII-1 (4.76); GIII-5 (23.8) TSI: 1 d	Con–: 20.55 ± 1.54 Con+: 21.10 ± 1.69	47.2	To identify relationship b/w con history and post-con cog symps	**ImPACT**
Covassin et al. (46), USA	72 (college)	College Sports Programs	TSI: 2 d	M: 19.52 ± 1.08 F: 18.94 ± 1.55	NR	To identify any age and sex differences in symps, neurocog testing, and postural stability post-con	**ImPACT**
Chen et al. (54), China	15 (placebo)	Medical University Hospital	TSI: 1 d Last F/U: 12 weeks p/i	42.3±14.05	66.67	To investigate effect of cerebrolysin therapy on cog recovery in mTBI	CASI, **MMSE**
Dikmen et al. (23), USA	421 overall: 130 (CT-) 133 (CT+, GCS 15) 158 (CT+, GCS 13-14)	Participants from 4 Prospective Longitudinal Investigations	GCS (CT–): 13–9 (7); 14–25 (19); 15–96 (74)/(CT+, GCS 15): 15–133(100)/ (CT+, GCS 13–14): 13–60 (38); 14–98 (62) TSI: 1 m	CT-: 28 ± 9.8 CT+, GCS 15: 35 ± 14.3 CT+, GCS 13-14: 38 ± 19	CT–: 71 CT+, GCS 15: 81 CT+, GCS 13-14: 73	To determine effect of com and uncom mTBI on outcome wrt controls	Finger Tapping; SRCL **TMT A & B; WAIS (DST, PIQ, Seashore Rhythm Test, VIQ)**
Failla et al. (58), USA	108	Level 1 Trauma Center	GCS: 8.02 ± 3.083 TSI: 6 m	34.19 ± 13.75	81.5	To determine if post-TBI cog rec is related to dopamine D2 receptor, and ankyrin repeat and kinase domain genes	**COWAT; CVLT-II;** D-KEFS (VF); **FIM-Cog; ROCF; Stroop; TMT A & B; WAIS-R (DG)**
Farbota et al. (24), USA	17	Level 1 Trauma Center	GCS–7.2 TSI–<3 m	34.5 ± 12.0	82.4	To examine brain volume loss in TBI patients using TBM and cog testing	**COWAT; TMT A & B**; **WAIS-III (DG);** WRAT-III (Reading)
Field et al. (47), USA	35 (college)	College Sports Programs	AAN: GI/II–23 (66); GIII–12 (34) TSI: ≤24 h	19.9 (17–25)	96	To evaluate patterns of rec wrt post-con symps and cognition	**HVLT**
Kersel et al. (25), New Zealand	65	Intensive Care Unit	GOS (6 m): Good–26 (40); mod–19 (29); sev–20 (31)/(1 y): Good–19 (29); mod–13 (20); sev–33 (51) TSI: 6 m	28 ± 11	75	To describe sev TBI effects wrt deficits and patterns of rec	AVLT; **COWAT**; **WAIS-R (BDT, DG, DST, FSIQ, Sim)**

(Continued)

TABLE 1 | Continued

Authors	TBI sample size	TBI study setting	Injury severity (% of total), time since injury (at initial assessment)	Mean age/ Mean age ± SD/ Mean age (range)/ Age group (%)	Sex (%M)	Study purpose	Instrument (s) used
Kontos et al. (60), USA	80	Army Medical Center	GCS: 15–80 (100) TSI: 1–7 d	Blast mTBI+: 31.05 ± 7.07 Blast mTBI-: 27.54 ± 5.57	100	To determine mTBI effect on cog performance and PTS symps in veterans w/ or w/o blast mTBI history	**ImPACT**
Kwok et al. (26), China	31	Hospital/ District Hospital	GCS: 13–15–31 (100) TSI: ≤1 w	38.60 ± 12.35	80.6	To examine changes in cog functioning of mTBI patients over a 3m period	AVLT; BVRT; DVT; FF; **SDMT**; VF; **WAIS (DG)**
Lee et al. (55), Korea	10 (placebo)	Hospital Trauma Center	CT: Ab−7 (70) TSI: 30.0 ± 6.5 d	35.5 ± 7.2	80	To compare effects of methylphenidate, sertraline and placebo for TBI neuropsych sequelae	CFFT; CRT (MRT, RRT, TRT); CTT; MAT; **MMSE;** STM; **WAIS (DST)**
Liberman et al. (27), USA	80 overall: 62 (APOE e4-) 18 (APOE e4+)	Shock trauma Center	GCS: 9–12–8 (8.0); 13–14–40 (50.0); 15–32 (40.0) LOC: #-64 (80.0) RGA: #-50 (62.5) TSI: 3 w	<30: 31.2% 30-49: 35.0% ≥50: 33.8%	60.0	To determine if short-term mTBI rec variability is related to *APOE* genotype	CRT; Dual Attention; GPT; Number Vigilance; **PASAT;** SRT1; **Stroop;** Word Recall; Word Recognition; Picture Presentation; Memory Scanning
Losoi et al. (28), Finland	74	University Hospital	ISS−3.9 ± 3.2 CT: Ab−7 (9.5) MRI: Ab−15 (20.3) LOC: #−27 (36.5); dur−0.9 ± 2.2 min PTA: #−68 (92.0) dur−2.6 ± 3.4 h TSI: 1 m	37.0 ± 11.8	60.8	To characterize mTBI rec	Finger Tapping; **RAVLT; Stroop; TMT A & B;** VF; **WAIS-III (DG, DST, SS)**
Macciocchi et al. (48), USA	24	College Sports Programs	AAN: GI−24 (100) LOC: <30 min−24 (100) TSI: 24 h	1 con: 19.5 2 cons:19.1	NR	To identify cog and behavioral effects of 1 vs. 2 cons	**PASAT; SDMT; TMT A & B**
Maksymiuk et al. (29), Poland	17	Air Force Institute of Aviation Medicine	GCS: 14–5 (29.4); 15–12 (70.6) LOC: Several s−7 (41.2); 1–20 min−6 (35.3); 30–60 min−5 (29.4) RGA: #−17 (100) PTA: #−17 (100)	22.1 (19-25)	100	To estimate rCBF and compare neuropsych results post-mTBI	Couve; **WAIS-R**
Mandleberg et al. (30), Scotland	149 overall: 51 (cohort 1) 98 (cohort 2)	Institute of Neurological Sciences	PTA: cohort 1–6 w (2 d-12 m); cohort 2–5 w (4 d-6 m) TSI: 3 m	1: 28.96 ± 13.14 2: 34.75 ± 15.11	1: 92.2 2: 87.8	To analyze relationship b/w PTA dur and cog functioning over time	**WAIS (PIQ, VIQ)**
McCrea et al. (49), USA	94	College Sports Programs	AAN: GI/II− 88 (93.2) LOC: #−6 (6.4); dur−30 s PTA: #−18 (19.1); dur−90 min RGA: #−7 (7.4); dur−120 min TSI: immediately	20.04 ± 1.36	NR	To characterize rate of impairment and rec following con	**COWAT** **HVLT;** SAC**; SDMT; Stroop TMT B**

(Continued)

TABLE 1 | Continued

Authors	TBI sample size	TBI study setting	Injury severity (% of total), time since injury (at initial assessment)	Mean age/ Mean age ± SD/ Mean age (range)/ Age group (%)	Sex (%M)	Study purpose	Instrument (s) used
Meier et al. (50), USA	17 (T1) 15 (T2) 13 (T3)	College Sports Programs	PTA: <1 min– 2 (11.8); 10–20 min−2 (11.8) RGA: <5 min−1 (5.9); 10–20 min−1 (5.9) LOC: #−0 (0) TSI: 1 d	20.57 ± 1.20	100	To characterize CBF rec and compare time of rec w/ cog and behavioral post-con symps	**ANAM (CDD, CDS, G/NG, memory search, MTH, MTS, procedural RT, spatial processing, SRT1 & 2)**
Ponsford et al. (31), Australia	123	Emergency & Trauma Center	GCS:13–15 −123 (100) LOC: #−111 (92.5; of 120 w/ known status); dur−61.44 ± 110 s PTA: #−118 (9.7); dur−103 ± 191 min TSI: ≤48 h	34.98 ± 13.13	74	To examine post-con symps, and cog, psych, and functional outcomes w/i uncom mTBI patients	**ImPACT**
Powell et al. (32), UK	35 (follow-up)	Hospital	GCS: 13–14 −5(14); 15 −27(77); UKN−3 (9) PTA: <1 h−15 (43); 1–24 h−11 (31) LOC: yes−19 (54); UKN−6 (17) TSI–≤48 h	34.5	66	To assess MHI patients at admission and 3m	AMIPB; SOMC; **TMT B; WAIS (DG, DG Backwards)**
Prigatano et al. (38), USA	17 (control)	Neuropsychological Rehabilitation Program	AIR−1.82 (of n = 10) TSI:15.9 ± 13.6 m	23.5 ± 5.1	88.2	To evaluate effectiveness of neuropsych rehab by comparing patients to untreated controls	**TMT A & B; WAIS (BDT, DST, PIQ, VIQ, Vocab); WMS (Memory Quotient, LM, VR)**
Register-Mihalik et al. (51), USA	132	College Sports Programs	TSI–pre-season and 5 d postinjury	18.59 ± 1.09	65.2	To determine reliable change parameters for con measures w/i healthy controls and apply to con athletes	**ANAM (CDS, MTH, MTS, PRT, SRT 1 & 2, Sternberg)**
Roberston and Schmitter-Edgecombe (39), USA	49	Rehabilitation Program	GCS: 4.472 ± 8.400 PTA: 13.945 ±18.268 d TSI: 45.00 ± 35.14 d	37.796 ± 18.294	73.5	To examine change in self-awareness over course of TBI rec and relate to community re-integration	**COWAT; RAVLT; SDMT; TMT A & B; WAIS (LNS)**
Sandhaug et al. (40), Norway	41 overall 15 (mod) 26 (sev)	Rehabilitation Clinic University Hospital	T3 severity: mod−15 (36.6); sev−26 (63.4) TSI: 3 m	T1: 41 ± 18	T1: 77 T2: 75	To describe functional level ≤24m post-TBI and evaluate pre-injury/injury-related predictors	**FIM-Cog**
Schmitter-Edgecombe and Robertson (41), USA	21	Rehabilitation Program	GCS: 8.05 ± 4.50 PTA: 18.81 ± 11.65 h TSI: 41.20 ± 19.85 d	33.57 ± 14.55	71	To observe recovery of visual search processes in individuals with mod-sev TBI	**COWAT;** Preattentive and Attentive Visual Search Tasks; **RAVLT; SDMT; TMT A & B; WAIS-III (LNS)**

(Continued)

TABLE 1 | Continued

Authors	TBI sample size	TBI study setting	Injury severity (% of total), time since injury (at initial assessment)	Mean age/ Mean age ± SD/ Mean age (range)/ Age group (%)	Sex (%M)	Study purpose	Instrument (s) used
Snow et al. (59), Australia	24	Community	PTA: ≥14 d–24 (100) TSI: 17.8 ± 4.2 w	26.2 ± 7.8	66.7	To describe pattern of rec, and association b/w discourse and injury severity, executive function/verbal memory abilities, and psychosocial handicap w/i sev TBI patients over 2 years	CDA-M; FAS; **RAVLT**; **TMT B**
Sosnoff et al. (52), USA	36	College Sports Programs	AAN: G1–8 (22.2); GII–24 (66.7); G3–4 (11.1) TSI–baseline and post-injury	21.21 ± 1.49	80.6	To analyze the impact of mTBI on the relationship b/w cognitive and motor function	CRI; **ImPACT**
Sours et al. (33), USA	41	Shock Trauma Center/ University Medical Center	CT: Ab–9 (22.0) TSI: 7.66 ± 2.36 d	43.68 ± 16.98	73.2	To examine relationship b/w ANAM and IH-FC 1m post-mTBI	**ANAM (CDS, MTH, MTS, PRT, SRT 1 &)**
Till et al. (42), Canada	33	Rehabilitation Institute/University Health Network	GCS: 6.48 ± 3.34 LOC: 38.09 ± 18.31 d TSI: 54.03 ± 17.10 d	35.36 ± 14.52	75.8	To assess long-term cog decline following mod to sev TBI	**COWAT;** GPT**; RAVLT; SDMT; TMT A & B; WAIS (BDT, DG Forwards & Backwards); WMS (LM I & II)**
Tofil and Clinchot (34), USA	24	Teaching Hospital	PTA: 6.4 w(2.5–13.5 w) TSI: 19.5 d, (1–7 d)	28.6 (19–57)	70.8	To assess rec of auto and cog functioning w/ FIM-Cog	**FIM-Cog**
Vanderploeg et al. (61), USA	105	Defense and Veterans' Brain Injury Center	PTA: >1 d–100 (95) LOC: >30 min–105 (100) TSI: 32.4 ± 12.8 d	25.2 ± 6.4	94.3	To determine course of rec of memory processes in 1st y post-TBI	**CVLT**
Wang et al. (56), China	20 (control)	Clinical Trials Registry Platform of World Health Organization	GCS: 6.92 ± 1.38 CT/MRI: Ab–17 (85) TSI: 5.86 ± 4.54 y	28.64 ± 10.13	75.00	To study effects of umbilical cord mesenchymal stem cell transplantation in TBI patients and compare to untreated controls	**FIM-Cog**
Whyte et al. (43), USA	108 overall: 72 (early rec) 36 (late rec)	National Institute on Disability and Rehabilitation Research	GCS: 25 %ile–3; 50 %ile–4; 75 %ile–6 LOS: 25 %ile acute/rehab–23/28 d; 50 %ile–32/45 d; 75 %ile–46/68 d TSI: 92.5 d	26.2 ± 15.5	68	To describe 5-year outcomes of TBI patients who could not follow commands at rehab admission	**FIM-Cog**
Wylie et al. (35), USA	18 overall: 8 (cog rec) 10 (no cog rec)	Tertiary Care Academic Medical Center	GCS: cog rec+-15; cog rec–−15 LOC: cog rec+-3 (38); cog rec—1 (13) CT (Ab): cog rec+-1 (13); cog rec—0 (0) TSI: cog rec+-2.2 ± 1.0 d; cog rec—2.0 ± 0.6 d	Cog rec+: 30.0 ± 15.6 Cog rec-: 26.2 ± 9.6	Cog rec+: 38 Cog rec-: 60	To understand early effect of con on working memory	**ImPACT**

(Continued)

TABLE 1 | Continued

Authors	TBI sample size	TBI study setting	Injury severity (% of total), time since injury (at initial assessment)	Mean age/ Mean age ± SD/ Mean age (range)/ Age group (%)	Sex (%M)	Study purpose	Instrument (s) used
Zafonte et al. (57), USA	509 (placebo)	8 Level 1 Trauma Centers	Initial n = 606 GCS: com mild−404 (66.7); mod/sev– 202 (33.3) Head AIS: ≤4–171 (28.5); >4–429 (71.5) PTA: ≤24 h−121 (25.8); >24 h−347 (74.2) TSI: 90 d	n = 606: 18-30: 199 (32.8) >30-45: 142 (23.4) >45-60: 184 (30.4) >60: 81 (13.4)	n = 606: 73.8	To determine effectiveness of citicoline on functional and cog status in com mild, mod and sev patients	**COWAT; CVLT;** GPT, **Stroop; TMT A & B; WAIS-III (DG, PSI)**
Zaninotto et al. (36), Brazil	40	USP Clinics Hospital	Severity: mod−16 (40.0); sev−24 (60.0) TSI: 6 m	28.7 ± 9.4	87.5	To evaluate visual memory performance post-TBI	GPT; **ROCF; WAIS-III**

Cognitive instruments discussed within this review are bolded.

AAN, American Academy of Neurology; Ab, abnormal; AGCT, Army General Classification Test; AIR, Average Impairment Rating; AIS, Abbreviated Injury Score; AMIPB, Adult Memory and Information Processing Battery; ANAM, Automated Neuropsychological Assessment Metrics; APOE e4, Apolipoprotein E; assoc, association; auto, automatic; AVLT, Auditory Verbal Learning Test; b/w, between; BCT, Bell Cancellation Task; BDG, backward Digit Span; BDT, Block Design Test; BVRT, Benton Visual Retention Test; CASI, Cognitive Abilities Screening Instrument; CBF, cerebral blood flow; CFFT, Critical Flicker Fusion Threshold; CM, Color Matching; cog, cognitive/cognition; com, complicated; con, concussion; COWAT, Controlled Oral Word Association Test; CPT, Continuous Performance Task; CRI, Concussion Resolution Index; CRT, Choice Reaction Time; CT, computed tomography; CTT, Compensatory Tracking Task; CVLT, California Verbal Learning Test; d, days; DA, Dual Attention; DCT, Digit Cancellation Task; DG, Digit Span Test; diff, different/differences; D-KEFS, Delis-Kaplan Executive Function System; DM, Design memory; DST, Digit Symbol Test; dur, duration; DVT; Digit Vigilance Test; EMQ, Everyday Memory Questionnaire; exec func, executive function; F, female; FDG, forward Digit Span; FF, Figural Fluency; FIM-Cog, Functional Independence Measure-Cognitive Subscale; FSIQ, Full Scale Intelligence Quotient; FT, Finger Tapping; func, functional; G, Grade; GCS, Glasgow Coma Scale; GOS, Glasgow Outcome Scale; GPT, Grooved Pegboard Test; h, hours; HVLT, Hopkins Verbal Learning Test; IH-FC, inter-hemispheric functional connectivity; ImPACT, IMmediate Post-concussion Assessment and Cognitive Testing; IQ, Intelligence Quotient; ISS, Injury Severity Score; LM, Logical Memory; LOC, loss of consciousness; m, months; M, male; MAT, Mental Arithmetic Test; max, maximum; min, minutes; MHI, mild head injury; MIST, Memory for Intentions Screening Test; MMSE, Mini-Mental Status Examination; mod, moderate; MQ, Memory Quotient; MRI, magnetic resonance imaging; MS, Memory Scanning; mTBI, mild traumatic brain injury; MTH, Mathematical Processing; MTS, Matching to Sample; neurocog, neurocognitive; neuropsych, neuropschyological; NR, not reported; NV, Number Vigilance; P/A VST, Pre-attentive/Attentive Visual Search Tasks, PASAT, Paced Auditory Serial Addition Test; perf, performance; PIQ, Performance Intelligence Quotient; plac, placebo; PP, Picture Presentation; PRO, Procedural Reaction Time; psych, psychological; PTA, post-traumatic amnesia; PTS, post-traumatic stress; RAVLT, Rey Auditory Verbal Learning Test; rCBF, regional cerebral blood flow; rec, recovery; rehab, rehabilitation; ROCF, Rey-Oesterrieth Complex Figure Test; RGA, retrograde amnesia; SD, standard deviation; SDMT, Symbol Digit Modalities Test; sev, severe; Sim, Similarities; SM, Symbol Matching; S-NAB, Neuropsychological Assessment Battery – Screening Module; SOMC, Short Orientation Memory and Concentration Test; SPA, Spatial Processing; SRCL, Selective Reminding Test Sum of Recall; SRT, Simple Reaction Time; ST, Stroop Test; STN, Sternberg Memory Search; symp, symptoms; T, time; TAPI, Test d'Attention Partagée Informatisé; TBI, traumatic brain injury; TBM, tensor based morphometry; TLM, 3 Letter Memory; TMT, Trail Making Test (full version, or part A/B); TOMM, Test of Memory Malingering; TSI, time since injury; UKN, unknown; uncom, uncomplicated; VEM, Verbal memory; vets, veterans; VF, Verbal Fluency; VIQ, Verbal Intelligence Quotient; Voc, Vocabulary; VR, Visual Reproduction; w, week; w/, with; w/i, within; w/o, without; WAIS, Wechsler Adult Intelligence Scale; WMS, Wechsler Memory Scale; WRAT, Wide Range Achievement Test; wrt, with respect to; y, years.

clinical evaluations and tests (30, 31, 33, 34, 36, 40, 42–44, 46–49, 53, 61–65). Five studies used the American Academy of Neurology (AAN) graded concussion assessment test (44, 53, 55, 59, 66), six used GCS scores (38, 39, 50, 56, 58, 67), one study assessed CT scans (60), one—MRI scans (57), and one assessed PTA (37) alone to confirm TBI. Two studies used other methods, including description of damage and/or lesions based on medical records, and diagnoses of referring professionals (29, 68).

Injury Severity in Samples Assessed

Three measures were used to assess cognitive functioning in mild TBI (mTBI) samples only (ANAM, HVLT, ImPACT), while the rest were applied to samples of varying injury severities. Among the most commonly used measures were the TMT, used in 11 studies, of which six (23, 28, 32, 42, 48, 49) comprised mTBI samples, three—mixed injury severity samples (24, 39, 41), and two—severe TBI samples (58, 59). The COWAT was used in eight studies, of which two (42, 49) featured mTBI samples, four (24, 39, 41, 57)—mixed injury severity samples, and two (25, 58)—severe TBI samples. Several versions of the WAIS were used seven times: once (23) in a study of mTBI participants, twice (36, 41) in samples of mixed injury severities, and four times (25, 30, 38, 58) in severe TBI samples (**Table 3**).

EVALUATION OF MEASUREMENT PROPERTIES

Construct Validity

Convergent, divergent, and/or known-groups validity (62) were reported for all instruments in TBI samples of all severities and mixed-severity samples (39, 53, 63–81). Where construct validity was evaluated, at baseline or follow-up assessments, correlation strength between scores of instruments measuring the same construct, or scores of groups of people with known differences in cognitive functioning, were not always in line with clinical expectations. There is evidence of moderate to strong convergent validity of the original version of CVLT in mixed severity TBI samples (64), FIM-Cog in severe and mixed TBI samples (67); ImPACT in mTBI samples (65, 66); MMSE in mixed severity TBI (80); PASAT in mild and mixed severity samples (69); ROCF in severe and mixed samples (70, 71); SCWT, and WAIS and WMS in all TBI severity samples (63, 72–75, 77, 78).

Divergent validity hypotheses were tested by analyzing the correlation of the PASAT with measures of intellectual, mathematical, and verbal abilities, academic achievement and complex motor skills (i.e., r =0.29–0.59, $p < 0.05$), all of which were significant positive correlations (69). Correlations of the ImPACT with difficulty concentrating and remembering were negative (i.e., $r = -0.48$– (-0.41), $p < 0.01$) (**Table 2**) (65).

Known-groups validity was reported for several domains of the ANAM and HVLT in mTBI samples (53, 68, 79); COWAT in mixed and severe TBI samples (72); list learning/delayed recall from the RAVLT in all injury severity samples (39); oral and written SDMT in mild and mixed severity samples (72); MMSE in a TBI sample of unknown severity (81); TMT, WAIS-R and WAIS-III in mixed severity samples (39, 72, 76, 77), and WAIS-IV in mTBI sample (82). Significant differences were observed between the scores of persons with TBI and healthy controls, and TBI and other neurological populations (**Table 2**).

Test-Retest Reliability

Test-retest reliability refers to the consistency of scores attained by the same patient over the course of several attempts at different times (62). It concerns the stability of the instrument's performance over a period of time, when a real change in the measured construct (i.e., cognition) is unlikely (62). The assumption is that while between-person differences in scores on a given measure are expected, the score for any individual will remain constant across successive administrations of the instrument. In our population of interest, persons with TBI, there is evidence for the test-retest reliability of the HVLT-R and the ANAM4. One study (83) reported the Pearson correlation coefficient (PCC) and the other (68) reported the intra-class correlation coefficient (ICC), the preferred statistic. The HVLT-R was administered twice to 75 adults with TBI of unknown injury severity (71% men, 46.5 $\pm$ 10.5 years of age, at 11.8 $\pm$ 9.6 years post injury), the two sessions occurring 6–8 weeks apart from one another (83). Correlation coefficients for two of the eight HVLT-R scores (total recall and delayed recall) reflected high test-retest reliability ($r = 0.82$) and the remaining six scores (T-score, delayed recall T-score, retention, retention T-score, recognition discrimination index and recognition discrimination index T-score) reflected moderate ($r = 0.64$) test-retest reliability. The ANAM4 was administered twice to 1,324 members of the Marine Corps unit (all men, 22.5 $\pm$ 3.4 years of age) with a known high rate of concussion from combat and blast exposure. The average interval between the two test sessions was 357 $\pm$ 88 days (range 99–637 days) (68). After injury classification, 238 members were designated to the concussed group and 264 to the non-concussed group. While there were no significant differences between the mean scores of the two groups at the first session, differences emerged at second session, with the concussed group having lower mean scores than the non-concussed group on the cognitive tasks assessing attention, memory, spatial processing, reaction time, and cognitive fatigue [i.e., code substitution delayed (CDD), matching to sample (M2S), procedural reaction time (PRT), and simple reaction time (repeat) (SRT, SRT2) subscales]. The test of simple effects revealed that the mean score for the concussed group decreased significantly from T1 to T2 on the SRT, SRT2, PRT, Code Substitution Learning, M2S, Mathematical Processing (MTH), and CDD subscales. The ICC between the scores from the first and second sessions was reported only for the non-concussed group: of the seven domains, the CDD and MTH domains met the cut-off for the mean score correlation between the two time points for the entire group (i.e., >0.70) but not in the comparison of scores of individual patients at the two time points (i.e., >0.90). Practice effects were reported for the ANAM, where it was noted that individuals with TBI displayed inconsistent performance in 30 administrations over four days, while controls showed consistent improvement (85) (**Table 3**).

TABLE 2 | Quality assessment of the 15 selected instruments based on criteria proposed by Holmbeck et al. (20).

Measures	Frequency of use by different investigators	TBI severity	Frequency of use by same team	Details for critical evaluation	Test-retest reliability/ responsiveness	Construct validity (concurrent, divergent/convergent, known-group)
ANAM	**4x** (33, 50, 51, 53)	Mild TBI (33, 50, 51, 53)	N/A	Can be purchased at vistalifesciences.com	ANAM4: T1 and T2 357 ± 88 d (range 99–637) NA/ decline in CDS, CDD, M2S, MTH, PRT, SRT, and SRT2; 48% w decline on ≥2 subtests (68)	**Known Groups** • SPA/MTH: sd b/w TBI and HCs ($p < 0.05$) (53) • CDS, CDP, PRT, SRT, SRT2: sd b/w concussed and non-concussed ($p < 0.05$) (68)
COWAT	**8x** (24, 25, 39, 41, 42, 49, 57, 58)	Mild TBI (42, 49) Severe TBI (25, 58) Mixed TBI (24, 39, 41, 57)	**2x** (39, 41)	Can be purchased at parinc.com	U/K	**Known Groups** • sd b/w TBI and HCs at BS ($p < 0.01$) (72)
CVLT	**3x** (57, 58, 61)	Version II Severe TBI (58) Original version Mixed TBI (57, 61)	N/A	Can be purchased at pearsonclinical.com	U/K	**Convergent** • CVLT w/ RAVLT: 1and5, 1–5, B, SDR, % SDR, and Int ($r = 0.49$–0.83; $p < 0.001$) (64)
FIM-Cog	**5x** (34, 40, 43, 56, 58)	Severe TBI (34, 41, 56) Mixed TBI (43, 58)	N/A	Not available online; must contact UDSMR to subscribe	U/K	**Convergent** • FIM-Cog w/ DRS, FIM+FAM mot and cog, LCFS, PTA: $r = 0.41$–0.95; $p < 0.05$ (67)
HVLT	**2x** (47, 49)	Mild TBI (47, 49)	N/A	Can be purchased at parinc.com	• HVLT-R TR, DR, % Retained, discrim.: $r = 0.64$–0.82; $p < 0.05$ (83)	**Known Groups** NS b/w TBI and HCs in HVLT total, sd in HVLT delayed ($p = 0.02$) (79)
ImPACT	**7x** (31, 35, 44–46, 52, 60)	Mild TBI (31, 35, 44–46, 52, 60)	**4x** (44–46, 60)	Can be purchased at impacttest.com	U/K	**Divergent** • VEM w/ difficulty concentrating and remembering: $r = -0.48$ to -0.41; $p < 0.01$ (65) **Convergent** • RT w/ SDMT, verbal/visual memory, feeling foggy, difficulty remembering: $r = 0.36$–0.70, $p < 0.05$) (66)
PASAT	**2x** (27, 48)	Mild TBI (48) Mixed severity TBI (27)	N/A	Can be purchased at pasat.us	U/K	**Convergent** • 2.0s and measures of attention ($r = 0.35$–0.49, -0.35, $p < 0.001$) (69) **Divergent** • 2.0 s and measures of intellectual ability, mathematical knowledge, verbal ability, academic achievement, and complex mot skills ($r = 0.29$–0.59, $p < 0.05$) (69)
RAVLT	**6x** (28, 37, 39, 41, 42, 59)	Mild TBI (28), Mixed severity TBI (37, 39, 41) Severe TBI **s** (42, 59)	**2x** (37, 42) **2x** (39, 41)	Can be purchased at wpspublish.com	U/K	**Known Groups** • List learning/delayed: sd b/w TBI and HCs at BS ($p < 0.01$) (39)
ROCF	**2x** (36, 58)	Mixed severity TBI (36) Severe TBI (58)	N/A	Can be purchased at parinc.com	U/K	**Convergent/divergent** • Copy w/ GPT NDH: $r = 0.37$; $p < 0.01$ (70) • IR w/ SDMT, GPT NDH: $r = 0.35$–0.37; $p < 0.01$ (70) • RCFT rec. w/ COWAT: $r = 0.35$;$p < 0.01$ (70) • RCFT total w/ total voxel # on L/R thalamic RSNs: $\rho = -0.55$; $p = 0.003$ (71)

(Continued)

TABLE 2 | Continued

Measures	Frequency of use by different investigators	TBI severity	Frequency of use by same team	Details for critical evaluation	Test-retest reliability/ responsiveness	Construct validity (concurrent, divergent/convergent, known-group)
MMSE	**2x** (54, 55)	Mild TBI (54), Mixed severity TBI (55)	N/A		U/K	**Convergent Validity** • w/ MoCA score ($r = 0.852$, $p < 0.001$) (80) **Known Groups** • sd b/w TBI and stroke at (t=3.13, $p < 0.001$, most difference in orientation domain) (81)
SCWT	**6x** (27, 28, 37, 49, 57, 58)	Mild TBI, (27, 28, 49) Mixed severity TBI, (37, 57, 58)	N/A	Can be purchased at parinc.com	U/K	**Convergent/divergent** • w/ informant CFQ: $r = 0.47$; $p < 0.05$ (72) • w/ SADI: $r = 0.41$; $p < 0.01$ (73) • CW w/ ADL, informant CFQ, QOLIBRI: $r = 0.40$–0.55, -0.40; $p < 0.05$ (74)
SDMT	**6x** (26, 39, 41, 42, 48, 49)	Mild TBI, (26, 48, 49) Mixed severity TBI (39, 41) Severe TBI (42)	**2x** (39, 41)	Can be purchased at wpspublish.com	U/K	**Known Groups** • Oral/Writ: sd b/w TBI and HCs at BS ($p < 0.01$) (72)
TMT	**14x** (23, 24, 28, 32, 37–39, 41, 42, 48, 49, 57, 59)	Mild TBI (23, 28, 32, 48, 49), Mixed severity TBI (37–39, 41, 58), Severe TBI (24, 42, 59)	**2x** (37, 42) **2x** (23, 57) **2x** (39, 41)	Can be purchased at www.mcssl.com	U/K	**Known Groups** • A/B: sd b/w TBI and HCs at BS ($p < 0.01$) (39) • B: sd b/w TBI and non-TBI ($p = 0.047$) (39)
WAIS	**17x** (23–26, 28–30, 32, 36–39, 41, 42, 55, 57, 58)	Mild TBI (23, 26, 28, 29, 32, 36, 55), Mixed severity TBI (37–39, 41, 57, 58) Severe TBI (24, 25, 30, 42)	**2x** (37, 42) **2x** (23, 57) **2x** (39, 41)	Can be purchased at pearsonclinical.com	U/K **Responsiveness** • Info, Comp, DST, PC, PA, PIQ, FSIQ: ↑0–3 to 7–12 m ($t = 2.24$–3.44; $p \leq 0.05$) (84) • DST, BDT, PA, OA, PIQ, FSIQ: ↑ 4–6 to >13 m ($t = 2.19$–2.68; $p \leq 0.05$) (84) • Info, Comp, Arith, DG, Vocab, DST, PC, BDT, PA, VIQ, PIQ, FSIQ: ↑ 0–3 to >13 m ($t = 2.06$–4.93; $p \leq 0.05$) (84)	**Convergent** • WAIS Vocab w/ early MRI: $r = -0.43$; $p < 0.05$ (75) • WAIS Sim, Vocab, DST, BDT, OA w/ late MRI: $r = -0.86$ to -0.48; $p < 0.01$ (75) • WAIS-R BDT w/ VFD Total and Rotation: $r = 0.47, -0.45$; $p < 0.05$ (63) **Known Groups** • WAIS-R DG: sd b/w TBI and HCs ($p \leq 0.001$) (76) • WAIS-III LNS: sd b/w TBI and HCs at BS ($p < 0.01$) (39) • WAIS-IV: sd b/w TBI and non-TBI ($p < 0.01$) (39) • WAIS-IV: mTBI positive vs negative combat-exposed military personnel ($p < 0.17$) (82)

(Continued)

TABLE 2 | Continued

Measures	Frequency of use by different investigators	TBI severity	Frequency of use by same team	Details for critical evaluation	Test-retest reliability/ responsiveness	Construct validity (concurrent, divergent/convergent, known-group)
WMS	**3x** (37, 38, 42)	Mild TBI (42) Mixed TBI (37) Severe TBI (77)	**2x** (37, 42)	Can be purchased at pearsonclinical.com	U/K	**Convergent** • WMS MQ/VM and L/R-brain: sig↓ pre- to post-operation (77) • WMSandWAIS FSIQ: $r = 0.75$–0.83 (77) • WMS-R VM and PTA: $r = -0.53$; $p < 0.05$ (78) • WMS-R VEM/VM/GM/Attention/ Concentration/DR and IMS: $r = -0.65$ to -0.44; $p < 0.05$) (78)

ADL, activities of daily living; ANAM, Automated Neuropsychological Assessment Metrics; Arith, Arithmetic; BDT, Block Design Test; BS, baseline; b/w, between; CFQ, Cognitive Failures Questionnaire; cog, cognitive/cognition; Comp, Comprehension; COWAT, Controlled Oral Word Association Test; CW, Color Word; d, days; DG, Digit Span; discrim., discriminability; DR, delayed recall; DRS, Disability Rating Scale; DST, Digit Symbol Test/Digit Symbol Coding/Coding; CVLT, California Verbal Learning Test; FAM, Functional Assessment Measure; FIM, FIM instrument, cognitive subscale (formerly Functional Independence Measure); Freq, frequency; FSIQ, Full Scale Intelligence Quotient; GM, General Memory; GPT, Grooved Pegboard Test; HCs, healthy controls; HVLT, Hopkins Verbal Learning Test; IMS, Inpatient Memory Impairment Scale; ImPACT, Immediate Post-concussion Assessment and Cognitive Test; Info, Information; Int, Intrusions; ICC, intraclass correlation coefficient; IR, Immediate Recall; LCFS, Levels of Cognitive Functioning Scale; LNS, Letter Number Sequencing; L/R, left/right; MoCA, Montreal Cognitive Assessment; mot, motor; MRI, magnetic resonance imaging; MTH, Mathematical Processing; MQ, Memory Quotient; N/A, not applicable; U/K, unknown; NDH, non-dominant hand; OA, Object Assembly; PA, Picture Arrangement; PASAT, Paced Auditory Serial Addition Test; PC, Picture Completion; perf, performance; PIQ, Performance Intelligence Quotient; PTA, post-traumatic amnesia; QOLIBRI, Quality of Life after Brain Injury; RAVLT, Rey Auditory Verbal Learning Test; RCFT, Rey Complex Figure Test and Recognition Trial; ROCF, Rey-Osterrieth Complex Figure Test; RSNs, resting state networks; RT, Reaction Time; SADI, Self-Awareness of Deficits Interview; sd, significant difference; SDMT, Symbol Digit Modalities Test; SDR, short delay recall; sess, sessions; Sim, Similarities; SPA, Spatial Processing; TBI, traumatic brain injury; TMT, Trail Making Test; TR, total recall; UDSMR, Uniform Data System for Medical Rehabilitation; w/, with; WAIS (-R/III/IV), Wechsler Adult Intelligence Scale (-Revised/Third Edition/Fourth Edition); WMS (-R/III/IV), Wechsler Memory Scale (-Revised/Third Edition/Fourth Edition); Writ, written; VEM, Verbal Memory; VFD, Benton Visual Form Discrimination Test; VIQ, Verbal Intelligence Quotient; VM, Visual Memory; Vocab, Vocabulary. Bold values designate number of uses of the instrument, meant to distinguish from the citations beside these values.

Responsiveness

Responsiveness, defined as the ability of an instrument to detect change over time in the construct being measured (62), was reported for the ANAM4 in a sample of concussed males (68) and for the WAIS in a sample of severe TBI (84). The former study of young men from the Marine Corps unit (68) tested the rate of performance decline on ANAM4 subscales from the first test session to the second, applying the reliable change (RC) methodology (86). Researchers reported that 48% of the concussed group demonstrated a decrease in performance on two or more subscales, compared to 28% of the non-concussed group.

When the WAIS was administered to 40 adults who sustained TBI and experienced posttraumatic amnesia (PTA) lasting at least 4 days (95% men, 28.3 ± 13.36 years of age) in the latter stages of their PTA and to a matched group of 40 non-injured persons, TBI group scores on the verbal subscales indicated less initial impairment and were restored to levels exhibited by the comparison group at a faster rate than were the scores on non-verbal subscales (84). The mean verbal intelligence quotient (IQ) of the TBI group approached that of the comparison group within the first year after injury, while performance IQ continued to improve over the course of 3 years (84, 87).

Classification of Instruments of Cognitive Functioning by Cognitive Domain(s) Assessed

The WAIS assesses all seven cognitive domains, qualifying as a "global" measure of cognitive functioning. The remaining instruments were "multi-domain" measures. The most represented domain was learning and memory, assessed in 13 instruments, and the least represented was social cognition, included in two instruments (**Table 3**; **Supplementary File 3**).

Information Relevant to Clinical and Research Applications

Instruments' manuals, assessment forms, and scoring instructions are available from their publishers; some are available online for free (**Table 2**). Information about the instruments (e.g., purpose, content, measurement properties, etc.) can be obtained online (**Supplementary File 3**).

All instruments require participants to complete one or more tasks, typically through written or spoken responses. The ANAM and ImPACT are computerized, the WAIS and WMS can be computer- or paper-based, and the FIM-Cog is administered via interview or participant observation. The number of items in each instrument varies: for instance, the COWAT presents three letters and relies on free word recall, while the PASAT contains a 61-item list of digits that the test-taker must sum up (i.e., adding each digit presented to the one that came just before it). The FIM-Cog, and larger batteries like the ANAM, ImPACT, WAIS and WMS, contain multiple tasks assessing different cognitive domains, ranging from five (e.g., FIM-Cog) up to 15 (e.g., WAIS), of which ten are core and five are supplementary subtests. Completion times range from 3 min (e.g., COWAT) to more than 90 min (e.g., ANAM, WAIS). Scoring procedures and score

TABLE 3 | Summary of domains assessed in instruments measuring cognitive functioning, and interpretation of scores.

Measures	Neurocognitive Domains						
	Learning and memory	**Language**	**Perceptual-motor**	**Complex attention**	**Executive function**	**Information processing speed, reaction time***	**Social cognition**
ANAM	CDS, CDD—higher score is better		SPA, MTS—higher score is better	CDS, CDD, PRO– higher score is better	MTH, PRO, CDS, CDD, CPT—higher score is better	ST2, ST4, PRO, SRT, SRT2—higher score is better GNG—lower score is better	
ImPACT	WM, WM-D, VERM, DM, DM-D, VISM—higher score is better		DM, DM-D, VISM—higher score is better	TL– higher score is better CL, XO ICC; XO—lower score is better	SM, TL, VERM, VISM—higher score is better CL, XO ICC; XO, CL, SM, RT—lower score is better	SM, TL, VERM, VISM—higher score is better CL, XO ICC; XO, CL, SM, RT—lower score is better	
HVLT	Higher score is better				Higher score is better		
TMT			TMT A/B—lower score is better	TMT A/B—lower score is better	TMT A/B—lower score is better	TMT A/B—lower score is better	
PASAT				Higher score is better	Higher score is better	Higher score is better	
WAIS Total IQ—higher score is better	WMS—higher score is better	VCI, VIQ—higher score is better	PRI, PIQ—higher score is better	SS, CODE/DSST, CAN, VIQ, PIQ—higher score is better	VCI, PRI, WMS, VIQ, PIQ—higher score is better	PSS—higher score is better	Crystallized intelligence (use of learned knowledge) –higher score is better
FIM-COG Total score—higher score is better	Mem	Expr, socint—higher score is better			Comp, expr, socint, probsolv, mem—higher score is better		Higher score is better
CVLT	Higher score is better				Higher score is better		
COWAT	Higher score is better	Higher score is better		Higher score is better	Higher score is better		
RAVLT	Recall—higher score is better Forgetting—lower score is better Learning—higher score is better				Information retention–higher score is better Information retrieval– higher score is better		
ROCF	Higher score is better		Higher score is better		Higher score is better		
MMSE Total score—higher score is better	Recall—higher score is better Lang—higher score is better		Orient, visconst—higher Score is better		Regist, att and calc—higher score is better		

(Continued)

TABLE 3 | Continued

Measures	Neurocognitive Domains						
	Learning and memory	**Language**	**Perceptual-motor**	**Complex attention**	**Executive function**	**Information processing speed, reaction time***	**Social cognition**
SCWT			Scoring varies		Scoring varies	Scoring varies	
SDMT			Higher score is better	Higher score is better		Higher score is better	
WMS Total MQ—higher score is better	LM, VR—higher score is better	PCI, ORI—higher score is better	ORI, VR—higher score is better		PCI, MC, MS, AL—higher score is better		

Learning and memory: immediate memory, recent memory (free recall, cued recall, recognition memory), very-long-term memory (semantic, autobiographical), implicit learning.
Language: expressive language (naming, word finding, fluency, grammar, syntax), receptive language.
Perceptual-motor: visual perception, visuoconstructional, perceptual-motor, praxis, gnosis.
Complex attention: sustained attention, divided attention, selective attention, processing speed.
Executive function: planning, decision making, working memory, responding to feedback/error correction, overriding habits/inhibition, mental flexibility.
Social cognition: recognition of emotions, theory of mind.
**Information processing speed and reaction time: not part of DSM-5 classification; additional for our purposes.*
AUTOMATED NEUROPSYCHOLOGICAL ASSESSMENT METRICS (ANAM): Sternberg memory search (ST2 and ST4), Mathematical processing (MTH), Spatial processing (SPA), Procedural reaction time (PRO), Simple reaction time (SRT), Simple reaction time repeat (SRT2), Code substitution (CDS), Code substitution-delayed (CDD), Continuous performance (CPT), Matching to sample (MTS), Go-no-go (GNG); IMMEDIATE POST-CONCUSSION ASSESSMENT AND COGNITIVE TESTING (ImPACT): Word memory (WM), Word memory-delayed (WM-D), Symbol match (SM), Three letters (TL), X's and O's (XO), Design memory (DM), Design memory-delayed (DM-D), XO (total correct answers on memory or distractor tasks), TL (avg counted correctly), Color match (CL); HOPKINS VERBAL LEARNING TEST (HVLT); TRAIL-MAKING TEST (TMT): Trails A (sequential connecting of numbers), Trails B (sequential connecting of numbers and letters); PACED AUDITORY SERIAL ADDITION TEST (PASAT); WECHSLER ADULT INTELLIGENCE SCALE (WAIS): Similarities (SIM), Vocabulary (VOCAB), Information (INFO), Comprehension (COMP), Block design (BD), Matrix reasoning (MR), Visual puzzles (VP), Picture completion (PC), Picture arrangement (PA), Figure weights (FW), Digit span (DSPAN), Arithmetic (ARIT), Letter-number sequencing (LNS), Symbol search (SS), Coding/digit symbol (CODE/DSST), Cancellation (CAN), Verbal intelligence (VIQ), Performance intelligence (PIQ), Full scale intelligence (FSIQ); FUNCTIONAL INDEPENDENCE MEASURE COGNITIVE DOMAIN(FIM-Cog): Comprehension (auditory), Expression (verbal), Social interaction, Problem solving, Memory; CALIFORNIA VERBAL LEARNING TEST (CVLT): Word list A (target words verbally delivered, 5 trials to learn), Word list B (distractor words); CONTROLLED ORAL WORDS ASSOCIATION TEST (COWAT); RAY AUDITORY VERBAL LEARNING TEST (RAVLT); REY-OSTERRIETH COMPLEX FIGURE TEST (ROCF); MINI-MENTAL STATE EXAMINATION (MMSE); STROOP COLOR-WORD TEST (SCWT); SYMBOL DIGIT MODALITIES TEST (SDMT); WECHSLER MEMORY SCALE (WMS).

interpretation varies across instruments. Scoring sheets/software and instructions are available with purchase of the instruments.

Evidence-Based Assessment of Cognitive Functioning Measures

All 15 instruments were utilized in at least two peer-reviewed studies by two different research teams. The WAIS and TMT were the most frequently used instruments: different versions of the WAIS were used 17 times by 14 different teams, and the TMT was used 14 times by 11 teams (**Table 2**). None of the instruments met the criteria for a "well-established," "approaching well-established," or "promising" rating in the TBI population (**Table 3**). Known-groups validity and responsiveness were reported for two versions of the ANAM in two concussion samples (53, 68). The hypotheses regarding known-groups validity were accepted for the HVLT-R delayed recall task but rejected for the total score in a mTBI sample (79), and test-retest reliability in a TBI sample of unknown severity met the correlation cut-off for the group, but not for individual patients for total recall and delayed recall only (83). Convergent and divergent construct validity hypothesis testing for other instruments were not supported for all subscales/tasks, and were not always in line with clinical expectations (69, 78).

Table 4 provides a summary of the measurement properties of measures of cognitive functioning in TBI samples.

DISCUSSION

This review provides a comprehensive overview of existing instruments used to evaluate cognitive functioning in clinical and non-clinical settings in persons with TBI. An extensive search strategy led to identification of 15 instruments; each was reviewed and comprehensively described (**Supplementary File 3**), providing information on content and level of evidence existing regarding measurement properties as they concern the use of these tools for evaluative purposes, i.e., their ability to measure change in a construct over time. Our results highlight that most scientific evidence pertains to construct validity, with limited evidence on test-retest reliability and responsiveness in TBI samples. This poses a risk to TBI researchers and clinicians when it comes to interpreting the results produced in longitudinal studies, with no certainty of the instruments' ability to measure change in cognitive functioning in persons with TBI longitudinally. The results are informative nevertheless, having implications for the understanding of and future research related to the measurement properties of evaluative instruments, and their subsequent utilization for studying the natural history and clinical course of cognitive functioning and treatment effects in clinical trials in persons with TBI.

Construct Validity

Construct validity refers to the development of a mini theory to describe how well an instrument measuring a construct of interest would agree with another instrument measuring a related construct (11, 62). In the measurement of cognitive functioning in persons with TBI, there does not exist a gold standard or criterion measure (11), and therefore understanding the domains each instrument is trying to measure (content validity) and whether the different instruments relate to one another in the way one would expect, is an important property to consider. It is important to highlight the basic principle of construct validation, which is that hypotheses about the relationship of scores of any instrument with scores on other instruments measuring a similar or different construct (convergent and divergent construct validity, respectively) should be formulated in advance; the specific expectations with regards to certain relationships can be based either on an underlying conceptual model or on the data in the literature (11). This review has found that only a few researchers tested hypotheses related to the relationship between the measures of cognitive functioning studies and measures of other constructs, stating ahead of analysis the expected direction and magnitude of associations, based on what was known about the constructs under study. In future studies, to assess similarity or dissimilarity between instruments' scores, when formulating hypotheses, one should first have a solid grasp of the contents of comparable instruments, which we provide in this review, as domains within any given instrument are expected to be correlated strongly with domains of conceptually similar instruments. There should also be a clear description of what is known about the TBI population under study, including but not limited to the circumstances surrounding injury, injury severity and mechanism, brain maturity and brain health at the time of injury, comorbid mental and physical disorders, coping ability, and psychotropic medication use, as each of these have the ability to influence cognitive functioning at assessment (88–92).

Known-groups validity (of construct validity) refers to an instrument's ability to discriminate between groups of individuals known to have a particular trait and those who do not have that trait (62). This property is most relevant for discriminative (i.e., diagnostic) instruments (11, 12), however is significant for evaluative instruments, where it is imperative that an instrument is responsive to all clinically important differences between constructs under investigation or different courses or outcomes of the construct (13). This includes identification and deletion of unresponsive items within a construct from the instrument over time. One way to identify such items within the cognitive functioning constructs assessed by instruments in the TBI population is to administer the instrument to a group of people with TBI of varying severities and associated cognitive impairments and to healthy people without impairments, and compare the scores yielded at baseline testing (known groups validity) and at follow-up after an intervention with known efficacy in improving cognition (e.g., cognitive training). Presence and absence of differences between the two groups in items will indicate items that are responsive and those that are not, respectively (longitudinal known-group construct validity). Only one study assessing measurement properties provided parameters of longitudinal known-group validity for the ANAM4 in young men with concussion (68) and those without.

Test-Retest Reliability

Not every change on a measurement instrument can be considered a real or true change in the construct the instrument is believed to measure (13). Observed changes in scores over

TABLE 4 | Summary of measurement properties of evaluative instruments of cognitive functioning in TBI samples.

Instrument	Target population when developed	Neurocognitive domains covered	Respondent burden*	Construct validity		Ability to detect change	
				Convergent or divergent	Known-group	Test-retest reliability	Responsiveness
ANAM	Healthy persons with environmental challenges	5/7	Up to 90 min	–	+	–	+
ImPACT	Athletes with concussion	5/7	25+ min	+	–	–	–
HVLT	General adult population	2/7	5–10 min testing + 25 min delay	–	+	+	–
TMT	Military personnel	4/7	5–10 min	–	+	–	–
PASAT	General population	3/7	15–20 min	+	–	–	–
WAIS	General adult population	7/7	60–90 min	+	+	–	+
FIM-COG	Rehabilitation in-patients	4/7	30–45 min	+	+	–	–
CVLT	General population	2/7	30 min testing + 30 min delay	+	–	–	–
COWAT	Persons with low education or limited writing	4/7	3+ min	–	+	–	–
RAVLT	General population	2/7	10–15 min	–	+	–	–
ROCF	Persons 6–89 years old	3/7	50–60 min	+	–	–	–
MMSE	Psychiatric and dementia patients	3/7	<5 min	+	–	–	–
SCWT	Psychiatric patients	3/7	5 min	+	–	–	–
SDMT	Persons 8 + years old with organic brain pathology	3/7	<5 min	–	+	–	–
WMS	General population	4/7	30–35 min	+	–	–	–

**As reported for original version; + = information available in TBI sample(s) of mild severity; – = no information available in TBI samples of any severity.*
COWAT, Controlled Oral Word Association Test; CVLT, California Verbal Learning Test; FIM, FIM instrument, cognitive subscale (formerly Functional Independence Measure); HVLT, Hopkins Verbal Learning Test; ImPACT, Immediate Post-concussion Assessment and Cognitive Test; MMSE, mini mental state examination; min, minutes; PASAT, Paced Auditory Serial Addition Test; RAVLT, Rey Auditory Verbal Learning Test; ROCF, Rey-Osterrieth Complex Figure Test; SDMT, Symbol Digit Modalities Test; TMT, Trail Making Test; WAIS (-R/III/IV), Wechsler Adult Intelligence Scale (-Revised/Third Edition/Fourth Edition); WMS (-R/III/IV), Wechsler Memory Scale (-Revised/Third Edition/Fourth Edition).

time may be due to measurement error, natural variability in a person's ability to concentrate throughout the day, i.e., peak in performance, mood at the time of investigation, which may determine positive or negative responses in case of doubt, evaluators' variability in applying criteria more or less strictly, or the natural course of the construct under study (i.e., recovery or deterioration) (11–13). Therefore, interpretation of change in score over time requires assessment of measurement error by test-retest of a stable population of interest (13). But what is a stable TBI population? By choosing a timeframe with 6–8 weeks between the two test sessions of the HVLT-R, researchers reported moderate to high test-retest reliability on all eight parameters tested (83). Unfortunately, the researchers did not ask their participants how their cognitive activity changed over the 6–8 weeks, and therefore, the stability of the group of TBI patients that took part in this study is unknown and thus the interpretability of the score and corresponding attribution of functional status is uncertain. When the researchers assessed test-retest reliability of the ANAM4 in young men in the chronic stage post-concussion and in their non-injured counterparts, the groups' scores were comparable at baseline, but differences in some but not all subscales (CDD, M2S, PRT, SRT, and SRT2) emerged at 357 ± 88 days after baseline assessment, with the concussed group exhibiting lower scores than the non-concussed group; the reason for this observation is not clear (68). Consequently, issues related to the meaning and interpretation of results of longitudinal studies utilizing instruments with unknown test-retest reliability in the population of interest remain pressing.

Responsiveness

Responsiveness, defined as an instrument's ability to accurately detect change when it has occurred, is key for instruments applied for the purpose of evaluation (13). Responsiveness is not an attribute of the instrument itself, but reflects the application of the instrument in a given context (e.g., for quantifying the benefit of an intervention in a clinical trial), or to a certain type of change (i.e., natural history, recovery, etc.). Responsiveness is the ability of an instrument to detect change when it has taken place, and can be expressed either as absolute difference within a person or group, or the effect size, referred to as the standardized response mean (91). Responsiveness is the least studied attribute of measures of cognitive functioning. The results of one study that investigated responsiveness of the WAIS in a sample with severe head injury supported the hypothesis of differential speed of recovery of different

domains of cognition in TBI (i.e., verbal IQ of the head injured group approached that of the comparison group within about one year of injury, while recovery of performance IQ continued to improve over about 3 years) (84). The results of another study assessing the ANAM4 in a concussed sample (68) reported that 48% of the concussed group demonstrated decreases in performance on two or more subscales compared with 28% of the non-concussed group, driven by the CDS, CDD, PRO, SRT, and ST2 subscales (assessing abilities related to information processing speed, reaction time, attention, memory, and learning). Neither study however, formulated specific hypotheses with respect to expected mean differences in scores in the studied groups a priori. Without the a priori hypotheses the risk of bias is high, because retrospectively, it is tempting to think of explanations for the observed results instead of concluding that an instrument might not be responsive. Also worth noting is that when measurement properties were assessed, participant samples consisted of mostly or strictly men. Without gender-related specifications on the applications of the ANAM and the HVLT, it impossible to draw any firm conclusions on the instruments' test-retest reliability and responsiveness, and therefore their ability to detect change over time.

Feasibility, and Clinical and Research Utility

Feasibility concerns practicality of administering an instrument to a person in the setting it which it needs to be administered (11). In order to accurately measure what it intends to measure, and ensure valid responses, self-administered instruments must be completely self-explanatory, and those administered by research or clinical personnel require personnel to be trained to collect the required information. None of the studies included in this review reported on the training of respondents and administrators, or lack thereof. This is important for ensuring the procedure is standardized and to confirm the ability of persons with TBI to complete the procedure and respond with insight. Instruments that require more than 30 min to complete can be tiring for persons with TBI, who commonly experience decreased stamina, especially during tasks involving novelty. Multi-domain instruments demand continuous, goal-directed activity, which would be affected by diminished motivation, impairments, psychological state, and age. In such cases, researcher or clinicians may administer combinations of relevant sub-tests over some time, which can present a challenge for calculation of an accurate score and interpretation of scores. A composite score is the most practical approach for researchers looking to quantify a population's global change over time: if sample sizes are sufficiently large, the between-person variation in certain subscales or domains will be balanced in the calculation of a mean global score for the group. In the clinical setting, however, where clinicians are working one-on-one with individuals to study the natural history of or intervention-induced changes in a construct over time, focus on the individual subscales is key. The implication is that the scores of each of the subscales of a global or multi-domain measure have to be validated separately in a population of interest. This is particularly relevant for certain domains of cognition such as crystalized intellectual abilities, which have been hypothesized to be resistant to the effects of TBI. Finally, study of the evaluative properties of measures of cognitive functioning that are reflective of everyday cognitive skills is needed.

STUDY LIMITATIONS

There are a number of limitations to this review. All of the studies included were published in English, and therefore instruments used in non-English-speaking populations and studies have not been captured. The review team did not contact authors of reviewed papers for additional methodological details that were not available in their publications. Further, the team appraised methodological quality utilizing Holmbeck et al.'s criteria (20), developed for measures of psychosocial adjustment and psychopathology, and therefore not specific for measures of cognitive functioning. Nevertheless, justifications for quality ratings given to each of the reviewed instruments were reported to clarify the resultant assessment grades. Several instruments [i.e., standardized assessment of concussion (SAS), short orientation-memory-concentration test (SOMT), and the neuropsychological assessment battery (NAB)] assessing orientation (i.e., time and place), were not reviewed in this work, as they were utilized just once within the articles identified in the primary search, and therefore did not meet the frequency of use criteria set for this review.

Another potential issue is that while the instruments themselves are standardized, there are a number of scores that could be derived from each one. For instance, CVLT scores can be based on the number of words recalled from multiple lists, recall after short/long delay, number of errors in recall, etc. The use of these scores was not consistent from study to study. This lack of consistency not only makes it challenging, if impossible, to compare scores across studies, but may impact evaluation of certain measurement properties, such as concurrent validity, if only certain scores are associated with instruments meant to measure similar/different constructs (**Table 3**; **Supplementary File 3**). There are limitations related to the identification of data on construct validity. For the purpose of this review, data on measurement properties was gathered from studies of longitudinal design only. Despite attempts to include all articles relevant to construct validity in the TBI population, it is possible some cross-sectional studies evaluating construct validity were missed.

Finally, while the potential application of the described instruments measuring cognitive functioning in TBI can be for diagnostic/descriptive and prognostic/predictive purposes, the focus of our work was to examine the evaluative properties of such instruments (i.e., their ability to measure the magnitude of change longitudinally), when no external criterion is available for validating the construct. Thus, the assessment of

properties of instruments included in this review, as descriptive or predictive measures of cognitive functioning, requires further study.

CONCLUSIONS

In research utilizing evaluative, or other, psychometrics, the suitability of the instruments, or lack thereof, in terms of their psychometric properties, is rarely discussed, or acknowledged as a limitation in the case of measures whose scores have not been validated. This review highlights the problematic use of certain measures that lack the properties necessary for their use as evaluative measures. The evidence on measurement properties of instruments used to assess cognitive functioning in TBI samples longitudinally is limited, and thus, the way forward appears to be consensus on a set of measures with the greatest potential for evaluative purposes in TBI, and assessment of these select measures to build the evidence on measurement properties and establish or refute rationale for their application in TBI research. Refinement and testing of this group of instruments in TBI samples of varying severities in terms of longitudinal construct validity, test-retest reliability, and responsiveness, not only to reliably study the course of cognitive functioning after brain injury, but also for quantifying treatment benefits in clinical trials, is timely. Assessment of psychometric properties should not be an afterthought, but rather should preface the application of a measure in any new population or context, serving as the deciding factor on whether to proceed with its use. It is important that future research on psychometric properties of evaluative psychometrics, take into account the heterogeneity in cognitive functioning of persons with TBI, and report stratified results for subgroups of people based on injury severity, mechanism, and baseline cognitive abilities, to mitigate some of the heterogeneity. Further, to present these results in the context of change in everyday functional capabilities as time since injury progresses or in response to intervention, which will provide valuable insights. Furthermore, emphasis on within-individual variability in the TBI population, where each person serves as their own control, is likely to be the best technique to analyse change, and to answer the question—to which extent is the inherent regenerative capacity affected by injury-related variables, as opposed to internally (age, sex, genetic profile, etc.) or environmentally driven variables, as well as brain-behavior relations. The trade-off with the latter, however, is limited standardization of individual outcome measures, and lack of current theories of psychometric properties that speak to single case experimental design studies only (relevant to personalized medicine theory) and limited external validity (i.e., generalizability).

ETHICS STATEMENT

This article does not contain any studies with human or animal subjects performed by any of the authors.

AUTHOR CONTRIBUTIONS

TM and AC contributed to the conception of the study. TM developed the idea, registered the review on PROSPERO, designed and published the protocol, and developed the study screening criteria and quality assessment criteria. TM, SM, NP, FJ and AD executed the study in accordance with the protocol protocol. AD and NP screened all abstracts. AD extracted the data. SM doubled checked all extracted data. AD, SM, and NP performed study quality assessment and abstracted the data. TM guided the process and checked all data. AD and SM performed data analyses. AD wrote the first draft of the review, which was then edited by SM and TM. TM and AC provided mentorship to AD, SM, NP, and FJ throughout the course of the study.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2019.00353/full#supplementary-material

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The handling editor declares a shared association, though no other collaboration, with one of the authors AC in the Canadian concussion consortium.

GLOSSARY

Glossary of terms adapted from Feinstein (11), Kirshner and Guyatt (12), and the COSMIN [Mokkink et al. (62)] definitions.

Discriminative instruments	Measures used to distinguish between individuals or group on an underlying dimension when no external criterion or gold standard is available for validating these measures. Key psychometric properties: construct validity (differentiate high/low levels, acts as expected) and reliability (internal consistency, inter-rater reliability)
Evaluative instruments	Measures used to assess the magnitude of longitudinal change in an individual or group on the dimension of interest. Key psychometric properties: construct validity (measures target construct), test-retest reliability, and responsiveness to change
Predictive instruments	Measures used to classify individuals into a set of predefined measurement categories when a gold standard is available, either concurrently or prospectively, to determine whether individuals have been classified correctly. Key psychometric properties: construct validity (measures target construct, predicts future events), reliability (internal consistency, inter-rater reliability), statistical association with gold standard (criterion measure)
Content validity	The degree to which an instrument adequately samples from the domain of interest
Construct validity	The degree to which the measure scores reflect the hypotheses; includes (1) convergent, (2) divergent, and (3) known-group validity
Convergent validity	The degree of relatedness between two constructs hypothesized to be related
Divergent validity	The degree of relatedness Between two constructs hypothesized to be different
Known-group validity	Ability of the measure to discriminate between group of individuals known to have a particular trait and those who do not have that trait (same as discriminative validity)
Reliability	The extent to which the measure is reliable, that is, free of errors in score not due to true state of construct measured in the patient; consists of (1) internal consistency, (2) test-retest, (3) inter-rater, and (4) intra-rater
Inter-rater reliability	Degree of agreement between the score given by one rater and that by another at one time with respect to the same respondent; addresses the interpretability of the measure; falls under the broader test-retest reliability category
Intra-rater reliability	Degree of agreement between scores given by the same respondent or rater at one time and those given at another time; falls under the broader test-retest reliability category
Feasibility	Practicality of administering the measure; completion time, and scoring formula
Responsiveness	Ability of an instrument to detect change over time in the construct to be measured

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CASE REPORT
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Using Functional Near-Infrared Spectroscopy to Study the Effect of Repetitive Transcranial Magnetic Stimulation in Concussion: A Two-Patient Case Study

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Background: Approximately 25% of concussion patients experience persistent post-concussion symptoms (PPCS). Repetitive transcranial magnetic stimulation (rTMS) has been explored as a treatment, and functional near-infrared spectroscopy (fNIRS) may be a cost-effective method for assessing response.

Objectives: Evaluate rTMS for the treatment of PPCS and introduce fNIRS as a method of assessing treatment response.

Methods: *Design*: Two-patient case study. *Setting:* Calgary Brain Injury Program. *Participants:* 47 and 49 years. male, with PPCS for 1–2 years (headache, cognitive difficulties, nausea, visual difficulties, irritability, anxiety, poor mood, sleep, and fatigue). *Intervention:* 10 sessions of rTMS therapy to the left dorsolateral prefrontal cortex (DLPFC), at 10 Hz (600 pulses) and 70% of resting motor threshold amplitude. Participants completed an 8-week headache diary and a battery of clinical questionnaires prior to each fNIRS session. *fNIRS:* Hemodynamic changes were recorded over the frontoparietal cortex during rest, finger tapping, and a graded working memory test. fNIRS was completed pre-rTMS, following rTMS (day 14), and at 1-month post-rTMS (day 45). For comparison, two healthy, sex-matched controls were scanned with fNIRS once daily for five consecutive days.

Results: Clinical scores improved (headache severity, MoCA, HIT-6, PHQ-9, GAD-7, QOLIBRI, RPSQ, BCPSI) or remained stable (PCL-5, headache frequency) post-rTMS, for both participants. Participant 1 reported *moderate* symptom burden, and a fNIRS task-evoked hemodynamic response showing increased oxyhemoglobin was observed following a working memory task, as expected. Participant 2 exhibited a *high* symptom burden pre-treatment, with *abnormal* fNIRS hemodynamic response where oxyhemoglobin declined, in response to task. One month following rTMS treatment, participant 2 had a normal fNIRS hemodynamic response to task, corresponding to significant improvements in clinical outcomes.

Conclusion: This case study suggests fNIRS may be sensitive to physiological changes that accompany rTMS treatment. Further studies exploring fNIRS as a cost-effective technology for monitoring rTMS response in patients with PPCS are suggested.

Keywords: concussion, post-concussion symptom, transcranial magnetic stimulation (repetitive), functional Near Infrared Spectroscopy (fNIRS), rehabilitation

BACKGROUND

Annually, up to 280,000 people in Canada (1) and 42 million worldwide (2, 3) experience a mild traumatic brain injury (mTBI). In patients with mTBI, symptoms experienced following injury usually resolve within 3 months. However, up to 25% of patients will experience persistent post-concussion symptoms (PPCS), which can continue up to 1 year following injury (4). Common symptoms include headaches, dizziness, fatigue, irritability, depression, anxiety, emotional lability, concentration or memory difficulties, insomnia, and reduced alcohol tolerance (ICD-10 post-concussion syndrome diagnostic criteria) (5–8).

Repetitive transcranial magnetic stimulation (rTMS) is a non-invasive neurostimulation treatment whereby a rapidly alternating magnetic field applied to the scalp induces an electrical stimulus in a targeted region of the brain (9). This may lead to neuronal depolarization and either excitation or inhibition, depending on the neurons stimulated. Clinically, TMS has been approved by the FDA for treatment-resistant depression (rTMS) (10, 11) and migraine with aura (single pulse TMS) (12) Recent preliminary studies have explored rTMS as a treatment option for PPCS (13–15), although the physiological changes associated with rTMS intervention remain relatively unknown.

Functional near infrared spectroscopy (fNIRS) is a neuroimaging technology that non-invasively measures changes in cerebral tissue oxygenation coupled to neuronal activity. Continuous traces of cerebral tissue oxygenation are recorded and changes in the optical absorption properties of the brain tissue are measured (16). These changes can then be used to map local changes in brain activity, similar to how the blood-oxygenation level-dependent (BOLD) signal is used to measure brain activity in functional MRI studies (17). In comparison to functional MRI, fNIRS is advantageous for clinical application because it is small, portable, and useful in a variety of environments where neuroimaging is not feasible. We propose functional near-infrared spectroscopy (fNIRS) as a cost-effective method for studying rTMS treatment response. In this case study, we utilized fNIRS to explore the relationship between physiological changes in brain function and clinical markers of recovery associated with rTMS treatment in two patients with PPCS.

OBJECTIVES

To evaluate the effectiveness of rTMS for the treatment of PPCS and to assess whether fNIRS could be a biomarker of rTMS treatment response.

PATIENT HISTORIES

Participant #1

A 47-year-old male accountant was seen in the Calgary Brain Injury Program (CBIP) at the Division of Physical Medicine and Rehabilitation Department, Foothills Medical Centre, Calgary, AB, Canada. He was originally referred with a history of persistent symptoms (headache, dizziness, vision, neck pain, nausea, poor sleep, and mood) following mild traumatic brain injury while playing soccer. He had a past medical history of migraine with aura, basal cell carcinoma (removed), and gastroesophageal reflux disorder (GERD).

The patient was hit in the head by a high-speed ball while playing in a soccer game. He did not lose consciousness nor report post traumatic amnesia. He finished playing the game and was later diagnosed with a sport-related concussion (SRC) by a sports medicine physician based on the Consensus statement on Concussion in sport—5th International Conference (18). Initial symptoms included feeling "off and foggy" for the first 3 days, with subsequent development of persisting headaches/head pressure sensations, vision difficulties, fatigue, slowed processing speed and dizziness. Approximately 2–3 weeks after the head injury, he had a CT scan of his head, which was normal. In regard to treatment, he had trialed craniosacral therapy, physiotherapy, vestibular and vision therapy with only mild improvement in his symptoms. As a result, he was on short term disability.

Physical exam at the initial assessment demonstrated evidence of saccades when looking to the left and left eye nystagmus when looking to the right. He had evidence of convergence insufficiency on exam. The remainder of his neurologic exam was normal. Investigations, including neuro-ophthalmology evaluation, CT head, and neuroendocrine testing (CBC, electrolytes, glucose, TSH, free T4, a.m. cortisol) were all within normal limits.

The patient was seen seven times at the CBIP over the course of 16 months with ongoing treatment for headache, neck pain/hyperalgesia, vision, mood and return to work counseling. Despite further treatment with oral pharmacologic medications (trazadone, amitriptyline, desvenlafaxine), topicals, greater occipital nerve blocks, cranial botox injections (PREEMPT protocol) (19), prism glasses, and exercise, he continued to experience PPCS.

Participant #2

A 49-year-old male elementary school teacher was originally referred to the CBIP with a history of PPCS (vision changes, headaches, confusion, slowed thinking, difficulty with multitasking, poor balance, postural dizziness, nausea, emotional lability, fatigue) following a motor vehicle accident. He had a

past medical history of a mild TBI (with loss of consciousness) at 19 years old, as well as remote history of lower extremity orthopedic injuries.

The patient was involved in a motor vehicle accident, which occurred at ∼50 km/h. The air-bags deployed and his car started on fire. He was unable to remove himself from the vehicle. He did not report amnesia or loss of consciousness, but did experience a sensation of nausea, vision changes, headache, dizziness, and fatigue following the event. He was diagnosed with a concussion by his family doctor in accordance with the World Health Organization Criteria (20), based on alteration in mental state and neurological deficits following the event. He tried to go back to work 3 days after the injury, however reported word-finding difficulties, problems concentrating, poor memory, and confusion. Treatment prior to assessment in the CBIP included acetaminophen, ibuprofen, physiotherapy, massage, and hyperbaric oxygen chamber therapy without significant benefit. The patient was on short-term disability from work as a Grade 5 teacher. He was previously active in Iron Man Triathlons but was unable to train since his accident.

Initial physical exam demonstrated convergence insufficiency. He became symptomatic with eye movement. The rest of his neurologic exam was normal. Investigations, including an MRI of the brain and neuroendocrine testing (CBC, electrolytes, glucose, TSH, free T4, IGF-1, a.m. cortisol, and urine electrolytes) were within normal limits.

He was seen five times at CBIP over the course of 8 months with ongoing treatment for vision, headaches, dizziness, mood, return to exercise, and general rehabilitation (occupational and physical therapy, social work, psychology, and productivity consultant). He was treated with oral medications (sertraline, rizatriptan), prism glasses, vestibular physiotherapy, vision therapy, and personal exercise training with ongoing post-concussion symptoms.

METHODS

Design

Two-patient case study.

Setting

Calgary Brain Injury Program, Calgary, Alberta, Canada.

Included Participants

The two included participants, described above, consented to participate in a case study using rTMS and fNIRS for possible treatment of their persistent post traumatic brain injury symptoms. Two male control subjects (19 and 28 years of age, respectively) with no history of concussion or mild TBI underwent five identical fNIRS scans across five consecutive measurement days, in an effort to demonstrate reproducibility of baseline fNIRS measurement. Participant 1 was maintained on oral pharmacologic management with amitriptyline throughout the trial, while participant 2 did not take any oral medications.

Intervention

Ten sessions of rTMS therapy using an air-cooled 70-mm coil (Airfilm; Magstim, Whitland, UK) to the left dorsolateral prefrontal cortex (DLPFC), over 2 weeks, at 10 Hz (600 pulses) and 70% of resting motor threshold amplitude. Participants clinical MRI scans were loaded onto the neuronavigation software platform (Brainsight2, Rogue, Montreal).

Assessments

Clinical questionnaires included the headache impact test-6 (HIT-6), Montreal cognitive assessment (MoCA), patient health questionnaire-9 (PHQ-9), generalized anxiety disorder scale-7 (GAD-7), post-traumatic stress disorder checklist for DSM-5 (PCL-5), quality of life after brain injury questionnaire (QOLIBRI), Rivermead PPCS questionnaire (RPSQ-3, RPSQ-13), and British Columbia post-concussion symptom inventory (BCPSI). fNIRS recordings and clinical questionnaires were completed at baseline, immediately following rTMS (day 14), and at one month (day 45) post-rTMS. An 8-week headache diary documenting frequency and severity was also completed (2 weeks at baseline, during treatment, post-treatment, and 1-month post treatment).

fNIRS

Functional near infrared spectroscopy (fNIRS) scans were recorded at baseline, immediately following rTMS (day 14), and at one month (day 45) post-rTMS to investigate changes in brain physiology associated with rTMS treatment. fNIRS data were recorded over the frontoparietal cortex at a sampling rate of 3.91 Hz, using the NIRScout fNIRS system (NIRx Medical Technologies, Berlin, Germany; **Figure 1**). Each recording consisted of a 5 min rest period, followed by a finger tapping exercise, and a graded working memory task, previously described by Hocke et al. (21). The fNIRS data was processed and analyzed for task-evoked activation using an ordinary least squares method of general linear modeling, as implemented in the NIRS Brain AnalyzIR Toolbox (22). See Huppert et al. for a detailed discussion of fNIRS principles, acquisition, and analysis (23).

RESULTS

Clinical Scores

Participant 1 reported moderate overall symptom burden at baseline based on symptom scores, with minor improvements in most clinical scores following rTMS (**Table 1**). Participant 2 had greater symptom burden at baseline, and experienced improvements in all clinical scores, with clinically significant improvements in headache frequency, functional impact, and depression post-rTMS treatment, which persisted at 1-month post-rTMS (day 45; **Table 1**).

Both participants reported decreased headache severity immediately following rTMS and the effect persisted at the 1 month follow up. Headache frequency did not change in participant 1, however, there was a gradual reduction in headache frequency in participant 2. Clinical questionnaire outcomes, including the MoCA, HIT-6, PHQ-9, GAD-7, and QOLIBRI,

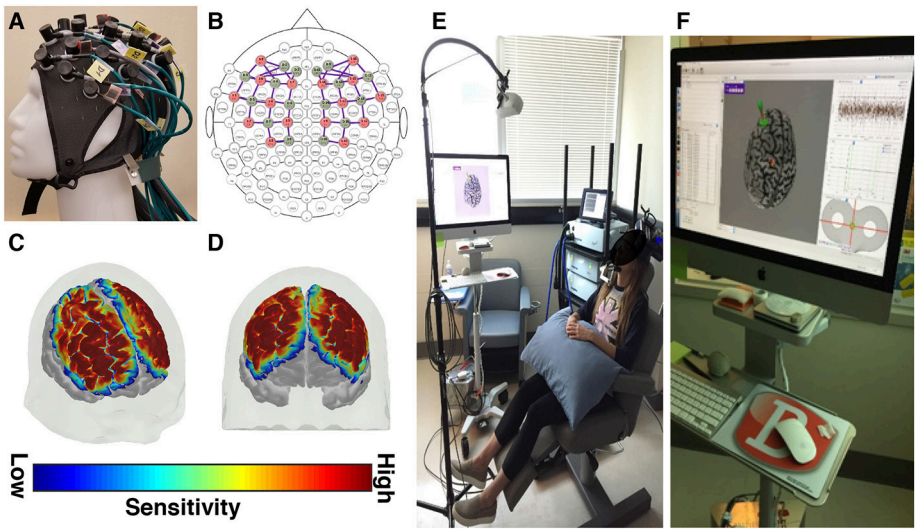

FIGURE 1 | fNIRS and rTMS equipment descriptions. **(A)** A custom fNIRS headcap and **(B)** optode configuration was used. The fNIRS headcap was designed to measure tissue oxygenation over fronto-parietal brain areas, including the dorsolateral prefrontal cortex and the primary motor cortex. **(C,D)** The sensitivity maps (shown here at 2 different angles) depict the areas of the cerebral cortex where tissue oxygenation was recorded, based on the custom optode configuration. These sensitivity maps are created by projecting the simulated photon paths for each fNIRS channel onto a 3D model of the brain. **(E)** rTMS equipment configuration and **(F)** rTMS neuronavigational system.

RPSQ-3, RPSQ-13, and BCPSI all either improved or stayed the same immediately following rTMS treatment for both participants (day 14). Further, follow up scores from the 1-month assessment (day 45) improved compared to baseline for both subjects, suggesting persistent effects on headache severity, function, mood, and quality of life (**Table 1**). Participant 1 maintained part time work following rTMS and participant 2 was able to return to work at the completion of treatment.

fNIRS

It has been shown previously that working memory tasks evoke a robust hemodynamic response in the DLPFC, characterized by an increase in oxygenated hemoglobin (29, 30). This expected hemodynamic response was observed across 5 measurement days in the controls, highlighting the reproducibility of the activation pattern (**Figures 2C,D**). In patients with PPCS, participant 1 demonstrated the expected task-evoked hemodynamic response to the working memory task at baseline and both post-rTMS time points (**Figure 2A**). Interestingly, participant 2 exhibited an *abnormal* fNIRS hemodynamic response to the working memory test (**Figures 2B**, **3**) whereby oxygenated hemoglobin in the left DLPFC was decreased at the baseline time-point. This response appeared to normalize by the 45-day follow-up.

DISCUSSION

This paper is a preliminary investigation of the feasibility and applicability of using fNIRS to quantitatively assess functional responses to rTMS treatment. Prefrontal cortex rTMS has shown promise as an effective treatment for multiple disorders, particularly depression (10, 11) and headache (12, 31–33) which are both prominent post-concussion symptoms. Consequently, rTMS has been proposed as a treatment for PPCS. Several studies report that rTMS in patients with PPCS may significantly reduce symptoms of headache, depression, dizziness, and improve quality of life (13–15, 34, 35), however these studies are limited by small sample sizes, weak study design, and/or a lack of objective tools to assess treatment response. Furthermore, little is known about the physiological mechanism of how rTMS influences symptoms and function in this population. Therefore, we propose using fNIRS technology to assess possible functional changes in PPCS patients following rTMS intervention.

Treatment of PPCS With rTMS

In this case study, two participants with PPCS who received 10 sessions of rTMS to the left DLPFC reported positive outcomes following treatment, with participant 2 reporting greater than the minimal clinically important difference (MCID) on several questionnaires. There were many similarities between the two participants with regards to the presence of symptoms that were reported at baseline (i.e., headaches, dizziness, vision changes, neck pain, fatigue, and mood difficulties), although, participant 2 reported overall more severe symptom burden prior to rTMS treatment, which may have contributed to their difference in post-rTMS treatment response.

In particular, at baseline, participant 2 had markedly higher headache frequency (39 vs. 28; participant 2 vs. participant 1, respectively), headache severity (5.56 vs. 2.75), mood symptoms (PHQ-9 depression score: 25 vs. 11; GAD-7 anxiety score: 18 vs. 7; PCL-5 post-traumatic stress score: 54 vs. 10), lower quality of life (QOLIBRI: 6 vs. 53), and more severe post-concussion symptom scores (RPSQ-3: 11 vs. 6; RPSQ-13: 48 vs. 25; BCPSI:

TABLE 1 | Clinical questionnaire outcome measures before treatment (day 1), immediately following rTMS (day 14), and at one-month post treatment (day 45).

Assessments		rTMS participant 1				rTMS participant 2			
Questionnaire	**MCID**	**Pre-rTMS (Day 1)**	**Post rTMS (Day 14)**	**Follow-up (Day 45)**	**Clinically Important Change**	**Pre-rTMS (Day 1)**	**Post rTMS (Day 14)**	**Follow-up (Day 45)**	**Clinically important change**
Headache Frequency	50% dec./month (15, 24, 25)	28	28	28	–	39	29	16	+
Headache Severity	2 (26)	2.75	2.42	2	–	5.56	4.06	4.37	–
MoCA		29	30	26		26	26	28	
HIT-6	8 (27)	64 (severe)	63 (severe)	61 (severe)	–	68 (severe)	65 (severe)	60 (severe)	+
PHQ-9	5 (28)	11 (mod.)	10 (mod.)	9 (mild)	–	25 (severe)	4 (minimal)	8 (mild)	+
GAD-7		7 (mild)	5 (mild)	6 (mild)		18 (severe)	4 (minimal)	10 (mod.)	
PCL-5		10	11	10		54 (further testing req'd)	16	15	
QOLIBRI		53 (severe)	56 (severe)	66 (mod.)		6 (severe)	53 (severe)	31 (severe)	
RPSQ-3		6	8	7		11	6	6	
RPSQ-13		25	22	22		48	29	22	
BCPSI total		65	42	47		106	38	59	

Clinical scores improved (headache severity, MoCA, HIT-6, PHQ-9, GAD-7, QOLIBRI, RPSQ, BCPSI) or remained stable (PCL-5, headache frequency) immediately post-rTMS, for both participants. All follow up scores from the one-month assessment (day 45), for headache severity, mood, function and quality of life, improved compared to baseline for both subjects, suggesting persistent effects following rTMS treatment.

MCID, minimal clinically important difference; MoCA, Montreal cognitive assessment; HIT-6 (functional impairment), headache impact test-6; PHQ-9 (depression), patient health questionnaire-9; GAD-7 (anxiety), generalized anxiety disorder scale-7; PCL-5 (post-traumatic stress), PTSD Checklist for DSM-5; QOLIBRI, quality of life in brain injury; RPSQ-3, RPSQ-13, Rivermead post-concussion symptom questionnaire; BC-PSI, British Columbia post-concussion symptoms questionnaire.

106 vs. 65), in comparison to participant 1 (**Table 1**). At follow-up (45 days post-rTMS intervention) participant 2 reported clinically significant improvements in headache frequency (59% decrease), functional impact of headaches (HIT-6: 8-point reduction), and depression (PHQ-9: 17-point reduction), as well as a large reduction in global post-concussion symptoms and improved quality of life. On the other hand, participant 1 reported improvement on most clinical questionnaire outcomes following rTMS, however changes were below the MCID (**Table 1**). This case study, although a limited sample, suggests that rTMS treatment response in PPCS patients is variable, and may relate to baseline function.

Despite persistence of lengthy post-concussion symptoms in both participants, there was an immediate positive effect on self-reported symptoms following rTMS treatment (headache severity, depression, anxiety, cognition, functional impact, quality of life). To date, few studies have investigated rTMS for the treatment of PPCS. Koski et al. performed rTMS to the DLPFC in patients with PPCS>3 months following injury (13). Although there were differences in rTMS stimulation protocol compared to our study (20 sessions, 10 Hz, 110% RMT, 600 pulses), they too found a decline in post-concussion symptom scores post-rTMS, which correlated with increased fMRI task-related activation peaks in the DLPFC.

fNIRS as a Tool to Explore rTMS Treatment Response

A number of studies report that chronic headache, depression, and mTBI are associated with alterations in prefrontal brain areas, characterized by reduced gray matter volume and/or cortical thickness, changes in frontal white matter microstructure, as well as altered function in studies of task-response and functional connectivity (36–44). Interestingly, many studies report functional and behavioral improvements following prefrontal rTMS treatment in patients with these disorders (14, 15, 34, 35, 45–49). This has led to the hypothesis that rTMS to the prefrontal cortex can alter its function and microstructure, and result in improved outcomes in patients with PPCS. As a cost-effective neuroimaging tool, functional near infrared spectroscopy (fNIRS) is well suited for assessing functional changes following rTMS treatment and has the potential to add to our understanding of the mechanism by which these changes occur.

fNIRS is a functional imaging technology that measures changes in cortical tissue oxygenation which correspond to local changes in brain metabolism, allowing for portable and non-invasive measurement of functional brain changes (16, 17). Our group has previously shown that fNIRS has the potential to detect alterations in brain function associated with concussion injury (21, 50). In addition to our findings, two other studies suggest that fNIRS is sensitive to altered function in the prefrontal cortex of patients with post-concussion symptoms, particularly while performing cognitive tasks such as visual attention or working memory (21, 51, 52). In this case study, we used fNIRS measures of functional activation in the left DLPFC, in response to a working memory task, as a method to assess baseline function and rTMS treatment response. A normal hemodynamic response recorded by fNIRS during a working memory task is characterized by a robust

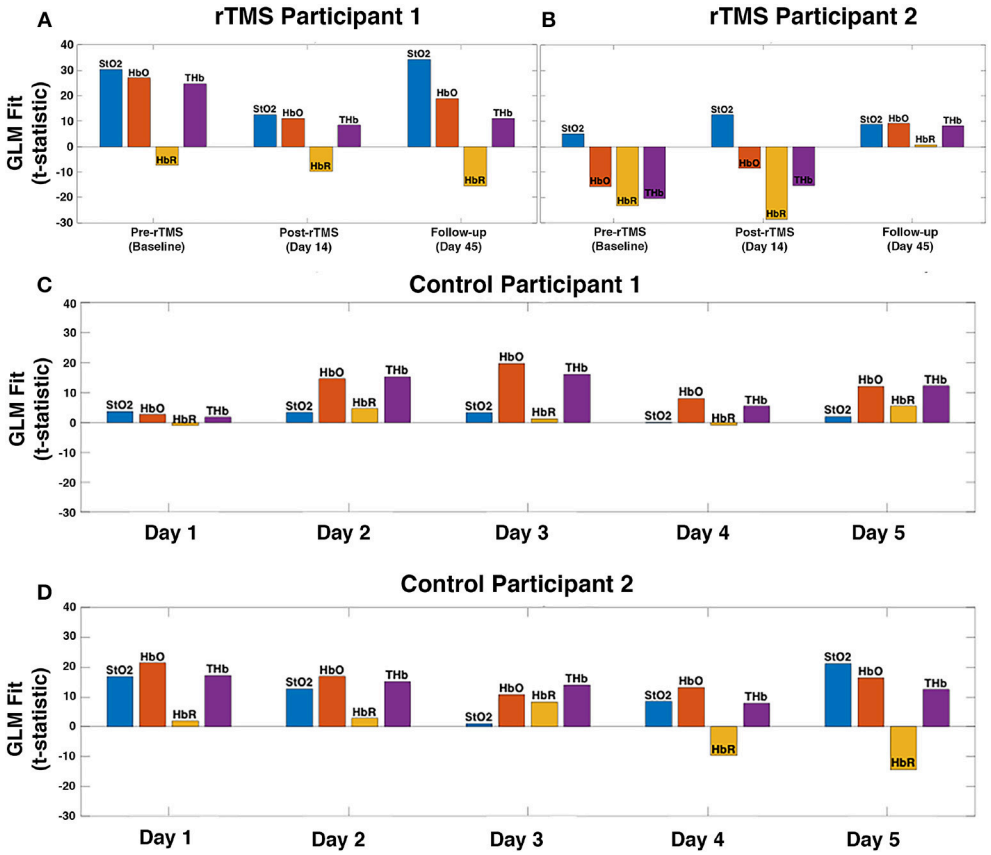

FIGURE 2 | fNIRS measured hemodynamic response to a working memory task in the left DLPFC of patients with persistent post-concussion symptoms (PPCS) who received repetitive transcranial magnetic stimulation (rTMS) treatment **(A,B)**. As an example of the reproducibility of the hemodynamic response pattern to this task, data from two healthy sex-matched controls across five measurement days is presented **(C,D)**. A general linear model (GLM) was used to calculate the location and magnitude of task-evoked changes in oxygen saturation (StO_2), oxyhemoglobin (HbO), deoxyhemoglobin (HbR), and total hemoglobin (THb) for each participant. **(A)** rTMS participant 1 exhibits normal task-evoked hemodynamic response (characterized by a large increase in HbO) at baseline, as well as post-rTMS (day 14 and follow-up day 45). **(B)** rTMS participant 2 exhibits abnormal task-evoked hemodynamic response (HbO decreased during working memory task execution) at baseline and post-rTMS day 14, however, is normalized 1 month after rTMS treatment (day 45). **(C,D)** As expected, a consistent hemodynamic response of increased oxygenation was observed in the control subjects across all five measurement days.

increase in oxygenated hemoglobin and a far less robust decrease (or no change at all) in deoxygenated hemoglobin, in the DLPFC (29, 30). This normal or expected response of a robust increase in oxygenated hemoglobin is evident in the two control subjects across five measurement time-points, highlighting the reproducibility of this measurement (**Figures 2C,D**). In addition, total hemoglobin (oxygenated + deoxygenated hemoglobin) and oxygen saturation (oxygenated/total hemoglobin) can also be calculated and are both expected to increase with task-activation.

Pre-treatment, participant 2 (high pre-treatment symptom burden) had a decrease in the oxyhemoglobin response to the working memory task, which is an abnormal task-evoked fNIRS hemodynamic response (29, 30). Forty-five days following the start of the rTMS treatment, participant 2's fNIRS response appeared more comparable to the normal response observed in the controls (**Figures 2C,D**), which paralleled the significant improvement in clinical scores. In participant 1, who had less severe symptom burden at baseline, we observed an expected task-evoked fNIRS hemodynamic response at baseline (similar to control subjects), as well as post-rTMS treatment (**Figure 2A**).

The exact mechanism by which rTMS treatment improves brain function is still a matter of debate, although one proposed mechanism that has gained traction is the hypothesis that rTMS helps to re-establish connections in areas of the brain that exhibit dysfunctional activity (53, 54). This hypothesis aligns with our preliminary findings in participant two who had a positive treatment response, after exhibiting high symptom burden and altered fNIRS response prior to treatment. Further, the idea that baseline physiological features may, in part, determine rTMS treatment response was recently explored in a cohort of individuals with depression. The authors of this study report that a baseline decrease in the ratio of blood flow in the dorsolateral prefrontal cortex (DLPFC) relative to the ventromedial prefrontal cortex (VMPFC) was predictive of treatment response (55), suggesting that those who experience the greatest treatment-response have decreased DLPFC cerebral blood flow at baseline.

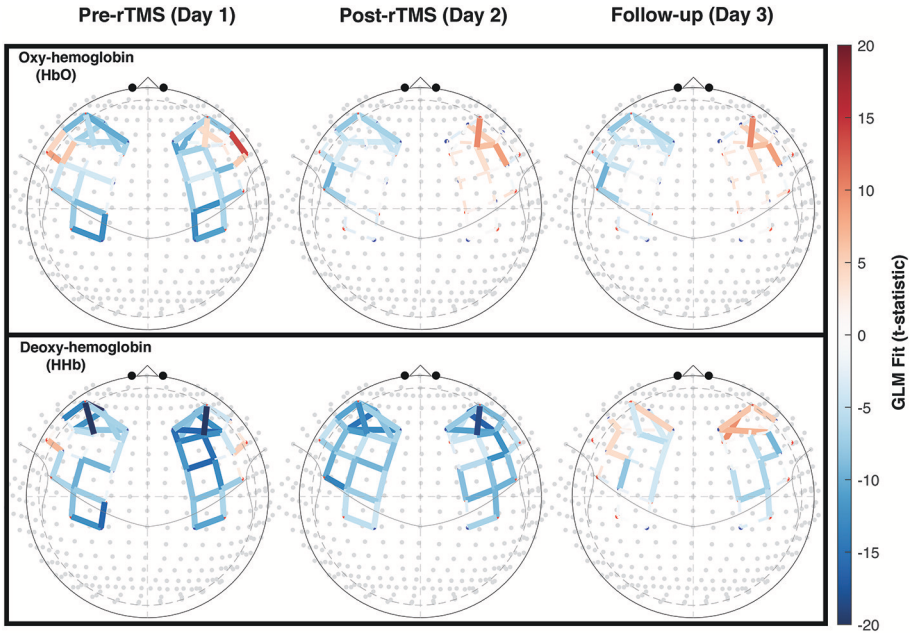

FIGURE 3 | Working memory task-activation color maps for rTMS participant 2, at each time point. Abnormal hemodynamic response (significant deactivation) is detected in the left DLPFC at pre- and post-rTMS timepoints (day 1 and 14) and appears to be normalized (significant activation) by follow-up (day 45). Statistical t-values from the GLM are mapped as red (positive or activation) and blue (negative or deactivation) for each channel pair. Colors increase in intensity as the absolute t-value increases. Solid colored lines represent significance at the level of $p < 0.05$, after correction for false discovery rate. Broken lines represent non-significant changes.

Abnormal vascular coupling or network activation may help to explain the unusual reduction in oxyhemoglobin we observed in participant 2.

Considering this is a case study of two participants, we cannot accurately determine the timeline or trajectory of recovery of fNIRS measured brain function, nor can we conclude with confidence that pre-injury function on fNIRS measures relate to treatment response. These preliminary findings do however suggest that fNIRS could be utilized in future studies as a means to better understand the acute and long term effects of rTMS treatment, and support the hypothesis that pre-treatment baseline function may play a role in who responds best to rTMS intervention. Taken together, this two-patient case study highlights a potential role for fNIRS imaging technology to be used as a tool for assessing rTMS treatment response in patients with PPCS.

Limitations

Potential limitations identified in our study include differences in the mechanism of injury and length of time between concussion to rTMS treatment, for the two participants. Participant 1 received rTMS treatment ∼3 years following a sport-related concussion, whereas participant 2 received rTMS treatment 8 months following a motor vehicle accident-related concussion. Pre-injury risk factors for developing post-concussion symptoms, including migraine, depression, life stressors, and personality characteristics may have played a role in persistence of symptoms in the two participants (56). In addition, a limitation of fNIRS is that it is only sensitive to hemodynamic changes in the cerebral cortex, limiting the ability to study deeper brain structures. Further, this study was completed on a small sample size with only one sex (male) represented, and control participants were not age matched to rTMS subjects. Although age-related effects on the magnitude of response to working memory have been observed previously, the direction of the task-effect (increase in oxygenation) does not differ between young and old healthy adults, suggesting the response we observed in participant 2 is unrelated to aging (57). Time since injury and mechanism of injury may factor into rTMS treatment efficacy and should be considered in future trials, along with a larger sample of mTBI patients and including age- and sex-matched controls.

CONCLUSION

To our knowledge, this is the first study to utilize functional near infrared spectroscopy (fNIRS) to explore rTMS treatment response in participants with persistent post-concussion symptoms. In this pilot trial, both participants reported symptom amelioration and improved quality of life after rTMS. Interestingly, participant 2, who had more severe symptomatology also showed abnormal oxyhemoglobin (hemodynamic) response to a working memory task as quantified with fNIRS. As participant 2's symptoms improved, the fNIRS hemodynamic response also changed to a more

typical or expected pattern (increased oxyhemoglobin) during task response.

This study demonstrates the feasibility of examining rTMS treatment response with fNIRS and suggests the possibility of a measurable relationship between the two technologies. fNIRS may be a sensitive tool to predict response to rTMS in patients with PPCS, providing a first step toward utilizing fNIRS as an objective assessment tool in future rTMS trials. To further evaluate rTMS treatment efficacy and gain a greater understanding of the physiological changes underlying rTMS intervention for PPCS, large longitudinal clinical trials with objective assessments at multiple time points are needed. As a cost-effective portable neuroimaging device, fNIRS is well-suited for this role.

ETHICS STATEMENT

This was a case study of two patients. We received written consent from these two patients in accordance with the University of Calgary Research Ethics board. However, as there was not a protocol, ethics was not approved for the protocol.

AUTHOR CONTRIBUTIONS

Conception and study design were completed by CCD, JMS, CTD, and JFD. Data collection was done by CCD, IO, JMS, and EP. Data analysis and interpretation was performed by CCD, JFD, JMS, and CTD. Drafting the article was done by JMS and CCD. Critical revision of the article was completed by all authors. Final approval of the version to be published was done by JMS, CCD, and CTD.

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REVIEW
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Network Analysis and Precision Rehabilitation for the Post-concussion Syndrome

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Some people experience persistent symptoms following a mild traumatic brain injury (MTBI), and the etiology of those symptoms has been debated for generations. Post-concussion-like symptoms are caused by many factors both before and after MTBI, and this non-specificity is the bedrock of the conundrum regarding the existence of the post-concussion syndrome. A latent model or common cause theory for the syndrome is inconsistent with the prevailing biopsychosocial conceptualization. It is the thesis of this paper that adopting a network perspective for persistent symptoms following MTBI, including the post-concussion syndrome, could lead to new insights and targeted treatment and rehabilitation strategies. The network perspective posits that symptoms co-occur because they are strongly inter-related, activating, amplifying, and mutually reinforcing, not because they arise from a common latent disease entity. This approach requires a conceptual shift away from thinking that symptoms reflect an underlying disease or disorder toward viewing inter-related symptoms as constituting the syndrome or disorder. The symptoms do not arise from an underlying syndrome—the symptoms are the syndrome. A network analysis approach allows us to embrace heterogeneity and comorbidity, and it might lead to the identification of new approaches to sequenced care. The promise of precision rehabilitation requires us to better understand the interconnections among symptoms and problems so that we can produce more individualized and effective treatment and rehabilitation.

Keywords: concussion, traumatic brain injury, rehabilitation, post-concussional syndrome, depression

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INTRODUCTION

A substantial minority of people report persistent symptoms following a mild traumatic brain injury (MTBI) for several months and sometimes years (1–9). Whether these symptoms represent a "post-concussion syndrome" has been controversial for generations. For decades, researchers, and clinicians have questioned whether this diagnosis is a true syndrome, disorder, or disease entity [e.g., (10–15)], and the etiology of the syndrome has never been agreed upon [see (16–21) for reviews]. Many have suggested that the etiology of persistent symptoms is due to the biological effects of a MTBI, psychological factors, psychosocial factors (broadly defined), chronic pain, depression, or a combination of factors (22–30). Regardless of etiology, persistent symptoms after MTBI are associated with high levels of disability and health care service utilization, and lower health-related quality of life (9, 31–40).

The International Classification of Diseases 10th edition (ICD-10) specific research criteria for the post-concussional syndrome require symptoms to be present for more than 1 month and the person must have symptoms and problems in three or more of the following domains (1) complaints of unpleasant sensations and pains, such as headache, dizziness (usually lacking the features of true vertigo), general malaise and excessive fatigue, or noise intolerance; (2) emotional changes, such as irritability, emotional lability, both easily provoked or exacerbated by emotional excitement or stress, or some degree of depression and/or anxiety; (3) subjective complaints of difficulty in concentration and in performing mental tasks, and of memory complaints, without clear objective evidence (e.g., psychological tests) of marked impairment; (4) insomnia; (5) reduced tolerance to alcohol; and/or (6) preoccupation with the above symptoms and fear of permanent brain damage, to the extent of hypochondriacal over-valued ideas and adoption of a sick role (41). The Diagnostic and Statistical Manual of Mental Disorders-Fourth Edition (DSM-IV) (42) included research criteria for the post-concussional disorder that differed from the ICD-10 criteria in a several ways, such as including somewhat different symptoms and requiring the presence of objectively measured cognitive deficits. For the 5th Edition (i.e., the DSM-5), published in 2013 (43), the post-concussional disorder was dropped and problems relating to MTBI can be coded as "mild neurocognitive disorder," but this diagnosis does not include post-concussion symptoms—it is based on objective evidence of a decline in cognitive functioning.

A fundamental challenge in defining the syndrome is the non-specificity of the symptoms. Post-concussion-like symptoms are common in healthy children and adults in their daily lives (44–51). They are also common in people seen for psychological treatment (52), outpatients seen for minor medical problems (53), personal injury claimants (53, 54), and people with post-traumatic stress disorder (PTSD) (55), orthopedic injuries (11), chronic pain (42, 56–59), whiplash (60), anxiety (61, 62), and depression (63). Biopsychosocial conceptualizations of the symptoms and syndrome (64–66) emphasize a diverse range of personality and social psychological factors that contribute to how symptoms are perceived, experienced, and reported, such as expectations and misattributions (47, 67–71), coping and illness perceptions (72), "good-old-days" bias (47, 73–79), cognitive hypochondriasis (80), fear avoidance (81, 82) cogniphobia (83, 84), nocebo effect (85, 86), perceived injustice (87), iatrogenesis (17, 27), resilience (88, 89), Type D personality (90, 91), and other personality characteristics, particularly compulsive, histrionic, dependent, and narcissistic traits (21, 61). A multidimensional model for conceptualizing the post-concussion syndrome suggests that setbacks in several aspects of a person's life (physical, emotional, cognitive, psychosocial, vocational, financial, and recreational) serve as cumulative stressors that interact with personality and pre-morbid physical and mental health factors, resulting in the syndrome (21, 92, 93). Clearly, post-concussion-like symptoms are caused by many factors both before and after a mild injury to the brain. This non-specificity problem incumbers the development of new and innovative approaches to conceptualizing the etiology of symptoms and developing new treatment and rehabilitation strategies.

As seen in **Figure 1**, a diverse array of physical, psychological, and cognitive symptoms and problems can be amplifying and mutually reinforcing in people who have experienced a mild TBI. Some of those symptoms might be caused directly or indirectly by injuries to the brain, head, peripheral vestibular system, or body, and some symptoms might be caused, amplified, or maintained by a diverse range of other factors. It is essential to appreciate that these diverse symptoms and problems occur within a *personal biopsychosocial context*, as seen in **Figure 1**. Individuals have unique pre-injury vulnerability factors, current environmental stressors, social psychological reactionary factors, and personality characteristics. As such, an individual's symptoms and problems (from **Figure 1**) occur within a unique personal context. The symptoms that a person experiences, their underlying causes, and the biopsychosocial context in which the person lives all are subject to change over time, from the initial days following injury to weeks and months later.

The biopsychosocial heterogeneity and complexity associated with outcome from MTBI is illustrated further in an interesting review by Kenzie et al. (94). They propose a conceptual framework, involving multiple nested scales, based on a complex systems theoretical approach. The four nested scales are cellular (e.g., axonal injury, neuroinflammation, and synaptic changes), network (e.g., intrinsic connectivity and neuronal population dynamics), experiential (e.g., physical, cognitive, and psychological symptoms), and social (e.g., access to healthcare, social support, work or school pressures)—and each of these interacting scales can be influenced by a diverse range of personal characteristics and external environmental factors [see Figure 1 in Kenzie et al. (94)]. Given the complexity of persistent symptoms following a mild injury to the brain, as reflected in the conceptual model of Kenzie and colleagues and in **Figure 1**, it is not surprising that there is no unified latent disease model etiology for the post-concussion syndrome.

NETWORK ANALYSIS AND PERSISTENT POST-CONCUSSION SYMPTOMS

It is the thesis of this paper that adopting a network perspective for persistent symptoms following MTBI, including the post-concussion syndrome, could lead to new insights and targeted treatment and rehabilitation strategies. To my knowledge, there are no published studies applying network analysis to persistent symptoms and problems following MTBI. Network theory and analysis (95–100) posits that mental disorders can be viewed as a set of interacting symptoms. Conceptually and philosophically, the network approach does not require that the post-concussion syndrome, or syndromes, have a single underlying cause (e.g., brain injury) that is *independent* of the symptoms. Instead, the presence of the interacting and inter-related symptoms *constitutes* the syndrome. A syndrome may

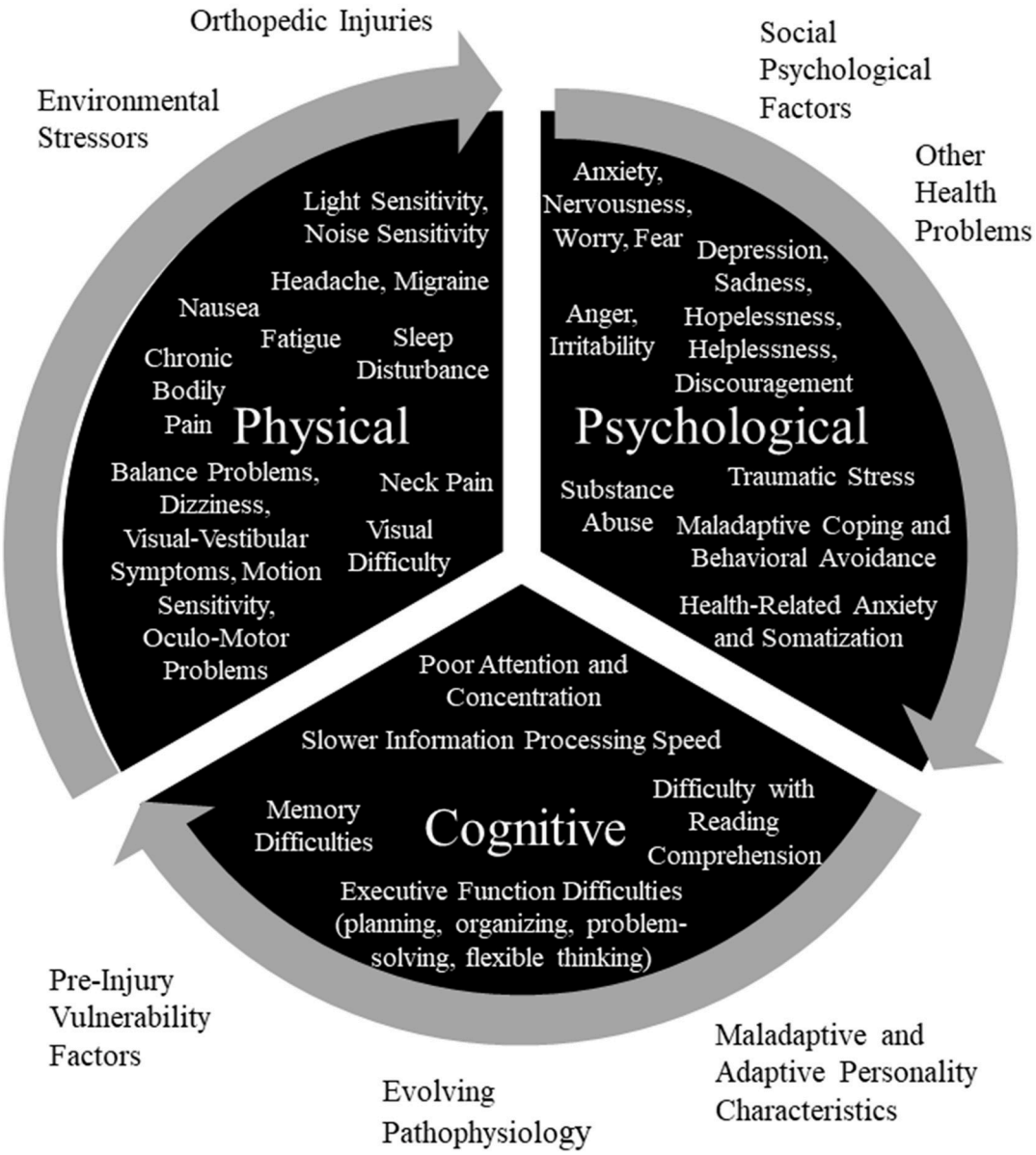

FIGURE 1 | Potentially Amplifying and Reinforcing Persistent Symptoms and Problems and Personal Biopsychosocial Context for Experiencing Persistent Symptoms and Problems. Pre-Injury Vulnerability Factors: personal or family history of mental health problems and associated genetic and environmental vulnerability (childhood abuse or neglect, depression, anxiety, or traumatic stress); prior brain injuries; personal history of, or vulnerability to, migraine or other headache disorder; and history of motion sickness or other visual-vestibular vulnerability factor. Environmental Stressors: financial/occupational stress; academic stress; marital, family, or relationship problems; and litigation, compensation-seeking or maintaining, or other secondary gain issues. Social Psychological Factors: maladaptive coping, catastrophizing, expectations, "good-old-days" bias (tendency to view oneself as healthier in the past and underestimate past problems), nocebo effect, diagnosis threat, cognitive hypochondriasis and preoccupation, lifestyle and family dynamics changes, avoidance behavior, cogniphobia (fear and avoidance of mental exertion out of concern for developing or exacerbating a headache), reinforced illness behavior, anger, bitterness, perceived injustice, justification/entitlement, or iatrogenesis. Personality Characteristics or Disorders: neuroticism (a personality trait characterized by a strong tendency to experience negative emotions such as anxiety, depression, anger, and self-consciousness. Individuals with this trait have considerable difficulty coping with stress), anxiety sensitivity (a trait comprised of physical, psychological, and social pre-occupations and concerns, is characterized by fear of anxiety-related bodily sensations), alexithymia (a cluster of traits characterized by difficulty identifying feelings, difficulty describing feelings to others, externally oriented thinking, and limited capacity for imaginal thinking), perfectionism, egocentrism, Type D personality (personality pattern is characterized by two stable personality traits: negative affectivity and social inhibition), disagreeableness (a personality trait characterized by antagonism, skepticism, and egocentrism), unconscientiousness (a trait characterized by reduced self-discipline and ambition, disorganization, and a more lackadaisical approach to life), narcissistic, dependent, histrionic, or passive-aggressive. Adaptive Personality Characteristics: resilience, grit (passion and perseverance toward long-term goals), and psychological hardiness (personality characteristic consisting of three psychological attitudes and beliefs: commitment, challenge, and control).

occur when a requisite number of symptoms become activated for a sufficient period of time. The network approach, applied to the post-concussion syndrome, posits that symptoms co-occur because they are strongly inter-related, activating, amplifying, and mutually reinforcing, not because they arise from a common latent disease entity. This approach requires a conceptual shift away from thinking that symptoms *reflect* an underlying disease or disorder toward viewing inter-related symptoms as *constituting* the syndrome or disorder. That is, the symptoms are the syndrome.

NETWORK ANALYSIS IN PSYCHIATRY AND PSYCHOLOGY

Network analysis is a statistical and psychometric methodology for studying the interrelationships among symptoms. A number of articles describe the methodology of network analysis (96, 101, 102). A network, graphically represented, is comprised of nodes and edges. For the purpose of this paper, a node is a symptom or clinical feature of PCS, and the edges are connections between symptoms. The edges represent the statistical associations between symptoms. When represented as a figure, symptoms (i.e., nodes) that activate each other are connected by lines (i.e., edges). The interrelations among the symptoms represent the network. Specific symptoms within the network can be influenced by things in the "external field." The external field is outside the symptom network, but not necessarily outside the person. The external field is comprised of intrinsic (e.g., microstructural brain injury, cervical injury, or peripheral vestibular injury) and extrinsic factors (e.g., life stress). The external field also includes the social and environmental context for the person, including being involved in personal injury litigation or a worker's compensation claim.

A network of symptoms is represented graphically, in a two-dimensional figure, by having circles representing symptoms and lines connecting circles representing the association (i.e., correlation) between the symptoms. These graphic depictions arise from statistical psychometric analyses of large databases, not from theory. The lines can be unweighted, which means that all statistically significant correlations are shown with the same thickness of lines, or they can be weighted, meaning that thicker lines represent stronger correlations. Line colors can also be used, such as green lines representing positive associations and red lines representing negative associations. The lines connecting the symptoms can be undirected (no arrows) or directed (one arrow). A directed line (i.e., edge) shows the hypothetical direction of the association between symptoms (e.g., symptom A activates symptom B). See **Figure 2** for a *hypothetical* network of nine symptoms in slow to recover high school and college students with pre-existing anxiety problems. Symptom *centrality* is an important concept in the network analysis. Central symptoms are those that are most important in the network, and there are several was to measure centrality including the degree, strength, expected influence, closeness, and betweenness. It is important to appreciate that a limitation of network analysis diagrams is that they can lead to the impression that inter-related and interacting between symptoms are static, when in fact they might be temporally sequenced and dynamic.

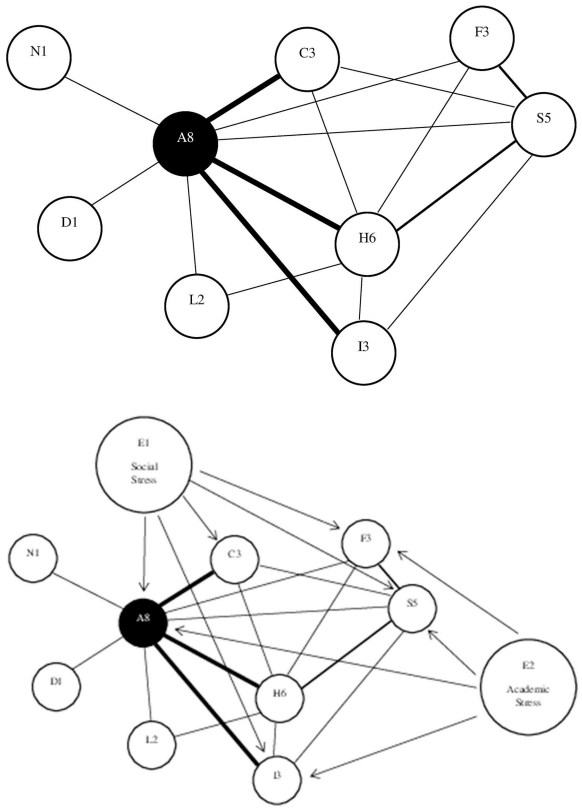

FIGURE 2 | *Hypothetical* network of nine symptoms in slow to recover high school and college students with pre-existing anxiety problems. The top figure shows that anxiety (A8) has the greatest degree (eight connections to other symptoms) and strength (three heavier lines) of centrality, followed by headaches (H6) and sleep (S5). Three symptoms are connected to three other symptoms (nodes): irritability (I3), concentration problems (C3), and fatigue (F3). Light sensitivity (L2) is connected to two other symptoms, and nausea (N1) and dizziness (D1) are connected to only one other symptom. The bottom figure illustrates the role of external factors, in the external field, that are amplifying the network of symptoms, such as social stress (E1) and academic stress (E2).

Fried and colleagues reviewed the literature on network analysis in psychology and psychiatry (95). Network analysis has been used to better understand the structure of emotional and behavioral problems in children (103), the central symptoms and syndromic pathways of traumatic stress in children and adolescents (104–106), longitudinal developmental associations between symptoms of depression and anxiety (107), and the associations between internalizing and externalizing psychopathology in the transition from childhood to adolescence (107). In adults, syndromic pathways between social anxiety, perceived stress, and problematic alcohol use have been identified (108). In fact, network analysis has been used to simultaneously study 12 major psychiatric diagnoses in a sample of more than 34,000 adults, with the resulting network illustrating differential associations between symptoms within the same

diagnosis and strong connections with symptoms from other diagnoses, illuminating the complexity of psychopathology and psychiatric comorbidity (100). Because depression and PTSD are so common in civilians, military service members, and veterans who have sustained MTBIs and who report long-term symptoms and problems, some recent advances in those areas, based on a network empirical and theoretical perspective, are discussed in the sections below.

Depression

Pre-injury mental health problems, such as depression and anxiety, are a risk factor for persistent symptoms following MTBI (21, 36, 109–112). Depression is common following TBIs of all severities (113–115). Depression is also common in people with chronic pain (116–119), chronic headaches (120–123), PTSD (55, 124–126), and substance abuse problems (127–131). Primary depression can mimic the post-concussion syndrome (132), and depression has a very large effect on post-concussion-like symptom reporting (48, 63, 132–134). Moreover, post-injury worry, stress, and anxiety are thought to be central features of long-term symptom reporting (17, 27, 41, 61).

Network analysis is leading to important new insights in depression (135–139). Depression can be viewed as a complex dynamic system of interacting symptoms, some of which are core syndromal symptoms of depression (e.g., sadness and anhedonia) and some of which are not (e.g., anxiety and sympathetic arousal) (137). It is well established in psychiatry that depression and anxiety are comorbid in many people (140), and cross-sectional network analysis studies have illustrated *how* major depressive disorder and generalized anxiety disorder are interconnected, entangled, and amplifying (141–143). Moreover, chronic pain and depression often co-occur (116–119), and new studies are examining associations between symptom networks in chronic pain and depression (144), and how self-efficacy, fear avoidance, and perceived disability might link the pain experience with affective disorder symptoms (145).

Network analysis has been used to better understand the course of illness and the probability of relapse. People in remission from a prior episode of depression are at increased risk for developing future depression, and resilience is central and important for successfully coping with stressors and maintaining good mental health (146). Moreover, transitional states from being healthy to being depressed are not well-understood. "Critical slowing" (147) is a phenomenon in depression characterized by dynamic networks of symptoms taking increasingly longer to adapt or recover to perturbations, eventually leading to a tipping point into the development of a syndrome. The concept of critical slowing is applicable to a pathway by which a person might develop persistent symptoms following an MTBI.

Post-traumatic Stress Disorder

Traumatic stress is fairly common in both civilians and military personnel who sustain MTBIs (148, 149). People with PTSD report symptoms that overlap with the post-concussion syndrome, such as irritability, cognitive problems, and sleep disturbance (55), and PTSD might have an amplifying or additive effect on symptom reporting following MTBI (150, 151). Network analysis has been used in diverse studies of PTSD (152–157). Researchers have used network analysis to examine (i) how specific combinations of symptoms might drive the development of PTSD in trauma-exposed adults (154); (ii) whether traumatic stress symptom presentations vary in association with different types of index traumas (158); (iii) the symptom connectivity and associations in combat veterans with PTSD and subthreshold PTSD (159, 160), and the interactions among traumatic stress symptoms, suicidal ideation, depression, and quality of life in veterans (153); (iv) the association between PTSD and alcohol use disorders (161); (v) the identification of central symptoms and bridging symptoms relating to the comorbidity of PTSD and major depressive disorder (162), and (vi) the comorbidity of GAD, depression, and PTSD (163). It is believed that better understanding of which symptoms of traumatic stress are more central and strongly interconnected than others may have implications for targeting clinical interventions.

CONCLUSIONS AND DIRECTIONS FOR FUTURE RESEARCH

It has long been believed by some researchers that no central underlying disease mechanism for the post-concussion syndrome has ever been found because it does not exist. The longstanding challenge for conceptualizing the post-concussion syndrome is that the constellation of symptoms comprising the syndrome are non-specific. Therefore, it is difficult to accept that post-concussion symptoms cohere as a syndrome because they share a single latent underlying cause, such as brain damage or a mental disorder. Multiple social psychological factors, such as expectations and misattributions (47, 67–71), "good-old-days" bias (47, 73–79), perceived injustice (87), fear avoidance (81, 82), socio-environmental factors such as compensation seeking (164–166), vulnerability factors such as pre-injury mental health problems (21, 36, 109–111), and neurological factors, such as microstructural changes to white matter (167), have been shown to be associated with persistent post-concussion symptoms. However, none have emerged as a latent common cause, and most in the field accept that post-concussion symptoms are multifactorial in causation. A latent model or common cause theory for the syndrome is inconsistent with a biopsychosocial conceptualization (64–66).

A network perspective makes it possible to study the architecture of persistent symptoms and problems following MTBI, allowing the identification of symptoms that are more central and strongly interconnected. A network perspective allows us to embrace the challenges of heterogeneity, non-specificity, comorbidity, and the latent disease model that have plagued the field of mild neurotrauma. The network perspective eschews the idea that a single latent dimension is the underlying cause of both symptom emergence and coherence. Symptoms can be causally connected through diverse biopsychosocial mechanisms. Network theory is agnostic with regard to how causal relations among symptoms are exemplified.

The direct causal associations between some symptoms might be predominately biological, whereas other symptoms might have associations that are more strongly psychological. Symptoms can form amplification and self-sustaining feedback loops. If the inter-relations among the symptoms are strong enough, the symptoms become entrenched, self-sustaining, and in combination they comprise and represent a syndrome. In this context, a post-concussion syndrome does not exist separately from the symptoms that constitute it. In fact, a network perspective might identify *multiple syndromes*, or at least clusters of prominent symptoms, that might occur in subgroups of people following MTBI.

Adopting a network perspective in clinical research might help us identify single, paired, or small clusters of strongly interconnected symptoms that could be initial targets for treatment and rehabilitation (168). In the hypothetical example set out in **Figure 2**, an aggressive treatment and rehabilitation strategy targeting the two most central symptoms, anxiety, and headaches, might dampen the amplifying inter-relations among multiple symptoms leading to improvement across the entire network of symptoms. In theory, and of particular relevance to sequenced care following MTBI, targeting one or two symptoms with a high degree of strength of centrality might dampen or even ameliorate other symptoms in the acute or subacute period following injury, potentially preventing entrenchment and persistence of symptoms. It might also help us better understand complex comorbidities, such as depression, anxiety, PTSD, chronic pain, peripheral vestibular problems, and substance abuse, how they are inter-related, and how they might bridge and amplify post-concussion-like symptoms. Future research using network analysis might reveal syndrome profiles and inter-relations with comorbidities that could be targets for time-sequenced precision rehabilitation—leading to more personalized health care. Precision rehabilitation requires us to better understand the interconnections among symptoms and problems so that we can produce more effective treatment and rehabilitation for them.

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The author confirms being the sole contributor of this work and has approved it for publication.

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The Association Between Moderate and Vigorous Physical Activity and Time to Medical Clearance to Return to Play Following Sport-Related Concussion in Youth Ice Hockey Players

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Design: Prospective cohort study.

Background: The recommendations regarding the optimal amount and type of rest for promoting recovery following concussion are based on expert opinion rather than evidence-based guidelines due to current a lack of high-level studies. There is an evident need for more research into the parameters of rest and activity and its effects on recovery from concussion.

Objective: To evaluate the association between the amount of moderate and vigorous physical activity (MVPA) during the first 3 days following concussion diagnosis and time to medical clearance (days) to return to play in youth ice hockey players.

Methods: Thirty youth ice hockey players (12–17 years) that were diagnosed with a concussion sustained during ice hockey were recruited to participate. The exposure was the cumulative amount of MVPA (minutes), measured using a waist-worn Actigraph accelerometer. Participants were dichotomized into high ($\geq$148.5) and low ($<$148.5) activity groups based on the median of cumulative time spent in MVPA over the first 3 days following injury diagnosis.

Results: Participants in both the low and high activity group reported to the clinic at a median time of 4 days post-injury (low activity IQR: 3–5 days; high activity IQR: 3–7 days). The low activity group completed a median time of 110.7 min (IQR: 76.2–131.0 min) in MVPA, whereas the high activity had a median of 217.2 min (IQR 184.2–265.2 min) in MVPA. Kaplan Meier survival curves with Log-rank tests of hypothesis revealed the high activity group took significantly more time to be medically cleared to return to play ($p = 0.041$) compared to the low activity group.

Conclusion: The results from this study suggest that more time in MVPA early in the recovery period may result in a greater time to medical clearance to return to full participation in ice hockey. Future research, using valid measures of activity, are required to better understand the relationship between early activity and recovery following concussion in youth.

Keywords: concussion, mild traumatic brain injury, ice hockey, youth, activity

BACKGROUND

Concussion is a mild traumatic brain injury that can present with a range of symptoms that may impair an individual's ability to perform activities of daily living and result in time away from activities, such as school, work, sport, and recreational activities (1). The current guidelines for the management of acute concussion, according to the 5th Consensus Statement on Concussion in Sport, include physical and cognitive rest until acute symptoms resolve, followed by a graded program of exertion prior to medical clearance to return to play (RTP). Currently, the literature suggests that youth may take longer to recover than adults and should therefore receive the appropriate accommodations to reduce cognitive and physical load (2). Although there are conflicting reports on the efficacy of rest, expert opinion suggests an initial period of rest (24–48 h) is advised for recovery following the injury (1, 3). To date, the optimal amount and type of rest and physical activity that are most beneficial for recovery following a concussion are not well-defined (4–6).

Concussion is a result of biomechanical forces to the brain (e.g., acceleration, deceleration, rotational) that initiate a complex cascade of neurometabolic and neurochemical events that result in altered cerebral functioning (7, 8). Exercise introduced within 6 days following injury has been shown to be detrimental in animal models, whereas delayed voluntary exercise beyond 14 days appears to be beneficial (9). Thus, rest is postulated to be potentially beneficial in reducing the chances of re-injury and neuronal cell damage during the acute phase of concussion (8, 10, 11).

Complete bed rest has been described as an unrealistic and impractical prescription following concussion, and a complete absence of physical or cognitive activity is impossible (12). Participation in physical activity has been reported to have positive benefits for youth health (13). Eliminating physical activity, especially for long periods, can be expected to have a negative effect, increasing symptoms of depression and anxiety (12). Two randomized controlled trials have examined rest time on symptom scores and neurocognitive outcomes in individuals following concussion (14, 15). The first study evaluated the effects of prescribed bed rest for 6 days vs. no rest on post-traumatic complaints in participants recruited from the emergency department (14). This study found no beneficial effect on participant's reported outcomes as a result of prescribed bed rest. The second study evaluated strict rest for 5 days vs. usual care (1–2 days of rest followed by step-wise return to activity) on neurocognitive, balance and symptom assessment (15). The authors used an intention to treat analysis and found that prescribed bed rest did not improve symptoms or neurocognitive and balance outcomes. Furthermore, this study found no significant differences in the actual amount of energy expenditure and cognitive activity between groups which was measured using self-report diaries. These studies both suffer from potential measurement biases related to the use of self-reported activity diaries to monitor physical activity participation and rest rather than an objective measure of activity.

The literature provides conflicting evidence regarding the efficacy of physical and cognitive rest for reducing time to medical clearance to return to play by a physician and improving symptom scores following concussion (16–18). In regards to physical activity, Majerske et al., found that student athletes reporting moderate levels of cognitive and physical activity (e.g., school activity, jogging) during the first month after a concussion showed better neurocognitive performance and reaction time than those reporting no activity or high levels of activity (19). Further, Grool et al., demonstrated a reduced risk of persistent post-concussion symptoms at 28 days in youth (ages 5–18) who self-reported participation in early physical activity (within 7 days post-concussion) compared to those who reported no physical activity (20). Although, it should be noted that more than 2/3 of the study population reported engagement in some form of physical activity at 1 week post-injury.

To effectively evaluate the effects of physical activity on concussion recovery, reliable and valid measurement tools are imperative. Accelerometry is commonly used to measure physical activity, as it is easily administered and has been found to be valid and reliable across numerous populations (21, 22). The Actigraph accelerometer has been used in both youth and adult populations and shown to be a reliable and valid measure when compared to oxygen consumption via VO_2 metabolic carts and other accelerometers (22–24). Whereas, self-reported activity has been shown to be an unreliable method of measuring activity, prone to a desirability bias based on the context of those observing behavior (25).

Previous literature indicates excessive rest or complete bed rest have not been shown to be beneficial for recovery from concussion; conversely, high levels of activity may slow recovery (14, 15, 19). Although previous research has attempted to evaluate the effects of activity following concussion, it is difficult to extrapolate the findings into recommendations because previous research in concussion has yet to use objective measurement devices. Therefore, studies of rest and physical activity following a concussion using improved methods for measurement are gravely needed to inform the type and amount

of rest and physical activity that is most beneficial for recovery from concussion.

The primary objective of this study is to evaluate the association between moderate and vigorous physical activity (MVPA) during the first 3 days following concussion diagnosis, and time (days) to medical clearance to return to play in youth ice hockey players. Secondary objectives of this study are to examine the association between MVPA and time to: (i) return to baseline symptom scores, (ii) first day of initiation of return to play protocol, (iii) first day of unrestricted return to school.

MATERIALS AND METHODS

Study Design

This was a sub-cohort nested within a larger cohort study that included youth ice hockey players between the who were diagnosed with concussion by a study sport medicine physician. This study was approved by the University of Calgary Conjoint Health Research Ethics Board (Ethics ID: REB15-2577). In the larger cohort study, participants reported baseline symptom scores at the beginning of the 2015–2016 ice hockey season, using the Sport Concussion Assessment Tool 3 (SCAT3) (26). The SCAT3 includes the Post-Concussion Symptom Scale (PCSS), an all-encompassing symptom scale with 22 symptoms ranging in severity from 0 (none) to 6 (severe). Thus, the corresponding PCSS severity score an individual can report is between 0 and 132. Data on demographics, concussion history, medical history and social history were collected through the Acute Sport Concussion Clinic (ASCC) at the University of Calgary Sport Medicine Center as part of the initial intake forms.

Subjects

Male and female youth ice hockey players between the ages of 12–17 who presented to the ASCC at the University of Calgary Sport Medicine Center following a suspected concussion following an ice hockey-related concussion mechanism were approached for participation in the study. Informed written consent to participate (including parent consent and player assent if <15 years of age) was provided by all participating players. Individuals were excluded from participation in this study if they were diagnosed with an injury that was supplementary to the SRC or refused to wear the Actigraph accelerometer.

Procedures

Players who sustained a sport-related concussion and consented to participate in this study attended an initial physician appointment, during which, they were assessed a sport medicine physician affiliated with this study. The players were required to complete standardized forms (e.g., SCAT3) and clinical tests including measures of vestibulo-ocular and cervical spine function. Concussion was diagnosed following a clinical assessment involving assessment of multiple domains that included physical signs, cognitive impairment, neuro-behavioral features, sleep disturbance and clinical symptoms which was performed by a sport medicine with clinical expertise in SRC. The physicians in the current study were blinded to the participant's physical activity levels and baseline symptom reports. Medical instructions were similar to all participants as physicians followed standard of care recommendations offered by the university clinic that advocated for participants to rest until their acute symptoms subsided followed by a gradual increase in activity using the return to play protocol (27).

Exposure

Exposure was defined as the total amount of time (minutes) spent in MVPA in the initial 3 days (72 h) immediately following concussion diagnosis. MVPA was measured using a waist worn Actigraph wGT3X-BT accelerometer (Actigraph LLC, Pensacola, FL, USA), with raw accelerometer data categorized into activity intensities of sedentary, light, moderate, and vigorous using cut-points for adolescents previously validated by Romanzini et al. (24) Participants were asked to wear the monitor above the right anterior superior iliac spine, only taking off the monitor when bathing to prevent water damage and skin irritation. In the absence of any previously established cut-point for physical activity in a youth population recovering from concussion, the median time in moderate to vigorous activity was chosen as the time point of relevance. Due to variations in time to receive medical clearance, 3 days was chosen as the exposure window to ensure accurate collection of the participants initial physical activity after receiving medical recommendations and to ensure adherence to wearing the accelerometer.

Outcomes

All participants completed the SCAT3 and were assessed by the physician at the initial and weekly follow-up appointments until full clearance to return to play. The primary outcome was the time from concussion to full medical clearance by a study sport medicine physician to return to full participation ice hockey. Physicians followed a standardized protocol of medical clearance to return to ice hockey, where the patient was required to be (i) asymptomatic at rest, (ii) asymptomatic with exertion, and (iii) no other reason to withhold clearance. Therefore, all participants were initially instructed to rest upon diagnosis of their SRC.

The outcome of symptom duration was defined as the number of days between the injury date and the date of return to baseline symptom scores (if available) or medical clearance by physician if no baseline was available. The outcome of number of days to the initiation of the activity portion of the return to play protocol (i.e., step 2) was recorded as the number of days from the injury date to the date the physician instructed the participant to begin the protocol. The date of return to school was self-reported by the participant to the researchers, and the number of days from the injury date was calculated.

Statistical Analysis

The exposure of MVPA was dichotomized into high (>148.5 min) and low (≤ 148.5 min) time in MVPA based on the cumulative minutes spent during the first 3 days after and including the initial appointment date. The primary outcome was the number of days from the injury date to the date medical clearance to return to play (e.g., full participation in ice hockey). Secondary outcomes were the number of days from the injury date to the date of (i) return to baseline symptom scores as

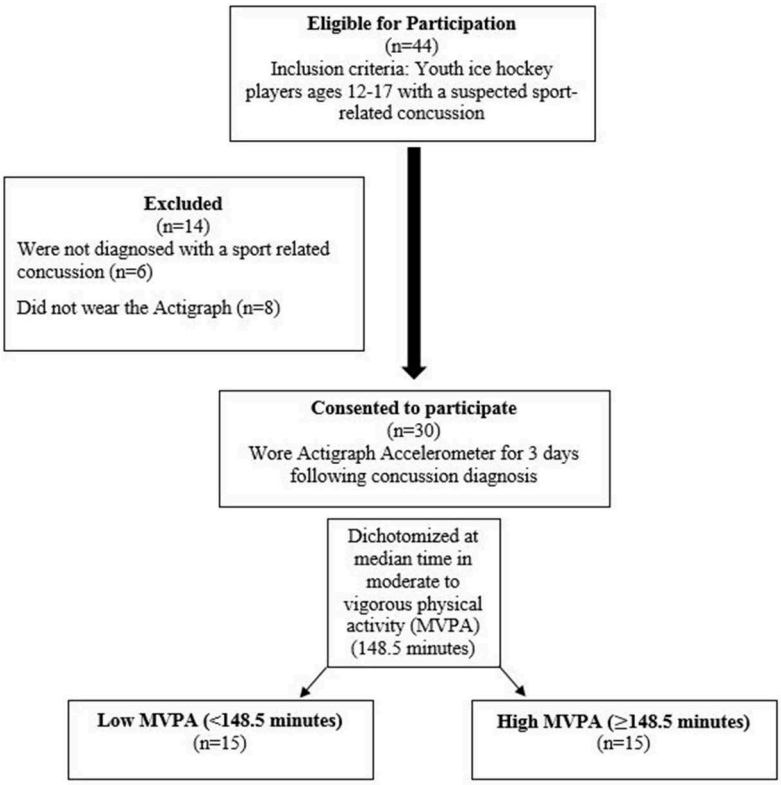

FIGURE 1 | Consent flowchart.

reported on the SCAT3, (ii) initiation of step 2 (transition from rest to light aerobic exercise) of the return to play protocol, (iii) return to full school participation. Descriptive statistics [e.g., median: interquartile range (IQR), counts (proportion)] of baseline characteristics, stratified based on low and high activity groups, were calculated. Kaplan-Meier survival analysis with log-rank tests of significance were used to evaluate the effect of high and low MVPA on time to medical clearance and the secondary outcomes. Significance was set a priori at an alpha of 0.05 for the primary outcome, with a Bonferonni correction for the secondary outcomes ($0.05/3 = 0.0167$). Due to the small sample size, inferential statistics assessing the effect of covariates on time to medical clearance were not possible. All statistical analyses were conducted using STATA (V.13) (28).

RESULTS

Forty-four youth with a suspected concussion presented to the sport medicine physician during the study period (December 16, 2015–April 7, 2016). Of those, six participants were not diagnosed with a concussion at the initial appointment and were not recruited into the study. An additional 8 participants initially consented to participate but did not wear the Actigraph after enrollment in the study. These participants were excluded from all analyses. A consent flowchart detailing those who did and did not participate is depicted as **Figure 1**. Thirty participants were included in the current study (29), with participant demographics summarized in **Table 1**. Participants in both the low activity and high activity groups presented to the clinic a median of 4 days post-injury (low activity: IQR 3–5 days and high activity: IQR 3–7 days). Using the PCSS from the SCAT3, the median number of total number of symptoms that participants reported at their initial appointment was 13 out of 22 (IQR 9–20) for the low activity group and 10 (IQR 6–14) for the high activity group. The median symptom severity score for the low activity group was 31 (IQR 14–51) out of a possible 132 for the low activity group and 14 (IQR 8–29) for the high activity group. The median time in MVPA was 148.5 min (range 10.5–349.3 min) and was used to dichotomize physical activity into low and high activity. The median amount of time that the participants in the low activity spent in MVPA was 110.7 min (IQR: 76.2–131.0 min). The high activity group performed a median of 217.2 min in MVPA (IQR: 184.2–265.2 min). The median time spent in the remaining physical activity categorizations for the low and high activity groups are summarized in **Table 2**. The number of days from the injury date to each outcome for the low and high activity groups are presented in **Table 2**. Four of the total sample participants (13.3%) did not miss any days of school and returned to full school participation the day after their injury.

Survival analysis using log-rank tests were used to compare the low and high activity groups for the primary and secondary outcomes. The results of these tests are presented in **Table 2**. The

TABLE 1 | Participant demographics.

Characteristic	Low activity group	High activity group
Sex	11 males, 4 females	14 males, 1 female
Age—years, median (IQR)	14 (14-15)	14 (13-15)
Height—cm, median (IQR)	166.1 (162.0–180.3)	166.2 (156.0–169.8)
Weight—kg, median (IQR)	56.6 (50.5–61.6)	53.2 (45.6–59.2)
Level of play, *n* (%)		
Elite (AAA, AA, A)	6 (40.0%)	3 (20.0%)
Non-elite (Tiers 1–7)	9 (60.0%)	12 (80.0%)
Previous history of concussion, *n* (%)		
0	9 (60.0%)	8 (53.3%)
1	4 (26.7%)	4 (26.7%)
2 or more	2 (13.3%)	3 (20.0%)
Initial total symptoms/22, median (IQR)	13 (9-20)	10 (6-14)
Initial symptom severity/132, median (IQR)	31 (14-51)	14 (8-29)
Number of days from concussion to initial appointment, median (IQR)	4 (3-5)	4 (3-7)
Median total time spent in sedentary (IQR)	3225.3 (3410.7–3400.0)	3050.0 (2908.8–3163.8)
Median total time spent in light (IQR)	269.3 (213.8–367.8)	434.7 (274.2–584.7)
Median total time spent in moderate (IQR)	72.3 (50.8–77.8)	117.0 (100.8–140.2)
Median total time spent in vigorous (IQR)	35.8 (23.3–52.0)	100.2 (80.2–127.8)
Median time in moderate to vigorous (IQR)	110.7 (76.2–131.0)	217.2 (184.2–265.2)

TABLE 2 | Outcomes by activity group.

Outcome	Low activity (MVPA <148.5 min)	High activity (MVPA ≥148.5 min)	Log-rank test	
			chi^2	*p*-value
Number of days to medical clearance to return to play (median, IQR)	16 (11-24)	19 (14-38)	4.18	0.0409*
Number of days to return to baseline symptom scores (median, IQR)	15 (11-23)	19 (14-36)	4.98	0.0256
Number of days to initiation of return to play protocol (median, IQR)	11 (10-14)	12 (9-21)	1.58	0.2090
Number of days to full return to school (median, IQR)	9 (8-13)	3 (2-9)	1.47	0.2246

**Significant difference (significance $p < 0.05$) in survivor function between low and high activity groups for primary outcome.*

high activity group took significantly more time to be medically cleared to return to play (chi$^2 = 4.18$, $p = 0.041$) compared to the low activity group (**Figure 2**). Following Bonferroni correction for the remaining three outcome measures ($0.05/3 = 0.0167$), there were no significant differences identified in any of the secondary measures between low and high activity groups.

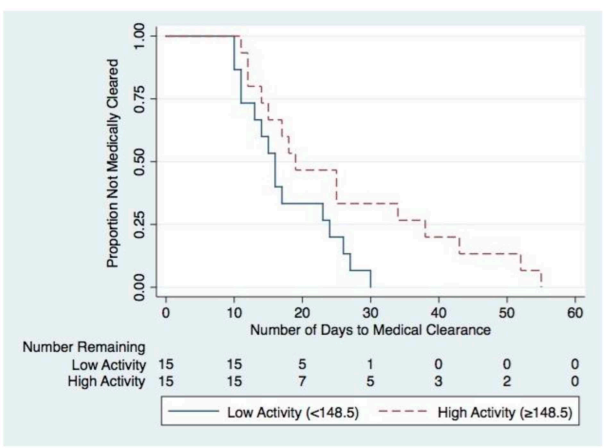

FIGURE 2 | Kaplan Meier survival curves for high and low MVPA.

DISCUSSION

This is one of the first studies to objectively assess the association of high and low different levels of physical activity using accelerometry during recovery with time to medical clearance to return to play. All participants in the current study performed at least some MVPA in the first 3 days after diagnosis, despite receiving instructions from their treating physician to rest following the initial appointment. Youth athletes in the current study who performed greater amounts of MVPA in the first 3 days following concussion diagnosis, which was within 7 days post-injury for most, experienced significantly greater time to receive medical clearance to return to sport. A study by Grool and colleagues demonstrated that youth who self-reported early physical activity participation, which was primarily in the form of

light aerobic exercise, had reduced risk of developing persistent symptoms compared to those who did not engage in any physical activity (20). Complete rest following concussion is unreasonable as youth participants are unlikely to comply (20). Instead of completely eliminating initial activity following a concussion, efforts should perhaps be made to limit the amount of higher intensity activities.

Our results suggest that more time spent in MVPA during the first 3 days following initial assessment and concussion diagnosis is associated with a greater time to medical clearance to return to play (i.e., full participation in ice hockey). These findings are different than the results of Howell et al., who reported that in adolescents, higher levels of physical activity and lower initial symptoms after concussion are associated with a shorter duration of symptoms (27). However, this may be due higher physical activity being associated with a less severe injury, as these individuals may be less symptomatic upon resuming activity and thus become asymptomatic sooner. Howell et al., also used a self-reported activity questionnaire, recording participants' activity levels during the entire duration of their recovery, which may be a source of reporting bias leading to different results than this study (30).

All participants in this study reached each outcome in a logical order by returning to full school participation first, followed by starting the return to play protocol, then returning to baseline symptom scores before being medically cleared. The low activity group obtained medical clearance for full participation in ice hockey in fewer days than the high activity group, however, the high activity group returned to school sooner.

LIMITATIONS

Due to the sample size, we were unable to evaluate the effect of additional covariates on time to medical clearance. Collectively, individuals in the low activity group appeared to have higher median PCSS symptom severity scores on presentation, although no statistical tests were performed. Previous research has suggested that total symptom severity score may be a possible confounder on time to recovery, as greater symptom burden would likely reduce initial physical activity levels and may lead to a longer recovery time (31, 32). Even despite higher PCSS score upon presentation, individuals in the low activity group achieved medical clearance to return to sport sooner than their high activity counterparts. Future studies evaluating time to medical clearance should include rigorous evaluation of these symptom-related covariates.

The difference between the Kaplan-Meier curves in the number of days to full return to school was not statistically significant. The point estimates for the median time of full return to school for the high activity group was smaller than for the low activity group. The high activity group returning to school earlier may have provoked and prolonged their symptoms, resulting in a longer time to return to baseline symptoms and time to obtain medical clearance. More research evaluating both physical and mental activity across the entire duration of recovery is needed.

Personality traits, such as risk-taking social behaviors may have also contributed to a stunted recovery for those in the high activity group. Future research should concurrently monitor social behavior and physical activity to determine its influence on recovery.

In the absence of any previous well-defined parameters for rest or physical activity for youth following concussion, the median of 148.5 min over the course of 3 days of MVPA was selected as the cut-point for high and low physical activity and has no known clinical significance. Three days was chosen in order to ensure adherence by all participants to wearing the accelerometer. Future studies with means of accurately tracking activity for an extended period of time, all the while maintaining compliance to wearing the device, are needed.

Examining the relationship between sedentary time and recovery from concussion is also important. Future research with larger sample sizes are needed to conjointly evaluate the amount of rest while taking into account MVPA is needed.

The participants in this study collectively reported to the clinic at a median of 4 days (IQR: 3–6 days) after their concussion and therefore the type and amount of physical activity that participants engaged in immediately after their concussion remains unknown. Thus, another potential confounder is the time to presentation to the sports medicine physician with a suspected concussion. Additionally, it is unknown what activity participants were doing immediately after the injury and how this would affect recovery.

Participants self-reported the date they first returned to school. The date of return to school may have been influenced by the timing of the date of the injury (i.e., if the injury occurred with an ensuing school break, the first date of return to school occurred after the break). This could have led to an over estimation of the amount of time to return to school, although we would expect this to be similar between both groups.

A Hawthorne effect may have occurred for both physicians and participants. Participants wore the accelerometer on the waist and were aware that their activity was being observed and measured. Knowing that they were being studied, participants may have then changed their behavior and activity may appear more compliant with the physician's instruction to rest in the initial time period following concussion and then gradually complete the return to sport protocol. This could lead to an underestimation of the true activity that may have otherwise been performed by participants if they were not having activity tracked. However, this effect is not expected to differ between study groups. Physicians may have also acted more conservatively in granting their return to play decision if they felt their decision was being monitored by the researchers in this study. This may have led to an overestimation of the actual amount of time, determined by the physician, to become ready for re-participation in sport. Again, this would not be expected to be different between the low and high activity groups.

The treating physicians in the current study followed their patients from injury diagnosis to medical clearance and followed standardized return to play protocols. This was done to reduce measurement error through inter-rater differences, which would have been present if multiple physicians were involved in the treatment of a single subject. Multiple physicians were allotted to the treatment of participants in this study. Therefore, although standardized procedures were in place, measurement error could have occurred if there were systematic differences

between physicians in their clinical judgment and their decisions to grant medical clearance. Future studies could address this potential limitation by operationalizing the instructions given to patients and further standardizing the criteria to obtain medical clearance.

CONCLUSION

Youth ice hockey players that participated in MVPA for more than 49.5 min per day, in the first 3 days after their initial assessment took significantly longer to receive medical clearance to return to play than players participating in <49.5 min of MVPA per day. Currently, the optimal amount and type of rest and physical activity that are most beneficial for recovery following a concussion are not well-defined (4–6). Complete rest following concussion diagnosis is unreasonable as individuals, especially youth, are unlikely to comply. Previous research has shown that early initiation of light intensity physical activity may facilitate recovery (20). Whereas, our results suggest that more time spent in MVPA during the first 3 days following concussion diagnosis is associated with a greater time to medical clearance to return to play. Thus, recommendations to limit the amount of time in MVPA initially for adolescent athletes may facilitate recovery following concussion.

ETHICS STATEMENT

This study was approved by the University of Calgary Conjoint Health Research Ethics Board (Ethics ID: REB15-2577). Informed written consent to participate (including parent consent and player assent if <15 years of age) was provided by all participating players.

AUTHOR CONTRIBUTIONS

JL and TR provided substantial contributions to the identifying the research question, acquisition of data and analysis, and development of the manuscript. The remaining authors critically revised all aspects of the manuscript and provided intellectual contributions. The corresponding author oversaw and contributed to all aspects of this project. All authors provided approval for publication of the content.

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CLINICAL TRIAL
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Pilot Randomized Controlled Trial of an Exercise Program Requiring Minimal In-person Visits for Youth With Persistent Sport-Related Concussion

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Objective: To evaluate feasibility and acceptability of a sub-threshold exercise program with minimal in-person visits to treat youth with persistent sport-related concussion, and explore efficacy for improving concussive symptoms, health-related quality of life, and fear-avoidance.

Study design: We conducted a pilot randomized controlled trial comparing a 6 week sub-threshold exercise program requiring only two in-person visits to active control (stretching) for 12–18 year old youth with persistent sport-related concussion. We measured moderate-to-vigorous physical activity pre- and post-intervention using accelerometry, and increased goals weekly via phone contact. We examined feasibility and acceptability using qualitative interviews. We used exponential regression to model differences in trajectory of concussive symptoms by experimental group, and linear regression to model differences in trajectory of health-related quality of life and fear-avoidance of pain by experimental group.

Results: Thirty-two subjects randomized, 30 completed the study ($n = 11$ control, $n = 19$ intervention), 57% female. Youth and parents reported enjoying participating in the study and appreciated the structure and support, as well as the minimal in-person visits. Exponential regression modeling indicated that concussive symptoms declined more rapidly in intervention youth than control ($p = 0.02$). Health-related quality of life and fear-avoidance of pain improved over time, but were not significantly different by group.

Conclusions: This study indicates feasibility and potential benefit of a 6 week subthreshold exercise program with minimal in-person visits for youth with persistent concussion. Potential factors that may play a role in improvement such as fear-avoidance deserve further study.

Keywords: brain concussion, child, fear-avoidance, pain, exercise, traumatic brain injury, treatment, sport

INTRODUCTION

Approximately 1.1–1.9 million youth sustain concussions annually (1), and up to 30% have persistent symptoms such as headache, fatigue, and difficulty concentrating for weeks or months (2–5). Persistent concussive symptoms can impact social development, cognitive function, and academic success, and result in greater utilization of sub-specialty care (6). A recent consensus statement called for research into treatments for persistent concussive symptoms (7), as the extant literature provides little guidance. One promising approach is the use of rehabilitative exercise. Individuals who sustain concussions have increased symptoms with exercise, and exercising at a "sub-symptom threshold" level appears to help them return to function more quickly (8, 9). A few studies have reported benefit for such an approach, but have required weekly in-person visits (8–16). Currently no exercise treatments have been designed for concussion that could be completed with minimal in-person visits and therefore be more easily disseminated. We proposed to address this gap, adapting a pre-existing exercise intervention for concussion to be delivered with only two in-person visits, and utilizing weekly check-ins via phone contact with the youth, as has been used effectively in previous studies (17).

Debate also exists regarding how sub-threshold exercise might produce benefit in patients with persistent concussive symptoms. Some have posited (8, 9, 12) that exercise improves cerebrovascular autoregulation, which appears to be impaired following brain injury. Participating in daily exercise at a level below that which exacerbates symptoms could assist with rehabilitation of neurologic adaptations to exercise, thus decreasing exercise-related symptoms occurring secondary to transmission of systemic pressure into the cerebrovascular space.

We conceptualized that exercise interventions for concussion might also have effects on "fear-avoidance" (18–22). The fear-avoidance model is a prominent theoretical model applied to adults and youth to understand processes through which an acute pain experience can become chronic (18–22), According to this model, individuals who perceive pain as threatening and place a catastrophic meaning on the pain experience (e.g., rumination and worry that pain will not go away), develop pain-related anxiety that maintains avoidance, leading to functional disability, depression, and persistence of pain. Pediatric specific models of fear-avoidance include the important role of parent behavioral and psychological responses to the child's pain experience, recognizing that the child's own experiences develop within the familial context (23, 24).

A few authors (25–27) have suggested a role for fear-avoidance in the persistence of concussive symptoms, and we theorized that fear-avoidance might be impacted by sub-threshold exercise programs post-concussion (**Figure 1**). Patients with acute concussion are initially instructed not to exercise, given concerns about the vulnerability of the injured brain. When symptoms worsen during exercise, concussed patients may fear such increases indicate greater injury. This fear leads them to become anxious about participating in exercise and avoid exercise, bolstering their fear, and generating a cycle of disability. Rehabilitative exercise challenges catastrophic assumptions about exercise, thus decreasing anxiety and avoidance of exercise, and improving function (28). Function in chronic illness states is often conceptualized as health-related quality of life (HRQoL), which can be measured using the Pediatric Quality of Life scale (PedsQL) (29). Prior research has suggested that youth with PPCS have deficits in function that can be measured with the PedsQL (30, 31), and that these deficits can improve with intervention (32).

We conducted a pilot randomized controlled trial (RCT) of a 6-week rehabilitative exercise program requiring minimal in-person visits for youth with persistent concussive symptoms, the Sub-Threshold Exercise Program (STEP). Our goals were to: (a) assess feasibility and acceptability of this approach, (b) collect pilot data regarding the effect of STEP on trajectory of concussive symptoms, and variation by demographic and injury factors (sex, age, prior concussion, time since injury), and (c) explore impact of the intervention on objectively measured moderate-vigorous physical activity (MVPA), standardized measures of fear-avoidance of pain, and health-related quality of life over time.

METHODS

Recruitment

We recruited youth 12–18 years old from concussion clinics at Seattle Children's Hospital and an on-line portal over a period of ∼9 months. The on-line portal consisted of a website with information about the study and targeted advertisements on social media platforms. Inclusion criteria included: (1) diagnosis of sports-related concussion consistent with Zurich definition by a clinician experienced with concussion management (33), (2) at least two concussive symptoms, (3) duration of symptoms 3 weeks−6 months after concussion, (4) no contraindication to performing physical activity, and (5) not currently receiving physical therapy to increase physical activity. Subjects completed a baseline exercise tolerance test (a modified Buffalo Concussion Treadmill Test) (8) and were eligible for the study if symptoms worsened during this test, consistent with prior studies (8, 9, 14). Subjects continued to receive usual care from their referring concussion clinician during the study. We did not collect information about other treatments pursued by subjects during the study. The study was approved by the Seattle Children's Hospital Institutional Review Board and registered at Clinicaltrials.gov, NCT02673112. All youth and parents completed written informed consent.

Procedures

All subjects completed in-person assessments at study entry (baseline) and 6 weeks later (post-intervention). Subjects were examined by a study physical therapist at baseline to ensure they had no concerning cervical spine or vestibular issues that would preclude exercise. The remainder of the assessments were completed online, including weekly assessments of concussion symptoms during intervention, and surveys at 3 and 6 month follow up. Accelerometer assessments were completed for 5–7 days at baseline and 6 weeks to measure moderate-vigorous physical activity (MVPA) in an objective manner. Youth and

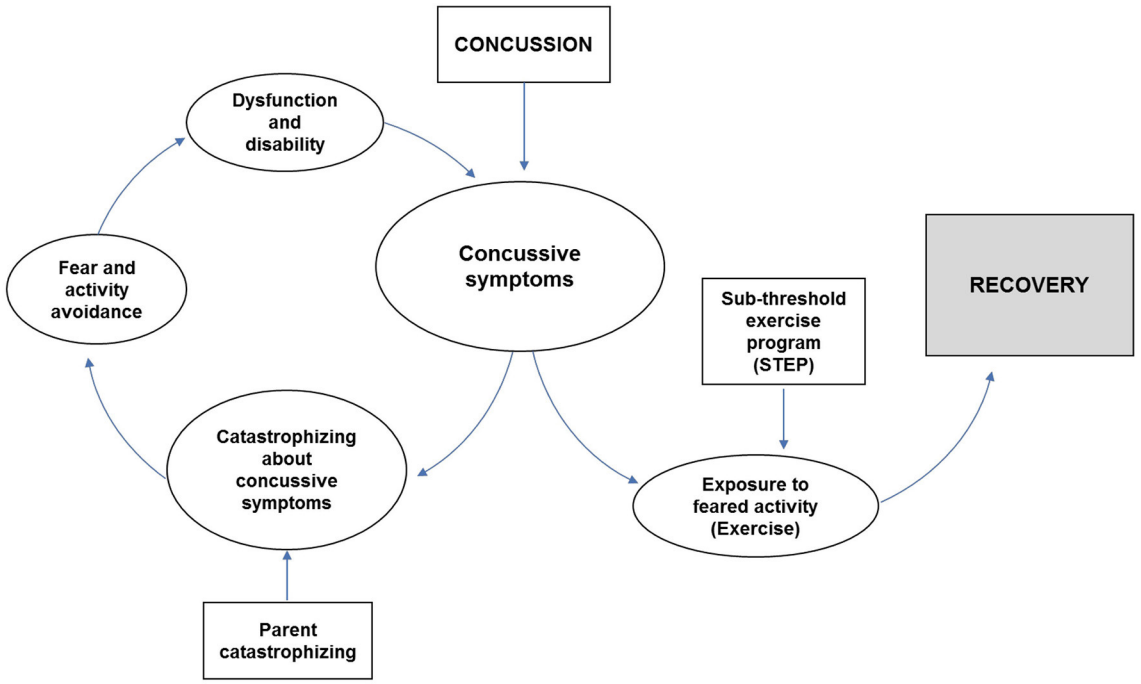

FIGURE 1 | Conceptual model of Fear-avoidance (19), adapted for concussion.

parents were provided incentives for completing accelerometry measurements and surveys using gift cards.

Randomization

Randomization was conducted by the study analyst (K.W.) using random number generation in blocks of four, stratified by age (11–13 and 14–18) and sex. Allocation was weighted 2:1: toward the intervention arm to provide maximum data for feasibility and acceptability. Study arm allocation details were placed into opaque envelopes and chosen sequentially.

Participants

Two hundred thirty youth were screened, but 69% did not meet inclusion criteria as concussion symptoms had resolved by the time of recruitment contact or they were already receiving physical therapy (**Figure 2**). Of the 72 patients who met criteria for participation, 45 were initially interested, 10 of whom did not have an increase in symptoms with the treadmill test, and three of whom later declined participation. Thirty-two individuals enrolled and were randomized to intervention or control. Only one of the enrolled participants came from the on-line portal, the remainder were patients at Seattle Children's Hospital. Two subjects discontinued participation in the study, both in the first week of the study, leaving 30 total subjects, 11 control, and 19 intervention.

Experimental Arms

a) **Stretching (Control)**: Individuals randomized to control were given a home stretching program and provided a handout with color illustrations. Stretches required 5–10 min to complete and were completed daily (see **Supplementary Material**). Research assistants (RAs) called subjects weekly to ensure they were tolerating the exercises.

b) **Sub-Threshold Exercise Program (STEP) (Intervention):** Individuals randomized to the intervention were given a 6 week daily home aerobic exercise program. The exercise prescription for participants included specifications for frequency, duration, and intensity as recommended by Howell et al. (34) Frequency was set at daily, with the understanding that youth might miss 1–2 days per week due to scheduling conflicts. Duration of exercise was started at 5–10 min per day greater than MVPA at baseline measured with accelerometry, and increased weekly by 5–10 minutes per/day via phone contact with the RA (for a goal of 60 min/day). Intensity was set at 80% of the heart rate that produced symptoms during the modified Buffalo Concussion Treadmill Test (i.e., "sub-threshold") (8, 9). Measuring MVPA using actigraphy provided information about quantity of physical activity at baseline, to ensure that the intervention was an increase from a participant's baseline. Utilizing the treadmill test provided information about the intensity of exercise a participant could tolerate, to ensure that the intervention would not provoke symptoms. If symptoms worsened during exercise, HR goal was decreased by 10%. Subjects were provided a wrist-based HR monitor to track heart rate. Participants were instructed to exercise in whatever manner they chose, and most utilized either exercise bike, treadmill, fast walking up an incline/stairs, or calisthenics. Exercise type was allowed to shift during the intervention to adapt to participant preferences and lifestyle.

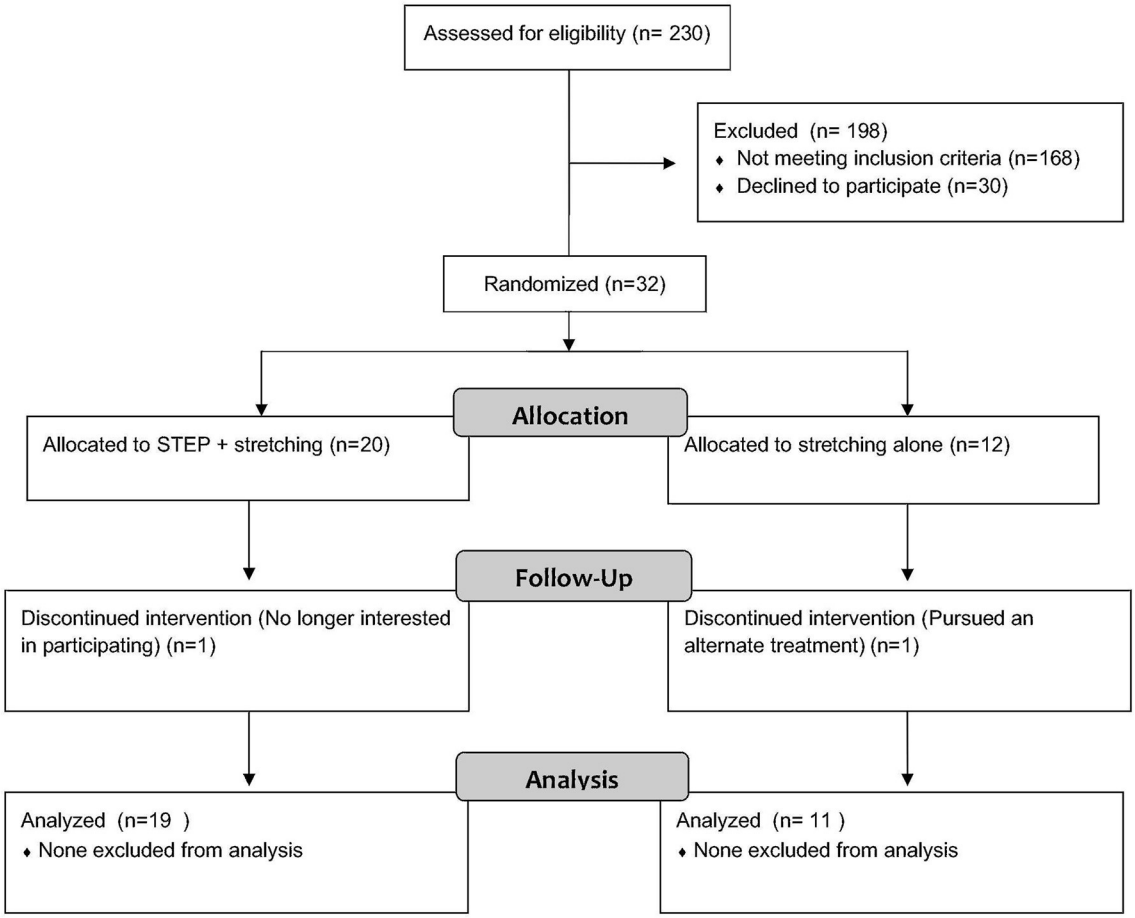

FIGURE 2 | CONSORT flow diagram for Sub-Threshold Exercise Program (STEP), Seattle WA 2016–17.

Blinding

Physical therapists conducting the modified Buffalo Concussion Treadmill Test were blinded to randomization status. Aside from accelerometry, all other assessments were completed via self-report.

Demographics, Past Medical History, and Family History

Youth and parents were interviewed together at baseline regarding: (a) date of injury, (b) mechanism, and (c) prior concussion. Parents completed surveys regarding (a) demographics (age, race, socioeconomic status) and (b) past medical history.

Baseline Exercise Tolerance

The Buffalo Concussion Treadmill Test (35) is a graded treadmill test used to determine heart rate threshold for concussive symptoms. The test was administered in accordance with prior studies (8, 9), beginning with a treadmill speed of 3.3 mph with 0% incline. After 1 min, the grade was increased to 2.0%. At the start of the 3rd min and each minute thereafter, the grade was increased by 1%. The same speed was maintained throughout. The test was stopped when the subject self-reported worsening of concussive symptoms, when they reached HR max for age or at 20 min, and HR was recorded using pulse oximetry. Participants who reached either the HR max for age or completed 20 min on the treadmill were excluded from the study. For the remaining participants, the HR at which they reported worsening was defined as the threshold HR and used to guide the intensity of exercise for the intervention arm.

Outcome Assessment

Feasibility and Acceptability

1. **Enrollment:** Recorded numbers of patients screened, eligible, and enrolled.
2. **Retention/attrition:** Tracked rates of participant withdrawal and loss to follow up. Recorded reasons for withdrawal, and tracked adverse events.
3. **Engagement:** Recorded visit completion rates, and rates of completion of surveys and other procedures.
4. **Satisfaction:** Subjects completed an end of study interview regarding satisfaction with study procedures and suggestions for improvement.

5. **Safety:** RA called subjects weekly to track exercise tolerance and any adverse events.

Preliminary Efficacy Outcomes

Trajectory of concussive symptoms, measured using the Health behavior inventory (5, 36)**:** The HBI is a 20-item instrument assessing post-concussive symptoms on a four-point Likert scale with higher scores indicating greater severity. This scale has demonstrated validity and reliability among adolescents with mild traumatic brain injury (mTBI) (36, 37). The HBI was measured at nine time points: Baseline, weekly during the intervention (weeks 1–6), 3 months, and 6 months.

Exploratory Outcomes

1. **Trajectory of Health-related quality of life, measured using the Pediatric Quality of Life Inventory (youth and parent report):** PedsQL© is a 23-item five point questionnaire that assesses physical, emotional, social, and school functioning, with established validity and reliability (29, 38). PedsQL was measured at four time points: Baseline, 6 weeks, 3 months, and 6 months.
2. **Change in physical activity, measured using accelerometry**: Physical activity was measured pre- and post-intervention (baseline and 6 weeks) in both experimental arms using a hip-mounted ActiGraph GT3X (ActiGraph LLC, Pensacola, FL). The GT3X accelerometers collect data at a frequency of 30 Hz, and data was processed into 1 s epochs (39–41). Participants wore the accelerometer for 1 week at baseline and in the last week of the intervention. We used the accelerometer data quality standards by Troiano et al. (42), including criteria for wear time and valid days (4–7 days, eight or more hours of accelerometer wear/day) (42). We used the accelerometer cut-points for moderate-to-vigorous physical activity (MVPA) developed by Evenson et al. (43), which has the highest classification accuracy (44). Total minutes above the threshold was divided by number of valid days to obtain minutes of MVPA per day pre- and post-intervention.
3. **Trajectory of Fear-avoidance, measured using the Fear of pain questionnaire** (45): The FOPQ-C and FOPQ-P are 24- and 23-item child and parent proxy versions of the Fear Of Pain Questionnaire, and have been shown to reliably and validly measure pain-related fear and pain-related avoidance of activities in youth (Cronbach's alpha 0.92) (23, 45). Fear-avoidance was measured at four time points: Baseline, 6 weeks, 3 months, and 6 months.

Analysis

Descriptive

Participant characteristics, including sociodemographic characteristics, were summarized overall and compared by study arm using chi-square. Continuous measures were summarized via means and standard deviations, or median and interquartile range for asymmetrically distributed variables, and were compared by Student's *T*-tests and Wilcoxon rank sum, respectively.

Feasibility and Acceptability

Feasibility and acceptability measures were descriptively summarized. Satisfaction was measured qualitatively and themes were summarized.

Preliminary Efficacy Outcome

We collected pilot data regarding trajectory of concussive symptoms (HBI), hypothesizing that intervention youth would have a more rapid decline in concussive symptoms than control youth. Our previous work (13) has suggested that injury recovery follows an exponential curve with a rapid rate of decline initially after injury, and thus we modeled trajectory of concussive symptoms using an exponential decay framework which fit well with the data.

$$HBI(t) = Nbl^{*}\, e^{-\lambda t}$$

In this model, N_{BL} represents mean HBI at study baseline, estimated as a linear function of random intercept (HBI at the time of injury, N_0) and covariates (duration of symptoms at entry into the study, age at concussion, and sex):

$$N_{BL} = N_0 + \boldsymbol{\beta}\mathbf{X}.$$

We modeled intercept as a random effect, modified based on factors that might impact concussive symptoms at study baseline (sex, age, prior concussion, and duration of symptoms). Rate of exponential decay (non-linear slope) was modified based on covariates expected to impact rate of symptom resolution (prior concussion, duration of symptoms). Rate of change at time t weeks from study baseline, denoted by $-\lambda_t$, was estimated as a linear function of study arm and covariates:

$$\lambda_t = \gamma_0 + \gamma_1\,(Intervention) + \boldsymbol{\gamma}\mathbf{X}.$$

A statistically significant intervention effect (λ_1) therefore denotes a difference in the rate of symptom resolution, accounting for duration of symptoms at entry into the study, age, sex, and prior concussion.

Exploratory Outcomes (MVPA, Fear-Avoidance and Health-Related Quality of Life)

Given skewness in MVPA data, we examined this outcome categorically, assessing the proportion in each group who achieved a minimum of 15 min per day of MVPA at 6 weeks with logistic regression. Fear-avoidance (FOPQ) and health-related quality of life (PedsQL©), were entered into separate linear mixed models. Models were covariate-adjusted for duration of symptoms at entry into the study, age, sex, and prior concussion. Within participant correlation was modeled via an autoregressive covariance structure.

RESULTS

Sample Description

Half of the participants were female, with average age 15.5 years (SD 1.6, **Table 1**). Approximately half the sample reported a

TABLE 1 | Demographic characteristics of concussed youth participating in Sub-Threshold Exercise Program (STEP) study, Seattle WA 2016–17.

	Control ($n = 11$) *Mean (SD) or N (%)*	Intervention ($n = 19$) *Mean (SD) or N (%)*	Total ($n = 30$) *Mean (SD) or N (%)*
Female	6 (54.6)	12 (63.2)	17 (56.7)
Age at baseline (years)	15.8 (1.1)	15.4 (1.8)	15.5 (1.6)
Race [a]			
White	7 (63.7)	17 (89.5)	24 (82.8)
African-American/Black	2 (18.2)	–	2 (6.6)
Asian	–	2 (10.5)	2 (6.6)
Missing	2 (18.2)	–	2 (6.6)
Ethnicity			
Hispanic	–	1 (5.2)	1 (2.9)
Non-hispanic	10 (90.9)	17 (89.5)	31 (88.6)
Missing	1 (9.1)	1 (5.3)	2 (6.7)
Household income			
$0–60,000/year	3 (27.3)	3 (15.8)	6 (20.0)
History of prior concussion	7 (63.6)	8 (42.1)	15 (50.0)
Duration of symptoms at baseline (days) [b]	75.9 (49.4) Range 22–202	48.8 (32.2) Range 21–175	58.8 (41.1) Range 21–202
Mechanism of injury			
Football	1 (09.1)	4 (21.1)	5 (16.7)
Soccer	2 (18.2)	3 (15.8)	5 (16.7)
Basketball	3 (27.3)	1 (5.2)	4 (13.3)
Wrestling	1 (9.1)	2 (10.5)	3 (10.0)
Swimming	–	2 (10.5)	2 (6.7)
Volleyball	–	2 (10.5)	2 (6.7)
Softball	1 (9.1)	1 (5.2)	2 (6.7)
Lacrosse	1 (9.1)	–	2 (6.7)
Tennis	1 (9.1)	–	1 (3.3)
Hockey	–	1 (5.2)	1 (3.3)
Ultimate frisbee	1 (9.1)	–	1 (3.3)
Gymnastics	–	1 (5.2)	1 (3.3)
Dance	–	1 (5.2)	1 (3.3)

[a] *Chi-square, $p = 0.06$.*
[b] *Wilcoxon rank sum, $p = 0.02$.*

prior concussion. Duration of concussion symptoms at the start of the study averaged about 2 months, but was quite skewed (median 48.5 days, IQR 33, 64). Concussions occurred from a wide range of sports (**Table 1**). The majority of youth (70%) reported headaches "often" at study entry. Approximately 40% had difficulty with concentrating and being tired. Only 17% reported history of chronic pain, but 73% had pain in the week before starting the study, all of whom had headaches. A smaller proportion reported neck pain (33%), back pain (23%), or pain in other locations (17%). Half the subjects reported family history of chronic headaches, 60% back or neck pain, and 47% other joint pain.

TABLE 2 | Exponential decay model examining the effect of the Sub-Threshold Exercise Program (STEP) on concussive symptoms over time (Health Behavior Inventory, or HBI), adjusted for age, sex, duration of time since injury and history of concussion, Seattle WA 2016–17.

		Estimate	95% Confidence limits		*p*-value
Intercept	mu	24.48	−27.60	76.56	0.36
Age (continuous)	c1	0.69	−2.63	4.01	0.69
Female	c2	−4.68	−15.55	6.19	0.40
Duration of symptoms					
<9 weeks (referent)	–				
9–22 weeks (int)	b2	−8.24	−12.85	−3.62	**0.0005**
>22 weeks (int)	b3	−3.97	−11.65	3.71	0.31
Rate	g0	0.12	0.05	0.19	**0.0009**
Duration of symptoms					
<9 weeks (referent)	–				
9–22 weeks (rate)	g2	−0.07	−0.14	0.00	**0.048**
>22 weeks (rate)	g3	−0.03	−0.06	−0.01	**0.01**
Prior concussion (y/n)	c3	−0.01	−0.03	0.01	0.25
Intervention	g1	0.02	0.00	0.04	**0.02**

Bold values indicate the highlighted results that are significant with p values <0.05.

Feasibility and Acceptability

Two participants discontinued the study after randomization but prior to starting the intervention as their symptoms had already resolved. Retention was excellent for participants who began the intervention, with 90% of youth and 83% of parents who began the intervention completing 6 month follow up. During interviews with parents and youth, 100% reported they would recommend the study to a friend. Other themes included: (1) enjoyment of the study (particularly incentives, weekly RA check-ins and use of wrist-based heart rate monitors) (2) appreciation of structure and organization, and (3) appreciation of minimal in-person study visits. Symptoms during exercise were reported by 2/11 subjects in the control group (18.2%) and 7/19 (36.8%) subjects in the intervention group, but were managed effectively by decreasing intensity of exercise, and no subjects chose to leave the study due to symptom exacerbations. Most symptom exacerbations occurred in the first few weeks of the study. Two individuals in the intervention group had symptoms exacerbate in later weeks, both of which were associated with participants engaging in a longer duration of exercise than was prescribed. No adverse events occurred during the study. We did not inquire as to whether participants were able to return to sporting activities.

Quantitative Outcomes

The exponential decay model revealed a significant effect of the intervention on rate of decline of concussive symptoms (HBI, $p = 0.02$, **Table 2** and **Figure 3**), after controlling for age, sex, and prior concussion. Rate of concussion symptom improvement was slower among youth with chronic symptoms (9–22 weeks, and >22 weeks) compared to those with acute symptoms (<9 weeks) in both intervention and control groups. However, the intervention effect (i.e., the difference in rates between intervention and control youth) was also most pronounced in youth with chronic symptoms. All subjects completed the pre-intervention accelerometry as it was a requirement for starting the study. Most subjects (26/30, 87%) completed the post-intervention accelerometry. The proportion of youth achieving a minimum of 15 min/day of MVPA was not significantly different by study arm. Parent-reported health-related quality of life (PedsQL©) was significantly improved in intervention compared to control youth ($\beta = 0.56$, $p = 0.05$; **Table 3**). Child-reported PedsQL© improved overall ($\beta = 0.75$, $p = 0.0045$; **Table 3**), but was not significantly affected by the intervention ($\beta = 0.19$, $p = 0.47$; **Table 3**). Parental fear-avoidance (FOPQ-P) significantly declined overall ($p = 0.0096$), but was not different by treatment group ($\beta = -0.0031$, $p = 0.99$, **Table 3**; **Figure 4**). Child fear-avoidance (FOPQ-C) was not significantly different by treatment group ($\beta = -0.29$, $p = 0.23$, **Table 3**; **Figure 4**).

DISCUSSION

While previous studies utilized sub-threshold exercise to treat youth with persistent concussion, this is the first study to measure MVPA using accelerometry, and the first to examine an intervention requiring minimal in-person visits. This is also the first study to explore the impact of exercise on fear-avoidance of pain in youth with concussion. We found the Sub-Threshold Exercise Program (STEP) was feasible and acceptable for youth with concussive symptoms. Youth reported enjoying the structure and support provided, and preferred the minimal visits. Preliminary data suggested potential benefit of this approach, as youth who received STEP had more rapid improvement in concussion symptoms compared to youth in a stretching control, and improvement was maintained at 6 months. Health-related quality of life improved significantly for all subjects and fear-avoidance of pain declined significantly for all subjects, but neither was significantly different by intervention group.

Our findings are in line with prior studies of exercise interventions for concussed youth, all of which report benefit (8–15). Much of our methodology was similar to prior studies: (a) utilizing the Buffalo Concussion Treadmill Test to determine HR threshold, (b) setting exercise goals at 80% of the HR threshold (8, 9), and (c) asking participants to exercise for 6 weeks (8–15). However, previous studies of sub-threshold exercise required weekly in-person visits, which present greater barriers for access and are difficult to scale. Instead, we utilized RAs as health coaches, phoning youth weekly to advance exercise goals, and required only two in-person visits, which we felt was a more

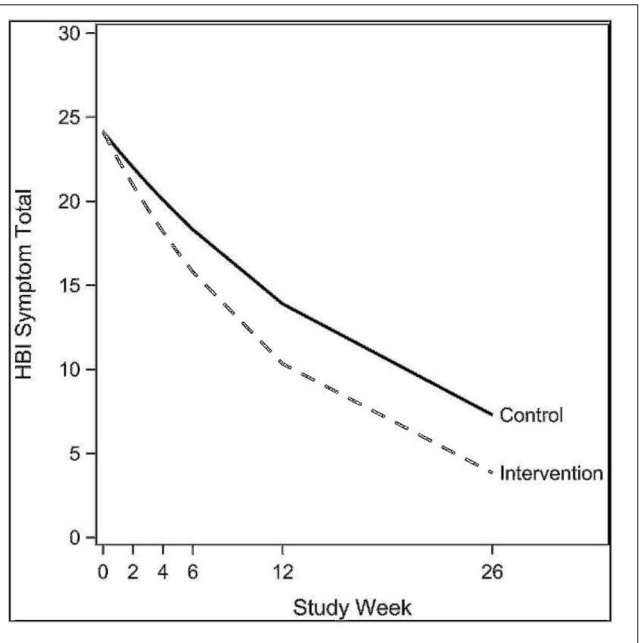

FIGURE 3 | Exponential decay models examining the effect of the Sub-Threshold Exercise Program (STEP) on concussive symptoms in youth, Seattle WA 2016–17.

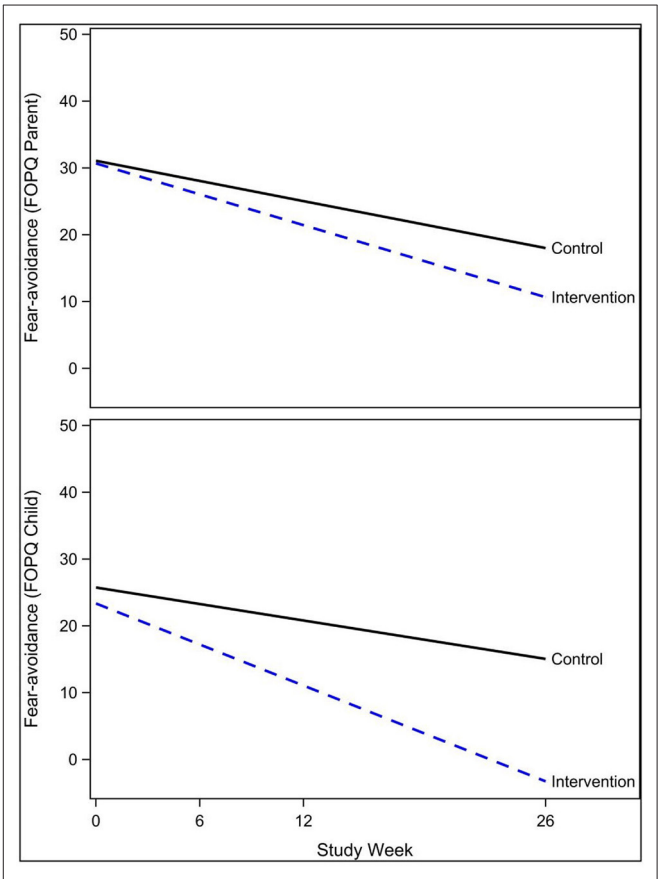

FIGURE 4 | Effect of the Sub-Threshold Exercise Program (STEP) on fear-avoidance in youth, Seattle WA 2016–17.

TABLE 3 | Linear mixed model examining the impact of the Sub-Threshold Exercise Program (STEP) intervention on concussed youth on outcomes of fear avoidance of pain and health-related quality of life, adjusted for age, sex, duration of symptoms, and prior concussion, Seattle WA 2016–17.

	FOPQ[a] (Child)			FOPQ[a] (Parent)			PEDsQL© [b] (Child)			PEDsQL© [b] (Parent)		
	B	**(SE)**	**p**	**B**	**(SE)**	**p**	**B**	**(SE)**	**p**	**B**	**(SE)**	**p**
Mean												
Intercept	−24.54	(28.54)	0.40	20.80	(28.80)	0.48	71.90	(22.91)	0.0044	57.97	(24.22)	0.02
Age (continuous)	3.24	(1.88)	0.10	1.03	(1.90)	0.59	−0.10	(1.51)	0.95	−0.06	(1.60)	0.97
Female	13.64	(5.45)	**0.02**	9.58	(5.42)	0.59	−6.49	(4.35)	0.15	−1.21	(4.53)	0.79
Prior concussion	−8.79	(6.02)	0.16	−9.02	(6.03)	0.15	−1.18	(4.84)	0.81	7.73	(5.12)	0.14)
Duration of symptoms												
<9 weeks (referent)	–	–	–	–	–	–	–	–	–	–	–	–
9–22 weeks	−7.26	(4.73)	0.13	−5.83	(4.49)	0.20	15.46	(3.04)	**<0.0001**	11.42	(3.49)	**0.0016**
>22 weeks	4.31	(3.62)	0.24	6.35	(3.33)	0.06	−11.46	(3.95)	**0.0048**	−0.82	(4.49)	0.86
Slope												
Week	−0.40	(0.26)	0.13	−0.63	(0.24)	**0.0096**	0.75	(0.26)	**0.0045**	0.22	(0.29)	0.44
Week x Intervention	−0.29	(0.25)	0.23	−0.0031	(0.23)	0.99	0.19	(0.25)	0.47	0.56	(0.29)	**0.05**

[a] *Fear of Pain Questionnaire, a measure of fear-avoidance of pain.*
[b] *Pediatric Quality of Life Inventory, a measure of health-related quality of life.*
Bold values indicate the highlighted results that are significant with p values <0.05.

scalable approach. We also provided youth with wrist-mounted HR monitors, to allow them to self-monitor HR goals. In addition, we objectively measured MVPA using hip-mounted accelerometers pre- and post-intervention, which allowed us to tailor the intervention to activity level, ensuring that the intervention was an increase from baseline MVPA. Utilizing accelerometry also allowed us to quantify changes in MVPA. Despite the impact of the intervention on concussive symptoms, it did not significantly change MVPA compared to controls in this pilot study.

Finding no significant change in MVPA and yet a positive effect of the intervention on rate of decline of concussive symptoms poses a new question—how can an aerobic exercise intervention be efficacious if it does not increase MVPA? We suggest caution in examining these MVPA data, given the relatively small sample size. In addition, accelerometry is an imperfect measure of MVPA, and certain types of physical activity such as swimming and cycling are not well-captured. The intervention and control groups also had differences in amount of MVPA at baseline, which makes it challenging to measure improvement. The lack of differences in MVPA does suggest we should consider other factors. In planning this study, we felt it would be beneficial to examine concepts from the chronic pain literature, given the prevalence of headache as a chronic symptom of concussion. One prevalent theory regarding the development of chronic pain is fear-avoidance of pain (18–22).

Prior studies (25–27) have measured high levels of fear-avoidance of pain and fear of physical activity ("kinesiophobia") in patients with persistent concussive symptoms. However, this is the first study to report decreases in fear-avoidance of pain in patients undergoing two different exercise treatments for concussion, and this finding deserves further study. Clearly further work needs to be done to examine the relationship between fear-avoidance and concussion symptom resolution longitudinally, as there are possible bidirectional relationships. In addition, "fear-avoidance" contains multiple concepts—pain-catastrophizing, fear of pain, and avoidance of activities that might result in pain. Future studies should disentangle these concepts, and better understand potential predictive relationships between children's psychological and behavioral response to concussion and their subsequent symptom experience using mediation analyses. It is of note that the intervention was most efficacious for youth with persistent symptoms (>9 weeks), fitting with a chronic pain model (18–22). Additional research is needed to explore whether mediators of exercise treatment effects vary with chronicity of symptoms.

It is notable that more than half of the youth in our study had parents who reported chronic pain. Parents play an important role in contextualizing pain and other negative symptoms for their children (23, 46–48). If a parent expresses fear about a child's pain, their child is more likely to be concerned about potential danger. Intervening with parents to decrease pain catastrophizing, pain fears and avoidance of potentially painful activities has proven beneficial for youth with chronic pain (49–51). While the STEP intervention included parents at the baseline visit, parents did not receive tailored education and were not significantly involved in weekly calls. Future studies might consider greater engagement with parents to help them support their child's exercise and lessen fear of concussive symptoms.

This study was limited by a lack of diversity, which affects the ability to generalize to other populations. We also had a small sample size and thus lacked the power to conduct a definitive assessment of efficacy or true mediation analysis regarding fear-avoidance of pain and MVPA, and future studies are needed to explore both of these areas. Hip-mounted accelerometry is also an imperfect measure of MVPA, and does not accurately capture a full range of activities such as swimming and cycling. Accelerometers are also relatively burdensome to wear, and must be used for brief periods of time, resulting in activity bias. We

attempted to defray such issues through standardized methods including recommendations regarding wear time, but the data remain imperfect. Finally, we had no direct measure of adherence such as a daily log, which would allow us to better estimate compliance with the exercise intervention.

In conclusion, this study found that a Sub-threshold Exercise Program (STEP) for youth with persistent concussive symptoms was feasible, and may increase the rate of improvement in concussive symptoms. The STEP intervention was acceptable to subjects even with a small number of in-person visits, and treatment benefits were maintained at 6 month follow-up. Future studies are needed to examine this type of intervention in a larger sample powered to assess efficacy and mediation of treatment effects.

DATA AVAILABILITY

The datasets generated for this study are available on request to the corresponding author.

AUTHOR CONTRIBUTIONS

SC conceptualized and designed the study, oversaw data analysis, drafted the initial manuscript and incorporated all revisions and comments. KW conducted data analysis, prepared the figures and reviewed and revised the manuscript. JM and FR assisted with conceptualization and design of the study, provided input regarding analysis, and critically reviewed the manuscript for important intellectual content. MB assisted with conceptualization and design of the study, and reviewed and revised the final manuscript. ES assisted with conceptualization and design of the study, assisted with data collection and reviewed and revised the final manuscript. AH and LF assisted with data collection and analysis, and reviewed and revised the final manuscript. TP provided input regarding analysis, and critically reviewed the manuscript for important intellectual content. All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2019.00623/full#supplementary-material

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Predictors for Psychological Distress 2 Months After Mild Traumatic Brain Injury

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Objective: To predict psychological distress at 2 months for patients with mild traumatic brain injury.

Method: A prospective cohort study of 162 patients with mild traumatic brain injury (MTBI) admitted consecutively to an outpatient clinic at Haukeland University Hospital, Norway. Demographic data were obtained from Statistics Norway and injury characteristics were obtained from the hospital records. Sick leave data from the last year before the injury were obtained from The Norwegian Labor and Welfare Service. Self-report questionnaires were used to obtain history about earlier disease and symptom profiles. The Hospital Anxiety and Depression Scale (HAD) detecting states of depression and anxiety were used as the dependent variable in a stepwise linear regression. Pre-injury factors and injury-related factors were examined as potential predictors for HAD.

Results: In the first steps we observed a significant association between HAD at 2 months and education, whiplash associated disorder (WAD), and earlier sick listed with a psychiatric diagnosis. In the final step there was an association only between HAD and self-reported anxiety and WAD. There were no associations between HAD and injury-characteristics like severity at Glasgow Coma Scale or intracranial injury.

Conclusion: Patients with low education, earlier psychiatric diagnosis, self-reported earlier anxiety and WAD were more likely to develop a psychological distress after a MTBI. These findings should be taken into consideration when treating patients with MTBI.

Keywords: mild traumatic brain injury, predictors, psychological distress, anxiety, depression, outcome, treatment

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INTRODUCTION

Mild traumatic brain injury (MTBI) is a major public-health concern, and more than 600 patients per 100,000 people are suffering a MTBI (1, 2). The annual incidence of hospital-treated MTBI is around 100–300 patients per 100,000, and in Norway <100 patients per 100,000 are hospitalized (1, 3).

Common acute symptoms are headache, fatigue, dizziness and cognitive impairment associated with pain, sleep disturbance and psychological distress (4, 5). For the majority of patients with a MTBI the symptoms resolve, but between 5 and 20% develops post-concussion symptoms (PCS) lasting more than 12 months (4, 6–11).

PCS are more common among MTBI-patients compared to other patients suffering a non-head trauma (4, 12). PCS can be divided into somatic, cognitive, and emotional complaints (13). Somatic complaints include headache, dizziness, nausea, fatigue, problems with vision, noise sensitivity, and sleeping problems. Cognitive symptoms include problems with memory or concentration and reduced speed of processing. Emotional symptoms include depression, anxiety, frustration, and irritability (6, 14).

There is a debate in the existing literature whether PCS result from organic injury in the brain, psychological factors or both (15–17). Some studies demonstrate that PCS are associated with pre-injury mental and physical health, injury-related stress and early post-injury cognitive impairment (4, 17). Other authors have found an association between stress, depression, anxiety, all-or-nothing behavioral, and negative expectations about recovery with the development of PCS (18, 19). It is stated that the development and maintenance of PCS can best be explained by a biopsychosocial model, including both neurobiological, psychological and social factors (20). This model that includes pre-injury factors can also explain the multifactorial etiology of persistent symptoms after MTBI (21).

Despite the favorable outcome of MTBI for the majority of patients, a substantial group of patients report symptoms and disability after MTBI. To improve the outcome, several authors have suggested a planned follow-up visit after MTBI to screen for specific treatable conditions, such as depression, anxiety, or other modifiable factors like expectations or coping strategies (22–25). Clinical guidelines, like those from Ontario, Canada recommend a rehabilitation model involving an early evaluation of signs and symptoms combined with education focusing on the normalization of symptoms and reassurance of the expected favorable outcome within 3 months (26). There is a consensus that treatment should be based on a biopsychosocial model and for a gradual return to daily activities and work (26). The guidelines recommends that somatic, cognitive, or behavioral difficulties should be treated symptomatically, and that a management strategy for each symptom including treatment for mental health disorders must be considered (26). It is important to identify characteristics of patients who are at risk of developing psychological distress like anxiety or depression after a MTBI. To improve research about the outcome after a traumatic brain injury (TBI) common data elements are developed, where several pre-defined variables are potential predictors for a functional outcome after a TBI (27). In addition, both pre-injury and early post-injury psychological factors are important predictors for the functional outcome after a MTBI (28, 29). Zahniser et al. found that early psychological distress after MTBI appeared to function as a precursor to functional impairment, and one study for MTBI patients aged 6–17 years found an association between a pre-injury diagnosis of anxiety and psychological distress after a MTBI (30, 31). To the best of our knowledge, pre-injury and injury-related factors have not been investigated as predictors of psychological distress after a MTBI among adults.

The objective of this study was to identify which clinical characteristics predict psychological distress at 2 months after injury for patients with MTBI.

METHODS

Patients and Settings

This is a prospective cohort study with 162 patients admitted to a planned clinical follow-up within 2 months after a MTBI at the Department of Physical Medicine and Rehabilitation at Haukeland University Hospital, Norway after a MTBI. All patients hospitalized for 5 h or longer at the Department of Neurosurgery at Haukeland University Hospital, Bergen, Norway, from January 2009 to July 2011, with an ICD-10 diagnosis of S06.0–S06.9 received a planned follow-up by a rehabilitation specialist 6–8 weeks after the injury at a multidisciplinary outpatient clinic. After finishing the planned follow-up, the sick-listed patients at an age 16–55 years were recruited to a randomized clinical trial. The aim of the main multicenter study was to find out if a specific multidisciplinary model improved return to work (32). Pre- injury-, injury-, and post-injury-related clinical variables were analyzed to find any significant associations with psychological distress 2 months post-MTBI.

Inclusion Criteria

In accordance with the Task Force on MTBI and the American Congress of Rehabilitation Medicine, MTBI was defined as a Glasgow Coma scale (GCS) measure of 13–15 within 30 min or the lowest score during the first 24 h post-injury, unconsciousness for <30 min and posttraumatic amnesia <24 h (33, 34). The participants lived in a mixed rural and urban community, and the majority of them were Norwegian residents (Caucasians). Patients attending the follow-up session, fitting the inclusion criteria and providing a written informed consent were consecutively recruited to the study.

Exclusion Criteria

We omitted patients on disability pension or unemployed in the last 6 months. Patients with a severe head trauma or other diseases that had a significant impact on working skills were excluded. Other exclusion criteria included the following: lack of informed consent, lack of Norwegian language skills or a history of substance abuse in the medical records.

Procedures

When discharged from neurosurgical service for clarity, MTBI patients received an information pamphlet about their MTBI and how to address their symptoms. They were also informed that they would receive a planned follow-up consultation within 2 months post-injury. The participants received a self-report questionnaire and an appointment with a specialist in physical and rehabilitation medicine 6–8 weeks post-injury. At follow-up a clinical interview and an examination was performed with reassurance of an expected favorable outcome after the injury. Patients meeting the inclusion criteria were then offered to participate in the study.

The Self-report questionnaires collected 6–8 weeks post-injury were used to obtain patients history about and screening for PCS, psychological distress, disability, and pain. Demographic data were obtained from the self-report questionnaire and information about education and income from Statistics Norway.

Injury characteristics including acute CT scan were obtained from the medical records during the patient's emergency stay. Data regarding sick leave and diagnosis the last year before the injury were obtained from a national register, the Norwegian Labor and Welfare Service (NAV). After 16 days on sick leave, every citizen in Norway are paid by NAV. The majority of patients were given a diagnosis and received their sick-leave certificate by a general practitioner, a minority by medical specialists. In addition, patient with a musculoskeletal disorder may be sick-listed for up to 12 weeks by a manual therapist or chiropractor.

An accredited third-party agency, Statistics Norway, linked the clinical data with the sick leave data from NAV.

Measures

Psychological distress measured with Hospital Anxiety and Depression Scale (HAD) at 6–8 weeks post-MTBI was used as the main outcome and was the dependent variable in a stepwise linear regression.

HAD is a self-reported questionnaire consists of 14 items assessing states of depression (seven items) and anxiety (seven items) (35). The patients rate each item using a four-point scale from 0 to 3: 0 = no symptoms during the last week; 3 = a severe symptom or symptoms most of the time during the last week. The HAD has been validated for traumatic brain injuries and documented to have high reliability (35, 36). The total sum of scores for HAD was used in the analyses. The subscale of anxiety and depression ranges from 0–21, 8–10 are mild cases and 11 are set as a cut-off for moderate or severe anxiety or depression (35, 37).

Pre-injury and injury-related factors were examined as potential predictors for psychological distress 2 months post-MTBI.

Pre-injury Factors

We obtained information about the income for 1 year (2010) from Statistics Norway, categorized above the mean or not. Pre-injury factors assessed from the self-report questionnaire consisted of age in years, sex, social status such as number of children still living with parents, education and employment status. Education was categorized either as primary education or secondary and higher with more than 10 years of education.

Injury-Related Factors

Injury mechanisms classified as traffic accidents, falls, violence and others (sports) were obtained from the self-report questionnaire. In addition, occupational injuries were also registered. The GCS, neurological status, seizures, headache, neck pain, whiplash associated disorder (WAD), findings on CT scan, alcohol intoxication and length of hospital stay were collected from the medical records from the emergency stay. Patients diagnosed with the ICD-10 diagnosis of S13.4 by a neurosurgeon at the emergency stay was defined as WAD, a non-medical term describing a sudden distortion of the neck. We defined those patients who did not undergo a CT as having no intracranial injury in the analysis, based on the information from the medical records. GCS, a clinical scale for assessing the depth and duration of unconsciousness and coma, was used to classify MTBI based on the first observed GCS within 30 min or the lowest score the during the first 24 h (38). In the preliminary analyses, findings on CT was categorized as type of bleeding, contusion, location of injury, intracranial injury or not, and fractures of the skull, face and neck. Length of post-traumatic amnesia (PTA) was measured using a standardized interview at the follow-up 6–8 weeks after the MTBI, asking the patients to retrospectively recall events. PTA was dichotomised into more or <1 h.

Pre-injury Factors Obtained From a National Registry and Retrospective Self-Rating Factors

We received information from the national registry NAV whether the participants had been sick-listed during the last year before injury and diagnosed with a psychiatric diagnosis, TBI, fatigue, attention deficit disorder, headache, neck pain, a musculoskeletal disorder, neurological disorders, or other diagnosis classified as other disease. The participants had to be sick-listed for more than 16 days to be registered in the national registry. In addition, the participants ticked off at the self-report questionnaire obtained 6–8 weeks post-injury if they at the pre-injury period had anxiety, depression, prior head injury, headache, neurological disorders, or other diseases.

Data registered in the study were entered into the database by two independent co-workers unfamiliar with the aim and content of the study. A biostatistician was responsible for performing and controlling the statistical analyses. The biostatistician was not involved in the treatment or collecting data.

Statistical Methods

Data analyses was completed with IBM SPSS Statistics for Windows, Version 24.0. Armonk, NY: IBM Corp.

We used a linear regression model to assess the predictors for the total sum score for HAD. In the preliminary analyses we estimated the unadjusted model for each of the pre-injury and injury-related factors, to detect all predictors with an association to psychological distress. In the preliminary analyses the significance level was set to 0.10.

In the first step in the fully adjusted model we estimated all significant pre-injury predictors and injury-related predictors, where the significance level was set to 0.05.

In the second step we added pre-injury predictors about sick leave from the national registry the NAV in the fully adjusted model.

Finally, in the third step we estimated the fully adjusted model for all significant predictors from the first two steps and retrospective self-report data about pre-injury diseases.

Additionally, to take into account potential confounding and reflect all aspects of the study in the fully adjusted model, we ensured to have age and sex as essential properties of the cohort in the model.

We used pairwise deletion for missing data to ensure that we used all available data and achieve maximal power in the estimated models. The significance level was set to 0.05 for all analyses in the fully adjusted model.

RESULTS

As presented in an earlier published paper, we identified 343 patients with MTBI admitted consecutively to the Departments of Neurosurgery from January 2009 to July 2011 (39). Of these, 96 patients decided to not attend the planned follow-up 6–8 weeks post-MTBI basically due to a favorable outcome (39). In addition, 92 were not eligible to the study at 6–8 weeks follow-up; 45 substance abuse, 22 significant somatic disease, five significant psychiatric disease, and four lack of language. Finally, 171 patients were eligible to the study, nine declined to participate, and 162 patients were included in the analyses.

As given in **Table 1**, the median age was 33 years, and 63% of the participants were men. The majority of the injuries comprised a fall (47%). Regarding education, 38% have only primary school education with 10 years or less. A CT scan was performed for 94% of the patients and showed intracranial injury for 19% of the patients. GCS was 15 for 77% of the patients, and 12% reported PTA for more than 1 h. It was 27% of the patients who meet the criteria for anxiety at HAD with a score of eight or higher on the subscale, 15% meet the criteria for a depression and 12% had both anxiety and a depression. The mean score of the HAD was 8, 52, standard deviation 7, 30 and range from 0 to 31.

The results of the linear regression analyses are given in **Table 2**. We abstain from presenting the non-significant results from the unadjusted model for each of the pre-injury and injury-related predictors presented in the measure section, which were not included in the fully adjusted models.

In the first step in the fully adjusted model we observed in the linear regression model at a 5% significance level a significant association between HAD at 2 months and WAD and lower education. WAD had the largest beta value of 3.77 (0.7, 7.5) and education beta of 3.67 (1.0, 6.4). The pre-injury and injury-related variables explained 13% of the variance in psychological distress.

In the second step in the fully adjusted model we observed in the linear regression model a significant association between HAD at 2 months and lower education and a psychiatric diagnosis the last year before injury. A psychiatric diagnosis had the largest beta value of 5.29 (1.7, 8.9) and education a beta of 3.40 (0.8, 6.0). The pre-injury diagnosis from NAV explained an additional 8% of the variance in psychological distress.

In the final step in the fully adjusted model we observed a significant association between HAD at 2 months and pre-injury retrospective self-reported anxiety and WAD. Pre-injury self-reported anxiety had the largest beta value 7.61 (3.6, 11.6) and WAD a beta of 3.55 (0.3, 6.8). The R square for the final model was 0.396 with an adjusted R Square of 0.338, explaining an additional 19% of the variance in psychological distress.

There were no association between HAD and other injury-related measures like severity at Glasgow Coma Scale, PTA or intracranial injury in any of the steps in the adjusted models.

TABLE 1 | Demographic data and clinical characteristics 6–8 weeks after mild traumatic brain injury.

Variable	Total	*n* (%)
Pre-injury factors		
Age, years[a]	162	33 [16, 55]
Sex, men	162	102 (63%)
Education, primary school, 10 years or less of education	162	62 (38%)
Income in thousand NOK[a]	149	339 [1.3, 1,145]
Injury-related Factors		
Cause of injury	162	
Traffic accident		31 (19%)
Fall		76 (47%)
Assault		36 (22%)
Sports injury and others		19 (12%)
Glasgow Coma scale (GCS)[a,b]	162	15 [13, 15]
GCS 13		7 (4%)
GCS 14		30 (19%)
GCS 15		125 (77%)
Radiological examination[b]		
Intracranial injury (CT-scan)	162	30 (19%)
Frontal intracranial injury	162	24 (15%)
Whiplash associated disorder	162	18 (11%)
PTA > 1 h	92	11 (12%)
Pre-injury factors from a national registry		
Diagnosed during last year before injury		
Psychiatric diagnosis	162	18 (11%)
Headache and other neurological disorders	162	4 (3%)
Traumatic brain injury	162	2 (1%)
Musculoskeletal disorder	162	37 (23%)
Pre-injury retrospective self-rating factors		
Anxiety	162	21 (13%)
Depression	162	35 (22%)
Headache	162	24 (15%)
Neurological disorders	160	7 (4%)
Traumatic brain injury	161	31 (19 %)
Other disease	162	48 (30%)
Psychological distress six to eight weeks post-injury		
HAD anxiety score eight or higher	162	44 (27%)
HAD anxiety score 11 or higher	162	20 (12%)
HAD depression score eight or higher	162	24 (15%)
HAD depression score 11 or higher	162	11 (7%)

[a] *Median [min, max].*
[b] *Measured at time of injury.*

DISCUSSION

The aim of this study was to identify which clinical characteristics predict psychological distress at 2 months after a MTBI. Several variables predicted psychological distress at 2 months post-MTBI. However, in our final model, two variables contributed uniquely to psychological distress at 2 months, namely pre-injury retrospective self-reported anxiety and WAD.

Among pre-injury variables, lower education, psychiatric diagnosis the last year before injury and pre-injury self-reported anxiety were associated with the development of psychological distress after a MTBI. Singh et al. found an association between pre-injury and post-injury depression among more severe TBI-cases where 55% of the patients had a moderate or severe TBI

TABLE 2 | Linear regression analyses of predictors in relation to psychological distress 2 months after mild traumatic brain injury.

		Step 1			Step 2			Step 3		
Fully adjusted models, *N* = 147	**N**	**B**	**CI (95%)**	***P*-value**	**B**	**CI (95%)**	***P*-value**	**B**	**CI (95%)**	***P*-value**
Pre-injury factors										
Age	162	0.11	(−0.0, 0.2)	0.069	0.08	(−0.0, 0.2)	0.194	0.09	(−0.0, 0.2)	0.104
Sex	162	−0.61	(−3.0, 1.8)	0.620	−0.75	(−3.1, 1.6)	0.522	−0.23	(−2.3, 1.9)	0.831
Education	162	**3.67**	**(1.0, 6.4)**	**0.008**	**3.40**	**(0.8, 6.0)**	**0.011**	2.17	(−0.2, 4.6)	0.074
Income	149	−2.73	(−5.5, 0.0)	0.053	−2.60	(−5.3, 0.7)	0.056	−2.11	(−4.5, 0.3)	0.086
Injury-related factor										
Whiplash associated disorder	162	**3.77**	**(0.7, 7.5)**	**0.046**	3.35	(−0.3, 7.0)	0.068	**3.55**	**(0.3, 6.8)**	**0.035**
Frontal intracranial injury	162	−2.23	(−5.5, 1.1)	0.183	−1.07	(−4.3, 2.2)	0.516	−1.22	(−4.1, 1.7)	0.405
Pre-injury factors from a national registry										
Sick-listed other diagnosis	162				1.80	(−1.1, 4.7)	0.223	1.84	(−0.8, 4.4)	0.164
Sick-listed musculoskeletal	162				1.69	(−1.2, 4.5)	0.242	0.76	(−1.8, 3.4)	0.564
Sick-listed psychiatric diagnosis	162				**5.29**	**(1.7, 8.9)**	**0.004**	2.04	(−1.6, 5.6)	0.263
Pre-injury retrospective self-rating factors										
Anxiety	162							**7.61**	**(3.6, 11.6)**	**<0.001**
Depression	162							1.88	(−1.6, 5.4)	0.289
Headache	162							1.12	(−1.8, 4.0)	0.446
Other disease	162							1.52	(−0.8, 3.8)	0.198

Significance: $p < 0.05$ marked bold.

(40). To our knowledge, earlier studies have not investigated predictors for psychological distress among adults after a MTBI. Among children and adolescents pre-injury anxiety, acute memory problems are associated with psychological distress at 4 weeks after a MTBI, and acute mental status predict psychological distress at 12 weeks (31). Among adults pre-injury depression is earlier demonstrated to be associated with post-injury anxiety and PCS (41). McCauley et al. found no association between sex, age, or education and the development of anxiety and PCS after a MTBI, equivalent to the lack of relationship between sex and psychological distress after a MTBI in our study (41). However, our findings are comparable with predictors for PCS after MTBI, where education and pre-injury mental health problems were among predictors for unfavorable outcome after a MTBI (4, 28, 42). Since psychological distress is a part of PCS, our findings support that PCS are associated with pre-injury mental health, emphasizing that PCS can best be explained by a biopsychosocial model and not as a result of neurobiological factors alone (4, 6, 14, 17, 20). In our study there were no association between pre-injury retrospective self-report of depression and the development of psychological distress post-injury, indicating the important role of pre-injury anxiety to explain the development of psychological distress after MTBI.

Several authors have found a non-linear association between age and outcome after a MTBI with a favorable outcome for patients aged 65 and older (28). In the main multicenter study the focus was to improve return to work. We therefore recruited only patients at the age between 16 and 55 years, which can explain the lack of association between age and outcome (32).

Among injury-related variables only WAD was associated with the development of psychological distress. In earlier literature it is described more pronounced psychological disorders among patients with chronic WAD (43). Further on, elements of anxiety like fear and catastrophizing are associated with the development of chronic WAD (44, 45). Finally, it is earlier demonstrated an association between elevated psychological distress after a motor vehicle crash and the development of MTBI and WAD (46). These findings may indicate an association between psychological distress and the development of both PCS and WAD after an injury. However, our finding is in accordance with earlier literature demonstrating an association between extracranial injuries and outcome after MTBI, indicating WAD as an indicator of the severity of the injury (42). In a biopsychosocial model the association between WAD and MTBI may then be a result of both psychological factors and the severity of the injury.

In this cohort there were no association between development of psychological distress at 2 months and other injury-related measures like severity at Glasgow Coma Scale, PTA or intracranial injury in any of the steps in the adjusted models. The impact of injury-related factor on PCS is debated, so far there is no consensus about the predicting value of MRI and the development of PCS (47). However, our findings are partly supported by studies that have found no association between the outcome after a MTBI and CT-abnormalities (28). In another study comparing a clinical model with adding a more advanced MRI brain morphometric characteristics to the model, the MRI-based measures had no additive value to predict outcome after MTBI (48).

It is noteworthy that several variables contributed to psychological distress at 2 months post-MTBI, including lower education, pre-injury psychiatric diagnosis, retrospective self-reported anxiety and WAD. However, only self-reported anxiety and WAD made a unique significant impact in our final model that explained 40% of the variance in psychological distress.

Because our sample size was relatively small, care must be taken when interpreting the findings.

STRENGTHS AND LIMITATIONS

The patients are recruited among the most severe MTBI-cases since they were hospitalized. A strength of this study was the use of clinical data about pre-injury diagnosis for sick-leave to avoid recall bias (49). However, short-term sick leave <16 days is missing, and we most likely have lost information about student sick-listed for <1 year, since students and unemployed must be on sick-leave for 1 year to receive any benefits from the NAV. In our study population 23 % were students.

However, a major limitation with our finding was that the strongest predictor for the development of psychological distress after a MTBI, was retrospective self-reported anxiety assessed in the self-report questionnaire 6–8 weeks post-injury, therefore these retrospective self-report predictors were added in step 3 in the model. According to earlier published studies self-reports may be more biased and less sensitive than more objective clinical characteristics (48). Patients reporting psychological distress after an injury, may be more likely to report earlier psychological problems at follow-up. In step 1 and 2 we avoided recall bias by using pre-injury data about sick leave from a national registry together with injury-related factors, where a pre-injury psychiatric diagnosis, education, and WAD predict the outcome. However, a major strength of this study was that both a pre-injury psychiatric diagnosis from the national sick-leave registry in step 2 and self-report anxiety in step 3 were associated with the development of psychological distress after a MTBI. To reduce the potential for selection bias, the guidelines from The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement was followed (50). By obtaining data from national registries, we improved the quality of the study and reduced the probability for data-collector bias.

However, we cannot exclude selection bias due to exclusion of patients out of work last 6 months before injury, and that potential participants did not attended the planned follow-up. According to an earlier publication from this cohort, the patients who did not attend the planned follow-up most likely had a favorable outcome and fewer needs for rehabilitation support (39). Many of the patients that were excluded from the study had a severe substance abuse, and was vulnerable to develop psychological distress after a MTBI (51). Our results cannot be transferred to this group of patients.

Another limitation is the assessment of clinical data in the medical records from the emergency hospital stay, where relevant information was missing such as the intensity of acute pain. CT scan was performed by 94% of the patients, which indicates that our results regarding intracranial findings are valid.

Acute emotional distress, coping style, and resilience are found to be associated with the outcome after a MTBI (28, 41). We have no information about coping style or resilience in our study, these factors may be important in predicting development of psychological distress after a MTBI. Further research should focus on determining which pre-injury factors including personal factors and coping style that have an association with the development of psychological distress after a MTBI, and implement these factors in future intervention studies. Our study may have some implications for rehabilitation after a MTBI. Clinically, a self-report questionnaire is easily administrated to screen for demographic data and psychological distress post-MTBI. Early detection of vulnerable patients with a thoroughly clinical interview about pre-injury mental health and offering them treatment may improve the outcome after a MTBI.

CONCLUSION

Patients with low education, earlier psychiatric diagnosis, self-reported earlier anxiety and WAD were more likely to develop a psychological distress after a MTBI. These findings should be taken into consideration when treating patients with MTBI.

DATA AVAILABILITY

All datasets generated for this study are included in the manuscript and/or the supplementary files.

ETHICS STATEMENT

This study was carried out in accordance with the recommendations of The Norwegian Social Science Data Services, identifier NSD 20425 and the National Committees for Research Ethics in Norway. All subjects gave written informed consent in accordance with the Declaration of Helsinki.

AUTHOR CONTRIBUTIONS

EV and JS contributed the conception and design of the study. EV organized the database. EV and JA performed the statistical analyses and contributed to the section of statistics and results. EV wrote the first draft of the manuscript. EV, KF, HN, and JS contributed to manuscript revision, read and approved the submitted version.

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Activity Level and Type During Post-acute Stages of Concussion May Play an Important Role in Improving Symptoms Among an Active Duty Military Population

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Background: Previous research demonstrates that early rest and gradual increases in activity after concussion can improve symptoms; however, little is known about the intensity and type of activity during post-acute time periods—specifically months post-injury—that may promote optimal recovery in an active duty service member (SM) population.

Objective: The objectives of this study were to investigate how activity level and type at the post-acute stages of concussion (at 1 and 3 month[s] post-injury) impact subsequent symptoms among SMs, and how this relationship might differ by the level of symptoms at the time of injury.

Methods: Participants included 39 SMs ages 19–44 years from 3 military installations who were enrolled within 72 h after sustaining a concussion. Linear regression was used to evaluate whether the association between activity level at 1 or 3 month(s) post-injury (as measured by a multi-domain Activity Questionnaire) and subsequent symptoms at 3 and/or 6 months (as measured by the Neurobehavioral Symptom Inventory) varied by the level of symptoms at acute stages of concussion. Partial correlation was used to evaluate relationships that did not differ by acute symptom level. Symptoms at the time of activity assessment (1 or 3 month[s]) were accounted for in all models, as well as activity level at acute stages of concussion.

Results: Greater physical and vestibular/balance activity at 1 month were significantly correlated with lower symptoms at 3 months, but not at 6 months post-injury. There were no significant associations found between activity (total or by type) at 3 months and symptoms at 6 months. The association between activity level at either 1 or 3 months and subsequent symptoms at 3 and/or 6 months did not differ by the level of acute symptoms.

Conclusion: The intensity and type of activities in which SMs engage at post-acute stages of concussion may impact symptom recovery. Although low levels of activity have been previously shown to be beneficial during the acute stage of injury, higher levels of activity may provide benefit at later stages. These findings provide support for the importance of monitoring and managing activity level beyond the acute stage of concussion.

Keywords: service members, military, concussion, mild traumatic brain injury, post-acute activity, symptoms

INTRODUCTION

Concussion, or mild traumatic brain injury, significantly impacts warfighter readiness for events such as deployment and combat. With over 380,000 diagnosed concussions among US service members (SMs) since 2000 (1), rehabilitation approaches to expedite symptom recovery after concussion are highly relevant to health and readiness in this population. A growing body of evidence has shown the importance of monitoring and regulating activity level in the first hours to days following a concussion (2–8); however, little attention has been given to the contribution of post-acute (i.e., ≥1 month[s]) activity level on symptom recovery in the weeks and months that follow. Furthermore, most of these studies have focused on sports-related concussion (2–5, 7, 8), while only a limited number provide information about active duty military personnel (9), who may have a greater risk for concussion, and among whom the consequences of persistent impairments impact military force readiness. Research has also been sparse in the evaluation of symptom recovery against activity by specific categories (e.g., cognitive, physical, vestibular/balance). This type of information could help to improve clinical guidance for primary care managers to educate and provide guidance to their patients on the most appropriate type and intensity of activities at different stages of recovery to optimize return to pre-injury activities and symptom resolution.

Activity participation, whether too little or too much, during the acute recovery period from concussion is known to impact recovery rates. Unrestricted physical activity during acute stages of concussion has been shown to negatively impact recovery (2, 4–6), and increased cognitive activity shortly following injury to lengthen recovery time (3). In contrast, studies have also demonstrated that too much rest may not provide clear benefits and may even negatively influence recovery (6, 10). In a systematic review of sports-related concussion studies, an initial period of moderate physical and cognitive rest has been shown to provide benefit during the acute post-injury phase (11). Prolonged physical and cognitive rest beyond the currently recognized recommendation by expert consensus of 2 days has also been demonstrated to be associated with higher levels of total symptoms over 10 days after injury (6, 12). Considering activity levels beyond the acute stage of injury, findings also support the importance of engagement in some activity, but an understanding of the appropriate activity level and activity type remains largely unknown. One study evaluating a cohort of student-athletes suggested that moderate physical and cognitive activity (vs. minimal activity) within 30 days of injury may be necessary for symptom recovery and better neurocognitive performance (5). In a study of concussed athletes and non-athletes, ages 16–53, with symptoms lasting at least 6 weeks post-injury but stable for 2–3 weeks, a treadmill exercise for 5–6 days per week was found to significantly decrease the level and number of symptoms after 6 weeks from measures prior to the treadmill exercise (7). Overall, these studies suggest that unrestricted activity at the acute stage of concussion may exacerbate symptoms or delay recovery; however, some level of activity in both acute and post-acute stages of concussion may be beneficial for recovery.

Regardless of outcome, existing studies have been limited to cohorts of pediatric and adult athletes (2–5, 7, 8), and findings may not be generalizable to a military population whose occupational environment differs significantly, potentially impacting the optimal types and intensities of activity during recovery. For athletes, the Consensus Statement on Concussion in Sport has recommended immediate physical and cognitive rest after a concussion, followed by a stepwise return-to-play after clearance by treating healthcare providers (13). A similar set of guidelines, the Progressive Return to Activity (PRA) Clinical Recommendation (CR), which emphasize gradual return to activity after rest at the acute stage of concussion, was developed specifically for SMs by military and civilian subject-matter experts and published by the Defense and Veterans Brain Injury Center (DVBIC) (1). Recent research among SMs suggests that activity participation within the acute stage of injury impacts symptom resolution over time (9); however, it is unknown how post-acute levels of activities, particularly the type of activities conducted to include military-specific tasks (e.g., combat training), may influence continued improvement in symptomatology.

Optimal patterns of activity during the course of concussion recovery may depend on the severity of symptoms experienced in the acute stage. In a recent study by our group, greater activity level at acute stages of concussion was associated with higher levels of symptoms over time, but only among those with high levels of acute symptoms (9). In the current study, we build upon our previous findings by evaluating the contribution of activities at later stages of concussion rehabilitation post-concussion. The primary objectives of this study were: 1) to evaluate the relationship between activity level (in total and by categories: cognitive, lifestyle, physical, vestibular/balance, and military-specific) at post-acute stages of concussion (specifically,

Abbreviations: SM, Service Members; DVBIC, Defense and Veterans Brain Injury Center; PRA, Progressive Return to Activity; CR, Clinical Recommendation.

at 1 and 3 month[s] post-injury) and subsequent symptom level among an active duty military population; and 2) to determine whether this association differs by acute symptom severity.

MATERIALS AND METHODS

Data for this study were drawn from the broader DVBIC (Defense and Veterans Brain Injury Center, RRID:SCR_004505) PRA CR Study, which investigated the impact of implementing the DVBIC PRA CR focused on gradual return to unrestricted activity post-concussion among SMs (1, 14). The parent study has been previously described in detail (15). Data from the current study included only concussed SM participants who received "usual treatment" from providers who had not yet received focused training on the PRA CR. "Usual treatment" refers to any treatment deemed appropriate by the treating clinicians; it was not experimentally controlled. This study was carried out in accordance with the recommendations of the Naval Medical Center San Diego Institutional Review Board, with concurrence from Womack Army Medical Center, and Human Research Protections Program administrative review by the Defense Health Agency. These committees approved the protocol in compliance with all applicable federal regulations governing the protection of human subjects. All subjects gave written informed consent in accordance with the Declaration of Helsinki.

Study Participants

Participants who received "usual treatment" included 64 SMs, 18–48 years of age, recruited from clinics and operational medical units at three U.S. military installations (Army [southeast U.S.], Navy [southwest U.S.], and Marine Corps [southwest U.S.]). Eligible participants had sustained a concussion within the previous 72 h of enrollment into the study. Those who suffered other concussions within 12 months of the concussion in question were excluded. Electronic medical records were reviewed to confirm concussion diagnoses, which must have met the Veterans Administration/Department of Defense definition for concussion (16). After enrollment, participants completed a face-to-face baseline assessment (i.e., within 72 h of injury), and were followed-up at 1 week, 1 month, 3 months, and 6 months post-injury via a telephone or in-person interview.

Of the 64 participants from the parent study, there were 39 with complete data to assess activity level at 1 month and symptom level at 3 months; 38 had complete data to assess activity level at 1 month and symptom level at 6 months; and 33 had complete data to assess activity level at 3 months and symptom level at 6 months. The demographic and military characteristics of the 39 participants evaluated for activity level at 1 month and symptom level at 3 months (the greatest number of participants in any of the proposed study analyses) were comparable to those of the "usual treatment" group from the parent study consisting of 64 participants.

Measures and Procedures

Assessment of Activities

This study utilized a 60-item Activity Questionnaire (9, 15), which included activities that are recommended to be avoided or encouraged at various stages of recovery according to the DVBIC PRA CR education materials (17). For each activity item, participants were asked "Since your concussion, did you [activity item stated]" during baseline and at 1 week, or, for other follow-up interviews, "In the last 2 weeks, did you [activity item stated]." Although psychometric properties are not yet available, this questionnaire was streamlined for analysis by removal of 11 items due to low variance, low correlation with other activity items, and inconsistent interpretation by SMs as demonstrated by questions asked of the interviewers during follow-up. An interdisciplinary group of investigators representing Epidemiology, Neuropsychology, Primary Care Sports Medicine and Physical Therapy (RR, JB, KS, KM, AC) reviewed the remaining 49 items and determined 6 individual categories: (1) cognitive (12 items); (2) lifestyle (10 items); (3) physical (20 items); (4) vestibular/balance (17 items); and (5) military-specific (6 items) (9). Eighteen items were included in multiple categories (e.g., walk briskly was categorized as both a physical and vestibular/balance activity). To ensure that scores represented the same direction, seven items (e.g., sleep 6–8 h a night) were reverse coded. Three items did not fit into any category ("wear dark glasses or sunglasses" and "do familiar tasks [e.g., vehicle maintenance check]," "rest all day"), but were included in the total activity score. Each item was scored 0–4 with responses such as "never" (0), "every few days" (1), "some days" (2), "most days" (3), and "every day" (4).

Assessment of Neurobehavioral Symptoms

The Neurobehavioral Symptom Inventory (NSI) was used to assess concussion symptoms (18). Participants were asked to evaluate 22 symptom items since their concussion (during baseline and at 1 week), or, in the last 2 weeks, during the 1-, 3-, and 6-month follow-up interviews. Based on previous exploratory analyses, these items were categorized into 4 factors: (1) cognitive (4 items); (2) vestibular (3 items); (3) somatosensory (7 items); and (4) affective (6 items) (19, 20). Two items regarding hearing difficulty and changes in appetite were only included in the total symptom score as they did not fit into any of the 4 factors. Responses ranged from 0 to 4 and included "none" (0), "mild" (1), "moderate" (2), "severe" (3), and "very severe" (4). Among SMs, NSI has been shown to have high internal consistency (total alpha = 0.95; subscale alpha = 0.88–0.92) (21). Further, external validity was exemplified with moderate correlation ($r = 0.41$) showing NSI differentiating veterans with TBI status from those without (21).

Calculation of Activity and Symptom Scores

To maximize the use of available data, a prorated summary score was calculated for activity and symptom level for participants with at least one missing item needed to calculate each variable (22). All non-missing values per variable were summed and multiplied by the total number of possible items. This, in turn, was divided by the actual number of items with non-missing values. For each category of activity or symptom, prorated scores were based on the items included within each category. A list of items within each category has been reported previously (9). In the current study, only one participant had 1 missing item for the calculation of activity level. Prorated scores were transformed

into z-scores for comparability across categories. Each mean and standard deviation were based on the type of activity or symptom level in question. For example, activity level was assessed as a total score and by categories such as cognitive activity. To calculate the z-score for total score, this took into consideration the mean and standard deviation of all of the activity item responses from all participants. To calculate the z-score for cognitive activity, this took into consideration the mean and standard deviation of activity items that were categorized as cognitive activity, also from all participants. All of these calculations were done at each time point.

Assessment of Covariates

Demographic characteristics (i.e., age, sex, and education) and military information (i.e., branch affiliation, current rank, and number of deployments) were assessed at baseline.

Statistical Analyses

To ascertain the contribution of demographic characteristics and military history on activity level during post-acute stages of symptom recovery, Spearman correlation was used for age, a continuous variable, and one-way analyses of variance for categorical variables. The modifying impact of symptom level at the acute stage of concussion was also analyzed and presented as a dichotomized variable (high vs. low) based on median cut-offs (total and by categories). Although evaluating this variable continuously would provide more statistical power, dichotomization was chosen to enhance clinical relevance. First-order interaction terms were created as a product of this variable with post-acute activity level. In these investigations, linear regression was utilized to assess the relationship between activity level at either 1 or 3 month(s) and subsequent symptoms (i.e., at 3 and 6 months, or at 6 months, respectively) among those with either high vs. low level of symptoms at the acute stage of injury (objective #2). Partial correlation (r_p) was used to evaluate relationships that did not differ by acute symptoms (objective #1). All models were adjusted for activity level within 72 h of injury and symptom level at the time of each activity variable being examined. To investigate assumptions for the utility of linear regression and Pearson correlation in our study, we used the following techniques: to identify non-linearities in the data, we used scatter plots and graphs of augmented component-plus-residual plots with LOWESS smoothing; to assess the assumption of normality, we evaluated graphs of standardized normal probability plots (P-P plots) to assess non-normality in the middle range of data, and quantiles of the residual against quantiles of a normal distribution (Q-Q plots) to assess non-normality at the tail-ends of data; to test the assumption of homoscedasticity, a plot of residuals vs. fitted (predicted) values were examined; and to evaluate evidence of auto-correlation, we utilized the Durbin-Watson statistic. All assessments were done between each activity level score (total and by categories) against each symptom level score (total and by categories). To address the presence of outliers that may significantly affect results, both the activity and symptom level data (z-scores) were truncated to +/−3 standard deviation from the mean.

Main effects and interaction were considered significant at a $p < 0.05$. All statistical analyses were completed using Stata statistical software (Stata, RRID:SCR_012763), release 15 (StataCorp, 2017, College Station, TX).

RESULTS

There was an overall decrease in symptom progression (total and by categories) over time (see **Figures 1A**,**B**). Among the 39 participants evaluated for activity level at 1 month and symptom level at 3 months, a significant decrease in total, cognitive and vestibular symptoms were found from 1 month to 3 months post-injury. Although the reduction continues to 6 months, the progression was not statistically significant. See **Figure 1A**. Among the 33 participants evaluated for activity level at 3 months and symptom level at 6 months, the decrease in symptom progression (total and by categories) was not statistically significant (see **Figure 1B**).

Table 1 illustrates the characteristics of the study sample. Participants had a mean age of 26 years (range = 19–41) and were mostly men (89.7%), married (46.0%), and had 12–15 years of education (82.0%). Most served in the US Army (69.2%), were non-commissioned officers (E4 and E5, 51.3%) and were deployed at least once (56.4%). There were no significant differences in total activity or symptom score at 3 months post-injury by any assessed demographic or military characteristic. Study participants had a median symptom score of 20 (range=2-61) at the acute stage of concussion.

Activity Level at 1 Month and Subsequent Symptoms at 3 and 6 Months

The association between activity level at 1 month (total or by categories) and subsequent symptoms at 3 and 6 months did not differ by the level of symptoms within 72 h of injury. **Table 2** provides the correlations between activity level at 1 month and symptom level at 3 and 6 months post-injury. Greater total activity at 1 month post-injury was significantly correlated with lower cognitive ($r_p = -0.41$, $p = 0.012$) and somatosensory ($r_p = -0.36$, $p = 0.028$) symptoms at 3 months. Subscale analyses suggested that total score correlations were driven primarily by physical and vestibular/balance activities. Greater physical activity at 1 month was significantly correlated with lower cognitive ($r_{p=}-0.44$, $p = 0.006$) and vestibular ($r_{p=}-0.37$, $p = 0.025$) symptoms at 3 months post-injury. Greater vestibular/balance activity at 1 month was also significantly correlated with lower total ($r_{p=}-0.39$, $p = 0.017$) and cognitive ($r_{p=}-0.55$, $p < 0.001$) symptoms at 3 months post-injury. No significant correlations were found between total, cognitive, lifestyle and military-specific activities at 1 month and symptoms (total or by category) at either 3 or 6 months.

Activity Level at 3 Months and Subsequent Symptoms at 6 Months

The relationships between activity level at 3 months and subsequent symptoms at 6 months post-injury did not vary by the

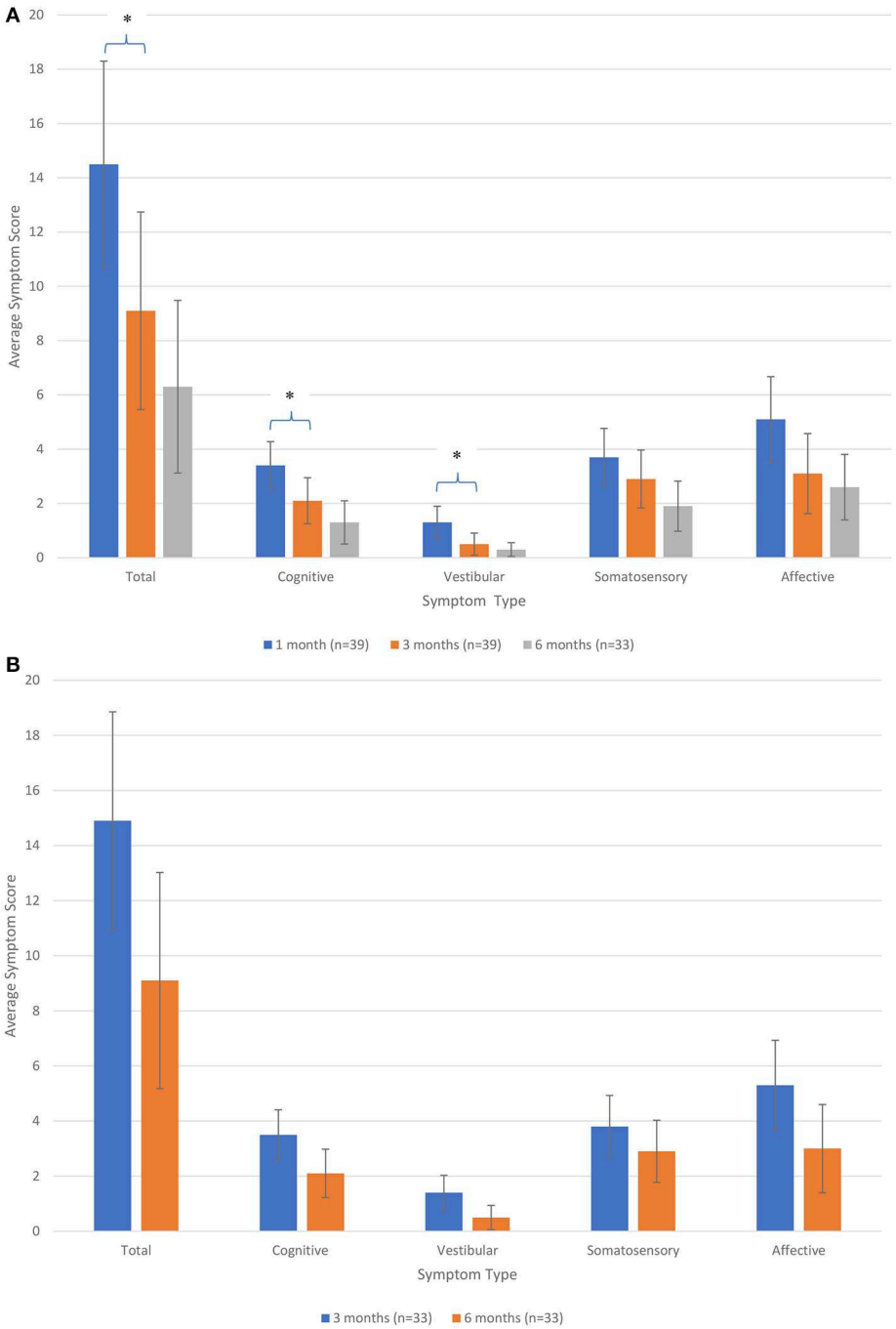

FIGURE 1 | (A) Average symptom level score over time (in total and by categories) for participants assessed for activity level at 1 month and symptom level at 3 months post-injury. *Significant at $p < 0.05$. **(B)** Average symptom level score over time (in total and by categories) for participants assessed for activity level at 3 months and symptom level at 6 months post-injury.

level of symptoms within 72 h of injury. Further, no significant relationships were found between activity level at 3 months (total or by categories) and symptoms at 6 months post-injury (data not shown).

DISCUSSION

This study provided preliminary evidence that activity level at post-acute stages of concussion may play an important role in

TABLE 1 | Demographic and military characteristics of service members and their relation to activity and symptom score at 3 months post-injury, overall ($n = 39$).

Variable	Value	Total activity score		Total symptom score	
		Mean (SD)	*p*	Mean (SD)	*p*
Age in years, mean (SD)	26 (6.2) (Range = 19–41)	NA	0.938	NA	0.393
Sex, *n* (%)			0.804		0.283
Men	35 (89.7)	107.3 (19.6)		15.2 (12.5)	
Women	4 (10.3)	109.8 (8.5)		8.3 (5.3)	
Education, *n* (%)			0.754		0.624
High school diploma or GED	13 (33.3)	103.6 (14.1)		12.3 (9.0)	
Some college (1–3 years)	19 (48.7)	111.2 (22.5)		16.1 (13.5)	
College graduate (4+ years)	4 (10.3)	103.0 (18.8)		19.5 (16.3)	
Some graduate school	1 (2.6)	118.0 (NA)		8.0 (NA)	
Graduate/professional program	2 (5.1)	102.0 (2.8)		6.0 (7.1)	
Marital status, *n* (%)[a]			0.821		0.496
Never married	15 (40.5)	104.3 (19.2)		17.4 (14.4)	
Married	17 (46.0)	107.4 (20.3)		13.9 (10.8)	
Divorced	4 (10.8)	114.5 (15.2)		10.5 (11.1)	
Separated	1 (2.7)	104.0 (NA)		1.0 (NA)	
Branch, *n* (%)			0.102		0.351
US Navy	3 (7.7)	96.3 (13.3)		5.7 (8.1)	
US Marine Corp	9 (23.1)	118.3 (13.7)		17.4 (11.6)	
US Army	27 (69.2)	105.2 (19.4)		14.4 (12.4)	
Rank, *n* (%)			0.870		0.883
Junior enlisted (E1-E3)	8 (20.5)	108.8 (15.9)		15.8 (10.0)	
Non-commissioned officer (E4-E5)	20 (51.3)	103.4 (19.7)		13.7 (13.0)	
Non-commissioned officer staff (E6-E9)	8 (20.5)	102.6 (22.9)		16.5 (14.6)	
Officers (O1-O10)	3 (7.7)	111.3 (9.9)		10.7 (2.5)	
Number of deployments, *n* (%)			0.895		0.211
0	17 (43.6)	107.1 (20.1)		17.2 (9.8)	
1+	22 (56.4)	108.9 (18.0)		12.3 (13.4)	
Acute symptom score, median (IQR)	20 (15–37) (Range = 2–61)	NA	NA	NA	NA

IQR = Interquartile Range. [a]*n = 37 for this variable.*

improving symptoms among SMs; specifically, SMs with higher activity levels at 1-month post-injury reported lower level of post-concussion symptoms 2 months later. These findings held even after controlling for severity of symptoms at 1 month and activity level shortly after injury, suggesting that the effects of post-acute activity levels on later symptom outcomes were not simply due to pre-existing differences in trajectory of recovery. The results of this study suggest that although low levels of activity have been previously shown to be beneficial during the acute stages of injury among SMs (9), higher levels of activity may provide benefit at later stages in this population. The effects of activity level on later symptoms appeared to level off after approximately 3 months, possibly due to a greater proportion of SMs having achieved successful symptom recovery around this time. As we reported previously in data drawn from the parent study (9), only 26.8% of SMs demonstrated clinically significant levels of post-concussive symptoms by 3 months post-injury.

Of interest, the type of activity was important to symptom resolution; specifically, higher rates of physical and vestibular/balance activities at 1 month were associated with reduced total, cognitive, and vestibular symptoms at 3 months. In contrast, cognitive, lifestyle and military-specific activities at 1 month were not associated with symptoms at 3 months. These findings were consistent with our previous study evaluating the impact of early post-injury activity, in which both physical and vestibular/balance activities were also shown to drive the relationship between activity level and symptoms over time (9). The current study did not find the association between activities at post-acute stages of concussion and subsequent symptoms to vary by the level of acute symptoms; however, other factors such as lifetime history of concussion could modify this relationship, as symptoms from previous injury may lower cerebral reserve that would otherwise be used for symptom recovery related to the current concussion. Future studies that evaluate the contribution of lifetime concussion history on symptom recovery among concussed SMs are warranted. The findings of this study demonstrate the importance of primary care managers to monitor specific types of activity for symptom recovery at the post-acute stages of concussion, as focusing on activity in total may overlook the specific

TABLE 2 | Partial correlation between activity level at 1 month (total and by categories) and symptom level at 3 and 6 months (total and by categories), adjusted for activities at acute stage of concussion and symptoms at 1 month post-injury.

Symptom level months post-injury	Activity level at 1 month post-injury, correlation coefficient (*p*-value)					
	Total	**Cognitive**	**Lifestyle**	**Physical**	**Vestibular/balance**	**Military- specific**
3 MONTHS (*n* = 39)						
Total score	−0.30 (0.070)	0.002 (0.992)	−0.06 (0.730)	−0.30 (0.068)	**−0.39 (0.017)***	−0.07 (0.661)
Cognitive	**−0.41 (0.012)***	−0.08 (0.622)	0.03 (0.868)	**−0.44 (0.006)***	**−0.55 (<0.001)***	−0.14 (0.423)
Vestibular	−0.17 (0.310)	0.13 (0.451)	0.18 (0.288)	**−0.36 (0.026)***	−0.31 (0.066)	0.09 (0.606)
Somatosensory	**−0.36 (0.028)***	−0.07 (0.683)	−0.17 (0.327)	−0.30 (0.076)	−0.30 (0.067)	−0.21 (0.203)
Affective	−0.17 (0.312)	0.03 (0.852)	0.03 (0.880)	−0.19 (0.270)	−0.30 (0.067)	−0.03 (0.847)
6 Months (*n* = 38)						
Total score	−0.11 (0.506)	0.06 (0.731)	−0.06 (0.727)	−0.19 (0.275)	−0.16 (0.343)	0.09 (0.617)
Cognitive	−0.21 (0.227)	0.10 (0.558)	0.08 (0.663)	−0.31 (0.064)	−0.30 (0.080)	−0.02 (0.893)
Vestibular	−0.15 (0.370)	0.10 (0.567)	−0.07 (0.695)	−0.28 (0.101)	−0.17 (0.319)	0.05 (0.761)
Somatosensory	−0.07 (0.667)	0.11 (0.514)	−0.04 (0.822)	−0.14 (0.411)	−0.13 (0.460)	0.08 (0.661)
Affective	−0.10 (0.576)	−0.10 (0.550)	−0.11 (0.535)	−0.12 (0.500)	−0.10 (0.560)	0.09 (0.585)

**Significant p-value at a level < 0.05 (bolded).*

impact of physical and vestibular/balance activities on symptom resolution. This could, in turn, lead to poor recovery. The preliminary findings from this paper also support exploration of rehabilitation programming/clinical care that includes physical and vestibular/balance activities, notably at chronic stages of concussion.

A limited number of studies have evaluated the contribution of activities at the post-acute stages of concussion on improving symptoms (7), and none among an active duty military population. Aside from our recent work examining acute activities (9), to our knowledge, no previous studies have considered multiple activity categories, including military-specific items, at a granular level as investigated in the current analyses. The PRA CR developed by DVBIC, from which the activities assessed in this study are obtained, provides an algorithm for activity progression, which can be standardized across military populations as a part of acute and post-acute concussion management (17). The use of this CR may improve outcomes by providing guidance to primary care managers, particularly in reengaging in physical and/or vestibular/balance activities as supported by our preliminary findings, to optimize the speed of recovery. This may not only guide the prescription of specific patterns of activity, but also, the determination of whether patients should receive medical waivers from engaging in usual duties. Future studies will include the evaluation of activity progression on improving symptom levels, comparing those who receive usual care to those who receive care according to the guidelines published in the DVBIC PRA CR.

The strengths of this study included the use of longitudinal activity and symptom data that extend 6 months post-injury within a population of military SMs. This study also evaluated demographic and military service information to assess for potential confounding factors. Additionally, data on activity items and categorization specific to a military population were collected to best address the objectives of this study. There were also limitations to consider. Although activity level was evaluated against symptom level at a later time point, controlling for symptoms at the time of activity assessment to support directionality of the association, we cannot infer causality in the significant relationships found. In addition, the Activities Questionnaire used in this study was developed *de novo* in order to be consistent with the recommendations found in the PRA CR education materials. It should be noted, however, that careful item screening was used to narrow the final list of items used in analyses. Further, this questionnaire not only included military-specific activities, but it also allowed for activity categorization not queried in previously studied and/or published surveys, most of which were aimed to evaluate a different population of individuals with moderate to severe traumatic brain injury. Along with activity level, the level of symptoms was self-reported which may be subject to recall bias. Although self-reported instruments are time- and cost-effective, future studies utilizing more objective assessment of activity (e.g., wearable devices, clinically-monitored activity, and symptom level) might help to validate the results of our findings. Finally, sample size was limited and, in part due to participant attrition over time, conservative corrections for multiple comparisons were not feasible in this study. However, even with a limited sample size, significant results were found. Nonetheless, the findings in this study were preliminary and analyses were exploratory. Future longitudinal studies with a larger sample size may be necessary not only to confirm the findings in this study, but also, to potentially detect significant effects that may have been missed in this study due to limited sample size. Additionally, with a larger sample, the trajectories of the residuals in the relationship between activity and symptom level might be better defined and might perhaps suggest the use of a more complex analytic approach.

Our findings provide preliminary evidence that activity level during the post-acute stages of concussion remains an important factor in improving symptoms, thus, advocating for continued monitoring and patient management even up to 1 month post-injury. Taken together with our recent finding that greater activity levels immediately following injury (i.e., within 72 h) result in poorer symptom status among SMs (9), these findings support recommendations for a gradual increase in activity (1, 10, 13, 14, 23–26)—rather than extended rest—to promote symptom resolution among SMs with recent concussion. Also consistent with our previous work (9), the results highlight the importance of physical and vestibular/balance activities in managing symptoms over time. Further research is necessary to evaluate the mechanisms of these associations and potential differences in the impact of various types of activities on symptom resolution. Future studies that evaluate how changes in activity level over time influence symptom recovery will also be critical to the continued development of clinical protocols for improving health outcomes of military personnel who have been diagnosed with concussion. Cumulative findings may inform how primary care managers and rehabilitation providers educate and guide their patients regarding progressive return to activity to optimize outcomes and military readiness.

DATA AVAILABILITY

The datasets analyzed for this study are not publicly available but will be submitted to FITBIR beginning in 2019. Requests to access the datasets should be directed to Dr. Rosemay Remigio-Baker (rosemay.a.remigio-baker.ctr@mail.mil).

ETHICS STATEMENT

This study was carried out in accordance with the recommendations of the Naval Medical Center San Diego Institutional Review Board, with concurrence from Womack Army Medical Center, and Human Research Protections Program administrative review by the Defense Health Agency. These committees approved the protocol in compliance with all applicable federal regulations governing the protection of human subjects. All subjects gave written informed consent in accordance with the Declaration of Helsinki.

AUTHOR CONTRIBUTIONS

RR-B, ME, JB, EG, and WC were involved in the development of concept and analytical approach. All analyses were conducted by RR-B. Screening and categorization of activity items used in the study were done by EG, RR-B, JB, KS, KM, and AC. KM and AC served as subject-matter experts regarding activity involvement during concussion recovery among service members. KS served as a topic expert on TBI and education, particularly as it pertains to the Progressive Return to Activity Clinical Recommendation. AC and TA were involved in data collection and provided information regarding study procedures and interaction with participants to interpret data. EG and FQ provided knowledge in the structure and content of the parent study that served as the source of data for this investigation. KS, PS, and LM provided insight into military physical and psychiatric environment. All authors contributed to the development and editing of the manuscript.

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The Stability of Retrospective Pre-injury Symptom Ratings Following Pediatric Concussion

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Objective: To determine the stability of children's retrospective ratings of pre-injury levels of symptoms over time following concussion.

Methods: Children and adolescents (n = 3,063) between the ages of 5–17 diagnosed with a concussion by their treating pediatric emergency department (PED) physician within 48 h of injury completed the Post-Concussion Symptom Inventory (PCSI) at the PED and at 1, 2, 4, 8, and 12-weeks post-injury. At each time point, participants retrospectively recalled their pre-injury levels of post-injury symptoms. The PCSI has three age-appropriate versions for children aged 5–7 (PCSI-SR5), 8–12 (PCSI-SR8), and 13–18 (PCSI-SR13). Total scale, subscales (physical, cognitive, emotional, and sleep), and individual items from the PCSI were analyzed for stability using Gini's mean difference (GMD).

Results: The mean GMD for total score was 0.31 (95% CI = 0.28, 0.34) for the PCSI-SR5, 0.19 (95% CI = 0.18, 0.20) for the PCSI-SR8, and 0.17 (95% CI = 0.16, 0.18) for the PCSI-SR13. Subscales ranged from mean GMD 0.18 (physical) to 0.31 (emotional) for the PCSI-SR8 and 0.16 (physical) to 0.31 (fatigue) for the PCSI-SR13. At the item-level, mean GMD ranged from 0.13 to 0.60 on the PCSI-SR5, 0.08 to 0.59 on the PCSI-SR8, and 0.11 to 0.41 on the PCSI-SR13.

Conclusions: Children and adolescents recall their retrospective pre-injury symptom ratings with good-to-perfect stability over the first 3-months following their concussion. Although some individual items underperformed, variability was reduced as items were combined at the subscale and full-scale level. There is limited benefit gained from collecting multiple pre-injury symptom queries.

Clinical Trial Registration: Clinicaltrials.gov through the US National Institute of Health/National Library of Medicine. (NCT01873287; http://clinicaltrials.gov/ct2/show/NCT01873287).

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INTRODUCTION

Concussions are a prevalent injury among children and adolescents throughout North America. In the US, concussions account for one in 220 PED visits, accumulating over 700,000 PED visits annually (1–3). Rates of reporting to the emergency department are even higher in Canada, where concussions are responsible for one in every 70 PED visits (4). Currently, an objective biomarker for concussion diagnosis and subsequent recovery is elusive. Instead, health care providers must rely upon a clinical examination in combination with symptom, balance, and cognitive assessments for concussion diagnosis and management (5, 6). This can be particularly difficult when evaluating children and adolescents, especially elementary-aged children, as current clinical assessments are developed for use with adults and are often not validated or developmentally appropriate for young patients (7).

Concussions can result in a number of somatic, emotional, cognitive, or sleep-related symptoms (8), with headache, imbalance/dizziness, and fatigue the most commonly reported post-concussion symptoms (8, 9). Most clinicians do not have access to a concussion symptom checklist completed by the child pre-injury to serve as a baseline level of normal functioning. One alternative approach is to rely on the injured child to retrospectively report pre-injury levels of their current post-injury symptoms. As concussion management requires serial assessment, and potentially oversight from multiple health care providers (10), it may require children to provide retrospective pre-injury ratings multiple times throughout recovery.

The Post-Concussion Symptom Inventory (PCSI) is a commonly used pediatric symptom checklist that is sensitive to concussion (8). The PCSI has three, developmentally appropriate versions for children aged 5–7, 8–12, and 13–18 years old. Several psychometric properties of the PCSI have been previously reported, including its factor structure, internal consistency, rater concordance, and convergent validity (8, 11, 12). The test-retest reliability of the PCSI has been assessed in healthy (i.e., non-injured) children and interclass correlation coefficients ranged from moderate-to-high ($0.65 < ICC < 0.89$) (8). However, the presence of concussion may alter the stability of this assessment, particularly when retrospectively recalling pre-injury ratings. Adults with concussion are suspected to engage in a "good-old-days" bias, whereby they idealize retrospective pre-injury levels compared to uninjured controls (13, 14). Recall bias in self-reported symptom outcomes is also highlighted in the scientific literature, with patient age and time since event named as important factors (15, 16). Therefore, it is critical to formally evaluate the stability of retrospective pre-injury ratings throughout pediatric concussion recovery, since pre-injury status can have important implications on clinical decision making following injury.

The primary purpose of this study is to determine the stability of retrospectively provided pre-injury ratings from children and adolescents over the first 3-months following a diagnosed concussion. Due to the relatively short follow-up period (12-weeks), we anticipate the effect of a "good-old-days" or recall bias will be relatively minimal and hypothesize that retrospective pre-injury ratings will be highly stable overall. However, we further hypothesize that individuals who report higher retrospective pre-injury symptom ratings will be less stable than individual who report few or no pre-injury symptoms.

MATERIALS AND METHODS

Participants

Data collection methods have been previously described in detail in other studies (17, 18). Briefly, children presenting to nine PEDs across Canada were eligible if they were between 5 and 17 years old, were diagnosed with a concussion using the definition reported by the 2012 Zurich consensus statement (19), presented to the PED within 48 h of injury, and were proficient in either English or French. Children were excluded if they had: (1) A Glasgow Coma Scale score $\leq$ 13; (2) Any abnormal findings on standard neuroimaging (if neuroimaging was clinically indicated); (3) Neurosurgical operative intervention, intubation, or intensive care stay, (4) Multisystem injuries with treatment requiring hospital stay; (5) Severe developmental delay resulting in communication difficulties; (6) Intoxication at time of PED presentation; (7) No clear primary mechanism of trauma (e.g., sports-related injury, motor vehicle accident, fall) for the current head injury; or (8) Previously enrolled in the same study. Research assistants were present at each PED from 12:00 to 22:00 h to screen for potential participants, assess eligibility, and explain study procedures to eligible patients. This study was carried out in accordance with the recommendations of the Research Ethics Board of each participating institution with written informed consent from all subjects. Written consent was obtained from all eligible and willing parents as well as children and adolescents capable of consenting on their own behalf in accordance with the Declaration of Helsinki. The protocol was approved by the Research Ethics Board of each participating institution.

Methods and Outcomes

Initial PED Visit

Once enrolled, a research assistant collected data from both the parent and child with an electronic survey in their primary language (English or French) on a portable computer tablet to gather demographic information. Along with demographic data, the parent and the child were then asked to complete the age-appropriate version PCSI prior to leaving the PED. Symptoms on the PCSI were rated once scoring the child's current level of post-injury symptoms and once retrospectively recalling the child's pre-injury levels of those same symptoms. In addition to data collection, each treating physician provided a routine clinical assessment of the child, provided discharge instructions, and gave follow-up information as per the normal standard-of-care procedures of that PED site. Prior to leaving the PED, contact information was obtained for all families.

Study Follow-Up

Parents chose to complete follow up measures either online using a web-based platform (REDCap) or over the phone (Email: $n =$

TABLE 1 | List of symptoms provided on each version of the PCSI.

	PCSI-SR5 ages 5–7	PCSI-SR8 ages 8–12	PCSI-SR13 ages 13–18
POST-CONCUSSION SYMPTOM INVENTORY			
Physical	1. Have you had headaches? Has your head hurt? 2.Have you felt sick to your stomach like you were going to throw up? 3. Have you felt dizzy? (like things around you were spinning)	1.Have you had headaches? Has your head hurt? 2. Have you felt sick to your stomach or nauseous? 3. Have you had any balance problems or have you felt like you might fall when you walk/run/stand? 4. Have you felt dizzy? (like things around you were spinning) 5. Have bright lights bothered you more than usual? (like when you were in the sunlight, when you looked at lights, or watched TV) 6. Have loud noised bothered you more than usual? (like when people were talking, when you heard sounds, watched TV, or listened to loud music) 7. Have things looked blurry? 8. Have you felt like you are moving more slowly?	1. Headache 2. Nausea 3. Balance problems 4. Dizziness 5. Sensitivity to light 6. Sensitivity to noise 7. Visual problems 8. Move slower than usual 9. Move in a clumsy manner
Sleep		9. Have you felt more tired than usual? 10. Have you felt more drowsy or sleepy than usual?	10. Fatigue 11. Drowsiness
Emotion	4. Have you felt grumpy or irritable? (like you were in a bad mood)	11. Have you felt grumpy or irritable? (like you were in a bad mood) 12. Have you felt sad? 13. Have you felt nervous or worried?	12. Irritability 13. Sadness 14. Nervousness 15. Feeling more emotional
Cognitive	5. Has it been hard for you to pay attention to what you are doing? (like homework or playing games)	14. Has it been hard to think clearly? 15. Has it been hard for you to pay attention to what you are doing? (like homework or chores, listening) to someone, or playing a game? 16. Has it been hard for you to remember things? (like things you saw or heard, or places you have gone) 17. Have you felt like you are thinking more slowly?	16. Feeling mentally "foggy" 17. Difficulty concentrating 18. Difficulty remembering 19. Answers questions more slowly than usual 20. Gets confused with directions of tasks
	3pt Guttman Scale: 0 = no, 1 = a little, 2 = a lot		7pt Guttman Scale: 0 = no problem, 3 = moderate, 6 = severe

2,776, Phone: $n = 276$, Missing: $n = 11$). Families choosing to complete the follow-up sessions over the phone were called by a research assistant, who read out all survey questions and recorded the participant's answers. For families choosing the web-based option, a link to a secure web-based survey was sent to the parent via email. If the survey was not completed within 48 h of the initial reminder email, phone calls were initiated. A maximum of five phone calls per patient was attempted. Once the patient was contacted, ratings of current symptoms and retrospective report of pre-injury levels were collected at all time points (1, 2, 4, 8, and 12-weeks post-enrollment).

Post-concussion Symptom Inventory (PCSI)

The PCSI is a developmentally-appropriate concussion symptom scale that was made for children and adolescents. The PCSI has three age-based versions (PCSI-SR5: Ages 5–7, 13-items, 3-point Guttman Scale; PCSI-SR8: Ages 8–12, 25-items, 3-point Guttman Scale; PCSI-SR13: Ages 13–18, 26-items, 7-point Guttman Scale). As the PCSI uses different scaling based on the age-appropriate version, the PCSI-SR5, and the PCSI-SR8 were transformed by multiplying each item by three to make the scale range equivalent to the PCSI-SR13 which used a 7-pt Guttman scale most commonly found in the literature. The PCSI was chosen because it is one of only two symptom scales with age-appropriate version for younger children, with appropriate psychometric data published in the literature (8, 11, 12). Additionally the PCSI-SR8 and PCSI-SR13 can be evaluated as physical, cognitive, emotional, and sleep subscales (8). The list of symptoms and which subscales they contribute to can be found in **Table 1**.

Statistical Analysis

All analyses were completed in *R* version 3.3.2 (Vienna, Austria) (20). Stability was evaluated by quantifying the mean absolute discrepancy of the retrospective pre-injury ratings for each patient, a quantity also known as the Gini's Mean Difference (GMD), and post-injury symptom ratings were not analyzed in this study. GMD is a descriptive outcome calculated by taking the average of the absolute value for all pair-wise comparisons between pre-injury ratings at all study time points (i.e., pre-injury rating at the PED and 1, 2, 4, 8, and 12-weeks follow-ups). GMD was chosen because no reference time-point must be declared (i.e., no single time-point was assumed to be more accurate than others) and it is free from distributional assumptions (i.e., remain valid under non-normal distributions). With six total time points throughout this study, a maximum of 15 pairwise comparisons were possible for each individual item. To be included in the analysis, individuals were required to complete the retrospective pre-injury ratings on the PCSI at least twice. Individuals who only completed the PCSI at one time point were excluded as GMD could not be calculated. Additional information about the

TABLE 2 | Descriptive statistics for the 5–7, 8–12, and 13–18-year-old age groups.

Item	Ages 5–7				Ages 8–12				Ages 13–18			
	No missing data ($n = 306$)	Some missing data ($n = 193$)	GMD unavailable ($n = 35$)	*P*	No missing data ($n = 631$)	Some missing data ($n = 572$)	GMD unavailable ($n = 79$)	*P*	No missing data ($n = 563$)	Some missing data ($n = 601$)	GMD Unavailable ($n = 83$)	*P*
Age, median (IQR)	6.7 (5.9, 7.3)	6.6 (5.9, 7.2)	6.6 (5.8, 7.2)	0.30	10.8 (9.7, 11.9)	10.7 (9.5, 11.9)	10.6 (9.5, 11.9)	0.95	15 (13.9, 16.0)	15.2 (14.1, 16.2)	15.2 (14.3, 16.5)	**0.02**
Sex, freq (%)												
Male	184 (60.1)	126 (65.3)	21 (60.0)	0.50	420 (66.7)	368 (64.3)	50 (63.3)	0.67	314 (55.8)	321 (53.5)	53 (63.9)	0.19
Female	122 (39.9)	67 (34.7)	14 (40.0)		211 (33.4)	204 (35.7)	29 (36.7)		249 (44.2)	279 (46.5)	30 (36.1)	
Concussion Hx, freq (%)												
Yes	273 (89.8)	173 (90.1)	30 (93.8)	0.79	528 (83.9)	464 (81.5)	60 (80.0)	0.66	395 (70.7)	374 (62.6)	51 (63.7)	0.16
No	31 (10.2)	17 (9.9)	2 (6.2)		101 (16.1)	105 (18.5)	15 (20.0)		164 (29.3)	223 (37.4)	29 (36.3)	
Personal Hx, freq (%)												
Migraine	16 (5.3)	10 (5.2)	0 (0.0)	0.41	64 (10.2)	60 (10.5)	7 (9.5)	0.96	99 (17.7)	119 (19.8)	17 (21.2)	0.58
Learning disability	8 (2.6)	13 (6.7)	1 (3.2)	0.08	51 (8.1)	39 (6.9)	13 (17.6)	**0.01**	46 (8.2)	62 (10.2)	11 (14.1)	0.19
Attention deficit	12 (3.9)	14 (7.3)	0 (0.0)	0.1	52 (8.3)	53 (9.3)	8 (11.0)	0.67	45 (8.0)	70 (11.7)	14 (17.7)	**0.01**
Anxiety	12 (3.9)	1 (0.5)	0 (0.0)	**0.04**	43 (6.8)	35 (6.1)	3 (4.1)	0.62	65 (11.6)	68 (11.4)	10 (12.7)	0.94
Depression	0 (0.0)	0 (0.0)	0 (0.0)	1	5 (0.8)	7 (1.2)	2 (2.7)	0.3	30 (5.3)	35 (5.8)	8 (10.0)	0.25
Sleep disorder	2 (0.7)	3 (1.6)	0 (0.0)	0.5	8 (1.3)	8 (1.4)	0 (0.0)	0.6	20 (3.6)	17 (2.8)	4 (5.1)	0.53
Other Psychiatric	2 (0.7)	1 (0.5)	0 (0.0)	0.89	5 (0.8)	4 (0.7)	0 (0.0)	0.74	10 (1.8)	8 (1.3)	2 (2.6)	0.65
Mechanism, freq (%)												
Sports/Rec	146 (47.7)	85 (44.3)	10 (31.2)	0.60	436 (69.2)	381 (66.6)	47 (64.4)	0.35	442 (78.5)	470 (78.2)	58 (72.5)	0.07
Non-Sport/fall	155 (50.7)	104 (54.2)	21 (65.6)		179 (28.4)	179 (31.3)	25 (34.2)		91 (16.2)	105 (17.5)	12 (15.0)	
MVC	3 (1.0)	2 (1.0)	1 (3.1)		10 (1.6)	3 (0.5)	0 (0.0)		18 (3.2)	16 (2.7)	4 (5.0)	
Assault	2 (0.7)	1 (0.5)	0 (0.0)		5 (0.8)	7 (1.2)	1 (1.4)		11 (2.0)	10 (1.8)	6 (7.5)	
Other	0 (0.0)	0 (0.0)	0 (0.0)		0 (0.0)	2 (0.3)	0 (0.0)		1 (0.2)	0 (0.0)	0 (0.0)	

Groups were further evaluated by missing data points, where No Missing Data = participants who completed all time points involved in the study (n = 6), Some Missing Data = participants completed between 2 and 5 time points, and GMD Unavailable = participant only completed one time point (GMD could not be calculated and were not analyzed in this study). Bold values are statistical significance (P < 0.05).

amount of missing data present throughout this study can be found in the **Supplementary Material.**

A GMD value was first calculated using the rating provided for each individual item listed on the PCSI. At the subscale and full-scale level, the GMD value was calculated by taking the average of all constituent items involved (i.e., if the subscale had three items, the GMD values calculated for those three individual-items were averaged to create a GMD value for the entire subscale). This approach allowed all GMD values reported in this study to range from 0 (perfect stability) to 6 (worst possible stability), providing consistency between all levels of analysis (full scale, subscale, and individual-items) and more appropriate comparisons for situations where all individual items were not completed at all time points. To calculate 95% confidence intervals for the GMD values, estimates were provided by percentile bootstrap based on 100 repetitions. As the number of items differs on each version of the PCSI, we chose to report GMD values separately for the PCSI-SR5, PCSI-SR8, and the PCSI-SR13. There is no literature available to define what level of stability is needed in clinical use, but some level of variability is to be expected. We defined an acceptable level of stability to be good-to-perfect to be a GMD < 1, which is 1/6th (16.7%) of the possible value given the PCSI range.

Previous concussion studies have shown that ∼40% of individuals report no pre-injury level of symptoms (21). Individuals who consistently report no pre-injury levels of problems across all study time-points would have perfect stability (GMD = 0); a large proportion of individuals with perfect stability may mask clinically important findings. Therefore, we completed a subgroup analysis by removing all individuals who reported no pre-injury symptoms at all six time points studied and re-analyzed stability only with individuals reporting some retrospective pre-injury symptom presence throughout the study (+ Pre-Injury Ratings). Stability results for the entire sample and for the + Pre-Injury Ratings subgroup are presented throughout the study.

RESULTS

A total of 3,063 children aged 5–17 were recruited through the Predicting and Preventing Postconcussive Problems in Pediatrics (5P) study. Of those 3,063 children, 2,866 (93.6%) completed the retrospective pre-injury PCSI rating during at least two time points and were included into the analysis (Ages 5–7: $N = 499$, Ages 8–12: $N = 1{,}203$, Ages 13–17: $N = 1{,}164$). In our sample, 207 (41.5%) participants aged 5–7, 343 (28.5%) participants aged 8–12, and 252 (21.6%) participants aged 13–17 retrospectively rated all pre-injury levels as zero throughout the entire study period (GMD=0) and were not included in the subgroup analysis. Descriptive statistics for the study sample can be found in **Table 2.**

PCSI-SR5

Full Sample

The full scale for the PCSI-SR5 was highly stable, with 94% of children displaying good-to-perfect stability. The mean GMD for

TABLE 3 | Mean (95% CI), median (95% CI), and percentage of individuals with good-to-perfect stability for the PCSI-SR5 (Ages 5–7).

Level	Outcome	Stability for PCSI-SR5 ($n = 499$)					
		Mean (95% CI)		Median (95% CI)		Good-to-perfect stability (N, %)	
		Full sample	+ Pre-injury ratings only	Full sample	+ Pre-injury ratings only	Full sample	+ Pre-injury ratings only
Item	Headache	0.39 (0.34, 0.46)	1.41 (1.32, 1.52)	0.00 (0.00, 0.00)	1.20 (1.20, 1.50)	413/499 (83%)	54/140 (39%)
	Nausea	0.27 (0.22, 0.33)	1.48 (1.34, 1.64)	0.00 (0.00, 0.00)	1.20 (1.00, 1.60)	447/499 (90%)	39/91 (43%)
	Dizziness	0.13 (0.10, 0.18)	1.52 (1.33, 1.73)	0.00 (0.00, 0.00)	1.35 (1.00, 1.60)	472/499 (95%)	17/44 (39%)
	Irritability	0.42 (0.37, 0.48)	1.52 (1.43, 1.68)	0.00 (0.00, 0.00)	1.50 (1.20, 1.60)	411/499 (82%)	51/139 (37%)
	Difficulty Concentrating	0.60 (0.53, 0.67)	1.60 (1.47, 1.73)	0.00 (0.00, 0.00)	1.50 (1.20, 1.60)	371/499 (74%)	60/188 (32%)
Full Scale	Overall Total	0.31 (0.28, 0.34)	0.53 (0.48, 0.58)	0.20 (0.20, 0.24)	0.40 (0.36, 0.48)	468/499 (94%)	259/290 (89%)

Outcomes are provided at the item and full-scale level for the full sample and for the + Pre-Injury Ratings subgroup only. No subscales exist in the PCSI-SR5.

the full 5–7-year-old sample ranged from 0.13 to 0.60 at the item-level. Dizziness was the most stable individual item and difficulty concentrating showed the lowest stability.

+ Pre-injury Ratings

When looking only at individuals who retrospectively reported at least one non-zero pre-injury rating throughout the study period, the overall stability was reduced but trends were similar to the full sample. The full scale remained highly stable for the + Pre-Injury sample, with 89% of children continuing to show good-to-perfect. Balance problems and difficulty concentrating remained the most and least stable individual items, respectively. Overall results for the PCSI-SR5 can be found in **Table 3**.

PCSI-SR8

Full Sample

Overall, the full scale for the PCSI-SR8 was highly stable (GMD = 0.19, 95% CI: 0.18, 0.20). The physical subscale showed the highest relative stability, with moving slowly and vision problems encompassing the most stable individual items. The emotional subscale showed the lowest stability among the four subscales. Headache had the lowest relative stability at the item-level, followed by difficulty concentrating.

+ Pre-injury Ratings

The PCSI-SR8 remained highly stable for the + Pre-Injury sample, but different trends emerged in this group. The physical domain continued to be the most stable subscale, but nausea and headache had the highest relative stability of individual-items. In disagreement with the full sample, fatigue (subscale), and vision problems (item-level) were the least stable relative to other outcomes. Full results for the PCSI-SR8 can be found in **Table 4**.

PCSI-SR13

Full Sample

The full scale for the PCSI-SR13 had high overall stability. Vision problems, answer slowly, and nausea were the most stable individual items and the physical domain was the most stable subscale. Conversely, fatigue, headache, and the fatigue subscale had the lowest relative stability.

+ Pre-injury Ratings

The overall stability for the full scale remained high for the + Pre-Injury sample. The physical subscale and dizziness (item) had the highest relative stability. On the low end, fatigue (subscale) and headache (item) had the lowest stability. Overall results for the PCSI-SR13 can be found in **Table 5**.

DISCUSSION

The results of this study confirm our hypothesis that the retrospective recall of pre-injury ratings is stable in children and adolescents. At the full-scale level, all mean GMD values were <5% of the scale range, suggesting little dispersion, and high stability in the retrospective recall of pre-injury levels in the 3-months post-concussion. Averaging over all items, including those with very low mean GMDs, and non-consistent retrospective reporting in opposing direction (i.e., retrospectively rating one symptom 1-point higher than previous reports while rating a different symptom 1-point lower than previous reports) likely contribute to the high stability seen across both the full scale and sub-scale level. The wider 95% confidence intervals and smaller percentage of individuals displaying good-to-perfect stability indicate that the youngest children (ages 5–7) may have slightly less stability in their retrospective symptom recall, in agreement with previous literature suggesting young children have the least reliable recall (15). Our results support the high overall stability of retrospective pre-injury ratings despite large, non-linear changes in post-injury symptoms ratings, which have been shown previously in this sample of concussed children and adolescents (22).

Every individual item on each version of the PCSI had a mean GMD $\leq$ 1/10th of the scale range and a median GMD of 0, indicating little dispersion. Headache, fatigue, and difficulty concentrating were among the least stable individual items across all versions of the PCSI. These particular symptoms are not specific to concussion and are among the most commonly reported baseline symptoms in healthy children and adolescents for their respective age groups (8, 23). Additionally, the severity at which these problems occur if present often fluctuates over time, which can account for the higher variability (less stability) seen in these items. This rationale is supported by previous research in children with headache history, which shows that children can accurately recall headache frequency but struggle with recalling headache intensity and duration (16). Conversely, the items with the highest individual stability (vision, balance/dizziness, and move/answer slowly) are among the least frequently endorsed baseline symptoms in our study, which agrees with previous literature (8).

The PCSI was highly stable as hypothesized. Previous studies show that the "good-old-days" and recall biases can elevate pre-injury symptom reports, which would theoretically decrease the stability of the assessment. However, reports of these biases are traditionally found over longer periods of time than evaluated in this study and in individuals with on-going symptoms (13, 15). The main objective of this study was to describe the overall stability of retrospective symptoms rating on the PCSI. Therefore, stability was examined only as a collective whole over the follow-up period (i.e., not specific to time intervals within the follow-up period) and with pre-injury symptom ratings [post-injury symptom scores and their progression over the follow-up period in this sample have been previously reported (22)]. As such, our methodology does not allow for a conclusive determine regarding the presence of the "good-old-days" in our sample, which should be evaluated further in future studies.

The primary strength of this study lies in the large, diverse sample. Our pediatric participants comprised a wide age range (5–17), included various mechanisms of injury, and embraced patients with behavioral, learning, and psychological problems [more specific information about our sample can be found in Zemek et al. (18)]. Our broad inclusion criteria increase the generalizability of findings. The use of a validated concussion symptom checklist, which has three, developmentally appropriate versions for children and adolescents, is an additional strength. Lastly, the analytical method of GMD

TABLE 4 | Mean (95% CI), median (95% CI), and percentage of individuals with good-to-perfect stability for the PCSI-SR8 (Ages 8–12).

Level	Outcome	Stability for PCSI-SR8 (n = 1,203)					
		Mean (95% CI)		Median (95% CI)		Good-to-perfect stability (N, %)	
		Full sample	+ Pre-injury ratings only	Full sample	+ Pre-injury ratings only	Full sample	+ Pre-injury ratings only
Item	Headache	0.59 (0.55, 0.64)	1.50 (1.45, 1.55)	0.00 (0.00, 0.00)	1.50 (1.50, 1.60)	904/1,203 (75%)	178/477 (37%)
	Nausea	0.26 (0.22, 0.28)	1.39 (1.32, 1.47)	0.00 (0.00, 0.00)	1.20 (1.09, 1.50)	1,080/1,203 (90%)	99/222 (45%)
	Balance	0.13 (0.10, 0.16)	1.53 (1.36, 1.65)	0.00 (0.00, 0.00)	1.20 (1.00, 1.60)	1,146/1,203 (95%)	43/100 (43%)
	Dizziness	0.14 (0.12, 0.17)	1.43 (1.32, 1.54)	0.00 (0.00, 0.00)	1.20 (1.20, 1.50)	1,133/1,203 (94%)	49/119 (41%)
	Fatigue	0.28 (0.25, 0.31)	1.50 (1.42, 1.59)	0.00 (0.00, 0.00)	1.20 (1.20, 1.50)	1,077/1,203 (90%)	101/227 (45%)
	Drowsy	0.19 (0.17, 0.23)	1.50 (1.40, 1.59)	0.00 (0.00, 0.00)	1.20 (1.20, 1.50)	1,113/1,203 (93%)	65/155 (42%)
	Sensitivity to Light	0.19 (0.17, 0.22)	1.51 (1.42, 1.63)	0.00 (0.00, 0.00)	1.50 (1.20, 1.60)	1,110/1,203 (92%)	62/155 (40%)
	Sensitivity to Noise	0.23 (0.20, 0.26)	1.47 (1.35, 1.56)	0.00 (0.00, 0.00)	1.20 (1.20, 1.55)	1,092/1,203 (91%)	81/192 (42%)
	Irritability	0.36 (0.33, 0.40)	1.43 (1.38, 1.48)	0.00 (0.00, 0.00)	1.35 (1.20, 1.50)	1,029/1,203 (86%)	130/304 (43%)
	Sad	0.25 (0.22, 0.28)	1.45 (1.35, 1.54)	0.00 (0.00, 0.00)	1.50 (1.20, 1.50)	1,080/1,203 (90%)	84/207 (41%)
	Nervous	0.40 (0.36, 0.44)	1.51 (1.43, 1.58)	0.00 (0.00, 0.00)	1.50 (1.20, 1.60)	1,004/1,203 (84%)	118/317 (37%)
	Move Slowly	0.08 (0.07, 0.10)	1.40 (1.30, 1.56)	0.00 (0.00, 0.00)	1.20 (1.00, 1.50)	1,163/1,203 (97%)	32/72 (44%)
	Think Slowly	0.12 (0.09, 0.14)	1.54 (1.43, 1.65)	0.00 (0.00, 0.00)	1.50 (1.20, 1.55)	1,143/1,202 (95%)	35/94 (37%)
	Mental Fog	0.15 (0.13, 0.18)	1.49 (1.40, 1.61)	0.00 (0.00, 0.00)	1.20 (1.00, 1.50)	1,133/1,203 (94%)	52/122 (43%)
	Difficulty Concentrating	0.46 (0.43, 0.51)	1.51 (1.42, 1.57)	0.00 (0.00, 0.00)	1.50 (1.20, 1.60)	978/1,203 (81%)	145/370 (39%)
	Difficulty Remembering	0.25 (0.21, 0.28)	1.47 (1.39, 1.55)	0.00 (0.00, 0.00)	1.50 (1.20, 1.60)	1,080/1,203 (90%)	78/201 (39%)
	Vision	0.10 (0.08, 0.12)	1.57 (1.40, 1.81)	0.00 (0.00, 0.00)	1.20 (1.20, 1.60)	1,158/1,202 (97%)	30/74 (41%)
Subscale	Physical	0.18 (0.17, 0.20)	0.34 (0.32, 0.36)	0.12 (0.12, 0.12)	0.25 (0.23, 0.25)	1,186/1,203 (99%)	632/649 (97%)
	Fatigue	0.23 (0.21, 0.26)	1.08 (1.02, 1.14)	0.00 (0.00, 0.00)	1.00 (0.82, 1.00)	1,104/1,203 (92%)	160/259 (62%)
	Emotional	0.31 (0.29, 0.34)	0.76 (0.73, 0.80)	0.00 (0.00, 0.00)	0.60 (0.60, 0.67)	1,098/1,203 (91%)	390/495 (79%)
	Cognitive	0.22 (0.21, 0.25)	0.60 (0.56, 0.64)	0.00 (0.00, 0.00)	0.45 (0.45, 0.50)	1,140/1,202 (95%)	386/448 (86%)
Full Scale	Overall Total	0.19 (0.18, 0.20)	0.26 (0.25, 0.28)	0.11 (0.09, 0.12)	0.18 (0.18, 0.21)	1,185/1,203 (99%)	841/859 (98%)

Outcomes are provided at the item, subscale, and full-scale level for the full sample and for the + Pre-Injury Ratings subgroup only.

TABLE 5 | Mean (95% CI), median (95% CI), and percentage of individuals with good-to-perfect stability for the PCSI-SR13 (Ages 13–18).

Level	Outcome	Stability for PCSI-SR13 (n = 1,164)					
		Mean (95% CI)		Median (95% CI)		Good-to-perfect stability (N, %)	
		Full sample	+ Pre-injury ratings only	Full sample	+ Pre-injury ratings only	Full Sample	+ Pre-injury ratings only
Item	Headache	0.39 (0.35, 0.43)	0.97 (0.89, 1.03)	0.00 (0.00, 0.00)	0.80 (0.67, 0.87)	1,015/1,164 (87%)	319/468 (68%)
	Nausea	0.13 (0.11, 0.15)	0.83 (0.76, 0.91)	0.00 (0.00, 0.00)	0.67 (0.60, 0.67)	1,115/1,164 (96%)	131/180 (73%)
	Balance	0.18 (0.15, 0.21)	0.88 (0.81, 0.95)	0.00 (0.00, 0.00)	0.67 (0.60, 0.70)	1,100/1,164 (95%)	178/242 (74%)
	Dizziness	0.15 (0.13, 0.17)	0.78 (0.71, 0.85)	0.00 (0.00, 0.00)	0.60 (0.53, 0.67)	1,117/1,164 (96%)	177/224 (79%)
	Fatigue	0.41 (0.37, 0.44)	0.91 (0.86, 0.97)	0.00 (0.00, 0.00)	0.67 (0.67, 0.87)	1,011/1,164 (87%)	369/522 (71%)
	Drowsy	0.25 (0.21, 0.27)	0.86 (0.80, 0.92)	0.00 (0.00, 0.00)	0.67 (0.60, 0.67)	1,082/1,164 (93%)	252/334 (75%)
	Sensitivity to Light	0.17 (0.14, 0.19)	0.86 (0.78, 0.95)	0.00 (0.00, 0.00)	0.67 (0.60, 0.67)	1,106/1,164 (95%)	166/224 (74%)
	Sensitivity to Noise	0.18 (0.15, 0.20)	0.88 (0.80, 0.96)	0.00 (0.00, 0.00)	0.67 (0.60, 0.80)	1,100/1,163 (95%)	175/238 (74%)
	Irritability	0.38 (0.34, 0.41)	0.93 (0.87, 0.99)	0.00 (0.00, 0.00)	0.73 (0.67, 0.87)	1,006/1,164 (86%)	316/474 (67%)
	Sad	0.23 (0.20, 0.26)	0.93 (0.85, 1.00)	0.00 (0.00, 0.00)	0.67 (0.60, 0.77)	1,082/1,164 (93%)	203/285 (71%)
	Nervous	0.36 (0.32, 0.40)	0.95 (0.89, 1.02)	0.00 (0.00, 0.00)	0.67 (0.67, 0.87)	1,029/1,164 (88%)	305/440 (69%)
	Emotional	0.28 (0.24, 0.31)	0.93 (0.85, 1.01)	0.00 (0.00, 0.00)	0.67 (0.67, 0.80)	1,054/1,164 (91%)	235/345 (68%)
	Move Slowly	0.15 (0.13, 0.17)	0.88 (0.80, 0.96)	0.00 (0.00, 0.00)	0.67 (0.60, 0.77)	1,109/1,164 (95%)	145/200 (73%)
	Mental Fog	0.14 (0.12, 0.17)	0.88 (0.78, 0.95)	0.00 (0.00, 0.00)	0.67 (0.60, 0.80)	1,108/1,164 (95%)	136/192 (71%)
	Concentration	0.36 (0.32, 0.39)	0.92 (0.85, 0.98)	0.00 (0.00, 0.00)	0.67 (0.67, 0.80)	1,042/1,164 (90%)	330/452 (73%)
	Memory	0.25 (0.22, 0.27)	0.87 (0.81, 0.93)	0.00 (0.00, 0.00)	0.67 (0.60, 0.80)	1,082/1,164 (93%)	247/329 (75%)
	Vision	0.11 (0.10, 0.13)	0.84 (0.74, 0.94)	0.00 (0.00, 0.00)	0.67 (0.57, 0.80)	1,128/1,164 (99%)	123/159 (77%)
	Confused	0.22 (0.20, 0.25)	0.86 (0.80, 0.93)	0.00 (0.00, 0.00)	0.67 (0.60, 0.82)	1,086/1,164 (93%)	219/297 (74%)
	Clumsy	0.26 (0.23, 0.29)	0.91 (0.82, 0.98)	0.00 (0.00, 0.00)	0.80 (0.67, 0.87)	1,066/1,164 (92%)	241/339 (71%)
	Answer Slowly	0.13 (0.11, 0.15)	0.81 (0.74, 0.89)	0.00 (0.00, 0.00)	0.60 (0.53, 0.67)	1,127/1,164 (97%)	156/193 (81%)
Subscale	Physical	0.16 (0.14, 0.17)	0.27 (0.24, 0.29)	0.07 (0.04, 0.08)	0.18 (0.15, 0.18)	1,147/1,164 (99%)	671/688 (98%)
	Fatigue	0.31 (0.28, 0.33)	0.65 (0.62, 0.70)	0.00 (0.00, 0.00)	0.50 (0.50, 0.58)	1,081/1,164 (93%)	469/552 (85%)
	Emotional	0.27 (0.25, 0.29)	0.49 (0.45, 0.53)	0.08 (0.08, 0.10)	0.35 (0.30, 0.39)	1,097/1,164 (94%)	572/639 (90%)
	Cognitive	0.18 (0.16, 0.19)	0.36 (0.34, 0.39)	0.00 (0.00, 0.00)	0.24 (0.22, 0.28)	1,133/1,164 (97%)	528/559 (95%)
Full Scale	Overall Total	0.17 (0.16, 0.18)	0.22 (0.20, 0.24)	0.09 (0.08, 0.10)	0.13 (0.12, 0.14)	1,145/1,164 (98%)	892/911 (98%)

Outcomes are provided at the item, subscale, and full-scale level for the full sample and for the + Pre-Injury Ratings subgroup only.

is considered a strength due its ability to tolerate non-normally distributed data and handle missing data (only two retrospectively PCSI rating were needed for inclusion). Even though missing data may mean different time intervals between assessments, there is no natural bias toward stability when this is the case which allows the inclusion of more patients and increases generalizability of our results.

Although the psychometric properties of the PCSI are a strength, the number of items and rating scales for the three different versions are not equivalent and represent a limitation. All reported pre-injury rating responses (0–2 scale) on the PCSI-SR5 and PCSI-SR8 were multiplied by three to make all response outcomes range of GMD 0–6. However, this induces more instability into the PCSI-SR5 and PCSI-SR8 and assumes a 1-point discrepancy on the 0–2 scale is equal to a 3-point discrepancy on a 0–6 scale. The multiple rating scales utilized in the PCSI complicates comparisons across age groups; however, rescaling prevents an inaccurate misinterpretation that younger children have higher stability because the scale range is smaller. Original GMDs values for the PCSI-SR5 and PCSI-SR8 can be found by dividing values reported in this manuscript by three. IN addition, GMD values reported are group averages. Therefore, some individuals may have had large changes (low stability) in their retrospective pre-injury recall. Clinicians should be aware of this when working on the individual patient-level.

Symptom reporting is limited by both floor and ceiling effects, floor effects being a larger concern in our study evaluating pre-injury ratings. The GMD looks at the absolute value of differences in pre-injury reporting over multiple time points. Patients who consistently report no symptoms would have a GMD of zero, thus increasing the stability of the group analysis. However, even patients at the floor (total score of zero) can have a large GMD if they report higher pre-injury ratings at subsequent assessments. Recovery status is not considered in this study. Some participants will have reached full concussion recovery during the follow-up period while other were still experiencing post-concussion symptoms and deficits. How recovery status may have affected retrospective symptom reporting is unknown. Nearly all patients preferred email follow-ups, but a minority of patients ($n = 276$) requested phone follow-ups. Similarly, very young children may need their parent to help read or understand the symptom checklist. It is possible that interacting with a research assistant via phone follow-ups or parent may influence the patient's response.

While some items underperformed relative to other and some minor differences in stability between the full sample and the + Pre-Injury Ratings reporters were apparent at the item-level, the stability for both groups was high at both the subscale and full-scale level. Based on the results of this study, there appears to be no additional clinical benefit to having patients retrospectively recall their pre-injury symptom levels multiple times throughout the recovery period and this can reduce burden on the healthcare provider and the injured child. If multiple retrospective pre-injury ratings are needed (e.g., seeing multiple providers), clinicians can be assured that children and adolescent will retrospectively rate pre-injury levels with relatively high stability. As long as clinical decisions are based on the subscale or the full-scale level, multiple pre-injury ratings will not have meaningful differences and provide equivalent results.

Children and adolescents retrospectively rate pre-injury levels of post-concussion symptoms with good-to-perfect stability over the first 3-months following their injury. Although some individual items underperformed, variability was reduced as items were combined at the subscale and full-scale level. There is limited benefit to multiple pre-injury symptom queries.

DATA AVAILABILITY

The dataset for this study can be requested through Ontario Brain Institute (OBI) BRAIN-CODE after registering using the following link: https://www.braincode.ca/user/register

ETHICS STATEMENT

This study was carried out in accordance with the recommendations of the Research Ethics Board of each participating institution with written informed consent from all subjects. All subjects gave written informed consent in accordance with the Declaration of Helsinki. The protocol was approved by the Research Ethics Board of each participating institution.

AUTHOR CONTRIBUTIONS

ET, RZ, GG, and IG were involved in the conception of this project. KT made substantial contributions to data analysis. ET, KT, MS, and CV were involved in the interpretation of the findings. ET drafted this manuscript and all authors critically revised the manuscript for important intellectual content. All authors approved the final version and agree to be accountable for all aspects of the work.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2019.00672/full#supplementary-material

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What Comes First: Return to School or Return to Activity for Youth After Concussion? Maybe We Don't Have to Choose

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Objectives: Return to School (RTS) and Return to Activity/Play (RTA) protocols are important in concussion management. Minimal evidence exists as to sequence and whether progression can occur simultaneously. Experts recommend that children/youth fully return to school before beginning RTA protocols. This study investigates recovery trajectories of children/youth while following RTA and RTS protocols simultaneously, with the following objectives: (1) to compare rates and patterns of progression through the stages of both protocols; (2) to evaluate symptom trajectories of youth post-concussion while progressing through stages of RTS and RTA; and (3) to propose a new model for concussion management in youth that involves the integration of Return to Activity and Return to School protocols.

Methods: In a 3-year prospective-cohort study of 139 children/youth aged 5–18 years with concussive injury, self-reported symptoms using PCSS and stage of protocols were evaluated every 48 h using electronic surveys until full return to school and activity/sport were attained. Information regarding school accommodation and achievement was collected.

Results: Sample mean age is 13 years, 46% male. Youth are returning to school with accommodations significantly quicker than RTA ($p = 0.001$). Significant negative correlations between total PCSS score and stage of RTS protocol were found at: 1-week ($r = -0.376$, $p < 0.0001$; $r = -0.317$, $p = 0.0003$), 1-month ($r = -0.483$, $p < 0.0001$; $r = -0.555$, $p < 0.0001$), and 3-months ($r = -0.598$, $p < 0.0001$; $r = -0.617$, $p < 0.0001$); indicating lower symptom scores correlated with higher guideline stages. Median full return to school time is 35 days with 21% of youth symptomatic at full return. Median return time to full sport competition is 38 days with 15% still symptomatic. Sixty-four percent of youth reported experiencing school problems during recovery and 30% at symptom resolution, with 31% reporting a drop in their grades during recovery and 18% at study completion.

Conclusions: Children/youth return to school faster than they return to play in spite of the self-reported, school-related symptoms they experience while moving through the protocols. Youth can progress simultaneously through the RTS and RTA protocols during stages 1–3. Considering the numbers of youth having school difficulties post-concussion,

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full contact sport, stage 6, of RTA, should be delayed until full and successful reintegration back to school has been achieved. In light of the huge variability in recovery, determining how to resume participation in activities despite ongoing symptoms is still the challenge for each individual child. There is much to be learned with further research needed in this area.

Keywords: children, adolescents, mild traumatic brain injury, concussion management, return to school, return to activity

INTRODUCTION

Concussion has become an epidemic in children and youth. The number of reported head injuries in Emergency Departments among youth playing sport has increased in the past decade by over 40% (1). The symptoms of concussions can often interfere with participation and performance in home, school, and community activities (2, 3). The current consensus for standard concussion management is the six-stage Berlin Return to Play recommendations (2). This statement and much of the literature now suggest a more conservative approach to the management of children/youth with concussion. It is, however, still unclear as to what "more conservative" entails. When they are symptomatic, children and youth are advised to rest for 48 h (4) then gradually resume regular activity with incremental increases in physical and cognitive activity within symptom tolerance (5, 6). Depression and anxiety may result as secondary sequelae if youth are socially isolated and removed from normal activity and participation for prolonged periods of time (7–10). Prolonged rest can lengthen recovery time and contribute to deconditioning (11, 12), therefore protocols for children must contain a balance of activity and rest to promote physical, emotional and cognitive recovery.

Both RTS and RTA protocols for pediatric concussion management should be conservative and individualized (2, 13–19). A number of protocols guiding families and youth through progressive recovery steps for safe Return to School (RTS) and Return to Activity/Play (RTA) have now been developed, are widely-accepted and are important aspects of pediatric concussion management (2, 20, 21).

Given that being a student is the primary occupation of childhood through to young adulthood, an emphasis on returning to school should be a top priority for children and families, more so than return to sport (22, 23). However, to date the emphasis in post-concussion management has been on return to play and sports (20, 21). A medical chart review showed that primary care physicians were providing return to school instructions to only 27.5% of patients as compared to return to sport instructions (51.6% of patients) (24). This imbalance may reflect the absence of research about post-concussive school issues (25, 26) and thus empirical evidence for specific methods and timelines for returning children to school is not yet available. An evaluation surrounding concussion education in Toronto schools found that 77% of responding schools have RTS protocols in place, in contrast to the 92% that had RTA protocols (27).

The CanChild Protocols for Concussion Management for children 5–18 years (Appendices 1, 2 in **Supplementary Materials**) (19, 28) were originally based on the Zurich return to play protocols and now the revised Berlin consensus recommendations (2). The CanChild protocols also have the same six stages of Return to Activity as the Zurich Return to Play recommendations, but they are more conservative in the way the child moves through the stages and have more detail about activities and intensity associated with each stage. Currently, there is minimal evidence supporting as to the sequence of RTS and RTA, whether they can be achieved simultaneously or whether RTS must be achieved before beginning RTA protocols. The focus now has shifted to the importance of return to school before return to activity/play. The Berlin Consensus (2) states that RTS must be completed before RTA begins, but this is ambiguous in clarifying whether that means fully back to school, or just starting to attend school. Others have suggested similar protocols. The Center for Disease Control and Prevention (29) recommends a gradual and cautious RTS, but does not mention how a RTS protocol can be integrated with a stepwise RTA protocol. Thomas et al. (11) noted that a majority of emergency department physicians instructed patients to rest for 1–2 days before returning to school whereas they instructed beginning a stepwise RTA protocol only after patients' symptoms resolved. Many Ontario school boards have adopted a similar approach, recommending full RTS prior to starting RTA protocols (30).

There is increased understanding, however, that youth may benefit from physical activity prior to complete symptom resolution, particularly among youth who are slow to recover (31–33). Moreover, a multisite, prospective cohort study by Canadian researchers indicates that youth who reported early physical activity post-injury (<7 days) have a 25% decreased risk in developing persistent post-concussive symptoms compared to youth who reported no early physical activity (34). These results suggest that early integration of a RTA protocol with RTS may lead to better health outcomes for youth with concussion.

The current scientific literature regarding concussion management has not adequately addressed how to integrate RTA and RTS protocols post-concussion in youth. Prior to doing so, it is important to understand the recovery trajectories of youth while following both RTS and RTA protocols.

Therefore, the objectives of this study were:

1. To compare rates and patterns of progression through the stages of both protocols;

2. To evaluate symptom trajectories of youth post-concussion while progressing through stages of RTS and RTA.
3. To propose a new model for concussion management in youth that involves the **integration** of Return to Activity and Return to School protocols.

METHODS

Participants

Participants were recruited between November 2014 and December 2016 through the Emergency Department at McMaster Children's Hospital in Hamilton, community referrals from family health teams or sports medicine clinics. The inclusion criteria were as follows: (1) diagnosed with concussion by a physician within the last year; (2) between the ages of 5–18 years; and (3) *still symptomatic* at recruitment. Children and youth were excluded from the study if they had a confirmed significant brain injury requiring resuscitation, surgical intervention or admission to the pediatric critical care unit. Informed written consent was obtained from all parents and participants. This study was approved by the Hamilton Integrated Research Ethics Board in Hamilton, Canada.

Procedures

These analyses are part of a larger prospective cohort study evaluating youth compliance to RTS and RTA concussion management protocols (35). Participating youth were monitored for up to 6-months post-recruitment. Upon enrollment to the study, the RTA and RTS protocols were explained to the participating youth and their parents by research staff including how to proceed through the stages and highlighting the importance of returning fully back to school before returning fully back to activity. The protocols were presented together, and youth were told to follow them both. Study data were collected and managed using REDCap electronic data capture software. While still symptomatic, youth were provided electronic questionnaires every 48 h where they were asked to report their current recovery stage within the RTA and RTS protocols, provide an indication of their level of cognitive and physical activity, and complete the Post-Concussive Symptom Scale (PCSS) (36). When enrolled in the study, participants were asked to record on the PCSS, how they were feeling 1-week prior to the injury. Being symptomatic was then based on the difference between the participants' identified pre-injury status and current reporting of symptoms. Upon symptom resolution, participants were asked to complete the same questionnaires biweekly until their final in-person assessment, which occurred 3-months post-symptom resolution.

Secondary outcomes, including reported school problems, grade changes, and use of school accommodations were also collected.

Statistical Analysis

SAS version 9.4 and SPSS Statistics version 23.0 were used to conduct the data analyses. Demographic and injury information variables are presented with mean and standard deviation (SD), or median and lower and upper quartiles (Q1, Q3, respectively), when distributions are highly skewed.

TABLE 1 | Participant characteristics.

	All participants ($n = 139$)	<1 month recovery ($n = 49$)[a]	Slow to recover (>1 month) ($n = 79$)[a]
Age, mean (SD) years	13.4 (2.87)	12.3 (2.72)	13.5 (2.79)
Sex, n (%)			
Males	64 (46.0)	26 (53.0)	29 (36.7)
Females	75 (53.9)	23 (46.9)	50 (63.2)
Time from Injury at Recruitment, median (Q1, Q3), days	7.8 (3.0, 33.0)	4.63 (1.82, 7.8)	19.9 (5.7, 75.5)
Cause of Injury, *n* (%)			
Sports-related	103 (74.1)	39 (79.5)	55 (69.6)
Fall	22 (15.8)	7 (14.2)	18 (22.7)
MVA	4 (3.0)	0 (0.0)	2 (2.5)
Other	10 (6.2)	3 (6.1)	4 (5.0)
Number of Previous Concussions, *n* (%)			
0	81 (58.3)	39 (79.5)	40 (50.6)
1–2	46 (33.3)	6 (12.2)	24 (30.3)
3+	12 (15.8)	4 (8.1)	15 (18.9)
Total PCSS Score at baseline, mean (SD)	40.1 (24.8)	30.7 (18.6)	43.4 (25.6)
Stratum Information based on Symptom Resolution, *n* (%)			
Symptom free within 1 month	49 (35.2)	–	–
Symptom free within 3 months	40 (35.2)	–	–
Symptoms last longer than 90 days	23 (16.5)	–	–
Never reached symptom resolution during study (i.e., 6 month follow-up)[a]	16 (11.5)	–	–

[a]*Missing data regarding symptom duration for 11 participants due to withdrawal from study or pending data collection.*

TABLE 2 | Parent and child comparison of time in days to return to school, return to activity, and reported school information.

	All participants ($n = 139$)	<1 month recovery ($n = 49$)[a]	Slow to recover ($n = 79$)[a]
Symptom Duration[a], median (Q1, Q3), days	29 (18, 57)	18 (14, 22)	57 (41, 108)
Days until Return to School, median (Q1, Q3), days			
Parent Report	18.5 (7.25, 48.5)	13.6 (5.9, 22.6)	28.3 (8.4, 76.2)
Participant Self-Report **RTS Stage 3**—Modified Academics	12.6 (9.3, 21.3)	13.4 (9.81, 18.6)	18.2 (10.8, 39.1)
Participant Self-Report **RTS Stage 5**—Full Return to School	35.3 (23.4, 78.1)	24.6 (17.9, 30.2)	69.2 (41.1, 139)
Days until Return to Activity, median (Q1, Q3), days			
Parent Report	48.4 (30.6, 73.9)	34.3 (27.9, 49.9)	62.4 (51.2, 113)
Participant Self-Report **RTA Stage 3**—Individual Sport Specific Activity	25.8 (12.9, 59.7)	12.4 (8.89, 23.1)	47.2 (23.5, 102)
Participant Self-Report **RTA Stage 6**—Full Return to Activity/Sport	38.5 (27.9, 75.3)	29.2 (24.9, 33.9)	74.1 (47.3, 151)
Reported School Problems, *n* (%)			
During recovery	89 (64.0)	28 (57.1)	49 (62.0)
At symptom resolution	42 (30.2)	21 (42.8)	17 (21.5)
Unknown	10 (7.1)	-	13 (16.4)
Reported School Accommodations, *n* (%)			
Yes	108 (74.0)	35 (71.4)	58 (73.4)
No	25 (19.7)	14 (28.5)	10 (12.6)
Unknown	6 (6.3)	-	11 (13.9)
Reported Drop in Grades, *n* (%)			
Yes	43 (30.9)	1 (2.0)	20 (25.3)
No	41 (29.4)	23 (46.9)	22 (27.8)
Unknown	55 (39.5)	25 (54.9)	37 (46.8)

[a]*Missing data regarding symptom duration for 11 participants due to withdrawal from study or pending data collection.*

A Spearman's rank order correlation analysis was used to investigate the relationship between a child's PCSS score and corresponding stage of RTS/RTA protocols, with a significance level being set as $p < 0.02$, as adjusted for the comparisons at the three-designated time-points. To approach this analysis comprehensively, three key time points were chosen: 1-week, 1-month and >1-month, because they represent the most commonly reported recovery times in the concussion literature (2, 37), and they reflect the symptom recovery strata in the CanChild concussion protocols.

T-tests were calculated to determine the mean differences in days to each stage during progress through RTS and RTA to completion. Statistical significance was set at $p \leq 0.05$. All data were tested for normality using the Shapiro-Wilk test.

RESULTS

The characteristics of all participants are shown in **Table 1**. The final sample consisted of 139 children and youth aged 5–18 included 64 boys (46%) and 75 girls (53%) with a mean age of 13.4 years. Sport-related injury was the most prevalent cause of injury (74%). Of these injuries, 28% occurred during recreational play in gym class or at recess, 27% were hockey-related, and 14% were basketball-related.

This was the first concussion for 58% of the participants. At recruitment, median time since injury was 7.8 days (with Q1 and Q3 being 3.0 days and 33.0 days, respectively) whereas the mean time since injury was 34.8 days with the minimum and maximum time being 2.9 h and 320.9 days, respectively. Fifty six percent were in the slow to recover group, that is symptoms persisting longer than 1-month. It should be noted that the recruitment sample purposely included a heterogenous sample of youth with possible time from injury any time within in 1 year post as long as they were still symptomatic. This was reflected in the large variability in symptom duration profiles.

The median return time to stage 3 of RTA was 25.8 days and 12.6 days to RTS. The median time to RTA step 6, full return to activity or sports competition, was 38.5 days (**Table 2**) with a median return to school time of 35.3 days ($p = 0.000$) (**Figure 1**). The median time in stage 3 RTA was 0 days (mean 12.3 days) while median time in stage 3 of RTS was 12.6 days (mean 14.9) (**Table 3**). **Table 4** shows the paired sample *t*-test for time to stages 3 and 5 and 6 for RTA and RTS.

Table 5 depicts the PCSS at stages 3 RTA/RTS and Stage 6 RTA and Step 5 RTS. The symptom score decreases over time, but symptom scores are consistently higher for RTS than RTA. Fifteen percent of participants were still reporting symptoms upon full return to activity, stage 6 RTA, while,

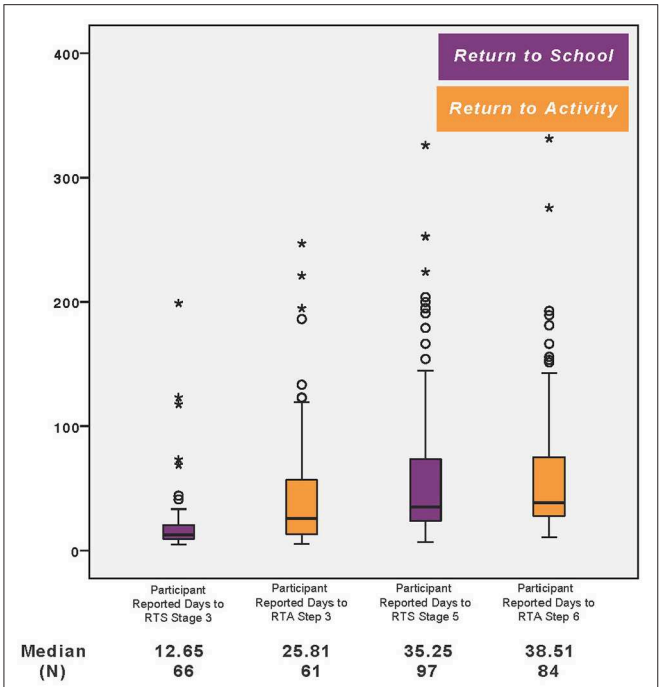

FIGURE 1 | Participant reported days to RTA and RTS stages. The star represents the outliers for the participants in the slow to recover group (>1 month). The circle represents the outliers for the participants in the <1 month recovery group.

21% of participants were still symptomatic at stage 5 of the RTS protocols.

The Spearman's rank order correlation analysis showed significant negative associations between the total PCSS score and the stage of RTS/RTA protocols at 1-week ($r = -0.376$, $p < 0.0001$; $r = -0.317$, $p = 0.0003$), 1-month ($r = -0.483$, $p < 0.0001$; $r = -0.555$, $p < 0.0001$), and 3-months ($r = -0.598$, $p < 0.0001$; $r = -0.617$, $p < 0.0001$).

Sixty-four percent of youth reported experiencing school problems during recovery and 30% at symptom resolution with 31% reporting a drop in their school grades during recovery and 18% at study completion. Seventy four percent of parents reported their child was receiving school accommodations during recovery from concussion.

DISCUSSION

Days spent at each stage of recovery and time to attain each stage of recovery in **Tables 2**, **3** show that these times are comparable despite huge variability. The time difference between days to RTS and RTA are statistically significant with RTS being quicker. But overall the median time for both full return to school and full competition is just over 1 month. The trajectory of PCSS symptom scores decreases as stage increases, demonstrating a positive recovery trend as youth progress at their own pace through the stages of protocols showing continuous improvement without harmful effect or significant regression in stages or increase in symptoms while they follow RTS and RTA at the same time. Of note is that symptoms scores are higher in RTS stages and youth are more symptomatic on completing RTS (21%) than RTA (15%). This is understandable as youth are returning to school more

TABLE 3 | Participant reported days in RTS and RTA stages.

Participant group	Step	*N*	Mean (*SD*)	Median	Minimum	Maximum
RETURN TO SCHOOL STAGES						
<7 days recovery	1	1	0.00	0.00	0.00	0.00
	2	2	3.00 (4.24)	3.00	0.00	6.00
	3	2	2.50 (3.54)	2.50	0.00	5.00
	4	2	3.50 (0.71)	3.50	3.00	4.00
	5	2	77.50 (6.36)	77.50	73.00	82.00
<1 month recovery	1	15	6.47 (8.98)	3.00	0.00	30.00
	2	32	3.88 (6.42)	0.00	0.00	24.00
	3	35	11.17 (9.51)	9.00	0.00	47.00
	4	38	8.84 (7.02)	6.00	0.00	29.00
	5	45	81.04 (40.08)	80.00	6.00	186.00
Slow to recover	1	33	14.76 (23.33)	6.00	0.00	111.00
	2	58	11.28 (23.30)	2.00	0.00	114.00
	3	64	58.25 (74.00)	33.50	0.00	405.00
	4	59	32.64 (44.22)	18.00	0.00	223.00
	5	55	93.69 (61.31)	92.00	0.00	353.00
RETURN TO ACTIVITY STAGES						
<7 days recovery	1	1	6.00	6.00	6.00	6.00
	2	2	2.50 (3.54)	2.50	0.00	5.00
	3	2	3.50 (0.71)	3.50	3.00	4.00
	4	2	0.00 (0.00)	0.00	0.00	0.00
	5	2	1.00 (1.41)	1.00	0.00	2.00
	6	2	76.50 (7.78)	76.50	71.00	82.00
<1 month recovery	1	15	5.47 (5.36)	3.00	0.00	16.00
	2	32	14.38 (8.02)	12.00	0.00	34.00
	3	35	5.69 (7.65)	2.00	0.00	24.00
	4	38	8.58 (12.39)	4.00	0.00	62.00
	5	45	2.27 (4.77)	0.00	0.00	21.00
	6	45	76.13 (42.30)	75.00	4.00	186.00
Slow to recover	1	33	15.91 (22.95)	9.00	0.00	96.00
	2	58	63.91 (84.97)	31.00	0.00	499.00
	3	64	26.66 (44.75)	11.50	0.00	278.00
	4	59	36.88 (58.74)	10.00	0.00	259.00
	5	55	12.75 (44.45)	0.00	0.00	326.00
	6	40	78.33 (43.07)	78.50	2.00	170.00

TABLE 4 | Paired sample *t*-test for time to stages 3 and stages 5 & 6 for RTA and RTS.

		Mean	*SD*	*df*	2-tailed sig
Pair 1	Days to RTS Stage 3 & Days to RTA Step 3	27.1 41.6	37.2 49.9	43	$P < 0.000$
Pair 2	Days to RTS Stage 5 & Days to RTA Step 6	51.6 62.9	56.7 59.6	83	$P < 0.000$

quickly and not too concerning as long as they are receiving school accommodations, as seen in 74% of this study sample, so that they can continue with school while symptomatic, avoiding unnecessary academic failure and the resulting anxiety it produces for the youth. As expected, time to move through stages and time in each stage is quicker for the youth in strata one, recovery within 1 week, and strata 2, recovery within 1 month, with longest recovery times in the slow to recover group (**Table 2**) (38–40). The fact that youth return to school sooner than return to activity including contact sport is in line with the recommendations that youth should return to school before return to sport (2, 20, 41), except that in our study they are doing them in unison but at different rates. It is recommended that RTS stages should be followed in conjunction with the RTA protocol (17–19), as suggested in **Figure 2**. Stages 1–3 can be carried out simultaneously. After stages 1–3 there is more variability in youth recovery (**Table 2**) and more risk in the activity stages. It is suggested that RTS should then proceed up to full return to school attendance and performance, stage 5 RTS, before moving onto stage 4–6 in RTA. If a youth cannot participate fully in his or her academic program, then he or she should not be playing full contact or step 6 full activity and contact sport (2). As long as youth are active and participating, they do not have to go to full risk and contact sport (17–19, 42). In this way they can concentrate on getting back to full academic achievement while avoiding physical risk, though still enjoying and benefiting from some physical activity (43–46). We now know depression can affect youth who are not allowed to participate (7, 47). Therefore, the balance and compromise is to participate in both school and physical activity until higher level cognitive activity is required and higher level risk is present in higher stages of RTA protocol. At this point higher priority should be given to academic success (22) which is vital to future vocational opportunities and then

TABLE 5 | Participant reported PCSS at RTA and RTS stages.

	Participant reported PCSS at RTS stage 3	Participant reported PCSS at RTS stage 5	Participant reported PCSS at RTA step 3	Participant reported PCSS at RTA step 6
N	66	97	60	84
Mean	14.89	5.71	12.27	3.17
Median	7	0.00	0.00	0.00
Minimum	0	0	0	0
Maximum	118	72	98	52
Percentiles 25	0.00	0.00	0.00	0
50	7.00	0.00	0.00	0
75	25.00	5.00	14.00	0

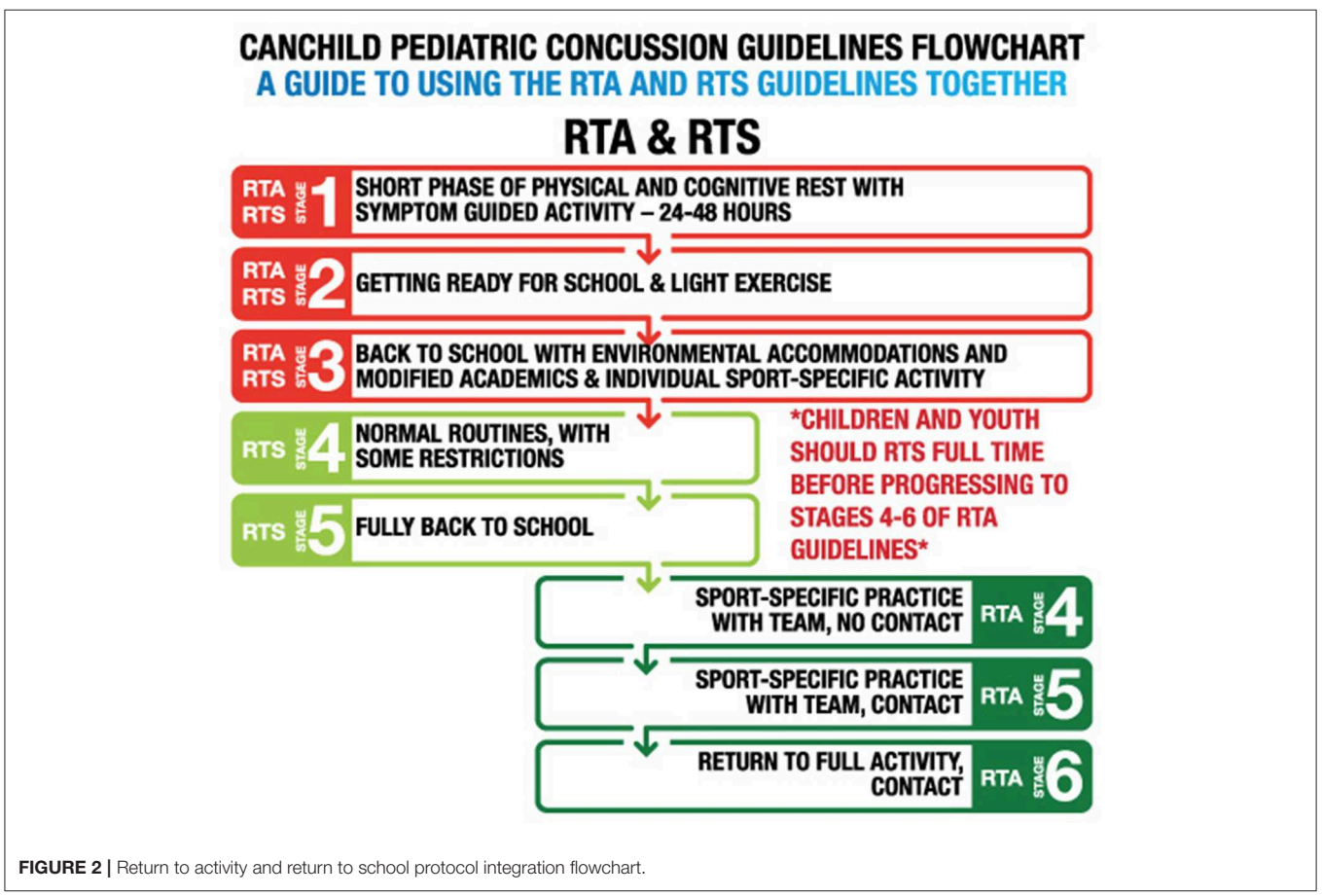

FIGURE 2 | Return to activity and return to school protocol integration flowchart.

proceed to higher risk physical activity as in stages 4–6 of RTA (2, 48).

The success of this approach is also greatly dependent on the school accommodations which we saw in 74% of youth. The accommodations allowed youth to progress successfully with both RTS and RTA. As presented in **Table 2**, the numbers of youth that have problems throughout recovery (64%) drops significantly by the end of symptom resolution (30%) and accommodations throughout by the school probably are likely a significant factor in this trend. It is interesting that quicker recovery of symptoms does not mean less problems as 43% of youth who recovered within a month had school problems as compared to 22% of those who had symptom resolution after 1-month post-injury. The fact that school problems decrease as recovery continues does not support the need to only complete school re-entry before activity resumption.

Limitations

There are several limitations with this present study. There are inherent limitations with the self-report method and the current analyses were unable to confirm the accuracy of the self-reported symptoms and stage of guidelines. Missing data and those lost to follow-up and different numbers of youth completing each stage make analyses challenging. In addition, the huge variability in times to reach stages affects the normal distribution of the data, so the analyses had to be adjusted for this phenomenon. However, we deliberately chose to include youth with varying times post-injury as long as they were symptomatic in order that a realistic spectrum of recovery could be explored.

CONCLUSIONS

Youth return to school faster than they return to play in spite of the self-reported, school-related symptoms they experience while moving through the protocols. Youth can progress simultaneously through the RTS and RTA protocols during the early stages 1–3. Considering the numbers of youth having school difficulties post-concussion, full contact sport, stage 6, of RTA, should be delayed until full and successful reintegration back to school has been achieved. In light of the huge variability in recovery, determining how to resume participation in activities despite ongoing symptoms is still the challenge for each individual child. There is much to be learned with further research needed in this area.

DATA AVAILABILITY

The datasets generated for this study are available on request to the corresponding author.

ETHICS STATEMENT

This study was carried out in accordance with the recommendations from the Hamilton Integrated Research Ethics Board with written informed consent and assent from all subjects. All subjects gave written informed consent in accordance with the Declaration of Helsinki. The protocol was approved by the Hamilton Integrated Ethics Research Board (HiREB).

AUTHOR CONTRIBUTIONS

CD contributed to study design and methodologies, data analysis and interpretation, manuscript preparation and critical revision, and final approval of the manuscript. SR contributed to data collection and analysis, manuscript development, critical revision, and final approval of the manuscript. C-YL contributed to data collection, data analysis and interpretation, manuscript development, critical revision, and final approval of the manuscript. EC contributed to data collection and analysis, manuscript development, and final approval of the manuscript.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2019.00792/full#supplementary-material

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Comprehensive Neuropsychiatric and Cognitive Characterization of Former Professional Football Players: Implications for Neurorehabilitation

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Objectives: To identify novel targets for neurorehabilitation of people with a remote history of multiple concussions by: (1) comprehensively characterizing neuropsychiatric and cognitive functioning in former professional football players, with a focus on executive functions; (2) distinguishing concussion-related findings from pre-morbid/cohort characteristics of professional football players; and, (3) exploring the relationship between executive functions and neuropsychiatric symptoms.

Participants: Sixty-one high-functioning former professional football players and 31 age- and sex-matched control participants without history of concussion or participation in contact sports.

Design: Between-groups analyses.

Main measures: *Neuropsychiatric*. Personality Assessment Inventory (PAI) clinical scales plus the Aggression treatment consideration scale; the Mini International Neuropsychiatric Interview (MINI). *Cognitive.* Comprehensive clinical neuropsychological battery assessing domains of verbal and visuospatial attention; speed of processing and memory; current and estimated pre-morbid IQ; and, executive functioning, including two experimental measures that were novel for this population (i.e., response inhibition and inconsistency of responding on a go/no-go task).

Results: (1) Compared to control participants, former professional football players scored significantly higher on the PAI Depression, Mania, and Aggression scales, and significantly lower on response inhibition. (2) Relative to controls, former players with >3 concussions ($\bar{x} = 6.1$), but not former players with ≤3 concussions ($\bar{x} = 2.0$), showed (i) significantly higher scores on the PAI Depression scale, (ii) significantly more MINI clinical diagnoses overall, and manic/hypomanic episodes specifically, and (iii) significantly poorer executive function. (3) Mediation analysis revealed that concussion exposure had a significant indirect effect on PAI Depression, Mania, and Aggression via inconsistency of responding on the go/no-go task.

Conclusions: Notable impairments to neuropsychiatric functioning and worse performance on a sensitive experimental measure of executive function were observed; these were related to both concussion history and pre-morbid (cohort) factors. Therefore, neuropsychiatric and executive functioning should be carefully assessed in those with a remote history of multiple concussions. Moreover, former players' neuropsychiatric symptoms were associated with inconsistency of responding; this suggests that treatments targeted at response inconsistency could help to mitigate neuropsychiatric dysfunction.

Keywords: sports concussion, neuropsychiatric functioning, cognitive dysfunction, executive function, neurorehabilitation

INTRODUCTION

Repetitive concussions are a growing public health concern due to their cumulative effects and evidence of down-stream neurodegenerative consequences (1–6). American football players endure higher concussion exposure (7) and thus former players can provide a window into the delayed effects of multiple concussions in the context of contact sport. While post-mortem research has established a link with chronic traumatic encephalopathy (CTE) in this population (3, 5, 6), there remains a gap in our understanding of the long-term neuropsychiatric and cognitive sequelae in retired players measured *in vivo*.

Studies examining *neuropsychiatric* function in former professional football players have focused predominantly on depression, with significantly higher symptom endorsement and rates of clinically elevated depression relative to control participants (8–14). In post-mortem studies using proxy reports of retired players who had developed CTE, symptoms of "explosivity," "impulsivity," "aggression," and "paranoia" have been reported (6, 15). In a pilot study of 17 former professional football players without a diagnosis of dementia, we observed significantly higher mania symptoms and aggression on the Personality Assessment Inventory (PAI) (16) as compared to control participants. In the former players, higher aggression scores were negatively associated with orbitofrontal cortex thickness and uncinate fasciculus axial diffusivity (17). Few other studies to date, however, have examined neuropsychiatric symptoms other than depression *in vivo*.

In studies examining *cognitive* functioning in former professional football players, learning and memory impairments have been the predominant deficits studied and observed (8, 14, 18–22). There is also some evidence that executive functioning is affected in retired professional football players (23) and related populations (e.g., former high school and college athletes with a history of multiple concussions) (24, 25). Executive functions refer to higher order mental control processes responsible for the management of behavior; they allow us to adapt to our environment from moment to moment as a function of current goals. One core component of executive functioning is inhibitory control, which can be generally defined as the ability to override an automatic behavior to achieve a task specific objective (26, 27).

A small number of studies have examined traditional measures of executive functioning in retired football players (e.g., verbal fluency, Trail Making Test B) (14, 22, 28), and impairments were found in one study (22). In our pilot study of retired professional football players mentioned above, performance on an experimental measure of inhibitory control (commission errors on a go/no-go task) was lower in retired players relative to control participants. More commission errors on this task were also negatively associated with orbitofrontal cortex thickness and uncinate fasciculus axial diffusivity in the former players (17).

An experimental measure of executive functioning that has yet to be used with this population is intra-individual variability (IIV) of reaction time, which represents inconsistency of responding across trials of a task. IIV has shown notable sensitivity to executive impairments in brain injury (29, 30). One study found ongoing impairments in IIV in otherwise fully cognitively recovered TBI patients (29). A study by our group found declines in IIV during the chronic stages of moderate–severe TBI, from 1 to 2+ years post-injury (30).

Disruption to executive functioning has been implicated in a predisposition for and maintenance of neuropsychiatric illnesses, including depression and mania (31–33). Given that higher concussion exposure may contribute to poorer executive functioning (24, 25), these findings raise the question of whether concussion-related executive functioning impairments might increase susceptibility to neuropsychiatric symptoms. To date, no previous study has examined whether executive and neuropsychiatric functioning are directly related in this population, nor whether executive function variables might mediate (i.e., give rise to) the relationship between concussion exposure and neuropsychiatric symptoms. If so, remediating executive dysfunction could prevent or mitigate expression of neuropsychiatric dysfunction in people with a history of multiple concussions.

The overarching aim of this study was to identify novel treatment targets for the long-term cognitive and neuropsychiatric sequelae of multiple concussions. Our first objective was to replicate and extend previous studies characterizing neuropsychiatric and cognitive functioning of former professional football players with a remote history of multiple concussions. Here, we comprehensively measured neuropsychiatric and cognitive functioning in retired players with a history of multiple concussions, and we added novel experimental measures of executive function. These were IIV and response inhibition on a go/no-go reaction time task. Based on past research (12, 17), we predicted greater symptoms of depression, mania, and aggression in comparison to age- and education-matched control participants. Also based on previous findings (8, 17, 19, 22), we predicted worse performance relative to control participants on tests of learning, memory, and executive functioning.

Our second objective was to discern whether any observed differences between retired players and control participants on our neuropsychiatric and cognitive measures were attributable to concussion history or, rather, to pre-morbid, cohort characteristics. To do this, we examined whether higher vs. lower concussion exposure—following the precedent of Guskiewicz et al. (12)—was associated with neuropsychiatric and cognitive outcomes. Greater impairments in the higher concussion exposure group for measures of depression, mania, and aggression, and for measures of learning, memory, and executive functioning, which we predicted based on past research (34–38), would offer evidence that impairments are secondary to concussion history rather than to pre-morbid traits.

Finally, we explored the *relationship* between cognitive and neuropsychiatric functioning in former professional football players as a function of concussion exposure. Our pilot research showed evidence that executive functioning deficits and neuropsychiatric elevations correlated with common structural findings (17); as well, studies of other populations have shown a relationship between executive functioning deficits and neuropsychiatric illness (31–33). Thus, we anticipated a relationship between executive functioning measures and neuropsychiatric findings in the former players. We also anticipated a possible mediating role of executive functioning in the relationship between concussion exposure and neuropsychiatric symptoms. In other words, in the absence of executive function impairments, symptoms might be less likely to manifest in people with a remote history of multiple concussions.

METHODS

Participants

Sixty-one former male Canadian Football League (CFL) players were recruited from across Canada through advertisements in alumni newsletters, presentations, and word of mouth by the Canadian Concussion Centre. Primary inclusion criteria: history of play in the CFL for 3 years or more, under 85 years of age, and currently employed or retired for reasons unrelated to disability (all participants were gainfully employed or voluntarily retired). Primary exclusion criteria: diagnosis of dementia, history of stroke, systemic illness (e.g., diabetes, lupus).

Former players were divided into higher and lower concussion exposure subgroups following the precedent of Guskiewicz et al. (12). Note that for 17 of the 61 retired athletes, partial data has been previously reported (17, 39).

Thirty-one male control participants ranging in age from 28 to 70 were recruited from the local community with the same exclusions as above. Additional exclusions were history of concussion, participation in contact sport (to reduce risk of undocumented concussions), and 2 z-scores below average or more on any neuropsychological test (40). Control participants were closely group-matched to the retired players on age, education, and estimated pre-morbid IQ (**Table 1**).

Measures

All participants were administered a neuropsychiatric assessment comprising the PAI (16) and the Mini International Neuropsychiatric Interview (41) (MINI), which are widely used in TBI and have strong psychometric properties (42, 43). The PAI is a self-report instrument of personality and neuropsychiatric function, with validity demonstrated by our group for TBI for all scales except the *Somatization* and *Schizophrenia* scales, which were excluded from this study (43). We report here on all remaining clinical scales, plus the *Aggression* treatment consideration scale. The MINI is a widely employed, structured, diagnostic interview that measures neuropsychiatric function and screens for 15 disorders based on DSM-IV criteria. We present here findings for all major Axis I diagnoses.

The cognitive battery included traditional clinical neuropsychological tests selected for known validity and reliability for TBI (see **Supplementary Table 1** for test name, description, and outcome measure). Experimental measurement of executive functioning was undertaken using the Sustained Attention to Response Task (SART), a go/no-go reaction time test. The SART was designed as a measure of sustained attention (44), a capacity that is developmentally linked to inhibitory control (45); and, as a go/no-go test, it has been employed to examine inhibitory control (34). Two SART outcomes were employed. The first was commission errors on the task (measuring inhibitory control). The second was IIV of reaction time (measuring inconsistency of responding). For IIV, standard deviation of the correct reaction time was recorded, from which

TABLE 1 | Demographics and concussion history of former professional football players, concussion exposure subgroups, and control participants.

Demographic and injury variables	All retired athletes (*N* = 61)	Lower concussion exposure (≤3; *n* = 26)	Higher concussion exposure (≥4; *n* = 35)	Control participants (*N* = 31)
M (SD) Range				
Age	55.0 (12.8)	55.7 (14.4)	54.5 (11.8)	49.7 (12.1)
	28–84	28–84	31–82	28–70
YOE	15.9 (1.8)	15.6 (1.8)	16.1 (1.7)	16.5 (2.3)
	12–21	12–20	12–21	13–22
Estimated premorbid IQ†	112.5 (7.8)	112.5 (7.0)	112.5 (8.6)	112.3 (8.8)
	95–125	95–122	95–125	
No. of years played in CFL	7.5 (3.6)	8.3 (3.7)	6.7 (3.5)	
	1–15	1–14	3–15	
No. of self-reported concussions	4.4 (2.8)	2.0 (0.9)	6.1 (2.4)	
	0–13	0–3	4–13	
Age of first concussion	19.7 (6.0)	22.1 (7.2)	18.4 (4.9)	
	8–33	8–33	9–32	
Age of last concussion	24.7 (4.5)	23.8 (5.0)	25.2 (4.3)	
	17–34	17–33	20–34	
Years since last concussion	30.7 (14.6)	34.9 (17.2)	28.6 (13.0)	
	5–58	5–58	5–49	
Years since last play	23.7 (13.8)	24.2 (14.3)	23.4 (13.6)	
	0–53	0–53	1–53	

M, mean; SD, standard deviation; YOE, years of education. †Estimated pre-morbid IQ was collected with the Wechsler Test of Adult Reading (WTAR) during neuropsychological assessment.

a coefficient of variation was calculated as an index of IIV (i.e., SD/mean RT) (46, 47).

Design and Procedures

A between-subjects design was employed. All participants provided their informed consent and were tested face-to-face with all measures completed in one testing session. All neuropsychiatric and neuropsychological tests were administered by a trained psychometrist or post-doctoral trainee. Inter-rater reliability was established between testers. The study was approved by the University Health Network Research Ethics Board, Toronto, ON, Canada.

Analysis

Objective 1: Analyses were conducted using the Statistical Package for the Social Sciences, version 21 (48). To compare former players to control participants on the demographic, neuropsychiatric, and cognitive measures, we employed between-group, independent *t*-tests. We used an alpha level of 0.05 (1-tailed) for directional hypotheses, and 0.05 (2-tailed) plus Holm-Bonferroni adjustment for multiple comparisons (49) for exploratory comparisons.

To examine the frequency of neuropsychiatric dysfunction in the groups, we compared the number of individual cases in each neuropsychiatric domain on the PAI and the MINI between groups using Fisher's exact test (with Bonferroni correction for *post-hoc* pairwise testing). Clinical elevations on the PAI were operationalized as a scaled T-score of 70 or greater, based on conventional clinical criteria for the test (16), and clinical diagnoses were made based on MINI interview clinical diagnosis employing the test's diagnostic criteria (41).

For the MINI diagnoses, "current" and "previous" diagnoses were combined for each scale to prevent over-representation of a domain. Similarly, anxiety diagnoses other than Generalized Anxiety Disorder were combined into an "Anxiety—Other" scale, where Panic Disorder, Agoraphobia, Social Phobia, Obsessive Compulsive Disorder, and Posttraumatic Stress Disorder were collapsed into a single outcome variable. Mania and hypomania diagnoses were also collapsed into a single variable. An additional "Diagnoses—Other" outcome variable was created for the remaining disorders (but for which there were no cases diagnosed).

To describe the frequency of neuropsychological impairments, we computed the number of participants in the borderline/mild (−1.4 to −1.9 z-scores), moderate (−2 to −2.9 z-scores), and severe (−3 or more z-scores) ranges for each test, based on clinical convention (50). We then compared the proportions of mild, moderate, and severe neuropsychological impairments between groups using Fisher's exact test.

Objective 2: To examine the effects of concussion exposure, a higher concussion exposure group and a lower concussion exposure group was created by separating retired athletes according to number of self-reported concussions. Higher concussion exposure was operationally defined as 4 or more ($n = 35$) and lower concussion exposure was defined as 3 or fewer concussions ($n = 26$). Concussion number was determined from the player's recall of concussions as defined by McCrea et al. (51). Self-reported concussions are considered a moderately though

not highly reliable index of concussion exposure (52). Therefore, we used a binary concussion exposure variable (high vs. low) rather than a continuous measure, based on the precedent of Guskiewicz et al. (12).

Using 1-way ANOVA, the higher and lower concussion exposure subgroups and the matched control group were compared on each of the demographic, neuropsychiatric, and neuropsychological variables (note that by chance, the subgroups remained demographically equivalent to one another and to the control group). We also compared the frequencies of PAI elevations, MINI clinical diagnoses, and neuropsychological impairments between the higher and lower concussion exposure subgroups and the control group using Fisher's exact test, as carried out between the full group of former players and control participants in Objective 1. For planned comparisons, we employed alpha levels as above.

Objective 3: Lastly, we investigated the relationship between executive and neuropsychiatric functioning as a function of concussion exposure in the former players, excluding controls. We first examined the contributions of concussion exposure and our experimental measures of executive functioning (SART commission errors and IIV) to neuropsychiatric scale scores from the PAI (*Depression*, *Mania*, and *Aggression*) using hierarchical linear regression. Separate regression analyses were run for each neuropsychiatric outcome, and predictor variables were entered in three steps in the following order: concussion exposure, then SART commission errors, and then SART IIV. In a follow-up set of analyses, we examined the mediating role of these novel executive functioning measures in the association between concussion exposure and neuropsychiatric functioning. Separate mediation analyses were performed for each neuropsychiatric variable previously included in the regression. Bootstrapping for mediation analysis with bias-corrected confidence estimates was performed using 5,000 bootstrap samples (53, 54).

RESULTS

We compared the demographic characteristics of the former professional football players to the control participants and found that the two groups were similar in age, educational attainment, and estimated premorbid IQ (see **Table 1**). After the former professional football players were divided into "higher concussion exposure" and "lower concussion exposure" subgroups, these subgroups did not differ significantly in age, education, or estimated premorbid IQ from one another or from control participants.

Objective 1: Neuropsychiatric and Cognitive Characterization

Independent t-tests were applied to compare neuropsychiatric and cognitive functioning of the former professional football players and control participants. Consistent with our hypotheses, former players scored significantly higher than control participants on the PAI's *Depression*, *Mania*, and *Aggression* scales (after accounting for multiple comparisons, except where a 1-tailed test applied), with medium to large effect sizes (see **Table 2**). Former players and control participants did not differ significantly on any of the other neuropsychiatric variables. All three subscale variables for *Mania* (i.e., *Grandiosity*, *Irritability,* and *Activity*) and two of three subscales for *Aggression* (i.e., *Aggressive Attitude* and *Physical Aggression*, but not *Verbal Aggression*) differed significantly between the two groups after controlling for multiple comparisons. Thus, former professional football players with a history of multiple concussions reported significantly greater depression and mania symptoms, as well as aggression, than community control participants.

We compared the frequencies of PAI clinical elevations and MINI diagnoses for all former professional football players and control participants using Fisher's exact test (as operationalized in the Methods; see **Supplementary Table 2**). Our results showed that a significantly greater proportion of former players met criteria for one or more clinical diagnoses on the MINI compared to control participants (36% vs. 16%, respectively, $p < 0.05$). Furthermore, 11 of 61 former professional football players compared to one of 31 control participants met clinical criteria for a current or past manic/hypomanic episode on the MINI, a difference in proportions that was statistically significant (18% vs. 3%, respectively, $p < 0.05$). We then compared the former players' and control group's performance on each of the cognitive tests. The former professional football players made significantly more go/no-go commission errors on the SART than control participants, with a medium effect size, in partial support of our hypotheses (see **Table 3**). Our hypothesis that former players would show significantly worse scores on tests of learning and memory was not supported. These results suggest that former professional football players were less able to withhold a prepotent motor response on the experimental SART task (an index of inhibitory control) compared to control participants. Furthermore, the results showed that former players' learning and memory abilities were similar to those of the control participants.

We also compared the frequencies of cognitive impairments observed in the full retired professional football player group and control group. Fisher's exact test results indicated that there were no statistically significant differences in the frequencies of impairments between the two groups for any of the neuropsychological measures (results presented in **Supplementary Table 3**).

Objective 2: Comparing Retired Athletes With Higher vs. Lower Concussion Exposure

For the neuropsychiatric outcomes, we performed a series of one-way ANOVAs comparing concussion exposure subgroups and control participants for all PAI variables. Our results showed that *Depression* [$F_{(2, 87)} = 4.63$, $p < 0.05$], *Mania* [$F_{(2, 87)} = 12.75$, $p < 0.001$], and *Aggression* [$F_{(2, 87)} = 6.83$, $p < 0.01$] scores were significantly different between groups. According to Levene's statistic, the assumption of homogeneity of variances was violated for *Aggression*. Welch's *F* statistic confirmed that the difference between groups was still statistically significant [$F_{(2, 53)} = 10.44$, $p < 0.001$]. *Post-hoc* comparisons using the Tukey HSD

TABLE 2 | Mean PAI clinical scale and sub-scale scores for former professional football players ($N = 61$) and matched control participants ($N = 31$).

	All retired athletes *M* (*SD*)	Control participants *M* (*SD*)	*T* (*df*), *p*	*d*
Depression+	49.3 (10.4)	44.7 (9.0)	2.09 (88), 0.040	0.47
Cognitive	47.6 (8.4)	45.9 (6.4)	0.99 (88), 0.324	0.23
Affective	50.0 (9.1)	46.6 (7.9)	1.75 (88), 0.042	0.40
Physiological	51.2 (10.9)	44.4 (9.8)	2.90 (88), 0.005	0.66
Anxiety	46.4 (8.1)	42.8 (8.7)	1.95 (88), 0.054	0.43
Anxiety-Related Disorders	46.0 (8.6)	42.5 (8.5)	1.81 (88), 0.074	0.41
Mania+	52.9 (10.2)	42.3 (8.2)	4.89 (88), <0.001	1.15
Activity Level	49.6 (9.0)	42.5 (9.2)	3.50 (88), 0.001	0.78
Grandiosity	56.8 (11.0)	46.3 (7.9)	4.62 (88), <0.001	1.10
Irritability	49.7 (9.9)	42.6 (8.5)	3.34 (88), 0.001	0.77
Paranoia	45.9 (8.0)	45.3 (8.8)	0.34 (88), 0.734	0.07
Borderline	47.4 (9.1)	43.3 (9.2)	2.01 (88), 0.047	0.45
Antisocial	50.1 (7.7)	47.6 (8.4)	1.41 (88), 0.163	0.31
Alcohol problems	53.5 (10.8)	48.9 (8.8)	2.01 (88), 0.047	0.47
Drug Problems	50.8 (9.1)	46.5 (5.2)	2.38 (88), 0.019	0.58
Aggression+	50.7 (11.0)	42.6 (6.0)	3.72 (88), <0.001	0.91
Aggressive Attitude	49.5 (12.1)	41.2 (6.2)	3.53 (88), 0.001	0.86
Verbal Aggression	51.4 (10.2)	46.1 (9.0)	2.39 (88), 0.019	0.55
Physical Aggression	50.7 (10.1)	44.3 (4.2)	3.29 (88), 0.001	0.83

Mean T-scores presented for all clinical scales (minus Somatization and Schizophrenia) plus Aggression. Mean sub-scale scores only presented where full clinical scale scores differed between groups. +Denotes 1-tailed test applies. Means and standard deviations presented in the table are T-scores. CFL, Canadian Football League (indicates former professional football player group).

TABLE 3 | Mean raw scores on cognitive measures for former CFL players ($n = 61$) and control participants ($n = 31$)[a].

	All retired athletes *M* (*SD*)	Control participants *M* (*SD*)	*T* (*df*), *p*	*d*
Go/no-go errors+	12.3 (5.7)	9.7 (4.9)	2.07 (88), 0.041	0.48
Go/no-go RT+	358.3 (92.4)	377.1 (80.9)	−0.95 (88), 0.346	−0.22
Go/no-go IIV+	28.2 (11.7)	24.9 (7.5)	1.43 (88), 0.156	0.34
RAVLT trials 1–5 total score+	45.1 (9.3)	46.9 (7.7)	−0.94 (90), 0.351	−0.21
RVDLT trials 1–5 total score+	39.4 (11.4)	39.9 (11.1)	−0.19 (90), 0.854	−0.04
SDMT-O total correct	61.2 (12.3)	63.3 (12.7)	−0.74 (90), 0.461	−0.16
Trails A total time (sec)	25.0 (7.5)	27.3 (11.1)	−1.19 (90), 0.238	−0.25
Trails B total time (sec)+	62.56 (23.7)	65.6 (25.4)	−0.56 (90), 0.579	−0.12
Spatial span forwards SS	11.4 (2.6)	11.3 (2.5)	0.07 (90), 0.947	0.02
Spatial span backwards SS	12.52 (2.8)	12.4 (2.8)	0.22 (90), 0.826	0.05
Digit span forwards %ile	63.5 (31.4)	52.1 (30.0)	1.67 (90), 0.098	0.37
Digit span backwards %ile	66.9 (27.8)	59.3 (24.9)	1.29 (90), 0.202	0.29

+Denotes 1-tailed test applies. [a]SART scores for one control participant and one retired professional football player were invalid and therefore excluded. SART, Sustained Attention to Response Task; RT, Reaction Time; RAVLT, Rey Auditory Verbal Learning Test; RVDLT, Rey Visual Design Learning Test; SDMT-O, Symbol Digit Modalities Test-Oral; CFL, Canadian Football League (indicates former professional football player group).

test indicated that, for the former professional football players who reported 4 or more previous concussions, mean T-scores for the PAI's *Depression* ($M = 51.71$, $SD = 11.13$), *Mania* ($M = 54.18$, $SD = 10.59$), and *Aggression* ($M = 50.71$, $SD = 12.51$) scales were significantly greater than those observed for the control group (*Depression* $M = 44.67$, $SD = 8.96$; *Mania* $M = 42.33$, $SD = 8.22$; *Aggression* $M = 42.63$, $SD = 5.95$). Former players who reported 3 or fewer previous concussions had significantly higher scores on the PAI's *Mania* ($M = 51.12$, $SD = 9.71$) and *Aggression* ($M = 50.62$, $SD = 9.02$) scales, but not the *Depression* ($M = 46.19$, $SD = 8.62$) scale, compared to the control group. Thus, regardless of self-reported concussion exposure, the retired professional football players had significantly higher scores on the PAI's *Mania* and *Aggression* scales, which was not consistent with our hypotheses. However, only the retired players with four or more self-reported past concussions had significantly higher

Depression scale scores compared to the control group, which was consistent with our hypotheses (see **Figure 1** for planned comparisons results).

Regarding PAI elevations and MINI clinical diagnoses, a greater proportion of participants in the higher concussion exposure subgroup had one or more MINI clinical diagnoses compared to the control group (49% vs. 16%, respectively, $p < 0.05$). The proportion of participants with one or more MINI clinical diagnoses in the lower exposure subgroup did not differ significantly from the higher exposure subgroup or the control group. Furthermore, of the 11 former players who met criteria for a current or past manic/hypomanic episode, 10 were in the higher exposure subgroup, a proportion that was significantly greater than the lower concussion exposure subgroup (18% vs. 4%, respectively, $p < 0.05$) and the control group (18% vs. 3%, respectively, $p < 0.05$). No other differences in proportions of PAI elevations or MINI clinical diagnoses were found between the concussion exposure subgroups and control group.

Cognitive outcomes for the concussion exposure subgroups and control participants were performed using one-way ANOVAs. In partial support of our hypotheses, ANOVA results indicated that errors of commission, $F_{(2,87)} = 3.27$, $p < 0.05$, but not IIV, $F_{(2,87)} = 3.04$, $p = 0.053$ (approaching significance), on the SART was significantly different between groups. *Post-hoc* comparisons showed that retired players with higher self-reported concussion exposure made significantly more go/no-go commission errors ($M = 13.18$, $SD = 5.95$) than control participants ($M = 9.73$, $SD = 4.88$). Retired players with 3 or fewer reported previous concussions did not differ significantly from the higher concussion exposure subgroup or control group for go/no-go commission errors (lower exposure group $M = 11.08$, $SD = 5.33$). Frequencies of mild, moderate, and severe impairments for each of the cognitive variables were also compared between the higher and lower concussion exposure subgroups and the control group. Comparisons using Fisher's exact test indicated that there were no statistically significant differences in the frequency of impairments between groups for any of the cognitive variables. Thus, retired professional football players with four or more self-reported concussions were significantly worse at inhibiting a prepotent motor response (i.e., SART commission errors, inhibitory control) than control participants, whereas retired players with 3 or fewer self-reported concussions did not differ from those with 4 or more concussions or from control participants (see **Figure 2**). There were no differences between any of the groups on any other measure of cognitive functioning, including learning and memory, which did not support our hypotheses.

Objective 3: Exploring the Relationship Between Concussion Exposure, Executive Functioning, and Neuropsychiatric Function

We performed hierarchical linear regression analyses to test models in which the former players' concussion exposure, SART commission errors, and SART IIV were used to predict their PAI *Depression*, *Aggression*, and *Mania* scale scores. The analyses yielded significant models in the prediction of PAI *Depression*, $F_{(3,58)} = 4.40$, $p < 0.01$, and *Aggression*, $F_{(3,58)} = 3.14$, $p < 0.05$, scores, and were marginal for the model predicting *Mania* scores, $F_{(3,58)} = 2.31$, $p = 0.086$. Regression coefficients revealed that IIV was a significant predictor in the PAI *Depression* (R-squared change for the addition of IIV to the model was 0.067) and *Aggression* (R-square change for the addition of IIV was 0.121) models. No individual predictors were significant in the model for PAI *Mania* (results presented in **Table 4**).

To address our final question, whether executive dysfunction was implicated in former players' neuropsychiatric symptoms, we examined whether IIV mediated the relationship between their concussion exposure and neuropsychiatric functioning. IIV was chosen as a mediating variable because it was the only significant predictor from the regression analysis. Results of the mediation analyses revealed a significant intervening effect of IIV in the relationship between concussion exposure and *Depression* ($B = 1.70$; CI = 0.13 to 5.21), *Mania* ($B = 1.41$; CI = 0.08 to 3.80), and *Aggression* ($B = 2.01$; CI = 0.20 to 4.58). The direct effect of concussion exposure on *Depression* ($B = 3.68$, $t_{(57)} = 2.01$, $p = 0.161$), *Mania* ($B = 1.65$, $t_{(57)} = 0.62$, $p = 0.540$), and *Aggression* ($B = -1.72$; $t_{(57)} = -0.61$, $p = 0.544$) was non-significant when controlling for IIV. Thus, concussion exposure had a significant indirect effect on *Depression*, *Mania*, and *Aggression* through IIV. These results are depicted in **Figure 3**.

DISCUSSION

This high-functioning group of retired professional Canadian football players showed disproportionate impairments to neuropsychiatric and executive functioning. The retired players showed significantly higher scores on the *Depression*, *Mania*, and *Aggression* scales of the PAI as compared to control participants. As well, more than double the percentage of retired players than control participants reached clinical threshold for a neuropsychiatric diagnosis on the PAI and on the MINI. Taken together, these results suggest a non-trivial neuropsychiatric burden in these high-functioning retired players that extends beyond the increased depressive symptoms reported in previous *in vivo* studies (11–13). Our findings are also compatible with the sporadic cases of *retrospectively* identified aggression and mania in post-mortem studies of retired football players (15).

Regarding the question of whether the findings above are attributable to having sustained multiple concussions or rather to pre-morbid characteristics of this unique cohort of individuals (i.e., retired CFL players), we examined the role of concussion exposure. We found a significant effect of exposure for the *Depression* clinical scale, but not the *Aggression* and *Mania* scale scores. However, on more fine-grained analyses, proportionately more former professional football players met threshold for a clinical diagnosis of mania/hypomania in the higher concussion exposure group than the lower exposure group. Moreover, unlike the low exposure group, the higher concussion exposure group had more clinical diagnoses on the MINI than control participants. Nonetheless, further research is needed to understand the role of concussion exposure (both

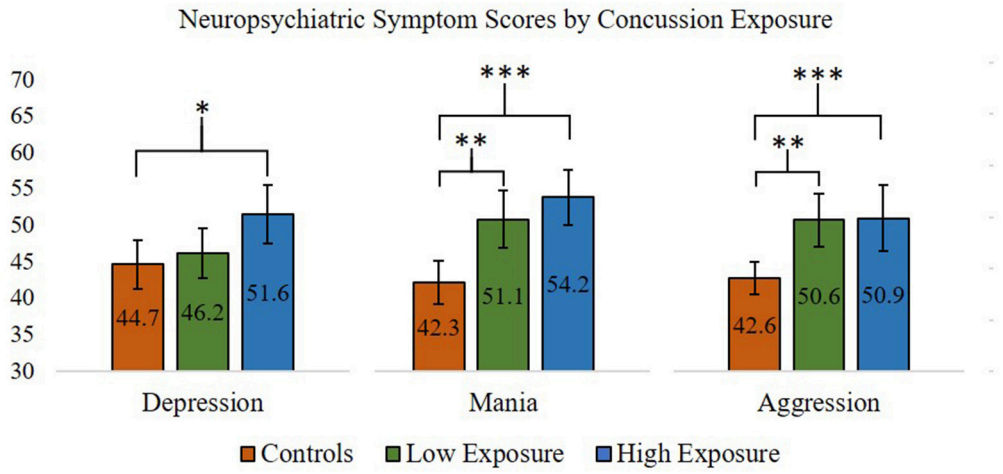

FIGURE 1 | ANOVA and *post-hoc* test results comparing Personality Assessment Inventory Depression, Aggression, and Mania scale scores (presented in T-scores) between former professional football players with higher (>3) and lower (≤3) self-reported concussion exposure and control participants. *$p < 0.05$; **$p < 0.01$; ***$p < 0.001$. Error bars = 95% confidence intervals.

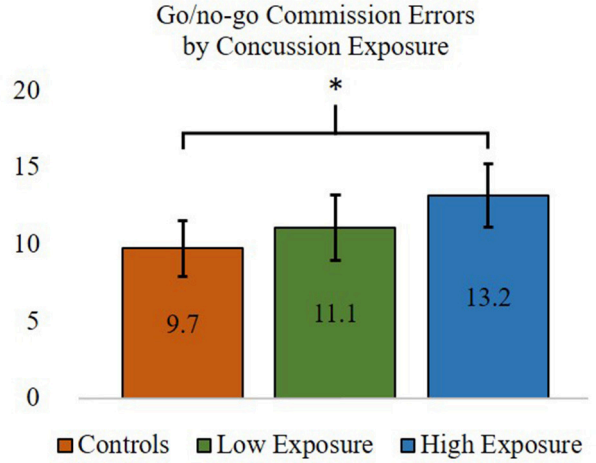

FIGURE 2 | ANOVA and *post-hoc* test results comparing inhibitory control—commission errors (out of a possible 25) between former professional football players with higher (>3) and lower (≤3) self-reported concussion exposure and the control group. *$p < 0.05$. Error bars = 95% confidence intervals.

number and severity) in neuropsychiatric functioning in this population, including research into the structural underpinnings of neuropsychiatric functioning given our prior pilot findings showing that higher aggression scores correlated negatively with orbitofrontal cortex thickness and uncinate fasciculus axial diffusivity (17). An alternative explanation for the current findings—that higher pre-morbid mania symptoms increase risk of sustaining more concussions—should be examined as well. In short, concussions appear to increase manifestation of certain neuropsychiatric characteristics. However, as elite football may select for traits associated with mania and aggression, some outcome variance may be explained by pre-morbid/cohort characteristics. Taken together, the above results suggest that people with a remote history of multiple concussions sustained in contact sports contend with non-trivial neuropsychiatric symptoms and should be considered for comprehensive neuropsychiatric assessment. Many efficacious treatments exist for neuropsychiatric dysfunction, both psychological (e.g., cognitive behavior therapy) and pharmacological (55, 56). Research is needed to evaluate the extent to which those with a remote history of multiple concussions sustained outside of contact sport may be suffering the same neuropsychiatric burden.

Turning to the cognitive characterization, the only measure that discriminated the full group of former professional football players from control participants was inhibitory control (i.e., commission errors on the SART). These results are partially consistent with a previous study in former professional football players, which found impairments to executive function, but not in the absence of other cognitive impairments (22). It was unexpected that no other cognitive measures, including learning and memory, discriminated former professional football players from control participants[1] (18). The pattern of findings may reflect both the higher functioning of our sample compared to those in other studies (8, 18, 22) as well as the sensitivity of the SART task—and the importance of inhibitory control—in this population.

Although inconsistency of responding (calculated using IIV on the SART) did not discriminate the retired players from controls or the higher concussion exposure group from the lower exposure group (though marginally significant differences were observed), it *was* predictive of neuropsychiatric outcomes in

[1]Given this deviation from past findings, we attempted to obtain a more sensitive index of memory impairment by individually bench-marking memory function against estimated pre-morbid IQ (i.e., an IQ-MQ split). However, again, there was no significant difference between the groups.

TABLE 4 | Hierarchical linear regression in the prediction of retired players' Depression, Mania, and Aggression scores on the Personality Assessment Inventory.

	β	ΔR^2
A. Regression predictors of PAI Depression		
Step 1		
Concussion exposure	0.26*	0.066*
Step 2		
Concussion exposure	0.21	
SART commission errors	0.25	0.060
Step 3		
Concussion exposure	0.17	
SART commission errors	0.11	
SART IIV	0.30*	0.067*
Total R^2: 0.194		
B. Regression predictors of PAI Mania		
Step 1		
Concussion exposure	0.15	0.022
Step 2		
Concussion exposure	0.11	
SART commission errors	0.21	0.042
Step 3		
Concussion exposure	0.07	
SART commission errors	0.09	
SART IIV	0.25	0.047
Total R^2: 0.112		
C. Regression predictors of PAI Aggression		
Step 1		
Concussion exposure	0.01	0.000
Step 2		
Concussion exposure	−0.02	
SART commission errors	0.16	0.025
Step 3		
Concussion exposure	−0.08	
SART commission errors	−0.03	
SART IIV	0.40**	0.121**
Total R^2: 0.146		

*$p < 0.05$; **$p < 0.01$. PAI, Personality Assessment Inventory; SART, Sustained Attention to Response Task.*

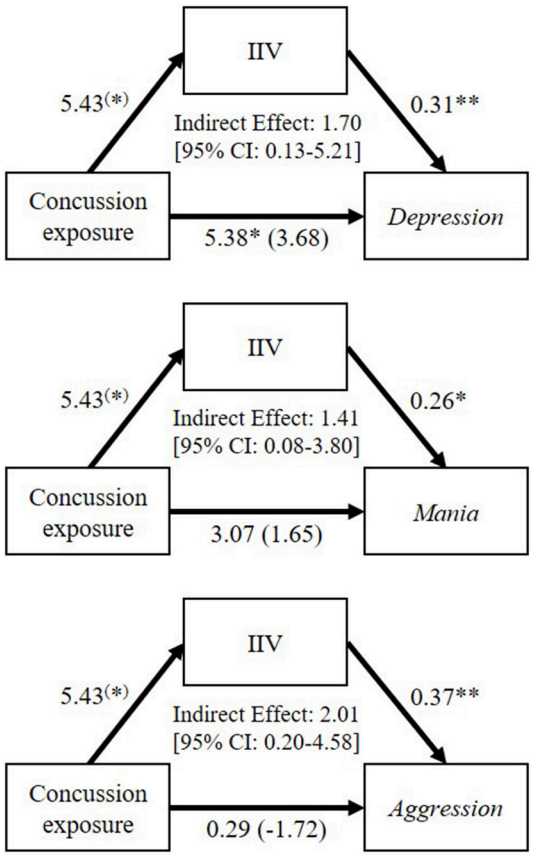

FIGURE 3 | Mediation analyses to examine the mediating role of go/no-go reaction time intra-individual variability (IIV; inconsistency of responding) on the relationships between former professional football players' self-reported concussion exposure and their Depression, Mania, and Aggression scores on the Personality Assessment Inventory. Values accompanying each arrow represent unstandardized regression weights. The unstandardized regression coefficients between concussion exposure and each neuropsychiatric variable, controlling for IIV, are in parentheses. $^{(*)}p < 0.10$; $^{*}p < 0.05$; $^{**}p < 0.01$.

the former players—in particular, PAI *Depression* and *Aggression* scores. We thus examined whether inconsistency of responding might mediate the relationship between concussion exposure and neuropsychiatric symptoms in the former players given that executive functioning has been implicated in neuropsychiatric dysfunction (31–33), and that in our pilot study of former professional football players, we found that executive function deficits and neuropsychiatric symptoms correlated with the same structural findings (17). A series of mediation analyses revealed that former players' concussion exposure had a significant indirect effect on their PAI *Depression*, *Aggression*, and *Mania* scores via inconsistency of responding. These results offer an interesting and novel hypothesis to be tested in future research: that impairment to one aspect of executive functioning (i.e., inconsistency of responding) renders individuals with a history of multiple concussions more vulnerable to the manifestation of neuropsychiatric symptoms including depression, mania, and aggression. In other words, in the absence of this deficit, these symptoms may not be manifested.

Our findings suggest that executive functioning should be assessed carefully, and with more than just traditional clinical measures; in this study, conventional measures were less sensitive than our experimental ones. Encouragingly, there are known treatments for executive dysfunction, including Goal Management Training (GMT) (57). GMT has been shown to improve executive functioning (measured using the same go/no-go task used in our study) in patients with frontal lobe brain damage (58). Notably, participants improved on inhibitory control (commission errors) from pre- to post-GMT, and benefits were maintained at 4-month follow-up (58). Participants also showed marginally significant improvements in inconsistency of responding (indexed by

IIV) from baseline to follow-up. Another intervention, with the potential to improve both executive and neuropsychiatric functioning is mindfulness training (59–61), which has been shown to decrease inconsistency of responding (62, 63) and to improve response inhibition accuracy (63). Previous research has also demonstrated that mindfulness meditation may enhance emotion regulation through improvements in executive functioning (59), results consistent with our finding that self-reported concussion exposure was indirectly associated with neuropsychiatric symptoms via IIV.

Our study has limitations that affect the generalizability of the current findings. The use of self-reported concussion history is problematic because recollection of concussion is considered only moderately reliable (52). We sought to address this limitation with our use of a binary concussion history variable as opposed to a continuous variable, a method for estimating concussion exposure employed in previous studies (12, 20). The current study may also be limited by self-selection biases. For example, participants in this study may represent former CFL players who were experiencing neuropsychiatric and cognitive concerns and therefore sought out a research study that would help to address them. It should be noted, however, that our sample comprised retired players with a history of concussion who were high-functioning (based on self-report of current occupational and social functioning). Most of the players reported that they entered the study to support their fellow players. Another potential limitation was our use of community control participants, as opposed to professional athlete control participants without a history of concussion. To help address this issue, we conducted subgroup comparisons within the former professional football player group to differentiate former players as a function of concussion exposure. Comparing individuals within the same population was done in an effort to distinguish cognitive and neuropsychiatric findings attributable to concussion exposure vs. cohort characteristics (64). Finally, in the current cohort study, we cannot ascertain whether the selective impairments observed represent the residual effects of original concussions or a *de novo* disorder, perhaps associated with the aging process.

In sum, we have presented a comprehensive neuropsychiatric and cognitive profile of high-functioning former professional football players and a disproportionate, but treatable, burden of neuropsychiatric and executive function deficits (the latter revealed on an experimental measure of executive function, the SART). Our findings also revealed a novel potential treatment target for remediating neuropsychiatric deficits—inconsistency of responding—that warrants further research. Future research should also examine the extent to which these findings generalize to those with a remote history of multiple concussions sustained *outside* the context of contact sport.

From a neurorehabilitative point of view, people with a remote history of multiple concussions, particularly when sustained in the context of contact sport, should be considered for comprehensive neuropsychiatric assessment (and treatment) and for careful evaluation of executive dysfunction, with an emphasis on both inhibitory control and inconsistency of responding (i.e., IIV).

DATA AVAILABILITY

The datasets generated for this study are available upon request to the corresponding author.

ETHICS STATEMENT

This study was approved by the University Health Network Research Ethics Board, Toronto, ON, Canada.

CONSENT STATEMENT

All participants of this study provided their informed consent in person prior to the face-to-face study assessment and written informed consent.

AUTHOR CONTRIBUTIONS

RG, AT, BC, and BV contributed conception and design of the study. BC and AT organized the database. AT and BV performed the statistical analyses. RG and AT wrote the first draft of the manuscript. BV wrote sections of the manuscript. MT, CT, KD, DM, RG, and RW were involved in the conceptualization and data collection for the larger study, of which the current study is a part. All authors contributed to manuscript reviewing and editing.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2019.00712/full#supplementary-material

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REVIEW
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Methylphenidate Treatment of Cognitive Dysfunction in Adults After Mild to Moderate Traumatic Brain Injury: Rationale, Efficacy, and Neural Mechanisms

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Positive effects of methylphenidate (MPH) on attention and cognitive processing speed have been reported in studies of patients with moderate to severe traumatic brain injury (TBI). Studies which have acquired functional brain imaging before and while using MPH have also found alteration of brain activation while performing a cognitive task; in some studies, this alteration of activation in selective brain regions was also related to improved performance on cognitive tests administered outside of the scanning environment. Enhanced cognitive performance has been reported after single doses of MPH and after daily treatment over durations of up to and exceeding 1 month. Preclinical research and both positron emission tomography and single photon emission tomography of humans have shown that MPH increases extracellular dopamine and norepinephrine; the dose effects of MPH have an inverted *U*-shaped function where high doses may cause insomnia, nervousness, and increased heart rate among other symptoms and impair cognitive performance, whereas too low a dose fails to improve cognitive performance. In the past 5 years, small clinical trials, and experimental pilot studies have found therapeutic effects of single and repeated low doses of MPH in patients with mild TBI who reported cognitive dysfunction. This literature also suggests that MPH may interact with concurrent cognitive interventions to enhance their effects. This focused review will critically evaluate the recent literature on MPH effects on cognitive dysfunction after mild to moderate TBI. To elucidate the neural mechanisms of MPH effects, this review will also include recent imaging research, preclinical, and experimental human studies.

Keywords: traumatic brain injury, methylphenidate, clinical trials, imaging, dopamine, cognition

INTRODUCTION

Methylphenidate (MPH) is a dopamine and noradrenaline agonist which has stimulant effects. It is widely prescribed in clinical settings (1) and is used in research. The primary objective of this review is to describe and critique clinical trials of MPH that have focused on improving cognitive performance and cognitive ("mental") fatigue in persons who sustain mild to moderate traumatic brain injury (TBI). Although other catecholaminergic medications will be briefly considered, we will focus on MPH because it is the most investigated drug in this category, it is widely prescribed in rehabilitation, and in follow-up care for TBI (2, 3). Related objectives include examining the premise for using MPH to treat cognitive dysfunction in TBI; brain imaging and experimental evidence for the neural mechanisms which underpin MPH's effects; methodological issues in clinical trials of MPH; and its potential role as an adjuvant in cognitive rehabilitation. The clinical trials listed in Clinical trials.gov (see https://clinicaltrials.gov; Accessed February 14, 2019) that enrolled adult participants with a spectrum of TBI severity will be summarized. Finally, we will review the subset of published investigations that studied adult participants with mild to moderate TBI.

MECHANISM OF EFFECTS, SCIENTIFIC PREMISE, AND INVERTED *U*-SHAPED FUNCTION OF PERFORMANCE BY DOSE

Mechanism of Therapeutic Effect on Cognition

The positive effects of MPH on cognition in conditions characterized by low dopamine are achieved by reducing reuptake of extracellular dopamine by the dopamine transporter (DAT) which is most densely represented in a group of contiguous subcortical structures in the forebrain, including the caudate, putamen, and nucleus accumbens and, to a lesser extent, in prefrontal cortex (3). Although MPH also affects reuptake of noradrenaline, the literature supports modulation of dopamine levels as the primary mechanism of clinical improvement in studies of TBI (3). MPH has also been the most frequently used dopamine agonist in clinical trials to treat cognitive deficit after TBI (3).

Premise for MPH Treatment of Post-TBI Cognitive Deficit

The premise for using MPH to ameliorate cognitive deficits is based on several related lines of research. First, evidence suggests mediation of cognitive function by stimulation of dopaminergic and noradrenergic receptors in prefrontal cortex and in subcortical regions (3, 4). Additionally, the architecture of these neuromodulatory transmitter systems renders them vulnerable to injury as they originate within brainstem nuclei, project widely throughout the brain, and include neurons with long fibers, diffuse arborization, high baseline activity, and little or no myelination (3, 5). This diffuse distribution and fragile neuronal structures make these systems especially susceptible to both mechanical and metabolic injury (e.g., diffuse axonal injury) (3). Third, animal and clinical studies have provided evidence for catecholaminergic disruption following TBI (6, 7). Finally, dopamine levels have been shown to increase during the acute post-injury period within brain areas that include the medial prefrontal cortex, striatum, brainstem, and hypothalamus (3, 8). Such increases are then followed by a hypodopaminergic state characterized by a reduction in dopamine release and other alterations that decrease the overall level of dopaminergic function (3, 9).

Similarly, shortly after TBI there is also an acute increase in noradrenaline which is then followed by a reduction in noradrenergic activity (3). Imaging studies have confirmed these changes; positron emission tomographic imaging (PET) and single photon emission computed tomography (SPECT) have shown reduced dopamine transporter (DAT) binding secondary to lower dopamine levels (3, 4, 10). Jenkins et al. (10) also found that slow cognitive processing speed after moderate to severe TBI was specifically related to reduced DAT binding in the caudate. A recent translational SPECT investigation of moderate to severe TBI patients found that those with low pretreatment DAT level in the caudate showed significant improvement in complex reaction time (RT) after taking 0.3 mg/kg MPH for 2 weeks in a randomized cross-over design (11). In contrast, complex RT did not change in a placebo condition and MPH effects on performance were not significant in patients who had normal baseline levels of DAT. Although self-rated fatigue was reduced in both the low and normal baseline DAT level subgroups, a diminution of self-rated apathy was found only in the low DAT subgroup. In summary, these studies support the premise that MPH-related improvement in cognitive performance is mediated by increased dopamine level.

FUNCTIONAL MAGNETIC RESONANCE IMAGING (FMRI) STUDIES OF MPH

Application of Task Related fMRI to Study Neural Mechanisms of Cognitive Dysfunction After TBI

Task-related fMRI has been used to explore cognitive dysfunction following TBI, including studies employing pharmacological interventions and working memory paradigms [e.g., (12, 13)]. Following mild traumatic brain injury (mTBI), fMRI showed problems with the allocation of neural resources while engaged in working memory tasks. Activation of brain regions such as dorsolateral prefrontal cortex was excessive at low to moderate task difficulty levels, while higher task demands resulted in little or no additional increase in neural processing resources (12, 14). Preliminary research has started to address how modulation of brain activation might be improved through pharmacological manipulations (6). Although most fMRI studies involving pharmacologic agents have focused on moderate to severe TBI, we included them in **Table 1** because they provide proof of principle concerning dopaminergic mechanisms in task-related activation and provide a framework for investigation of

TABLE 1 | MPH interventions in adults with a history of TBI ranging from mild to severe (see ClinicalTrials.gov).

Study title and identifier	Brief description	Design and study population	Treatment schedule	Outcome measures	Study results and limitations
Cognitive remediation after trauma exposure trial = CREATE Trial (CREATE) NCT01416948	To evaluate the efficacy of MPH and galantamine in the treatment of persistent cognitive symptoms associated with PTSD and/or TBI	Randomized, double-blind, placebo-controlled, parallel assignment; adults with mild to moderate TBI and/or PTSD	MPH 20 mg b.i.d., or galantamine 12 mg b.id., or placebo for 12 weeks	RNBI, RPSQ, RAVLT, TMT, subtests of WAIS-III, BVMT-R, PASAT, CPT, PTSD Checklist—specific event version, and Patient Health questionnaire-9	Study was terminated due to lack of recruitment-−32 participants out of proposed 159; Limitation- mixed TBI/PTSD population
Dopamine receptor imaging to predict response to stimulant therapy in chronic TBI NCT02225106	To evaluate PET imaging with [11C]-raclopride, a D2/D3 receptor ligand, before and after administering MPH, to measure endogenous dopamine release in TBI patients with problems in cognition, attention, and executive function	Non-randomized one-time placebo and one-time MPH, after that MPH for 4 weeks; adults with moderate to severe TBI	MPH 60 mg one-time, after that 30 mg b.i.d.; 4 weeks	CVLT, TMT, Subtests of the WAIS-IV, RPSQ, Sustained arousal and attention task 50/50; Dual task; Distraction task; Sustained attention to response, and Test of everyday attention	Study was completed with actual enrollment of 11 out of proposed 30; No results available; Limitations- small sample size, no randomization
MPH (Ritalin) and Memory/Attention in traumatic brain injury (TBI) NCT00453921	To compare the results of three interventions: memory and attention training, MPH, and memory/attention training in combination with MPH and use functional MRI to characterize changes in activation of the neural circuitry of memory and attention in study groups	Randomized, double-blind, placebo-controlled, parallel assignment; adults with mild to severe TBI	MPH 0.3 mg/kg b.i.d.; 7 weeks	CVLT, CPT, and Functional MRI task performance and brain activation (N-back)	All $p < 0.05$; Limitations- small sample size (18–20 participants in each group), wide range of TBI severity, and no info regarding participants' distribution of TBI severity
The relationship between traumatic brain injury and dopamine (a chemical in the brain) NCT02015949	To investigate if treatment with MPH improves cognitive functions in TBI, whether the mechanism involves a normalization of brain functioning and whether brain dopamine levels (measured by the SPECT and MRI) can predict the magnitude of any improvement in symptoms.	Randomized, cross-over, placebo controlled; adults ≥3 months post- moderate to severe TBI	MPH 0.3 mg/kg b.i.d. or placebo for 2 weeks	CRT and relationship of CRT to specific binding ratio of the dopamine transporter (DAT) in the striatum. Patients were divided into low vs. normal DAT level based on their DAT binding ratio on SPECT.	All participants completed trial ($n = 40$, 20 assigned to each MPH-placebo sequence). CRT was reduced (faster) in the low DAT subgroup while on MPH as compared to placebo; fatigue improved when on MPH.

MPH, methylphenidate; TBI, traumatic brain injury; b.i.d., bis in die (latin) or two times a day; BVMT-R, Brief Visuospatial Memory Test-Revised; CPT, Continuous Performance Test; CRT, Choice Reaction Time task; CVLT, California Verbal Learning Test; MRI, Magnetic Resonance Imaging; RAVLT, Rey Auditory Verbal Learning Test; RNBI, Ruff Neurobehavioral Inventory—Post-morbid Cognitive Scale; RPSQ, Rivermead Post-concussion Symptom Questionnaire; PASAT, Paced Auditory Serial Addition Test; PTSD, post-traumatic stress disorder; SPECT, Single Photon Emission Computed Tomography; TMT, Trail Making Test; WAIS, Wechsler Adult Intelligence Scale.

drug effects to treat persistent cognitive dysfunction after less severe TBI.

Current Status of fMRI Studies Using Catecholaminergic Agents

MPH is thought to act through mechanisms that block the reuptake of dopamine and noradrenaline, as well as an increase in dopamine release (3). Together, such actions elevate extracellular concentrations of both of these catecholamines to produce stimulatory effects. However, the only pharmacological studies that have used functional neuroimaging to study mTBI have used other catecholaminergic agonists, bromocriptine and guanfacine, and their action differs from that of MPH (13, 15). Bromocriptine is a selective D_2 dopamine receptor agonist with complex, dose-dependent effects (3). This agonist binds to presynaptic auto-receptors which inhibit dopamine release, as well as post-synaptic sites. At high doses, the excitatory post-synaptic effect is thought to predominate with a net result that facilitates dopaminergic function. In contrast, guanfacine is a selective α-2A adrenergic agonist which acts on receptors that are concentrated predominantly within the prefrontal cortex and the locus coeruleus, resulting in stimulation of the noradrenergic system (3, 6).

Using a single-dose pharmacological challenge approach with block design fMRI, Mcallister et al. (13) and Mcallister et al. (15) examined the effects of bromocriptine or guanfacine on activation during an auditory letter n-back working memory task. In one study, they administered guanfacine to 13 mTBI patients and 14 healthy control subjects within 1 month of injury as part of a double blind, placebo-controlled crossover design (15). The n-back task had three levels of difficulty and, for mTBI patients, noradrenergic stimulation improved performance at the intermediate level (i.e., 2-back), while the control subjects experienced a decline. Functional neuroimaging with the mTBI patients revealed an activation increase within the right frontal lobe (e.g., middle frontal gyrus) during the guanfacine condition, while the control subjects had activation increases within areas outside of working memory circuitry.

Mcallister et al. (15) used the same working memory paradigm and study design with 26 mTBI patients and 31 control subjects to investigate the D_2 dopamine receptor agonist bromocriptine. This manipulation did not alter performance for the control subjects, but mTBI patients experienced declines during the 0-back and 3-back task conditions. The activation patterns found with bromocriptine were essentially the opposite of those observed with guanfacine, including increased frontal activation in the control subjects and increases outside of working memory circuitry for subjects with mTBI. When considered in combination, the findings for bromocriptine and guanfacine are consistent with different neural and behavioral responses to different types of catecholaminergic intervention after mTBI.

According to Mcallister et al. (6), alterations in central catecholaminergic sensitivity impair working memory and contribute to cognitive complaints shortly after mTBI, but the effectiveness of different pharmacological interventions for improving cognitive function likely depends upon factors such as the type of catecholaminergic stimulation and the dose. In particular, stimulation of the prefrontal noradrenergic system appears to have the potential to enhance working memory performance following mTBI (15). Although these studies (13, 15) did not examine MPH in patients with mTBI, others have used functional neuroimaging to study activation changes associated with MPH in patients with injuries of greater severity [e.g., (16)].

Current Status of fMRI Studies Using MPH

Newsome et al. (16) examined the effects of a 1-month MPH intervention in patients with moderate to severe TBI. Using a double blind, placebo-controlled design, they administered either a placebo or 15 mg of the drug twice a day for a month with pre-treatment and end-of-treatment scanning performed using a block design visual n-back task with face stimuli. Four TBI patients received MPH and the other five were in the placebo group. In a whole brain analysis examining the 2-back minus 0-back contrast, this MPH treatment, relative to placebo, reduced activation within areas thought to have a role in working memory, such as the anterior cingulate gyrus, cuneus, and cerebellum. An *a priori* region of interest analysis also found treatment-related reductions within the anterior cingulate gyrus.

Studies of moderate to severe TBI using single-dose pharmacological challenge approaches have also provided evidence for alterations in working memory activation following MPH administration (17, 18). Manktelow et al. (18) used a double blind, placebo-controlled crossover design to study the effects of a single 30 mg. dose in 15 patients with moderate to severe TBI and 15 healthy controls. Using a block design visual letters n-back task, Manktelow et al. reported that the controls performed better than the TBI patients during the placebo condition, but there was no significant between-group difference after administration of the MPH. In TBI patients the drug increased task-related activation within a portion of the left cerebellum to a level comparable to controls and this change was correlated with the improvement in working memory performance. Kim et al. (17) used perfusion fMRI and a block design visual letters n-back task with 21 moderate to severe TBI patients. The pharmacological challenge consisted of a single dose (0.3 mg/kg) of MPH that was delivered as part of a randomized double-blind, placebo-controlled crossover study design. The MPH improved RT, with a trend toward greater task accuracy, and on functional neuroimaging there was also a trend toward a global reduction of cerebral blood flow under all of the task conditions, including the rest blocks. These findings suggest the possibility of a general mechanism of action for cognitive enhancement associated with MPH in patients with moderate to severe TBI.

Visual attention and response inhibition are cognitive functions that have also been studied in moderate to severe TBI patients using MPH (17, 19). In addition to the n-back working memory paradigm that was described above, Kim et al. (17) also employed the Visual Sustained Attention Task (VSAT) block design fMRI paradigm with 18 of their study participants. The administration of a single dose of MPH (0.3 mg/kg) improved both VSAT RT and accuracy. Also, during the MPH condition, there was deactivation within the left posterior

superior parietal cortex that was correlated with improved RT. These authors concluded that suppression of activation within this brain region may represent a mechanism through which MPH improves visual attention impairment following TBI. Use of a single 30 mg dose has also been found to be related to activation on event-related fMRI using the stop signal task, which is a challenging measure of response inhibition. Moreno-López et al. (19) used this fMRI paradigm in a randomized double blind, placebo-controlled crossover study with 14 moderate to severe TBI patients and 20 healthy controls. Under the placebo condition the TBI patients had decreased task-related activation, relative to control subjects, within the right inferior frontal gyrus. However, the administration of MPH increased activation within this structure to a level that was similar to that of the control subjects.

In summary, fMRI research addressing neural mechanisms associated with MPH's cognitive effects following TBI has been limited. Although previous fMRI research has often reported the presence of greater and more diffuse activation following TBI (20–22), the more recent task-related fMRI studies of MPH found that the drug altered activation in the direction approximating healthy controls. However, the brain regions most affected by MPH depended on the specific tasks used as represented in **Figure 1**. These changes in activation were generally correlated with improved cognitive performance.

These findings were interpreted as providing evidence for the normalization of working memory activation following the 1-month MPH intervention. To our knowledge, no studies have specifically studied activation changes in patients with mTBI using MPH, but the other catecholaminergic drugs guanfacine and bromocriptine have been examined using a working memory paradigm, and the findings suggest the possibility of different effects associated with the stimulation of dopaminergic and noradrenergic systems (6, 13, 15). Since MPH acts on both of these neuromodulatory systems (i.e., MPH is a dual agonist), there is a justification for further research to determine how this particular drug alters brain function to improve performance following mTBI. However, several studies with moderate to severe TBI have been conducted and, although the details of their findings are inconsistent, there is some preliminary evidence that administration of MPH may normalize the pattern of activation in a way that enhances performance.

High variability in the cognitive response and functional imaging findings may reflect heterogeneity of the neuropathology associated with TBI (3). Current status of fMRI studies using individual differences in the level and type of injury-related cognitive impairment (3, 6), non-linear relationships between catecholamine levels and cognitive function (23), subject factors such as age and genetics (3, 6), and between-study differences in research design and statistical power, also contribute to the variability in findings across studies (22). Differences in the reduction of dopamine among patients sustaining TBI of apparently similar acute severity is another source of variability in response to MPH both in changes of task related activation and improvement in cognitive performance.

CLINICAL TRIALS OF MPH AND OTHER CATECHOLAMINERGIC DRUGS

Clinical trials of MPH have studied neurologic disorders involving low levels of brain dopamine, especially in the striatum. Currently over 300 clinical trials of MPH have been posted on the ClinicalTrials.gov website with 195 of them on adults (see https://clinicaltrials.gov/ct2/results?term=methylphenidate&cond=brain+injury, accessed February 01, 2019). The majority of these studies involve developmental attention-deficit/hyperactivity disorder (ADHD), followed by narcolepsy and chronic fatigue syndrome due to multiple sclerosis, other autoimmune conditions, or as a result of cancer treatment. Several trials of MPH were designed to enhance gait and balance in Parkinson's disease and to alleviate apathy in patients with Alzheimer's disease or other dementia. In contrast, relatively few trials of MPH were designed to improve cognitive functioning following TBI.

Clinical trials of MPH to treat cognitive deficits after TBI have mostly enrolled moderate to severely injured patients and these studies have been reviewed recently (2, 3, 10). **Table 1** summarizes those trials in Clinical Trials.gov that focused on moderate to severe TBI or enrolled patients representing a spectrum of TBI severity. **Table 2** summarizes the clinical trials of MPH and related drugs that have enrolled mild to moderate TBI patients. These clinical trials to date have aimed at treating cognitive deficit rather than impacting disability. The clinical

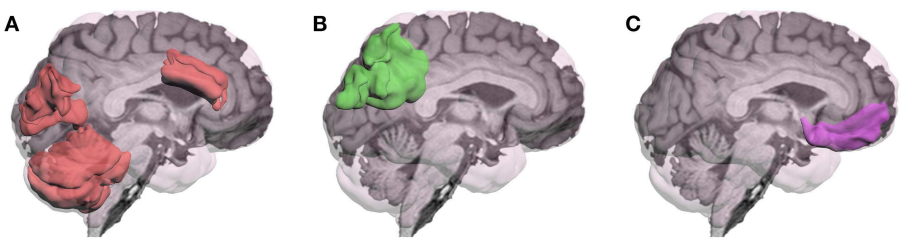

FIGURE 1 | Brain regions in which methylphenidate (MPH) has modulated activation during performance of cognitive tasks in patients with TBI have varied depending on the specific cognitive task: **(A)**Visual Working Memory: activation by an n-back task for photos of faces was modulated in anterior cingulate gyrus, cuneus, and cerebellum (16), and for letters in left cerebellum (18); **(B)** Visual Sustained Reaction Time (RT): MPH modulated deactivation of left posterior superior parietal region (17); **(C)** Response Inhibition: MPH modulated activation by the stop signal RT task in the right inferior frontal gyrus (19).

TABLE 2 | Clinical Trials of Methylphenidate in Adults with History of Mild to Moderate TBI.

Article (First author and year)	Participants in each group (N), mean age (SD), Chronicity	Study design, max MPH dose, duration of treatment	Cognitive measures	Results/ *p*-values	Limitations
Lee et al. (24)	MPH ($N = 10$); 35.3 (8.0) Placebo ($N = 10$); 35.5 (7.2); Chronicity: 2weeks-1 year;	Randomized, double-blind, placebo-controlled, parallel design; 20 mg; 4 weeks	Critical flicker fusion threshold, CRT, CTT, MAT, Sternberg memory scanning task, DSST, and MMSE	Significant treatment effect $p < 0.05$	All participants were diagnosed with major depression; small sample size
Johansson et al. (25)	$N = 29$; 38.6 (11.1); Chronicity:8.6 years (5.1)	Prospective, open-label, crossover; No MPH, Low dose MPH, Normal dose MPH- 4 weeks/each; max dose- 20 mg	MFS	Significant treatment effect with $p < 0.001$	No placebo-control; small sample; no cognitive testing; participants Selected or mental fatigue and pain $\geq$ 12m
Johansson et al. (26)	$N = 44$; 38.9 (10.8); Chronicity: 8.2 years (5.7)	Prospective, open-label, crossover; No MPH, Low dose MPH, Normal dose MPH- 4 weeks/each; max dose- 20 mg	DSC and DS (WAIS-III), TMT, and MFS	DSC: $p = 0.04$ MFS: $p < 0.001$ All other: $p > 0.1$	Lack of placebo-control; patients selected for moderate disability, mental fatigue, pain
Mcallister et al. (27)	MPH ($N = 9$); 36.7 (9.3) Placebo ($N = 12$): 44.4 (8.2) Chronicity: N/A	Randomized, double-blind, placebo-controlled; 20 mg; 12 weeks	RAVLT, DS, RNBI, RPSQ, and TMT	RNBI: $p = 0.004$ DS: $p = 0.011$ All other: unknown	Small sample size; mixed mTBI/PTSD population in both groups
Johansson et al. (28)	$N = 30$; 39.7 (12.5); Chronicity: 8.6 years (5.9)	Prospective, open-label, max dose- 20 mg; 6 months; patients were responders to MPH in prior phase	DSC and DS (WAIS-III), TMT, and MFS	All $p < 0.001$	Lack of placebo-control; small sample size;
Zhang and Wang (29)	MPH ($N = 18$); 36.3 (10.9); Placebo ($N = 18$): 34.9 (12.1); Chronicity: 46.5 days (6.8), MPH; 46.1 days (7.2), placebo	Randomized, double-blind, placebo-controlled; 30 weeks	MFS, CRT, CTT, MAT, DSST, and MMSE	MFS: $p = 0.005$ MAT: $p = 0.02$ All other: $p < 0.001$	Small sample size
Jonasson et al. (30)	$N = 18$; 44.9 (10.4); Chronicity: ~22 months post-injury; patients were responders in prior trial	Prospective, open-label, max dose- individual; 4 weeks after a 4 weeks period off MPH	DSC and DS (WAIS-III), and MFS	DSC: $p < 0.001$ DS: $p = 0.011$ MFS: $p < 0.001$	Lack of placebo-control design; small sample size

MPH, Methylphenidate; TBI, traumatic brain injury; CRT, Choice Reaction Time task; CTT, Compensatory Tracking Task; DS, Digit Span; DSC, Digit Symbol Coding; DSST, Digit Symbol Substitution Test; MAT, Mental Arithmetic Test; MFS, Mental Fatigue Scale; MMSE, Mini-Mental State Examination; N/A, not applicable; RNBI, Ruff Neurobehavioral Inventory-Post-morbid Cognitive Scale; RPSQ, Rivermead Post-concussion Symptom Questionnaire.

trials included in **Table 2** were identified by searching PubMed, published meta-analyses, and reviews.

The trials described below used MPH to treat persistent cognitive symptoms, cognitive impairment, and cognitive (or "mental") fatigue following mild to moderate TBI, including patients who had mild or no impairment of consciousness but sustained brain lesions or other pathology identified by imaging ("complicated mTBI"). The rationale for focusing on mild to moderate TBI is that this range of severity accounts for over 80% of the 2.8 million acute TBI population treated in emergency departments annually in the USA (31). The subgroup of the mild to moderate TBI population who have cognitive impairment persisting for 3 months or longer is estimated to be ∼15–30% which represents a large, underserved population (32). However, there is a paucity of high-quality longitudinal follow-up studies using cognitive tests to evaluate recovery in patients with this range of acute TBI severity. This gap in clinical trials of MPH for cognitive deficit after mild to moderate TBI is concerning because cognitive dysfunction impacts return to work and other activities which affect quality of life. In addressing this gap in clinical trials of MPH, it is important to consider the methodological issues in study design and conduct as described below.

MATERIALS AND METHODS

Methodological Issues in MPH Clinical Trials

Variation in Severity and Chronicity of TBI

There is wide variation in the severity and chronicity of TBI represented in trials that have enrolled a spectrum of TBI severity (**Table 1**). However, the studies summarized in **Table 2** are more homogeneous as they enrolled patients with mild to moderate TBI.

Eligibility Criteria for Enrollment

There is also variation across trials in the eligibility criteria for enrollment; some screened for impaired cognitive performance in addition to self-report of cognitive dysfunction, whereas other studies relied on self-report, clinical observations and clinical judgment, and/or report by a collateral source. Studies have also differed in screening for co-morbidities, including depression, anxiety, post-traumatic stress disorder and ADHD; some trials excluded depressed patients to isolate cognitive effects of MPH from MPH- related improvement of mood. Screening for symptom validity and effort is also an issue because patients seeking compensation may exaggerate their cognitive impairment or expend less than full effort in their performance on cognitive tests.

Study Design

Table 2 shows variation in study design; randomized, clinical trials using placebo-control groups have been limited by small sample sizes, whereas crossover designs have mitigated this problem. An additional advantage of crossover designs is that they are robust to the considerable heterogeneity in TBI pathology even in patients with equivalent TBI severity. The short washout (≈24 h) of MPH is also well-suited for crossover designs as placebo and drug conditions can be scheduled with separation by a brief interval. Administering MPH at the same time each day is also recommended to mitigate confounding by chronobiologic variation. However, practice effects on cognitive tests are a potential confound, arguably more so in crossover designs, especially those that are open label. In addition, patients may experience increased arousal which cues them to the MPH phase of the study.

MPH Dose and Duration

Studies have ranged in duration of treatment from single administration of MPH and same day "challenge" testing to the cohort followed by Johansson et al. (30) who maintained MPH responders for 2 years following a 4-months interval without treatment. **Table 2** shows that the dose of MPH has ranged from 20 to 30 mg in studies using a fixed dose; other studies have used 0.3 mg/kg with the constraint of a maximum dose. Johansson et al. (30) have used an individualized dose escalation strategy which is atypical in the literature. Johansson et al. (30) maintained MPH responders for 2 years following a 4-months interval without treatment. She reported that MPH effects dissipated during this 4-months drug-free period, but the therapeutic effects of MPH on processing speed, working memory, and cognitive fatigue were reinstated when the patients resumed MPH according to the regimen described below.

In a crossover trial to treat cognitive fatigue, Johansson et al. (30) used a Latin Square design wherein each patient had 4 weeks in each of three different conditions: (1) no medication, (2) low dose MPH, and (3) normal dose MPH. There was no washout period because a short-acting preparation of MPH was used. The low and normal dose conditions included dose escalation during weeks 1–3, which rose to 60 mg/day in the fourth week of the normal dose condition. Of 29 patients (age 18–65 years) who were enrolled in the trial, 5 dropped out including 4 subjects who reported adverse events. Reduction of symptoms as measured by the Mental Fatigue Scale (MFS) (33), was greater in the normal and low dose MPH conditions as compared to no medication and symptom reduction under the normal dose exceeded that of the low dose condition. Conceptually, the MFS has ecological relevance because it queries about variation in fatigue at different times of the day and its effects on psychological health and sleep. In this respect, the MFS compliments measures of cognitive performance which may take an hour or two but possibly overlook the cumulative effects of work or study over hours in the course of the patient's daily schedule (33).

Although dose escalation adds complexity to a trial, it may be more representative of clinical practice and is advisable for older patients. To this point, Jonasson et al. (30) screened for cardiovascular health, including electrocardiography at each visit. The Jonasson et al. study's dose escalation approach is noteworthy because it may have optimized MPH treatment, ostensibly reaching the top of the inverted *U*-shaped function as represented in **Figure 2**.

Inverted U-Shaped Relation of Dose Level to Performance and Adverse Effects of MPH

The results of experimental research using animal models and clinical studies are consistent with an inverted U-shaped relation of cognitive performance to dose of MPH. **Figure 2**

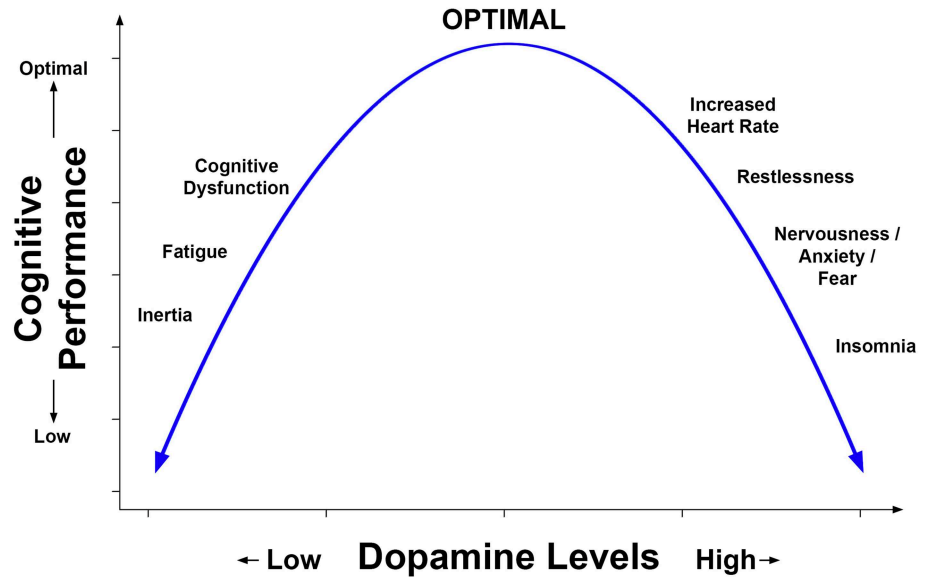

FIGURE 2 | Representation of the inverted *U*-shaped relation of prefrontal dopamine level to cognitive performance and symptoms. This relation is based in part on animal models including the work by Arnsten et al. (4) and has been described in reports concerning the effects of dopamine agonists on cognition and behavior in humans.

is a hypothetical representation of the results showing that cognitive performance is optimized by a moderate level of dopamine. This relation has been inferred (but not proven) from dose ranging studies of MPH which lacked a measure of dopamine. Suboptimal levels of brain dopamine are associated with fatigue, whereas excessively high levels can increase heart rate and produce symptoms such as nervousness, increased motor activity, and sleep disturbance. Baseline levels of dopamine are lower in older adults and reduced in neurologic conditions such as Parkinson's disease. A recent clinical SPECT investigation indirectly measured dopamine level by evaluating the binding of a radio ligand to DAT which was especially evident in the caudate (10). Consistent with the inverted *U*-shaped relation, these investigators found that moderate to severe TBI patients responded better to MPH on cognitive tests and reduction of fatigue if their baseline levels of brain dopamine were low, whereas patients who had normal levels of dopamine did not respond as well. Based on the above studies, screening for medical history and substance abuse, serial recording of adverse effects reported by the participant, and repeated measurement of vital signs is good practice for clinical trials of MPH.

Outcome Measures

Similar to variation in the enrollment criteria, clinical trials have varied in their use of self-report vs. cognitive performance measures. As described in the preceding section, cognitive ("mental") fatigue is a frequent complaint in the TBI population wherein the individual may be capable of performing the cognitive demands of a task or activity, but finds the process to be effortful and tiring as compared to her/his pre-injury level. Patients also reported that cognitive fatigue was present throughout the day. Interestingly, rating scale and visual analog scale measures of fatigue have been sensitive to MPH effects (30). In a recent translational study in moderate to severe TBI patients, Jenkins et al. (10) found that cognitive fatigue was sensitive to MPH in subgroups of participants who differed in level of pretreatment dopamine in the caudate based on SPECT using a ligand for dopamine.

Of the cognitive performance measures, complex RT, go no-go RT, cognitive processing speed, and set shifting tests have been widely used. Episodic multi-trial recall memory and working memory tests have also been employed, but less frequently than processing speed and RT tests. **Tables 1**, **2** show that some studies have relied on self-report of cognitive functioning in everyday activities as measured by various scales. From the perspective of ecological validity, a combination of cognitive performance and self-report measures is recommended as used by Jenkins et al. (10).

Few clinical trials of MPH have used composite measures to assess cognitive performance. Although a composite measure has the advantage of evaluating diverse cognitive operations, specific cognitive tasks such as working memory are supported by preclinical research implicating prefrontal dopamine receptors (4) and measures of cognitive processing speed have been especially sensitive to MPH in clinical trials. As seen in **Table 2**, timed tests that have been sensitive to MPH include Trail Making, Complex RT, Digit Symbol Substitution and Coding subtests, and Sternberg Memory Scanning, which measures changes in RT depending on the number of items to be held in memory.

Concurrent Cognitive Training and MPH Treatment

In view of the positive effects of MPH on attention, processing speed, and fatigue, it is plausible that MPH may enhance the effects of cognitive training. In a study which enrolled patients

representing a wide spectrum of acute TBI severity, Mcdonald et al. (34) found that 0.3 mg/kg of MPH taken over 7 weeks enhanced the effects of memory and attention training in a controlled study.

DISCUSSION

Despite relatively few postings on ClinicalTrials.gov, there is a considerable body of literature related to using MPH to treat cognitive complaints, cognitive deficits, and mental fatigue following mild to moderate TBI (2). Most of the previous reviews included studies with a wide range of TBI severity (with majority of them on moderate to severe range) (35, 36) and age (from children to older adults) (37). All of the above-mentioned studies have considerable limitations due to small sample sizes, enrollment of individuals with co-morbid depression (24, 27) or use of open-label design (25, 26, 28, 30). Hence, there is an evident need for well-designed and adequately powered, double blind, placebo-controlled clinical trials that will extend our knowledge of neural mechanisms of MPH effects and provide valuable information for clinicians and researchers.

Of considerable note, there is no consensus on whether to include screening measures of cognitive performance to substantiate self-report of cognitive dysfunction in everyday activities. If cognitive performance measures are used to screen for eligibility, they should tap the constructs that patients complain about. Few studies have obtained ratings of cognitive function by collateral sources and measures of symptom validity or effort expended during testing have generally not been used. Based on Mcdonald et al.'s (34) work, trials combining MPH with cognitive training also appear to be justified. Imaging biomarkers of dopamine and/or MPH effects also enhance the rigor of clinical trials.

CONCLUSIONS

The extant evidence supports further investigation of MPH for use in treating cognitive dysfunction and mental fatigue following mild to moderate TBI. However, there is a need for phase 3 clinical trials to evaluate the effectiveness of MPH and identifying the specific context of use in which it is most strongly indicated.

AUTHOR CONTRIBUTIONS

HL, RS, and MT wrote the main manuscript text. EW, TA, and JP edited the paper. TA designed and produced the figures. JH reviewed and verified manuscript and figures. JP revised and formatted the manuscript according to the journal's guidelines.

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Neurocognitive and Quality of Life Improvements Associated With Aerobic Training for Individuals With Persistent Symptoms After Mild Traumatic Brain Injury: Secondary Outcome Analysis of a Pilot Randomized Clinical Trial

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Objective: To report secondary neurocognitive and quality of life outcomes for a pilot randomized clinical trial (RCT) of aerobic training for management of prolonged symptoms after a mild traumatic brain injury (mTBI) in adolescents.

Setting: Outpatient research setting.

Participants: Thirty adolescents between the ages of 12 and 17 years who sustained a mTBI and had between 4 and 16 weeks of persistent post-concussive symptoms.

Design: Secondary outcome analysis of a partially masked RCT of sub-symptom exacerbation aerobic training compared with a full-body stretching program highlighting cognitive and quality of life outcomes.

Main Measures: The secondary outcomes assessed included neurocognitive changes in fluid and crystallized age-adjusted cognition using the National Institutes of Health (NIH) toolbox and self and parent-reported total quality of life using the Pediatric Quality of Life Inventory.

Results: Twenty-two percent of eligible participants enrolled in the trial. General linear models did not reveal statistically significant differences between groups. Within group analyses using paired *t*-tests demonstrated improvement in age-adjusted fluid cognition [$t_{(13)} = 3.39$, $p = 0.005$, Cohen's $d = 0.61$] and crystallized cognition

[$t_{(13)} = 2.63$, $p = 0.02$, Cohen's $d = 0.70$] within the aerobic training group but no significant improvement within the stretching group. Paired *t*-tests demonstrated significant improvement in both self-reported and parent-reported total quality of life measures in the aerobic training group [self-report $t_{(13)} = 3.51$, $p = 0.004$, Cohen's $d = 0.94$; parent-report $t_{(13)} = 6.5$, $p < 0.0001$, Cohen's $d = 1.80$] and the stretching group [self-report $t_{(14)} = 4.20$, $p = 0.0009$, Cohen's $d = 1.08$; parent-report $t_{(14)} = 4.06$, $p = 0.0012$, Cohen's $d = 1.045$].

Conclusion: Quality of life improved significantly in both the aerobic exercise and stretching groups; however, this study suggests that only sub-symptom exacerbation aerobic training was potentially beneficial for neurocognitive recovery, particularly the fluid cognition subset in the NIH Toolbox. Limited sample size and variation in outcomes measures limited ability to detect between group differences. Future research should focus on developing larger studies to determine optimal timing post-injury and intensity of active rehabilitation to facilitate neurocognitive recovery and improve quality of life after mTBI.

Clinical Trial Registration: www.ClinicalTrials.gov, identifier: NCT02035579.

Keywords: mTBI (mild traumatic brain injury), aerobic training, neurocognitive, quality of life, pediatrics

INTRODUCTION

Mild traumatic brain injury (mTBI) is a significant cause of morbidity in adolescents, however, little research exists on how best to aid neurocognitive recovery and maximize quality of life for these children. Children and young adults are estimated to have over one-million emergency department visits annually in the United States (1). While physical symptoms such as headache, nausea, and blurry vision are common after mTBI, neurocognitive deficits also need to be addressed to ensure the highest level of recovery. Children often present with neurocognitive changes including poor concentration, decreased processing speed, and slowed reaction time after mTBI (2–4). These symptoms can make return to school more difficult and every day functioning challenging for the children and their families. After mTBI, the majority of children have complete resolution of their symptoms in the first few weeks, however, a small portion continue to face recovery challenges, with ∼12% of children showing persistent symptoms 3 months post-injury (5). Studies indicate a history of multiple mTBIs and pre-existing psychiatric conditions put children at risk for prolonged recovery and potentially, a reduction in quality of life related to persistent problems (6).

Mild traumatic brain injury causes dysregulation of cerebral blood flow and neurochemical changes in the brain resulting in a metabolic and energy imbalance that can persist months post-injury (4, 7). Evidence supports that these physiologic alterations are responsible for mTBI symptoms including mental fogginess, fatigue, mood changes, and emotional disturbances (8). These symptoms may contribute to known neurocognitive changes after mTBI including altered attention, processing time, and working memory (3, 8).

Currently, there is no definitive treatment for persistent symptoms after mTBI. Aerobic exercise is a potentially promising intervention as it is believed to improve cerebral blood flow and neurometabolic physiology in the brain (9, 10). Aerobic exercise is felt to improve physiologic brain dysfunction and consequently have a positive impact on neurocognitive symptoms (9, 10). Aerobic exercise programs have emerged as a safe and feasible rehabilitation strategy for patients with mTBI (11–15).

Multiple studies focusing on mTBI recovery provide preliminary evidence for the efficacy of aerobic exercise in promoting symptom improvement (11–15). A recent systematic review identified a variety of positive outcomes related to exercise training after mTBI (12). Exercise has been associated with reduced symptoms, faster return to full function, reduced days of recovery, and improved reaction times (11, 13–15). However, these prior findings were limited with regard to other outcome measures, including neurocognitive and neuropsychological outcomes, and there is a paucity of RCTs characterizing how exercise may specifically result in improvements in such outcomes. Animal models evaluating aerobic exercise have demonstrated positive changes in gene plasticity of the hippocampus, which is responsible for memory (16), raising the possibility of improvements on neurocognitive testing in adolescents who engage in aerobic exercise training. It is critical to evaluate the range of potential advantages of aerobic exercise as a treatment, especially in the adolescent population, for whom a non-invasive and non-pharmacologic option may be particularly beneficial.

In the original report of this exploratory randomized clinical trial (RCT), participants in both the aerobic and stretching groups demonstrated a downward trend in Post-Concussion Symptom Inventory (PCSI) ratings, with the aerobic

training group showing a greater decrease in PCSI ratings than the stretching group (11), indicating that a sub-symptom exacerbation aerobic exercise program may be beneficial to patients with post-concussive symptoms compared to a full-body stretching program. Since the stretching group showed improvement as well, minimal activity may even be beneficial in the recovery process.

The goal of this paper was to characterize the effect of aerobic training on the secondary outcomes of neurocognitive functioning and quality of life. Neurocognitive outcomes were assessed using the fluid and crystallized cognitive subsets of the NIH Toolbox (17, 18). Fluid cognition includes episodic and working memory, processing speed, attention and executive function while crystallized cognition encompasses language (18). We hypothesize that fluid cognitive function would improve with aerobic exercise as it is often affected after mTBI (3, 9). Furthermore, crystallized cognition, which is considered a fixed measure, is not expected to change with intervention. Additionally, we hypothesized that aerobic training would also be associated with improvements in quality of life.

METHODS

Design

We conducted an exploratory RCT to determine the benefits of a 6-week, sub-symptom exacerbation aerobic training compared to a full-body stretching intervention in adolescents with persistent symptoms after injury. This clinical trial was registered through clinical trials and the registration number is NCT02035579. Randomization was stratified by age (12–14 and 15–17 years) and sex. The study was single blinded; evaluators were unaware of group assignment (11).

Participants

As described previously (11), adolescents between the ages of 12 and 17 years were recruited from outpatient clinics, emergency departments, and communities throughout the Cincinnati, Ohio area between September 1, 2013 and February 1, 2015. Individuals were considered for participation if they had sustained an mTBI, experienced between 4 and 16 weeks of persistent symptoms, and endorsed that these symptoms were exacerbated with physical activity. **Table 1** lists exclusion criteria that were applied.

As reported previously (11), a total of 395 individuals were evaluated for eligibility and 136 were deemed eligible (**Figure 1**). Of the eligible participants, 102 declined participation due to lack of interest, time commitment, ongoing recovery, and "other" reasons. Thirty-four completed a baseline assessment. At the baseline assessment, four individuals were excluded because of medication usage or lack of symptoms during the biking protocol. A total of 30 participants were randomized. All participants provided written informed consent and assent in accordance with good clinical practices and local IRB standards. Written parental consent was obtained for all participants under the age of 16.

TABLE 1 | Exclusion criteria.

1. Unable to speak and or read English
2. Evidence of more severe TBI
3. Preexisting neurological impairment
4. Cognitive disorders
5. History of psychological diagnosis
6. Developmental delay
7. Genetic disorders
8. Metabolic disorder
9. Cognitive disorders
10. Hematologic disorders
11. Cancer
12. Neck pain
13. Pre-injury diagnosis of ADHD
- Requiring 2+ medications
- Medication changes in last 1 month
14. Current participation in other therapy
15. History of cardiovascular problems
16. Recent/upcoming medication dose changes
- Beta-blockers
- Antidepressants
- Antianxiety medications
- ADHD medications
- Prophylactic headache medications
- Mood behavioral medications

Study Procedure

At the baseline visit (week 0), participants were evaluated for eligibility and an aerobic bike test was conducted. Participants began biking at a speed consistent with a Borg rate of perceived exertion (RPE) of 11 (fairly light), with the bikes (Exerpeutic upright exercise bike) set at resistance at level 2, for 5 min, then increased RPE by 1 at 5-min intervals for 30 min (max intensity of 16) or until they experienced symptoms. Participants unable to complete at least 2 min of cycling before experiencing symptoms and participants able to complete the full 30 min test without experiencing symptoms were excluded from further participation in the trial. Participants who were not excluded moved to a run-in period, allowing an opportunity to monitor for any changes in symptoms that may occur as part of natural recovery (**Figure 1**).

At the week 1 visit, participants were again evaluated for eligibility then randomized into either the sub symptom exacerbation aerobic training group or the full body stretching group (11). The aerobic training group repeated the aerobic cycling test that was performed at the baseline assessment in order to create a customized home exercise program. Participants were given the same model exercise bike to use at home for the duration of the study and were asked to complete their individually tailored cycling program 5–6 days per week at 80% of the duration that exacerbated symptoms during study visits. The cycling program was repeated at each of the following six visits and based on the results, the home exercise program was adjusted for each participant in the aerobic training

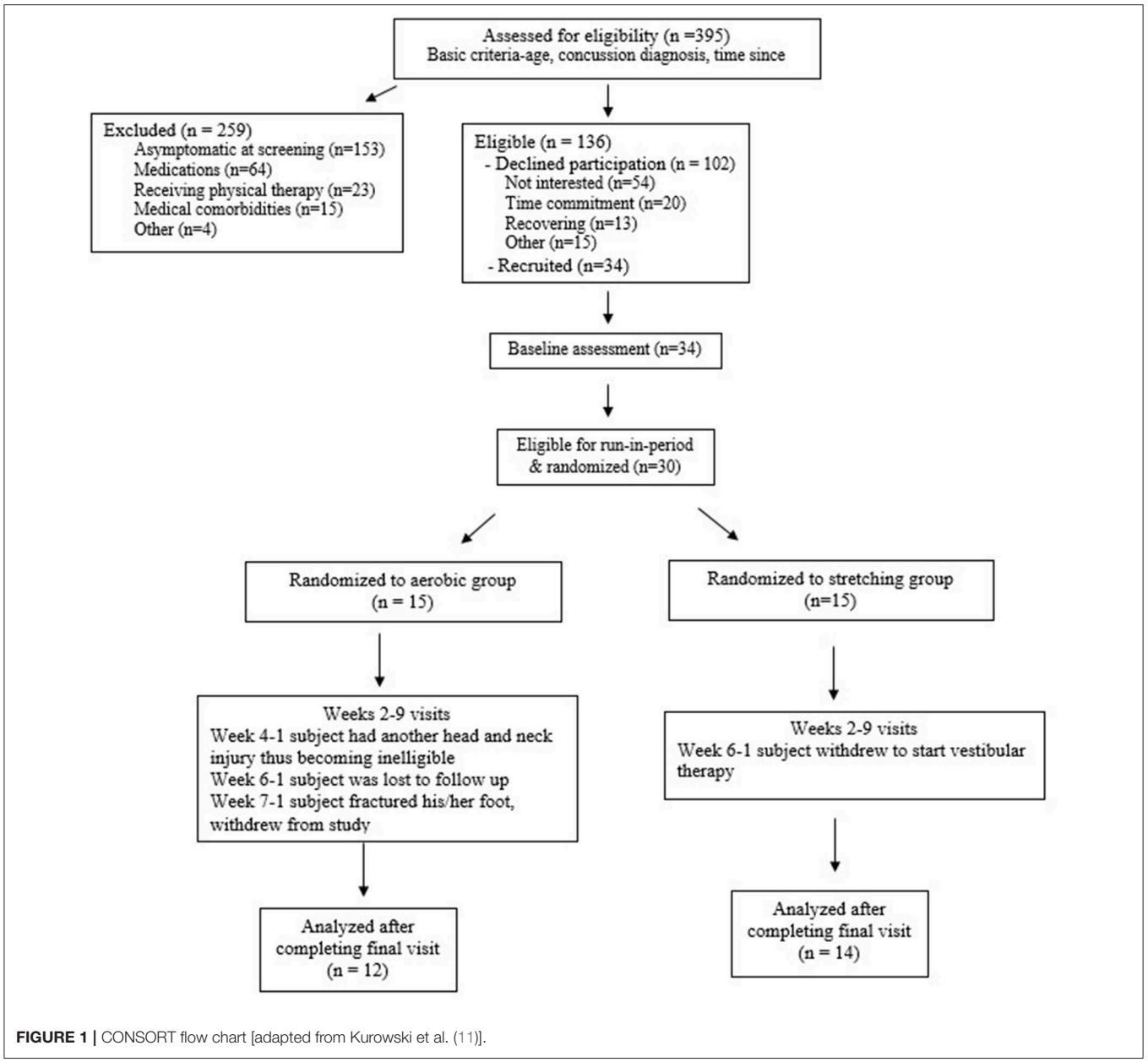

FIGURE 1 | CONSORT flow chart [adapted from Kurowski et al. (11)].

group. Participants returned the bikes at study completion. Participants in the stretching group were instructed on a full-body stretching program to be completed at home 5–6 days per week. The stretching group reviewed the program at weekly intervals and received a new group of stretches every 2 weeks, targeting a variety of upper extremity, lower extremity, and trunk muscles (11).

Participants in each arm of the study were asked to complete at least 6 weeks of training. They were considered fully recovered and transitioned to a run-out period if they were able to complete the cycling test without symptom exacerbation. Those who did not return to their baseline after 6-weeks of training remained in the program for up to two additional weeks prior to moving to the post-intervention run-out period (11).

Adherence and Adverse Events

Adherence and adverse events for this study were reported previously (11). Participants in the stretching group reported completing sessions more times per week than the aerobic exercise group, mean number of times per week were 5.85 (1.37) and 4.42 (1.95) ($p < 0.0001$), respectively (11). Adverse events encountered during the study were unrelated to the study protocol itself, for example one subject fractured his/her foot and another had a new head and neck injury (11).

Outcome Measures

Both the NIH Toolbox and PedsQL (self-report and parent proxy forms) were administered at baseline and at the end of the intervention. The NIH Toolbox is a multidimensional

set of measures that can be used to assess cognitive, sensory, motor, and emotional function in individuals ages 3–85 years (17). The Toolbox has been validated and normed in a broad sample of the US population. The NIH Toolbox Cognition Battery was used to assess global cognition (17). It consists of tests of executive function, attention, episodic memory, language, processing speed, and working memory (17). This battery yields the following summary scores, in addition to individual measure scores: Cognitive Functioning Composite Score, Fluid Cognition Composite Score, and Crystallized Cognition Composite Score. Composite scores (age-adjusted crystallized cognition, age adjusted fluid cognition, and age adjusted total cognition scores) were used as dependent variables.

The pediatric Quality of Life Inventory (PedsQL) generic core was used to assess quality of life. The PedsQL is composed of 23 items that measure physical, emotional, social, and school functioning (19–21). Self-report forms are validated for children 5–18 years and parent-report forms have been developed for children 2–18 years. The PedsQL has been used in pediatric TBI as a measure of quality of life (22–25). PedsQL total score was used as the dependent variable in analyses.

Other outcome variables and results from this RCT have previously been published, including findings that aerobic exercise training may result in faster symptom recovery (11) and improved structural connectivity in brain networks (26).

Sample Size

In the primary outcome paper (11), we determined that 15 participants would be needed per group to detect an effect size of 1.25 at an alpha of 0.05, power of 0.9 and a 10% drop out rate (11). Effect sizes of 0.2, 0.5, and 0.8 are consider small, medium, and large, respectively (27). Power and sample size calculations were based on symptom recovery trajectory.

Analysis

General linear models were used initially to examine the effect of group (aerobic vs. stretching) status on post-intervention scores, controlling for baseline scores. No significant group effects were noted in any of the post-intervention outcomes. Due to the pilot/exploratory nature of this study, separate paired samples *t*-tests were used to explore pre-post differences within each group, and Cohen's *d* was used to characterize the magnitude of change within each group. The Shapiro-Wilk (28) test indicates that data are unlikely to violate normality for all outcomes evaluated ($p > 0.05$), except for the post-intervention self-report PedsQL ($p = 0.04$) and parent-report PedsQL ($p = 0.01$) in the aerobic group (see **Supplemental Table 1**).

RESULTS

There were no between group differences noted for participant race, sex, age, primary caregiver level of education, household income, prior history of concussion, and time since injury. The full body stretching group was more likely to have a non-sports related mechanism of injury but both groups had the same number of participants in organized sport (**Table 2**). In the aerobic training group, six out of 12 did not return to baseline and required a further 2 weeks of training. Individuals in the aerobic group that returned to baseline earlier were similar to individuals that did not return to baseline with respect to age, sex, race, time since injury, and initial symptom ratings (11).

TABLE 2 | Comparison of baseline data between intervention and comparison groups [adapted from Kurowski et. al. (11)].

	Cycling ($n = 15$)	Stretching ($n = 15$)	*P*-value
Age at enrollment, mean (SD), *y*	15.22 (1.37)	15.50 (1.80)	0.64
Time since injury, mean (SD), *d*	52.30 (19.93)	55.95 (22.16)	0.64
Sex (males), *n*	5	8	27
Race (non-white), *n*	2	2	1.00
Primary caregiver education (with bachelor degree or higher), *n*	9	7	0.46
Income ($70,000 and above annual income), *n*	9	9[a]	0.81
Mechanism of injury (sports-related), *n*	6	12	0.03
Number reporting typical participation in an organized sport prior to injury, *n*	13	13	1.00
History of two or more concussions (including injury related to this study), *n*	10	6	0.14

[a] *The value is based on n = 14, primary caregiver unavailable or declined to provide information.*

General linear models did not reveal statistically significant effect of treatment group (aerobic and stretching groups) on any of the neurocognitive or quality of life measures. However, paired *t*-test models demonstrated significant pre-post differences in the fluid and crystallized age-adjusted test measures from the NIH Toolbox (**Table 3**) within the aerobic training group but not the stretching group. The aerobic training group demonstrated a significant pre-post increase in age-adjusted fluid cognition [$t_{(13)} = 3.39$, $p = 0.005$, Cohen's $d = 0.611$] and age-adjusted crystallized cognition scores [$t_{(13)} = 2.63$, $p = 0.02$, Cohen's $d = 0.704$]. The stretching group failed to demonstrate significant pre-post changes in fluid cognition [$t_{(13)} = 1.08$, $p = 0.30$, Cohen's $d = 0.338$] or crystallized cognition scores [$t_{(14)} = 1.79$, $p = 0.09$, Cohen's $d = 0.425$]. A significant pre-post increase in the age-adjusted total cognition score was noted for both the aerobic training [$t_{(13)} = 5.13$, $p = 0.0002$, Cohen's $d = 1.370$] and stretching groups [$t_{(13)} = 3.10$, $p = 0.01$, Cohen's $d = 0.82$].

Individual subgroups of fluid cognition in the aerobic exercise group showed statistically significant improvement on all subtests including attention, reaction time, cognitive flexibility, episodic memory, working memory, and processing speed tested by flanker inhibition [$t_{(13)} = 3.90$, $p = 0.0018$, Cohen's $d = 1.040$], dimensional change card sorting [$t_{(13)} = 3.16$, $p = 0.01$, Cohen's $d = 0.844$], picture sequencing [$t_{(13)} = 3.09$, $p = 0.0085$, Cohen's $d = 0.827$], list sorting [$t_{(13)} = 3.07$, $p = 0.0090$, Cohen's $d = 0.820$] and pattern comparison [$t_{(13)} = 4.0$, $p = 0.0015$, Cohen's $d = 1.070$].

Paired *t*-tests also revealed substantial within group differences with pediatric quality of life total score (**Table 3**).

TABLE 3 | Neurocognitive and quality of life scores.

Measure	Aerobic exercise group					Stretching group				
	Visit1	Visit2	*t*-test	*p*-value	Cohen's d	Visit1	Visit2	*t*-test	*p*-value	Cohen's *d*
Fluid mean (SD)	88.98 (23.66)	107.36 (17.97)	$t_{(13)} = 3.39$	$p = 0.005$	0.611	99.38 (22.78)	105.28 (19.31)	$t_{(13)} = 1.08$	$p = 0.30$	0.338
Crystallized mean (SD)	101.29 (1.25)	107.60 (13.61)	$t_{(13)} = 2.63$	$p = 0.02$	0.704	107.27 (11.64)	110.48 (14.50)	$t_{(14)} = 1.79$	$p = 0.09$	0.463
Self-report PedsQL Mean (SD)	72.25 (14.68)	85.64 (12.09)	$t_{(13)} = 3.51$	$p = 0.004$	0.9375	71.09 (14.55)	81.64 (13.68)	$t_{(14)} = 4.20$	$p = 0.0009$	1.084
Parent-report PedsQL Mean (SD)	60.29 (12.25)	86.94 (12.46)	$t_{(12)} = 6.50$	$p < 0.0001$	1.802	61.59 (16.37)	80.00 (15.85)	$t_{(14)} = 4.06$	$p = 0.0012$	1.048

Significant pre-post increases on the PedsQL Total score were noted for both the aerobic [$t_{(13)} = 3.51$, $p = 0.004$, Cohen's $d = 0.938$] and the stretching [$t_{(13)} = 4.2$, $p = 0.0009$, Cohen's $d = 1.084$] groups. A similar pattern was noted for the equivalent parent-reported PedsQL measure with significant increases in Total PedsQL score in the aerobic [$t_{(12)} = 6.50$, $p < 0.0001$, Cohen's $d = 1.802$] and stretching [$t_{(12)} = 4.06$, $p = 0.0012$, Cohen's $d = 1.048$] groups.

DISCUSSION

Secondary findings of this exploratory RCT suggest sub-symptom exacerbation aerobic training is potentially beneficial (or at least not detrimental) for neurocognitive recovery and quality of life. This is consistent with the shift in current literature to support active rehabilitation programs in mTBI recovery instead of the classically prescribed rest (11, 12, 15, 29). Overall, age-adjusted scores in the fluid cognition category showed within-group improvement for the aerobic exercise participants but not those receiving the stretching intervention. These results are generally consistent with findings in a meta-analysis demonstrating improvement in reaction time scores, a fluid measure, with exercise after mTBI (12). Another recent study has also demonstrated improvement in quality of life when children with mTBI participate in an active exercise rehabilitation program (30). Understanding the presumed relationship between aerobic exercise and neurocognition improvements in the mTBI population requires a deeper look at a cellular and molecular level. Aerobic training has been shown to impact neuroplasticity through variety of mechanisms (31). With exercise, nerve growth factor (NGF) increases in the brain, leading to neurogenesis in the dentate gyrus of the hippocampus, which is ultimately responsible for learning and memory. Increased cerebral blood flow with aerobic exercise is thought to be the result of angiogenesis related to increased vascular endothelial growth factor (VEGF). Both of these mechanisms potentially may help explain why the improvement in fluid cognition were most notable in the aerobic exercise group. Timing is a key consideration when recommending aerobic exercise following mTBI. We studied adolescents starting aerobic exercise at least 4 weeks post-injury and were able to see significant improvements in fluid cognition. Recent studies demonstrated that earlier initiation of such protocols potentially leads to faster resolution of symptoms and earlier return to sport and school (14, 15), specifically initiating activity within 7 days may lead to a decrease in symptoms at a month (32). Our results may have shown even more dramatic improvement if aerobic exercise was initiated sooner in the recovery course. Determining the optimal timing of initiation and intensity of exercise that is optimal for each individual in their recovery course is critical needed for the field.

The ideal exercise intensity that should be utilized for managing recovery after TBI is unclear. The study described in this paper utilized a moderate intensity biking protocol which has been consistently demonstrated to be beneficial. Majerske et al. found that moderate intensity exercise after mTBI resulted in better outcomes on computerized neurocognitive testing when compared with high or low intensity activities (33). Another study demonstrated that strenuous exercise protocols are associated with improved post-concussive symptoms; however, neurocognitive recovery declined from day 2 to day 10 after initiation of the protocol (13). Studies in healthy children, adolescents and adults have shown that strenuous activity immediately to up to 3 h before testing can negatively affect cognitive assessment (34, 35). However, in other healthy and neurologic populations, high-intensity exercise seems to have a greater impact on brain plasticity and brain health (36–44). There is a critical need to continue to develop improved evidence to inform exercise prescription for children and adolescents after mTBI.

Our results supported the hypothesis that exercise may have a greater influence on fluid cognition, such as working memory, processing speed, and executive functioning, than crystallized cognition after mTBI. This finding is in agreement with other work that has demonstrated that fluid abilities are most affected by mTBI (3). Although learning effects typically are accounted for by the NIH Toolbox for crystallized cognition (17), due to the close, repetitive testing performed in this study, some learning effects may be present (45). Therefore, learning effects could

account for the subtle improvements in crystallized cognition seen in both the aerobic and stretching groups. For subsets of fluid cognition, the largest effect size was seen in the aerobic training group for the processing speed tests. Because both groups' scores at the final visit in our study were above the average fluid cognition subset score, the possibility of a learning effect should be considered.

We must also consider the fact that a truly "inactive" control group was not utilized since the stretching group still received an active, albeit minimal activity, intervention. Therefore, the improvement seen with the aerobic exercise may be more striking if compared to a true physical rest placebo (46). One study examined the effect of strict rest for 5 days following concussion and found higher report of symptoms and slower recovery in those with strict rest compared to those with 1–2 days of rest and progressive, gradual resumption of activity (46).

This secondary analysis also evaluated overall quality of life and demonstrated improvement in overall quality of life for both the self- and parent-reported PedsQL in the aerobic and stretching groups. This suggests that even a small amount of activity may have a positive influence on adolescent quality of life after mTBI in the setting of persistent post-injury symptoms. Alternately, since both protocol groups improved, these findings may be an artifact of natural recovery.

LIMITATIONS

The generalizability of this exploratory trial is limited by a variety of factors including sample size, high non-participation rate during selection process, exclusion of patients with neck and cervicogenic symptoms, and limited racial and socioeconomic diversity (11). Age and sex characteristics were similar between groups; however, due to the small sample size, subgroups analyses based on these factors is unwarranted; future larger studies are needed to better understand the association of age and sex with response to exercise. Additionally, this study focused on adolescences; therefore, extrapolation of findings to younger populations should be done with caution and future studies should potentially focus on this younger age range. Also, due to the small sample size, the study is at risk for non-normal distribution of data; therefore, interpretation of findings should be done with caution. Overall, there is a need for future studies with larger sample sizes to confirm the results of this study and characterize the association of an array of individual and injury factors on response to the intervention and outcomes to develop better precision medicine approaches. The full body stretching group was more likely to have a non-sports related mechanism of injury; however, reports of participation in sports was similar between groups. Higher baseline fluid cognition scores were noted in the stretching group compared with the aerobic group at initial testing. This may be due to an unknown characteristic which was not accounted for during study randomization. The higher baseline would have made it more difficult for the stretching group to improve compared to the aerobic group.

It is also important to note that fluid and crystallized cognition scores for both groups generally fell within the normal range. The average crystallized cognition scores before and after the protocols were above average for age. In addition, the baseline fluid cognition scores were below average and lower in the aerobic group compared to the stretching group which may have contributed to the significant changes found in this cognition subset. Another consideration is a ceiling effect may potentially be present since the post-intervention scores were above average in both fluid and crystallized cognition. The practice effect is another limitation of the study. It has been demonstrated that practice effects unlikely exist for crystallized cognition but might be important for fluid cognition (45). Therefore, it is difficult to say with absolute certainty how much of the improvement in fluid cognition is related to intervention, expected recovery, and practice effects.

Outcome reporting may have been biased since the structure of the study did not allow for double blinding. Reporting bias should be considered in regards to adherence as this was assessed by self-reported and parent-report only. It is possible that participants may have participated in activities outside of the study protocol that were unaccounted for and could have influenced the results.

CONCLUSION

Secondary findings from this exploratory RCT support that sub-symptom exacerbation aerobic training may potentially have positive effects on the neurocognitive recovery of fluid cognitive abilities such as working memory and executive function skills in adolescents with persistent symptoms after mTBI. Data also suggests that improvements in quality of life may be seen with both stretching and aerobic exercise protocols in this population. There is a critical need for continued development of evidence-based treatments for management of mTBI. Future studies should aim to determine optimal intensity and timing of physical activity after mTBI and how this can positively influence neurocognitive outcomes, quality of life, and global functioning.

DATA AVAILABILITY

The datasets generated for this study are available on request to the corresponding author.

ETHICS STATEMENT

This study was carried out in accordance with the recommendations of Cincinnati Children's Institutional Review Board (IRB) with written informed consent from all subjects. All subjects gave written informed consent in accordance with the Declaration of Helsinki. The protocol was approved by the Cincinnati Children's IRB.

AUTHOR CONTRIBUTIONS

Each author has made substantial contributions to study design, implementation, analysis, and/or write-up. All authors accept responsibility for reported research, and all authors

have participated in the concept and design, analysis and interpretation of data, drafting or revising of the manuscript, and have approved the manuscript as submitted.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2019.01002/full#supplementary-material

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Methodology and Implementation of a Randomized Controlled Trial (RCT) for Early Post-concussion Rehabilitation: The Active Rehab Study

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Background: Sports-related concussion (SRC) is a complex injury with heterogeneous presentation and management. There are few studies that provide guidance on the most effective and feasible strategies for recovery and return to sports participation. Furthermore, there have been no randomized studies of the feasibility, safety, and efficacy of early rehabilitation strategies across multiple sports and age groups. This international cluster-randomized pragmatic trial evaluates the effectiveness of early multi-dimensional rehabilitation integrated with the current return to sport strategy vs. the current return to sport strategy alone.

Methods: The study is a cluster-randomized pragmatic trial enrolling male and female athletes from 28 sites. The sites span three countries, and include multiple sports, levels of play (high school, college, and professional), and levels of contact. The two study arms are Enhanced Graded Exertion (EGE) and Multidimensional Rehabilitation (MDR). The EGE arm follows the current return to sport strategy and the MDR arm integrates early, MDR strategies in the context of the current return to sport strategy. Each arm employs a post-injury protocol that applies to all athletes from that site in the event they sustain a concussion during their study enrollment. Participants are enrolled at pre-season baseline. Assessment timepoints include pre-season baseline, time of injury (concussion), 24–48 h post-injury, asymptomatic, and 1-month post-injury. Symptoms and activity levels are tracked post injury through the return to play process and beyond. Injury and recovery characteristics are obtained for all participants.

Primary endpoints include time to medical clearance for full return to sport and time to become asymptomatic. Secondary endpoints include symptom, neurocognitive, mental status, balance, convergence insufficiency, psychological distress, and quality of life trajectories post-injury.

Discussion: Outputs from the trial are expected to inform both research and clinical practice in post-concussion rehabilitation across all levels of sport and extend beyond civilian medicine to care for military personnel.

Ethics and Dissemination: The study is approved by the data coordinating center Institutional Review Board and registered at clinicaltrials.gov. Dissemination will include peer-reviewed publications, presentation to patients and public groups, as well as dissemination in other healthcare and public venues of interest.

Clinical Trial Registration: www.ClinicalTrials.gov, identifier: NCT02988596

Trial Funding: National Football League.

Keywords: traumatic brain injury, exercise, clinical intervention, post-concussion activity, return to play

INTRODUCTION

Concussion is a complex injury. Athletes who sustain a sports-related concussion (SRC) present with a diverse array of symptoms and recovery trajectories (1). Unfortunately, there is limited empirical evidence for clinicians to use in selecting the most effective and feasible strategy for recovery, rehabilitation, and return to sport. Currently, return to activity recommendations are based on expert consensus, with relatively few randomized controlled studies directly evaluating return to sport strategies (2). There are few clinically directed and pragmatic options to guide clinicians responsible for implementing concussion treatment/rehabilitation, particularly during the early acute/sub-acute presentation phase. A conservative strategy of restrictive physical and cognitive rest (i.e., removing athletes from participation and placing him/her on rest until normal brain functioning returns), was long considered to be the preferred therapeutic option for athletes post-concussion and was endorsed as the standard of practice by expert panels (3). This strategy is often frustrating for athletes, given they tend to be physically-focused, task-orientated individuals. In fact, recent evidence suggests that strict, total rest may actually prolong functional recovery following concussion (4). Over the past 5 years the evidence base concerning active management and rehabilitation strategies for concussion has significantly grown and suggests various interventions may be beneficial, especially in athletes with prolonged symptoms (5–7) However, it remains unclear to what extent these active strategies can be employed without negatively affecting recovery (e.g., exacerbating symptoms, prolong symptom recovery, etc.). There is scientific and clinical concern that prematurely implementing overly-aggressive activities has the potential to worsen symptoms and delay return to activity in athletes (8, 9).

There are limited data promoting a systematic approach to early rehabilitation and post-concussion activity that is modifiable throughout the return to sport process based on symptom presentation and sport specific requirements. Young adults with cervicogenic and vestibular symptoms experiencing prolonged concussion symptoms demonstrated improved outcomes and accelerated recovery when engaged in targeted therapy to address these dysfunctions (10–12). Aerobic exercise within a symptom limited heart rate range also improves recovery and outcomes in individuals with prolonged symptoms (6, 13). However, such interventions may not consider other areas such as balance or visual disturbance and have not been fully evaluated in the context of the current return to sport paradigm in a pragmatic field setting. While some of these studies were published after the current trial protocol development, they serve as evidence for the need to further evaluate various intervention methods post-concussion, even today.

To date, no studies have addressed key and focused strategies that can be feasibly implemented at a low cost and with few resources early in the treatment process. Furthermore, no studies have prospectively evaluated the current return to sport strategy and direct integration of early, multifaceted activities into this paradigm. Additionally, no studies to date have developed a comprehensive strategy for providers to begin engaging athletes with clinically directed and symptom-based activities immediately following the recommended (14) 24–48 h rest period. Such studies are needed for application across a wide variety of sports medicine and clinical settings. In order to develop best practices for the safe and effective use of these new therapies, there is a need for **pragmatic field trials** to support the accurate development of guidance for the use of early, active rehabilitation therapies, relative to current practice.

To address this gap, we are conducting a pragmatic cluster-randomized trial with two parallel groups. Of note, the trial was designed in 2016 and the outcomes and interventions selected were based on the following factors most relevant and applicable at that time: (1) common data elements in large-scale concussion studies (15); (2) pragmatic assessments and exercises that would apply in a variety of settings and that do not require extensive resources; and (3) logical intersection with the current return to sport paradigm. The trial includes athletes of varying age and levels of skill, from multiple countries, from multiple sports, and across multiple care models to understand the influence of early activity in the context of the return to sport strategy on outcomes following sport-related concussion. The two Specific Aims for this trial are to: (1) evaluate the effectiveness of the enhanced graded exertion (EGE) progression (current return to sport strategy) vs. an early, activity rehabilitation [multidimensional rehabilitation (MDR)] strategy; and (2) evaluate the safety and feasibility of these protocols.

METHODS AND ANALYSIS

Overview and Structure of the Active Rehab Study

The Active Rehab Study Consortium was initially proposed in 2014 through an international meeting that included representation from the scientific community and sporting organizations. The core idea of a multi-sport, multi-age, and multi-country study evaluating treatment and management of concussion was refined into a formal protocol over a period of months by an executive research consortium. They titled this project "Role of Active Rehabilitation in Concussion Management: A Randomized Controlled Trial (The Active Rehab Study)." The final consortium, led by The University of North Carolina at Chapel Hill and Medical College of Wisconsin, includes collaborators and sites from the Canadian Football League (CFL, 9 team sites), New Zealand Super Rugby (NZR, 5 team sites), North American Colleges/Universities (6 school sites), and Wisconsin and North Carolina High Schools (8 school sites). Sports represented in the study include collision, contact, and non-contact sports for both males and females. Should professional cohort sample size not approximate anticipated numbers, an additional professional ice-hockey cohort may be included. The study is conducted in compliance with US and international guidelines for research under the primary protocol approval from The University of North Carolina at Chapel Hill Institutional Review Board. All participants provide written and informed consent prior to participation. Informed consent documentation is verified via an informed consent tracking form in the study data collection system and through communication with study cohort leads and sites throughout the course of the study.

Allocation to Study Arm

The two treatment arms (multidimensional active rehab and EGE progression) are assigned at random to the 28 sites in the study. Site level (cluster) randomization is utilized because the study team considered that patient-level randomization at a site would be prone to contamination between arms. Thus, all athletes at a given site receive the same protocol. All study sites are randomized to either the MDR (early rehabilitation) or the EGE [current return to sport strategy (16)]. To ensure a balanced of treatment arms across cohort, site randomization is stratified by (i.e., conducted within) cohort (NZR, CFL, College, HS). Colleges/universities and high school sites are stratified by size of school prior to randomization; CFL and NZR sites are not stratified. Due to the nature of the early and active treatment delineation, no allocation concealment such as masking or blinding is possible. The clinicians (site personnel) at the sites know their allocated arm. However, participants are not explicitly told about the role of their respective study arm. Site personnel at the MDR sites are trained to deliver the treatment separately from the site personnel at the EGE sites.

Participants and Eligibility Criteria

The inclusion criteria for participants in the trial are individuals rostered as an athlete at the study sites who consent to the study. Written, informed consent is administered during a pre-season baseline assessment. Target participant enrollment across all settings is estimated to be 3,500 at baseline and 100–200 in each study arm (total $n = 200–400$) post-injury. The post-injury protocol includes all consented athletes with a SRC at each site and meeting the following criteria.

Our current trial aligns with common elements from the NCAA-DOD Grand Alliance Concussion Assessment, Research, and Education (CARE) Consortium (15). As such, we have defined SRC in accordance with the Department of Defense (DoD) operational definition as *a change in brain function following a force to the head, which may (or may not) be accompanied by temporary loss of consciousness (if LOC, temporary is defined as <30 min based on the Mayo TBI severity guidelines), but is identified in awake individuals with measures of neurologic and cognitive dysfunction, as indicated by 1 or more of the 22 symptoms from the Sport Concussion Assessment Tool (SCAT) symptom checklist* (16). No athlete with a Glasgow Coma Scale <13 enters the treatment progression of either arm.

As is standard with SRC studies (15), identifying the SRC is determined by medical professionals at each site involving a physician and other team-based healthcare provider (based on clinical exam and their interpretation of objective findings inclusive of the definition above). If medically diagnosed with a SRC, and no other indicators of more moderate to severe TBI as defined in the Mayo definition above (17), consented participants are eligible for enrollment in the treatment protocol. Documentation of the clinical diagnosis and identification of the medical personnel making the diagnosis are recorded in study case report forms. For inclusion in the post-injury protocols, the SRC must occur in a rostered sport for a high school or collegiate sport at their school or for their specific rostered sport (and team sanctioned activity) for the professional cohort. Individuals with any positive/abnormal clinical neuroimaging finding(s) following injury are not entered into the post-injury protocol or are discontinued from their arm treatment protocol

if these findings are observed after the protocol has been initiated. Although these individuals are discontinued from the treatment protocol, we continue to collect assessment time point data on these individuals and documentation for their overall care.

We anticipate ∼10–15% attrition due to study demands and seasonal nature of sport through full clearance to return to sport. However, we expect 20–30% attrition for the 1-month timepoint due to this timing and other potential participant follow-up issues. The study protocol incorporates contacting participants to keep them engaged.

Study Arms and Treatment Protocols

The two study arms are EGE and MDR. The EGE arm primarily follows the current consensus return to sport progression (**Table 1**). The MDR arm includes early, active rehabilitation that is integrated into the EGE/return to sport progression. Overall, the difference between study arms is the inclusion of early, active rehabilitation (**Figure 1**).

Participants in both arms, and at all sites, are enrolled into the overall study at pre-season baseline. However, the site's treatment protocol is only activated following concussion injury. Specifically, the post-injury protocol for both arms is only activated if the consented athlete suffers a concussion related to their rostered sport of interest at a team sanctioned event and meet enrollment criteria post-injury.

Following activation of the protocol post-injury, all concussed participants are given guidance on recommended physical activities in which they can engage. This guidance is consistent with the 5th International Consensus Statement on Concussion in Sport (16). Of note, our study was designed prior to the 2016 strategy being released, however, in anticipation of Stage 1 changing to limited/symptom guided activity, our design always included this type of language as part of Stage 1, as well as more generic descriptions of each stage. Participants are also instructed by their site medical staff on how to be observant for increases in symptoms. This guidance—which focuses on guided activity rather than restriction—is provided via a hardcopy educational instruction sheet and a short video. These materials are provided to all participants following injury. All concussed participants also keep a daily physical and cognitive activity summary log from 24 to 48 h post-injury through 7 days post return to play. A small subset of participants wears activity tracking technology to track physical activity from time of injury to full return to play. There is no predetermined sample size for the activity trackers as this is an ancillary component only. The activity log information serves as the primary compliance measure, as well as measures of activity that may affect recovery (covariates). To enhance compliance for log completion, participants are sent email reminders where applicable and completion is monitored by site clinicians for all sites.

TABLE 1 | 5th International Consensus Statement on concussion in sport return to sport strategy.

Rehabilitation Stage	Functional exercise at each stage of rehabilitation	Objective of each stage
1. Symptom-limited activity	Daily activities that do not provoke symptoms	Gradual reintroduction of work/school activities
2. Light aerobic exercise	Walking or stationary cycling at slow to medium pace. No resistance training	Increase HR
3. Sport-specific exercise	Skating drills in ice hockey, running drills in soccer. No head impact activities.	Add movement
4. Non-contact training drills	Progression to more complex training drills (e.g., passing drills in football and ice hockey). May start progressive resistance training	Exercise, coordination, and increased thinking
5. Full contact practice	Following medical clearance, participate in normal training activities	Restore confidence and assess functional skills by coaching staff
6. Return to play	Normal game play	

From McCrory et al. (16) 5th International Consensus Statement on Concussion in Sport (NOTE: Our study was designed prior to the 2016 strategy being released, however, in anticipation of Stage 1 changing to limited/symptom guided activity, our design always included that as part of Stage 1 and the remainder of the strategy remained the same).

Guided Rest + Enhanced Graded Exertion (EGE Arm)

Participants in the EGE arm complete the activities described above and guided rest prior to progressing past Stage 1 of the graded exertion (**Table 1**) (16). The term EGE was chosen as sites are directed to be sports specific in their choice of activities throughout the progression. A medical professional determines the symptom status of the athlete and when Stage 2 of the graded exertion for return to sport will begin. Once the athlete has been asymptomatic for 24 h (within at least 85% of their baseline symptom score—definition of asymptomatic for the study) they may begin the EGE progression. This protocol follows the 5th International Consensus Statement on Concussion in Sport return to sport strategy (16), but encourages enhancement to include sports and skill specific activities. Each step is recommended for completion on a separate day, at the clinician's discretion. Clinicians complete session logs for each graded exertion session for Stage 2 and for subsequent stages that include the following information: initial symptom checklist, phase of graded return to play progression, specifics on session activities, percentage of rest during the session, participants rating of perceived exertion, final symptom checklist, session satisfaction rating, and overall session feedback.

Guided Rest + Multidimensional Rehabilitation + Enhanced Graded Exertion (MDR Arm)

The term MDR was chosen to illustrate more than one area of activity would/could be addressed. Participants in the MDR arm complete the same activities as the EGE arm participants (as described above). However, once the participants' symptoms become "stable" (i.e., not getting worse), they are progressed into the MDR activity phases. "Stable" is defined as no significant increase utilizing Reliable Change Indices (RCI) metrics [symptom score not increasing by 10 or more over a

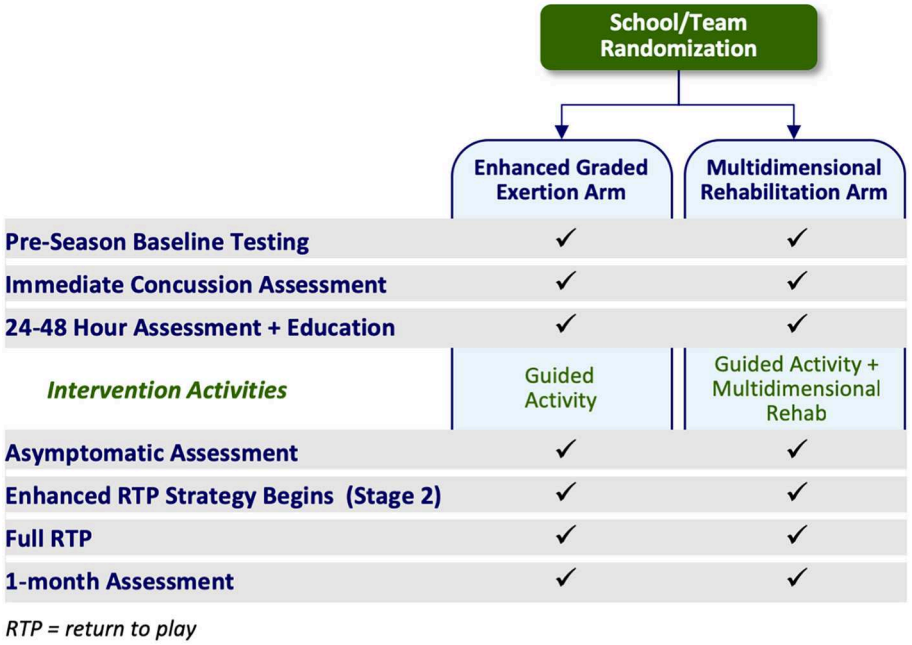

FIGURE 1 | Key study activities by study arm.

24-h period from their initial (first) symptom assessment] and no significant development of new symptoms over 24 h. Prior to beginning the exercises in the intervention, clearance to do so is obtained and documented by the athlete's healthcare team. The intervention includes 5 progressive phases: symptom control, perceived impairment reduction, activity integration, recovery acceleration, and sport specific application (**Figure 2**).

The choice of activity type in each phase is dependent on the nature of the athlete's reported symptoms and noted assessment deficits via a symptom assessment and clinical interview at each phase. Once an athlete is asymptomatic these activities may be chosen based on sport-specific performance needs. Activities are grouped into categories (termed "buckets") that are matched to a participant's symptom reports (**Figure 3**). The activity "buckets" include: balance, cognitive, comfort (symptom/emotional stability), and visual-vestibular. Some symptoms do not necessarily match the activity buckets and should be monitored. Activities that meet the intensity of targeted buckets are selected by the clinician, and are extensively documented, similar to the documentation process utilized by Schneider et al. (12).

Active, MDR sessions consist of guided exercises directed by a team clinician. Participants are asked to complete four sessions per week until full return to play, at their healthcare team's discretion. During each session, clinicians complete session documentation logs that include the following information: initial symptom checklist, phase of graded return to play progression, specifics on session activities, percentage of session spent resting, participants rating of perceived exertion, and final symptom checklist, session satisfaction rating, and session feedback. Should a participant state they are feeling worse during a session or request to stop, symptoms will be immediately assessed by the clinician. Sessions are stopped if a participant exceeds reliable change on total symptom severity (10 or more total point increase) (18, 19), if the participant requests to stop, or if the provider feels the participant is too symptomatic to continue. The symptom scale utilized is the SCAT 22-item (each item scored 0–6) post-concussion symptom scale. The metric utilized from this is total symptom burden (severity), which is calculated by summing the score of each item for a possible score range of 0–132.

Progression through the MDR protocol follows a standardized set of rules (**Table 2**). Progression from Phase I (Symptom Control) to Phase II (Perceived Impairment Reduction) requires that an individual's symptoms must not increase 10 or more points compared to their lowest symptom assessment since injury, and they must not have any symptoms with a symptom score of 5 or 6 at the beginning of a subsequent intervention session. When the participant completes activities in the phase where symptoms remain stable/do not increase beyond reliable change from beginning of one session to beginning of another (see "stable" above), the participant will be progressed to the next phase. We expect some increase from beginning to the end of a session, but we expect this to decrease by the start of the next session. Participants should on average, complete four sessions per week until fully returned to play. One session each week may be completed at home (i.e., unsupervised) as directed by a team healthcare provider. Each session lasts ∼20 min and is conducted at the clinician's discretion. Once enrolled into the MDR study arm, each participant completes a minimum of two sessions in Phase I (Symptom Control). The MDR activities may commence prior to beginning the EGE progression and

FIGURE 2 | Multidimensional Rehabilitation (MDR) framework and progression.

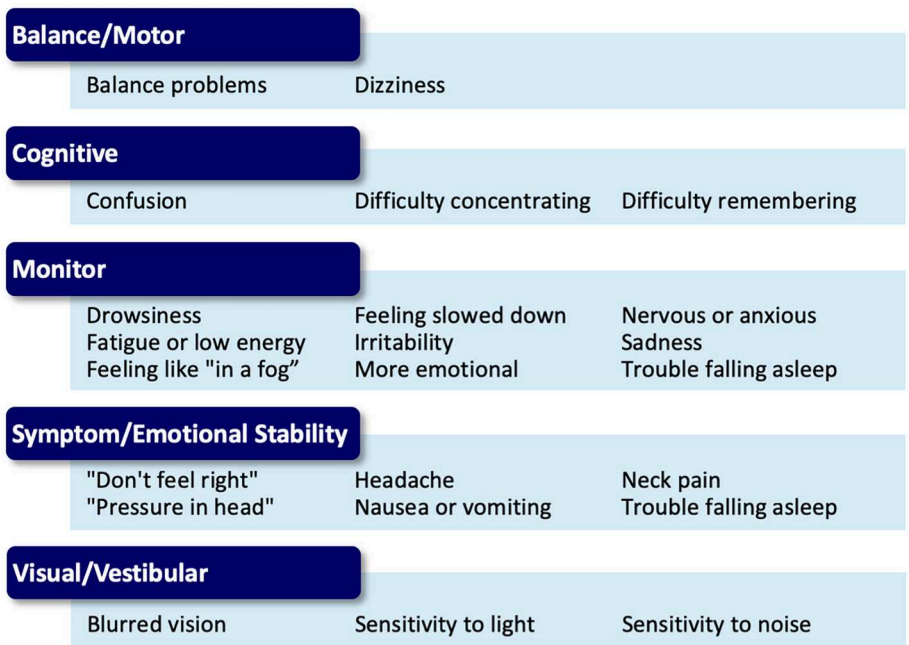

FIGURE 3 | Symptom presentation and activity bucket matches for the Multidimensional Rehabilitation (MDR) progression.

should be integrated with EGE activities once a participant is asymptomatic.

Specifically, progression from one phase to the next in Phases II through V requires that the participant does not experience any significant increase in symptoms from the beginning of one intervention session to the beginning of the subsequent session (as measured by a RCI of 10 of more total severity point increase), and no symptom score at the beginning of an intervention session is a 5 or 6 on the self-reported symptom severity scale. Once determined to be clinically recovered ("asymptomatic" by study definition or at clinician discretion), they begin the EGE progression (16) (**Table 1**) with sport and skill specific

TABLE 2 | Multidimensional rehabilitation progression (Active Rehab).

Rehabilitation stage	Notes	Goal
Entry into Phase I (to the intervention progression)	*Symptoms not getting worse.* ○ Symptom score not increasing by 10 or more over a 24 h/1 day period from their initial symptom assessment (6 h or 24–48 h assessment) ▪ Most people will be eligible at this time ▪ The earliest someone could start the intervention would be 24–48 h post-injury	Stabilization of symptoms
Phase I	*Must complete a minimum of **2 sessions** in this phase* Progression to Phase I may occur when: ○ An individual's symptoms must **not** increase 10 or more points **compared to their lowest symptom score since the injury** ○ They must not have any individual symptom items with a severity score of **5 or 6** when assessed at the beginning of a subsequent intervention session at Phase II (this would be the third session or beyond)	Symptom control and introduction to the intervention
Phases II–III, Phases III–IV, and Phases IV–V	*Must be a minimum of 1 day spent at each phase. Two phases cannot be completed on the same day.* Progression from one of these phases to the next (2–3, 3–4, and 4–5) may occur when: ○ An individual's total symptom severity score does **not** increase by 10 or more points from beginning of one intervention session to beginning of the subsequent session ○ No individual symptom item severity score symptom score at the beginning of the subsequent intervention session is a **5 or 6**	• Phase II- Perceived Impairment reduction • Phase III- Activity integration • Phase IV- Recovery acceleration • Phase V- Sport specific application

Considerations for care and progression

Clinicians should consult their site medical team regarding issues of pre-existing conditions and presentation that may affect care. Some of these may include:

- Migraine headaches
- Sleep related conditions/symptoms
- Gross vestibular dysfunction

Documentation of all additional care and treatment should be completed including but not limited to:

- Medications
- Additional therapies (e.g., physical therapy, vision therapy, vestibular therapy, etc.)
- All referral sources and those involved in the individual's care

Return to full participation

Return to full participation will occur at the physician/site medical professional's discretion of patient full recovery and will be documented. The intervention progression will stop.

enhancements at each phase. This MDR protocol should not delay the return to play process as when the participant becomes "asymptomatic" (by the study definition) they begin the enhanced graded return protocol (as the standard of care states) and will continue MDR exercises throughout this process. MDR activities are integrated with the return to sport progression at each Stage once the return to sport progression begins (**Figure 4**). Participants continue the rehabilitation progression during the EGE protocol and may continue the MDR exercises after full return for maintenance and/or to complete the last phases of the MDR progression at their clinician's discretion. **Figure 5** provides an example of cognitive activity progressions through each Phase. The **Supplemental Table 1** outline activity "bucket" progressions by MDR phase.

FIGURE 4 | Example illustration of Multidimensional Rehabilitation (MDR) activities being integrated to the Enhanced Graded Exertion (EGE) progression. This figure illustrates the overlap in activities. MDR activity may be integrated as soon as the participant is asymptomatic.

Safety Procedures

As with any trial, safety-related procedures were decided *a priori* by the study team in concordance with current literature. Potential risk of the study assessments and interventions were evaluated. Based on previous studies and clinical fortitude, it was determined *a priori* that discomfort is likely (10–25%) to occur as the participants are progressed in the interventions. We specifically anticipated more discomfort among those in the multidimensional activity group, as discomfort may increase slightly during rehabilitation sessions, as often occurs within any type of rehabilitation session. All rehabilitation is monitored and progressed by medical professionals and individuals are referred to their team physician as deemed medically appropriate. If at any point the participant or clinician feels the intervention should be discontinued, this is done and documented. Injury risk is rare,

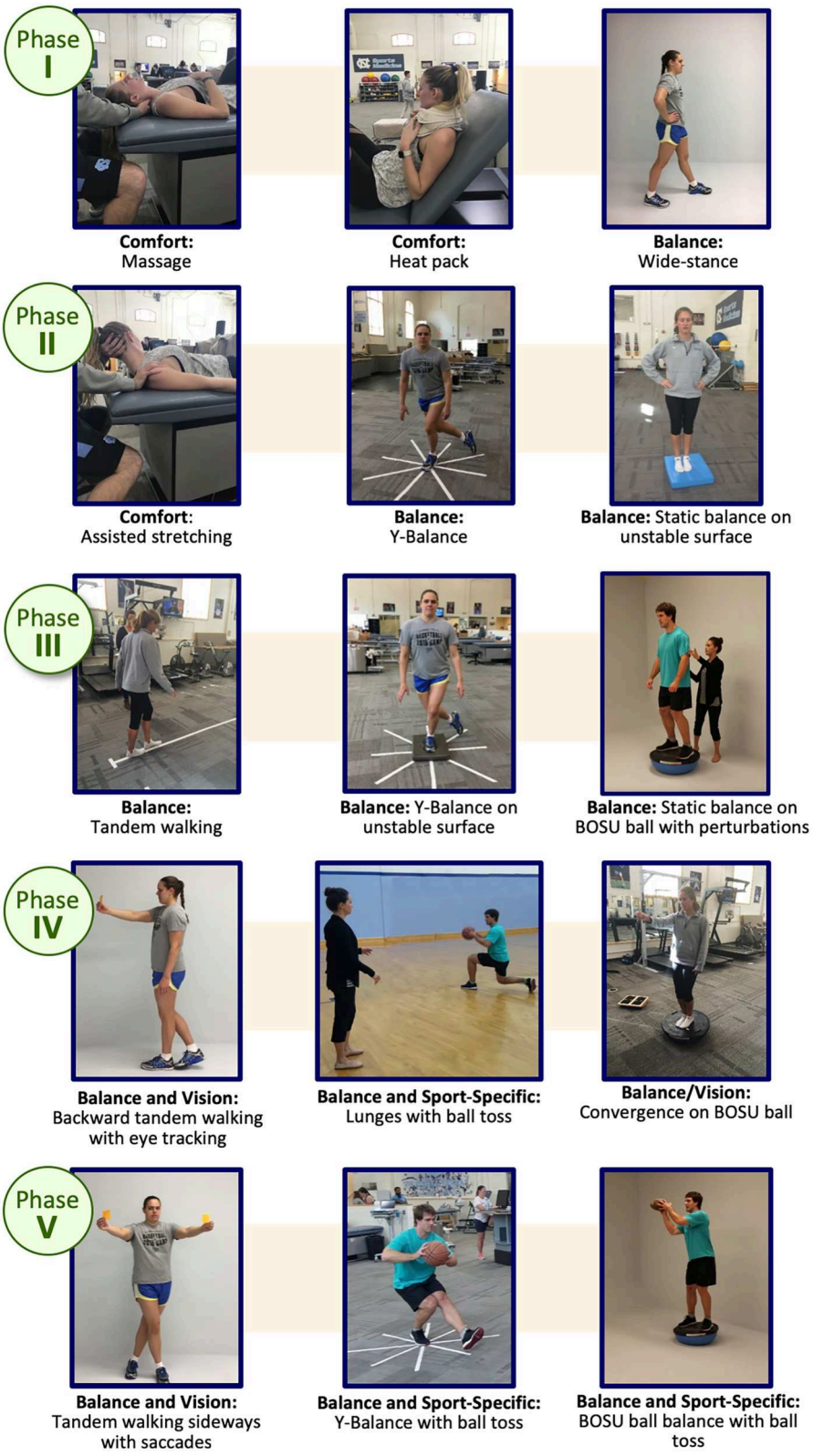

FIGURE 5 | Example Balance Activity Progression through the Multidimensional Rehabilitation (MDR) framework. Written informed consent was provided by all individuals in the images for publication.

however, there is the small possibility that symptom exacerbation or injury may occur during the interventions or testing. As all participants will be studied and progressed in environments with medical professionals, any potential significant symptom exacerbation or injury is documented, and participants are referred to the physician at the institution as deemed appropriate. The physician and medical team at each site will determine status and ability to continue the study activities. All events of this nature are documented appropriately via study administrative forms. A symptom-based adverse event was determined to be, as outlined in the progression, if an individual's symptoms increased by a reliable change of 10 or more points and remained elevated at that change in the subsequent session. An independent safety officer reviews quarterly study safety reports provided by the study team study and provides feedback on any overall concerns or safety issues. If the safety officer deems the study unsafe after corrective actions have been put into place, the study will be halted, or significant changes may be made to the study methods.

Data Management

All data are managed on secure servers through the data coordinating site via a central database or through site-based collection measures. All participants are registered with an identification code. Source data includes any original documentation to the study. The database is monitored by the data coordinating site and kept current to ensure monitoring of data and appropriate follow-up of participants throughout the study protocol. Monthly, quarterly, and individual injury monitoring occurs across the entire study period by the data coordinating site to ensure data quality and timely entry.

Study Outcomes and Assessments

The primary trial endpoints include time to asymptomatic/symptom free and time to full clearance for return to sport, in days. The secondary endpoints include clinical and quality of life outcomes assessed from baseline through 1-month post return to play, as well as safety and feasibility outcomes. An assessment protocol similar to the NCAA-DOD Grand Alliance Concussion Assessment, Research, and Education (CARE) Consortium's is utilized for both baseline measurements and post-injury assessments and to achieve the primary and secondary endpoints (15). The assessment time-points for the study (**Table 3**) include: pre-season baseline, time of injury (optional), 24–48 h following injury, daily symptom and activity tracking through 7 days post-return to play, athlete satisfaction at 7 days post-return to play, and 1-month following full return to play. Each of the assessment timepoints are collected at the approximate windows, i.e., within 5 days, due to the nature of athletic schedules. Study measures are administered by trained site personnel and clinicians. Assessments take place at site medical and training facilities. Below are brief descriptions of all study measures.

Demographics: Demographic information is collected on a separate form depending on the study cohort (i.e., High School, College/University, and Professional Setting). This assessment includes standard demographic information such as date of birth, sex at birth, place of birth, and race. In addition, information regarding sports history and academic level/achievement will be collected. *Time point collected: Baseline.*

Concussion History: The concussion history form provides the participant with a definition of concussion prior to asking the participant to provide a self-report of concussion history. Participants are directed to a concussion summary report for each concussion they report to have experienced. In the summary report the participant is asked to identify whether the concussion was sport-related or not, if the concussion was diagnosed, the approximate date of injury, their age at the time of injury, whether or not they lost consciousness (for how long), if they experienced any form of amnesia, and the number of days they experienced symptoms related to this particular concussive injury. *Time point collected: Baseline.*

Medication History: The medication history form requires the participant to identify any prescription medications she/he is currently taking as well as any over the counter medications. Prescription medications are broken up into categories (antidepressants, anti-psychotics, narcotics, non-narcotic pain medication, sleep aids, psychostimulants, birth control, allergy medication, asthma medication, and medication for acid reflux). The participant is asked to identify the exact name of any type of medication they are currently using. Three over the counter medications are listed for the participant to identify using including ibuprofen, acetaminophen, and loratadine. The participant is given space to identify any other over the counter medications they are currently using that are not listed. Lastly, the participant is asked to identify any supplements they may be using, and to report their tobacco, marijuana, and alcohol use. *Time point collected: Baseline.*

Medical History: The medical history form contains questions regarding the following self-reported information: height, weight, handedness and headache history. Participants are also asked about diagnosis of the following: meningitis, seizures, diabetes, sleep disorders, balance disorders, vestibular disorders, vertigo, motion sickness, Meniere's disease, psychiatric disorders, and other conditions. Participants are asked to provide information regarding previous diagnosis of conditions such as: learning disorders, attention deficits, hyperactivity disorder, vision and hearing issues, stroke, Parkinson's, and memory disorders. Participants also report any family history of headaches, migraines, Parkinson's, and memory disorders. Lastly, participants are asked to report their sleep patterns. *Time point collected: Baseline.*

Symptomology: The Standardized Concussion Assessment Tool symptom checklist (3, 16) includes a 22-item symptom inventory, self-reported hours of sleep inquiry, and questions regarding factors that may influence the severity of a participant's symptoms (i.e., mental/physical activity). Each participant is asked to rate how they feel "on a normal day" at baseline and "now" post-injury, with respect to each particular symptom, on a 6-point scale ranging from "none to severe" (0–6, respectively). Reliability and validity of the symptom checklist is well-established (20). Each symptom item score is added together to determine overall symptom burden (symptom

TABLE 3 | Assessment schedule.

	Demographics	Personal and family history	SCAT symptom checklist	QOL	BSI-18	Neurocognitive assessment	SAC	BESS	NPC	Dual-task	Start and end fatigue rating
Pre-season baseline	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Time of injury (within 6 h—if possible)			✓				✓	✓			
24–48 h post-injury			✓		✓	✓	✓	✓	✓	✓	✓
Asymptomatic post-injury			✓	✓	✓	✓	✓	✓	✓	✓	✓
1-month post return to play post-injury			✓	✓	✓	✓	✓	✓	✓	✓	✓

- Symptoms and activity assessed daily from the first assessment point until 7 days post return to play
- Concussion Index completed following injury
- Recovery Form completed following return to play
- *Participant Satisfaction completed at 7-days post return to play*

QOL, Quality of Life; BSI-18, Brief Symptom Inventory 18 item; SAC, Standardized Assessment of Concussion; NPC, Near Point of Convergence; SCAT, Sport Concussion Assessment Tool.

severity score); higher scores indicate greater symptom burden (severity). For this study, a reliable change is considered as a change of 10 points or more (18, 19). The possible score range for burden is 0–132. (*Time points collected: Baseline, Time of Injury, 24–48 h post injury, Asymptomatic, and 1-month post return to play. Note that participants who are injured and enter into the post-injury protocol are also asked to complete symptom checklists at the beginning and end of each intervention session.*

Brief Symptom Inventory-18 (BSI-18): Psychological distress is measured utilizing the BSI-18. The BSI-18 is a brief symptom inventory with high reliability (21). The assessment gathers athlete-reported data to help measure psychological distress in primary care settings (21). Participants rate their level of distress associated with 18 symptom items on a scale from 0 (not at all) to 4 (extreme). Ratings are then added together to compute an overall symptom distress score. *Time points collected: Baseline, 24–48 h Post-Injury, Asymptomatic Post-Injury, and 1-month post return to play.*

Health-Related Quality of Life (HRQL): Participants' HRQL is assessed using the Athlete-Reported Outcomes Measurement Information System (PROMIS-29), and the Quality of Life in Neurological Disorders (Neuro-QOL) Cognition and Fatigue Scales. These scales have high reliability and validity concerning overall quality of life (22–24). Outcomes will include the PROMIS-29 and Neuro-QOL summary scores (anxiety, physical function, depression, sleep disturbance, social role/activities, pain interference, pain intensity, Neuro-QOL cognition, and Neuro-QOL fatigue). These scales ask the participant to rate items on a Likert type scale ranging from 1 to 5 (higher or lower score indicating "worse" is dependent upon the item). *Time points collected: Baseline, Asymptomatic, 1-month post return to play.*

Computerized Neurocognitive Testing: Participant neurocognitive performance at baseline and post-injury will be assessed utilizing the computerized neurocognitive testing platform currently used clinically at each site. The platforms to be included by study sites include Immediate Postconcussion Assessment and Cognitive Test (ImPACT), CogSport, and Concussion Vital Signs. Reliability and validity of computerized tests varies and has been established in previous literature (25, 26). Each platform includes alternating forms and presentation variation. *Time points collected*: *Baseline, 24–48 h post injury, Asymptomatic, and 1-month post return to play.*

Mental Status: The Standardized Assessment of Concussion (SAC) (varied forms) (27, 28) will be used to assess mental status. The SAC is a clinical measurement to determine an individual's cognitive orientation, concentration ability, and immediate/delayed memory recall. The SAC has been shown to be a reliable and sensitive measure of concussion (27, 28). Alternate forms are used at each time point. *Time points collected: Baseline, Time of Injury, 24–48 h post injury, Asymptomatic, and 1-month post return to play.*

Balance: Balance is assessed utilizing the Balance Error Scoring System (BESS), as it is an objective postural stability measure that can be implemented in an office, field, or clinic setting. The test is administered as the participant completes three 20 s stance trials (i.e., double leg, single leg, tandem stance) on firm and foam surfaces (**Figure 6**). The administrator tracks errors during the trials. The BESS has been shown to have high reliability and sensitivity and specificity (30). The outcome from the BESS will be the total error score. *Time points collected: Baseline, Time of Injury, 24–48 h post injury, Asymptomatic, and 1-month post return to play.*

Near Point Convergence: The Near Point of Convergence (NPC) test will function as the visual/oculomotor exam for this study (31). NPC is measured by drawing a tongue depressor with a dot in 14-point font from arm's length toward the participant's nose. The participant is instructed to stop the approximation at the point the visual target is seen in double (diplopia). The clinician then measures the distance between the tip of the nose and the tongue depressor in centimeters. Three trials are

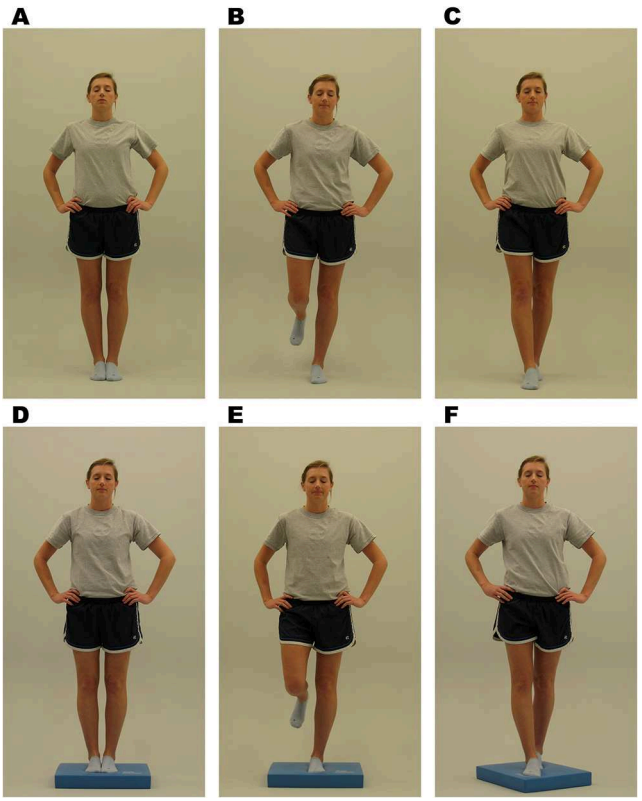

FIGURE 6 | Balance Error Scoring System (BESS) stances. Written informed consent was provided by the individual in the image for publication. **(A)** Double leg firm, **(B)** single leg firm, **(C)** tandem stance firm, **(C)** double leg foam, **(E)** single leg foam, and **(F)** tandem stance foam (29).

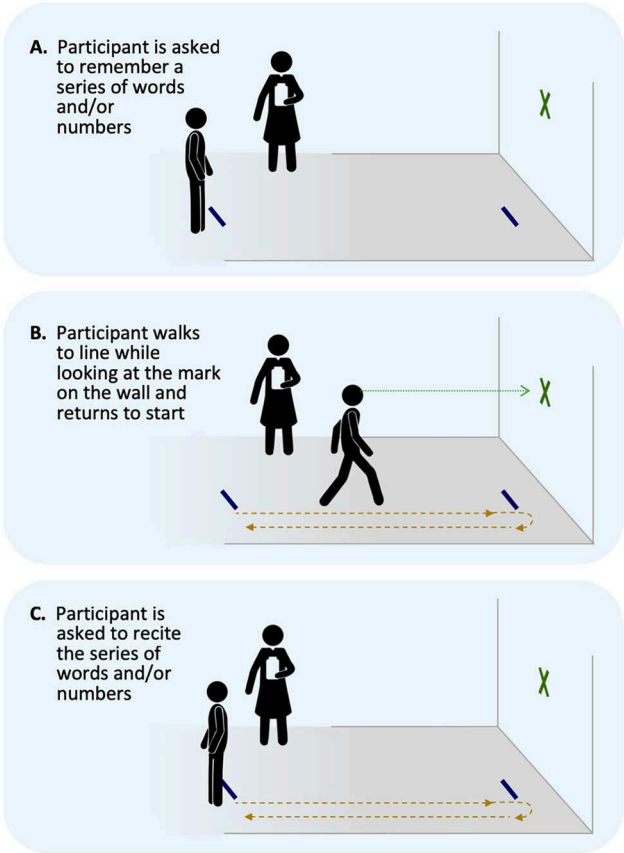

FIGURE 7 | Dual-task schematic. **(A)** Memory task begins, **(B)** walking task, and **(C)** memory recall.

collected and averaged. NPC has been shown to be a reliable measure (32). *Time points collected: Baseline, 24–48 h post injury, Asymptomatic, and 1-month post return to play.*

Dual-task: Dual-task performance will be assessed via the Walking and Remembering Dual-Task Assessment (ISAW-Grid Task) (33) which has been previously reported as potentially useful for physically active individuals (34) and evaluates divided attention cost across a gait and cognitive task. Participants walk 3.5 m toward a target and then turn and walk back to the start line and the walk time is recorded. Participants are then given 2 numbers and 6 letters from the military phonetic alphabet and asked to recall the information accurately and in order. Alternate word list are given at each time point. Following these single tasks, the individual is then asked to combine the task. The examiner gives the individuals 2 numbers and 6 letters to remember, the participant completes the gait task, and upon return to the start line, the participant is asked to recall the numbers and letters (**Figure 7**). Gait time and accuracy are scored and coded as the initial outcomes. Performance in the dual-task is then compared for each of these outcomes to the single task, yielding the primary outcome of dual-task cost. Participants will be asked to complete a cognitive (immediate recall) task while also completing a walking task of 7 m. *Time points collected: 24–48 h post injury, Asymptomatic, and 1-month post return to play.*

Daily Activity and Symptom Tracking: All concussed participants complete a daily activity and symptom tracking survey (cognitive and physical) from time of injury through 7 days post return to play. The survey can be completed on paper or via Qualtrics and includes questions about mental and physical activity as well as symptoms. *Time point collected: Daily through 7-days post return to play.*

Participant Satisfaction: The participant will be asked to complete a questionnaire regarding his/her satisfaction with the rehabilitation sessions and the intervention. This measure is adapted from the PSQ-18 which is a publicly available scale that measures general athlete satisfaction with care. The PSQ-18 was designed based on feedback from athletes using input from providers about the care they receive and has been used in various settings. *Time point collected: 7 days post return to play.*

Concussion Injury Index: This form documents all aspects of a participant's concussion. It is completed by the clinical research staff at the study site. Information gathered on this form includes: sport at time of injury, number of years playing sport, date and time of injury, date reported injury, loss of consciousness, etc. *Time point collected: This form is to be completed over the course*

of the injury and should be finalized by the 1-month post-return to play time point.

Recovery Tracking: A recovery tracking form documents all aspects of a participant's recovery from a concussion. It is completed by the clinical research staff at the site throughout the time it takes the participant to recover. Length of symptoms, medication usage, therapies/treatments, psychiatric issues, and return to play information will be reported. It also includes information on completion or discontinuation of the study treatment activities (e.g., discontinuation of the intervention for medical reasons). *Time point collected*: *This form should be completed over the course of the injury and should be finalized by the time entry is completed for the 1-month post-injury assessment.*

Planned Data Analysis

We conduct quarterly, interim analysis for descriptive outcomes to determine continued safety and feasibility of the study and to prepare safety reports.

Specific Aim 1 *(evaluation of effectiveness):* For analyses of our primary endpoints, Cox proportional hazards regression models (35) will be used to compare time to return to play and time to asymptomatic between the EGE and MDR groups. The specific outcomes for the Cox models will be time from date of injury to: (1) date of medical clearance for full return to participation and (2) asymptomatic date. The Wei-Lin robust variance estimator will be used to account for the effect of cluster-randomization by site (36).

For our secondary endpoints (clinical and quality of life measures), recovery trajectories will be examined by use of General Linear Mixed regression models and non-parametric smoothers. Random effects will be utilized to account for the effect of clustering by site and the effect of repeated observations over time within an individual participant. The time axis to be modeled in both sets of analyses is time from initiation of the treatment (defined as stable symptoms for 24 h), and time will be treated as a continuous variable in all analyses.

We will also assess potential predictors of attrition (e.g., gender, race, socioeconomic status). If no predictable patterns are observed for missing data (i.e., missingness occurs at random), no imputations will be conducted. Inverse probability of attrition weights based on the factors influencing attrition will be used to account for potential selection bias due to attrition. We will assess the differences between the EGE and MDR group participants (those with SCR) at baseline and before starting the treatment protocol.

For sensitivity analyses of primary and secondary, we will conduct intent-to-treat analysis (prescribed treatment), per-protocol analysis (adhered treatment) and use inverse probability weighting to determine potential outcomes had everyone adhered to their prescribed treatments.

To test the effectiveness of randomization, we will compare key variables at baseline and immediately post-injury (24-48 h timepoint) to determine differences between arms. These variables at a minimum will include: age, gender, previous history of concussion, contact/collision sport, baseline symptom severity score, 24–48 h symptom severity score. Should any differences be observed these factors will be controlled for in the models. Additionally, 24–48 h symptom severity will be considered in all analyses.

Specific Aim 2 (safety and feasibility): We will utilize descriptive statistics, qualitative analyses for open ended text of perceptions (exploratory based; triangulation) to understand overall safety, adverse event prevalence, and protocol perceptions.

Sample size (determined based on primary outcomes): Given that each participant will be recruited between 6 and 48 h post-concussion and will be followed for a month after their return to play (average total time of ∼37 days), if we estimate that each arm will have at least 100 participants, we will have 83% power to estimate an effect size of 0.64 in the MDR group as compared to the EGE group concerning days to asymptomatic. **Table 4** shows the available power for varying sample and effect sizes.

DISCUSSION

A major success of the study thus far is the international collaboration between researchers and clinicians across multiple collision sports and competitive levels in exchanging ideas regarding the understanding early rehabilitation for SRC and the current return to sport paradigm. This multidisciplinary collaboration engineered strategic solutions for the challenges encountered in implementing a large pragmatic randomized controlled trial. This seamless collaboration is critical to the successful launch and execution of the Active Rehab Study.

Varied Models of Clinical Care

Basic models of SRC care differ with varied settings across several countries, sports, and competitive levels. In the US, Athletic Trainers are commonly engaged and are often the primary clinicians delivering the intervention. In Canada, Athletic Therapists are most commonly the frontline providers directing care. In New Zealand, physicians and physiotherapists are the providers who deliver the intervention. Within these medical structures, there are differences in the standard protocol based on the site's overarching sport governing body (e.g., National Collegiate Athletic Association, Canadian Football League, World Rugby, High School Federation, etc.). The Active Rehab Study protocol, while prescriptive, also allows for clinical decision-making to ensure practical application and implementation on a larger scale. Funding to support front-line staff across these care models is also important and considering

TABLE 4 | Power and effect size based on number of participants in each arm.

	Hazard ratio for MDR vs. EGE comparing time to asymptomatic				
Randomized arm size	*4/7 (0.57)*	*4.5/7 (0.64)*	*5/7 (0.71)*	*5.5/7 (0.79)*	*6/7 (0.80)*
100	95%	83%	60%	36%	18%
150	>99%	94%	78%	50%	24%
200	>99%	98%	88%	62%	30%
250	>99%	>99%	94%	72%	37%

how this funding may be implemented locally is also a key factor for success. Additionally, given that many participants are professional athletes, it is important for leagues, schools, and administrators to understand that participants' medical providers are still responsible for their medical care and return-to-play decision-making to ensure compliance with the study trial. Without allowing site-specific medical oversight, many of the sites agreeing to participate in our study would have declined.

Changing Landscape of SRC Management

Implementing a multiyear pragmatic clinical trial involves understanding the rapidly changing landscape of SRC management. With a rapidly growing evidence base and new treatment and management strategies emerging, it is important to provide a protocol to capture any of these adaptations that may occur in clinical care across the trial. Our trial does not prohibit additional care and clinical decisions outside of the study protocol due to these potential changes. As such, we capture all treatments and activities outside of the study protocol to be able to control and assess how these factors may influence our study outcomes. Additionally, as the study began, the 5th International Consensus Statement on Concussion in Sport (16) had not yet been released. However, we felt symptom limited activity during Stage 1 was often clinically practiced vs. no activity. As such, this has been our protocol from the beginning of the study.

Clinical Variability of SRC

SRC presents in various ways and often involves an individualized approach. As such, it is important that the protocol allow for clinical-decision making within the context of the protocol. Additionally, participants may present with other symptoms or signs of medical conditions needing additional treatment. As such, allowance for additional treatments are a necessary part of a study like the current trial. Activities outside of the study protocol are closely documented to be able to control and assess how these factors may influence study outcomes.

Data Collection, Integrity, and Analysis

Quality assurance is a top priority to ensure maximum rigor of methods and confidence in the results of the study. Integrity of data collection and study arm/intervention documentation is an ongoing process that includes initial trainings for sites and onboarding of clinicians who will administer assessments and/or interventions. Yearly refreshers for those continuing with the study in multiple years are provided either in-person or via video training. Additionally, clear, concise, and specific study manuals for each aspect of the study are available to all study sites and team members, but are arm specific for the intervention portions. Post-injury checklists, specific to the study arm are available to all sites to ensure each participant follows the designated protocol and subsequent study specific activities in his/her arm. The coordinating institution is notified of an injury to ensure the study protocol steps are followed. Additionally, while there is a central study data system, one cohort utilized an application that collected the data and these data are merged with the larger array of data. The data systems all meet security requirements for the various institutions with individual password access and tracking. All data entry mechanisms contain data type and value range limitations to control for extraneous data entry. Monthly, quarterly, and injury specific monitoring occur by the project manager and project coordinator to ensure timely and accurate collection and entry. Following these monitoring mechanisms, sites are notified of issues with corrective actions and asked to correct and notify the data coordinating site when corrections have been made. These corrections are then verified by the data coordinating center. Data are cross-checked for quality within the monitoring system and via the quarterly preliminary analysis exports. Quarterly detailed data checks are run for standard distributions, missingness, and detailed data quality. Sites may be asked to further review and verify data with the oversight of the project manager to correct data through this mechanism. Additionally, in-person meetings and trainings are conducted to build relationships, answer questions about the study, and promote data quality and study success.

Intervention Compliance

Due to the interventional nature of both study arms, a high level of intervention compliance and documentation of activities during the rehabilitation and return to play process is essential. As described above, regular training, study manuals, and monitoring are key to ensuring site compliance and corrective actions when deviations occur such as missing study assessment timepoints and incorrect post-injury rehabilitation or return to play progressions. Additionally, having a clinician coordinator who manages the SRCs at various levels of sport being the primary point of contact for the rehabilitation (MDR) and return to sport (EGE) progressions continues to be essential to increase clinician buy-in and compliance. To increase athlete compliance, the sessions are clinician guided and include activities important to the participant.

Limitations and Future Considerations

As with any trial, the current protocol does not include every potential treatment area for concussion. However, the intent of the trial is to address key areas of concerning in a patient-centered and pragmatic manner in an effort to translate findings to a variety of clinical settings. Future trials and evaluation work may consider additional domains or assessment strategies as well as utilizing these assessments in areas of progression in more targeted populations and settings in which more clinical time and capacity may be available.

Anticipated Outcomes

Outcomes from the ongoing trial will contribute to research efforts to better understand the effects of early rehabilitation and the current return to sport paradigm on recovery time. Research efforts like this ongoing trial provide a pragmatic framework for research that seeks to produce the highest-level evidence possible concerning management and treatment of SRC across sports and across various levels of play in differing medical care environments. Lastly, the study data will provide guidance to safely and effectively use early, active rehabilitation therapies in the current clinical landscape. In order to achieve these outcomes we expect to see a positive effect of the MDR and that both arms will illustrate both MDR and EGE to be

safe and feasible. We anticipate then being able to develop implementation manuals and strategies to be used in a variety of clinical settings.

ETHICS AND DISSEMINATION

The study is carried out in accordance with international standards of research and under the guidance of the data coordinating center Institutional Review Board. Additional approvals and reviews are conducted as necessary for all study sites. Consideration is given to local needs and cultural considerations in the ethics review and implementation process. Written, informed consent is provided by each participant. For minors in the high school cohorts, guardian consent is also obtained. The trial is registered at clinicaltrials.gov (NCT02988596). Participants are enrolled at pre-season baseline to provide an opportunity to consent prior to a concussion occurring and reduce respondent burden post-injury. The model consent form may be obtained from the corresponding author upon request. All intervention and study activities occur with site medical professional guidance. Site investigators and clinicians explain the study protocol to participants are available to participants for questions and concerns. After completion of the trial and statistical analysis of the trial data, findings will be published in peer-reviewed medical journals and will adhere to CONSORT standards. The current plans for these primary papers include: (1) a primary paper addressing effectiveness of the intervention arms on the primary outcomes of time to clearance for full return to sport and time to asymptomatic, (2) a paper addressing effectiveness of the interventions on the secondary clinical outcomes, (3) a paper concerning overall safety and symptom provocation for both intervention arms, and (4) a paper addressing implementation evaluation and feasibility of the study interventions. Additional dissemination of results will include presentation at relevant scientific meetings, to the general public, and through peer-reviewed publications.

ETHICS STATEMENT

The study was approved by the Institution Review Board at the University of North Carolina at Chapel Hill (and associated site ethics boards where needed) and is registered as a clinical trial (clinicaltrials.gov; NCT02988596). Prospective participants are fully informed of the procedures of the study. Informed consent (and guardian consent) is provided by all participants prior to engaging in any study activities. Reporting procedures are in place to ensure any serious adverse events are report to the Principal Investigator.

AUTHOR CONTRIBUTIONS

JR-M, KG, MMc, and SM contributed to study design, data analysis and interpretation, initial drafting, and revision as well as final approval of the manuscript. KM, JM, MMr, IM, DN, KS, and PG contributed to study design, revision, and final approval of the manuscript. SR contributed to study design, data analysis, revision, and final approval of the manuscript. The Active Rehab Consortium investigators contributed to data collection, revision, and final approval of the manuscript.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2019.01176/full#supplementary-material

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Atypical Somatic Symptoms in Adults With Prolonged Recovery From Mild Traumatic Brain Injury

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Somatization may contribute to persistent symptoms after mild traumatic brain injury (mTBI). In two independently-recruited study samples, we characterized the extent to which symptoms atypical of mTBI but typical for patients suffering from somatization (e.g., gastrointestinal upset, musculoskeletal, and cardiorespiratory complaints) were present in adult patients with prolonged recovery following mTBI. The first sample was cross-sectional and consisted of mTBI patients recruited from the community who reported ongoing symptoms attributable to a previous mTBI ($n = 16$) along with a healthy control group ($n = 15$). The second sample consisted of patients with mTBI prospectively recruited from a Level 1 trauma center who had either good recovery (GOSE = 8; $n = 32$) or poor recovery (GOSE < 8; $n = 29$). In all participants, we evaluated atypical somatic symptoms using the Patient Health Questionnaire-15 and typical post-concussion symptoms with the Rivermead Post-Concussion Symptom Questionnaire. Participants with poor recovery from mTBI had significantly higher "atypical" somatic symptoms as compared to the healthy control group in Sample 1 ($b = 4.308$, $p < 0.001$) and to mTBI patients with good recovery in Sample 2 ($b = 3.169$, $p < 0.001$). As would be expected, participants with poor outcome in Sample 2 had a higher burden of typical rather than atypical symptoms [$t_{(28)} = 4.750$, $p < 0.001$, $d = 0.88$]. However, participants with poor recovery still reported atypical somatic symptoms that were significantly higher

(1.4 standard deviations, on average) than those with good recovery. Our results suggest that although "typical" post-concussion symptoms predominate after mTBI, a broad range of somatic symptoms also frequently accompanies mTBI, and that somatization may represent an important, modifiable factor in mTBI recovery.

Keywords: somatization, concussion, post-concussion syndrome, somatic symptoms, mild traumatic brain injury (mTBI)

INTRODUCTION

An estimated forty-two million people experience mild traumatic brain injuries (mTBI) worldwide annually (1). Symptoms generally resolve within the first week; however, a substantial number of patients experience chronic symptoms for months or years after injury, leading to significant disability and functional impairment (2, 3). Although there are many factors that influence the recovery trajectory, pre- and post-injury mental health problems are the strongest established contributor to poor recovery and functional limitation after mTBI (4, 5).

The term post-concussion syndrome (PCS) dates back to at least World War II where, based mainly on studies of soldiers with blast injury (i.e., "shell shock"), it was characterized by headache, dizziness, fatigue, tinnitus, memory impairment, poor concentration, and nervousness (6). The Rivermead Post-Concussion Syndrome questionnaire (RPQ) was developed in 1995 by aggregating the 16 most commonly reported post-concussion symptoms (7), and remains endorsed by the National Institute for Neurological Diseases and Stroke Common Data Elements as the instrument of choice for evaluating post-concussion symptoms in adults. Although there is significant ongoing debate as to the etiology of some of the symptoms, the endurance of this legacy instrument, unmodified, reflects at least some consensus that these are the cardinal features expected after a brain injury.

Somatization is a process whereby psychological distress manifests as physical symptoms, which can occur in the presence or absence of organic pathology (8). When symptoms occur in the context of an identifiable medical condition (e.g., TBI), somatization would be considered when the nature, severity, or course, of the symptoms differ from what can be attributed to the medical condition.

There is an emerging literature pointing to an etiological role for somatization in prolonging the recovery process after mTBI (9–14). Two previous studies in pediatric patients recruited from emergency departments have examined measures of somatization after mTBI, both finding that higher measures of somatization were associated with prolonged symptom duration (12, 14). A recent study of high school and collegiate athletes found pre-injury somatic symptom scores to be the strongest pre-morbid predictor of post-concussive symptom duration (13). However, like most other studies analyzing somatic symptoms after mTBI, Nelson et al. (13) evaluated somatization using a composite score reflective of somatic complaints across multiple body systems, and did not distinguish the somatic symptoms that would be conventionally associated with mTBI (e.g., headache and dizziness) from others that could not logically be attributed to the trauma (e.g., intestinal upset, diffuse body pains, etc). In so doing, they are potentially conflating organic brain injury with psychopathology.

Three studies, performed in the context of comprehensive health assessments in military personnel, have used somatic symptom scales broken down by item to evaluate somatic symptoms post-TBI, allowing for an assessment of the type of somatic symptoms experienced after mTBI. These studies consistently document an elevated level of somatic symptoms not plausibly related to head injury after TBI (e.g., chest pain, heart pounding or racing, shortness of breath) (9–11). Critically, these atypical somatic symptoms may be prognostic, as a study in military personnel by Lee et al. (11) found that an aggregated metric of pre-injury somatic symptoms was associated with the subsequent development of post-concussion syndrome (11). However, while these military studies suggest significantly heightened somatic symptoms post-TBI, the high prevalence of psychiatric comorbidities confounds causative inference. For example, Hoge et al. (9) documented a 44% prevalence of post-traumatic stress disorder (PTSD) and 27% prevalence of major depression after mTBI with loss of consciousness (LOC), and concluded that PTSD and depression are strongly associated with physical health problems upon return from deployment (9). They further suggest that PTSD or depression mediate the majority of the relationship between mTBI and subsequent somatic complaints (9). If this is correct, given lower rates of PTSD and depression in the civilian population as compared to military members (15), after civilian mTBI we might expect lower levels of somatization than in a military sample. However, if elevated somatization contributes to poorer recovery from mTBI independent of other mental health concerns, then rates in civilians with persistent symptoms might also be high.

Our aim was to evaluate symptoms *atypical* of mTBI (i.e., symptoms not typically related to the mechanism of injury) in adult civilians who had poor recovery from their mTBI and who had no other pre-injury history of psychopathology. First in an initial pilot study, and subsequently replicated in a prospectively-recruited sample, we administered a modified version of the most widely used assessment instrument for somatization symptoms, the Patient Health Questionnaire (PHQ-15), that had the four questions that reflect typical post-concussion complaints (i.e., headache, dizziness, insomnia, and fatigue) removed. We hypothesized that mTBI patients with poor recovery would report a higher severity of symptoms not typically associated with brain injury (e.g., gastrointestinal upset, sexual dysfunction, etc.) compared to those with good

recovery and also as compared to a healthy control group. Support for this hypothesis would provide further evidence for an association between somatization and prolonged recovery from mTBI.

METHODS

This study occurred in two phases and drew from two independently-recruited sources (recruitment flow chart shown in **Figure 1**). Informed consent was provided by all participants, and studies were approved by the University of British Columbia (UBC) Clinical Research Ethics Board (H16-01307 and H15-01063).

Participants and Study Design: Sample 1

Initially, in the context of an exploratory pilot study, we recruited a cross-sectional sample of 16 patients who had sustained an mTBI more than 30 days previously and who self-reported persistent symptoms from that mTBI. We also recruited 15 healthy controls from the community. Both mTBI patients and controls were recruited through an institutional newsletter and all participants were from an urban city (Vancouver, Canada). Healthy controls were included if they reported no TBI during their lifetime. The presence of an mTBI was verified using information about the injury collected with the Ohio State University TBI identification method in conjunction with the World Health Organization definition of mTBI [WHO: (16, 17)]. MTBI participants must have reported an injury to the head and at least one of: confusion or disorientation, LOC for 30 min or less, post-traumatic amnesia for <24 h, and/or other transient neurological abnormalities (16). MTBI participants and healthy controls were between 18 and 50 years of age and fluent in English, and were excluded if they self-reported any diagnosed psychiatric illness or substance abuse.

Participants and Study Design: Sample 2

Based on results from our initial pilot study we then assessed an additional subset of participants from an ongoing prospective observational study of TBI patients entitled "A national biobank and database for patients with TBI (CanTBI)." Participants were included in the broader CanTBI study if they (i) had a diagnosis of a mild, moderate, or severe TBI made by a physician, or were assessed for a head injury with mTBI being verified by chart review; (ii) had at least one blood draw for research purposes within 24 h of injury; and (iii) were fluent in English or French. Participants were excluded from CanTBI if they (i) had any neurodevelopmental or ongoing neurological disorder; (ii) had suffered a stroke, cardiac arrest, or had significant disruptive neurological issues; (iii) were brain dead or suffered from a terminal illness (life expectancy < 12 months at assessment); (iv) or were currently a prisoner, patient in custody, or enrolled in an intervention trial. From this broader CanTBI study, we evaluated somatic symptom scores in adult patients with mTBI who had no other diagnosed psychiatric illness or substance abuse (**Figure 1**). Participants were excluded from our analysis if they had (i) sustained a moderate or severe TBI; (ii) were <18 years of age; (iii) had not completed both the Rivermead and the Patient Health Questionnaire-15 at a follow-up time point 3 months post-TBI or greater; and (iv) had a history of diagnosed psychiatric illness. CanTBI participants were classified into either a "good recovery" group or "poor recovery" group based on the Glasgow Outcome Scale Extended (operationalized below). CanTBI participants completed follow-up interviews at three, six, and 12-months post-injury. For the present study, we assessed data from the first post-injury time point that was <30 days post-injury.

Measures

In both study samples, mTBI symptoms were assessed with the Rivermead Post-Concussion Symptoms Questionnaire

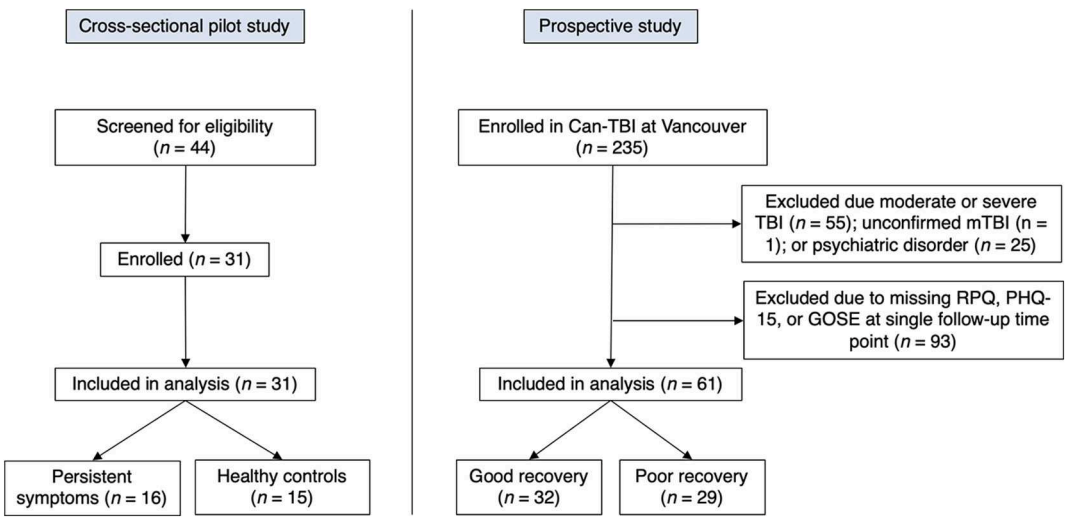

FIGURE 1 | Flow chart outlining participant recruitment for both study samples.

(RPQ) (7). The RPQ consists of 16 questions about post-concussion symptoms on a Likert scale ranging from 0 ("not experienced at all") to 4 ("a severe problem"). All scores of 1 or greater were included in total score calculations, for a potential maximum score of 64. In both study samples, somatic symptoms experienced in the 4 weeks preceding evaluation were measured using the Patient Health Questionnaire (PHQ-15), which is a 15-question subset of the full PHQ (18). The PHQ-15 is a commonly used instrument for the assessment of somatic symptoms that is both a valid and reliable proxy measure of somatization (19, 20). It is used to assess 15 non-specific physical symptoms spanning multiple organ systems (18). PHQ-15 scores possess moderate-to-good diagnostic accuracy for identifying somatic symptom disorder assessed with a structured interview for the DSM-V (21). Each PHQ-15 item can be rated as "not bothered at all," "bothered a little," or "bothered a lot," resulting in a score of 0, 1, or 2 points per question respectively, for a range from 0 to 30. A score of 1 or more on a PHQ-15 item was considered a positive endorsement of that somatic symptom. All data were collected with the secure, electronic REDCap Data Capture Tool hosted at the BC Children's Hospital Research Institute (22).

To examine symptoms atypical of mTBI in both study samples, we excluded PHQ-15 items *a priori* that were most likely etiologically related to mTBI [a method previously employed by Lee et al. (11)]. Specifically, we excluded the questions about headaches, dizziness, feeling tired or having low energy, and trouble sleeping. The remaining eleven PHQ-15 items were considered "atypical" for mTBI, and included stomach pain, back pain, pain in arms, legs or joints, menstrual cramps, chest pain, fainting spells, heart pounding or racing, shortness of breath, problems during intercourse, constipation, loose bowels or diarrhea, or nausea, bloating, or indigestion. Where listed, "PHQ-15" is the total score on the full PHQ-15 (maximum score 30 and including all 15 questions) and the "atypical" symptom subset is the total score for the 11-question subset of the PHQ-15 which queries only the symptoms that would be considered "atypical" after mTBI (maximum score 22).

In the prospectively-recruited sample, we used the Glasgow Outcome Scale Extended (GOSE) to evaluate outcome from mTBI (23). The GOSE has eight categories to measure global neurological function or death; it is a sensitive outcome measure across the injury severity spectrum, including in mTBI (24, 25). It parallels other indicators of recovery including post-concussion symptoms (26), and is endorsed as one of the few core mTBI outcome measure by the NINDS Common Data Elements group (27). As in other large multi-site mTBI studies participants with a GOSE score of 8/8 were considered to have "good recovery," while participants with a GOSE score < 8 were considered to have "poor recovery" (28). Of the 62 participants 33 had good recovery, and 29 had poor recovery at the time of assessment.

Statistical Analysis

For between-group comparisons we used independent-samples *t*-tests for continuous variables if normally distributed (as assessed with a Shapiro-Wilk test) or Mann-Whitney *U*-tests for non-normally distributed continuous variables, and Chi-squared tests for categorical variables or Fisher's Exact Tests for categorical variables if the expected cell count was <5. To test for differences in RPQ, PHQ-15 total score, and atypical symptom scores from the PHQ-15, we used multiple linear regression models (with R^2 as the measure of effect size), adjusting for age and sex in the cross-sectionally recruited sample, and adjusting for age, sex, and number of days post-injury in the prospectively recruited sample. For each multiple linear regression model, we generated 95% confidence intervals from 10,000 bootstrap samples using the *boot* package in R (29).

In the prospectively-recruited sample, we assessed the relative symptom burden of typical mTBI symptoms (RPQ), global somatic symptoms (PHQ-15 total score), and atypical somatic symptoms from the PHQ-15 in the group with poor recovery. To do this, we first internally standardized participant scores on each measure into z-scores, using the good recovery group as the reference. We then compared mean z-scores on each of the three outcomes within the poor recovery group using paired *t*-tests with Cohen's *d* to calculate effect size. This allowed us to determine the predominant symptom burden reported by individuals with poor recovery after mTBI. Statistical analysis was performed using *R* version 3.6.0 (30).

RESULTS

Demographic and injury-related data, as well as unadjusted RPQ and PHQ-15 scores for both study samples are presented in **Table 1**. In the cross-sectionally recruited sample, there were no statistically significant differences in age or sex between the symptomatic and healthy control groups. There were no statistically significant differences in age and sex between the good and poor recovery groups in the prospectively recruited study, nor were there statistically significant differences in peri-injury variables including LOC, GCS, mechanism of injury, whether or not participants received a head CT scan or had acute trauma-related finding on those CT scans. The cross-sectionally recruited symptomatic group and the prospectively recruited poor recovery group were not statistically significantly different in the number of days post-injury ($U = 209$, $p = 0.843$), nor were the prospectively-recruited good and poor recovery groups ($U = 402.5$, $p = 0.378$).

In the cross-sectional study, as anticipated, post-concussion symptom scores ($b = 31.650$, 95% CI: 25.10–37.73, $p < 0.001$, adjusted $R^2 = 0.77$) and global somatic symptom scores ($b = 8.757$, 95% CI: 6.34–10.99, $p < 0.001$, adjusted $R^2 = 0.64$) were higher in the symptomatic group as compared to the control group, adjusting for age, and sex. Our hypothesis was initially affirmed in this pilot study, as the group with persistent symptoms from their mTBI had significantly higher atypical somatic symptoms as compared to healthy controls adjusting for age and sex (**Figure 2**; $b = 4.308$, 95% CI: 2.54–6.13, $p < 0.001$, adjusted $R^2 = 0.39$). We found a similar pattern of results in the prospectively recruited sample: The poor recovery group had significantly higher post-concussion symptom scores ($b = 15.297$, 95% CI: 10.03–22.26, $p < 0.001$, adjusted $R^2 =$

TABLE 1 | Demographic, injury, and outcome metrics for the both study samples.

	Study 1 (cross-sectional community)			Study 2 (prospectively recruited from ER)		
	Healthy controls ($n = 15$)	**Symptomatic mTBI ($n = 16$)**	***p*-value**	**Good recovery ($n = 32$)**	**Poor recovery ($n = 29$)**	***p*-value**
Age, mean (SD)	31.1 (8.0)	31.6 (6.4)	0.862	40.6 (17.6)	45.1 (16.1)	0.177
% female	80	81.3	> 0.99	28.1	41.4	0.413
Years of education, mean (SD)[a]	N/A	N/A	N/A	16.6 (3.7)	15.7 (3.4)	0.553
Months post-TBI, mean (SD)	N/A	5.6 (3.6)	N/A	8.4 (5.4)	6.5 (4.7)	0.378
Cause of injury						
MVA, *n*	N/A	5	N/A	12	11	> 0.99
Sport, *n*	N/A	7	N/A	7	4	0.627
Fall, *n*	N/A	3	N/A	8	7	> 0.99
Other, *n*	N/A	1	N/A	5	7	0.608
LOC after injury[b]						
Yes, or suspected, *n*	N/A	2	N/A	14	9	0.386
No, *n*	N/A	11	N/A	14	17	
GCS (best prehospital)[c]	N/A	N/A	N/A			
15, *n*	N/A	N/A	N/A	13	14	0.288
13-14, *n*	N/A	N/A	N/A	7	3	
CT scan						
Performed, *n*	N/A	N/A	N/A	22	19	0.878
Acute findings, *n*	N/A	N/A	N/A	13	6	0.148
Questionnaire scores						
RPQ, mean (SD)	2.3 (3.5)	34.1 (11.3)	< 0.001	3.0 (5.3)	18.1 (14.1)	< 0.001
PHQ-15, mean (SD)	2.1 (1.8)	10.9 (4.2)	< 0.001	2.7 (2.8)	8.2 (6.1)	< 0.001

[a] *Years of education data not available for eight participants.*
[b] *LOC data not available for ten participants.*
[c] *GCS data not available for 25 participants.*
TBI, traumatic brain injury; MVA, motor vehicle accident; LOC, loss of consciousness; GCS, Glasgow Coma Scale; CT, computed tomography; RPQ, Rivermead Post Concussion Symptoms Questionnaire; PHQ, Patient Health Questionnaire.

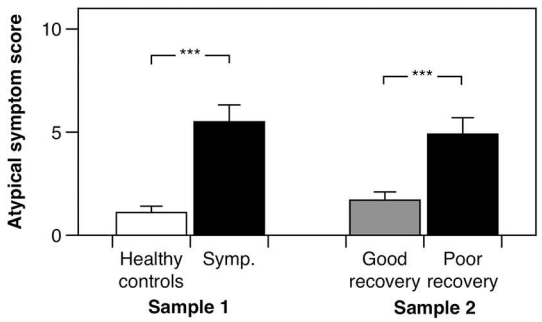

FIGURE 2 | Atypical somatic symptom scores for the cross-sectionally recruited sample (Sample 1) and the prospectively recruited sample (Sample 2). "Symp." is the subjectively symptomatic group in the cross-sectionally recruited sample. Error bars denote one standard error, and "***" denotes a $p < 0.001$.

0.32) and global somatic symptom scores ($b = 5.539$, 95% CI: 3.15–8.51, $p < 0.001$, adjusted $R^2 = 0.25$), adjusting for age, sex, and time since injury. Our hypothesis was again supported in the prospectively recruited sample, with the poor recovery group endorsing significantly higher atypical somatic symptoms than the good recovery group adjusting for age, sex, and time since injury (**Figure 2**; $b = 3.169$, 1.28–5.43, $p < 0.001$, adjusted $R^2 = 0.18$).

We then sought to determine the relative burden of symptom subtypes experienced by those with poor recovery in the prospective sample. Participants with poor recovery endorsed typical post-concussive symptoms (RPQ) 2.8 (SD = 2.7) standard deviations higher, on average, than those with good recovery, global somatic symptoms (PHQ-15) 2.0 (SD = 2.1) standard deviations higher than those with good recovery, and atypical somatic symptoms 1.4 (SD = 1.9) standard deviations higher than the group with good recovery. Using paired *t*-tests, we found that participants with poor outcome from mTBI had a higher burden of typical post-concussive symptoms than global somatic symptoms [$t_{(28)} = 3.656$, $p = 0.001$, $d = 0.68$] and atypical symptoms [$t_{(28)} = 4.750$, $p < 0.001$, $d = 0.88$], **Figure 3**.

DISCUSSION

Corroborating the limited prior work in this area, we found that heightened post-concussive and global somatic symptoms were associated with prolonged recovery following mTBI. Additionally, we provide evidence that civilians with poor recovery from mTBI experience a significantly greater degree of somatic symptoms *atypical* for mTBI, as compared to healthy

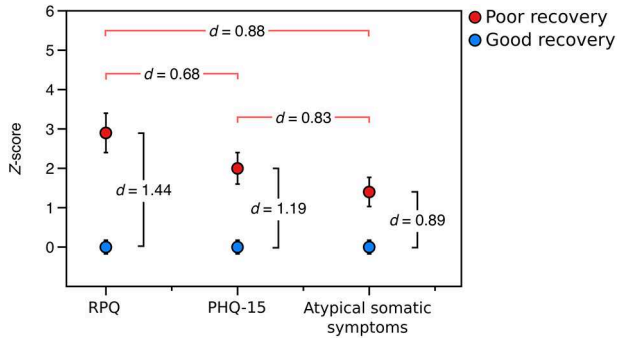

FIGURE 3 | Relative symptom burden in the poor recovery group relative (red) to the good recovery group (blue) in the prospectively-recruited sample (Sample 2). *d*-values between red brackets are values of Cohen's *d* from paired *t*-tests comparing the relative symptom burden in the group with poor recovery, and *d*-values between black brackets are values of Cohen's *d* from independent-samples *t*-tests comparing the symptom burden in the poor recovery group to that of the good recovery group. "RPQ" is the Rivermead Post-concussion Questionnaire, "PHQ-15" is the Patient Health Questionnaire-15, and "atypical somatic symptoms" are a subset of questions from the PHQ-15 that exclude those symptoms most plausibly related to mTBI.

controls and those with good recovery from mTBI. These results provide further evidence for the diagnostic role of unexplained medical symptoms in somatization (i.e., atypical symptoms and duration of symptoms following trauma), and our findings, in conjunction with the confluence of data reported in a variety of samples, help demonstrate a role of somatization in persistent symptomatology following mTBI.

The only prospective civilian study to link somatization to prolonged recovery from mTBI was recently reported by Nelson et al. (13). Although they did not specifically examine "atypical" symptoms, they did demonstrate a pronounced effect of pre-injury somatization on post-mTBI recovery in athletes. In a univariate analysis on the Brief Symptom Inventory-18 (31), somatization scores were the strongest pre-injury predictor of recovery duration, even when considered alongside a comprehensive list of pre-injury demographic and history variables (i.e., sex, education, learning disabilities, headache history, number of prior concussions, or type and duration of sporting history), psychiatric symptoms (depression, anxiety), cognitive performance, and balance scores. Path analysis indicated that these somatization symptoms likely affected recovery through a mediating effect on post-concussion symptoms, and the authors therefore conclude that somatization may heighten the experience of post-concussion symptoms or increase symptom reporting, subsequently leading to prolonged recovery.

Our study expands on the work of Nelson et al. (13) by highlighting that not only typical somatic symptoms but also somatic symptoms, etiologically unrelated to mTBI, are associated with poor outcome after adult civilian mTBI. This raises the possibility that somatization may be a potentially important modifying factor in the recovery trajectory, and emphasizes the clinical need for measurement of a broad array of somatic symptoms following mTBI. Specifically evaluating "atypical" somatic symptoms may also help to identify individuals suffering from somatization, that is primarily responsible for, or significantly magnifying their persistent symptomatology. This distinction is critical as treatment for somatization (which is treatment of the underlying psychiatric condition) is distinctly different than treatment for mTBI. Without appropriate identification of somatization, patients cannot be connected with effective interventions. This puts them at high risk for iatrogenic effects from unnecessary medical treatments (32), as well as potential worsening by well-meaning clinicians advising typical interventions for mTBI such as rest and symptom avoidance (33). When somatization is left undiagnosed and untreated, these physical symptoms and associated dysfunction typically persist or worsen, which leads to considerable costs to society and the health care system (34).

Prior authors have raised skepticism about whether symptoms after mTBI represent a true syndrome—a constellation of symptoms that predictably and uniquely co-occur (35, 36). If somatization is a major mechanism underlying persistent symptoms, we might expect unclear boundaries between what are typically referred to as "post-concussion" symptoms and other kinds of somatic symptoms, and that the PHQ-15 and the modified 11-item version would have been similarly elevated as compared to the RPQ in patients with prolonged recovery from mTBI. We found that both mTBI-related symptoms and symptoms atypical of mTBI were significantly higher among patients with poor recovery from mTBI when compared to both the control and good recovery groups. However, our results indicate that relative to atypical somatic symptoms, mTBI-related symptoms are more strongly associated with poor outcome. Several explanations are possible. First, somatization may only play a role in a subset of patients in our sample. In a cohort with higher depression and anxiety scores (more typical in patients with continued symptoms and poor recovery), for example, we might expect to see somatization as a more robust variable. Had we therefore not excluded those participants with a prior history of psychiatric problems it is possible that our effect sizes for the atypical symptom scores would be higher. Second, somatization may exacerbate symptoms from the mTBI. Thus, "typical" symptoms may be higher due to the combination of both the organic symptoms and somatization. Third, knowledge about mTBI and past experience of concussion and its typical symptoms may modify expectations or direct attention (somatic vigilance) (37), and support symptom misattributions. Somatization, which often coincides with these phenomena, would therefore be more likely to produce typical "post-concussion" symptoms than atypical symptoms (e.g., GI upset) in individuals with more extensive experience and knowledge about concussion.

This study has several limitations. It is comprised of modest sample sizes, and for this study we inventoried symptoms at only a single point in time. As we did not measure pre-injury somatization, we were unable to determine whether the somatic symptoms were present before, or appeared *de novo*

following injury. In parallel, we are unsure if somatization scores pre-injury were a risk factor for protracted recovery, or whether protracted recovery led to higher somatization scores. Further, we examined somatic symptoms using the PHQ-15, a proxy for examining somatization. While the PHQ-15 has moderate-to-good accuracy for diagnosing somatization, the gold standard for diagnosis is a physician administered structured interview based on the DSM-V and neurological examination demonstrating incongruent findings. This interview and examination may also have confirmed any psychopathology that may not have met the threshold for exclusion (e.g., subsyndromal post-traumatic stress disorder or adjustment disorder with anxious mood), that may have been associated with a greater likelihood of associated somatization. A lack of a structured interview and examination also means the diagnosis of somatization could not be corroborated based on the presence of psychological distress, as suggested by Lipowsky, or based on the incongruence of findings, as suggested by Stone and Carson (38), but rather was inferred based on the atypicality of symptoms (38).

Some group differences between the good and poor recovery groups in the prospective study are also worth mentioning. Previous literature suggests that females are more likely to have elevated somatization scores post mTBI (39) and there were slightly more females (41 vs. 30%) in our poor recovery group in comparison to the good recovery group, although this difference was not statistically significant in our sample. Similarly, the poor recovery group had a longer time-post injury interval (8.2 vs. 6.5 months) and was older (45 vs. 40 years), though again, neither of these were statistically significant in our sample. In order to mitigate the possible confounding effects of these variables we chose to include them as co-variates in our regression analysis. Finally, we do not know to what extent other psychological variables may have mediated the relationship between mTBI and somatization. As an example, a recent study suggest that alexithymia positively correlates with somatization post-TBI (40). Future research is required in order to determine what other psychological or medical factors may influence somatization, and to ascertain whether somatization is a cause or consequence of persistent symptoms after mTBI.

In contrast, the greatest strength of this study was that our work occurred in two phases, first as a cross-sectional pilot study followed by a prospectively recruited validation cohort which confirmed the findings of our cross-sectional study. Second, we specifically excluded individuals with diagnosed psychiatric illness, which helped to control for more serious depressive or anxiety symptoms that may influence somatization processes separately from mTBI.

In summary, we present evidence for a higher burden of somatic symptoms which are atypical for mTBI in individuals with poor recovery from mTBI, when compared with healthy controls and those with good recovery. While we found more typical mTBI somatic symptoms in those with poor recovery—as would be anticipated—we also found a significantly higher severity of somatic symptoms atypical of mTBI in individuals with poor recovery from mTBI. Though future research is needed, these results provide evidence that somatization identifiable by symptoms dissociable from trauma (medically incongruent or unexplained), may be a significant contributor to persistent symptomatology following mTBI and highlight a need to comprehensively assess for the presence of somatization as a part of mTBI care.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation, to any qualified researcher.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Clinical research ethics board, University of British Columbia. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

JS, KG, and WP conceptualized the study. JS performed the statistical analysis and wrote the initial draft with KG. All authors contributed to the interpretation of the results and the final manuscript.

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Conflict of Interest: WP is the founder and CEO of Translational Life Sciences, an early stage biotechnology company. He is also on the scientific advisory board of Medipure Pharmaceuticals and Vitality Biopharma, and in the past has been on the board of directors for Abbatis bioceuticals and on the advisory board of Vinergy Resources. All of these companies are early stage biotechnology enterprises with no relation to brain injury.

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