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Autonomic nervous system dysfunction in pediatric sport-related concussion: a systematic review

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Objective: *To identify, appraise and synthesize the evidence of autonomic nervous system (ANS) dysfunction following sport-related concussion in pediatric populations.*

Methods: *A literature search was conducted using MEDLINE (Ovid), SportDiscus (EBSCO), CINAHL (EBSCO), EMBASE (Ovid) and PsycINFO (Ovid). Studies were selected and appraised using the Joanna Briggs Institute (JBI) critical appraisal tools. Data was extracted from the included studies and qualitatively synthesized.*

Results: *Eleven studies were included in the synthesis. There was variability in the methods used to measure*

Dysfonctionnement du système nerveux végétatif dans les commotions cérébrales liées au sport chez l'enfant: une revue systématique

Objectif: *Identifier, évaluer et synthétiser les preuves du dysfonctionnement du système nerveux végétatif (SNV) à la suite d'une commotion cérébrale liée au sport dans les populations pédiatriques.*

Méthodes: *Une recherche documentaire a été effectuée sur MEDLINE (Ovid), SportDiscus (EBSCO), CINAHL (EBSCO), EMBASE (Ovid) et PsycINFO (Ovid). Les études ont été sélectionnées et évaluées à l'aide des outils d'évaluation critique du JBI (Joanna Briggs Institute). Les données ont été extraites des études incluses et ont fait l'objet d'une synthèse qualitative.*

Résultats: *Onze études ont été incluses dans la synthèse. Les méthodes utilisées pour mesurer la fonction du SNV varient d'une étude à l'autre, et*

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ANS function between studies, and sample populations and time to assessment following concussion varied considerably. There was also variability in the direction of change of ANS function between some studies.

Conclusion: *This systematic review identifies that concussion is associated with dysregulation of ANS function in pediatric athletes. We identified some weaknesses in the extant literature which may be due to existing logistical and financial barriers to implementing valid ANS measurements in clinical and sports settings.*

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KEY WORDS: sport-related concussion, concussion, mild traumatic brain injury, autonomic nervous system, dysautonomia, pediatric, athlete

les populations d'échantillons ainsi que le délai d'évaluation après une commotion cérébrale varient considérablement. La direction du changement de la fonction du SNV variait également d'une étude à l'autre.

Conclusion: *Cette étude systématique montre que les commotions cérébrales sont associées à une dysrégulation de la fonction du SNV chez les athlètes enfants. Nous avons identifié certaines faiblesses dans la littérature existante, qui peuvent être dues aux obstacles logistiques et financiers existants pour mettre en œuvre des mesures valides du SNV dans les environnements cliniques et sportifs.*

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MOTS CLÉS : commotion cérébrale associée au sport, commotion cérébrale, lésion cérébrale traumatique légère, système nerveux végétatif, dysautonomie, pédiatrie, athlète.

Introduction

Concussion, or mild traumatic brain injury (mTBI), is considered a subset of traumatic brain injury (TBI) that results from a direct or indirect biomechanical force transmitted to the head.[1] Concussion is described as a complex pathophysiological entity that results in functional, rather than structural disturbance to the nervous system including perturbations of normal cellular and physiological processes.[2]

Concussions account for 90% of all TBI's.[3, 4] Children have the highest incidence rate with 692 out of every 100,000 suffering a concussion at some point[3], with adolescent concussions accounting for 3% to 8% of all sport-related emergency department visits[5, 6]. As such, concussion remains a serious health concern for youth athletes, as estimates suggest that American children aged up to 18 years suffer between 1.1 to 1.9 million concussions per year in the context of sport and recreation, however this number may be an underestimation due to underreporting.[7-9]

Concussion is typically considered a self-limiting condition, with the majority resolving in 10-14 days, however up to 30% of individuals may experience persistent symptoms beyond four weeks.[10, 11] For youth, persistent symptoms may have significant impact on social, academic and sporting activities during critical stages of development.[10] Empirically, variability in the time to recovery has been observed between pediatric and adult populations[10] and the 2016 Consensus Statement on Concussion in Sport suggests that normal clinical recovery from concussion differs between pediatric individuals and adults.[1] Studies have also demonstrated that factors such as sex and age may influence concussion recovery, with females and adolescents exhibiting protracted recovery times.[12-16] Additionally, identification of TBI in pediatric individuals differs from that of adults due to developmental and physiological variances in the nervous system that exist during different stages of maturation.[17] One example of this includes pupil size and the pupillary light reflex (PLR), which provide insight into autonomic nervous system (ANS) activity.[18] Normative values for pupil size and the PLR have been described, with adults exhibiting decreased pupil size with increasing age[19, 20, 21], and adolescent boys showing slower maximum constriction velocities and smaller percent constriction compared to younger children[21, 22]. This is one example of a measurable physiological biomarker that allows us to quantify not only normal function, but also the variability we may see following concussive injury across different age categories and throughout recovery.

It is well understood that concussion can cause symptoms of headache[23, 24], nausea[17, 23], balance difficulties[23, 25], light and noise sensitivity[23, 25], sleep disturbances[25], cognitive changes[23, 25-28], emotional disturbances[23, 29] and visual disturbances[30, 31] among others. The vast number of symptoms that may coexist following a concussion may highlight an intricate functional relationship between different areas of the nervous system, despite having anatomically distinct regions.[32-34] Thus, concussion should not be thought of as a focal or localized injury to the nervous system, but rather a diffuse injury that affects interneuronal communication.[2, 32]

An area of study that is of particular interest is the effect that concussion may have on the autonomic nervous system (ANS), as the ANS is intricately intertwined within the CNS and may be affected by head trauma.[33-35] A recent high quality systematic review by Pertab *et al*.[36] synthesized studies of individuals who had experienced a concussion and the resultant impacts on ANS functioning. The authors concluded that "it is likely that concussion causes anomalies in ANS functioning".[36] Due to the anatomical pervasiveness of the ANS within the central nervous system (CNS) it is reasonable to suggest that a concussive injury may contribute to the common symptomatology clinicians see via autonomic mechanisms, in certain individuals.

The autonomic nervous system (ANS):

The autonomic nervous system's role in human function includes involuntarily bodily monitoring to maintain a stable internal environment of the various organ systems. Within the CNS, there is extensive interconnectedness between cortical, subcortical and brainstem regions, many of which comprise the ANS and help us respond and cope with different internal and external environmental stressors.[33, 34] The efferent output of the ANS is largely mediated by autonomic reflexes. In the majority of these reflexes, afferent information is transmitted to homeostatic control centers located in the brainstem and hypothalamus.[33] Reciprocally connected nuclear areas such as the nucleus tractus solitarius, ventrolateral medulla, parabrachial nucleus, amygdala and thalamus play a major role in autonomic control.[33] Importantly, various supraspinal centers including the insula, anterior cingulate cortex, medial prefrontal cortices and portions of the limbic system control and modulate autonomic responses through various cognitive, behavioral and emotional mechanisms.[33] These areas remain salient as a concussion may influence the projection fibres connecting deep and superficial regions of the CNS through rotational and shearing mechanisms.[37-40] The widespread distribution of injury may result in common concussion symptoms including behavioral, emotional, cognitive and motor dysfunctions which may subsequently include dysregulation of ANS function.[26-29] Therefore, it is mechanistically plausible that concussion may result in ANS dysfunction, as suggested by existing preliminary studies and literature reviews.[35, 36, 41-44]

Some studies have demonstrated dysfunction in autonomic and neuroendrocrine systems across the entire spectrum of TBI.[41, 45-47] More recently, studies have measured ANS function and its integrity in concussed athletes, specifically.[21, 48-56] Physiologic measures of the ANS in the research and clinical setting include measures of heart rate variability (HRV)[54, 56-58], tilt table testing[59], baroreflex responsiveness[60], arterial pulse contour analysis[61], pupillometry[21, 62-65], exercise tolerance testing[66, 67], cerebrovascular reactivity[68], and cerebral blood flow[69]. However, the latter two markers are non-specific measures of ANS functioning, as there are complex arrays of local vascular mechanisms that influence a given hemodynamic response in brain tissue.[70-72]

There has been a surge of research into the effects of concussion on ANS functioning in the pediatric population. This is particularly important due to the aforementioned high incidence rates of concussion amongst youth and the considerable number of children participating in sports.[5-7, 14, 16] Comparable to studies that have defined age-specific features for concussion identification, symptom presentation, and recovery, it may be essential to compare the degree of ANS impairment following concussion in different age categories. Pertab *et al*.[36] conducted a systematic review, however included all ages and to our knowledge there has yet to be a systematic review of the literature on the pediatric population specifically.

McCrory *et al*.[1] state in the 2016 Consensus Statement on Concussion in Sport that child and adolescent (e.g., pediatric) guidelines for sport-related concussion should refer to individuals 18 years of age or less. Due to inconsistencies with the "pediatric" reference age range definition in the literature and between international health organizations, we decided to include studies of individuals aged 2-18 for the purpose of this systematic review.[73-75] Therefore, the objective of this review is to identify, appraise and synthesize the evidence of ANS dysfunction in a population aged 2-18 who have a history of a sport-related concussion.

Methods

This review follows the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA).[76] A full protocol for this systematic review was registered on Open Science Framework registries.[77]

Inclusion and exclusion criteria

To be included in the systematic review studies must have fulfilled the following criteria: 1) English language, 2) published in a peer-reviewed journal, 3) cohort studies, case-control studies, cross-sectional studies, other observational studies, 4) data includes analysis of individuals who have a history of concussion; when mixed brain injury samples are studied, it is required that results be separately specified for a subgroup of participants with concussion in order to be included (no mixed mild-moderate-severe groups), 5) participant ages 2-18 (inclusive), 6) data must have measured at least one variable of interest for ANS function. This outcome of interest was required to be primarily representative of an autonomic process. For the purpose of this review measures of cerebral blood flow, cerebral autoregulation and cerebral vasoreactivity were not used as proxies for ANS function due to factors independent of the ANS contributing to these processes.

Studies fulfilling any of the following criteria were excluded from the systematic review: 1) Publication types including: guidelines, letters, editorials, commentaries, unpublished manuscripts, dissertations, government reports, books and book chapters, conference proceedings, meeting abstracts, lectures and addresses, consensus development statements, guideline statements. 2) Study designs including case reports, case series, qualitative studies, non-systematic and systematic reviews, clinical practice guidelines, and studies not reporting on methodology. 3) animal or cadaveric studies, 4) studies of individuals with diagnoses of: Parkinson's disease, Alzheimer's disease, multiple systems atrophy, familial dysautonomia, multiple sclerosis, spinocerebellar ataxia (all types), severe traumatic brain injury, spinal cord injuries, ischemic brain injury, intracranial hemorrhage, autism-spectrum disorders and cerebral palsy.

Search methods

A search strategy was developed in consultation with a health sciences librarian, and reviewed by a second librarian using the Peer Review of Electronic Search Strategies (PRESS) checklist.[78] The following electronic databases were systematically searched from inception to May 30, 2021: MEDLINE (Ovid), SportDiscus (EBSCO), CINAHL (EBSCO), EMBASE (Ovid) and PsycINFO (Ovid). Search terms consisted of subject headings and text words relevant to 'concussion' and 'autonomic nervous system/autonomic nervous system dysfunction' and are included in Appendix I. Subject headings were specific to each database – e.g., MeSH in Medline. In addition to database searches, reference lists of included studies and previous systematic reviews on this topic were hand searched to ensure all relevant studies were identified. Authors' personal libraries were also hand searched for relevant studies that were not captured with the search strategy.

Data collection and analysis

Screening

The citations identified by the search strategy included as Appendix I were exported into EndNote X9 for reference management and tracking of the screening process. Pairs of reviewers screened articles in two phases (titles and abstracts; full text articles) using a standardized pre-piloted Excel spreadsheet. The first phase included screening of titles and abstracts for irrelevant and potentially relevant citations based on the outlined inclusion and exclusion criteria. Potentially relevant citations from the first phase were reviewed in the second phase using the full text article. At each phase of screening, consensus ratings were automatically populated within screening Excel spreadsheets for citations where there was agreement between reviewers. Any disagreement was resolved by discussion between the paired reviewers to reach consensus. According to the study protocol, if consensus could not be reached, a third reviewer would independently appraise the citation and discuss with the other two reviewers to reach consensus. However, this step was not utilized as it was not necessary during our screening process.

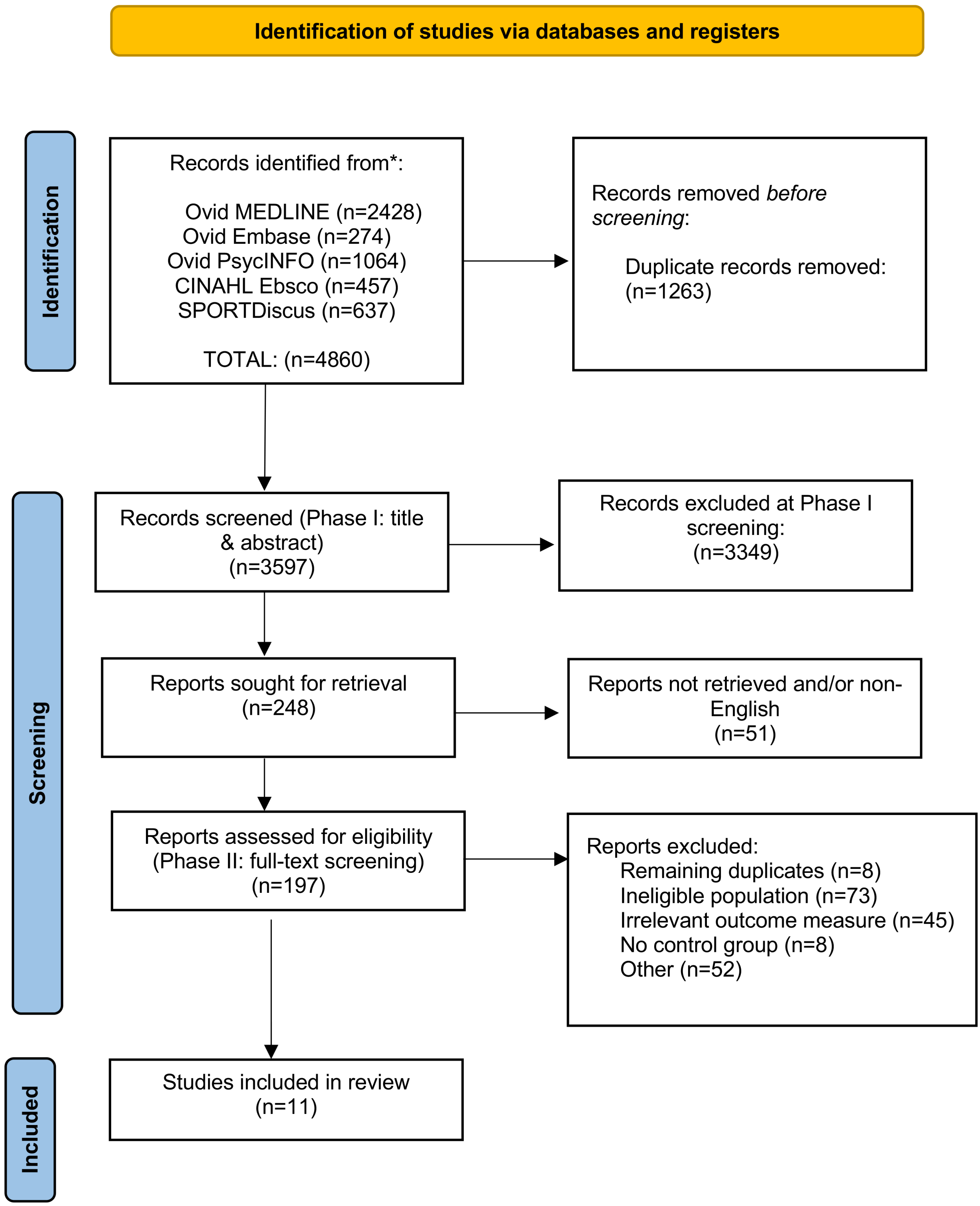

Figure 1.
PRISMA flow diagram

Critical appraisal
Critical appraisal of all articles that were deemed to be relevant was completed by pre-established pairs of reviewers, and consensus was reached through discussion. The internal validity of each study was assessed using the Joanna Briggs Institute (JBI) critical appraisal tools based on epidemiological study design.

Data extraction
The lead author (AP) extracted the data from studies with low risk of bias (n=11) and created evidence tables. A second reviewer (SHJ) checked the data extraction for accuracy and completeness. The research team used the results of the evidence tables to outline the evidence on each topic and to identify consistencies and limitations within the existing body of literature. Data tables describe the populations included in each study while also identifying the specific sport involved where applicable.

Statistical analysis
Ratings from the pairs of reviewers at phase 1 and phase 2 were compared and agreement was described using percent agreement and Kappa statistic with 95%CI. Results from low risk of bias studies were summarized in evidence tables and qualitatively described in text as we anticipated that data would not be able to be pooled for meta-analysis in any meaningful way, due to predicted heterogeneity in populations, ANS outcome measurements, time to assessment following concussion and study design.

Results
A total of 4860 citations were captured from database inception to May 2021 (Figure 1). Following removal of duplicates, we screened 3597 titles and abstracts in Phase I. The inter-rater percent agreement for Phase I screening between pairs of reviewers was 96.6% (95%CI – 96.0%-97.2%), kappa = 0.76 (95%CI – 0.72-0.80). Following Phase I screening, we sought 248 citations for full-text screening, however 51 articles could not be retrieved or were not obtainable in the English language. A total of 197 full-text articles were ultimately screened by the reviewers. The inter-rater percent agreement for Phase II screening between pairs of reviewers was 96.8% (95%CI – 93.7%-98.6%), kappa = 0.75 (95%CI – 0.58-0.92). In

Table 1.
Risk of Bias

Authors, Year	Research question	Criteria for inclusion	Subjects and setting	Matched controls	Valid exposure measurement	Valid measurement of outcome(s)	Confounding factors	Study taking place at multiple sites
Balestrini, 2021[48]	WC	AA	WC	Y	AA	Y	AA	N
Haider, 2021[52]	WC	WC	WC	Y	WC	Y	AA	Y
Hinds, 2016[53]	WC	AA	WC	Y, PA	AA	Y	AA	N
Memmini, 2021[50]	WC	WC	WC	Y	AA	Y	AA	N
Haider, 2020[51]	WC	AA	WC	Y	AA	Y	AA	N
Gall, 2004[55]	AA	WC	WC	Y	PA	Y	PA	N
Gall, 2004[54]	AA	WC	WC	Y	PA	Y	AA	N
Snyder, 2021[79]	WC	WC	WC	Y	AA	Y	AA	N
Woehrle, 2020[49]	WC	PA	AA	Y	AA	Y	AA	N
Paniccia, 2018[56]	WC	WC	WC	Y	WC	Y	WC	N
Master, 2020[21]	WC	WC	WC	Y	WC	WC	WC	N

Abbreviations: JBI, Joanna Briggs Institute; AA, adequately addressed; WC, well covered; NR, not reported, NAp, Not applicable; NAd, Not addressed; PA, poorly addressed; Y, Yes; N, No total, 11 studies fulfilled the inclusion criteria and were deemed to be relevant for appraisal and synthesis.

Methodological quality

Risk of bias for each of the 11 studies was evaluated by pairs of reviewers using the JBI checklist for cross-sectional studies, and consensus was reached following discussion. All eleven relevant studies were deemed to be low risk of bias based on their methodological quality. A risk of bias table (Table 1) describes results from critical appraisal as well as other relevant information that may have been described in the included studies.

Study characteristics

As described above, the JBI critical appraisal checklist for analytical cross-sectional studies was used for all eleven studies. The authors of the majority of the eleven studies identified their study methodology as being case-control or cohort, however these study classifications were not consistent with their respective epidemiological study design definition. For example, the authors of five studies identified their respective study as using case-control methodology, however upon review, the presence or absence of an exposure (concussion or history of concussion) in all studies was used to dictate the grouping prior to measurement of the outcome of interest (ANS functioning).[49-51, 56, 79] Thus, the disease/outcome was identified after a known exposure. To be of case-control methodology, subjects would be sampled based on the outcome of interest (presence or absence of ANS dysfunction), with a historical observation determining those who had sustained a concussion and those who had not. Thus, the analytical cross-sectional critical appraisal tool was the best fit during appraisal. An additional four studies were identified as being prospective cohort studies, however most measurements took place within a short timeframe and not over the long term.[21, 48, 52, 53] Two studies did not state their proposed study design and were deemed to best fit a cross-sectional design.[54, 55] Upon appraisal we deemed all 11 studies to be low risk of bias and there is a more detailed description in Table 1.

Due to the variability and rapidly changing diagnostic criteria for concussion, different criteria were used for diagnosis or determination of past concussion between studies. Five studies stated clearly that concussion diagnosis was made by a physician.[21, 48, 52, 53, 56] Others stated that diagnosis was determined using combinations of medical history, reported mechanism of injury, medical chart review, or self-report of previous physician diagnosis.[49-51, 79] Two older studies utilized the Canadian Hockey Association guidelines to define concussion where diagnosis relied on team trainers and spectators to detect events suspicious of concussion while observing game play.[54, 55]

There was variability in how ANS function was measured in the eleven studies. Cardiovascular and cardioautonomic metrics such as blood pressure (BP), systolic blood pressure (SBP), diastolic blood pressure (DBP), heart rate (HR), heart rate variability (HRV), and mean arterial pressure (MAP) were used.[48-56] Various combinations of these metrics were often included. The most common HRV sub-metric used was root mean square of successive RR interval differences (RMSSD)[48-51, 56], where the RR interval represents the time elapsed between two successive R-waves of the QRS signal of an electrocardiogram[80]. Studies also calculated the standard deviation of the NN intervals (SDNN)[50] and standard deviation of the RR intervals (SDRR)[54], where "NN" represents different nomenclature for "RR". However, the use of "NN" is used to distinguish that the RR interval of successive heart beats are "normal" and with the absence of artifacts.[80] Both of these sub-metrics are considered to be time domain measures of HRV, which quantify the inter-beat interval of a normal heart rhythm.[80] Other studies used frequency domain measures such as high frequency power (HF)[51, 54], low frequency power (LF)[51, 54], and the ratio of low frequency to high frequency power (LF:HF)[51, 54] as sub-metrics of HRV. Frequency domain measurements estimate the distribution of power (e.g., signal energy) into different frequency bands within the electrocardiogram.[80]

These cardioautonomic responses were commonly measured before, during or after various protocols of aerobic or isometric exercise.[49, 50, 53-55] Some studies examined cardioautonomic variables at rest, in different postures, or during autonomic reflex testing.[48, 51, 52] One study measured HRV over a 24-hour period during the participants' normal day-to-day activities.[56] A sole study evaluated cardiorespiratory function using respiratory rate, pulse-oximetry (SpO2), and end-tidal carbon dioxide (EtCO2).[79] Lastly, one study measured the multiple metrics of the autonomically controlled pupillary light reflex (PLR).[21]

Table 2.
Study location, sample populations and concussion diagnostic criteria.

Author(s), year	**Location/setting**	**Sample and control population descriptions, number enrolled (n), age in years**	**Concussion diagnostic criteria used in study**
Balestrini *et al*. 2021[48]	Sports medicine clinic, University of Western Ontario, Canada	Recreational and competitive adolescent athletes in a variety of sports from local adolescent sporting organizations. Concussed (mTBI) group and age and activity matched controls. mTBI: n = 65 (26M, 39F) age 15 +/- 1 yr CTRL: n= 54 (29M, 25F) age 14 +/- 1 yr	Diagnosed by a sports physician. Control participants with a previously diagnosed concussion were only included if they had not experienced symptoms in the 6-month period prior to testing (n=16).
Woehrle *et al*. 2018[49]	Sports medicine clinic, University of Western Ontario, Canada	Adolescents with sport-related concussion. Healthy, age and activity matched individuals recruited from community sports teams were used as controls. mTBI: n=19 (11M, 8F), age 15 +/- 2 yrs CTRL: n=16 (10M, 6F), age 15 +/- 2 yrs	Diagnosis was based on injury history, mechanism of injury and SCAT3 symptom score. The authors did not mention the presence or absence of a remote/resolved concussion history in the control population.
Memmini *et al*. 2021[50]	Recruitment from a minor hockey program. Quebec, Canada.	Asymptomatic Midget-AAA (age 15-18) male hockey players were divided into groups: concussion history (Chx) and no concussion history (CTRL). Chx group was divided further into those with 1 concussion (Chx1) and those with 2 or more concussions (Chx2). All groups were demographically matched. CTRL: n=18, age 16 +/- 1 Chx (total): n=16, age 16 +/- 1 Chx1: n=11, age 16 +/- 1 Chx2: n=5, age 16 +/- 1	Concussion history was determined by completion of a medical history and evaluation of de-identified health information. All concussion diagnoses were confirmed by medical records and by a resident neuropsychologist. Athletes who were currently experiencing persistent symptoms or those who sustained a concussion within 6-months of the assessment were excluded.

Author(s), year	Location/setting	Sample and control population descriptions, number enrolled (n), age in years	Concussion diagnostic criteria used in study
Haider *et al*. 2021[52]	University affiliated concussion management clinics in Buffalo, Philadelphia, and Albuquerque, USA.	Individuals presenting within 10 days of injury were considered for the concussion (mTBI) group. Healthy controls were age, activity, height, and weight matched and were obtained from regular pre-season health screening and examination. CTRL participants had no history of concussion within 12-months. mTBI: n=297 (174M, 124F), age 15.05 +/-1.7, prev. concussions 0.10 +/- 0.3, history of OH =1.4% (n=4) CTRL: n=214 (125M 89F), age 14.96 +/- 1.5, prev. concussions 0.62 +/- 1.0, history of OH = 0.5% (n=1) Sport related mTBI = 235/297 (79.4%)	Concussions were diagnosed according to international Concussion in Sport Group (CISG) guidelines by experienced clinicians based on history (including a standardized concussion symptom checklist) and clinical assessment. Diagnosis of concussion was standardized between all study physicians prior to enrollment. The CTRL group must not have been symptomatic or experienced a concussion within 12-months.
Hinds *et al*. 2016[53]	Concussion Clinic, Buffalo NY, USA	Recently symptomatic concussed (mTBI) patients with a mean time since injury of 5 days (n=40). Healthy, asymptomatic (n=30) athletes were selected as the control (CTRL) group. mTBI: n=40 (23M, 17F), age 15.5 (range 12-18) CTRL: n=30 (18M, 12F), age 15.9 (range 13-18)	Diagnosis based on physician evaluation and SCAT2. CTRL participants (no concussion) were selected if they were asymptomatic and had not experienced a concussion within 6-months prior to assessment. They also needed to be considered safe to exert themselves to exhaustion.
Haider *et al*. 2020[51]	University of Buffalo, New York, USA	Healthy, asymptomatic athlete participants. Included those with a remote concussion history >1 year ago (CH) and those without concussion history (CN). Age ranges in both groups were from 13-24 years. Individuals with >3 concussions were excluded. CH: n=9 (4M, 5F) age=18.3 +/-2.4 Prev. concussions (one=6, two=2, three=1) CN: n=21 (14M,7F), age=16.7 +/- 3.0	Self-reported concussion history. Only concussions that were recalled to be physician (or another relevant clinician) diagnosed, were included. However no comprehensive details of past concussion (loss of consciousness, recovery time, mechanism of sporting injury etc.) were collected. Those reporting no history of concussion diagnosis could be included in the CTRL group.

Author(s), year	Location/setting	Sample and control population descriptions, number enrolled (n), age in years	Concussion diagnostic criteria used in study
Gall *et al*. 2004 (BJSM)[55], 2004 (J. of ACSM)[54]	Simon Fraser University, British Columbia, Canada. Pacific International Junior B Hockey League (PIJHL)	Baseline data from 147 male Junior B players including a medical history and concussion (mTBI) history were obtained. Fourteen of 147 players sustained a concussion. Fourteen healthy non-concussed teammates (matched for position, playing time, body stature and team) served as the control group (CTRL). mTBI: n=14 (n=9 missed time, age=17.8 +/- 0.5) (n=5 did not miss time, age=18.8 +/- 0.8) CTRL: n=14 (n=9 matched controls for missed time group, age=18.7 +/- 0.4) (n=5 matched controls for no missed time group, age=19.0 +/-0.8)	Canadian Hockey Association concussion symptom guideline was used to diagnose a concussion, as applied through observation by team trainers and game attendees during game play.
Snyder *et al*. 2021[79]	University-Affiliated (UCLA) concussion clinics in Los Angeles, California	Individuals were part of a separate case-control study investigating the effect of psychological intervention in youth with persistent concussion symptoms. Controls were age-matched and recruited from local communities. PPCS: n=13 (4M, 9F), age = 16.15 (SD = 1.86), prev. concussions = 2 (SD = 1.08) CTRL: n=12 (6M, 6F), age=18.50 (SD=3.12), prev. concussions = 0.0	Concussion diagnosis by a medical provider within the past 2-16 months. Non-injured CTRL group could not be experiencing symptoms or have sustained a concussion within the 12-months prior to the study.
Master *et al*. 202021	Children's Hospital of Philadelphia, Pennsylvania, USA	Athletes aged 12-18 were prospectively enrolled. Healthy controls were athletes recruited from a local sub-urban high school with pupillometry measurements obtained prior to pre-season competition. mTBI: n=98 (43M, 55F), Age=15.7 (SD=1.54) CTRL: n=134 (56M, 78F), Age=15.3 (SD=1.61)	Concussion diagnosis was made by a sports medicine pediatrician according to the most recent consensus statement for concussion in sport. CTRL participants were healthy and had not sustained a concussion. Ten CTRL subjects subsequently sustained a concussion and thus were included in the concussed cohort.

Author(s), year	Location/setting	Sample and control population descriptions, number enrolled (n), age in years	Concussion diagnostic criteria used in study
Paniccia *et al*. 201856	Children's rehabilitation hospital, Toronto ON, Canada	Convenience sample of 553 youth athletes aged 13-18 was recruited from local sport organizations, as part of a larger pre-injury baseline testing study. Youth athletes who sustained concussion were placed in mTBI group and age/sex matched participants were then selected from the baseline cohort as the CTRL group. mTBI: n=29 (8M, 21F), Age=15 (SD=1.48) CTRL: n=15 (4M, 11F), Age=15 (SD=1.66)	Diagnosis of concussion was made by a physician. CTRL group consisted of those who did not sustain a concussion and who had undergone the same pre-injury baseline testing.

Abbreviations: M, male; F, female; mTBI, mild traumatic brain injury; n, number of participants; SCAT2/3, Sport Concussion Assessment Tool-2/3; CTRL, control group; CH, concussion history; CN, concussion naïve; SD, standard deviation; Chx, concussion history; Chx1, history of 1 concussion; Chx2, history of 2 or more concussions; PPCS, persistent post-concussion symptoms

Table 3.
Time to concussion evaluation, physiologic measurements, and findings.

Author(s), year	Time to assessment after concussion exposure	Specific ANS outcome measurements assessed	Key findings/conclusions
Balestrini *et al*. 2021[48]	When individuals pursued care at a sports medicine clinic (15 +/- 2 days after injury).	Heart rate variability (HRV, RMSSD), HR, and BP (MAP and DBP).	HR was greater in concussed group. HR in concussed group was also increased in each posture (supine vs. seated vs. standing). Smaller RMSSD values were observed in concussed females during seated posture compared to controls. Concussion may impair cardiovagal function in a sex- and posture-dependent manner. Cardiovagal dysfunction as measured by RMSSD persisted beyond clinical symptom resolution.
Woehrle *et al*. 2018[49]	12 +/- 10 days following concussion. Participants completed 2 separate testing sessions: immediately after diagnosis and at clinical discharge. The control group completed 2 test sessions separated by a minimum of 1 week.	HR, SBP, DBP, MAP, HRV (RMSSD) at rest and during 30% MVC isometric handgrip testing.	Change in HR was less in mTBI group during IHG test compared to CTRL ($p<0.05$). There is an impaired HR response at the onset of the IHG test in mTBI, which improved between the first and last visit.
Memmini *et al*. 2021[50]	Participants needed to be asymptomatic and have not sustained a concussion within 6-months of the assessment date.	Heart rate variability measures of mean N-N interval, RMSSD, and SDNN measured using ECG.	Pre-exercise: Mean RMSSD and SDNN were significantly higher for Chx2 than for Chx1. Post exercise: HR was higher for Chx compared to CTRL at all times points. Chx2 group differed significantly ($p<0.05$) from Cx1 and CTRL when measured 1-3min and 7-9min post exercise for recovery of NN/HR, SDNN and RMSSD. Elevated resting HR and longer return to baseline HRV was seen in concussed patients following exercise, when compared to controls. Having 2 or more concussions suppressed cardioautonomic function to a larger degree.

Author(s), year	Time to assessment after concussion exposure	Specific ANS outcome measurements assessed	Key findings/conclusions
Haider *et al*. 2021[52]	Concussed individuals who presented to the clinic within 10 days of the original injury.	BP, HR, PP using an automated BP cuff. Change in DBP, SBP and HR from supine to standing was calculated.	Concussed male and females experience symptoms of dysautonomia upon postural change more than healthy adolescents. These symptoms may have been due to cardioautonomic dysfunction as acutely injured adolescents with concussion had lower HRs and smaller changes in HR when moving from supine to standing, when compared to controls.
Hinds *et al*. 2016[53]	Concussed group was assessed within 5 days +/- 1.1 days, post-injury.	HR and RPE.	Concussed participants had lower HRs at the start of exercise compared to controls, but relative HR increase during each successive increase in exercise intensity was not significantly different between groups. RPE in the concussed group was higher for comparable workload when compared to controls. CTRL group exhibited no differences in HR or RPE between visits.
Haider *et al*. 2020[51]	Remote history of concussion of greater than 1-year	HRV metrics (HR, RMSSD, R-R interval were derived from the time-domain data and HF and LF HRV, and LF:HF were derived from the frequency domain data of HRV).	Athletes who reported a remote history of concussion showed a blunted cardiac parasympathetic response to a face cooling test compared to athletes without a reported history of concussion. There may also be a sympathetic predominance during face-cooling in athletes with history of concussion.
Gall *et al*. 2004 (BJSM)[55], 2004 (J. of ACSM)[54]	(BJSM, 2004) Exercise protocol completed within 72 hours of being asymptomatic at rest. Repeat protocol completed 5 days after initial assessment. (J. of ACSM, 2004) Baseline resting HRV measurement taken at 1.8 +/- 0.2 days following concussion injury. Exercise protocols completed once symptomatology has return to baseline.	(BJSM, 2004) HR and blood lactate. (J. of ACSM, 2004) HRV time domain measures (R-R interval means, SDRR). Estimation of LF power and HF power were calculated at rest and exercise. LF:HF ratio was also calculated.	(BJSM, 2004) Capacity to perform high intensity exercise did not seem to be influenced by concussion. However, although no detectable difference in symptoms from mTBI to control, the mTBI group did show an adverse CV response to steady state exercise. (J. of ACSM, 2004) No significant difference in any variable of HRV between concussed and controls while at rest, but there was difference during exercise.

Author(s), year	Time to assessment after concussion exposure	Specific ANS outcome measurements assessed	Key findings/conclusions
Snyder *et al*. 2021[79]	Within 2-16 months post-injury.	EtCO2 measured via capnometry. HR, RR, SpO2 also measured.	Baseline cardiorespiratory responses may be different in youth with PPCS compared to control participants and may be lower than normative ventilatory characteristics. These cardiorespiratory changes in the PPCS may be mediated by dysregulation in ANS functioning.
Master *et al*. 2020[21]	Measurements occurred within 28 days of injury (median 12 days, IQR 5-18 days). If injured participant had multiple assessments, the first assessment was used in the analysis.	Pupillometry. Eight pupillary dynamic metrics were quantified: maximum pupil diameter (steady-state pupil size before the light stimulus); minimum pupil diameter (pupil size after maximum constriction in response to the light stimulus); percentage pupil constriction; latency (time to maximum constriction in response to the light stimulus); peak and average constriction velocity; average dilation velocity; and T75 (time for pupil re-dilation from minimum diameter to 75%).	There were statistically significant differences in all PLR metrics between groups, except latency. Thus, testing the PLR identified a significant difference in pupillary autonomic control in concussed vs CTRL participants, and may serve as an objective biomarker of concussion.
Paniccia *et al*. 2018[56]	Concussed patients were followed weekly while symptomatic, and then at 1-, 3-, and 6-months following cessation of concussion symptoms. The same measures were collected for CTRL group.	HRV metrics: SDNN, RMSSD, pNN50, HF, HFnu. Mean HR was also calculated.	A decrease in RMSSD occurred in mTBI by day 15 and decreased until day 30, followed by levelling by day 50. mTBI were found to have increased HF and HFnu as days post-injury increased. Findings suggest an increasing trend of HRV along the recovery trajectory following concussion, although this recovery in physiology may be non-linear. There was a general increase in all HRV variables except SDNN, with increasing days post-injury.

Abbreviations: M, male; F, female; mTBI, mild traumatic brain injury; CTRL, control group; HR, Heart rate; RR, Respiratory rate; DBP, diastolic blood pressure; SBP, systolic blood pressure; MAP, mean arterial pressure; HRV, heart rate variability; RMSSD, root-mean square of successive N-N differences; SDNN, standard deviation of N-N intervals; SDRR, standard deviation of R-R intervals; CH, concussion history; CN, concussion naïve; Chx, concussion history; Chx1, history of 1 concussion; Chx2, history of 2 or more concussions; ECG, electrocardiogram; PP, pulse pressure; RPE, rating of perceived exertion; RRI, R-R interval; PPCS, persistent post-concussion symptoms; EtCO2, End-tidal carbon dioxide; SpO2, Blood oxygen saturation; PLR, pupillary light reflex; IQR, interquartile range; MVC, Maximum voluntary contraction; HF, high frequency power; HFnu, normalized power in HF band, LF, low frequency power; LF:HF, ratio of low frequency power to high frequency power; p, significance level

Summary of evidence

The eleven studies that were included in the data synthesis were heterogenous and could not be pooled for meta-analysis in any meaningful way as the methods of ANS measurement differed between studies. Additionally, sample populations, sample sizes, criteria for concussion diagnosis, time between concussion and initial ANS assessment, and number of repeat measures all varied between studies. Ten of the eleven studies clearly identified that the pediatric population studied were athletes. Three studies included ice hockey players[50, 54, 55], while another seven studies included "athletes from varying sports", or did not specify[21, 48, 49, 51-53, 56]. One study did not clearly state if participants were athletes, however the data collection took place at a university affiliated concussion clinic.[79]

Heart rate and blood pressure

Nine of eleven studies[48-55, 79] included measures of HR and/or BP. Measures of HR took place in different contexts, as some studies measured HR at rest and during or after exercise[50, 53, 55], while one study measured HR and BP responses to different postures[52]. One study measured heart rate and HRV during a 24-hour recording, but only reported on HRV.[56]

Hinds *et al*. suggest that resting HR is lower in concussed individuals versus controls (p=0.015), however the relative HR response to a standardized exercise-testing protocol is not significantly different between concussed athletes and controls.[53] Haider *et al*. found that concussed individuals had a statistically significant lower resting supine and standing HR, compared to controls (p<0.001; mTBI supine 66.9 +/- 12.2 bpm, standing 80.3 +/- 14.2 bpm; CTRL supine 71 +/- 12.9 bpm, standing 87.0 +/- 15.6 bpm). In this study, concussed individuals also had a smaller increase in HR compared to controls during a sit stand transition, however this was not statistically significant.[52] In contrast, Balestrini *et al*. found that HR was greater in concussed individuals in supine, seated and standing positions (supine p=0.03, seated p=0.006, standing p=0.009) compared to controls.[48] In this study, the concussed group also exhibited elevated DBP and MAP at their first visit, which was similar to controls by clinical discharge, however the elevated HR that was observed in concussed individuals did not recover by clinical discharge (p>0.5).[48] Memmini *et al*. also suggest that athletes with a history of concussion have higher resting HR, as well as higher post-exercise HR.[50] Lastly, although not statistically significant, Snyder *et al*. qualitatively identified a wider distribution of HR values amongst the participants in the concussed group when compared to the control group.[79]

In another study, there were smaller changes in HR within individuals in the concussed group during an isometric hand-grip exercise compared to controls (p<0.05; d=0.77, mTBI 95%CI 3.6-9.2 bpm, CTRL 95%CI 8.0-18.0 bpm).[49] Relative percentage change in HR was also less in the concussed group (% change in bpm; p=0.03; d=0.80, mTBI=9.5%; CTRL=20%).[49] During a different exercise task which involved steady-state aerobic exercise, Gall *et al*. reported that HR responses appeared to be greater in concussed individuals versus controls (p<0.05), with a significantly higher mean HR in the concussed group during an 8-minute aerobic test (mTBI, 126 bpm +/- 3.4 vs. CTRL, 116 bpm +/- 1.9, p<0.05).[55] However, the decreases in HR during a 5-minute recovery were not different between groups in this same study.

During cardioautonomic reflex testing (e.g., face cooling), individuals with a remote history of concussion (CH) showed overall positive changes in HR (% change in bpm), while control participants (CN) exhibited the expected negative change in HR at multiple timepoints of measurement (minute 1, CH +8.9% [−9.6, +27.4], CN −7.5% [−13.3, −1.7]; minute 2, CH +15.0% [−8.0, +38.1] CN −10.3% [−15.8, −4.7]; minute 3, CH +6.9% [−10.1, +24.4] CN −8.3% [−12.6, −4.1]).51 There was a difference over time between groups (p=0.021) that was not affected by sex (p=0.792) or age (p=0.097).

Heart rate variability

Six of the eleven studies[48-51, 54, 56] included HRV analysis. Like HR measurements, HRV was measured in different contexts and at different timepoints between the studies.

Balestrini *et al*. identified reduced RMSSD in concussed females while in a seated posture compared to controls (42 +/- 4ms vs. 61 +/- 7ms; p=0.01), which also correlated with their concussion symptom report (r2=0.07, p=0.005). In females, the RMSSD did not increase by clinical discharge (mean=37 days). This was the only study to identify a sex and posture dependent difference in HRV as a metric of cardioautonomic function.[48]

Woehrle *et al*. also identified reduced RMSSD in the concussed group compared to the control group at baseline (72 +/- 58ms vs 82 +/- 53ms) and during isometric handgrip testing (IHG) (37 +/- 30ms vs 44 +/- 44ms). The group/time interaction was not statistically significant (p=0.824).[49] Isometric handgrip testing involves participants sustaining a brief isometric contraction (usually ~ 30% of maximal voluntary contraction) using a handheld dynamometer, however the intensity, duration and number of repetitions of IHG varies widely within the literature, and there is no agreed upon consensus as to the ideal duration of the test.[81, 82]

Memmini *et al*.[50] and Gall *et al*.[54] both measured HRV during five-minutes of resting, prior to having athletes exercise. Memmini *et al*. observed significantly higher mean RMSSD and SDNN in those with a history of two or more concussions (CHx2) compared to those with a history of only one concussion (CHx1) at rest (RMSSD, CHx2: 77+/- 17 vs CHx1: 49 +/- 13 ms; SDNN, CHx2: 92 +/- 197 vs CHx1: 66 +/- 14 ms). There was no comparison to concussion-free controls reported. Post-exercise, there were significant increases over time in RMSSD for both those with a history of one concussion and the concussion-free control group, but the groups were not statistically different.[50] Those with a history of two or more concussions had statistically significant differences in the recovery of RMSSD and SDNN after exercise when compared to those with a history of one concussion and the control group.[50] In contrast, Gall *et al*. reported no significant difference in concussed athletes and their matched controls in the RR interval or other parameters of HRV while at rest. However, during exercise the concussed group had significantly lower (p<0.01) mean RR intervals than matched controls (466.2 +/- 8.9 ms vs 508.1+/- 9.1 ms). The concussed group also displayed lower SDRR compared to controls at rest, but this failed to reach significance (10.7ms +/- 0.9 vs. 13.1ms +/- 0.9).54 Low and high frequency powers were also significantly reduced in the concussed versus control group across exercise protocols.

Haider *et al*. measured responses to face cooling in those with a remote history of concussion (CH) and those with no concussion history (CN). Face cooling has been shown to elicit transient but measurable increases in cardiac parasympathetic activity.[83] At baseline, the CH group had lower LF:HF ratios (p=0.050). During face cooling, there was no difference in RR interval over time between groups (p=0.161) and there was no effect of sex (p=0.582) or age (p=0.385). There was a difference in RMSSD over time between groups (p=0.048) that was not affected by sex (p=0.084) or age (p=0.597). Changes (% change in ms) were present at all minutes (Minute 1, CH +31.8% [-44.8, +109.4], CN +121.8% [+82.1, +161.5]; Minute 2, CH +23.4 [-56.1, +102.8], CN +167.7 [+88.7, +235.5]; Minute 3, CH +83.6 [+12.9, +154.2], CN +100.9 [+51.2, +150.7]).[51] There were no differences in other sub-metrics of HRV including HF, or LF:HF during face cooling.

Paniccia *et al*. was the only study to have pre-injury baseline HRV values for individuals who went on to sustain a concussion, as well as for the control group. All baseline measurements were taken prior to an athletic season. All HRV variables were similar at baseline between groups and there were no significant sex differences, with the exception of females having lower HF (normal units) compared to males. In the concussed group there was a decrease in RMSSD at 15 days post-injury that continued to decline until day 30. This decline subsequently levelled off at day 50 (p=0.02). Concussed participants also had increasing HF (p=0.005) and HF (normal units) (p<0.001) values with increasing days post-injury. The only variable that did not increase in the concussed group post-injury was SDNN. However, in the initial 30-40 days post injury, HRV in general was shown to decrease by 14-25%.[56]

Capnometry

One study used capnometry to measure various cardiorespiratory variables as a proxy of ANS regulation of respiration.[79] The authors found that there was no statistical differences in respiratory rate, HR or SpO_2 between concussed and control groups, however there was a larger range of HR distribution values within the concussed group compared to controls. There was a significantly lower $EtCO_2$ that was observed in the concussed group compared to the control group (mean=36.30 mmHg [SD=2.86] vs. 39.80 mmHg [SD=2.30], p=0.003). The control group demonstrated a strong negative correlation between $EtCO_2$ and SpO_2 using Spearman's rank correlation (r=-0.71, p=0.009), however no significant intercorrelations between $EtCO_2$ and other cardiorespiratory variable existed in the persistent post-concussion symptom group.[79]

Pupillometry

A study by Master *et al*. utilized pupillometry to measure the ANS control of the PLR in concussed athletes and controls.[21] Athletes with concussion had larger maximum pupil diameters (4.83 vs 4.01mm; difference, 0.82; 99.44% CI, 0.53-1.11), larger minimum pupil diameters (2.96 vs 2.63mm; difference, 0.33; 99.4% CI, 0.18-0.48), and greater percentage constriction following light stimulus (38.23 vs 33.66%; difference, 4.57; 99.4% CI, 2.60-6.55). Enhanced pupillometry metrics revealed faster average constriction velocity (3.08 vs 2.50mm/s; difference, 0.58; 99.4% CI, 0.36-0.81), faster peak constriction velocity (4.88 vs 3.91mm/s; difference, 0.97; 99.4% CI, 0.63-1.31), faster average dilation velocity (1.32 vs 1.22mm/s, difference, 0.10; 99.4% CI, 0.00- 0.20), faster peak dilation velocity (1.83 vs 1.64mm/s; difference, 0.19; 99.4% CI, 0.07-0.32), and faster time to 75% re-dilatation (1.81 vs 1.51s; difference, 0.30; 99.4% CI, 0.10-0.51) in concussed athletes compared to matched controls.[21]

Discussion

The purpose of this systematic review was to investigate if pediatric sport-related concussion is associated with dysfunction of the ANS when compared to healthy pediatric populations. In a previous systematic review, Pertab *et al*. identified that "it is likely that concussion causes anomalies in ANS function", however these authors synthesized data from all populations.[36] In our review, we were able to identify that there is evidence to support that sport-related concussion impairs various functions of the ANS in a pediatric population, specifically.

Monitoring following concussion has largely focussed on athletes' symptom levels during daily and athletic tasks, and has served as primary criteria for recovery and return to sport.[1, 84, 85] More recently, focus has been placed on objective biomarkers to detect concussion and to determine recovery in hopes of providing more accurate and safe return to sport.[30, 31, 86, 87] This focus has gained some acceptance as it is becoming apparent that subjective symptom reporting has its limitations, and can be readily modified by the reporting athlete. Concussion-like symptoms also exist in numerous conditions such as depression[88, 89], anxiety[90], chronic pain syndromes[88, 91], cervical spine injuries[92] and can also vary by sex[26, 93], making it challenging to determine the etiology of reported symptoms in the presence of co-existing conditions. Existing literature on moderate and severe TBI in pediatric populations suggest that injury results in profound negative influences on cardioautonomic functioning, respiratory function, cerebral oxygenation, and consciousness following injury, all of which that can be monitored objectively.[94-98] As concussions are considered a milder form of TBI, it behooves researchers and clinicians to understand the potential for these autonomic consequences to fall along a spectrum of dysfunction, similar to the already recognized spectrum of injury under the umbrella of TBI diagnosis.

In the studies we synthesized we identified that concussion is associated with dysregulation in cardioautonomic regulation and functioning in pediatric athletes. Haider *et al*.[42] and Hinds *et al*.[43] reported that concussed individuals exhibit lower resting HR and lower HR while in different postures at rest when compared to controls. These findings suggest that there may be a parasympathetic predominance of cardiovascular control in individuals following concussion. In contrast, Balestrini *et al*.[37] and Memmini *et al*.[39] found that concussed individuals have higher HR at rest suggesting the contrary – that there may be a sympathetic dominance following concussion. The latter is a generally accepted consequence following moderate and severe TBI, and mechanistically, increased sympathetic nervous system activity leads to neuroinflammation and oxidative stress, both of which are known to be present following concussion.[2, 94, 95] One potential contribution to the differences observed between studies is that the environmental context in which cardioautonomic measurements are taken may influence the results. This is important to recognize as exercise[99, 100], body temperature[101], time of day[102] and psychological state[89, 103] have all been shown to produce variations in cardioautonomic measurements. Nevertheless, despite the presence of positive and negative changes in resting HR, all the studies exhibited a measurable difference in the cardioautonomic control of HR when comparing concussed athletes to controls, thus suggesting some degree of dysregulation of the ANS following concussion.

There may also be different HR responses that occur when athletes are exposed to distinctive forms of exercise following concussion. Woehrle *et al*.[49] reported that concussed individuals have an impaired ability to elevate their HR at the onset of a dynamic IHG task. A brief IHG task and the concomitant HR response that should occur reflects a reduction in vagal inhibition on the heart.[104-106] This should result in a brief but measurable increase in HR upon the onset of the exercise. The authors hypothesized that because concussed individuals have an impaired response to an IHG task it may suggest that they have a reduced ability to withdraw cardiovagal control of the heart as a result of disrupted ANS function.[49] Cardiovagal withdrawal is largely dictated by supratentorial and brainstem regions of the ANS, which may be susceptible to concussive impacts. During an aerobic exercise task, Gall *et al*.[55] reported that the HR response in concussed athletes is larger resulting in a higher mean HR. Unfortunately, due to the mechanistic complexity of cardioautonomic and cardiovagal control under different conditions, the responses observed in these two studies cannot be directly compared with confidence. Different exercise paradigms (e.g., dynamic exercise vs steady-state aerobic activity) produce different physiological effects.[104-106] Thus, it is not surprising that these authors observed different autonomic responses in their respective populations, as the environmental context of testing and measurement was different.

Another form of physiological monitoring following concussion that is also objective is autonomic reflex testing.[107] Autonomic reflexes are largely responsible for the maintenance of homeostasis within an organism while providing ongoing adaptation to both internal and external environmental stressors, and reflect reflexive activity of the sympathetic or parasympathetic components of the ANS.[33, 107] Technically, the ANS as a whole is reflexive in nature, as it automatically responds to perturbations in pre-established physiological set points. Still, there are specific reflexes within the ANS that can be isolated, measured and compared to their expected normal values. In humans these reflexes are innate, thus, dysregulation can lead to aberrant physiology, illness, and somatic symptoms.[108-110]

Two studies assessed the integrity of autonomic reflexes in individuals who had sustained a concussion. Haider *et al*.[51] evaluated the cardioautonomic response to a face-cooling procedure which is based on the mammalian dive reflex physiology. The dive reflex triggers bradycardia in order to conserve oxygen stores which is a protective response to cold water submersion.[83] The authors observed a profound reduction in the reflexive bradycardia that was expected during face-cooling in the group with a remote history of concussion, as they exhibited the contrary – a profound and measurable increase in HR during all timepoints of the procedure. The control group exhibited the expected bradycardia at all timepoints, which reflects an appropriate parasympathetic response to face cooling. These results provide evidence that there may be persistent deficits in reflexive ANS control in asymptomatic individuals who report a history of concussion, that are not present in those without a history of concussion. These findings may suggest the importance of having objective clinical measures to assess ANS integrity and athletic readiness for return to sport, in hopes of preventing return prior to full physiological recovery.

Master *et al*.[21] evaluated the utility of the PLR, which has been shown to be adversely affected by concussion in previous studies.[18, 111] Resting pupil size, responsiveness to light, and re-dilatation of the pupils are mediated by regions of the ANS and they are readily measurable by technologies such as pupillometry.[112-114] Pupillary defects and aberrant responsiveness to light stimuli are well documented in all forms of TBI[64, 65, 115] which has led to increasing utility of pupillometry in the diagnosis and management of concussion. Master *et al*.[21] found that all advanced pupillometry metrics were different in a concussed pediatric population compared to controls. Specific findings such as larger resting maximum pupil diameter and larger minimum pupil diameter suggest a sympathetic predominance while greater constriction and dilation velocities may suggest an aberrant and exaggerated response to a light stimulus. Areas of the CNS including the superior colliculus, pretectal olivary nucleus, locus coeruleus and the Edinger-Westphal nucleus all modulate the PLR with the help of higher cognitive brain centres.[116] Thus, an injury to any combination of these areas may lead to an aberrant PLR through disruption of communication between these modulatory regions.

Collectively in the studies we synthesized, we identified significant heterogeneity in study methodology which made it impossible to perform a meta-analysis of the results. However, upon qualitative synthesis it became apparent that the ANS may be disrupted in some way following concussion – a concept that is already generally accepted in existing literature.[35, 43, 44, 117]

Our systematic review identified weaknesses in the existing literature which include but are not limited to small sample sizes, lack of baseline ANS measurements, variability in the concussion diagnostic criteria used, and variability between times to assessment post-injury. Some studies examined concussed individuals as acutely as 1.8 days following injury[54, 55] while others examined individuals who were asymptomatic and only reported a history of concussion[51], or reported ongoing post-concussion symptomatology up to 16-months after injury[79]. This limits our ability to compare these studies with certainty as asymptomatic individuals may differ substantially from individuals still suffering from post-concussive symptoms when considering psychological state[88, 90] and aerobic capacity[118], both of which may confound ANS measurement.

Additionally, having strict age criteria in our methodology ended up being a limitation of our review as there were multiple relevant studies that were not included due to sample population age.[61, 119-122] A large proportion of studies in the existing literature include college and university aged participants, as institutions may have access to varsity athletes for data collection. Unfortunately, most of these studies had populations with mean ages of 19-22 years of age, which falls outside of our pre-established pediatric definition. So, although the methodology of such studies was generally acceptable and included concussed and non-concussed populations along with valid measures of ANS function, they could not be included in our review. Widening the scope of a future review to include individuals up to the age of 25 may result in more sound conclusions due to more potential studies being included in the synthesis.

Lastly, the pervasive lack of baseline ANS data in the existing literature is a major limitation and impairs our ability to make conclusions with directional certainty. Improving pre-season ANS measurement and including repeated measurement at regular intervals throughout the season will substantially improve the validity of making post-injury comparisons within individuals in future studies. Repeated measurements during a sporting season would likely be necessary to maintain the validity of the comparison as the improved fitness and aerobic capacity that one may gain throughout a season may increase an individual's HRV and decrease their resting HR and BP.[118, 123] Thus, even a single pre-season measurement may not be a valid comparator following injury, especially if an injury occurs in the peak of an athletic season.

Conclusion

In conclusion, our systematic review identified evidence to support that concussion likely leads to dysfunction of the ANS in pediatric athletes. This is in line with another recent systematic review of all ages and populations.[36] We identified some significant limitations in the methodology of the existing literature. Additionally, certain measurements of ANS function can be cumbersome and expensive, which is a barrier to widespread adoption in the sporting community particularly at the grassroots level. Future studies should focus on standardization of measurement methods, gathering baseline data, and performing repeat measurements of athletes throughout an athletic season. Implementation of these methods may lead to more accurate descriptions and quantification of the influence that concussion has on the ANS and may improve diagnosis and management of concussion in sport.

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