Assessing and characterizing Vestibulo-Ocular Reflex function following pediatric mild traumatic brain injury

Adrienne Crampton
B.SC (Kinesiology), M.HK (Human Kinetics)

School of Physical and Occupational Therapy

Faculty of Medicine
McGill University, Montreal

December, 2020

A thesis submitted to McGill University in partial fulfillment of the requirements of the degree of Doctorate in Philosophy (Rehabilitation Science)

To my family, the crew and the core, for supporting every journey I choose to embark upon.

To concussions… You have heavily influenced my life path. You have made me develop patience, resilience, perseverance and introspection… thank you. I hope this work contributes to decreasing the burden you will have on future generations.

Table of Contents

List of tables

List of figures

List of abbreviations

ADL	*Activity of daily life*
CFRT	*Cervical flexion rotation test*
CI	*Caloric irrigation*
CNS	*Central nervous system*
CVAQ	*Cardiff visual acuity questionnaire*
DAI	*Diffuse axonal injury*
DHI	*Dizziness handicap inventory*
DVA/cDVA	*Dynamic visual acuity/Computerized dynamic visual acuity*
ENG/EOG	*Electronysagmography/ Electrooculography*
GCS	*Glasgow coma scale*
GEE	*Generalized estimating equations*
GST/cGST	*Gaze stability test/Computerized gaze stability test*
HIT	*Head impulse test*
vHIT	*Video head impulse test*
HST	*Head shaking test*
HTT	*Head thrust test*
LARP	*Left-anterior/right-posterior*
LogMAR	*Logarithm of the minimum angle of resolution*
MI	*Multiple imputation*
NCAA	*National collegiate athletic association*
NPC	*Near point of convergence*
OM	*Oculomotor*
OR	*Odd ratio*
PRO	*Patient-reported outcome*
RALP	*Right-anterior/left-posterior*
RCT	*Rotary chair test*
ROM	*Range of motion*
SCC	*Semi-circular canal*
SD	*Standard deviation*
SHA	*Sinusoidal harmonic acceleration*
SP	*Smooth pursuit*
SPEM	*Smooth pursuit eye movements*
TBI	*Traumatic brain injury*
mTBI	*Mild traumatic brain injury*
USA	*United States of America*
VCR	*Vestibulo-collic reflex*
VMS	*Visual motion sensitivity*
VO	*Vestibulo-ocular*
VOG/VNG	*Video-oculography/videonystagmography*
VOMS	*Vestibular/ocular motor screening tool*
VOR	*Vestibulo-ocular reflex*
VSR	*Vestibulo-spinal reflex*

Abstract

Background: The high reported rates of pediatric mild traumatic brain injury (mTBI) and the potential persistent symptoms associated, have made this injury a pressing health concern across the globe. The direct and/or indirect forces associated with the traumatic event causing mTBI result in diffuse pathologies and heterogeneous clinical profiles among this young population. While a majority of individuals recover within two to four weeks of injury, a significant portion experience persistent symptoms beyond three months. Such a long recovery period can significantly impact a child or adolescent's ability to perform recreational activities and activities of daily life. Moreover, there can be serious consequences to their psychological, psychosocial and physical well-being. While previous management and treatment of mTBI was relatively conservative, scientific advances in recent years have supported more active approaches to rehabilitation. In order to continue to develop more targeted treatment strategies, assessments across the various domains known to be affected by mTBI must be refined. More comprehensive and precise yet accessible assessments will lead to a more detailed understanding of the pathophysiological mechanisms underlying impairments and symptoms that present and/or persist following mTBI. It has recently been demonstrated that vestibulo-ocular reflex (VOR) impairments and symptoms presenting in the acute stage following injury can lead to a greater symptom profile and a generally more negative prognosis. At the present time, the reasons underlying these relationships are poorly understood. To address this, it is necessary to more conclusively determine how to assess VOR function in order to understand the specific characteristics of related impairments that may occur following mTBI in pediatric populations.

Objective: The overarching goal of our work is to characterize VOR function following mTBI in children and adolescents, with a special focus on its assessment, using patient-reported and clinician administered measures. The first line of inquiry focuses on understanding the breadth of measures used to assess VOR function and how they relate to one another (manuscript 1 and 2). The second line of inquiry focuses on determining the extent to which clinician-administered measures of VOR function and the oculomotor (OM) system relate to patient-reported outcome (manuscript 3). The third and final line of inquiry determines if performance on measures of VOR function and the supporting OM system vary over the first 6 months following pediatric mTBI (manuscript 4).

Methods and results: The focus of the *first line of inquiry* was fulfilled in two parts. First, through a scoping review whose objective was to identify the tests administered and tools used to evaluate VOR function after TBI in all ages and severities. An electronic search across seven databases, including all relevant literature until November 2019 was performed. Our results identified various tests performed, among which were the gold standard Caloric Irrigation and Rotary Chair tests. Our results identified alternatives to these, each performed with computerized or clinical tools. Overall, the findings outline three types of measures (computerized, clinical, and symptom-based) that can be further grouped into three categories: 1) measures focusing on symptom provocation in response to tasks requiring eye and head movements, 2) measures of gaze stability in response to unplanned high velocity head movements, and 3) measures of gaze stability in response to voluntary or expected high velocity head movements. Second, an agreement study was performed to determine the level of agreement between symptom-based and performance-based tests of VOR function in a pediatric mTBI population. Agreement was obtained using Cohen's kappa statistic. Little agreement was found between performance-based and symptom-based tests of VOR function. The second objective was to characterize the level of symptoms provoked by VOR tests in individuals with cervical findings and those without. Our findings demonstrated greater symptom provocation in individuals with cervical findings. This study supports the notion that 1) each test has a distinct role in VOR assessments and thus, one cannot be substituted for another, and 2) there is a need to further understand the contributions of co-existing cervical impairments to the symptom provocation experienced following VOR tasks.

The focus of the *second line of inquiry* was addressed through a relationship study for which the objective was to determine the extent to which clinician administered measures of VOR and OM function relate to patient-reported levels of activity limitations and participation in children and adolescents within 21 days of mTBI. Linear regression was used to examine the associations present between the relevant clinician-administered and patient-reported measures included in this study. Our models demonstrated a significant association between symptoms induced by VOR tasks and the Dizziness Handicap Inventory (DHI) and symptoms induced by version tasks and the Cardiff Visual Ability Questionnaire (CVAQ). These findings highlight the need to encourage treatment strategies targeting VOR and version-related symptoms experienced, as they cause important and limiting vestibular and visual burdens to the pediatric mTBI population.

The focus of the *third line of inquiry* was addressed through a longitudinal study for which the objective was to determine the extent to which performance on clinical and computerized tests of VOR function and of its supportive OM system vary over time in children and adolescents at 21 days, 3 months, and 6 months after mTBI. The secondary objective was to determine the proportion of this sample presenting with abnormal scores on VOR and OM tests at each timepoint. Generalized estimating equations were used to estimate the effect of time on outcome measures at 3 separate timepoints. For each outcome measure the proportion of the sample demonstrating results above or below predetermined cut-offs was determined. Significant changes over time were observed in global VOMS symptom provocation (driven by VOR subcomponents), right VOR gain, vertical saccade performance and vertical smooth pursuit performance. The version performance variables were found to have the highest proportions demonstrating abnormal results. These findings highlight that the importance of including both symptom-based and performance-based outcome measures when evaluating subcomponents of VOR function. Additionally, the results suggest potential impairments along the VOR pathway (causing sensory mismatch) and along the pathways supporting vertical version performance.

Conclusion: The findings from the three lines of inquiry demonstrate the need to refine what outcome measures should be used when evaluating VOR function following pediatric mTBI in order to develop a battery of tests that is accessible, efficient and comprehensive. The results emphasize the importance of accounting for co-existing cervical impairments in assessments and of treating symptoms induced by VOR and OM tasks due to the significant effect they can have on one's daily functioning. This work underlines the value of including symptom-based and performance-based outcome measures when assessing VOR function, and identifies subcomponents of VOR function that demonstrate change over time following pediatric mTBI.

Abrégé

Contexte: L'incidence élevée des traumatismes craniocérébraux légers (TCCL) chez les enfants ainsi que la possibilité que les symptômes associés puissent persister font en sorte que cette blessure représente un problème de santé majeur à travers le monde. Les forces externes directes et/ou indirectes impliquées pendant l'évènement traumatique causant le TCCL produisent des pathologies diffuses et des profils cliniques hétérogènes chez cette jeune population. Alors qu'une majorité d'individus se rétablissent au cours des deux à quatre semaines suivant la blessure, une proportion importante d'entre eux aura des symptômes qui persistent au-delà de trois mois. Pour un enfant ou un adolescent, une plus longue période de récupération peut avoir d'importantes conséquences sur leur bien-être psychologique, psychosocial et physique, ainsi que sur leur capacité d'effectuer des activités récréatives et des activités de la vie quotidienne. Jusqu'à récemment, les approches de réadaptation et de traitement recommandées pour traiter une personne avec un TCCL étaient axées sur le repos, mais de récents progrès scientifiques ont démontré le potentiel thérapeutique de certaines approches de réadaptation plus actives. Afin de développer des interventions en réadaptation plus ciblées, les évaluations doivent, elles aussi, évoluer afin de mieux comprendre les multiples domaines de fonctionnement pouvant être affectés après un TCCL. Une évaluation plus complète, précise et accessible, fera en sorte que les mécanismes physiopathologiques associés aux déficiences et aux symptômes qui se présentent et/ou persistent après un TCCL seront identifiés d'une manière plus détaillée. Récemment plusieurs troubles et symptômes liés au réflexe vestibulo-oculaire (RVO) ont été rapportés suite à un TCCL et associés à un pronostic plus négatif. Cependant, les raisons expliquant cette relation sont présentement mal comprises. Afin de résoudre ce problème, il est nécessaire de mieux définir comment évaluer la fonction du RVO et de mieux comprendre les caractéristiques des déficiences pouvant survenir à la suite d'un TCCL chez les enfants et les adolescents.

Objectif: Le but principal de notre travail est de décrire la fonction du RVO à la suite d'un TCCL chez l'enfant et l'adolescent en mettant l'emphase sur son évaluation utilisant des mesures auto-rapportées ou administrées par des cliniciens. Le premier aspect traité vise à décrire le spectre des outils de mesure qui sont utilisés pour évaluer la fonction du RVO et leurs associations les uns aux autres (manuscrits 1 et 2). Notre deuxième champ d'investigation vise à déterminer dans quelle mesure les tests de la fonction du RVO et du système oculomoteur (OM), administrés par des

cliniciens, sont associés à certaines mesures auto-rapportées (manuscrit 3). La troisième et dernière piste d'investigation vise à déterminer si la performance des enfants et adolescents aux mesures de la fonction du VOR et du système OM, varie au cours des 6 premiers mois suivant leur TCCL (manuscrit 4).

Méthodes et résultats: L'objectif de la première investigation a été atteint en deux étapes. Premièrement, une revue de la portée a été effectuée afin d'identifier (dans la littérature scientifique) les tests administrés et les outils utilisés pour évaluer la fonction du RVO après un TCC de toutes sévérités auprès de personnes de tous âges. Une recherche électronique dans sept bases de données et incluant la littérature pertinente jusqu'en novembre 2019 a été effectuée. Nos résultats ont identifié divers tests utilisés, parmi lesquels se sont retrouvés deux tests de référence soit « l'Irrigation Calorique » et la « Chaise Rotative ». Nos résultats ont identifié des alternatives à ces derniers, réalisées avec des outils informatisés ou cliniques. Les résultats décrivent trois types de mesure (informatisées, cliniques et basées sur les symptômes) pouvant être regroupées en trois catégories soit : 1) mesure axée sur la provocation des symptômes en réponse à des tâches nécessitant des mouvements des yeux et de la tête; 2) mesure de la stabilité du regard en réponse à des mouvements non planifiés de la tête à haute vélocité; et 3) mesure de la stabilité du regard en réponse à des mouvements volontaires ou anticipés de la tête à haute vélocité. Comme deuxième étape, une étude de concordance a été réalisée pour déterminer le niveau d'accord entre les tests basés sur les symptômes et les tests basés sur la performance de la fonction du RVO auprès d'un échantillon d'enfants et d'adolescents à l'aide de la statistique kappa de Cohen. Nos résultats démontrent peu de concordance entre les tests basés sur les symptômes et les mesures basées sur la performance de la fonction du RVO. L'étude de concordance a aussi permis de déterminer le niveau de symptômes provoqué par les tests du RVO chez les individus ayant des résultats positifs à divers tests de fonction cervicale et ceux n'ayant pas de tels résultats. Nos résultats ont démontré qu'une plus grande provocation de symptômes était présente chez les personnes ayant des déficiences au niveau cervical. Cette étude conclue donc que 1) chaque test a un rôle distinct dans les évaluations de la fonction du RVO et que l'un ne peut être remplacé par un autre, et que 2) il est nécessaire de mieux comprendre les contributions des déficiences cervicales co-existantes lors de la provocation des symptômes ressentis, à la suite des tâches de RVO.

L'objectif de *la deuxième* piste d'investigation a été abordé dans le cadre d'une étude corrélationnelle dont l'objectif était de déterminer dans quelle mesure les tests de la fonction du RVO et du système OM administrés par les cliniciens étaient associés aux limitations d'activités et restriction de participation des enfants et des adolescents à l'intérieur des 21 jours suivant un TCCL. Une analyse de régression linéaire a été utilisée à cet effet. Nos modèles ont démontré une association significative entre les symptômes induits lors des tâches du RVO et le *Dizziness Handicap Inventory* (DHI) ainsi qu'entre les symptômes induits lors des mouvements de version et le *Cardiff Visual Ability Questionnaire* (CVAQ). Ces résultats soulignent la nécessité d'encourager les stratégies de traitement ciblant les symptômes liés au RVO et aux mouvements de version, car ils causent des difficultés importantes sur le plan vestibulaire et visuel auprès de la population pédiatrique ayant subi un TCCL.

L'objectif de la *troisième piste investigation* a été abordé dans le cadre d'une étude longitudinale dont l'objectif était de déterminer dans quelle mesure la performance des enfants et adolescents aux tests cliniques et informatisés de la fonction du RVO et du système OM varie à 21 jours, 3 mois et 6 mois après un TCCL. L'objectif secondaire de cette étude visait à déterminer la proportion d'individus de ce groupe présentant des scores anormaux aux tests du RVO et du système OM à chacun de ces moments d'évaluation. Des équations d'estimation généralisées ont été utilisées pour estimer l'effet du temps sur les mesures des résultats au cours de la période d'évaluation. Des changements significatifs au fil du temps furent observés au niveau de la provocation globale des symptômes, du gain du RVO droit, de la performance lors d'épreuve de saccade verticale et de la performance lors de la poursuite verticale. Les variables de performance lors des mouvements de version présentaient les proportions anormales les plus élevées. Ces résultats soulignent l'importance d'inclure à la fois des mesures de résultats basées sur les symptômes et basées sur la performance lors de l'évaluation des sous-composantes de la fonction du RVO. De plus, les résultats suggèrent des altérations potentielles le long de la voie du RVO (qui provoque une discordance sensorielle) et le long des voies qui soutiennent les performances de mouvement de version verticale.

Conclusions Les résultats de ces travaux démontrent la nécessité d'affiner quelles mesures devraient être utilisées lors de l'évaluation de la fonction du RVO après un TCCL pédiatrique afin

de développer une batterie de tests pouvant fournir une évaluation accessible, efficace et complète. Les résultats soulignent l'importance de tenir compte des déficiences cervicales co-existantes et de traiter les symptômes induits par des tâches stimulant le RVO et le système OM en raison de leur effet significatif sur le fonctionnement d'un enfant ou d'un adolescent. Ces études soulignent l'importance d'inclure à la fois des mesures basées sur les symptômes et d'autres basées sur la performance dans les évaluations de la fonction du RVO. De plus, elles identifient des changements dans certaines sous-composantes de la fonction du RVO suivant un TCCL pédiatrique.

Acknowledgements

To my supervisor Dr. Isabelle Gagnon. I have always believed in following my heart and my instinct above all else. Years ago, immersed in a very unrelated field of study, I reached out to you demonstrating interest in joining your lab. Following one short phone call I was convinced that beginning my journey into the world of mTBI under your supervision was *the* next move. I am most thankful that you also accepted this next move, welcoming me with open arms into such a cohesive and supportive lab environment. You accepted my "unconventional" background and were ever-so patient with me throughout the years when I needed support climbing the steep learning curve of academia. With regards to research and academia, your mentorship and tactful guidance has taught me more than I can describe in words. Equally important, are the life skills I have learned from your leadership, empathy, flexibility and poise in all situations. Thank you for the invaluable lessons and immeasurable support.

To Dr. Liz Teel, you were by my side on a daily basis through the many ups and downs. I am *very* grateful for this. Your mentorship, guidance and wisdom (yes you are wise!) kept me on track when I felt I was derailing.

Thank you to Dr. Isabelle Gagnon, the RI-MUHC, the School of Physical and Occupational Therapy and the FRQS-REPAR for providing me with financial support and thus the opportunity to benefit from such an enriching PhD curriculum and experience.

To my supervisory committee members Ms. Lisa Grilli and Dr. Kathryn Schneider. Your expertise, clinical insights and thought-provoking questions encouraged me to pursue important lines of thinking key to making this body of work what it is today. Thank you.

To the clinical team at the Montreal Children's Hospital Concussion clinic; Lisa Grilli, Christine Beaulieu, Meghan Straub, Carlo Galli and Debbie Friedman. Thank you for welcoming and supporting my research project. Such a study would not have been feasible without you!

Joanna and Mike… There is no better pair to spend countless days and evenings with at the hospital. When the pandemic hit, I missed our daily interactions. Thank you for supporting me

throughout these years and being such a dynamic duo! Thank you to my participants and their families for contributing to science, making my PhD and the SiMPLy Rehab project possible ☺

To the SiMPLy Rehab team and other contributors; Drs. Isabelle Gagnon, Mathilde Chevignard, Kathryn Schneider, Michal Katz-Leurer, Miriam Beauchamp and Chantel Debert. Trainees and staff members: Gilad Sork, Aurelie Garat, Julie Joyce, Michaela Chadder, Joanna Mazza, Michael Skalak and Heather Shepherd. Thank you for the many meetings, constructive discussions, comments, timely assistance and overall support.

To lab members Scott, Guido, Julien and Dakota. Our time was short, but rest assured it was sweet! To the row; our shared Wusband Christophe Alarie, Drs. Danielle Dobney, Eda Cinar, Laurie Corbin-Berrigan (Wom #1) and Liz Teel (Wom #2). I feel blessed to have had such a wonderful group to navigate these last few years with. Thank you for the laughs, deep conversations, support and ridiculous moments. Thank you for the valuable contributions you all had in helping me (Waby) evolve as a person and academic.

To the members of our crazy Irish family across the country/world and to the loving Spada & Wyczynskis. Every ounce of encouragement you sent my way was felt and appreciated.

Thank you to all my friends near and far who supported me throughout this journey in many unique and creative ways. This kept me driving forward energetically! A special thank you to my core trio in Ottawa/Toronto and to my main humans in Montreal for *always* being there.

Jesc. Merci pour tout ton support au cours de ces dernières années. Tu étais là pour célébrer les victoires autant que pour m'encourager de passer à travers les obstacles. Tu as été une étincelle incroyable dans ma vie et pour cela je t'en remercie.

To my fam-jam. Mam (Bichenette), Dad, Steffi, Bren and Miss Gabby (The Gabster). You are my rocks and always will be. You are my biggest cheerleaders and my most faithful fans. Your unconditional love, support, guidance and advice has allowed me to achieve this milestone and become who I am today. Thank you from the bottom of my heart for supporting my dreams.

Preface

Statement of originality

This thesis contains original work completed by Adrienne Crampton, the doctoral candidate, in order to contribute to the existing literature focusing on visuo-vestibular functioning in pediatric mild traumatic brain injury (mTBI). Chapters 5, 7, 9 and 11 constitute the original scholarship in this thesis. Unless specifically outlined, the material in this work has not been previously published. Original scholarship in this thesis includes:

i) Identifying the various test administered and tools used to evaluate vestibulo-ocular reflex function following TBI in children and adults across the spectrum of TBI severities
ii) Determining the level of agreement between symptom-based and performance-based tests of vestibulo-ocular reflex function in a pediatric mTBI population.
iii) Determining the extent to which clinician administered measures of vestibulo-ocular reflex and oculomotor function relate to patient-reported levels of activity limitations and participation in children and adolescents within 21 days post-injury
iv) Determining the extent to which performance on clinical and computerized tests of vestibulo-ocular reflex function and of its supportive oculomotor system vary over time in children and adolescents at 21 days, 3 months, and 6 months after a mild TBI.

The results of these studies and of the overall work contribute to 1) understanding the breadth and characteristics of the outcome measures used to assess vestibulo-ocular reflex function in pediatric mTBI in order to further refine assessment strategies; 2) identifying the relationship between clinician-administered measures of vestibulo-ocular reflex and ocular-motor function and patient reported measures of similar constructs to support better clinical interpretation of these measures; and 3) determining if changes are present over time in specific subcomponents of VOR function in order to inform treatment strategies.

Studies in this thesis were supported by a greater parent project, SiMPLy Rehab (funded by ERA-NET NEURON). Outcome measures included in this thesis were selected by the research group as a whole in order to ensure alignment in research findings. The methods for each study included

in this thesis were determined independently from the parent project. The vast majority of participants and data used for the studies included in this thesis were recruited and evaluated at the Montreal Children's Hospital-McGill University Health Center. Few additional participants were recruited at the University of Calgary Sport Medicine Centre or Acute Sport Concussion Clinic and evaluated at the university's Concussion Lab.

Contribution of authors

The four manuscripts included in this thesis are the work of Adrienne Crampton working under the direct supervision of Dr. Isabelle Gagnon and supported by supervisory committee members Dr. Kathryn Schneider and Ms. Lisa Grilli. Dr. Gagnon was closely involved in guiding the methodology, analyses and reviewing all studies.

Study 1 (Manuscript 1, chapter 5)

Is under revision by Brain Injury, the official journal of the International Brain Injury Association. Adrienne Crampton was the primary author of this review and was the lead contributor to all steps completed. Design of the study was undertaken with author Dr. Aurélie Garat. Screening and data extraction were undertaken with Dr. Garat and Heather Shepherd. Drs. Kathryn Schneider, Michal Katz-Leurer, Mathilde Chevignard and Isabelle Gagnon were consulted when interpreting study findings. Dr. Gagnon assisted with revising the manuscript and providing mentorship throughout the review.

Study 2 (Manuscript 2, chapter 7); Study 3 (Manuscript 3, chapter 9) and Study 4 (Manuscript 4, chapter 11)

Study designs and methodology were developed by Adrienne Crampton and Dr. Isabelle Gagnon. Recruitment of participants and data collection was performed by Adrienne Crampton with the support of laboratory research coordinators and clinicians at the Montreal Children's Hospital Concussion Clinic. Statistical analyses were performed by Adrienne Crampton and statistician Mr. Xun Zhang. Ms. Lisa Grilli, Dr. Kathryn Schneider and Dr. Gagnon reviewed the manuscripts and contributed insights to interpretations and the discussions. Drs. Michal Katz-Leurer, Mathilde Chevignard, Miriam Beauchamp, Chantel Debert will have reviewed the manuscripts prior to

journal submission. Dr. Gagnon provided extensive guidance throughout the three studies and manuscript revisions.

* While not authors, Ms. Joanna Mazza and Mr. Michael Skalak supported in participant recruitment and evaluations. Ms. Christine Beaulieu, Ms. Meghan Straub, Ms. Debbie Friedman and Mr. Carlo Galli provided assistance in referring participants to our study and supported the research program as a whole.

Chapter 1: Introduction

Mild traumatic brain injury (mTBI) can result in cognitive, physical, emotional and psychosocial effects. A mTBI sustained by an adult is experienced differently than one sustained by a child or adolescent due to physiological, developmental and environmental factors at play. With rates of pediatric mTBI estimated as high as 1.1-1.9 million each year in the USA (1), as well as nearly 40% of children with mTBI experiencing symptoms beyond one month and 11-14% beyond 3 months (2), research in this field is accelerating. The acute, sub-acute and chronic symptoms experienced by children and adolescents following mTBI can have long-lasting effects on their overall quality of life, ability to perform activities of daily life, navigate their environment as well as excel in academics, athletics and other activities of choice.

While pediatric mTBI has always demonstrated much heterogeneity with regards to symptom presentation, recent advances in the field have suggested the existence of specific clinical profiles which emerge as a result of distinct risk factors, symptom presentations and clinical outcomes (3). Among them, the vestibular (dizziness and balance-related) and the ocular (vision-related) profiles are of particular interest as visual and vestibular complaints following mTBI can prove burdensome to a young individual's ability to complete schoolwork and participate in daily recreational activities.

When attempting to identify the source of such visual and vestibular complaints, clinicians and researchers will often consider vestibulo-ocular reflex (VOR) function. VOR function allows one to maintain a steady gaze when one's head is in movement. This successfully occurs when the VOR mobilizes eye movement responses in an equal and opposite direction to head movements (1:1 ratio). The oculomotor (OM) system, or the coordinated action of eye muscles, supports the eye movements required for an accurate VOR. The OM system allows one to track objects and respond to moving visual stimuli through version eye movements (eyes moving in the same direction), such as smooth pursuit and saccades, and vergence eye movements (eyes moving in opposite direction). In pediatric mTBI, high rates of abnormalities and/or impairments to VOR function and the OM system have been identified (24-73%) (4-9). While the presence of VOR impairments within 14 days of injury has been linked to prolonged recovery (9, 10), their contributions to the overall symptom burden following mTBI remain poorly understood.

In order to further understand the nature of the impairments to VOR function which can arise following pediatric mTBI, the characteristics of both VOR function and of the supporting OM system must be more precisely determined during both the acute/sub-acute phase and in the months following the injury. At the moment, little research has focused on VOR function beyond the timepoint at which a young individual is "medically cleared" to return to school or sports. Furthermore, as no existing guideline advocates for a specific standardized assessment battery to assess VOR function in pediatric mTBI, various outcome measures are currently being used. These measures may not provide the most comprehensive, efficient and/or clinically practical assessment of overall VOR function.

The overarching goal of our work is to characterize VOR function following mTBI in children and adolescents, with a special focus on its assessment, using patient-reported and clinician administered measures. To achieve this, the thesis is organized around three lines of inquiry: 1) to better understand the breadth of measures used to assess VOR function and how they relate to one another in order to inform the selection of optimal test batteries, 2) to determine the extent to which clinician-administered measures of VOR and OM function relate to patient-reported outcome, and 3) to determine if performance on measures of VOR function and of the supporting OM system varies over the first 6 months following pediatric mTBI.

Together these lines of inquiry will not only provide an increased understanding of VOR function following mTBI over time, but they will provide both insight on how to interpret clinical findings, and direction on the optimal choice of comprehensive assessment strategies. This work will also support the development of a more homogeneous approach to evaluating VOR function amongst clinicians working with pediatric mTBI populations and may help to inform future targeted treatment approaches.

This thesis has been organized in a manuscript format with chapters linking each manuscript. Preceding the manuscripts is a literature review providing an overview of pediatric mTBI injury mechanisms, of the state of the evidence regarding both VOR function and the OM system in the context of pediatric mTBI, and of how VOR function is currently assessed. Manuscript 1 consists

of a scoping review undertaken to provide a more global perspective on the tools and measures used to assess VOR function. Manuscript 2 explores the level of agreement between commonly used measures of VOR function in a sample of children and adolescents after mTBI. Manuscript 3 presents the relationship between clinician-administered measures of VOR and OM function and patient-reported outcome capturing activity limitations and participation restrictions related to vision and dizziness. Finally, Manuscript 4 provides a characterization of the evolution of VOR function and of its supporting OM system in children and adolescent over the first 6 months following mTBI. Figure 1.1 is a schematic representation of the thesis contents. Individual manuscript titles and objectives can be found in Table 1.1.

Figure 1.1: *Thesis contents*

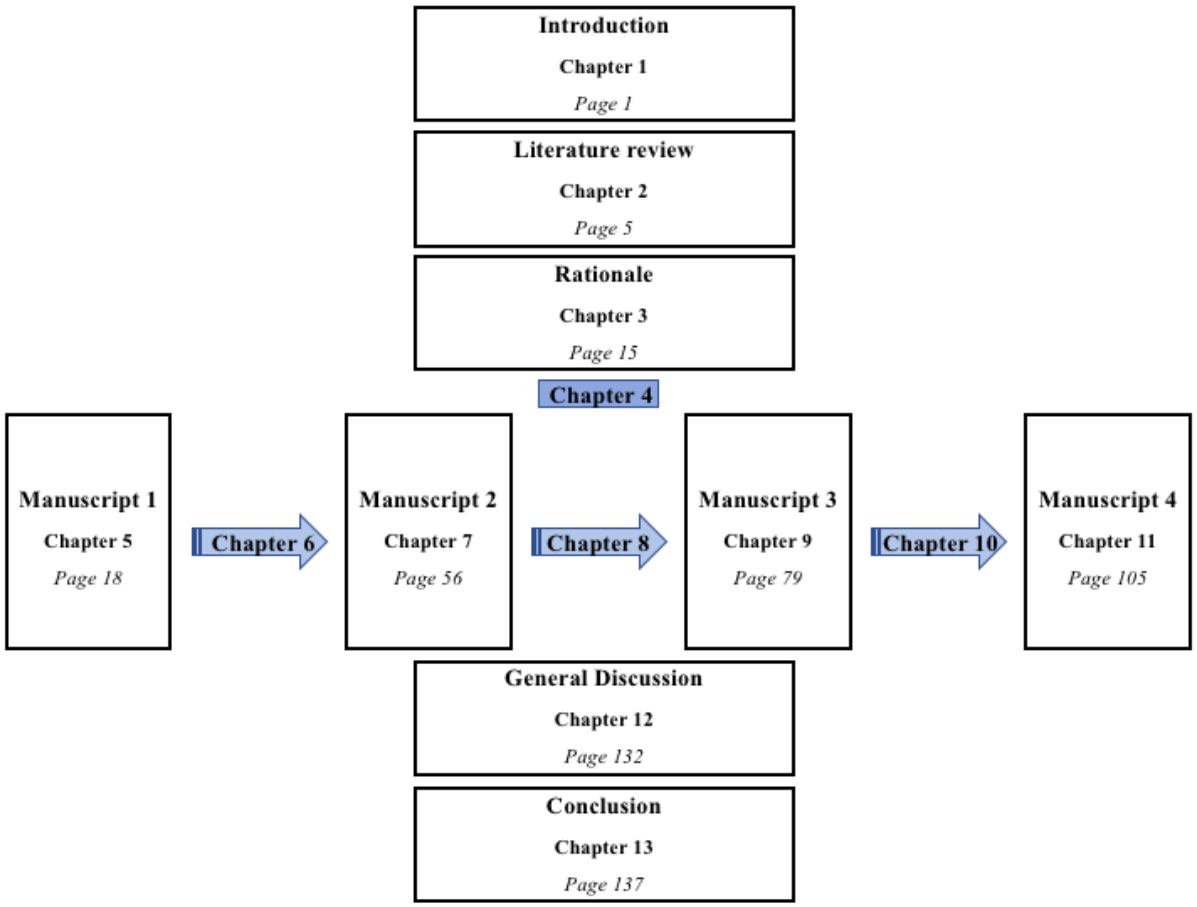


Table 1.1: Manuscript titles and objectives

Manuscripts and objectives	P.
1	
Evaluating the Vestibulo-Ocular Reflex following traumatic brain injury: A scoping review	18
The objective of this review is to identify the tests administered and tools used to evaluate VOR function following TBI in children and adults across the spectrum of TBI severities.	
2	
Determining the agreement between common measures of VOR function after a mild traumatic brain injury in children and adolescents	56
The first objective of this study is to determine the level of agreement between symptom-based and performance-based tests of VOR function in a pediatric mTBI population. The second objective was to characterize the level of symptom provocation induced by VOR tests in individuals with cervical findings and those without.	
3	
Quantifying the relationship between clinician-administered measures of vestibulo-ocular reflex and oculomotor function and patient-reported outcome after pediatric mTBI	79
The objective of this study is to determine the extent to which clinician administered measures of VOR and OM function relate to patient-reported levels of activity limitations and participation in children and adolescents within 21 days post-injury.	
4	
Characterizing the evolution of vestibulo-ocular reflex function over time in children and adolescents after a mild traumatic brain injury	105
The primary objective of this study is to determine the extent to which performance on clinical and computerized tests of VOR function and of its supportive OM system vary over time in children and adolescents at 21 days, 3 months, and 6 months after a mild TBI. The secondary objective is to determine the proportion of children and adolescents with mTBI presenting with abnormal scores on VOR and OM tests at each timepoint.	

Chapter 2: Literature review

Traumatic brain injury

Traumatic brain injuries (TBI) are one of the most frequently occurring injuries across the globe, with an incidence of approximately 69 million individuals per year (11). A TBI is defined as an "alteration in brain function, or other evidence of brain pathology, caused by an external force" (12), and its severity can be separated into three main categories: mild, moderate, or severe. This injury has tremendous repercussions on the daily functions of injured individuals, as well as on that of their caregivers, friends/families, and on our healthcare system. Leading causes of TBI are falls, motor vehicle collisions, struck by or against events, sports and recreation activities, and assaults (13-15).

Mild TBI and the pediatric population

Epidemiology and definition

Mild traumatic brain injuries (mTBI) represent an estimated 80-85% of all TBIs (11, 16, 17) with the approximated incidence at more than 600 individuals per 100, 000 (18), and the highest rates in children aged 0-14 years (19). In the US pediatric population, estimates of the number of mTBI/concussion from sports and recreation alone range between 1.1-1.9 million each year (1). Moreover, in Canada, a 5.5-fold increase in concussion-related emergency department and physician office visits was observed between 2003 and 2013, with the highest increase and overall rates reported in adolescents 13-18 years old (20).

According to the WHO collaborating center for neurotrauma task force on mTBI, the "*operational criteria for clinical identification include: i) 1 or more of: confusion or disorientation, loss of consciousness for 30 min. or less, post-traumatic amnesia for <24 hrs, and/or other transient neurological abnormalities such as focal signs, seizure, and intracranial lesion not requiring surgery; and ii) a GCS score of 13-15 after 30 min post-injury or later upon presentation for healthcare".* In addition, it is noted that "*These manifestations of mTBI must not be due to drugs, alcohol, medications, caused by other injuries or treatment for other injuries (e.g. systemic injuries,*

facial injuries or intubation), caused by other problems (e.g. psychological trauma, language barrier or coexisting medical conditions) or caused by penetrating craniocerebral injury" (21). Following mTBI, individuals experience symptoms which usually fall into four broad categories: cognitive, emotional/behavioral, physical, and sleep disturbances (22, 23). While most individuals become asymptomatic within 2-4 weeks following the injury, a significant proportion still experience persistent symptoms 3 months to over one-year post-mTBI (24-26). When they persist, the nature of these symptoms influences functioning and restricts the individual's ability to resume their usual daily activities (27, 28).

Mechanisms involved in the traumatic event

A mTBI results from direct or indirect forces transmitted to the brain, often associated with events such as motor vehicle accidents, falls, sports and recreation collisions, assault and/or other incidents. The acceleration, deceleration and rotational forces involved in each traumatic event can cause the brain to collide against the skull (often referred to as a coup-contrecoup mechanism) and/or rotate within this enclosed space (29). The resulting mTBI can result in both focal and diffuse pathology. The former is more often associated with direct blows to the head (30) while the latter is a result of the inertial loading, rotation, acceleration, and deceleration forces endured by the mechanism of injury (30, 31). The stretching and shearing experienced by the brain structures can cause diffuse axonal injury (DAI) leading to damaged axonal membranes and impaired intracellular transport (32, 33). A series of neurometabolic events, often coined, the *neurometabolic cascade*, occur causing dysregulation in neurotransmitter release and ion fluxes temporarily changing cellular pathology during the acute and sub-acute period (33, 34). The ionic imbalance caused by excessive extracellular potassium, decreased cerebral blood flow and decreased glucose metabolism causes a series of neurochemical disturbances which can contribute to the loss of consciousness, amnesia and/or other cognitive disturbances common following mTBI (33, 34).

Beyond the neurometabolic repercussions, structural damages can also occur as pathways, cortical and subcortical structures are vulnerable to the forces at play in mTBI (35). In fact, white matter abnormalities have been identified in both cortical and subcortical structures (33, 36). Such

structural changes along specific neural pathways can result in or contribute to distinct functional abnormalities (36, 37).

The unique attributes of each mechanism involved in mTBI, as well as various intrinsic and extrinsic risk factors contribute to the heterogeneous pathological outcome, and phenotype, observed in each individual (38). In pediatric populations, the response to brain trauma can further differ due to the maturation of the developing skull and of the nervous system as well as to the evolving size/mass of the brain (39, 40). Factors such as incomplete ossification and myelination, compliant cranial bones, greater head-to body ratio (skull, brain, size, face-to-cranium ratio, neck muscles), differences in injury thresholds and plasticity all increases a young person's vulnerability (39, 41-45). From a biochemical standpoint the developing brain is also more vulnerable to the excitatory amino acid surges that occur and cerebral swelling experienced can be more diffuse and prolonged (46). In addition to one's functional and anatomic development, the injury mechanism, primary and secondary complications, and neurological deficits can be influenced by one's age/physiologic maturity (47).

The vestibular and visual systems in pediatric mTBI

The highly interconnected visual and vestibular systems are particularly vulnerable following mTBI due to the wide range of neural pathways, cortical and subcortical structures involved in the functioning of these systems (48-50). Understanding deficits to the visual and vestibular systems in pediatric mTBI is of particular importance as injury to an immature visual or vestibular system may result in long lasting repercussions which can affect the healthy development of young individuals.

The vestibulo-ocular (VO) and oculomotor (OM) systems in pediatric mTBI

The vestibular and visual systems contribute, separately and together, in numerous ways to support one's overall functioning and their ability to interact with the environment that surrounds them. In pediatric mTBI populations, impairments and/or positive findings associated with the VO and the OM system are frequently reported. The former, through vestibulo-ocular reflex (VOR) function,

allows us to maintain gaze stability when our head is in movement. The later (OM system) supports VOR function by helping to produce the necessary eye movement responses. With respect to VOR and/or OM dysfunction, rates in pediatric mTBI populations range from 29-69% (4, 51, 52). Such numbers prove troubling as recent literature demonstrates poorer prognosis (measured through longer time to recovery) in individuals demonstrating symptom provocation following visuo-vestibular assessment (9, 52, 53). In addition to being at a greater risk for re-injury (54), individuals with alterations in these functions may experience difficulty in school, recreational activities, return to sport and day-to-day life (9, 55, 56). Presently, the mTBI literature relevant to VOR function focuses heavily on adult population and sport-specific pediatric populations, emphasizing a need to focus on more general pediatric mTBI populations.

The Vestibulo-Ocular Reflex

The vestibular system consists of a peripheral sensory apparatus, a central integration center, and a motor output (57, 58). It can be divided into two subsystems: i) the vestibulo-ocular system, responsible for visual/gaze stabilization, visual acuity, and the development of visual spatial and perception abilities (59-63) and ii) the vestibulo-spinal system, responsible for maintaining the body's orientation in space and contributing to ensuring postural tone (63-65). The peripheral sensory apparatus lies in the bony labyrinth of the inner ear and is composed of 3 semi-circular canals (SCC: lateral, anterior, and posterior), as well as 2 otolith organs (the utricle and the saccule) (64-67). The SCCs and their neural elements detect angular acceleration in the three planes of motion (64, 68, 69), while the otolith organs detect linear acceleration and gravitational changes (64, 65, 69). The SCCs work in pairs and are the primary sensory input driving the vestibulo-ocular reflex (VOR) response. The central vestibular system receives and processes the majority of the afferent signals in the vestibular nuclei (as well as receiving extravestibular sensory input) (58, 63, 65, 70, 71), with the cerebellum receiving the remaining signals (65, 71). The integration of vestibular, visual, and somatosensory inputs occurs in the vestibular nuclei allowing interactions with the oculomotor nuclei, the spinal cord, the cerebellum, the autonomic system, the thalamus, and the contralateral nuclei (65, 69, 72). The resulting motor output addresses posture, locomotion, spatial orientation, and gaze stabilization (63, 65, 73). The motor output that results from vestibular stimulation translates into three reflexes: the vestibulo-ocular reflex (VOR, helps maintain gaze

stability while head is in motion), vestibulo-spinal reflex (VSR, helps maintain posture and orientation of the body in space through the myotatic reflex), and vestibulo-collic reflex (VCR, helps to stabilize the head and neck) (58, 64, 65, 69, 74). The cerebellum provides input to, and receives outflow from, the vestibular nuclei, monitoring vestibular processing and adjusting responses if necessary (58, 64).

The VOR, in particular, facilitates eye movements in equal and opposite direction to head movement (1:1 gain ratio). An impairment anywhere along the VOR pathway can compromise an individual's ability to integrate visual and vestibular information and potentially affect their gaze stability. Abnormalities to VOR function have been identified in 43-69% of pediatric mTBI populations (8, 9, 51, 75). Certain physical implications arising from an inefficient VOR can include blurred vision, dizziness, vertigo, swaying sensations, and balance-related difficulties (76-80). As a result, the reported rates of dizziness, visuo-vestibular and/or visual complaints which range from 29-72% in pediatric mTBI (6, 9, 81) are particularly pertinent. From a more psychosocial standpoint, dizziness in mTBI populations has been linked to mental health difficulties, as well as functional limitations affecting mTBI patients' return to work/daily life (82-87). Better understanding the VOR contributions to dizziness, and vision-related difficulties following pediatric mTBI is an important step to addressing important restrictions to ADLs.

Oculo-motor system and VOR function

A healthy functioning of the OM system is needed to integrate motor outputs from the VOR and prompt an appropriate eye-movement response to the associated vestibular input. In mTBI, vision-related symptoms and oculomotor (OM) abnormalities have been identified by many (54, 88-91), with varying prevalence estimates. Particular to the pediatric population, Master et al. (2016) reported one or more vision diagnoses in 69% of their pediatric concussed sample (relevant functions included: accommodation, convergence, and/or saccades) (4). Additionally, it has been shown that up to 81% of individuals presenting with vision-related symptoms (e.g. blurry vision, double vision) post-mTBI may have one or more underlying OM impairments (92). OM contributions to VOR function can come from *version* and *vergence eye movements.*

Version eye movements are conjugate eye movements that keep an image stable on the fovea while tracking and/or glancing back and forth between targets (93), and include saccades and smooth pursuit eye movements.

Saccades are rapid ballistic eye movements that allow one to change fixation from one target to another (such as looking towards a stimulus that suddenly appears) (94, 95). The parietal eye fields, frontal eye fields, supplementary motor areas, cingulate eye field and dorsolateral prefrontal cortex each have a dominant role in different elements of saccadic function (96-99).

Poorer anti-saccades, memory-guided saccades, and self-paced saccades have been observed following mTBI (37, 100), along with impaired accuracy (100-103), increased latencies (14, 104), greater variability (100, 105), and lower control or generation and inhibition (104-106). Additionally disturbances in information transfer and coordination between the saccadic system and other OM subsystems have been found following mTBI (37). Potential pathophysiological mechanisms for the deficits mentioned are any mTBI-related lesions in the saccadic pathways and structures extensively identified in literature (97, 107-110). Studies with pediatric mTBI samples have demonstrated saccadic deficits in 29-82% of samples (4, 7, 9).

Smooth pursuit eye movements (SPEM) are slow eye movements allowing one to track moving objects smoothly by focusing the image on the eye's fovea (such as visually tracking a ball that has been thrown) (94, 95). They involve the frontal, parietal, and cerebellar regions (101). The smooth pursuit of a predictable target is based on both retinal and extraretinal higher cortical input and programmed by the cerebellum (111-113).

Decreased target predictions, increased position error (114-116) increased variability in SPEM (114-118), and reduced gain and velocity (118) were all identified in SPEM following mTBI. Findings highlight lesions in the frontal eye field, paramedian reticular formation, rostral mesencephalon, parietal cortex, basal ganglia, superior colliculus or cerebellum (flocculus) (108, 119, 120) may affect SPEM, while lesions in the medial temporal area have the capacity to completely restrict SPEM (121). Pediatric-specific mTBI literature has demonstrated abnormalities in smooth pursuit abilities (122) at rates between 33-66% (7, 9, 123).

Saccadic eye movements and SPEM combine to orient the visual axis and optimize visual feedback yet are different modes of ocular control (94, 100, 108). These systems share certain common brain regions, premotor neural areas, neural pathways, that coordinate their outputs (94). Saccades can also act as a compensatory mechanism for both the VOR (through overt and/or covert saccades) and smooth pursuit eye movements (through catch-up saccades). In addition, smooth pursuit eye movements can contribute to VOR responses at lower velocities and when gaze stability is required in conjunction with visual tracking. Version function as a whole is vulnerable to local and diffuse axonal injury (100, 120) with injuries to one system potentially affecting the other.

Vergence eye movements are disconjugate movements of the eyes that require simultaneous adduction or abduction of the eyes to maintain a binocular fusion on near targets (96, 124). They include *convergence*, and *divergence* eye movements, as well as contributions from the *accommodation* system. Vergence functions can contribute to VOR responses, as the gaze that is being stabilized requires a specific near (convergence) or far (divergence) focus.

Vergence eye movements are integrated through a neural feedback loop driving the eyes inward (convergence) and outward (divergence) when the object is in focus (accommodation), in order for images in both eyes to be fixated on the appropriate areas of the retina (125). The integrity of this system is crucial to eye teaming and focusing (such as watching an object coming towards you) (125, 126). The mechanism of accommodation keeps a focused retinal image of an object at the fovea when the depth of the object is changing (108). The specific details of the pathway and neural circuity involved in vergence (convergence and divergence) are less well understood than other oculomotor movements (79, 127), with conflicting literature surrounding signal pathways (79, 127). Following mTBI, different elements of vergence may be affected with convergence insufficiency being the most prevalent (92, 120). Abnormalities are also found in static and dynamic parameters (120, 128-130), such as receded near point convergence and reduced fusional vergence reserves (118, 120, 131, 132), decreased velocity (14), overall slowed dynamic responses (129, 133, 134) and restricted relative change (120, 135). In pediatric-specific literature such abnormalities can be observed in mTBI samples at rates ranging from 24-73% (4-7).

Each of the eye movements involve multiple pathways spanning various areas of the brain and require complex coordination of related neural circuits (136, 137). The extraocular muscles (muscles surrounding the eyes) and the cranial nerves associated with their function are imperative to maintaining uncompromised eye movement responses (124, 138). The forces involved in mTBI (mentioned previously) have been shown to affect the structures and pathways that support the OM system (4, 100). OM changes following mTBI are important to understand as the overall process of rehabilitation from mTBI involves multiple components (physical, psychological, vestibular, occupational) that interact with the visual system (120). It has been shown that visual impairments may compromise one's ability to optimize their rehabilitation in these other realms, as it is a primary sensory input for many (108, 120, 139, 140).

Assessing VOR function in pediatric mTBI

When seeking to understand visuo-vestibular symptoms in pediatric mTBI populations, assessing one's VOR function and supporting OM system can provide insight as to where an underlying impairment may be located (9, 51). As much complexity is involved in integrating afferent sensory information and in producing the appropriate motor output to support an optimal VOR response, precision and objectiveness are important when assessing VOR function. However, due to the high rates of mTBI in pediatric populations and the significant burden this injury can place on our healthcare system and on clinicians, the efficiency and accessibility of these assessment is also of utmost importance. At the present time, various measures are used when assessing VOR function in pediatric mTBI populations, yet best practice recommendations remain to be determined.

In specialized clinical settings, VOR function is commonly assessed using gold standard measures of vestibular function. Preferably this consists of bithermal caloric irrigation (CI) however, as CI is relatively invasive and uncomfortable for pediatric populations, rotary chair testing (RCT) is often considered as an alternative (141, 142). Unfortunately, despite being considered the gold standard for overall vestibular function testing, when specifically considering VOR function and its more precise characteristics, these two tests present certain limitations. CI can lack sensitivity and specificity, while the RCT is unable to detect laterality in the measured variables (143). Additionally, the protocols followed when administering these tests lack standardization and

neither the CI nor the RCT is able to assess the VOR at high frequencies most representative of daily demands (144, 145). Most importantly, there can be long wait times and/or high costs associated with the specialized clinical settings in which such tests are administered. As children with mTBI most often present for initial care in non-specialized clinical settings, more accessible gold standard measures are required.

While no one measure exists for use in such general clinical settings, the results of a scoping review performed by our group highlight various tools and tests used to assess the VOR following TBI (Crampton et al, *under review)*. In studies assessing the VOR in mTBI populations which highlight tests that may address certain limitations of the previously outlined gold standard measures, three main categories of measures, can be identified: 1) measures focusing on how symptoms are provoked in response to tasks requiring eye and head movements, 2) measures of gaze stability in response to unplanned high velocity head movements, and 3) measures of gaze stability in response to voluntary or expected high velocity head movements. Within the first category a commonly used measure is the vestibular-oculomotor screening tool (VOMS) measuring symptom-provocation following VOR and OM tasks (123). Within the second category, common VOR measures are the clinical head thrust/head impulse test (HTT/HIT) (143) and video HIT test (vHIT)(146). Finally, measures falling within the third category are the horizontal head shaking test (HST)(143), dynamic visual acuity test (DVA) (147), and gaze stability (GST) test (148) (Crampton et al. *Under-review*).

Within each of these categories, the measures can be administered using clinical or computerized tools. Those that do not require computerized tools (symptom-based and clinical measures) provide a useful means to evaluate VOR function quickly, with minimal equipment and at a low-cost. These would therefore prove much more accessible than current gold-standard vestibular measures. Unfortunately, such measures often lack precision and/or objectiveness as they rely on clinician observation and/or an individual's report of symptom provocation (9, 149). Measures that are administered with computerized tools, such as videonystagmography (48, 150) or computerized DVA tools (151-153) address certain of these limitations by adding precision and objectiveness when evaluating elements of VOR function. These measures also provide a means to evaluate VOR function at high frequencies, a limitation to gold-standard vestibular measures. However, these

tools are expensive, and often lack psychometric properties or normative data across all tests and manufacturers (Crampton et al. *Under-review*).

As the literature focused on VOR function assessments in pediatric mTBI populations is still in its infancy, little consensus exists surrounding what may constitute an optimal assessment of VOR function that is efficient and accessible, yet precise and objective, in this population. Moreover, of the pediatric mTBI literature that has been published, few studies have focused on non-athlete samples (Crampton et al. *Under-review*). The high rates, the developmental implications and the psychosocial repercussions of pediatric mTBI bring and urgency to understanding, diagnosing and treating this injury in all children and adolescents. With impairments to VOR function and the supporting OM system identified in much published pediatric mTBI literature (9, 54, 55, 75, 154, 155), it is important to attach meaning to these findings. Such impairments following pediatric mTBI can have important implications to a child or adolescent's ability to perform at school, in sports, navigate their ADLs, and experience an overall QOL (9, 56). Understanding the underlying pathophysiology, obtaining further information on how these impairments evolve following injury, and gaining an understanding of how they contribute to a child/youth's overall functioning must be further clarified.

Chapter 3: Rationale and objectives

Our literature review has highlighted the diffuse nature of mTBI, underlining the wide-reaching impacts this injury can have on various structures and neural pathways. Specifically, we have outlined the potential repercussions of mTBI on VOR function, as well as on supporting eye movement control in pediatric populations. At the present time, best practices and standardized recommendations on how to optimally assess VOR function, do not exist. There is a need to better understand what tests and tools are used when assessing VOR function, as well as how they may differ from one another. Furthermore, while the literature review clearly demonstrates that various impairments to VOR function and supporting eye movements can present following pediatric mTBI, many of the mechanisms underlying these impairments remain unclear and their functional implications are poorly understood.

Research focused on VOR function following pediatric mTBI can provide a more precise understanding of the vestibular and ocular clinical profiles, as well as an avenue to explore the development of more precise targeted treatment approaches for this population. While many questions remain to be answered, the literature review highlights the need to 1) provide clinicians with more evidence to inform their choice of measures used to assess the VOR, 2) determine how elements of VOR and OM function relate to one's more global daily activities, and 3) determine if VOR function changes over time in order to inform potential targeted treatment recommendations, in pediatric mTBI populations. The following presents the three lines of inquiry and specific aims which will be the underlying pillars of this doctoral work:

1- To provide clinicians with a greater understanding of the breadth of measures used to assess VOR function and how they relate to one another in order to inform their selection of optimal test batteries

Understanding how commonly used measures relate to one another will support the development of best practice recommendations as to what battery of tests should be used when assessing VOR function in pediatric mTBI populations. This general objective was separated into two aims:

a. To provide a broad representation of the tests administered and tools used to assess VOR function in TBI populations of all ages and across the spectrum of injury severity in order to understand the current state of practice and inform future research avenues.

b. To determine the relationship between measures commonly used to assess VOR function in pediatric mTBI populations in order to support the development of best-practice clinical recommendations.

2- To determine the extent to which clinician-administered measures of VOR function and of the OM system relate to patient-reported outcome capturing activity limitations and participation restrictions related to dizziness and vision.

As the ecological implications of VOR impairments are poorly understood, this line of inquiry strives to add context to positive findings on measures of VOR function and the supporting OM system. This will be achieved by determining the extent to which clinician-administered measures of VOR and OM function, relate to the Dizziness Handicap Inventory (measuring dizziness' impact on quality of life) and the Cardiff Visual Ability Questionnaire (measuring the daily degree and nature of difficulty experienced by children as a result of a visual impairment) respectively. Determining these relationships will allow clinicians to more fully interpret and understand the impact of positive VOR and OM findings on their young patients, assisting the development of patient-centered treatment recommendations

3- To determine if performance on measures of VOR function and the supporting OM system varies over the first 6 months following injury in pediatric mTBI

This line of inquiry will provide valuable insight as to whether specific subcomponents may demonstrate change over time and/or identify greater proportions of children with impairments. As VOR impairments remain poorly understood, this more granular information could help targeted treatment approaches to be developed. The longitudinal nature of this line of inquiry will provide a unique representation of subcomponents of VOR function over time as the timepoints included are not contingent upon medical clearance/clinically determined "recovery" of each individual (most often seen in existing literature). Identifying if VOR function changes over time and whether this change is driven by specific subcomponents will inform treatment recommendations and clinical considerations when supporting a child or adolescent in their return to play and/or learn.

Chapter 4: Introduction to the 1st Manuscript

In the past decade, advances in the field of pediatric mTBI have resulted in many changes to clinical practice when it comes to the assessment and treatment of this population. Of great importance are the recommendations (22, 156) that support the transition from the previous more passive management of mTBI to the current more active approach. To support this active approach, more comprehensive assessments must be performed in order to appropriately determine which domains should be targeted when developing and prescribing early intervention recommendations.

VOR function is of particular interest to clinicians and researchers. Both the structures involved and the pathways responsible for afferent and efferent responses are vulnerable to injury when one suffers a mTBI. While deficits, abnormalities and/or impairments have been identified in relation to the VOR in pediatric mTBI populations, best practices to guide assessments of VOR function remain unclear. Much heterogeneity exists in the tests administered, tools used, protocols followed, and interpretations made when assessing the VOR in this population. As such, it is challenging to compare and combine findings across the literature in order to develop a more coherent understanding of VOR function following pediatric mTBI. This presents a barrier to developing standardized recommendations for clinical practice with regards to the assessment of VOR function.

To begin developing a solution that may address these challenges, and in order to help develop more standardized recommendations when evaluating VOR function in pediatric mTBI, it is important to obtain a broader understanding of the present state of practice in this field. This will allow specific gaps to be identified and enable specific research questions to be developed to address them. Assessments used in adult populations often provide a foundation upon which to build pediatric-specific recommendations. Moreover, practices used in more severe TBI can inform potential avenues to explore in mild and moderate TBI populations. As such, Study #1 (Manuscript 1) is a scoping review outlining the tests administered and tools used when evaluating VOR function following TBI of all severities in children and adults.

Chapter 5: Manuscript 1

Evaluating the Vestibulo-Ocular Reflex Following Traumatic Brain Injury: A Scoping Review

Adrienne Crampton[a]*, A. Garat[b,c], H. A. Shepherd[d], M. Chevignard[b,c,e], K. J. Schneider[d,f,g], M. Katz-Leurer[h] and I.J. Gagnon[a,i]

[a]*School of Physical and Occupational Therapy, McGill University, Montréal, Canada*

[b]*Laboratoire d'Imagerie Biomédicale, Sorbonne Université, Paris, France*

[c]*GRC 24 Handicap Moteur et Cognitif et Réadaptation, Sorbonne Université, Paris, France*

[d]*Sport Injury Prevention Research Centre, Faculty of Kinesiology, University of Calgary, Alberta, Canada*

[e]*Rehabilitation Department for Children with Acquired Neurological Injury and Outreach Team for Children and Adolescents with Acquired Brain Injury, Saint Maurice Hospitals, Saint Maurice, France*

[f]*Alberta Children's Hospital Research Institute, University of Calgary, Alberta, Canada*

[g]*Hotchkiss Brain Institute, University of Calgary, Alberta, Canada*

[h]*Physical Therapy Department, University of Tel-Aviv, Tel-Aviv, Israel*

[i]*Montréal Children's Hospital-McGill University Health Centre, Montréal, Canada*

*Corresponding author: Adrienne Crampton

5252 Boul de Maisonneuve Ouest, Office 3E.17

Montréal, QC H4A 3S5

Phone: 514-607-5330

Email: adrienne.crampton@mail.mcgill.ca

ORCID: https://orcid.org/0000-0002-5069-2389

Biographical Note

Adrienne Crampton, B.Sc, M.HK, is a doctoral candidate at McGill University (Montréal, Canada) within the School of Physical and Occupational Therapy. Her research focuses on oculomotor and vestibulo-ocular function in children following mild traumatic brain injury.

Dr. Aurélie Garat, PT, PhD, is a physiotherapist working at the Institut Gustave Roussy. Dr. Garat completed her PhD at Sorbonne University (Paris, France) focusing on oculomotor function following traumatic brain injury in children and adults.

Heather Shepherd, OT, MSc. is an occupational therapist and a doctoral student at University of Calgary (Calgary, Canada) within the Sport Injury Prevention Research Centre. Her research focuses on return-to-learn following a sport-related concussion and on knowledge translation within this field.

Dr. Mathilde Chevignard, MD, PhD, is a medical doctor specialized in physical medicine and rehabilitation. Dr. Chevignard works in a rehabilitation department devoted to children and adolescents with acquired neurological injury and in an outreach team devoted to children, adolescents and young adults who sustained acquired brain injury (Saint-Maurice Hospital, France).

Dr. Kathryn J. Schneider, PT, PhD, DipManipPT, is an assistant professor and clinician scientist (Physiotherapist) at the Sport Injury Prevention Centre at the University of Calgary (Calgary, Canada). Her research focuses on the prevention, detection and treatment of sport-related concussion.

Dr. Michal Katz-Leurer, L.P.T, M.P.H, PhD, is a senior lecturer and chair within the department of Physical Therapy at the Steyer School of Health Professions, Tel Aviv University. Her research focuses on the cardiac autonomic system among brain damaged patients.

Dr. Isabelle J. Gagnon, PT, MSc, PhD, is an associate professor at the School of Physical and Occupational Therapy (McGill University) and a clinician scientist (Physiotherapist, trauma/child development) at the Montréal Children's Hospital. Dr. Gagnon's research focuses on how children and adolescents, function after traumatic injury as well as on how rehabilitation services can contribute to achieving the best outcomes possible.

Evaluating the Vestibulo-Ocular Reflex Following Traumatic Brain Injury: A Scoping Review

Purpose: To identify the tests and tools used to evaluate vestibulo-ocular reflex (VOR) function after traumatic brain injury (TBI) in all age groups and across TBI severities. **Methods:** An electronic search was conducted to include relevant peer-reviewed literature published up to November 2019. Studies included those done with humans, of all ages, and had assessments of oculomotor and/or vestibulo-ocular function in TBI. **Results:** Of the articles selected (N=48), 50% were published in 2018/2019. A majority targeted mild TBI, with equal focus on non-computerized versus computerized measures of VOR. Computerized assessment tools used were videonystagmography, dynamic visual acuity/gaze stability, rotary chair and caloric irrigation. Non-computerized tests included the head thrust, dynamic visual acuity, gaze stability, head shaking nystagmus, rotary chair tests and the vestibular/oculomotor screening tool. High variability in administration protocols were identified. Namely: testing environment, distances/positioning/equipment used, active/passive state, procedures, rotation frequencies, and variables observed. **Conclusions:** There is a rapid growth of literature incorporating VOR tests in mild TBI but moderate and severe TBI continues to be under-represented. Determining how to pair a clinical test with a computerized tool and developing standardized protocols when administering tests will help in developing an optimal battery assessing the VOR in TBI.

Keywords: traumatic brain injury; concussion; measurement; technology; vestibulo-ocular reflex; vision

Keywords: Traumatic brain injury; concussion; vestibulo-ocular reflex; assessment; measurement

Introduction

The peripheral vestibular system enables clear vision during head motion via the vestibulo-ocular reflex (VOR). To ensure optimal VOR function, normal functioning of the peripheral vestibular system (three semicircular canals (SCC), and two otolith organs), and an intact vestibular nerve and central vestibular system (which receives and processes many sensory inputs), is crucial. The primary sensory input influencing the compensatory eye response to head movement comes from the SCCs (inhibiting one side while facilitating the other through a push-pull mechanism) (1), while secondary sensory inputs and motor responses essential to regulating the VOR are coordinated in the cerebellum (1, 2).

Following rotational head acceleration, the SCCs provide this primary sensory input via the vestibular nerve to the vestibular nuclei (1, 2). As there exist various connections between the vestibular nuclei and other central structures, a coordinated motor response is produced through the VOR signalling the extraocular muscles to appropriately respond to head movements. The excitatory stimulus directs the extraocular muscles to produce eye movements in equal and opposite direction to head movements to enable clear vision while the head is in motion (VOR gain). A normal VOR gain (head movement velocity over eye movement velocity) is considered to be 1 (i.e., head velocity is equal and opposite to eye velocity).

The VOR is vulnerable, both in function and structure, when one experiences a traumatic brain injury (TBI) (3-6). Rates of vestibular abnormality or dysfunction in TBI groups can range between 25-87% (7-10). As the incidence of TBIs across the spectrum of mild to severe is estimated at 1.7 million per year in the USA (11), and 69 million per year globally (12), vestibular abnormalities are a pressing concern. An impairment anywhere along the VOR pathway can compromise the VOR's ability to integrate visual and vestibular information. Identifying the sources of dysfunction in the VOR pathway and understanding the underlying pathophysiology is imperative as a compromised VOR may result in disabling sensations including dizziness, poor balance, or nausea (1, 13-15). Moreover, an inability to suppress the VOR and/or integrate visual and vestibular information can lead to difficulties with visual motion sensitivity and vertigo (16, 17).

The underlying impairments that cause dizziness or balance difficulties in individuals with TBI may stem from different physiologic sources. Vestibular disorders such as benign paroxysmal positional vertigo, central vertigo, temporal bone fracture, Menière's disease, labyrinthine concussion and perilymphatic fistula have been highlighted in TBI populations (1, 9). Furthermore, the VOR and visual motion sensitivity (VMS) sub-tests on the vestibular-oculomotor screening tool (VOMS) have been correlated with higher post-concussion symptom scores in milder forms of TBI (6). Symptom provocation following the VOR subtest on the VOMS was identified in 40-45.3% of a concussed sample (18). Currently, VOR assessment in patients following a TBI may not be included regularly as part of a typical clinical assessment. Rather, sensory organization, balance testing, and assessments of the vestibulo-spinal pathway are more prevalent (1, 19-21). When considering batteries evaluating the vestibular system following TBI, it is crucial that assessments of the VOR pathway be included to provide a more complete representation of a patient's vestibular function.

Intact SCC function drives the VOR. However, identifying the specific cause of a VOR impairment can often be difficult as the peripheral vestibular system structures involved in VOR function contribute to various reflexes beyond the VOR. Such reflexes include the vestibulocollic reflex (VCR), the cervico-ocular reflex, the cervicospinal reflex, and the cervicocollic reflex (1, 22). As there are many interconnections between the vestibulo-spinal reflex (VSR), VCR, and VOR (1, 3, 23, 24), compensation can be observed when one or more reflexes are compromised (22, 25). Vestibular compensation is a complex process coordinated centrally and involves the integration of many CNS structures (26). Evaluations must be sensitive and specific in order to identify impairments along the VOR pathway.

Currently, clinical practice lacks clarity surrounding which assessment or battery of assessments best evaluates VOR function. While patient-reported outcome measures exist to evaluate dizziness, they do not provide information specific to the function of one's VOR. Existing clinical outcome measures of the VOR, such as the head thrust test (HTT), horizontal head shaking test (HST), dynamic visual acuity test (DVA), gaze stability test (GST), and vestibular/oculomotor screening tool (VOMS) tend to rely on imprecise measurement (e.g., clinician observation and/or symptom provocation (27, 28)). Sensitivity and specificity of these tests vary greatly in the literature based

on the type of vestibular impairment and the reference test chosen (6, 29-31). As each clinical test measures a different component of the VOR, these tests must be administered in a complementary manner when assessing a patient's VOR. Consistency of findings among test results can assist with differential diagnosis suggesting a potential peripheral hypofunction or alteration in VOR function.

More objective measures, such as the rotary chair test and caloric irrigation that use videonystagmography to measure eye movement, have been considered the gold standard for detecting bilateral and unilateral vestibular impairment (32). The rotary chair test and caloric irrigation provide objective measures of horizontal SCC function; however, they do so at low frequencies and the former does not allow one to determine the side of vestibular hypofunction. When evaluating the VOR it is important to stimulate the SCCs at high frequencies to best isolate the VOR and better mimic normal head movement frequencies (33). The scleral search coil and electronystagmography/electrooculography (ENG/EOG) are objective tools previously used to support eye-movement measurement at high frequencies. While enabling higher frequency stimulation of all SCCs, these tools are seldom used. Limitations are the scleral search coil's invasiveness and EOG/ENG's inability to measure specific positional variables of the eyes.

Emerging technologies are beginning to address gaps in clinical tests used to assess the VOR. These computerized versions of clinical tests (often pairing a technology-based tool with a clinical test) may provide increased precision when assessing components of the VOR pathway. Videonystagmography (VNG), computerized DVA/GST (cDVAT/cGST) testing and enhanced computerized rotary chair testing and caloric irrigation have the potential to provide objective and precise measures of components contributing to VOR function. Variables of interest measured by these technologies are the VOR gain (ratio of head to eye movements), phase (difference between actual eye velocity and ideal eye velocity to perfectly compensate head motion (34)), asymmetry (comparison of right to left VOR response), and time constant (measured nystagmus response following a velocity step test). Measures of an individual's behavioral VOR are computed through LogMAR values from the cDVA/cGST. Behavioral VOR represents one's ability to stabilize an image and see it clearly while moving their head, without record of their eye movements (35). Recently, the use of these technologies in mTBI populations has gained interest. This is evident by publications such as Snegireva et al.'s systematic review (2018) of eye-tracking technologies used

in sport-related concussions (36) as well as this group's work on the awareness and perceived value of such technologies (2019) (37).

Many of these tests were developed for populations with primary vestibular impairments, and psychometric properties were obtained in populations suffering from vestibular pathologies not induced by TBI. As etiology is known to contribute to the underlying pathophysiology of an impairment (38, 39) tests demonstrating strong psychometric properties in one population cannot be assumed to maintain these properties when used in another (40). The properties and application of these tests and tools within TBI populations must be further explored in order to draw appropriate conclusions and generalizations, across ages and TBI severities (41-43). Current published literature using these novel technologies describes varied methodologies, variables of interest, and metrics making it difficult to compare findings, make conclusions, or determine clinical significance (36). Comprehensive and standardized assessments of the VOR are important within the TBI population (4, 44-47). Understanding the breadth of measures used in TBI populations, their established properties, their recommended administration procedures, and which variables to analyse, is necessary in order to develop a battery of complimentary tests assessing VOR function.

The state of practice in targeted assessments of the VOR following TBI requires further maturity to warrant a systematic review. Thus, a scoping review was deemed appropriate and Arksey and O'Malley's criteria was used to guide the process (48). This scoping review facilitated a summary and broad representation of the current clinical tests and computerized tools used in research and clinical settings when evaluating VOR function in TBI populations. *The objective of this review was to identify the tests administered and tools used to evaluate VOR function following TBI in children and adults across the spectrum of TBI severities.* All severities of TBI were included in this review as the most recent recommendations suggest that previously used classifications did not capture the multidimensional nature of TBI (38).

Methods

This scoping review used the six step iterative framework identified by Arksey and O'Malley (2005) and enhanced by Levac et al. (2010) to guide its methodology (48, 49).

Step 1: Identifying research question

The question guiding this review was developed with input from clinicians and researchers involved in an international research group interested in the topic of vestibulo-ocular and oculomotor outcomes after TBI and reads as: What tests are administered and what tools are currently used in clinical practice or research to assess VOR function following TBI of all severities in children and adults?

Step 2: Search strategy

Studies relevant to this scoping review were identified through searches in seven databases in November 2018: Ovid MEDLINE, EMBASE, Cochrane Library, CINAHL, Sportdiscus, Psychinfo, and HAPI (Health & Psychosocial instruments). The search strategy was developed by two authors (AC & AG) with the assistance of two health sciences librarians (JB & LK). No restrictions on time period or language were initially applied. Ovid MEDLINE was selected as the database to build the original search strategy as it facilitated translation to other Ovid-based databases (50). The search strategy contained a list of Medical Subject Heading (MESH) terms and keywords to comprehensively cover the breadth of literature. Boolean logic and adjacencies were used to combine terms with keyword truncations and to remove animal studies. As oculomotor function is closely tied to VOR function, and treatment-based studies often include assessments, both treatment and oculomotor-related articles were included in the search strategy. Authors (AC, HS & AG) screened articles for inclusion and hand-searched the bibliographies of review articles. The original search strategy was translated into the remaining databases and searches saved. See Figure A1.1 (Appendix 1) for Ovid MEDLINE search strategy.

*The original search strategy (November 2018) was re-run on all platforms restricting dates from Nov. 2018-Nov. 2019 to include the latest published literature.

Step 3: Study selection

The screening process aligned with the Joanna Briggs Institute recommendations (51)**.** The majority of study selection occurred over two phases, using the inclusion and exclusion criteria below. For inclusion in the title and abstract screen as well as for the full-text screen, inter-rater reliability was ensured at a percentage agreement of >80 percent in each. This was completed by randomly selecting 100 articles per round and 25 percent of full text articles, respectively.

Reviewers (AC, AG, HS) met at the beginning, middle, and end of each stage to clarify criteria. As screening occurred in pairs (AC & AG, AC & HS, and AG & HS), conflicts were resolved by the third reviewer.

Inclusion and exclusion criteria

Title and abstract screening phase - **Inclusion:** peer-reviewed literature, all ages, human studies, articles specifically assessing elements of oculomotor and/or VOR function, in a TBI population. **Exclusion:** Abstracts, conference proceedings, articles focused on general TBI outcome prediction, narratives on management, articles on diagnostic measures for TBI, epidemiological studies on incidence or prevalence of TBI, articles assessing strictly OM without VOR, and articles focusing on the vestibulo-spinal system without separate VOR assessment.

Additions to the exclusion criteria occurred at both full text screening and data extraction phases. At full text screening phase - Added to exclusion: Studies not focused on the clinical or research assessment of VOR in TBI, but whose objective was to establish the measurement properties of a specific tool, non-English. At data extraction phase - Added to exclusion: Guidelines, commentaries, reviews, clinical frameworks, narratives, consensus recommendations, articles solely focused on treatment with no assessments performed.

Step 4. Charting the data

Three authors (AC, AG, & HS) developed the data charting form and piloted the data extraction form. Two rounds of data extraction from 10 randomly selected articles were performed with all three reviewers to ensure consistency (49). Data of interest extracted to characterize studies were: title, first two authors, year of publication, country of study, study design, study setting, number of participants, age, sex, male/female, injury severity (mild, moderate, and/or severe). Data of interest extracted to inform our objectives were: inclusion and exclusion, purpose, objective and/or aims, VOR outcomes, limitations as identified by the study, key findings, barriers or challenges to evaluation, accessibility of assessment, recommended use of assessment and protocol followed when administering assessment.

Step 5. Collating, summarizing and reporting results

Step five in this review followed the three-stage process recommended by Levac et. al (49): analysing the data, reporting the results, and applying meaning to them (49). This review includes a descriptive numerical summary (Table 5.1) and thematic summaries (Table 5.2 and 5.3) according to Arksey and O'Malley framework recommendations (48). The results are reported below with a final step discussing the implications of the findings. In order to add depth to this section, findings were discussed with clinicians and expert researchers in this field. Insights obtained were used to help guide the discussion section of this article.

Step 6. Consultation

The larger team was consulted throughout the process. The consultation stage allowed for expert perspectives on the clinical implications of our findings and on recommendations for future research directions.

Results

Descriptive characteristics of the articles included (Table 5.1)

Electronic databases yielded 7575 articles. Duplicates were removed and 5390 articles remained. Title and abstract screening by two authors (AC & HS) resulted in the selection of 297 texts for full-text screening. Re-running the search strategy to include Nov. 2018-Nov. 2019 yielded 680 additional articles, of which 86 were included for full-text screening. A PRISMA flowchart provides a diagram of the article inclusion process (Figure A1.2, Appendix 1). A total of 48 (33 + 15) articles were included in this review.

A large majority (80%) of studies took place in the USA and focused on mild TBI and concussion populations (85.4%). A smaller proportion of studies focused on pediatric samples (39.6%) compared to adult samples (56.25%), with few studies including both populations (4.15%). An equal proportion of studies used computerized (45.8%) versus clinical (45.8%) tools or measures to assess the VOR. The remaining studies included a mix of both (6.25%) or did not specify (2.10%). Of note was the very recent growth of published literature in this field. Half of all articles included in this review (n=24/48) were published in 2018 or 2019.

Computerized tools used when evaluating VOR function (Table 5.2)

In this review, *Videonystagmography (n=14)* was used to evaluate VOR gain, asymmetry and gaze stability (24, 46, 52-61). Certain studies simply added VNG equipment to provide objective measurement to a non-computerized clinical test protocol (i.e., HIT or HST wearing Frenzel goggles). Alternatively, many of the included VNG test batteries followed the protocol for administration developed by their manufacturer. While manufacturer protocols were often based upon existing clinical tests, heterogeneity was observed in many elements of their administration. Differences across tools included sampling frequencies (frequency of stimulation at which eye movements are recorded), number of repetitions administered (ranging from 5-30/side for the HIT), speeds at which gain values were recorded (40ms, 60ms, 80ms), equipment set-up, lighting of environment, position of both evaluator and subject, distances from stimuli or fixation points, monocular versus binocular, and variables of interest (gain, asymmetry, general unspecified gaze stability).

Computerized DVA/GST (n=9) was used to evaluate behavioural VOR using both gaze stability and dynamic visual acuity (DVA) (4, 52, 60, 62-67). Among the measures identified, both tumbling E and C optotypes were observed. The administration of cDVA/cGST varied on the following elements: active versus passive head rotations, yaw versus pitch plane testing, velocity at which head rotations occurred, algorithms used in optotype progression in cGST, equipment set-up, lighting, and testing distance.

Rotary Chair Testing (n=7) was used to evaluate VOR gain, phase, asymmetry, and time constants (24, 58, 62, 68-71). Rotary chair tests evaluating VOR function included sinusoidal harmonic acceleration (SHA), step tests, and test batteries with visual fixation, visual suppression and visual enhancement. Variations were observed across test batteries, oscillation frequency (ranging from 0.01-0.64 Hz), VOR variables of interest (gain, phase, asymmetry), set up and testing environment, eye-movement recording techniques (VNG technology used), and tests included in the protocols.

Caloric irrigation (n=7) was not often thoroughly described in the selected articles (10, 24, 60, 62, 70-72). In the three instances it was described, variations existed in choice of caloric irrigation including air versus water, temperatures, and protocols.

Electronystagmography (n=1), did not specify which battery was used (72). *Galvanic labyrinth polarization stimulation (n=1)* used VNG to record spontaneous eye movement response and targeted both labyrinths (59).

Table 5.1: Descriptive characteristics of included studies

	Type of tool				**Country**		**Date of publication**			**Severity**		**Population**		
	Computerized	Manual	Both	Unspecified	USA	Other	Pre-2015	2015-2017	2018-2019	mTBI/ Concussion	Mod/Sev/ All*	Ped.	Adult	Both
# of articles (Total N=48)	22	22	3	1	40	10	9	15	24	41	7	19	27	2
%	45.80	45.80	6.25	2.10	80.00	20.00	18.75	31.25	50	85.4	14.6	39.6	56.25	4.17

Note: TBI: traumatic brain injury; m: mild; mod: moderate; sev: severe; ped: pediatric; *all: mix of mild, moderate, severe

Table 5.2: Computerized tools used when assessing VOR components

	Computerized tool used	Test or protocol administered with tool	P/A *	Differences in administration observed in VNG
VNG	Micromedical technologies Visual Eyes™ (Interacoustics, AS)	Tracking of sinusoidal smooth-moving visual target in horiz. & vert. planes. **Stated use:** Unspecified head and eye movements assessed (52)	P A	- Non-specified software versions. - Sampling frequency - Tests used in evaluations - Standing or sitting - Velocities used to perform same tests - Number of thrusts in HTT - Velocities at which variables were recorded - Distance from fixation point - Environment in which VNG administered - Variables of interest computed differently based on software
	Micromedical technologies Visual eyes™ 4 system. Version 9.0 Spectrum software (VORTEQ option, Interacoustics, AS)	HST: Shaking head in horiz. plane (2 Hz for 20s). Subject looked straight ahead without fixation until any provoked nystagmus ceased. Horizontal vHIT: Min. 30 thrusts/side. Subject fixated on visual target on wall. Impulses below 50 deg/s. or velocities below 150 deg/s. excluded. **Stated use:** Assess VOR (24)	A	
	Multisensory Jazz-Novo measurement system	Tracking of sinusoidal smooth-moving visual target in horizontal & vertical planes. **Stated use:** Assess gaze stability (52)	P A	
	Frenzel goggles (Interacoustics AS, video Frenzel lens VF 405 Unit Monocular vision)	HTT. Halmagyi and Curthoys method. **Stated use:** VOR (53)	P	
	ASL Eye Tracking H7 system (Applied Science Laboratory) + Vicon® Motion capture system (Nexus, Version Motion Systems)	Eye movements captured at 120 Hz. Gaze stabilization measured using % of time gaze fixed on the center of game screen and # of gaze deviations made away from the screen during Nintendo WiiFit soccer heading game. **Stated use:** Gaze stability (46, 54)	P A	
	EyeSeeCam Software (Interacoustics, AS)	Recorded overt & covert saccadic movement with VOR gain (ms) and left-right asymmetry (%). Gain calculated for horiz. Impulses at 40ms, 60ms, and 80ms. **Stated use:** VOR Gain, Asymmetry (55)	A	
		Subjects sat 1.5m facing wall and target. Horizontal HIT randomly administered (~ 20 deg. & 150-300 deg/s). 5 acceptable impulses recorded/direction. Gain & asymmetry calculated. **Stated use:** VOR Gain, Asymmetry (56)	P A	
		Subject sat 1.5m facing a wall. Eyes fixated on target, HIT provided unpredictably by examiner (small, high-velocity, right & left, 10-20deg, 150-300 deg/s). 10 impulses recorded/direction. **Stated use:** VOR Gain (57)	P	
		Assessed at a sampling rate of 220Hz. Subjects fixated gaze 1m in front of them while examiner performed 10 horizontal thrusts in left & right directions. Gain values at 60ms used. **Stated use:** VOR Gain (53)	P	
	I-Portal®-Neuro Otologic Test Center (Neurokinetics)	Computer controlled rotation head impulse. Gain and asymmetry calculated. **Stated use:** VOR gain, asymmetry (58)	A	
	Chronos Vision, IRIS Software package (Chronos Vision)	VOG right-eye movement response recorded at frame rate of 50 Hz, using head-fixed camera system mounted on infrared eye tracking goggles. Recorded spontaneous eye movements for 1 min. during Galvanic Labyrinth polarization (GaLA) stimulation of both labyrinths. **Stated use:** VOR (59)	A	
	Unspecified VNG	Unspecified administration. Stated use: VOR, Gaze stability (60, 61)	A	

cDVA	DVA Micromedical technologies (VORTEQ™ option, Interacoustics, AS)	Active head movements at or > 100 deg/sec. 10 feet from monitor. Wearing a yaw axis angular rate sensor. In dedicated DVA testing room meeting consistent criteria for room luminance and isolated testing. Computer-generated optotype "C". **Stated use:** DVA (4)	A	- Type of Optotype used - Speed of head movements used to calculate DVA - Algorithm used to determine GST velocity - Environment in which DVAT administered - Testing in both pitch and yaw directions not consistent
		Unspecified administration. **Stated use:** DVA (62)	P	
	Neurocom® InVision™ system [63-66] & Neurocom® SMART balance master InVision™ software [60]	Darkened room with an effective viewing distance of 10 feet. DVA tested at a velocity of 100 deg/s. GST calculated as deg./sec. at which subject could hold a visual target and recognize it during active horizontal or vertical head motion. **Stated use:** DVA & GST (65)	A	
		DVA maintained 85 deg/s. head velocity while decreasing size of tumbling E optotype. GST calculated with consistent sized optotype at increasing head velocity. **Stated use:** DVA & GST (64)	A	
		Subject tested in yaw and pitch. Began at 60-99 deg/s or 100-139 deg/s based on practice performance. Algorithm to determine GST velocity based on experimentally determined parameters to facilitate clinical testing. Reliability of this method not established. **Stated use:** DVA & GST (63)	A	
		As described by the technology manual. Tumbling E. DVAT was tested at 85 deg/s. **Stated use:** DVA & GST (60)	A	
		Administered with patient seated 2 meters from screen and measured at 120 deg/sec. **Stated use:** DVA & GST (66)	P	
		Unspecified procedures for DVA, GST, Target following and perception time. Seated position. **Stated use:** DVA & GST (67)		
	C3 Logix complete concussion management system	Unspecified DVA module. **Stated use:** DVA (52)	P A	
RCT	I-Portal®- Neuro Otologic Test Center (Neurokinetics)	SHA (with visual enhancement & with visual suppression). Participant was in computer-controlled rotational chair <36 inches from a black featureless enclosure wall. Movements for 2 eyes recorded with head-mounted goggles using off-axis IR lighting & black pupil technique. High frequencies. **Stated use:** VOR Gain, Phase, Asymmetry (58)	A	- Range and incremental change of oscillation frequency - Variables of interest - Environment of administration - Test batteries used
		SHA (with visual fixation). SHA testing screened at 0.01, 0.08 & 0.32 Hz at 60deg/sec peak velocity. 0.02, 0.04 & 0.16 Hz added if screening abnormal. Visual fixation performed with 0.08 Hz SHA & peak velocity of 60 deg./sec. **Stated use:** VOR Gain, Phase (24)	A	
		As described in (58). **Stated use:** VOR Gain, Phase, Asymmetry (68)	A	
		SHA with infrared measured eye movements (100Hz). Right & left oscillations at 0.02/0.04/0.08/0.32/0.64 Hz. Visual enhancement at 0.64Hz. VOR cancellation at 0.64Hz. Step test: chair rotated right, stopped, left, stopped (60s each). **Stated use:** VOR Gain, Phase, Time constant (69)	A	
	Micromedical technologies system 2000 (Interacoustics, AS)	SHA 0.01 Hz to 0.64 Hz (SHA), Stationary optokinetic stripes (enhancement of VOR), Laser projected dot rotated with patient (Visual Fixation) + Velocity step test. **Stated use:** VOR Gain, Phase, Asymmetry (62)	P	
		SHA 0.01, 0.04, 0.16 and 0.64 Hz. Participants seated in light-proof booth with head upright so rotation occurred in plane of both hSCCs. Mentally alerted to prevent VOR suppression. Phase, gain, and asymmetry calculated for slow component eye velocity (SCEV). SCEV scores abnormal when phase, gain or asymmetry was abnormal at two or more adjacent frequencies. **Stated use:** VOR (70)	A	
	Unspecified computerized RCT	Stated as VOR pathway testing. This study used trapezoidal rotations (100 deg/sec) and SHA (0.02-0.64). **Stated use:** VOR pathway (71)	A	

CI	ICS Chartr® air caloric stimulator model NCA-200	Warm irrigations (50 deg/f) followed by cool (24 deg/f). All irrigations performed for 60s with flow rate 8 L/min. **Stated use:** Unspecified (24)	A	- Temperature of water - Length of irrigation - Air vs. water
	ICS NCI-440	Irrigations using 250ml of water for 30 sec @ temperatures of 44 deg. &/or 30 deg. with participants supine and head elevated. Calculated slow component eye velocity of the 3 strongest beats of nystagmus. **Stated use:** Unspecified (70)	A	
	Micromedical technologies Visual Eyes™ with AquaStim (Interacoustics, AS)	Bithermal caloric tests. **Stated use:** Unspecified (62)	P	
	Unspecified Caloric irrigation	Fitzgerald hallpike method. **Stated use:** Unspecified (10)	A	
		Stated use: Unspecified (60, 71, 72)	A	
GALA	Galavanic stimulator (Neurotronix)	Galvanic labyrinth polarization (GALA) stimulation of both labyrinths occurred. GALA applied via circular silver chloride adhesive surface electrodes of 50mm diameter attached to right and left mastoids and an electrode attached to the interscapular. Stimulus applied right and left. One labyrinth polarized to maximum while the opposite to minimum. Sinusoidal waveform 0.41Hz and 180mA used. **Stated use:** VOR (59)	A	N/A
ENG	Electronystagmography (ENG)	Unspecified testing vestibular function. **Stated use:** Unspecified (72)	A	N/A

*Note: *P/A: pediatric/adult; HST: horizontal head shake test; vHIT: video head impulse test; HTT: head thrust test; VOR: vestibulo-ocular reflex; DVA: dynamic visual acuity; GST: gaze stability test; SHA: sinusoidal harmonic acceleration; hSCC: horizontal semicircular canals; RCT: rotary chair testing; CI: caloric irrigation*

Non-computerized tests used to evaluate VOR function (Table 5.3)

Articles included administered the *Head Thrust/Impulse Test* (HTT/HIT, n= 6 articles) to evaluate horizontal SCC function (55, 64, 66, 73-75). While many stated using the Halmagyi and Curthoys protocol (76), variations were observed in fixation point, use of head flexion, amplitude of head rotations (20-30 deg.), active versus passive impulses, range of motion testing prior to administration, hand placement of administrator, and observations recorded. The use of the Scleral search coil (n=1) in conjunction with the HTT was identified in only one article (77).

The *clinical DVA (n=7), Gaze Stability (n=3) and HST (n=2) tests* targeted behavioral VOR. Variations for the *DVA test* were observed in optotypes used (EDTRS, E, Snellen), active versus passive head movements, velocity and amplitude of head rotations (30-60 deg.), scoring methods, and distance from the optotype (15, 66, 73, 74, 78-80). The *gaze stability test* observed these differences as well as varied fixation points and was administered in both the pitch and yaw planes (28, 74, 81). Methods resembling Active Head Rotation tests using VNG/ENG seemed to have been employed in certain unspecified gaze stability protocols (28, 74). The *HST* relied primarily on examiner-observed induced nystagmus and symptoms (78, 82).

Rotary chair tests (n= 4) were identified in non-computerized settings (65, 72, 83). Rotary chair tests targeted VOR gain, time constants, and VOR cancellation. Variations in the method of observation, the type of chair, and the speed of rotation were identified.

The *Vestibular/Ocular-Motor Screening (VOMS) Tool (n=11)* explored symptom provocation resulting from Oculomotor, VOR and Visual Motion Sensitivity tests (18, 57, 73, 84-91). While administration often followed the intended protocol, certain variations either excluded or substituted a subtest or adapted the scoring methodology. The VOMS appeared more often in recently published articles. *Four studies assessed the VOR, however did not specify certain tests used *(n=4)* (27, 72, 75, 92).

Table 5.3: Clinical tests used to assess VOR components (without computerized tools)

Test	Key elements in how test was administered	P/A *	Differences in administration observed
Head thrust /Head impulse test	Unspecified in article. **Stated use:** VOR (73)	P	- Deg. of head rotation differed. - Scoring with observation vs adding symptom provocation reports - Test of ROM prior to administration not always mentioned - Head flexion
	Referenced Halmagyi and Curthoys method (55). This methodology required subject to fixate at a target 3m away and examiner to turn subject's head as quickly as possible to one side. **Stated use:** VOR	A	
	Subject seated, fixating on examiner's nose. Head & neck relaxed. Examiner's hands on subject's occiput and thumbs on temples. Participant's head flexed 30 deg. Head gently rotated left/right to 45 deg. to test range of motion. Test performed with quick movements in horizontal planes randomly 30 deg. right/left 3-4 times. Symptom provocation using VAS recorded (pre-post) & examiner observed catch up saccades. **Stated use:** VOR (74)	A	
	Patient fixated on a target (generally clinician's nose), while head was quickly turned "a small excursion" right or left. The head was flexed 30 deg. Test was positive if patient lost visual fixation and needed to refixate. **Stated use:** VOR (64)	A	
	Referenced Halmagyi and Curthoys method. Method would have required subject to sit, head in 20-30 degrees of flexion, examiner would have held subject's head bilaterally, unexpectedly and quickly rotated the head approximately 20 deg. to the left or right while instructing the subject to keep their eyes fixed on the examiner's nose. **Stated use:** VOR (75)	P	
	Participant was asked to fixate on a target and a small amplitude (5-10 deg.), high acceleration head thrust were applied right & left. Examiner observed presence or absence of corrective saccades. **Stated use:** VOR (66)	P	
	HIT with scleral search coil. Head velocity data collected with a rate sensor attached to a specifically modified head-mounted assembly. Eye velocity data collected with monocular 2D wireless scleral search coil system. Eye movements sampled at 1, 000 Hz. Subjects seated 1.5m from a 2cm red dot and calibration grid in room lit conditions. Active and passive head impulses recorded in yaw and pitch. 20 impulses in each direction generated at approx. ~25 deg. **Stated use:** VOR (77)	A	
Dynamic Visual Acuity Test	Lines lost (SA vs. DVA) calculated. Unspecified procedure, assumed to use Longridge and Mallinson Tumbling E due to information in article. **Stated use:** DVA (73)	P	- Speed of head movement differed - Type of chart used - Cut off for abnormality differed. - Distance from chart differed - Sitting vs. standing - Cut-off for last line-read differed - Scoring method differed - Active vs. passive head rotations
	Tumbling E chart. Participant stood 2.0m from the chart & read orientation of E starting from top of chart moving down until errors occurred. This was repeated with active head movements 30 deg. to the left/right in the horizontal plane to the beat of the metronome (180bpm). Lines lost (SA vs. DVA) recorded. Cut off 3 or > lines suggested vestibular dysfunction. **Stated use:** DVA (74)	A	
	Clinical DVA used a Snellen eye chart with horizontal head movement at a frequency of 2 Hz. Stated to be used to reflect one's ability to stabilize gaze during head movements. **Stated use:** DVA (78)	P	
	Longridge & Mallinson method (modified). Patient seated in chair, 6m from Snellen chart. Visual acuity determined. Inequality in visual acuity tested first. Head grasped by examiner & turned right-left in an arc of ~ 60 deg, at approx. 120 deg/sec. Modification: SA vs DVA calculated. Each figure in a row received a value and the number of figures missed while head moved was multiplied with their value and the result added to SA score. **Stated use:** DVA (15)	A	
	EDTRS chart mounted on wall at eye-height, subject was seated 20 feet away. SA obtained with subject's head still and DVA obtained with examiner assisted head rotation timed with a metronome at 2Hz. Line correct if less than 3 errors occurred. Difference in DVA & SA lines recorded. **Stated use:** DVA (80)	A	
	EDTRS chart. SA measured first. Line considered correct if one or less errors. DVA measured during active assisted head rotations at 2 Hz. Difference in number of lines recited recorded. **Stated use:** DVA (66)	P	

	Unspecified DVA. **Stated use:** DVA (79)	A	
Gaze Stability Test	Subject stood fixating a single visual target (X on piece of paper, Arial, Bold, 48 font) at eye level, arm's length away. Instructed to turn their head approx. 30 deg. right/left to a metronome (240bpm) for 1 min. Instructed to report target blurriness or bouncing. Pre & post symptoms recorded. Increase of 2 or more on VRS was considered a positive test. Examiner observations recorded. **Stated use:** Gaze stability (74)	A	- Target of fixation - Distance from target - Speed at which head shaking occurs - Directions of head shaking (solely horizontal vs. both)
	Examiner observed ability of participant to fixate on single point while rapidly rotating their head back and forth indicating "no". Symptom provocation. **Stated use:** Gaze stability (28)	A	
	Fixation of eyes on examiners thumb while head nodded up and down and shook side to side. **Stated use:** Gaze stability (81)	P	
Horizontal Head Shake Test	Modified HST. Subject asked to focus on a stationary object 1m from bridge of the nose and rapidly shook their head horizontally at least 30 deg. from neutral (10 sec). Abnormal test indicated by nystagmus or dysconjugate eye movements. Examiner observations and symptom provocation recorded. **Stated use:** VOR (82)	P	N/A
	Unspecified procedure. **Stated Use:** VOR (78)	P	
Rotating chair Test	Rapid office chair rotation used in lieu of HTT to "eliminate neck inputs". **Stated use:** VOR (83)	A	- Function being assessed - Speed of chair rotation differed - Type of chair
	Performed using 240 deg./sec. chair rotation. **Stated use:** VOR gain, Time constant (72)	A	
	Subject rotated while seated in office chair, clasped both hands together thumbs in front. Chair rotated back and forth while fixating on thumbs. Abnormal test was inability to keep eyes directly on the target. **Stated use:** VOR cancellation (83)	A	
	Unspecified. **Stated use:** Vestibular (65)	A	
VOMS	Adapted so only symptomatic response was recorded (reproduction of patient symptom). **Stated use:** VOR, VMS (73)	P	- Symptom response calculations - Additions/omissions of certain subcomponents
	VMS excluded. **Stated use:** VOR (18)	P	
	Specified to follow assessment protocol in VOMS however added gait/balance testing and dysmetria. **Stated use:** VOR, VMS (84)	P	
	No alterations. **Stated use:** VOR, VMS (57, 85-91)	6P 2A	
Unspecified	VOR tested at three timepoints & speeds (slow, 56/25bpm, 90/65 bpm). VOR cancellation (slow, 25bpm, 65bpm) **Stated use:** Unspecified test of VOR and VOR cancellation (92)	P	N/A
	Similar to VOMS protocol, symptom provocation. Headache, nausea, dizziness, fogginess (on a scale 0-10). **Stated use:** Unspecified test of VOR (27)	P	
	Subject seated, examiner grasped subject's head with both hands and moved while instructing subject to follow the examiner's nose as head was passively moved. **Stated use:** Unspecified test of VOR cancellation (75)	P	
	Stated use: Unspecified test of VOR and VOR cancellation (72)	A	

*Note: *P/A: pediatric/adult; VOR: vestibulo ocular reflex; DVA: dynamic Visual Acuity; SA: static acuity; VMS: visual motion sensitivity; VOMS: vestibular/oculomotor screening tool; N/A: not applicable; HIT: head impulse test; HTT: head thrust test; HST: horizontal head shake test; VRS: verbal rating scales; VAS: visual analogue scale*

Discussion

The descriptive statistics of our work emphasized certain important observations. Research focused on VOR function in TBI populations is gaining momentum in both pediatric and adult populations. However, there is limited research focused on moderate-severe TBI populations. One explanation for this could be the lower frequency at which moderate-severe injuries occur when compared to mTBI. Another consideration is that assessments for associated motor, cognitive and behavioural impairments, independence and quality of life may take precedence over those of specific physiological impairments when considering clinical management in more severe TBI. As VOR impairments may have deleterious consequences to the overall burden of injury following moderate-severe TBI, understanding VOR impairments in this population remains important to provide optimal targeted rehabilitation interventions.

This review highlighted a need for consensus on the use of VOR tests within the TBI population in order to generalize findings, make recommendations, and interpret results when administering these measures. Our results highlighted an augmented use of computerized tools measuring elements of the VOR; however, information on certain psychometric properties of these tools is limited in TBI populations. While many tools have established normative values (93-98), test-retest reliability, and inter-rater reliability in healthy populations, few have established psychometric properties within the TBI population. Literature discusses the sensitivity, specificity, and diagnostic accuracy of the tools in question however these studies are often conducted in populations with vestibular pathologies such as vestibular migraines, vestibular schwannoma, sudden sensorineural hearing loss, unexplained unilateral or bilateral vestibular failure, or Menière's disease (30, 99-106). The properties of these tools should be determined within the TBI population as the etiology of TBI is multidimensional resulting in diffuse and heterogeneous injury responses in individuals (38, 40).

Our findings identified both conventional clinical tests and the addition of computerized tools in research surrounding the assessment of VOR function in TBI populations. Clinical tests, which included HST, HTT, clinical DVA & GST, VOMS, and clinical versions of rotary chair tests were identified in our review. These tests provide valuable preliminary information, allowing evaluators to observe abnormal nystagmus presentation, overt catch-up saccades, exaggerated loss of visual

acuity, blurred vision provocation, symptom provocation, and an inability to suppress the VOR, respectively. Due to the nature of these tests, factors such as examiner experience, human error, or lack of precision can result in false negatives or lack of sensitivity or specificity (105-107). Observing subtle characteristics of eye movement responses in these tests can provide evaluators with valuable information on the source of the impairment. However, these subtleties may not be visible to the naked eye (e.g., direction of nystagmus, catch up saccade or covert saccades) and administration of these tests require specific training. To address these limitations, computerized tools to enhance assessment of the VOR continue to be refined. The tools identified in this review, their strengths and weaknesses will now be discussed.

In this review, three of seven studies that used caloric irrigation techniques specified more recent systems (24, 62, 70). While adding VNG during caloric irrigation provides additional precision to results, there are limitations to caloric irrigation when assessing VOR function. These may include the appropriate choice of method (bithermal versus unithermal, closed-loop, open-loop, air caloric) (108), the lack of certainty surrounding established norms (109), the recommendation for each clinical setting to establish their own normative values (96), the discomfort of testing (110), and the low frequency stimulation (0.002-0.004 Hz (111, 112)). Additionally, the results may vary according to the physiological features of an individual (e.g. temporal bone, external ear features, middle ear fluid) (110, 112).

With regards to the seven studies using computerized rotary chair tests in this review, four used Neurokinetics' I-Portal-NOTC system, two used Interacoustics' Micromedical technologies system 2000, and one did not specify their technology. Differences were present across site administration, choice of subtest used, and VOR-related variables of interest. While rotary chair test normative values have been explored (112), study results often related to specific frequencies of stimulation and lacked large sample sizes (97, 108). As the rotary chair test is a bilateral vestibular test, most often administered at mid-low frequencies between 0.01-0.64 Hz (97, 112), it is incapable of determining the side of the impairment or assess VOR response to high-frequency stimulation. Positive elements of rotary chair test are its tolerability (97), ability to provide information on VOR phase, gain, asymmetry (108, 112), and increased diagnostic accuracy when paired with ENG/VNG methods (97).

Computerized assessments identified in our work stimulating the VOR at higher frequencies were VNG and computerized DVA/GST. Within VNG, the video head impulse test (vHIT) demonstrates results comparable to the gold-standard scleral search coil technique (111, 113, 114). While our review provides information on certain technologies used in the TBI population, a review by Alhabib (2017) further discusses five vHIT systems and their applications amongst various populations (115). vHIT tests are quick to administer, well tolerated by various ages amongst mTBI, provide objective results, are able to measure VOR response to high frequency stimulation, and can evaluate all six SCCs (110, 111, 113, 115). The measurement of SCCs using high frequency stimulation allows for the accurate assessment of the SCCs without contributions from other systems and at speeds more relevant to those experienced in daily life (113). However, vHIT assessments require further refinement as goggle slippage and subtleties in administration caused artefacts to be recorded, affecting the quality of the eye-movement recordings. The validation of many commercial technologies also remains to be determined. Additional VNG tests identified resembled active head rotation tests. Such tests may provide measures of visual fixation (108), however their added-value to testing VO function is unclear.

Lastly, common symptoms in TBI such as dizziness and blurred vision with head motion have prompted the use of behavioural VOR tests such as cDVAT and cGST in TBI populations (3, 4, 60, 116). cDVAT and cGST systems identified in this review are easy to administer and provide an objective measure of DVA and gaze stability at high frequency when compared to their non-computerized counterparts. While normative values have been reported in both pediatric and adult populations (98), these values, along with appropriate psychometric properties, are necessary with each commercial system. Despite cDVAT and cGST providing valuable information on behavioral VOR, contributions from other physiological systems and compensatory mechanisms may influence one's overall results on these tests. Such contributions from other systems can be amplified when the testing is performed with active versus passive head rotations. Such considerations must be accounted for when interpreting results.

Amongst the tests identified in this review, it is important to underline that the horizontal SCCs are most commonly assessed. While these structures contribute to VOR function, additional emphasis on assessing anterior and posterior SCCs is important to provide a more complete

representation of SCC contributions to the VOR. While vHIT protocols and clinical HTTs can assess left-anterior/right-posterior and right-anterior/left-posterior (RALP and LARP, respectively) SCCs, such assessments are seldom observed in TBI populations. This may be due to: i) varying disinhibitory signals from the non-test ear depending on head velocity when testing vertical SCCs, potentially affecting the variability of the results (103); or ii) the challenges and inconsistencies observed when administering RALP and LARP impulses (62). With regards to the otolith organs, while more recent assessments are emerging (e.g., vestibular evoked myogenic potentials), as their contribution to VOR function is minimal they have not been discussed in this review.

Concluding statements/implications

The rapid growth of published literature that incorporates VOR tests following TBI demonstrates a promising research avenue in the evaluation and treatment of this patient population. VOR impairments following TBI are gaining importance in research as they display consequential effects on one's progression towards recovery. To better understand the underlying pathophysiology of dizziness and vestibular impairments in this population, assessments of the VOR pathway and its function must continue to be refined. This review highlighted the tests administered and tools used to evaluate VOR function in children and adolescents following TBI of all severities.

The information gathered from the 48 selected articles reinforces the need to develop more standardized protocols for the identified tests and when using the computerized tools discussed. Factors for consideration in these protocols include: test administration procedures, subject and evaluator positioning, frequency of head or chair rotations or impulses, distance from subject to target, testing environment, fit of equipment, variables of interest, and testing state (active versus passive). The identified factors should be appreciated by clinicians and researchers alike as each have implications on the results obtained and conclusions drawn regarding each patient's VOR.

Research supporting how to optimize the use of novel technologies when evaluating the VOR in TBI populations is needed. A large discrepancy exists in the literature with a greater focus on mTBI and concussion when compared with more severe TBI populations. Avenues to explore

across the spectrum of TBI severities may be: i) to clarify the appropriate pairing of clinical tests with computerized tools; ii) to outline clear detailed protocols that may be adopted with precise guidelines; iii) to further establish psychometric properties for clinical and technology-based versions of tests in TBI populations; and iv) to establish normative data for each tool. These avenues would support the development of an optimal battery of assessments to evaluate the VOR in TBI populations which would include reliable and validated tests and follow standardized protocols. From a clinical standpoint, this will support clinicians, adding objectiveness and precision to their assessments as well as ensuring a comprehensive evaluation of the VOR in patients with TBI.

Limitations

Limitations of this review include the iterative development of inclusion and exclusion criteria. While this is accepted practice in scoping reviews, it may have resulted in unwanted exclusion of certain published literature. An additional limitation includes the screening phases. While inter-rater reliability was ensured for each pairing at each phase, it is possible that subtle differences in decision-making may have occurred. Finally, as limited information was provided in certain studies within the methods sections specific intricacies surrounding the administration and/or details of certain tools used may be incomplete.

Acknowledgements

Authors AC and AG contributed to the conceptualization and design of this scoping review. AC and AG drafted the protocol and undertook to complete the study. AC and HS modified the proposal and iteratively adapted the proposal and screening process. AC, AG, and HS completed the screening steps. Drs. Isabelle Gagnon, Kathryn Schneider, Michal Katz-Leurer, and Mathilde Chevignard provided mentorship, aided the development of the research questions and revised the manuscript. Expert health science librarians Jill Boruff and Lucille Kiester provided guidance in developing the search strategy for this scoping review. Colleagues Christophe Alarie and Dr. Elizabeth Teel provided additional support throughout. We acknowledge the support and input of the research team as a whole as well as all stakeholders involved in the consultation phase of this research project. This work was funded by the Canadian Institute of Health Research under grant

number EIN 150763; and the Fonds de recherche du Québec under grant number 3679 as part of an ERA-NET NEURON JTC Cofund Program.

Declaration of Interest

The authors declare no potential conflicts of interest.

References

1. Wallace B, Lifshitz J. Traumatic brain injury and vestibulo-ocular function: Current challenges and future prospects. Eye & Brain. 2016;8:153-64. doi: 10.2147/EB.S82670.
2. Schubert MC, Minor LB. Vestibulo-ocular physiology underlying vestibular hypofunction. Phys ther. 2004;84(4):373-85. doi: 10.1093/ptj/84.4.373.
3. Peterson M. A case-oriented approach exploring the relationship between visual and vestibular disturbances and problems of higher-level mobility in persons with traumatic brain injury. J Head Trauma Rehabil. 2010;25(3):193-205. doi: 10.1097/HTR.0b013e3181dc82fa.
4. Gottshall K, Drake A, Gray N, McDonald E, Hoffer ME. Objective vestibular tests as outcome measures in head injury patients. The Laryngoscope. 2003;113(10):1746-50. doi: 10.1097/00005537-200310000-00016.
5. Hoffer ME, Gottshall KR, Moore R, Balough BJ, Wester D. Characterizing and treating dizziness after mild head trauma. Otology & Neurotology. 2004;25(2):135-8. doi:10.1097/00129492-200403000-00009.
6. Mucha A, Collins MW, Elbin RJ, Furman JM, Troutman-Enseki C, DeWolf RM, et al. A brief vestibular/ocular motor screening (VOMS) assessment to evaluate concussions: preliminary findings. Am J Sports Med. 2014;42(10):2479-86. doi: 10.1177/0363546514543775.
7. Corwin DJ, Wiebe DJ, Zonfrillo MR, Grady MF, Robinson RL, Goodman AM, et al. Vestibular deficits following youth concussion. J of Ped. 2015;166(5):1221-5. doi: 10.1016/j.peds.2015.01.039
8. Marcus HJ, Paine H, Sargeant M, Wolstenholme S, Collins K, Marroney N, et al. Vestibular dysfunction in acute traumatic brain injury. J of Neurology. 2019;266(10):2430-3. doi: 10.1007/s00415-019-09403-z.
9. Brodsky JR, Shoshany TN, Lipson S, Zhou G. Peripheral vestibular disorders in children and adolescents with concussion. Otolaryng Head & Neck Surgery. 2018;159(2):365-70. doi:10.1177/0194599818770618.
10. Skora W, Stanczyk R, Pajor A, Jozefowicz-Korczynska M. Vestibular system dysfunction in patients after mild traumatic brain injury. Ann. of Agricultural and Environ Med. 2018;25(4):665-8. doi:10.26444/aaem/81138.
11. Faul M, Xu L, M.M. W, Coronado VG. Traumatic brain injury in the United States : emergency department visits, hospitalizations, and deaths, 2002-2006. Atlanta, GA: Centers for

Disease Control and Prevention, National Center for Injury Prevention and Control; 2010.
12. Dewan MC, Rattani A, Gupta S, Baticulon RE, Hung YC, Punchak M, et al. Estimating the global incidence of traumatic brain injury. J Neurosurg. 2018;2018:1-18. doi:10.3171/2017.10.JNS17352.
13. Hoffer ME, Balaban CD, Gottshall K. Vestibular rehabilitation after mild traumatic brain injury with vestibular pathology. NeuroRehabilitation. 2011;29(2):167-71. doi: 10.3233/NRE 2011-0691.
14. Buch VN. Relationship between presence of clinical oculomotor and vestibular impairments to functional mobility in children and adolescents in the sub-acute stage following mild Traumatic Brain Injury [Masters]. Montreal, Quebec, Canada: McGill University 2014.
15. Herishanu YO. Abnormal cancellation of the vestibulo-ocular reflex (VOR) after mild head and/or neck trauma. Neuro-Opthalmology. 1992;12(4):237-40. doi: 10.3109/01658109209058144.
16. Diaz DS. Management of Athletes with Postconcussion Syndrome. Sem in Speech & Lang. 2014;35(3):204-10. doi: 10.1055/s-0034-1384682.
17. Akin FW, Murnane OD, Hall CD, Riska KM. Vestibular consequences of mild traumatic brain injury and blast exposure: a review. Brain Inj. 2017;31(9):1188-94. doi: 10.1080/02699052.2017.1288928.
18. Anzalone AJ, Blueitt D, Case T, McGuffin T, Pollard K, Garrison JC, et al. A Positive Vestibular/Ocular Motor Screening (VOMS) Is Associated With Increased Recovery Time After Sports-Related Concussion in Youth and Adolescent Athletes. Am J Sports Med. 2017;45(2):474-9. doi: 10.1177/0363546516668624.
19. Covassin T, Elbin R, Harris W, Parker T, Kontos A. The role of age and sex in symptoms, neurocognitive performance, and postural stability in athletes after concussion. Am J Sports Med. 2012;40(6):1303-12. doi: 10.1177/0363546512444554.
20. Kontos AP, Elbin R, Schatz P, Covassin T, Henry L, Pardini J, et al. A revised factor structure for the post-concussion symptom scale: baseline and postconcussion factors. Am J Sports Med. 2012;40(10):2375-84. doi: 10.1177/0363546512455400.
21. Nandi R, Luxon LM. Development and assessment of the vestibular system. International J Audiol. 2008;47(9):566-77. doi: 10.1080/14992020802324540.
22. Herdman S, Clendaniel RA. Vestibular rehabilitation. Philadelphia: F.A. Davis

Company; 2014.
23. Yorke AM, Smith L, Babcock M, Alsalaheen B. Validity and reliability of the vestibular/ocular motor screening and associations with common concussion screening tools. Sports Health. 2017;9(2):174-80. doi:10.1177/1941738116678411.
24. King JE, Pape MM, Kodosky PN. Vestibular Test Patterns in the NICoE Intensive Outpatient Program Patient Population. Military Medicine. 2018;183:237-44. doi: 10.1093/milmed/usx170.
25. Demer JL. Evaluation of visual and vestibular oculomotor function. Otolaryng Head & Neck Surg. 1995;112(1):16-35. doi: 10.1016/S0194-5998(95)70301-2.
26. Pfaltz C. Vestibular compensation: Physiological and clinical aspects Acta Oto Laryngologica.95(5):402-6. doi: 10.3109/00016488309139422.
27. Master CL, Master SR, Wiebe DJ, Storey EP, Lockyer JE, Podolak OE, et al. Vision and Vestibular System Dysfunction Predicts Prolonged Concussion Recovery in Children. Clin J of Sports Med. 2018;28(2):139-45. doi: 10.1097/JSM.0000000000000507.
28. Cheever KM, McDevitt J, Tierney R, Wright WG. Concussion recovery phase affects vestibular and oculomotor symptom provocation. Int J of Sports Med. 2018;39(2):141-7. doi: 10.1055/s-0043-118339.
29. Schubert MC, Herdman SJ, Tusa RJ. Vertical dynamic visual acuity in normal subjects and patients with vestibular hypofunction. Otol & Neurotol. 2002;23(3):372-7. doi:10.1097/00129492-200205000-00025.
30. Walther LE, Lohler J, Agrawal Y, Motschall E, Schubach F, Meerpohl JJ, et al. Evaluating the Diagnostic Accuracy of the Head-Impulse Test: A Scoping Review. JAMA Otolaryng Head & Neck Surg. 2019;145(6):550-60. doi: 10.1001/jamaoto.2019.0243.
31. Angeli SI, Velandia S, Snapp H. Head-shaking nystagmus predicts greater disability in unilateral peripheral vestibulopathy. Am J Otolaryng. 2011;32(6):522-7. doi: 10.1016/j.amjoto.2010.11.004.
32. Fife T, Tusa R, Furman J, Zee DS, Frohman E, Baloh R, et al. Assessment: vestibular testing techniques in adults and children: report of the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology. Neurology. 2000;55(10):1431-41. doi: 10.1212/WNL.55.10.1431.
33. Halmagyi GM, Chen L, MacDougall HG, Weber KP, McGarvie LA, Curthoys IS. The

Video Head Impulse Test. Front in Neurol. 2017;8(258). doi: 10.3389/fneur.2017.00258.
34. Ramachandran R, Lisberger SG. Normal performance and expression of learning in the vestibulo-ocular reflex (VOR) at high frequencies. J Neurophy. 2005;93(4):2028-38. doi: 10.1152/jn.00832.2004.
35. Paolo C, Silvia C, Maurizio V, Stefano R. A new tool for investigating the functional testing of the VOR. Front in Neurol. 2013;4. doi: 10.3389/fneur.2013.00165.
36. Snegireva N, Derman W, Patricios J, Welman KE. Eye tracking technology in sports related concussion: a systematic review and meta-analysis. Physiolo Meas. 2018;39(12). doi: 10.1088/1361-6579/aaef44.
37. Snegireva N, Derman W, Patricios J, Welman KE. Awareness and perceived value of eye tracking technology for concussion assessment among sports medicine clinicians: A multinational study. Physician & sportsmed. 2019. doi:10.1080/00913847.2019.1645577
38. Gravesteijn BY, Sewalt CA, Ercole A, Akerlund C, Nelson D, Maas AIR, et al. Toward a new multi-dimensional classification of traumatic brain injury: A collaborative european neurotrauma effectiveness research for traumatic brain injury study. J Neurotrauma. 2020;37(7):1002-10. doi: 10.1089/neu.2019.6764
39. Mucha A, Fedor S, DeMarco D. Vestibular dysfunction and concussion. Handb Clin Neurol. 2018;158:135-44. doi: 10.1016/B978-0-444-63954-7.00014-8
40. Chandrasekhar SS. The assessment of balance and dizziness in the TBI patient. NeuroRehabil. 2013;32(3):445-54. doi: 10.3233/NRE-130867
41. Reneker JC, Cheruvu V, Yang J, Cook CE, James MA, Moughiman MC, et al. Differential diagnosis of dizziness after a sports-related concussion based on descriptors and triggers: an observational study. Inj epid. 2015;2(1). doi: 10.1186/s40621-015-0055-2.
42. Lynch W. Options for Evaluating and Tracking Pediatric Concussion. J Head Traum Rehabil. 2018;33(5):354-61. doi:10.1097/HTR.0000000000000436.
43. Riska KM, Hall CD. Reliability and Normative Data for the Dynamic Visual Acuity Test for Vestibular Screening. J Otol and Neurol. 2016;37 545-52. doi:10.1097/MAO.0000000000001014.
44. Ellis MJ, Leddy J, Cordingley D, Willer B. A Physiological Approach to Assessment and Rehabilitation of Acute Concussion in Collegiate and Professional Athletes. Front in Neurol. 2018;9:1115. doi:10.3389/fneur.2018.01115.

45. Whitney SL, Sparto PJ. Eye Movements, Dizziness, and Mild Traumatic Brain Injury (mTBI): A Topical Review of Emerging Evidence and Screening Measures. J Neurol Physl Ther. 2019;43:International Conference on Vestibular Rehabilitation:S31-S6. doi:10.1097/NPT.0000000000000272.

46. Murray NG, Ambati V, Contreras MM, Salvatore AP, Reed-Jones RJ. Assessment of oculomotor control and balance post-concussion: A preliminary study for a novel approach to concussion management. Brain Inj. 2014;28(4):496-503. doi: 10.3109/02699052.2014.887144.

47. Sufrinko AM, Kegel NE, Mucha A, Collins MW, Kontos AP. History of High Motion Sickness Susceptibility Predicts Vestibular Dysfunction Following Sport/Recreation-Related Concussion. Clinical J Sport Med. 2017;20:20. doi: 10.1097/JSM.0000000000000528.

48. Arksey H, O'Malley L. Scoping studies: towards a methodological framework. Int J Social Res Meth. 2005;8(1):19-32. doi: 10.1080/1364557032000119616.

49. Levac D, Colquhoun H, O'Brien KK. Scoping studies advancing the methodology. Imp Sci. 2010;5:69-78. doi: 10.1186/1748-5908-5-69.

50. Shen N, Sockalingam S, Abi Jaoude A, Bailey SM, Bernier T, Freeland A, et al. Scoping review protocol: education initiatives for medical psychiatry collaborative care. BMJ Open. 2017;7(9):e015886. doi: 10.1136/bmjopen-2017-015886.

51. Peters MD, Godfrey CM, Khalil H, McInerney P, Parker D, Soares CB. Guidance for conducting systematic scoping reviews. Int J of Ev-Based Healthcare. 2015;13(3):141-6. doi: 10.1097/XEB.0000000000000050.

52. Carrick FR, Clark JF, Pagnacco G, Antonucci MM, Hankir A, Zaman R, et al. Head-Eye Vestibular Motion Therapy Affects the Mental and Physical Health of Severe Chronic Postconcussion Patients. Front in Neurol. 2017;8:414. doi: 10.3389/fneur.2017.00414.

53. Leung FT, Rahmann A, Mendis MD, Franettovich Smith MM, Sonsearay C, Low Choy N, et al. Vestibulo-ocular dysfunction in adolescent rugby union players with and without a history of concussion. Musculoskeletal Science & Prac. 2019;39:144-9. doi: 10.1016/j.msksp.2018.12.007

54. Murray NG, D'Amico NR, Powell D, Mormile ME, Grimes KE, Munkasy BA, et al. ASB clinical biomechanics award winner 2016: Assessment of gaze stability within 24–48 hours post concussion. Clin Biomech. 2017;44:21-7. doi: 10.1016/j.clinbiomech.2015.03.009.

55. Hides JA, Franettovich Smith MM, Mendis MD, Smith NA, Cooper AJ, Treleaven J, et

al. A prospective investigation of changes in the sensorimotor system following sports concussion. An exploratory study. Musculoskel Sci & Prac. 2017;29:7-19. doi: 10.1016/j.msksp.2017.02.003.

56. Alshehri MM, Sparto PJ, Furman JM, Fedor S, Mucha A, Henry LC, et al. The usefulness of the video head impulse test in children and adults post-concussion. J of Vest Res. 2016;26(5):439-46. doi: 10.3233/VES-160598.

57. Alkathiry AA, Kontos AP, Furman JM, Whitney SL, Anson ER, Sparto PJ. Vestibulo Ocular Reflex Function in Adolescents With Sport-Related Concussion: Preliminary Results. J Sports & Health.11(6):479-85. doi: 10.1177/1941738119865262.

58. Hoffer ME, Balaban C, Szczupak M, Buskirk J, Snapp H, Crawford J, et al. The use of oculomotor, vestibular, and reaction time tests to assess mild traumatic brain injury (mTBI) over time. Laryngoscope Invest Otolaryng. 2017;2(4):157-65. doi: 10.1002/lio2.74

59. Schlosser HG, Lindemann JN, Vajkoczy P, Clarke AH. Vestibulo-ocular monitoring as a predictor of outcome after severe traumatic brain injury. Crit Care. 2009;13(6):R192-R. doi: 10.1186/cc8187

60. Jones W, Silkworth W, Dusto N, Pelak VS, Berliner J, Buard I, et al. Central Visual Oscillopsia: Case Report and Review of the Literature. Cog & Behav Neurol. 2018;31(2):86-95. doi:10.1097/WNN.0000000000000151

61. Swingen LA, Goldsmith R, Boothby J, McDermott T, Kleibel C. Video Nystagmography to Monitor Treatment in Mild Traumatic Brain Injury: A Case Report. Integrative Medicine. 2017;16(2):46-52.

62. Zhou G, Brodsky JR. Objective vestibular testing of children with dizziness and balance complaints following sports-related concussions. Otolaryng-Head & Neck Surg. 2015;152(6):1133-9. doi: 10.1177/0194599815576720.

63. Dunlap PM, Mucha A, Smithnosky D, Whitney SL, Furman JM, Collins MW, et al. The Gaze Stabilization Test Following Concussion. J Am Acad of Audiol. 2018;29:29. doi: 10.3766/jaaa.18015.

64. Peterson MD. A Case-Oriented Approach Exploring the Relationship Between Visual and Vestibular Disturbances and Problems of Higher-Level Mobility in Persons With Traumatic Brain Injury. J Head Trauma Rehabil. 2010;25(3):193-205. doi: 10.1097/HTR.0b013e3181dc82fa.

65. Gottshall KR, Hoffer ME. Tracking recovery of vestibular function in individuals with blast-induced head trauma using vestibular-visual-cognitive interaction tests. J Neurol Phys Ther. 2010;34(2):94-7. doi: 10.1097/NPT.0b013e3181dead12.
66. Schneider KJ, Meeuwisse WH, Palacios-Derflingher L, Emery CA. Changes in measures of cervical spine, vestibulo-ocular reflex, dynamic balance and divided attention following sport related concussion in elite youth ice hockey players. J Orthopaed & Sports Phys Ther. 2018;48(12):974-982. doi: 10.2519/jospt.2018.8258.
67. Gottshall KR, Sessoms PH. Improvements in dizziness and imbalance results from using a multi disciplinary and multi sensory approach to Vestibular Physical Therapy - a case study. Front in Syst Neuro. 2015;9:106. doi: 10.3389/fnsys.2015.00106.
68. Balaban C, Hoffer ME, Szczupak M, Snapp H, Crawford J, Murphy S, et al. Oculomotor, Vestibular, and Reaction Time Tests in Mild Traumatic Brain Injury. PLos One. 2016;11(9). doi: 10.1371/journal.pone.0162168.
69. Christy JB, Cochrane GD, Almutairi A, Busettini C, Swanson MW, Weise KK. Peripheral Vestibular and Balance Function in Athletes With and Without Concussion. J Neurol Phys Ther. 2019;43(3):153-9. doi: 10.1097/NPT.0000000000000280.
70. Gattu R, Akin FW, Cacace AT, Hall CD, Murnane OD, Haacke EM. Vestibular, balance, microvascular and white matter neuroimaging characteristics of blast injuries and mild traumatic brain injury: Four case reports. Brain Inj. 2016;30(12):1501-14. doi: 10.1080/02699052.2016.1219056.
71. Bogle JM, Barrs D, Wester M, Davis L, Cevette MJ. Labyrinthine concussion following gunshot injury: A case report. Int J Audiol. 2016;55(7):425-8. doi: 10.31091/14992027.2016.1166398.
72. Herdman SJ. Treatment of vestibular disorders in traumatically brain-injured patients. J Head Trauma Rehabil. 1990;5(4):63-76 14p.
73. Gunter KB, Shields CJ, Ott SD, Coronado RA. Rehabilitation of an adolescent equestrian athlete with a history of multiple concussions: A case report describing an adapted return to sport protocol. Journal Orthopaed & Sports Phys Ther. 2018:1-31. doi: 10.2519/jospt.2018.8214.
74. McDevitt J, Appiah-Kubi KO, Tierney R, Wright WG. Vestibular and Oculomotor Assessments May Increase Accuracy of Subacute Concussion Assessment. Int J Sports Med. 2016;37(9):738-47. doi:10.1055/s-0042-100470.

75. Reneker JC, Cheruvu VK, Yang J, James MA, Cook CE. Physical examination of dizziness in athletes after a concussion: A descriptive study. Musculoskel Sci & Prac. 2018;34:8 13. doi: 10.1016/j.msksp.2017.11.012.
76. Halmagyi GM, Curthoys IS. A clinical sign of canal paresis. Arch Neurol. 1988;45(7):737-9. doi: 10.1001/archneur.1988.00520310043015.
77. Scherer MR. Characterizing high velocity angular vestibulo ocular reflex function in service members post blast exposure. Exp Brain Res. 2011;71(8):4669. doi:10.1007/s00221-010 2490-1.
78. Wee SK. Vestibular rehabilitation for a patient with severe traumatic brain injury: a case study. Physiotherapy Singapore. 2002;5(3):59-65.
79. Kelly KM, Kiderman A, Akhavan S, Quigley MR, Snell ED, Happ E, et al. Oculomotor, vestibular, and reaction time effects of sports-related concussion: Video-oculography in assessing sports-related concussion. J Head Trauma Rehabil. 2019;34(3):176-88. doi:10.1097/HTR.0000000000000437.
80. Reneker JC, Babl R, Pannell WC, Adah F, Flowers MM, Curbow-Wilcox K, et al. Sensorimotor training for injury prevention in collegiate soccer players: An experimental study. Phys Ther in Sport. 2019;40:184-92. doi:10.1016/j.ptsp.2019.09.012.
81. Desai N, Wiebe DJ, Corwin DJ, Lockyer JE, Grady MF, Master CL. Factors affecting recovery trajectories in pediatric female concussion. Clin J Sports Med. 2019;29(5):361-7. doi:10.1097/JSM.0000000000000646.
82. Ellis MJ, Cordingley D, Vis S, Reimer K, Leiter J, Russell K. Vestibulo-ocular dysfunction in pediatric sports-related concussion. J Neurosurg Pediatr. 2015;16(3):248-55. doi:10.3171/2015.1.PEDS14524.
83. Hammerle M, Swan AA, Nelson JT, Treleaven JM. Retrospective Review: Effectiveness of Cervical Proprioception Retraining for Dizziness After Mild Traumatic Brain Injury in a Military Population With Abnormal Cervical Proprioception. J Manip & Physiol Therapeutics. 2019;42(6):399-406. doi: 10.1016/j.jmpt.2018.12.002.
84. Corwin DJ, Propert KJ, Zorc JJ, Zonfrillo MR, Wiebe DJ. Use of the vestibular and oculomotor examination for concussion in a pediatric emergency department. Am J Em Med. 2019;37(7):1219-23. doi:10.1016/j.ajem.2018.09.008.
85. Mayer AR, Wertz C, Ryman SG, Storey EP, Park G, Phillips J, et al. Neurosensory

Deficits Vary as a Function of Point of Care in Pediatric Mild Traumatic Brain Injury. J Neurotrauma. 2018;35(10):1178-84. doi:10.1089/neu.2017.5340.
86. Sherry NS, Fazio-Sumrok V, Sufrinko A, Collins MW, Kontos AP. Multimodal Assessment of Sport-Related Concussion. Clin J Sports Med. 2019;0:1-6. doi:10.1097/JSM.0000000000000740.
87. Sinnott AM, Elbin RJ, Collins MW, Reeves VL, Holl CL, Kontos AP. Persistent vestibular-ocular impairment following concussion in adolescents. J Sci & Med in Sport. 2019;22(12):1292-7. doi:10.1016/j.jsams.2019.08.004.
88. Eagle SR, Nindl BC, Johnson CD, Kontos AP, Connaboy C. Does Concussion Affect Perception-Action Coupling Behavior? Action Boundary Perception as a Biomarker for Concussion. Clin J Sports Med. 2019;0:1-8. doi:10.1097/JSM.0000000000000731.
89. Elbin RJ, Kontos AP, Sufrinko A, McElroy M, Stephenson-Brown K, Mohler S, et al. Motion Sickness Susceptibility and Baseline Vestibular and Ocular-Motor Performance in Adolescent Athletes. J Ath Trng. 2019;54(9):939-44. doi:10.4085/1062-6050-347-18.
90. Kontos AP, Collins MW, Holland CL, Reeves VL, Edelman K, Benso S, et al. Preliminary Evidence for Improvement in Symptoms, Cognitive, Vestibular, and Oculomotor Outcomes Following Targeted Intervention with Chronic mTBI Patients. Milit Med. 2018;183:333-8. doi:10.1093/milmed/usx172.
91. Sufrinko AM, Mucha A, Covassin T, Marchetti G, Elbin RJ, Collins MW, et al. Sex Differences in Vestibular/Ocular and Neurocognitive Outcomes After Sport-Related Concussion. Clin J Sports Med. 2017;27(2):133-8. doi:10.1097/JSM.0000000000000324.
92. Ziaks L, Giardina R, Kloos A. Integration of Vision and Vestibular Therapy for Vestibulo-Ocular Post-Concussion Disorder -- A Case Study. Internet J Allied Health Sci & Prac. 2019;17(3):1-13.
93. Moran RN, Covassin T, Elbin R, Gould D, Nogle SJTAjosm. Reliability and normative reference values for the Vestibular/Ocular Motor Screening (VOMS) tool in youth athletes. The Am J Sports Med. 2018;46(6):1475-80. doi:11.77/0363546518756979.
94. Mossman B, Mossman S, Purdie G, Schneider E. Age dependent normal horizontal VOR gain of head impulse test as measured with video-oculography. J Otolaryngol Head Neck Surg. 2015;44:29. doi:10.1186/s40463-015-0081-7.
95. Alizadeh S, Nariman R, Ahadi M, Sameni SJ. Normative vestibulo-ocular reflex data in

6-12 year-old children using video head-impulse test. Aud Vestib Res 2017;26(3):145-50.
96. Van Der Stappen A, Wuyts FL, Van De Heyning PH. Computerized electronystagmography: normative data revisited. Acta Otolaryngol. 2000;120(6):724-30. doi:10.1080/000164800750000243.
97. Chan FM, Galatioto J, Amato M, Kim AH. Normative data for rotational chair stratified by age. Laryngoscope. 2016;126(2):460-3. doi:10.1002/lary.25497.
98. Riska KM, Hall CD. Reliability and normative data for the Dynamic Visual Acuity Test for Vestibular Screening. J Otol & Neurotol. 2016;37:545-52. doi:10.1097/MAO.0000000000001014.
99. Kaufman DR, Puckett MJ, Smith MJ, Wilson KS, Cheema R, Landers MR. Test–retest reliability and responsiveness of gaze stability and dynamic visual acuity in high school and college football players. Phys Ther in Sport. 2014;15(3):181-8. doi:10.1016/j.ptsp.2013.10.002.
100. Christy JB, Payne J, Azuero A, Formby C. Reliability and diagnostic accuracy of clinical tests of vestibular function for children. Pediatr Phys Ther. 2014;26(2):180-9. doi:10.1097/PEP.0000000000000039.
101. Schubert MC, Migliaccio AA. Stability of the aVOR to Repeat Head Impulse Testing. Otol & Neurol. 2016;37(6):781-6. doi:10.1097/MAO.0000000000001055.
102. Law MC, Polatajko HJ. Diagnostic tests in occupational therapy: A model for evaluation. Occ Ther J Research. 1987;7(2):111-22. doi:10.1177/153944928700700204.
103. Abrahamsen ER, Christensen AE, Hougaard DD. Intra- and Interexaminer Variability of Two Separate Video Head Impulse Test Systems Assessing All Six Semicircular Canals. Otol & Neurotol. 2018;39(2):e113-e22. doi:10.1097/MAO.0000000000001665.
104. Mezzalira R, Bittar RS, Bilécki-Stipsky MM, Brugnera C, Grasel SS. Sensitivity of caloric test and video head impulse as screening test for chronic vestibular complaints. Clinics. 2017;72(8):469-73. doi:10.6061/clinics/2017(08)03.
105. Jorns-Haderli M, Straumann D, Palla A. Accuracy of the bedside head impulse test in detecting vestibular hypofunction. J Neurol Neurosurg Psychia. 2007;78(10):1113-8. doi:10.1136/jnnp.2006.109512.
106. Cohen HS, Stitz J, Sangi-Haghpeykar H, Williams SP, Mulavara AP, Peters BT, et al. Utility of quick oculomotor tests for screening the vestibular system in the subacute and chronic populations. Acta Otolaryngol. 2018;138(4):382-6. doi:10.1080/00016489.2017.1398838.

107. Harvey SA, Wood DJ, Feroah TR. Relationship of the head impulse test and head-shake nystagmus in reference to caloric testing. Am J Otol. 1997;18:207-13.
108. Henry DF, DiBartolomeo JD. Closed loop caloric, harmonic acceleration and active head rotation tests norms and reliability. Otolaryng Head & Neck Surg. 1993;109:975-87. doi:10.1177/019459989310900602.
109. Henry DF. Test-retest reliability of open-loop bithermal caloric irrigation responses from healthy young adults. American J Otol. 1999;20:220-2.
110. McCaslin DL, Jacobson GP, Bennett ML, Gruenwald JM, Green AP. Predictive properties of the video head impulse test: Measures of caloric symmetry and self-report diziness handicap Ear & Hearing. 2014;35:185-91. doi:10.1097/AUD.0000000000000047.
111. Rambold HA. Testing of the semicircular canal function in vertigo and dizziness. Up to Date on Meniere's Disease. 2017:119. doi:10.5772/66688.
112. Ahmed M. Standardization of rotatory chair velocity step and sinusoidal harmonic acceleration tests in an adult population. Adv Arab Academy of Audiovestibulogy. 2014;1(2). doi:10.4103/2314-8667.149016.
113. Curthoys IS, Manzari L. Clinical application of the head impulse test of semicircular canal function. Hear, Bal and Comm. 2017;15(3):113-26. doi:10.1080/21695717.2017.1353774.
114. MacDougall HG, Weber KP, McGarvie LA, Halmagyi GM, Curthoys IS. The video head impulse test. Neurol. 2009;73:1134-41. doi:10.3389/fneur.2017.00258.
115. Alhabib SF, Saliba I. Video head impulse test: a review of the literature. Eur Arch Otorhinolaryngol. 2017;274(3):1215-22. doi:10.1007/s00405-016-4157-4.
116. Gottshall KR, Hoffer ME. Tracking recovery of vestibular function in individuals with blast-induced head trauma using vestibular-visual-cognitive interaction tests. J Neurol Phys Ther. 2010;34(2):94-7. doi: 10.1097/NPT.0b013e3181dead12.

Chapter 6: Integration of Manuscript #1 and Manuscript #2

Study #1 (Manuscript 1) was a scoping review outlining the tests administered and tools used in the evaluation of VOR function following TBI of all severities in both children and adults. In this review a vast majority of included studies focused on mTBI population samples. The protocols administered and variables of interest within, and across, measures identified tended to vary significantly. Of importance, as gold-standard measures of vestibular function remain difficult to access and also do not measure VOR function during high-frequency head movements, this scoping review highlighted various alternative measures that address either or both of these limitations. From these, three main categories of VOR function outcome measures can be extracted: 1) measures focusing on how symptoms are provoked in response to tasks requiring eye and head movements, 2) measures of gaze stability in response to unplanned high velocity head movements, and 3) measures of gaze stability in response to voluntary or expected high velocity head movements.

From a clinical rehabilitation standpoint, the benefits and limitations of selecting certain outcome measures over others remain to be determined. As clinical practice requires cost effective, efficient, reliable and user-friendly assessments, consideration should be put towards identifying whether to use clinical or computerized tools. Specific tests included when assessing the VOR should focus on distinct, complementary elements of the VOR response in order to avoid redundancy. Determining these characteristics, will support the development of an optimal battery of tests to assess VOR function in a manner suitable to clinical settings and resources.

In addition to the specific characteristics of tests, when assessing VOR function in the context of mTBI, the possibility of co-existing injuries to the cervical structures should also be considered as these can result in symptoms resembling those induced by VOR impairments. As targeted treatment recommendations are developed, and informed by results obtained from clinical assessment, it is important to better understand whether cervical injuries influence findings on symptom-based measures of VOR function. As such, in order to appropriately interpret positive findings, reduce false positives, and develop an accurate treatment plan, the potential influence of co-existing injuries on measures of VOR function should be determined.

In order to identify whether tests commonly used to assess VOR function in pediatric mTBI populations provide overlapping, rather than complementary information, our second study (Manuscript II) seeks to determine the level of agreement between symptom-based and performance-based tests of VOR function in this population. The tests included each fall into one of the three main categories of VOR measures identified from the results in Study 1 (Manuscript 1). Additionally, in order to explore the potential influence of cervical injuries on measures of VOR function, this study will characterize the level of symptom provocation induced by a VOR test in individuals with cervical findings and those without. This study will provide information to support clinical decision-making when interpreting and selecting outcome measures to include in test batteries when assessing VOR function in pediatric mTBI population. Such information would also provide a steppingstone for future studies seeking to explore certain avenues of research recommended in Study #1 (manuscript 1).

Chapter 7: Manuscript 2

Determining the agreement between common measures of VOR function after a mild traumatic brain injury in children and adolescents

Adrienne Crampton[a], K. Schneider [b,c,d] , L. Grilli [e] , M. Chevignard[f,g,h], M. Katz-Leurer[i], M. Beauchamp [j,k], C. Debert[l] and I. J. Gagnon[a,e]

[a]*School of Physical and Occupational Therapy, McGill University, Montréal, Canada*

[b]*Sport Injury Prevention Research Centre, Faculty of Kinesiology, University of Calgary, Alberta, Canada*

[c]*Alberta Children's Hospital Research Institute, University of Calgary, Alberta, Canada*

[d]*Hotchkiss Brain Institute, University of Calgary, Alberta, Canada*

[e]*Montreal Children's Hospital-McGill University Health Centre, Montréal, Canada*

[f]*Sorbonne Université, CNRS, INSERM, Laboratoire d'Imagerie Biomédicale, LIB, F-75006, Paris, France*

[g]*Sorbonne Université, GRC 24 Handicap Moteur et Cognitif et Réadaptation, Paris, France*

[h]*Rehabilitation Department for Children with Acquired Neurological Injury and Outreach Team for children and Adolescents with Acquired Brain Injury, Saint Maurice Hospitals, Saint Maurice, France*

[i] *Physical Therapy Department, University of Tel-Aviv, Tel-Aviv, Israel*

[j]*ABC's Laboratory, Ste-Justine Hospital Research Center, Montréal, Canada*

[k]*Department of Psychology, University of Montréal, Montréal, Canada*

[l]*Department of Clinical Neuroscience, University of Calgary, Calgary, Canada*

To be submitted to -

Abstract

Background: Alterations to vestibulo-ocular reflex (VOR) function and cervical spine injury may contribute to dizziness reported following pediatric mild traumatic brain injury (mTBI). Moreover, dizziness has been correlated with a more negative prognosis. While various measures are used to assess VOR function, there is no consensus on what the optimal battery of tests may be. The influence of cervical injury on findings from these tests remains unclear. **Objectives:** i) to determine the level of agreement between symptom- and performance-based tests of VOR function in a pediatric mTBI sample; ii) to characterize the level of symptom provocation induced by VOR tests in individuals with and without cervical findings. **Design:** Cross-sectional. **Setting:** Tertiary care pediatric hospital. **Participants:** 101 participants (54.5% female), mean age 13.92 years (2.63), completed a VOR assessment (mean time since injury 18.26 days (6.16)). **Outcome measures:** *Symptom provocation* was measured by the Vestibular/Ocular Motor Screening Tool (VOMS). *Performance* was measured by VOMS VOR performance, the Head Thrust Test (HTT), the computerized Dynamic Visual Acuity Test, and the video Head Impulse Test. *Cervical impairment* was measured by the Cervical Flexion Rotation Test, Range of Motion Test and Self-reported Neck Pain. **Analysis:** Agreement was evaluated using Cohen's kappa statistic. **Results:** No outcomes demonstrated agreement with VOR symptom provocation (k=-0.15-0.14). Among performance-based measures, fair agreement was demonstrated between VOMS VOR performance and the clinical HTT (k=0.32), while little to no agreement was demonstrated between the remaining measures. VOR dizziness symptoms were reported in a greater proportion of individuals with cervical findings (41.1-41.8%) than without (2.3-6.8%). **Conclusion:** The findings indicate i) that symptom-based VOR tests measure a different construct than performance-based tests, ii) the distinct role of each measure when assessing VOR function should be further understood, and iii) cervical injury may contribute to symptoms induced by tests of VOR function.

Keywords: Mild traumatic brain injury; vestibulo-ocular reflex; assessment; measurement; pediatric.

Background

A mild traumatic brain injury (mTBI) is an injury to the brain that can occur from direct or indirect forces. This injury is estimated to affect approximately 55.9 million people each year (1). In the USA, yearly rates specific to the pediatric population are estimated between 1.1-1.9 million (2). As mTBI often leads to cognitive, emotional/behavioral and/or somatic symptoms, these can greatly affect a young individual's ability to navigate their environment and pursue various activities of daily life.

While symptom presentation is unique in each individual due to various intrinsic and extrinsic factors at play, complaints relating to dizziness and vision are among the most commonly reported. Complaints of dizziness, visuo-vestibular and/or visual difficulties vary between 29-72% in children and adolescents following mTBI (3-5). The vestibulo-ocular reflex (VOR), a key reflex in gaze stabilization, may be altered following mTBI and is thus of great interest to clinicians and researchers focusing on pediatric mTBI populations. The VOR allows one to maintain gaze stability during head motion by facilitating eye movements in equal and opposite direction to head movement. The primary sensory input acting to trigger the VOR motor response originates from the semi-circular canals, situated in the peripheral sensory apparatus within the inner ear, which detect angular acceleration in the three planes of motion (6-8). The semicircular canals are in turn interconnected with the visual system, as well as with both central and peripheral structures involved in processing and coordinating the VOR response.

Difficulties with VO and/or VOR function have been identified in 29-69% of children and adolescents post-mTBI (5, 9-11). Such deficits can have important consequences on activities such as school, sports and general recreation. In addition, as dizziness has been identified as a predictor for prolonged recovery following mTBI (9, 12, 13) there is an urgency to understand its underlying pathophysiology, and to understand how to best evaluate for the presence of VOR dysfunction in children and adolescents presenting for care after a mTBI.

A variety of different measures have been developed and are used to assess the VOR in both clinical and specialized contexts. While in specialized contexts gold standard vestibular tests such as rotary chair testing (14) and caloric testing (14) are often used, these tests are not able to evaluate

the VOR at high frequencies and can be challenging to tolerate by symptomatic patients. Moreover, such tests are often costly and inaccessible due to long appointment wait times. In clinical contexts, there is little consensus with regards to best practices when assessing VOR function in mTBI populations. Our group (Crampton et al., *under review*) recently completed a scoping review (Manuscript 1, Chapter 5) which provided a broad representation of the breadth of tools and tests currently used to measure VOR function in TBI populations across severities and populations. In the results pertaining to pediatric mTBI samples, the measures used to evaluate the VOR could be grouped under three categories: 1) measures focusing on how symptoms are provoked in response to tasks requiring eye and head movements, 2) measures of gaze stability in response to unplanned high velocity head movements, and 3) measures of gaze stability in response to voluntary or expected high velocity head movements. Tools in all three categories could be found in clinical or computerized versions, with varying costs, ease of use and accessibility.

With this diversity and in the face of uncertainty regarding what constitutes a useful but not redundant battery to capture VOR function in their patients after mTBI, clinicians need increased clarity to better inform their practice and the development of optimal test procedures. This is especially true when it comes time to choose between clinical or computerized versions of performance-based tests which purport to address similar constructs. For example, current commonly used clinical tests often require little equipment, are low cost and are accessible to both practitioners and patients. However, they present shortcomings with regards to their precision and ability to quantify deficits observed (4, 15). Computerized versions of tests conversely are more precise, but may not be accessible, as they are more expensive, require training to administer and require a certain level of expertise to interpret more granular results. Finally, while symptom-based measures involving eye-head movements, are low in cost, require little equipment, and are easy to administer, these measures focus more on the symptoms induced by a VOR test than on VOR function itself. These measures may also be influenced by contributions from confounding injuries such as cervical impairments (16-18) which have been associated with dizziness and other visuo-vestibular symptoms in mTBI populations (17-19).

While previous literature has explored the psychometric properties of clinical and computerized performance-based VOR tests, as well as VOR symptom-based measures in pediatric populations

(20-23), to our knowledge no published literature exists exploring the agreement between commonly used measures assessing VOR function in pediatric mTBI. Understanding this agreement will be useful for clinicians and patients alike as the use of a shorter yet effective battery of tests to assess the VOR could be beneficial from a time, comfort, energy and economic perspective, while providing a more comprehensive understanding of the potential pathophysiological mechanisms that may underlie positive findings.

In order to provide clinicians and researchers with further information on which to base their choice of assessments and interpretation of results the purpose of this study was to determine the level of agreement between symptom-based and performance-based tests of VOR function in a pediatric mTBI population. In order to explore the potential influence of cervical impairments on symptom-based measures of VOR function, our second objective was to characterize the level of symptom provocation induced by VOR tests in individuals with cervical findings and those without, using the Vestibular/Ocular Motor Screening (VOMS) VOR test.

Methods

This study was a cross sectional study evaluating the agreement between symptom-based, and performance-based tests of VOR function. A consecutive convenience sample of participants were recruited at a tertiary care pediatric hospital, the Montréal Children's Hospital (McGill University Health Center) in the Emergency Department and at the Institutions' Concussion Clinic as well as at the University of Calgary Sport Medicine Centre or the Acute Sport Concussion Clinic (University of Calgary). Assessment took take place at the Kids Concussion Lab within this hospital (Montréal participants) or at the Concussion Lab at the University of Calgary (Calgary participants). The study was approved by the Pediatric panel of the McGill University Health Center Research Ethics Board and by the Conjoint Health Research Ethics Board at the University of Calgary. All participants provided informed consent (parent) and assent (child) to the study.

Participants: Participants enrolled in a larger project (SimplyRehab, funded by ERA-NET NEURON) aged 6 to 18 and assessed within 3 weeks of a medically diagnosed mTBI (24) were included in this study. Participants were excluded if one or more of the following were present: i)

history of TBI in the preceding 6 months or any previous TBI with unresolved symptoms/impairments; ii) presence of comorbidities that prevent or limit the participant's ability to complete the assessment; iii) medications which affect neural adaptation; iv) participants who consented to participate in the study, but withdrew prior to baseline assessment. Standard acute concussion care provided by family physicians, pediatricians, walk-in clinics or the emergency department was received by all participants.

Procedures: Consent and medical history of participants were obtained. Prior to arrival for their assessment, participants were asked to complete developmentally appropriate versions of patient-reported outcome measures and questionnaires in order to thoroughly characterize the sample. As the Post-Concussion Symptom Inventory and Pediatric Quality of Life Inventory provide separate versions for ages 5-7, 8-12, and 13-18 years old, total scores were presented according to age-group (Table 7.1). Upon arrival to the assessment, a trained evaluator performed the battery of assessments beginning with the symptom-based measures and followed by the performance-based measures. Additional balance and cervical measures, administered as part of the larger project, were included to more fully describe the sample. A description of patient-reported outcome measures, balance and cervical measures can be found in Table A2.1, Appendix 2.

Outcome measures: Five outcome measures from four VOR tests were included in this study. Together these included the three broad categories of VOR measures often administered when assessing VOR function in mTBI populations. Gaze stability in response to voluntary head movements was assessed first clinically looking at alterations in the child or adolescent's performance on the VOR task included in the quantified version of the Vestibular/Ocular-Motor Screening Tool (VOMS) and second, with a computerized test of Dynamic visual acuity (DVA). VOR symptom provocation in response to tasks requiring eye head movements was assessed following the same VOMS task. Finally, gaze stability in response to unplanned passive high velocity head movements was assessed with the clinical Head Thrust Test (HTT) and with a similar computerized test, the video Head Impulse Test (vHIT).

The Vestibular/Ocular-Motor Screening Tool (23, 25) (VOMS) was developed as a screening tool to assess symptom provocation (headache, dizziness, nausea, and fogginess) induced by common

VOR and OM tasks in individuals following concussion (23). The VOMS includes seven tasks: smooth pursuits, vertical saccades, horizontal saccades, convergence, vertical VOR, horizontal VOR and visual motion sensitivity. For the purpose of this study, only the vertical and horizontal VOR tasks were included. The VOR tasks of the VOMS consisted of asking the patients to face the examiner and rotate their head 20 degrees each side at 180 bpm horizontally while maintaining a focus on the examiner's nose. Ten repetitions (back and forth) were performed. This test was then repeated in the vertical direction. Symptom provocation was considered to be present, or abnormal, when the participant reported experiencing an increase of ≥ 2 points (on four combined 0-10 point symptom scales) on horizontal and/or vertical VOR task.

The VOMS VOR task was also used as a clinical test of gaze stability in response to voluntary head movement. The evaluator observed the performance of participants during the task of horizontal and vertical head motion while the participant actively rotated their head at 180 bpm. The evaluator noted the presence of corrective saccades (yes/no) during either or both horizontal and vertical VOR tasks which was then considered as abnormal VOMS VOR performance.

To complement the VOMS VOR task, a computerized DVA test (cDVA) was performed using the NeuroCom InVision System[1] (26). cDVA testing was selected as it has demonstrated high positive predictive value (96%) for individuals with vestibular disorders (unilateral vestibular loss and bilateral vestibular hypofunction), as well as high negative predictive values for those without (93%) (27)**.** The patient first completed the static visual acuity test through a series of tumbling E displays of varying sizes determined by an algorithm while sitting 10 feet from the screen. A head tracking device to capture head velocity was then placed on the patient's head and the DVA test was performed with fixed minimal velocity active head rotations at 120 deg/sec. Abnormal DVA change was considered to be a >0.3 LogMAR change when comparing static visual acuity and DVA. A standard clinical DVA Tumbling E/EDTRS test was not included as a clinical comparison as this test uses active assisted head rotations and not active head rotations. As this would reduce the central preprogramming at play, the cDVA test scores would not provide true comparisons.

[1] NeuroCom® InVision System, Natus®

The Head Thrust Test (28) (HTT) was included as a clinical measure of VOR function in the context of unplanned high velocity head movements, as it is often used as part of a clinical examination to identify individuals with peripheral vestibular hypofunction (28). In this test, the assessor administered quick, small amplitude and unpredictable high-acceleration head rotations (29). The patient was instructed to maintain their gaze on a stable point directly in front of them (the examiner's nose). The presence of catch-up saccades as observed by the assessor indicated abnormal VOR function.

The computerized Head Impulse Test (vHIT) was performed using the ICS Impulse software[2] to assess the horizontal semicircular canals in the peripheral vestibular labyrinth and as a computerized alternative to the HTT. In this test, the patient was sitting, facing the wall, and maintaining their gaze on a fixation dot, while the tester rotated the patient's head horizontally 10-20 degrees in a short abrupt manner, unpredictably to the left and right (30). The mean gain of the VOR was used for analysis with an abnormal cut-off of <0.8.

To address our second objective, individuals were categorized into two subgroups using five outcome measures assessing cervical spine function. The outcome measures selected included both physical measures of motion limitation as well as self-reported measures of pain. The presence of pain or abnormal function on one or more cervical spine measure categorized the individual into the NECK group (group with cervical findings). The absence of positive findings on any of these measures categorized the individual into the NONE group (group without cervical findings). Outcome measures used to evaluate the cervical spine included:

The cervical flexion and rotation test (CFRT) (31, 32), assessing *performance*, (CFRT, abnormal if range of motion is limited or firm resistance encountered, evaluator interpretation) and the *presence of pain* (abnormal if pain is present, patient self-report).

[2] ICS ® Impulse software, Natus®

The cervical range of motion test, assessing *performance* (abnormal if limited range of motion is present on rotation, side flexion, flexion or extension, evaluator interpretation) and the *presence of pain* (abnormal if pain is present on ROM test, patient self-report).

Self-reported neck pain, measured using self-report of neck pain in past 48 hours on a numeric pain scale from 0-2 for children under 13 years old and from 0-6 for adolescents 13-18 years old (abnormal if patient reported any *neck pain* that was not present prior to mTBI).

Analysis: As our data was categorical (binary), agreement among symptom-based and performance-based measures included was assessed using Cohen's kappa coefficients. These coefficients were selected as they provide more robust measures than simple percent agreement calculation, as kappa takes into account the possibility of the agreement occurring by chance.

Results

Our sample consisted of 101 participants and was composed of 45.5% males (54.5% females) (Table 7.1). The mean age was 13.92 years (SD= 2.63, range= 7-17) and mean time from injury to assessment was 18.26 days (SD= 6.61, range= 2-38) days. With regards to injury mechanism, 70.3% of participants in our sample sustained their mTBI from sport and 29.7% recreational play or other reasons. When considering prior mTBI/concussion history, 58% of our sample did not have any previous history of injury. Pain was reported during assessment of cervical ROM (26.0% of sample), during the CFRT (13.1% right and 15.2% left) and through self-report on the numeric pain scale (45.7%).

Table 7.1: Descriptive characteristics and additional outcome measures

Outcome		Mean (SD) or %	N
Descriptive characteristics			
Age in years, mean (SD)		13.92 (2.63)	101
Sex, male, %		45.5	101
Time to assessment, days (SD)		18.26 (6.16)	101
Participants seen in physio prior (>1 week) to T1, %		13.9	101
Previous history of concussion, %		42.0	101
mTBI from a sport, %		70.3	99
mTBI from recreation, other or unspecified, %		29.7	99
Post-concussion symptoms			
PCSI total score, mean (SD)			
	5-7 years	1.5 (1.92)	95
	8-12 years	6.95 (8.24)	
	13-18 years	26.38 (24.20)	
SCAT 5 symptom total, mean (SD)		30.08 (27.21)	71
Dizziness present on PCSI, %		51.1	94
Cervical exam			
Normal cervical ROM, %		94.0	100
Pain present on cervical ROM, %		26.0	100
Cervical flexion endurance, mean seconds (SD)		27.13 (16.12)	99
Normal cervical flexion rotation right, %		94.9	99
Normal cervical flexion rotation left, %		94.9	99
Cervical flexion rotation pain right, %		13.1	99
Cervical flexion rotation pain left, %		15.2	99
Self-reported neck pain present post injury, %		45.74	94
1 or more of above neck observations present, %		55.44	101
Global outcome			
Peds QL total score, mean (SD)			90
	5-7 years	92.39 (4.16)	
	8-12 years	81.06 (15.98)	
	13-18 years	71.92 (17.28)	
Glasgow outcome scale – extended, mean (SD)		2.32 (0.90)	98

SD: standard deviation; PCSI: post-concussion symptom inventory; SCAT: sport concussion assessment tool; ROM: range of motion; PedsQL: pediatric quality of life questionnaire

Performance on outcome measures assessing VOR function

On the performance-based measures included, very few participants had clinician-observed corrective or catch-up saccades during the VOMS VOR performance assessment (1/98) and the HTT (5/98), and few demonstrated abnormal VOR gain ratios on the vHIT (right/left average 3/88). Conversely, a large number of participants demonstrated abnormal performance on the cDVA test (31/80). When considering the measure of symptom provocation induced on one or both VOMS VOR tasks (horizontal and/or vertical), 29/93 participants reported a symptom increase of ≥ 2.

Level of agreement between symptom provocation and performance-based measures

No performance-based outcomes included in this study demonstrated more than slight agreement with VOMS VOR symptom provocation (Table 7.2). Cohen's Kappa coefficients ranged from -0.15 (left vHIT gain) to 0.14 (cDVA).

Table 7.2: Agreement between symptom provocation and measures of VOR function

Measure	**Cohen's Kappa with VOMS symptom provocation**	**95% CI**
VOMS VOR performance	0.05	-0.04 to 0.14
Head thrust test	0.11	-0.03 to 0.26
ICS Impulse left vHIT gain	-0.15	-0.25 to -0.06
ICS Impulse right vHIT gain	-0.05	-0.11 to 0.02
ICS Impulse average vHIT gain	-0.07	-0.14 to <0.01
InVision left DVA	-0.04	-0.25 to 0.18
InVision right DVA	0.07	-0.15 to 0.29
InVision average vHIT	0.14	-0.09 to 0.36

VOMS: vestibular/ocular motor screening tool; VOR: vestibulo-ocular reflex; vHIT: video head impulse test; DVA: dynamic visual acuity; CI: confidence interval

Level of agreement between performance-based measures

Of the outcomes included, fair agreement was only observed between VOMS VOR performance and the clinical HTT (kappa=0.32). All other comparisons showed poor to slight agreement (Table 7.3).

Table 7.3: Kappa values between performance-based outcomes

	VOMS VOR Performance (95% CI)	**HTT (95% CI)**	**vHIT (95% CI)**	**cDVA (95% CI)**
VOMS VOR Performance	-	0.32 (-0.16 to 0.80)	N/A	N/A
HTT	0.32 (-0.16 to 0.80)	-	-0.04 (-0.07 to -0.01)	0.05 (-0.06 to 0.17)
vHIT	N/A	-0.04 (-0.07 to -0.01)	-	0.08 (-0.03 to 0.18)
cDVA	N/A	0.05 (-0.06 to 0.17)	0.08 (-0.03 to 0.18)	-

VOMS: vestibular/ocular motor screening tool; VOR: vestibulo-ocular reflex; HTT: head thrust test; vHIT: video head impulse test; cDVA: computerized dynamic visual acuity

Second objective results: symptom provocation according to cervical findings

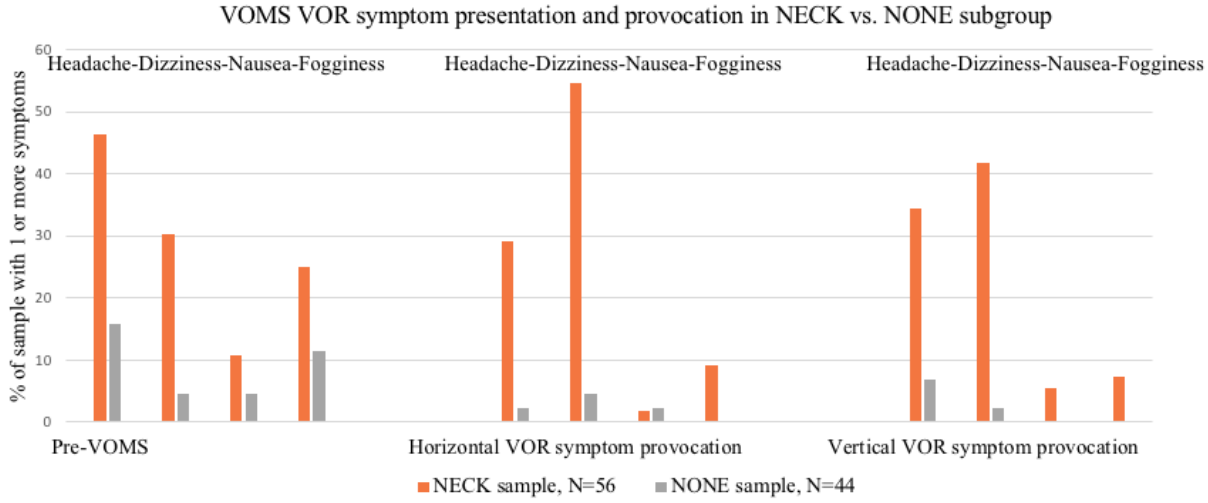
In both outcomes demonstrating higher abnormal frequencies, further descriptive statistics were obtained. When considering both the horizontal and vertical VOMS VOR test, the symptom provocation induced was driven mainly by the headache and dizziness symptom types (Table 7.4). Separating the sample into the NECK and NONE groups previously described, more participants in the NECK group reported headache and dizziness symptoms at rest (pre-VOMS) and provocation of these symptoms induced with VOMS VOR testing (Figure 7.1).

Table 7.4: VOR symptom provocation by symptom type

Variable	Headache	Dizziness	Nausea	Fogginess	Total change
Horizontal VOR (mean symptom change)	0.49	1.21	0.02	0	1.70
Horizontal VOR (total symptom change)	24	60	1	0	84
n	98	98	97	98	98
Vertical VOR (mean symptom change)	0.75	1.07	0.02	0.12	1.94
Vertical VOR (total symptom change)	37	53	1	6	96
n	98	98	97	98	98

VOR: vestibulo-ocular reflex; mean symptom change: sample mean symptom increase reported by symptom type following VOR task; total symptom change: sum of symptom increase reported by all participant following VOR task

Figure 7.1: Proportion of sample reporting symptoms at rest and provocation with testing by sub-group (NECK vs NONE)



**NECK sample, N=55 for horizontal and vertical symptom provocation and N=54 for horizontal VOR nausea. VOMS: vestibular/oculomotor screening tool; VOR: vestibulo-ocular reflex*

Additional results characterizing unusual cDVA abnormal proportions

When considering the proportions demonstrating abnormal performance on performance-based measure of VOR function, there were unusually high abnormal proportions on the cDVA test. In order to further discuss these proportions in the following section, the mean LogMAR change and mean velocities at which head movements occurred during cDVA testing were described. The mean LogMAR change was 0.29 (SD=0.16, 0.18-0.40) for the left and 0.29 (SD=0.16, 0.20-0.38) for the right. The mean velocity of all individuals as well as the mean velocity of sub-groups categorized over and under the 0.3 LogMAR cut-off can be found in Figure 7.2. Mean values range between 149.77 (20.98) and 169.78 (36.09) degrees/second highlighting true velocities to be greater than the minimal velocity threshold of 120 degrees/second.

Figure 7.2: Mean velocity of head movement

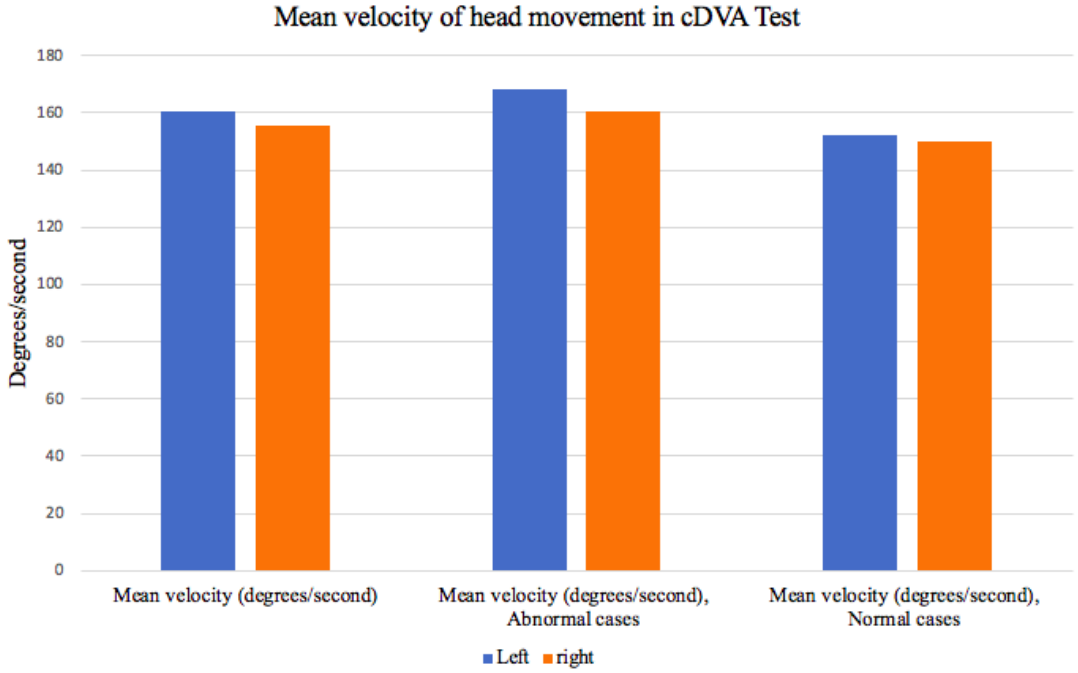


Figure 7.2: Mean velocity of head movement when patient responded to optotype presentation

Discussion

Our study's objective was to determine the level of agreement between symptom-based and performance-based tests of VOR function in a pediatric mTBI population. Our second objective was to characterize the level of symptoms provoked by VOR tests in individuals with cervical

findings and those without. Our results demonstrate a lack of agreement between symptom-based and performance-based tests (Table 7.2). These findings, along with the high proportion of participants reporting abnormal symptom provocation induced by the VOMS VOR test, and our findings outlining the potential contribution of coexisting cervical injuries on symptom provocation (discussed below), suggest that VOR functional abnormalities may not be the only source contributing to the symptoms induced by VOR testing. It would seem that symptom provocation induced by VOR testing may not measure the same construct as performance-based outcome measures of VOR function, reinforcing the value of including both symptom-based and performance-based measures when assessing VOR function.

Comparing performance-based measures: Of the performance-based measures included in this study, the two clinical measures of VOR, the VOMS VOR performance outcome and the clinical HTT demonstrated fair agreement (kappa=0.32). These findings may indicate that despite the contributions from additional systems and central preprogramming involved with active, voluntary head movements, positive performance findings on the VOMS VOR test may still be sensitive and specific to the VOR as the HTT with which it agrees, uses unplanned, passive head movements that better isolate VOR function. As these results are based on a small number of observations, they should be further explored in future research.

An additional point of interest among the performance-based outcome measures is the high proportion of participants demonstrating abnormal results on the cDVA test, but not on VOMS VOR performance, on the HTT or on the vHIT. As these results merit attention, they will be further discussed at the conclusion of this section.

Comparing clinical and computerized measures: In this study, our data allowed for the agreement between a clinical and a computerized measure of gaze stability during unplanned, passive high-velocity head movements to be assessed. When comparing the vHIT and the HTT, no agreement was observed (kappa= -0.04). As literature in recent years has investigated the use of the vHIT in mTBI and TBI populations (33, 34), this finding can contribute to discussions surrounding the added value of the vHIT to clinical practice. If the HTT and vHIT do not agree, the value may not lie in substituting the HTT for the vHIT, but rather, in using them for different purposes. The

former to obtain a more general, functional measure of the VOR, while the latter could provide extensive information on multiple variables in order to characterize the VOR response with a higher level of detail.

Symptom provocation and cervical spine findings: In order to further understand the underlying source of the symptom provocation induced by VOMS VOR testing, our study described symptom provocation by subcomponent (Table 7.4), highlighting headaches and dizziness to be driving symptom provocation as well as symptom presentation at rest. When considering explanations for these findings, the role of cervical contributions should be considered as the mechanisms leading to mTBI may affect this highly mobile region of the spine. Compromises to the afferent input in the cervical region are known to be capable of causing various symptoms, including dizziness and visual impairments (35). Moreover, literature within mTBI/concussed populations has identified cervical impairments to be potential sources contributing to symptoms such as headaches and dizziness (16, 17, 36). As our sample demonstrated pain on cervical flexion in 13.1% and 15.2% (right, left respectively), and on the cervical ROM test in 26.0%, as well as self-reported neck pain in 45.7%, it is possible that some of the symptoms experienced are a result of physiological impairments to the cervical spine structures and/or pathways.

To explore this relationship our group descriptively outlined the symptom provocation induced by VOMS VOR tests by symptom type and also by group (NECK vs. NONE). A clear difference was present with the NECK group experiencing larger proportions of headache and dizziness symptoms both prior to VOMS VOR test and induced by VOMS VOR testing (Figure 7.1). These findings support previous literature highlighting the similarities between the characteristics of cervical spine findings in concussed populations and those of non-concussed individuals experiencing headaches and dizziness (16, 17). As the often forceful mechanisms involved in mTBI can result in simultaneous injury to the cervical spine, considering these structures when assessing individuals and developing targeted treatment plans can result in more favorable prognosis and overall recovery (16, 17, 36).

Interpreting cDVA findings: While the high velocity of head movements (Figure 7.2) may marginally contribute to the high proportion of participants demonstrating abnormal results on the

cDVA test, we do not believe the difference in mean velocity observed between normal and abnormal groups is sufficient to be the sole reason for this observation. Supporting this, a study performed by Riska et al. (2016) in healthy adult populations showed little difference between the mean head velocity for trials incorrectly identifying the optotype and the mean head velocity of all trials (37). Nevertheless, as a small difference in velocity was observed between the normal and abnormal groups, further research should explore ways to more strictly monitor the velocity of head movements in order to ensure testing occurs at the velocity specified in the procedures.

An alternative consideration that may contribute to explaining our cDVA test results, is the use of a cut-off value of 0.3 LogMAR. While cut-off values of 0.2 and 0.3 are commonly used in clinical DVA assessments, these may not be adequate in the cDVA test. One particular study highlights this with a sample mean cDVA LogMAR change as high as 0.23 (0.13) when tested at 150 deg/sec. in healthy NCAA division 1 athletes (38). As such a population would be expected to have superior performances to most, these findings are perplexing. A more reliable approach to cut-off scores when administering the cDVA test may be that used by Goebel et al. (2007) who determined a cut-off of 0.33 LogMAR based on 2 SD from the mean of healthy control values obtained in this same study (39). As a whole, our findings highlight the need to further explore the psychometric properties of the InVision DVA test. Presently opinions on the reliability of the InVision DVA test are not uniform (21, 37, 40). Further research is required to determine the reliability and validity of the cDVA test when used in a pediatric mTBI population.

Limitations

Four outliers beyond the 21-day evaluation period were included due to scheduling difficulties. Additionally, it should be noted that the InVision software used in this study identified elevated perception times in 5 individuals (out of the 80 included in DVA analyses) thus affecting the validity of their DVA LogMAR change values. Finally, as limited abnormal observations were present in certain of the outcome measures included in this study, findings of agreement and lack of agreement among these measures must be considered loosely as the kappa values determined were heavily influenced by each individual observation.

Conclusion

Overall, the findings of this study do not demonstrate agreement between symptom-based and performance-based measures of VOR function. Our findings suggest there is value to including both symptom-based measures as well as performance-based measures when assessing VOR function in pediatric mTBI populations. Symptom-based measures, such as the VOMS VOR test, could prove useful in flagging additional systems (cervical spine) that may contribute to disabling sensations provoked (i.e., dizziness and headaches). As little to no agreement was demonstrated between clinical and computerized measures, the role and added value of computerized measures to clinical practice remains unclear. A potential confounding factor that may have been a source of the symptom provocation reported is the cervical spine as nearly half of our participants reported neck pain.

Future directions

Future research to evaluate the role of the cervical spine or perhaps central processing on symptom provocation induced by the VOMS in the presence of normal vestibulo-ocular testing is warranted. Research in pediatric mTBI populations, with a larger sample size, a shorter time since injury and a control group would provide additional clarity and more conclusiveness on the relationship between measures of VOR function included in this study. This will assist clinicians and researchers in selecting the most appropriate tests when assessing the VOR in pediatric mTBI.

References

1. Dewan MC, Rattani A, Gupta S, Baticulon RE, Hung YC, Punchak M, et al. Estimating the global incidence of traumatic brain injury. J Neurosurg. 2018;140(4):1-18.
2. Bryan MA, Rowhani-Rahbar A, Comstock RD, Rivara F. Sports - and recreation-related concussions in US youth. Pediatrics. 2016;138(1).
3. Cross E, Podolak OE, Lockyer J, Corwin DJ, Storey EP, Grady MF, et al. Prevalence of vestibular and vision problems following concussion in children under 12. Am Acad Pediatrics; 2018.
4. Master CL, Master SR, Wiebe DJ, Storey EP, Lockyer JE, Podolak OE, et al. Vision and vestibular system dysfunction predicts prolonged concussion recovery in children. Clin J Sport Med. 2018;28(2):139-45.
5. Master CL, Curry AE, Pfeiffer MR, Metzger KB, Kessler RS, Haarbauer-Krupa J, et al. Characteristics of concussion in elementary school-aged children: Implications for clinical management. J Pediatr. 2020;223:128-35.
6. Suvundra P, Luxon LM. The physiology of equilibrium and its application to the dizzy patient. In: Gleeson M, editor. Basic Sciences, Scott-Browns otolaryngology. 1. 6th ed. Oxford: Butter-Worth-Heinemann; 1997. p. 1-65.
7. O'Reilly R, Grindle C, Zwicky EF, Morlet T. Development of the vestibular system and balance function: differential diagnosis in the pediatric population. Otolaryngol Clin North Am. 2011;44(2):251-71.
8. Mehta Z, Stakiw D. Childhood vestibular disorders. Commun Disord Q. 2004;26(1):5-16.
9. Corwin DJ, Wiebe DJ, Zonfrillo MR, Grady MF, Robinson RL, Goodman AM, et al. Vestibular deficits following youth concussion. J Pediatr. 2015;166(5):1221-5.
10. Ellis MJ, Cordingley D, Vis S, Reimer K, Leiter J, Russell K. Vestibulo-ocular dysfunction in pediatric sports-related concussion. J Neurosurg Pediatr. 2015;16(3):248-55.
11. Ellis MJ, Cordingley DM, Vis S, Reimer KM, Leiter J, Russell K. Clinical predictors of vestibulo-ocular dysfunction in pediatric sports-related concussion. J Neurosurg Pediatr. 2017;19(1):38-45.
12. Hoffer ME, Gottshall KR, Moore R, Balough BJ, Wester D. Characterizing and treating dizziness after mild head trauma. Otol. Neurotol. 2004;25(2):135-8.

13. Suh M, Kolster R, Sarkar R, M, liss B, Ghajar J, et al. Deficits in predictive smooth pursuit after mild traumatic brain injury. J Neurosci Lett. 2006;401(1):108-13.
14. Fife TD, Tusa RJ, Furman JM, Zee DS, Frohman E, Baloh RW, et al. Assessment: Vestibular testing techniques in adult and children. Neurology. 2000;55(10):1431-41.
15. Cheever KM, McDevitt J, Tierney R, Wright WG. Concussion recovery phase affects vestibular and oculomotor symptom provocation. Int J Sports Med. 2018;39(2):141-7.
16. Schneider KJ. Cervicovestibular rehabilitation therapy in sport-related concussion: a randomised controlled trial. Br J Sports Med. 2014;48(17):1294-8.
17. Marshall CM, Vernon H, Leddy JJ, Baldwin BA. The role of the cervical spine in post-concussion syndrome. Phys Sportsmed. 2015;43(3):274-84.
18. Nacci A, Ferrazzi M, Berrettini S, Panicucci E, Matteucci J, Bruschini L, et al. Vestibular and stabilometric findings in whiplash injury and minor head trauma. J Acta Otorhinolaryngol Ital. 2011;31(6):378-89.
19. Reneker JC, Cheruvu VK, Yang J, James MA, Cook CE. Physical examination of dizziness in athletes after a concussion: A descriptive study. Musculoskelet Sci Pract. 2018;34:8-13.
20. Rine RM, Braswell J. A clinical test of dynamic visual acuity for children. Int J Pediatr Otorhinolaryngol. 2003;67(11):1195-201.
21. Kaufman DR, Puckett MJ, Smith MJ, Wilson KS, Cheema R, Landers MR. Test–retest reliability and responsiveness of gaze stability and dynamic visual acuity in high school and college football players. Phys Ther Sport. 2014;15(3):181-8.
22. Ross LM, Helminski JO. Test-retest and interrater reliability of the video head impulse test in the pediatric population. Otol Neurol. 2016;37(5):558-63.
23. Mucha A, Collins MW, Elbin RJ, Furman JM, Troutman-Enseki C, DeWolf RM, et al. A brief vestibular/ocular motor screening (VOMS) assessment to evaluate concussions: preliminary findings. Am J Sports Med. 2014;42(10):2479-86.
24. Carroll L, Cassidy JD, Holm L, Kraus J, Coronado V. Methodological issues and research recommendations for mild traumatic brain injury: the who collaborating centre task force on mild traumatic brain injury. J Rehabil Med. 2004;36(0):113-25.

25. Kontos AP, Sufrinko A, Elbin RJ, Puskar A, Collins MW. Reliability and associated risk factors for performance on the vestibular/ocular motor screening (VOMS) tool in healthy collegiate athletes. Am J Sports Med. 2016;44(6):1400-6.
26. NeuroCom International I. Clinical integration manual- Invision system. Clackamas, OR: NeuroCom International, Inc.; 2008.
27. Herdman SJT, R. J.; Blatt, P.; Suzuki, A.; Venuto, P. J.; Roberts, D. . Computerized dynamic visual acuity test in the assessment of vestibular deficits. Journal Ontol. 1998;19(6):790-6.
28. Schubert MCT, R. J.; Grine, L. E.; and Herdman, S. J. Optimizing the sensitivity of the head thrust test for identifying vestibular hypofunction. Phys Ther. 2004;84(2):151-8.
29. Chang T-P, Zee DS, Kheradmand A. Chapter 2 - Technological advances in testing the dizzy patient: The bedside examination is still the key to successful diagnosis. In: Gleason AT, Kesser BW, editors. Dizziness and Vertigo Across the Lifespan: Elsevier; 2019. p. 9-30.
30. McGarvie LA, MacDougall HG, Halmagyi GM, Burgess AM, Weber KP, Curthoys IS. The video head impulse test (vHIT) of semicircular canal function - Age-dependent normative values of VOR gain in healthy subjects. Front Neurol. 2015;6:154.
31. Schneider KJ, Meeuwisse WH, Palacios-Derflingher L, Emery CA. Changes in measures of cervical spine, vestibulo-ocular reflex, dynamic balance and divided attention following sport-related concussion in elite youth ice hockey players. J Orthop Sports Phys Ther. 2018:1-29.
32. Ogince M, Hall T, Robinson K, Blackmore AM. The diagnostic validity of the cervical flexion–rotation test in C1/2-related cervicogenic headache. J Man Ther. 2007;12(3):256-62.
33. Leung FT, Rahmann A, Mendis MD, Franettovich Smith MM, Sonsearay C, Low Choy N, et al. Vestibulo-ocular dysfunction in adolescent rugby union players with and without a history of concussion. Musculoskelet Sci Pract. 2019;39:144-9.
34. King JE, Pape MM, Kodosky PN. Vestibular Test Patterns in the NICoE Intensive Outpatient Program Patient Population. Mil Med. 2018;183:237-44.
35. Kristjansson E, Treleaven J. Sensorimotor function and dizziness in neck pain: implications for assessment and management. J Orthop Sports Phys Ther. 2009;39(5):364-77.
36. Kennedy E, Quinn D, Chapple C, Tumilty S. Can the neck contribute to persistent symptoms post concussion? A prospective descriptive case series. J Orthop Sports Phys Ther. 2019;49(11):845-54.

37. Riska KM, Hall CD. Reliability and normative data for the dynamic visual acuity test for vestibular screening. J Otol Neurotol. 2016;37:545-52.
38. Marquez C, Lininger M, Raab S. Establishing normative change values in visual acuity loss during the dynamic visual acuity test. Int J Sports Phys Ther. 2017;12(2):227-32.
39. Goebel JA, Tungsiripat N, Sinks B, Carmody J. Gaze stabilization test: A new clinical test of unilateral vestibular dysfunction. Otol Neurotol. 2007;28(1):68-73.
40. Mohammad MT, Whitney SL, Marchetti G, Sparto PJ, Ward B, Furman JM. The reliability and response stability of dynamic testing of the vestibulo-ocular reflex in patients with vestibular disease. J Vestib Res. 2011;21(5).

Chapter 8: Integration of Manuscript #2 and Manuscript #3

Study #2 (Manuscript 2) sought to determine the level of agreement between commonly used symptom-based and performance-based tests of VOR function in a pediatric mTBI population. Our results demonstrated little agreement between the symptom-based measure (VOMS), and the performance-based measures included in this study. Amongst the performance-based measures, two clinical measures demonstrated fair agreement, while those remaining did not exceed slight agreement. It is of importance to note however, that individually, each performance-based measure did identify individuals with abnormal test results according to the predetermined cut-off values. Together, these results seem to indicate that each individual measure could be sensitive to impairments to different components of VOR function. Such findings would indicate that a battery of multiple tests would be best suited to comprehensively assess VOR function.

Understanding the functional impairments to the VOR that result from pediatric mTBI is an important step required in order for a clinician to be able to develop an effective treatment plan. An additional crucial step is understanding the burden and/or impact that these impairments could be imposing on one's day to day life. First, this would provide valuable insight to assist in identifying treatment priorities and flag environmental challenges. Second, this would provide clinicians with an indication as to the level of discomfort likely experienced following certain exercises prescribed in a treatment plan. Understanding this would allow the clinician and patient to work at a threshold that is most effective while increasing the likelihood of patient adherence. Lastly, understanding the burden/impact of functional impairments would allow potential negative psychological, behavioral and/or psychosocial repercussions to be monitored.

Currently the impact of VOR impairments on one's daily experience is poorly understood. While Studies #1 and #2 focused on the assessment of VOR function in controlled settings, when exploring the impact of VOR impairments in a more ecological context, contributions from the OM system should also be considered as daily activities contain a variety of sensory stimuli which will often prompt one's vestibular and visual systems to produce quickly interchanging and/or integrated motor responses from both the VOR and the OM system. In light of this, Study #3 (Manuscript 3) seeks to further understand the impact of VOR and OM impairments on one's more

global vestibular and visual function by determining the extent to which clinician-administered measures of VOR and OM function, relate to patient-reported levels of activity limitations and participation in children and adolescents within 21 days post injury. Findings from this study could support more patient-centered strategies and ecologically relevant treatment solutions to be developed.

Chapter 9: Manuscript 3

Quantifying the relationship between clinician administered measures of vestibulo-ocular reflex and oculomotor function and patient-reported outcome after pediatric mTBI

Adrienne Crampton[a], K. Schneider [b,c,d] , L. Grilli [e] , M. Chevignard[f,g,h], M. Katz-Leurer[i], M. Beauchamp [j,k], C. Debert[l] and I. J. Gagnon[a,e]

[a]*School of Physical and Occupational Therapy, McGill University, Montréal, Canada*

[b]*Sport Injury Prevention Research Centre, Faculty of Kinesiology, University of Calgary, Alberta, Canada*

[c]*Alberta Children's Hospital Research Institute, University of Calgary, Alberta, Canada*

[d]*Hotchkiss Brain Institute, University of Calgary, Alberta, Canada*

[e]*Montreal Children's Hospital-McGill University Health Centre, Montréal, Canada*

[f]*Sorbonne Université, CNRS, INSERM, Laboratoire d'Imagerie Biomédicale, LIB, F-75006, Paris, France*

[g]*Sorbonne Université, GRC 24 Handicap Moteur et Cognitif et Réadaptation, Paris, France*

[h]*Rehabilitation Department for Children with Acquired Neurological Injury and Outreach Team for children and Adolescents with Acquired Brain Injury, Saint Maurice Hospitals, Saint Maurice, France*

[i] *Physical Therapy Department, University of Tel-Aviv, Tel-Aviv, Israel*

[j]*ABC's Laboratory, Ste-Justine Hospital Research Center, Montréal, Canada*

[k]*Department of Psychology, University of Montréal, Montréal, Canada*

[l]*Department of Clinical Neuroscience, University of Calgary, Calgary, Canada*

To be submitted to -

Abstract

Background: Forces involved in mTBI can lead to visual and vestibular impairments. In pediatric mTBI, high rates of abnormalities are observed in vestibulo-ocular reflex (VOR) and oculomotor (OM) function. There remains a lack of understanding of how measured impairments may affect a child or adolescent's daily functioning. **Objectives:** to determine the extent to which clinician administered measures of VOR and OM function relate to patient-reported levels of activity limitations and participation in children and adolescents within 21 days post-injury. **Design:** Cross-sectional design**. Setting:** Tertiary care pediatric hospital. **Participants:** 101 participants with mTBI aged 6 to 18. **Procedures:** Participants were assessed on a battery of VOR and OM tests within 21 days of injury. **Outcome measures:** The Dizziness Handicap Inventory (DHI) and Cardiff Visual Ability Questionnaire (CVAQ) measured patient-reported vestibular and visual function. The Vestibular/Ocular Motor Screening Tool (VOMS) (symptom provocation and performance), Head Thrust Test, computerized Dynamic Visual Acuity (DVA) Test and video Head Impulse Test were administered to assess VOR and OM function. **Analysis:** Linear regression examined the associations between clinician-administered measures of VOR and OM function and patient-reported functional outcomes. **Results:** Our sample consisted of 101 youth (54.4% female) with a mean age of 13.92 (2.63) and mean time since injury of 18.26 (6.16) days. Associations were found between: 1) DHI score and age (1.773, SD:0.01), VOR symptom provocation (18.499, SD:<0.001) and DVA (-29.433, SD:0.03): and 2) version symptom provocation and CVAQ score (0.796, SD:0.01). High abnormal proportions were found on VOMS performance. **Discussion:** The symptom provocation induced by VOR and OM tasks is associated with patient reported functional outcome, highlighting the detrimental impact of symptoms on one's daily functioning. Elevated proportions of abnormal function demonstrated on VOR and version performance variables emphasize a need for both objective and symptom-based measures. **Implications:** Our findings will assist clinicians when interpreting patient-reported measures activity limitation and participation.

Keywords: Mild traumatic brain injury; oculomotor; vestibulo-ocular reflex; measurement; pediatric.

Background

Mild traumatic brain injury (mTBI)

Mild TBI occurs when direct or indirect forces cause the brain to undergo a coup-contrecoup motion inside the skull. The pressure transmitted (1), the linear and rotational forces (2, 3), and the various intrinsic and extrinsic factors (4) all contribute to the diffuse pathology observed in mTBI. Among children and adolescent populations, such injuries are of particular concern as a recent summary of reported rates in pediatric mTBI outlined a 1.3 to 4.0 fold increase between 2003 and 2017 (5).

Vestibulo-ocular and oculomotor functions

Following mTBI, axonal injury from mechanical forces and/or the neurometabolic cascade (causing ionic shifts and disruptions to glucose metabolism) can occur affecting neural structures and connectivity (6, 7). Many pathways, cortical and subcortical structures are vulnerable to this injury due to the various forces involved in the traumatic event (8). The human vestibular and visual systems both include pathways crossing various cortical and subcortical regions of the brain with all four lobes of the brain involved in vision (9-11). Within the vestibular system, the vestibulo-ocular reflex (VOR) is responsible for helping to maintain one's gaze stability when the head is moving. The 3 semi-circular canals found in the inner ear act as the primary sensory stimulus for the VOR. Within the visual system, the oculomotor (OM) system is responsible for controlling many of our eye movements. The coordination of neural circuits across multiple pathways throughout the brain is required to support OM function (12, 13). As VOR and OM function are heavily interconnected, impairments in one often affect the other. Pediatric mTBI impairments to VOR and OM function can often range form 29-69% (14-16).

VOR function facilitates eye movements in equal and opposite direction to head movements (1:1 gain ratio). This allows one to maintain a stable gaze while their head is in movement. Impairments to VOR function have been identified at rates ranging from 43-69% in pediatric mTBI (14, 17-19).

Oculomotor eye movements are composed of both version and vergence eye movements. Versions are conjugate eye movements that keep an image stable while tracking and/or glancing from one object to another (20). Smooth pursuits are the slow eye movements supporting one's ability to

track an object (21, 22), while saccades are rapid ballistic eye movements that allow one to change fixation from one target to another (21, 22). Vergence movements (convergence and divergence) are disconjugate eye movements requiring one's eye to simultaneously adduct and abduct to maintain focus on targets both near and far (23, 24). Deficits to saccades and smooth pursuits in pediatric mTBI samples can range from 29-82% (16, 18, 25) and 33-66% (18, 25, 26) respectively. Deficits to vergence in pediatric samples have been reported between 24-73% (16, 25, 27, 28).

The elevated rates of VOR and OM abnormalities in pediatric mTBI, as well as the important role of these functions to support one's overall vision in basic tasks of daily life has led to a growth of literature on this topic (29-32). When outlining the impact of abnormal VOR and OM function it is particularly important to identify how these abnormalities may affect daily functions supported by the VOR and the OM system.

The impact of VOR and OM impairments

Prior literature in adult populations has explored the impact of VOR and OM impairments to some extent looking at their effects on activities of daily life, quality of life and health status.

Significant correlations between OM measures and the Rivermead Postconcussion Symptoms Questionnaire (RPSQ), the Rivermead Head Injury Follow-up Questionnaire (RHIFQ), as well as the SF-36 Health survey (13) were demonstrated in adults following concussion and with persisting abnormalities in eye movement function. In addition, Wagener and Kreiger (2019) found moderate negative relationships between visual symptoms and both participation and QOL, such as reading, computer use, and driving in adults with acquired brain injury-related OM impairments as measured by the PROMIS Global Health Scale and Assessment of Life Habits (33).

With regards to vestibular patient-reported outcomes, Gotshall et al. (2003) found a significant correlation between the self-reported Dizziness Handicap Inventory (DHI) and the Dynamic Visual Acuity (DVA) test at initial evaluation post-mTBI (34). Finally, when considering vision-related patient-reported outcomes, Suleiman et al. (2019) outlines significant correlation between

convergence insufficiency and the headache, dizziness and nausea item scores of the Rivermead Post-Concussion Questionnaire in adults (35).

In pediatric populations, literature exploring the effects of VOR and OM impairments on overall function is scarce. Recently, a study performed by Howell et al. (2019) separated Post-concussion Symptom Scores into domains, finding longer symptom duration associated with more severe VO domain symptoms in adolescents (36). Trbovich et al. (2019) investigated the use of the Convergence Insufficiency Survey (CISS) to identify adolescents and young adults with receded near point of convergence post-concussion. The CISS was found to have poor sensitivity and poor discriminatory value in patients with concussion (37). Of interest, this study stated that CISS scores may be capturing patients who have more "severe" concussions, additional vision diagnoses and potential vestibular dysfunctions (as there are no concussion grades, this can be interpreted in present times as "complex") (37).

Findings outlined above from Trbovich et al. (2019) and Gottshall et al. (2003) proved to be an important first step comparing a physical OM and VOR test to a construct-specific patient-reported functional outcome measure (respectively). In light of the gaps identified by our short overview of previous literature, our study will begin to address certain of these within the pediatric mTBI population. Our objective is to determine the extent to which clinician administered measures of VOR and OM function, relate to patient-reported levels of activity limitations and participation in children and adolescents within 21 days post-injury.

Methods

This study used a cross-sectional design to determine the extent to which clinician-administered measures of VOR and OM function, relate to patient-reported outcome within 21 days post-injury. A consecutive convenience sample of participants were primarily recruited at a tertiary care pediatric hospital, the Montréal Children's Hospital (McGill University Health Centre) in the emergency department and at the mTBI Program/Concussion Clinic, as well as at the University of Calgary Sport Medicine Centre or the Acute Sport Concussion Clinic (University of Calgary). Assessment took place at the Kids Concussion Lab within this hospital (Montréal participants) or

at the Concussion Lab at the University of Calgary (Calgary participants). This study was approved by the Pediatric panel of the McGill University Health Center Research Ethics Board and by the Conjoint Health Research Ethics Board at the University of Calgary.

Participants: All participants in this study were enrolled in a larger project (SimplyRehab, funded by ERA-NET NEURON). In this study, our sample was composed of 101 French or English-speaking participants aged 6 to 18 and assessed within 21 days of a medically diagnosed mTBI (38). Participants were excluded if they had a: i) history of any TBI in the preceding 6 months or any previous TBI with unresolved symptoms/impairments; ii) presence of comorbidities or related impairments that limit the ability to complete the testing protocol; iii) medications which affect neural adaptation; iv) participants who consented but withdrew prior to baseline assessment. Standard acute concussion care (pain management, observation and/or nausea management, recommendations for early management and return to activities) was received by all participants by their family physician, a pediatrician, a walk-in medical clinic or the emergency department.

Procedures: Eligible participants provided written consent to participate and completed their evaluation within 21 days of injury. Participants completed patient-reported outcome measures online prior to arrival for the in-person assessment. A trained evaluator performed the VOR and OM evaluation, as well as balance and gait assessments, and overall global outcome measures (secondary outcome measures), at the Kids Concussion Lab (Montréal) or the Concussion Lab (Calgary). Sessions lasted approximately 75 minutes.

Outcome measures:

Patient-reported outcome measures - Two patient-reported functional outcome measures were used in this study to represent activity limitations and participation in children and adolescents: i) the Dizziness Handicap Inventory (DHI), which was used to assess patient-reported vestibular function (39). This measure is a reliable and valid (39) 25-item self-assessment tool composed of three sub-scales (physical, emotional and functional), to assess one's perception of the handicap they experience due to dizziness. It is the most widely used measure for individuals with dizziness (40). The version included in this study ensured adapted language for children. DHI scores range from 0 (no self-perceived disability) to 100 (maximum self-perceived disability) points and ii) the

Cardiff Visual Ability Questionnaire for children (CVAQ) was used to assess patient-reported visual function (41). This measure is a reliable 25-item self-assessment tool (in children 7 years and older) with good content validity, construct validity and temporal stability (41), and which characterizes the nature and degree of difficulty experienced daily due to their visual impairment. CVAQ scores range from -2.8 (best score) to 2.9 (worst score) logits. The visual ability reported in this outcome measure specifically pertains to activities and vision-related elements across seven subscales: education, near vision, distance vision, getting around, social interaction, entertainment and sports (41).

Quantified assessments of VOR and OM - The battery of clinical and computerized assessments used to evaluate VOR and OM function in our sample included: i) The Vestibular/Ocular-Motor Screening Tool (42, 43) (VOMS) measuring symptom provocation and performance on VOR and OM tasks; ii) the Head Thrust Test (44) (HTT) clinically measuring VOR response to passive high velocity head thrusts; iii) the video Head Impulse Test (vHIT) measuring VOR response to passive high velocity head thrusts using a computerized measure (ICS Impulse software[3])(45); iv) the computerized Dynamic Visual Acuity (cDVA) test measuring one's ability to maintain visual acuity during active high-frequency head movements (InVision System[4]) (46); and v) the reflexive saccade test measuring the latency of eye-movement response to a series of stimuli presented in the horizontal plane (ICS Impulse software) (45). In addition to the standard administration of the VOMS (recommended by Mucha et al. (26)), our study included clinician-observed performance quantifiers added to each task in order to quantify VOR and OM performance (47).

Our measures evaluated the following variables:

The Vestibular/Ocular-Motor Screening tool evaluated *symptom provocation* induced by the standardized administration/performance of smooth pursuits, horizontal voluntary saccades, vertical voluntary saccades, convergence, horizontal VOR, vertical VOR and visual motion sensitivity (VMS, measuring VOR suppression). *Performance* on all tasks was additionally evaluated as normal or abnormal. Performance was considered abnormal by the evaluator

[3] ICS ® Impulse software, Natus®
[4] NeuroCom® InVision System, Natus®

according to the following criteria: 1) smooth pursuit task – presence of any intruding saccades; 2) horizontal and vertical saccade tasks – presence of any hypometric, hypermetric, long latency or poor conjugacy; 3) convergence task – any abnormality in synchronicity of eye abduction, and convergence greater than 6 cm (average of 3 trials); 4) horizontal and vertical VOR tasks – presence of any catch-up saccades; and 5) visual motion sensitivity task – presence of any inability to maintain gaze on point of fixation.

The Head Thrust test evaluated VOR function through clinician observation of participants' eye movement following short, brisk unpredictable head movements in both left and right directions and with head in 30 degrees flexion. VOR function was considered *abnormal* if catch-up saccades were observed following head thrust.

The NeuroCom InVision System evaluated the left and right DVA of each participant using fixed velocity head movements at 120 degrees/second. Right and left values were averaged due to correlation between the variables. *LogMAR change* values between static visual acuity and DVA measured by the InVision system were used to measure DVA.

The ICS Impulse software evaluated mean left and right *VOR gain* using the video head impulse test (vHIT) delivering 10 impulses/side. This software also evaluated reflexive horizontal saccade performance. *Mean latency* values were obtained from saccades performed horizontally in response to unpredictable laser stimuli appearing in front of the seated participant. Right and left values were averaged due to correlation between the variables.

For the purpose of the analysis the variables from our outcome measures were redefined and categorized. VOR function was categorized as being the response to head-eye movements. OM function was categorized as being version movements (eyes moving in the same direction) and vergence movements (eyes moving in opposition directions). Tables 9.1 and 9.2 provide all variables included in the analysis and their definitions separated by VOR and OM function.

Table 9.1: Variables relating to VOR function.

Variable	Definition of outcome measure	Outcome measure	Unit
VOMS VOR responses			
Symptom provocation	Participant reported increase of ≥ 2 points on four combined 0-10 point symptom scales in horizontal VOR, vertical VOR and/or VMS tasks	VOMS	N/A
Performance	Observed abnormality present as described in outcome measures in horizontal VOR, vertical VOR or VMS tasks	VOMS	N/A
VOR responses			
VOR function	Observed abnormality present in either or both left and right direction for HTT	HTT	N/A
VOR gain	Mean gain value of head to eye movement ratio measured by ICS Impulse software for vHIT in right and left direction	vHIT, ICS software	ratio
DVA	Mean LogMAR value of dynamic visual acuity for head movements to the right and left	cDVA, InVision system	LogMAR

VOMS: vestibular/ocular-motor screening tool; VO: vestibulo-ocular; VOR: vestibulo-ocular reflex; VMS: visual motion sensitivity; HTT: head thrust test; vHIT: video head impulse test; DVA: dynamic visual acuity; cDVA: computerized dynamic visual acuity; N/A: normal/abnormal

Table 9.2: Variables relating to OM function.

Variable	Definition of outcome measure	Outcome measure	Unit
Version movements			
Symptom provocation	Participant reported increase of ≥ 2 points on four combined 0-10 point symptom scales in smooth pursuits, horizontal and/or vertical saccade tasks	VOMS	N/A
Performance	Observed abnormality present as described in outcome measures in smooth pursuits, horizontal and/or vertical saccade tasks	VOMS	N/A
Reflexive Saccades	Mean latency of right and left reflexive saccades	ICS software	ms
Vergence movements			
Symptom provocation	Participant reported increase of ≥ 2 points on a 0-10 symptom scale on measured near point of convergence task	VOMS	N/A
Performance	Inability to symmetrically abduct eyes as thumb moves towards nose. Abnormality observed by clinician.	VOMS	N/A

VOMS: vestibular/ocular-motor screening tool; N/A: normal/abnormal

Analysis: Descriptive statistics were compiled to characterize our sample. Means (SD) and proportions with abnormal tests (or participant reported increase of ≥ 2 points for the VOMS symptom-based outcome) were determined for each outcome measure. Separate linear regression models were used to examine i) the association between clinician-administered measures of VOR function and patient-reported vestibular functional outcomes; and ii) the association between

between clinician-administered measures of OM function and patient-reported visual functional outcomes. Regression models adjusted for potential confounders including sex, age, and time since injury. Model selection was based on AIC (Akaike information criterion). The two initial models included all relevant VOR and OM outcomes (Tables 9.1 and 9.2 above). There were substantial proportions of missing values in vestibular and visual functional outcomes. Multiple imputation (MI) (48, 49) was used to impute missing data. Instead of filling in a single value for each missing value, this Markov chain Monte Carlo technique replaces each missing value with a random sample from the joint distribution based on the observed data and reflects the uncertainty due to missing values. Our regression analysis with multiple imputation was based on 20 copies of imputed data. All analyses were conducted using Statistical Analysis System version 9.4 (SAS Institute, Cary NC). The SAS procedure PROC MI was used to impute the missing values 20 times, and the SAS procedure PROC MIANALYZE was used to analyze the imputed data sets.

Results

Our sample consisted of 101 youth (54.5% female, 45.5% male) with a mean age of 13.92 (SD= 2.63, range= 7-17) years. The mean time from injury to assessment was 18.26 (SD= 6.16, range= 2-38) days. In our sample, 70.30 % of participants sustained their mTBI in the context of sports, 27.7% from recreational play or other activities and 2% from unknown mechanisms. No previous history of mTBI/concussion was reported in 58% of participants (Table 9.3). Peds QL scores ranged from 72.92 (17.28; teenagers) to 92.39 (4.16; young children). Sample mean or abnormal performance proportions on all VOR and OM outcome measures, as well as on additional measures of balance and global outcome can be found in Table 9.4.

Table 9.3: Descriptive characteristics

Variable (N=101 unless otherwise specified)	Mean (SD) or %
Age in years, sample mean (SD)	13.92 (2.63)
Sex, %	
Female	54.5
Male	45.5
Time to initial assessment (days, SD)	18.26 (6.16)
Participants seen in physio prior (>1 week) to assessment	13.9
Any psychiatric disorder**, %	10.0
Any developmental disability***, %	14.0
Personal history of migraines, % (N=100)	14.0
# of previous concussions, %	
0	58.0
1	21.0
2	14.0
3+	7.0
Mechanism of injury, % (N=99)	
Sports	70.3
Recreational play or other	27.7
Unknown	2.0
Location of injury, % (N=95)	
Frontal	25.3
Temporal	21.0
Parietal	14.8
Occipital	26.3
Neck	1.1
Indirect force	8.4
Other body part/multiple locations	11.6
mTBI from less forceful blow than previous TBIs, % (N=40)	55.0
Participants playing a sport competitively, % (N=75)	66.7

mTBI: mild traumatic brain injury

Table 9.4: Means and proportions for outcome measures. Additional balance and global outcome measures

Outcome	Mean (SD) or %	n
Variables included in DHI model		
VOMS VOR symptom provocation, % abnormal	35.79	95
VOMS VOR performance, % abnormal	21.21	99
VOR function, % abnormal	5.10	98
VOR gain, average (left & right), mean (SD)	0.97 (0.09)	91
DVA LogMAR change, average (left & right), mean (SD)	0.29 (0.15)	80
Variables included in CVAQ model		
Version symptom provocation, % abnormal	23.66	93
Version performance, % abnormal	56.70	97
Convergence symptom provocation, % abnormal	21.35	89
Convergence function, % abnormal	12.22	90
Reflexive saccades, mean (SD)	201.71 (35.45)	89
Visual/vestibular functional impact		
DHI total score, mean (SD)	23.63 (19.85)	87
Cardiff total score, mean (SD)	-1.67 (1.13)	90
Balance/vestibulospinal impact		
Average time in seconds tandem walk, mean (SD)	16.88 (6.53)	97
BESS score, mean (SD)	22.61 (8.85)	97
Functional Gait Assessment total, mean (SD)	29.24 (1.26)	93
Global outcome		
Peds QL total score, mean (SD)		
Young Child (5-7 years old)	92.39 (4.16)	4
Child (8-12 years old)	81.06 (15.98)	19
Teen (13-18 years old)	71.92 (17.28)	67
Glasgow outcome scale – extended, mean (SD)	2.32 (0.90)	98
Post-concussion symptoms		
SCAT 5 total, mean (SD)	30.08 (27.21)	71
PCSI total score, mean (SD)		
Young child (5-7)	1.5 (1.92)	4
Child (8-12)	6.95 (8.24)	20
Teen (13-18)	26.38 (24.20)	71

VOMS: vestibular/oculomotor screening tool; VOR: vestibulo-ocular reflex; DVA: dynamic visual acuity; LogMAR: logarithm of the minimum angle of resolution; Cardiff: Cardiff visual ability questionnaire; DHI: Dizziness handicap inventory PCSI: post-concussion symptom inventory; SCAT: sport-concussion assessment tool; DHI: dizziness handicap inventory; Peds QL: pediatric quality of life inventory; BESS: balance error scoring system; FGA: functional gait assessment.

Time since injury, sex and age were included in both MI and non-imputed models. No significant effects were demonstrated by time since injury and sex variables in the MI models. Age demonstrated a statistically significant negative association with DHI score 1.773 (p=0.008). Clinically, this value is not significant considering the minimum detectable change discussed in sections below. Time since injury, sex and age were thus not considered further for the MI model.

Relationship between VOR and functional dizziness-related problems (Table 9.5): Mean DHI score was 23.63 (19.85) demonstrating a self-perceived mild handicap experienced by dizziness. Our MI

model demonstrated that VOR symptom provocation (18.499 (11.312 to 25.686, p<0.001)) and DVA LogMAR change (-29.433 (-56.206 to -2.660, p=0.031) were significantly associated with scores on the DHI. However, while 21.21% of the sample demonstrated abnormalities on VOMS VOR performance, this variable was not associated with DHI score. In addition, neither VOR function nor VOR gain demonstrated associations with DHI score.

Relationship between OM and functional visual problems (Table 9.5): Mean CVAQ score was -1.67 (1.13) logits. As the optimal score for the CVAQ is -2.8 these results indicate the presence of self-perceived difficulties with vision in this sample. Our MI model demonstrated that version symptom provocation was significantly associated with an increase of 0.796 (0.185-1.406, p=0.011) logits on CVAQ. This underlines a negative effect of symptoms induced by version tasks on self-reported visual ability. While 56.7% of the sample demonstrated abnormalities on VOMS version performance this variable was not associated with CVAQ score. No associations were shown by convergence and reflexive saccade variables.

While both imputed and non-imputed models were considered, the MI model was selected for the following discussion as it presents more complete and thus unbiased data. Additional information can be found in Table 9.4 (means and proportions for variables included in the initial model) and Table 9.5 (reduced MI model). Values found to be significant in the original non-imputed models can be found in Table A3.1 (Appendix 3).

Table 9.5: Reduced multiple imputation models

Variable	Estimate	p-value	Lower & upper control limit means
DHI			
Age	1.773	(0.008)*	0.473 to 3.073
Sex	2.406	(0.488)	-4.393 to 9.204
Time since injury	-0.381	(0.179)	-0.937 to 0.175
VOR symptom provocation	18.499	(<0.001)*	11.312 to 25.686
DVA LogMAR change	-29.43	(0.031)*	-56.206 to -2.660
CVAQ			
Age	0.060	(0.168)	-0.025 to 0.144
Sex	0.191	(0.413)	-0.266 to 0.648
Time since injury	-0.035	(0.055)	-0.070 to 0.001
Version symptom provocation	0.796	(0.011)*	0.185 to 1.406

DHI: Dizziness handicap inventory; CVAQ: Cardiff visual ability questionnaire; VO: Vestibulo-ocular; DVA: Dynamic visual acuity; LogMAR: logarithm of the minimum angle of resolution

Discussion

The objective of this study was to determine the extent to which clinician administered measures of VOR and OM function, relate to patient-reported levels of activity limitations and participation in children and adolescents within 21 days post-injury. Our findings showed that significant associations could be identified i) between VOR symptom provocation as well as DVA LogMAR change and total DHI score and ii) between version symptom provocation and CVAQ score.

Association between VOMS VOR symptom provocation and DHI score

The significant association found between VOR symptom provocation and the DHI demonstrates that if a participant reported an increase of ≥ 2 points on four combined 0-10 point symptom scales following a VOMS VOR and/or VOR suppression task, the DHI total score would increase by 18.50 points. Considering that a score greater than 10 on the DHI tends to prompt patient referral to a specialist (30), that minimal detectable/important change ranges from 11-17 points (50, 51) and that scores from 0-30 indicate mild impairments (52), this finding is both statistically and clinically significant. As the DHI measures self-perceived handicap from dizziness, the association highlights a burden imposed by symptom provocation induced when performing movements stimulating a VOR response. It would seem that such symptoms prove debilitating in children and adolescents due to increased perceived dizziness. Considering our sample's mean score on the DHI was 23.63 (SD:19.85), the magnitude of the association (18.50 points) is of clinical importance. As DHI subscale scores can be calculated (emotional, physical and functional), future research contributions could explore the relationship of each subscale with VOR function to determine if one specific subscale is driving the association identified in this study.

Association between DVA and DHI score

The final significant association in this first model was demonstrated between averaged DVA change scores and the DHI. The model estimate ($p=0.031$) indicates that an increase of 0.1 LogMAR in DVA change score would result in -2.943 points on the total DHI score. While statistically significant, this finding is not clinically significant as it is well below the minimal detectable/important change previously stated. This finding was deemed negligible at this time,

however future studies could explore potential associations with DHI subscale in order to confirm the absence of an association.

Association between version symptom provocation and CVAQ score

The association between version symptom provocation and CVAQ score indicates that if children or adolescents report an increase of ≥ 2 points on four combined 0-10 point symptom scales following a VOMS OM version task, the CVAQ score would increase by 0.796 points, demonstrating an increased difficulty in perceived visual ability. As there is currently no literature on minimal clinically-relevant change, further research is needed to explore the clinical significance of this association. Proportional to the overall score range (2.9 + 2.8 = 5.7) the magnitude of the association would represent 14% of the overall score range.

The value of including objective performance-based measures of VOR and OM function

At the present time, the VOR and OM components of the VOMS tool look at symptom provocation and measured near point of convergence to screen for possible concussion (26). Emerging literature has questioned the usefulness of relying solely on symptom provocation due to the lack of objectiveness, precision and reliability (34, 53-55), suggesting more objective measures may be beneficial in order to quantify deficits (32, 34, 56). For this reason, our study included the quantified measurement of VOR and OM eye movements through clinician-observed abnormalities and computerized measurements. Of importance, while our sample demonstrated high abnormal proportions on VOR performance (21.21%, Table 9.4) and version performance (56.70%), neither (respectively) associated with the DHI or the CVAQ total score (Table 9.5).

The presence of an association between the patient-reported measures and the symptom-based measures, but not with the performance-based measures is of interest. This observation may reflect the subjective and more person-dependent nature of both the patient-reported outcome measures included and the symptom-reporting. The DHI measures *self-reported handicap* experienced by dizziness and the CVAQ measures visual ability in activities *most important* to this population. Considering the subjectivity of both measures, a young individual's response when completing them may be primarily driven by the more noticeable feelings of discomfort or "symptoms", thus explaining the association demonstrated. The performance-based abnormalities may prove to be

more challenging to recognize and therefore more challenging to report on patient-reported outcome measures such as the DHI or CVAQ.

For such reasons, the use of clinical performance-based measures to complement symptom-based measures when assessing VOR and OM systems in pediatric mTBI populations is encouraged (57). Our findings demonstrate a benefit to including both performance-based measures and symptom-based assessments. The abnormal performance-based findings on the VOMS can provide more objective information to direct further VOR and visual evaluation. Meanwhile, measures of symptom provocation induced by relevant tasks can provide valuable insight on the burden/handicap experienced by a patient in their day-to day life. To add weight to this discussion point, our group provides descriptive characteristics of our sample (Figures A4.1, A4.2, A4.3, Appendix 4) according to three sub-groups: *1) those demonstrating symptom provocation and abnormal function; 2) those demonstrating symptom provocation, yet normal function; and 3) those demonstrating no symptom provocation, but abnormal function.* The characteristics reinforce previous findings demonstrating the detrimental impact of symptoms on quality of life and more global measures such as the PedsQL, the SCAT-5, and Glasgow outcome score (33).

For a clinician, it is important to understand both how a patient is experiencing their injury and to address the underlying functional abnormalities. Prioritizing targeted treatment that reduces one's symptoms experienced all while working on the rehabilitation of specific functions is of great benefit to the patient's overall quality of life and ability to complete daily activities. In particular, vestibular rehabilitation therapy, emphasizing habituation and adaptation exercises, is a viable option for individuals with dizziness and impaired gaze stability (58, 59), addressing both symptoms and functional impairments. More recently, such approaches have been recommended in mTBI populations to desensitize one's response to head and body motion (habituation) as well as activate alternate neural pathways (adaptation) to support gaze stability (60, 61). As such patient-centered active treatment strategies can prove effective, motivating and engaging for patients, they should be further developed and validated within pediatric mTBI populations.

Limitations

A limitation of this study is the natural recovery that may have occurred in our sample due to our mean time since injury, as well as a potential small treatment effect in 14 participants that were seen by a physiotherapist prior to evaluation. In order to increase recruitment, our average time since injury was well into the sub-acute stage of mTBI and four outliers beyond the 21-day evaluation period were included due to scheduling difficulties. It is possible that these limitations contribute to our sample having lower rates of symptom provocation or impairments in VOR and OM variables included. Finally, the validity of five of the DVA LogMAR change values included may be questionable due to prolonged perception times noted by the InVision software.

Conclusion

Our findings demonstrate an association between symptom provocation induced by a VOR and/or VOR suppression task and the DHI as well as between symptom provocation induced by a VOMS version task and the CVAQ. Despite a notable portion of our sample displaying abnormalities in objectively measured VOMS VOR and version performance, these variables did not associate with the DHI and CVAQ. Our findings highlight the functional burden of symptoms experienced, when considering activity limitations and participation, in a pediatric mTBI sample. This reinforces the urgent need to further develop targeted treatment approaches to reduce VOR- and OM-related symptoms experienced in pediatric mTBI. Further exploring treatment approaches promoting habituation and adaptation in this young population may well support their return to activities of daily life and encourage a better overall quality of life.

Future Directions

To more specifically understand the role of the symptom provocation reported in this population, future studies using regression analyses would benefit from including each variable of the VOMS separately, and further by symptom type (i.e., smooth pursuit, dizziness). Additionally, as clinical practice is beginning to look at abnormalities in performance and symptom provocation in the VOMS, it would be beneficial to measure the statistical correlation between the two. Obtaining a

precise understanding of the underlying pathophysiology driving symptom provocation will inform targeted treatment approaches to minimize VOR and OM symptom burden in pediatric mTBI. Including precise objective measures when also recording participant-reported symptom-increase may allow future studies to correlate symptom-increase following specific eye movement tasks with mapped neural pathways associated with those eye movements.

References

1. Pinto PS, Meoded A, Poretti A, Tekes A, Huisman TAGM. The unique features of traumatic brain injury in children. Review of the characteristics of the pediatric skull and brain, mechanisms of trauma, patterns of injury, complications, and their imaging findings-part 2. J Neuroimaging. 2012;22(2):e18-e41.

2. Bandak FA, Ling G, Bandak A, De Lanerolle NC. Chapter 6 - Injury biomechanics, neuropathology, and simplified physics of explosive blast and impact mild traumatic brain injury. In: Grafman J, Salazar AM, editors. Handbook of Clinical Neurology. 127: Elsevier; 2015. p. 89-104.

3. Guskiewicz KM, Broglio SP. Chapter 10 - Acute sports-related traumatic brain injury and repetitive concussion. In: Grafman J, Salazar AM, editors. Handbook of Clinical Neurology. 127: Elsevier; 2015. p. 157-72.

4. Schneider KJ, Emery CA, Black A, Yeates KO, Debert CT, Lun V, et al. Adapting the dynamic, recursive model of sport injury to concussion: An individualized approach to concussion prevention, detection, assessment, and treatment. J Orthop Sports Phys Ther. 2019;49(11):799-810.

5. Keays G, Friedman D, Gagnon I, Beaudin M. Determining the accuracy of the Canadian hospitals injury reporting and prevention program for the representation of the rates of mild traumatic brain injuries in Quebec. Health Promotion and Chronic Disease Prevention in Canada [Internet]. 2019; 39(11):[291-7 pp.].

6. Dixon CE, Taft WC, Hayes RL. Mechanisms of mild traumatic brain injury. J Head Trauma Rehabil. 1993;8(3):1-12.

7. Giza CC, Hovda DA. The Neurometabolic Cascade of Concussion. J Ath Train. 2001;36(3):228-35.

8. Johansson J, Nygren de Boussard C, Oqvist Seimyr G, Pansell T. The effect of spectacle treatment in patients with mild traumatic brain injury: a pilot study. J Clin Exp Optom. 2017;100(3):234-42.

9. Helvie RE. Disruptions in physical substrates of vision following traumatic brain injury 2010 In: Traumatic Brian Injury - Rehabilitation, treatment, case management [Internet]. Boca Raton, FL CRC Press, Taylor & Francis Group 3rd. [307-55].

10. Suter PS. Rehabilitation and management of visual dysfunction following traumatic brain injury. 2010 In: Traumatic Brain Injury - Rehabilitation, treatment, case management [Internet]. Boca Ranton, FL CRC Press, Taylor & Francis Group 3rd. [307-55].
11. Kelts EA. Traumatic brain injury and visual dysfunction: a limited overview. NeuroRehabilitation. 2010;27(3):223-9.
12. Cifu DX, Wares JR, Hoke KW, Wetzel PA, Gitchel G, Carne W. Differential eye movements in mild traumatic brain injury versus normal controls. J Head Trauma Rehabil. 2015;30(1):21-8.
13. Heitger MH, Jones RD, Macleod AD, Snell DL, Frampton CM, Anderson TJ. Impaired eye movements in post-concussion syndrome indicate suboptimal brain function beyond the influence of depression, malingering or intellectual ability. J Brain Inj. 2009;132:2850-70.
14. Ellis MJ, Cordingley DM, Vis S, Reimer KM, Leiter J, Russell K. Vestibulo-ocular dysfunction in pediatric sports-related concussion. J Neurosurg Pediatr. 2015;16(3):248-55.
15. Ellis MJ, Cordingley DM, Vis S, Reimer KM, Leiter J, Russell K. Clinical predictors of vestibulo-ocular dysfunction in pediatric sports-related concussion. J Neurosurg Pediatr. 2017;19(1):38-45.
16. Master CL, Scheiman M, Gallaway M, Goodman A, Robinson RL, Master SR, et al. Vision diagnoses are common after concussion in adolescents. Clin Pediatr (Phila). 2016;55(3):260-7.
17. Corwin DJ, Wiebe DJ, Zonfrillo MR, Grady MF, Robinson RL, Goodman AM, et al. Vestibular deficits following youth concussion. J Pediatr. 2015;166(5):1221-5.
18. Master CL, Master SR, Wiebe DJ, Storey EP, Lockyer JE, Podolak OE, et al. Vision and vestibular system dysfunction predicts prolonged concussion recovery in children. Clin J Sports Med. 2018;28(2):139-45.
19. Gray M, Wilson JC, Potter M, Provance AJ, Howell DR. Female adolescents demonstrate greater oculomotor and vestibular dysfunction than male adolescents following concussion. Phys Ther Sport. 2020;42:68-74.
20. Strupp M, Kremmyda O, Adamczyk C, Bottcher N, Muth C, Yip CW, et al. Central ocular motor disorders, including gaze palsy and nystagmus. J Neurol. 2014;261 Suppl 2:S542-58.

21. Liversedge SP, Gilchrist ID, Everling S. The Oxford handbook of eye movements. Oxford: Oxford University Press; 2011.
22. Orban de Xivry J-J, Lefèvre P. Saccades and pursuit: two outcomes of a single sensorimotor process. J Physiol. 2007;584(1):11-23.
23. Ventura RE, Balcer LJ, Galetta SL. The neuro-ophthalmology of head trauma. Lancet Neurol. 2014;13(10):1006-16.
24. Singman EL. Automating the assessment of visual dysfunction after traumatic brain injury. Med Instrum. 2013;1(1).
25. Reneker JC, Cheruvu VK, Yang J, James MA, Cook CE. Physical examination of dizziness in athletes after a concussion: A descriptive study. Musculoskelet Sci Pract. 2018;34:8-13.
26. Mucha A, Collins MW, Elbin RJ, Furman JM, Troutman-Enseki C, DeWolf RM, et al. A brief vestibular/ocular motor screening (VOMS) assessment to evaluate concussions: preliminary findings. Am J Sports Med. 2014;42(10):2479-86.
27. Storey EP, Master SR, Lockyer JE, Podolak OE, Grady MF, Master CL. Near point of convergence after concussion in children. Optom Vis Sci. 2017;94(1):96-100.
28. Cross E, Podolak OE, Lockyer J, Corwin DJ, Storey EP, Grady MF, et al. Prevalence of vestibular and vision problems following concussion in children under 12. Am Acad Pediatr. 2018.
29. Hunt AW, Mah K, Reed N, Engel L, Keightley M. Oculomotor-based vision assessment in mild traumatic brain injury: A systematic review. J Head Trauma Rehabil. 2016;31(4):252-61.
30. Kontos AP, Deitrick JM, Collins MW, Mucha A. Review of vestibular and oculomotor screening and concussion rehabilitation. J Athl. Train. 2017;52(3):256-61.
31. Whitney SL, Sparto PJ. Eye movements, dizziness, and mild traumatic brain injury (mTBI): A topical review of emerging evidence and screening measures. J Neurol Phys Ther. 2019;43:International Conference on Vestibular Rehabilitation:S31-S6.
32. Howell DR, Brilliant AN, Storey EP, Podolak OE, Meehan WP, 3rd, Master CL. Objective eye tracking deficits following concussion for youth seen in a sports medicine setting. J Child Neurol. 2018;33(12):794-800.
33. Wagener SG, Kreiger R. Participation and quality of life for persons with oculomotor impairments after acquired brain injury. Br J Occup Ther. 2019;82(8):475-84.

34. Gottshall K, Drake A, Gray N, McDonald E, Hoffer ME. Objective vestibular tests as outcome measures in head injury patients. Laryngoscope. 2003;113(10):1746-50.
35. Suleiman A, Lithgow BJ, Anssari N, Ashiri M, Moussavi Z, Mansouri B. Correlation between ocular and vestibular abnormalities and convergence insufficiency in post-concussion syndrome. J Neuro Ophthalmol. 2019.
36. Howell DR, Kriz P, Mannix RC, Kirchberg T, Master CL, Meehan III WP. Concussion symptom profiles among child, adolescent, and young adult athletes. Clin J Sport Med. 2019;29(5):391-7.
37. Trbovich AM, Sherry NK, Henley J, Emami K, Kontos AP. The utility of the convergence insufficiency symptom survey (CISS) post-concussion. J Brain Inj. 2019;33(12):1545-51.
38. Carroll L, Cassidy JD, Holm L, Kraus J, Coronado V. Methodological issues and research recommendations for mild traumatic brain injury: the who collaborating centre task force on mild traumatic brain injury. J Rehabil Med. 2004;36(0):113-25.
39. Treleaven J. Dizziness handicap inventory (DHI). Aust J Physiother. 2006;52(1):67.
40. Mutlu B, Serbetcioglu B. Discussion of the dizziness handicap inventory. J Vestib Res. 2013;23(6):271-7.
41. Khadka J, Ryan B, Margrain TH, Court H, Woodhouse JM. Development of the 25-item cardiff visual ability questionnaire for children (CVAQC). Br J Ophthalmol. 2010;94(6):730-5.
42. Mucha A, Collins MW, Elbin RJ, Furman JM, Troutman-Enseki C, DeWolf RM, et al. A brief vestibular/ocular motor screening (VOMS) assessment to evaluate concussions: preliminary findings. Am J Sports Med. 2014;42(10):2479-86.
43. Kontos AP, Sufrinko A, Elbin RJ, Puskar A, Collins MW. Reliability and associated risk factors for performance on the vestibular/ocular motor screening (VOMS) tool in healthy collegiate athletes. Am J Sports Med. 2016;44(6):1400-6.
44. Schubert MCT, RJ; Grine, LE; and Herdman, SJ. Optimizing the sensitivity of the head thrust test for identifying vestibular hypofunction. Phys Ther. 2004;84(2):151-8.
45. McGarvie LA, MacDougall HG, Halmagyi GM, Burgess AM, Weber KP, Curthoys IS. The video head impulse test (vHIT) of semicircular canal function - age-dependent normative values of VOR gain in healthy subjects. Front Neurol. 2015;6:154.

46. NeuroCom International I. Clinical integration manual- Invision system. Clackamas, OR: NeuroCom International, Inc. ; 2008.
47. Sharma I, Codd C, Virani S, Emery C, Schneider KJC. Clinical assessment of vestibulo-ocular and oculomotor function in youth ice hockey players compared to symptom provocation on the vestibular/ocular motor screening tool. Clin J Sports Med. 2018;28(3):e71-2.
48. Schafer JL. Multiple imputation: a primer. J Stat Methods Med Res. 1999;8(1):3-15.
49. Rubin DB. Inference and missing data. J Biometrika. 1976;63(3):581-92.
50. Tamber AL, Wilhelmsen KT, Strand LI. Measurement properties of the dizziness handicap inventory by cross-sectional and longitudinal designs. Health Qual Life Outcomes. 2009;7:101.
51. Jacobson GP, Newman CW. The development of the dizziness handicap inventory. Arch Otolaryngol Head Neck Surg. 1990;116(4):424-7.
52. Whitney SL, Wrisley DM, Brown KE, Furman JM. Is Perception of handicap related to functional performance in persons with vestibular dysfunction? Otol Neurotol. 2004;25(2):139-43.
53. Iverson GL, Silverberg ND, Mannix R, Maxwell BA, Atkins JE, Zafonte R, et al. Factors associated with concussion-like symptom reporting in high school athletes. JAMA Pediatr. 2015;169(12):1132-40.
54. Asken BM, Snyder AR, Smith MS, Zaremski JL, Bauer RM. Concussion-like symptom reporting in non-concussed adolescent athletes. Clin Neuropsychol. 2017;31(1):138-53.
55. Hunfalvay M, Roberts CM, Murray NP, Tyagi A, Barclay KW, Bolte T, et al. Vertical smooth pursuit as a diagnostic marker of traumatic brain injury. Concussion. 2020;5(1).
56. Murray NG, Szekely B, Islas A, Munkasy B, Gore R, Berryhill M, et al. Smooth pursuit and saccades after sport-related concussion. J Neurotrauma. 2020;37(2):340-6.
57. Master CL, Curry AE, Pfeiffer MR, Metzger KB, Kessler RS, Haarbauer-Krupa J, et al. Characteristics of concussion in elementary school-aged children: implications for clinical management. J Pediatr. 2020;223:128-35.
58. Deveze A, Bernard-Demanze L, Xavier F, Lavieille JP, Elziere M. Vestibular compensation and vestibular rehabilitation. Current concepts and new trends. Neurophysiol Clin. 2014;44(1):49-57.

59. Tee LH, Chee NW. Vestibular rehabilitation therapy for the dizzy patient. Ann Acad Med Singapore. 2005;34(4):289-94.
60. Alsalaheen BA, Whitney SL, Mucha A, Morris LO, Furman JM, Sparto PJ. Exercise prescription patterns in patients treated with vestibular rehabilitation after concussion. Physiother Res Int. 2013;18(2):100-8.
61. Szczupak M, Hoffer ME, Gottshall K, Viirre ES. Vestibular consequences of mild traumatic brain injury (mTBI). In: Tsao JW, editor. Traumatic Brain Injury: A Clinician's Guide to Diagnosis, Management, and Rehabilitation. Cham: Springer International Publishing; 2020. p. 151-8.

Chapter 10: Integration of Manuscript #3 and Manuscript #4

Study #3 (Manuscript 3) determined the extent to which clinician-administered measures of VOR and OM function, relate to patient-reported levels of activity limitations and participation in children and adolescents within 21 days post-injury. The study demonstrated a significant association between symptom provocation induced by a VOR and/or VOR suppression task and patient-reported vestibular functioning as well as between symptom provocation induced by eye movements during certain OM tasks and patient-reported visual functioning. These results underline the significant burden imposed by such symptoms on one's daily functioning. Additionally, a large proportion of our sample demonstrated poor performance during VOR and OM version tasks of the VOMS. While those impairments were not significantly related to patient-reported activity limitations or participation restrictions, such findings support the value of adding performance indicators when administering the VOMS in order to increase sensitivity of this tool to performance impairments.

The associations between measures as well as the proportions of children with impairments highlighted in this study reinforce the findings in Study 2 (manuscript 2), by once again underlining the importance of considering both symptom-based and performance-based outcome measures when assessing VOR function in pediatric mTBI. Additionally, the associations found in Study 3 (manuscript 3) may improve the interpretation of symptom-based and patient-reported outcomes in a manner that promotes effective patient-centered clinical care.

While such findings allow initial observations to be made and recommendations to be developed, an increased understanding of how VOR function and its supportive OM system evolve over a prolonged time period following pediatric mTBI is required. This would contribute valuable insight to clinicians supporting patients with longer rehabilitation periods. Additionally, understanding the evolution over time will identify potential clinical considerations to account for when making return to learn/play recommendations and monitoring the re-integration of children and adolescents recovering from mTBI.

In order to address this gap, Study 4 (Manuscript 4) determines the extent to which performance on clinical and computerized tests of VOR function and of its supportive OM system vary over

time in children and adolescents at 21 days, 3 months and 6 months after a mild TBI. This study also determines the proportion of children and adolescents with mTBI presenting with abnormal scores on VOR and OM tests at each time points. This study will allow us to identify whether specific subcomponents demonstrate change over time and/or if they identify greater proportions of children with impairments. Previous literature published in this field has almost exclusively concluded follow-up at medical clearance response and/or return to play. As our study did not include timepoints determined according to recovery, we provide a unique longitudinal representation of the evolution of VOR function and its supporting OM system over time.

Chapter 11: Manuscript 4

Characterizing the evolution of vestibulo-ocular reflex function over time in children and adolescents after a mild traumatic brain injury

Adrienne Crampton[a], K. Schneider [b,c,d] , L. Grilli [e] , M. Chevignard[f,g,h], M. Katz-Leurer[i], M. Beauchamp [j,k], C. Debert[l] and I. J. Gagnon[a,e]

[a]*School of Physical and Occupational Therapy, McGill University, Montréal, Canada*

[b]*Sport Injury Prevention Research Centre, Faculty of Kinesiology, University of Calgary, Alberta, Canada*

[c]*Alberta Children's Hospital Research Institute, University of Calgary, Alberta, Canada*

[d]*Hotchkiss Brain Institute, University of Calgary, Alberta, Canada*

[e]*Montreal Children's Hospital-McGill University Health Centre, Montréal, Canada*

[f]*Sorbonne Université, CNRS, INSERM, Laboratoire d'Imagerie Biomédicale, LIB, F-75006, Paris, France*

[g]*Sorbonne Université, GRC 24 Handicap Moteur et Cognitif et Réadaptation, Paris, France*

[h]*Rehabilitation Department for Children with Acquired Neurological Injury and Outreach Team for children and Adolescents with Acquired Brain Injury, Saint Maurice Hospitals, Saint Maurice, France*

[i] *Physical Therapy Department, University of Tel-Aviv, Tel-Aviv, Israel*

[j]*ABC's Laboratory, Ste-Justine Hospital Research Center, Montréal, Canada*

[k]*Department of Psychology, University of Montreal, Montréal, Canada*

[l]*Department of Clinical Neuroscience, University of Calgary, Calgary, Canada*

To be submitted to -

Abstract

Background: Impairments to vestibulo-ocular reflex function (VOR) function following pediatric mTBI have been demonstrated but are poorly understood. Such impairments can be associated with more negative prognosis, affecting one's physical and mental well-being, emphasizing the need to more fully understand how these evolve. **Objectives:** i) to determine the extent to which performance on clinical and computerized tests of VOR function and of its supportive OM system vary over time in children and adolescents at 21 days, 3 months, and 6 months after a mTBI; ii) to determine the proportion of children and adolescents with mTBI presenting with abnormal scores on VOR and OM tests at each timepoint. **Design:** Prospective longitudinal design **Setting:** Tertiary care pediatric hospital. **Participants:** 36 participants with mTBI aged 6 to 18. **Procedures:** Participants were assessed on a battery of VOR and OM tests within 21 days of injury. **Outcome measures:** clinical measures included the *Vestibular/ocular motor screening tool (VOMS)* measuring the symptom provocation induced and performance on VOR and OM tasks; computerized measures included a *reflexive saccade test* measuring response latency, a *video head impulse test* measuring VOR gain, and a *dynamic visual acuity test* measuring LogMAR change. **Analysis:** Generalized estimating equations (parameter estimates and odd ratios) estimated the effect of time. Proportions above and below normal cut-off values were determined. **Results:** Our sample consisted of 52.8% females, with a mean age 13.98 (2.4) years and assessed on average 19.07 (8-33) days following injury. An effect of age on visual motion sensitivity (OR 1.43, p=0.03) and of female sex on near point of convergence (OR 0.19, p=0.03) was identified. Change over time was demonstrated by VOMS global symptom provocation (OR 9.90, p=0.012), vertical smooth pursuit performance (OR 4.04, p=0.03), vertical voluntary saccade performance (OR 6.06, p=0.005) and right VOR gain (0.068, p=0.013). Version performance and VOR symptom provocation showed high abnormal proportions at initial assessment. **Discussion:** Results indicate impairments to the VOR pathway may be present, driving symptom provocation. Vertical version findings underline the need to include relevant tasks in assessment batteries. **Implications:** Findings demonstrate the added value of including symptom and performance-based measures when assessing the VOR, as well as the relative stability of constructs measured beyond 3 months post mTBI.

Key words: Mild traumatic brain injury, pediatric, vestibulo-ocular reflex, oculomotor, assessment.

Background

Children and adolescents are susceptible to mTBI/concussion (1, 2) with rates of pediatric mTBI estimated between 1.1-1.9 million each year in the USA (3). This may be due to anatomical, physiologic and developmental factors (4) (i.e. continuing maturation (5), incomplete myelination of the brain and a more flexible skeletal structure (4, 6)). Environmental factors and activities of daily life in this age group can also contribute to their overall exposure to potentially high-risk situations. While most recover within 2-4 weeks, approximately one third of individuals can suffer persistent symptoms 3 months post-mTBI (7) and 12-14% will present symptoms for greater than 1 year post-mTBI (8, 9). Persisting symptoms can put children and adolescents at risk of negative physical and/or psychosocial repercussions resulting from a longer recovery process.

While mTBI can lead to a wide range of disturbances, the impact on vestibulo-ocular reflex (VOR) function in pediatric mTBI has recently attracted a large amount of interest. Relevant literature has outlined high rates of abnormalities and/or impairments to VOR function ranging from 43-69% (10-13). Moreover, similar rates of impairments (24-73%) have also been reported for eye movements involved in supporting VOR function and controlled by the oculomotor (OM) system (14-17). Such a high prevalence of abnormalities and/or impairments can have a significant impact on one's ability to navigate their environment and participate in recreational activities. In children and adolescents this may consequently affect their overall mental, physical, emotional and psychosocial health and wellbeing.

The VOR and the ability to suppress this reflex allows one to maintain gaze stability on static and dynamic targets respectively while the head is in motion. Uncompromised functioning of the OM system enables the eyes to move to allow for clear, binocular vision, as well as maintain un-impaired tracking and smooth movements of the eyes (18). Such eye movements are heavily involved in supporting the VOR responses required when navigating one's environment and performing activities of daily life.

Impairments and/or symptoms related to VOR function and the OM system present in the acute phase of recovery following pediatric mTBI are leading predictors of prolonged recovery (11, 19).

However, their underlying pathophysiology and evolution over time is poorly understood. Such questions have prompted recommendations for studies to measure VOR and OM function over time beyond the acute and subacute phase (20, 21) to better understand their overall recovery process. While a small number of studies have started to address this recommendation in pediatric mTBI populations, the relevant studies almost exclusively end follow-up assessments at time of medical clearance and/or return to play (11, 12, 19, 22-24) and their focus has mostly been limited to sport-related concussion (12, 19, 22-25). In addition, these studies display much heterogeneity with regards to the time from injury to initial evaluation including samples with initial assessment in the acute time period (<10 days) (23, 24), the sub-acute time period (<21 days) (11, 12, 19, 22) and some approaching the more sub-acute to chronic period (>21days to >1 month) (11, 25). Such limitations should be addressed to: 1) understand the evolution of VOR and OM function post mTBI during and beyond the acute/sub-acute phase in order to determine further characteristics of impairments that may persist; and 2) in order to confirm that VOR and OM functions indeed remain uncompromised in the initial period of one's re-integration to sport and daily life.

While VOR and OM studies in pediatric mTBI often include only two timepoints of interest in their results (initial clinical presentation and time to recovery) and are performed retrospectively (11, 12, 19, 22), two recent studies included data from multiple timepoints. The first by Sinnott et al. (2019), assessed VOR and OM function initially within 10 days, at 11-21 days and followed 63 adolescent athletes with concussion to medical recovery (time to recovery of 3 groups ranging from 22.95 to 34.94 days) (23). This study provides assessments in the acute, subacute and prolonged/persistent phase. However, its generalizability remains limited (athletic populations and sport-related concussion) and it only represents the evolution of these functions to medical clearance. The second, by Zaslow et al. (2020), included 3 timepoints: initial evaluation, return to play clearance and one month following RTP clearance. This study produced findings demonstrating stable OM function beyond RTP clearance. However, limitations to this study were a lack of VOR variables, a very small sample size (13 adolescents) and a restricted demographic (athletes) (25).

Overall, there are very few studies examining VOR function over time in youth post-mTBI (26, 27), particularly in younger school aged children (6-12 years) and non-athletes (28). More fully

understanding the specific impairments that may compromise VOR function following mTBI, the rate at which such impairments present, as well as characterizing how they resolve, will help guide treatments delivered to ultimately hasten the return to activities of daily living in these youths.

The primary objective of this study was to determine the extent to which performance on clinical and computerized tests of VOR function, and of its supportive OM system, varies over time in children and adolescents at 21 days, 3 months, and 6 months after a mild TBI. The secondary objective of this study was to determine the proportion of children and adolescents with mTBI presenting with abnormal scores on VOR and OM tests at each timepoint when compared to cut-off scores pre-determined from published literature.

Methods

This study used a prospective longitudinal design to characterize the evolution of children and adolescents' performance in VOR function and its supportive OM system within 21 days of injury, as well as 3 months and 6 months after a mTBI. A consecutive convenience sample of participants were recruited at a tertiary care pediatric trauma center, the Montréal Children's Hospital (McGill University Health Center) in the emergency department and the Concussion Clinic as well as at the University of Calgary Sport Medicine Centre or the Acute Sport Concussion Clinic (University of Calgary). All assessments took place at the Kids Concussion Lab within the same institution (Montréal participants) or at the Concussion Lab at the University of Calgary (Calgary participants). The study was approved by the Pediatric panel of the McGill University Health Center Research Ethics Board and by the Conjoint Health Research Ethics Board at the University of Calgary.

Participants: Participants in this study were a subsample of children and adolescents aged 6 to 18, diagnosed with an mTBI (29) and enrolled in a larger project (SimplyRehab, funded by an ERA-NET NEURON grant) who had completed 3 planned evaluations during the follow-up period. We excluded from the study individuals with any of the following: i) history of a previous TBI in the preceding 6 months or any previous TBI with unresolved symptoms/impairments; ii) presence of comorbidities that prevent or limit the participant's ability to complete the assessment; iii)

medications which affect neural adaptation; iv) participants who consented but withdrew prior to initial assessment. All participants received standard acute concussion care from either the emergency department, a walk-in medical clinic, a pediatrician or a family physician. For the majority of participants (Montréal-based), care was guided by the Montréal Children's Hospital Concussion KiT (30), providing a plan for general activity management, return to learn and return to physical activity/sports.

Procedures: Participants were approached, screened for inclusion and consented to participate. They then completed three evaluations over a period of 6 months. Initial (T1) within 21 days, T2 within 3 months, and T3 within 6 months of injury. Prior to scheduled assessments at each time point, participants completed patient-reported outcome measures online. In-person evaluation consisted of clinical and computerized measures of VOR function (outlined below) as well as additional assessments of balance and gait included to better describe our sample. Sessions lasted approximately 75 minutes.

Outcome measures: There is currently no gold standard measure to assess VOR function post-mTBI. As such, a battery of tests was included to assess VOR response, gaze stability, VOR suppression and eye movements supporting VOR function (the OM system). Computerized and standard clinical assessments were included and are described below.

Clinical outcome measures:

Vestibular/Ocular-Motor Screening (27, 31) The VOMS was used as a clinical outcome measure for VOR function. The VOMS is a clinical screening tool of the vestibulo-ocular and OM systems that was developed specifically to assess symptom provocation (headache, dizziness, nausea, and fogginess) induced by common VOR and OM tasks in individuals who have sustained a concussion (27). The VOMS includes 7 tasks covering OM function (smooth pursuit, horizontal saccades, vertical saccades, and near point of convergence), VOR function (horizontal VOR and vertical VOR) and visual motion sensitivity (VMS, measuring VOR suppression). Prior to beginning the VOMS each participant rated their current symptoms using a 0 (no symptom) to 10 (severe symptoms) point scale for four symptom types. They then rated their symptoms following each task and change from initial symptom score on the four combined symptom scales was

obtained. Symptoms included headache, dizziness, nausea, and fogginess. For the purpose of our study, we created a variable which we named global symptom provocation and defined it as an increase of 2 or more points on any task in the VOMS. Previous literature demonstrated the presence of symptom provocation on at least 1 VOMS task to have negative effects on recovery (19). This study recommended the use of the VOMS as a whole, rather than by individual subcomponents, when considering prognosis (time to recovery) in a pediatric mTBI population (19). While the study at hand emphasizes change over time rather than prognosis, our group included this global variable to determine the change over time in VOMS symptom provocation as a whole.

In addition to noting the symptom provocation induced by each task, assessors also noted performance-based observations for each VOMS task (normal-abnormal, qualitative descriptors). Our primary analysis included the global symptom provocation variable, as well as performance on individual VOMS subcomponents: smooth pursuit (vertical and horizontal), voluntary saccades (vertical and horizontal), convergence, VOR (vertical and horizontal) and VOR suppression (VMS task), as well as measured near point of convergence (NPC, cm). Symptom provocation for each subcomponent was included to fulfill our secondary objective and thus described using proportions and means.

Additional clinical outcome measures to comprehensively characterize our sample at each timepoint include patient-reported outcome measures, cervical measures and balance measures (full descriptions can be found in Table A2.1, Appendix 2).

Computerized outcome measures included:

a) The saccade test of the *ICS Impulse OM Module*. This allowed for computerized testing of reflexive saccades performed using the ICS Impulse software[5]. This product's hardware is composed of accelerometers and a camera. It is combined with rapid computerized pupil tracking software. In this test the patient is required to wear goggles that project visual

[5] ICS ® Impulse software, Natus®

horizontal saccade stimuli (laser dots appearing horizontally) onto a flat surface while eye position data is captured. The variable of interest for this test was latency (32).

b) The video head impulse test (vHIT) using the ICS Impulse software (33). This test was selected to quantify VOR gain, assessing the corresponding horizontal semicircular canals. In this test, the patient is sitting, facing the wall, maintaining their gaze on a fixation dot, while the tester rotates the patient's head horizontally 10-20 degrees in short abrupt unpredictable movements left and right (33).

c) The dynamic visual acuity (DVA) test using the InVision System[6] (34). This test was selected to provide a behavioral measure of VOR. To perform this test, the patient is seated 10 feet from the screen. The software first determines the static visual acuity through participant responses to a series of tumbling E displays of varying sizes determined by an algorithm. The test is then performed dynamically (DVA test) with fixed velocity head movements at 120 deg/sec. For the duration of the DVA test, a head tracker with built in accelerometers is worn by the patient in order to precisely quantify the head velocity at which their responses occur.

The outcome measures included measure a wide range of unique variables. Table 11.1 outlines and defines the study variables, providing cut-off values for normal vs. abnormal findings in each outcome.

[6] NeuroCom® InVision System, Natus®

Table 11.1: *Variables analyzed to determine changes over time in subcomponents contributing to VOR function.*

Variable	Outcome measure	Components of variable	Abnormal cut-off (Units)
Global Symptom provocation	VOMS	Combined symptom findings on the VOMS tasks (smooth pursuits, saccades, convergence, vestibulo-ocular reflex and visual motion sensitivity). Abnormal if participant-reported increase of ≥ 2 points on four combined 0-10 point symptom scales on **any** domain	2 or more symptoms (N/A)
Smooth pursuit performance (vertical and horizontal)	VOMS	Clinician-observed performance measured as abnormal upon presentation of catch-up saccades. Horizontal and vertical directions observed and rated separately.	Observed (N/A)
Voluntary saccade performance (vertical and horizontal)	VOMS	Clinician-observed performance. Measured as abnormal if saccade performance is observed to be/have: hypometric, hypermetric, long-latency or poor conjugacy. Horizontal and vertical directions observed and rated separately.	Observed (N/A)
Reflexive saccades	ICS Impulse Software	Average latency left/right as measured by the ICS Impulse software (computerized, continuous).	>240 (ms)
Convergence performance	VOMS	Clinician-observed performance on near point of convergence task. Measured as abnormal if any inability of the eyes to converge synchronously.	Observed (N/A)
Near point of Convergence	VOMS	Distance at which participant's eyes fail to converge synchronously or at which participant sees two distinct images of the target in focus (participant's thumb). Measured distance from thumb to tip of nose.	>6cm
VOR Performance (vertical and horizontal	VOMS	Clinician-observed performance. Measured as abnormal if catch-up saccades were observed. Horizontal and vertical directions observed and rated separately.	Observed (N/A)
VOR suppression performance	VOMS	Clinician-observed performance on VMS task. Measured as abnormal if participant is unable to maintain gaze on thumb during body rotations.	Observed (N/A)
VOR gain (left & right)	ICS Impulse Software	Defined by the vHIT test as measured by the ICS Impulse software. Right and left mean gain obtained.	<0.80
DVA (left & right)	InVision Software	Defined by the DVA test as measured by the InVision Software. Right and left LogMAR obtained.	>0.3 (LogMAR)

OM: oculomotor; VOMS: vestibular ocular motor screening tool; N/A: normal/abnormal; VOR: vestibulo-ocular reflex; DVA: dynamic visual acuity; vHIT: video head impulse test; LogMAR: logarithm of the minimum angle of resolution

Analysis: Means (Standard Deviations, SD) and proportions were used to characterize our sample. Patient reported outcome measures, cervical measures and balance measures part of the larger study were included in our description of the sample. All outcome variables were assessed at each time point by categorizing the sample into proportions demonstrating normal versus abnormal results for categorical data and by means with standard deviation for continuous data. To address

our *primary* objective, generalized estimating equations (GEE) taking account of within-patient variation were used to estimate the effect of time on VOMS global symptom provocation, performance on VOMS subcomponents (smooth pursuit, horizontal and vertical saccades, convergence, horizontal and vertical VOR and VOR suppression), NPC, reflexive saccades, VOR gain and DVA.

Models included the fixed effect of time with adjustment for covariates including age, sex and time since injury at the time of initial evaluation. Odds ratios (OR) for dichotomized outcome variables and differences in continuous outcome variables were estimated with 95% confidence intervals for variables listed in Table 11.1. Significance level was set at 0.05.

Proportions above and below previously outlined normal cut-off values were determined for outcome variables at each evaluation time point in order to address our secondary objective.

Results

Descriptive characteristics of our sample can be found in Table 11.2. Our sample consisted of 52.8% females and 47.2% males, with a mean age of 13.98 (SD: 2.40, 7-17 years) and among which the majority were right-handed (89%). The average time from injury to initial assessment was 19.07 days (SD: 5.93, 8-33 days). Injuries in our sample occurred from sport (80.6%) or recreation/other (19.4%) with the most common location of injury being the frontal (20.6%), left temporal (23.5%) and occipital region (20.6%). In our sample, 50% of participants did not have a history of previous concussion, 25% had suffered one, and 25% had suffered two to three previous concussions. To further characterize our sample, Table 11.3 contains participant scores on post-concussion symptoms, cervical examination, balance/vestibulospinal measures, and global outcome at each timepoint. Improved means or proportions can be observed on global outcome from T1 to T2. Scores from T2 to T3 either continued to improve or remained stable.

Means for all outcome variables as well as symptom provocation characteristics by VOMS component can be found in Table 11.4.

Table 11.2: *Descriptive characteristics of sample*

Variable	Mean (SD) or %	N
Age in years, sample mean (SD)	13.98 (2.40)	36
Sex, %	-	36
Female	52.8	-
Male	47.2	-
Time from injury to baseline assessment, days	19.07 (5.93)	36
Participants seen >1week prior to initial assessment	16.7	36
Any psychological disorder**, %	11.1	36
Any developmental disability***, %	13.9	36
Personal history of migraines, %	16.7	36
Participant playing a competitive sport, %	66.7	27
# of previous concussions, %	-	36
0	50.0	-
1	25.0	-
2	19.4	-
3	5.6	-
Mechanism of injury, %	-	36
Sport	80.6	-
Recreational play or other	19.4	-
mTBI from less forceful blow than previous, %	47.1	17
Location of injury, %	-	34
Frontal	20.6	-
Left temporal	23.5	-
Right temporal	14.7	-
Left parietal	2.9	-
Right parietal	2.9	-
Occipital	20.6	-
Other body part or multiple locations	14.7	-

N: Number of responses obtained upon which to base relevant variable's mean or %
*** Presence of anxiety, depression, sleep disorder or other*
****Presence of learning disability, ADHD, dev. disorder*

For our primary objective, our GEE model adjusted change estimates and OR showed no effect of time since injury on any of the outcomes analyzed. Time since injury was therefore not considered further in the GEE models for the primary objective. An age effect was identified on VOR suppression (OR 1.43, p=0.03) demonstrating that the odds of having normal VOR suppression performance increases with age. Finally, female sex increased the odds of having abnormal NPC according to the 6cm cut-off (OR 0.19, p=0.03).

Outcomes showing significant change from T1 to T2 were VOMS global symptom provocation (OR 9.90, p=0.01), vertical smooth pursuit performance (OR 4.04, p=0.03), vertical voluntary saccades performance (OR 6.06, p=0.01), and VOR gain to the right (0.07, p=0.01, 95% CI: 0.01-0.12). Outcomes showing significant changes from T1 to T3 were vertical smooth pursuit

performance (OR 3.12, p=0.04) and vertical voluntary saccade performance (OR 5.91, p=0.01). See Table 11.5 for detailed results related to the GEE analysis.

For our secondary objective, proportions above and below cut-off values for all outcomes can be found in Table 11.4 and Figure 11.1 (VOMS only). Of interest, the performance variables with the highest proportions of observed abnormal tests were the VOMS version subcomponents while the highest proportion of abnormal symptom provocation variables were the VOMS VOR subcomponents.

Table 11.3: *Post-concussion symptoms, cervical, balance, functional and global outcome measures over time* (see Table A2.1, Appendix 2 for explanation of outcome measures)

Outcome measure	N	Mean 1 (SD)	Mean 2 (SD)	Mean 3 (SD)
Post-concussion symptoms				
PCSI total (mean)				
8-12 yr/old (score out of 50)	8/8/7	7.5 (8.26)	1.63 (2.56)	4.57 (6.40)
13-18 yr/old (score out of 156)	27/25/22	20.78 (19.39)	8.12 (15.86)	8.77 (14.77)
Dizziness present on PCSI, %	34/35/35	38.2	5.7	5.6
SCAT 5 total (mean, 13-18 yr/old)	27/25/22	24.44 (22.31)	8.92 (16.86)	9.77 (16.56)
Cervical exam				
Neck ROM normal, %	36/36/36	97.2	100	88.9
Neck pain present, %	36/36/36	13.9	0	0
Cervical flexion rotation pain, % yes	35/36/36	11.4	0	0
Cervical flexion endurance, seconds	35/35/36	25.98 (14.03)	31.59 (12.83)	34.80 (14.50)
Balance/vestibulospinal				
Tandem best score, seconds	35/35/35	16.09 (6.44)	16.75 (7.38)	15.94 (5.54)
BESS score	35/34/35	23.74 (8.916)	19.38 (8.791)	19.71 (9.636)
FGA Score	34/35/35	29.47 (0.896)	29.56 (0.695)	29.63 (0.646)
Visual/vestibular functional impact				
DHI total score	32/34/28	21.56 (19.63)	6.53 (17.904)	4.21 (8.93)
Cardiff total score (Logits)	33/34/33	-1.65 (1.024)	-2.44 (0.805)	-2.64 (0.673)
Global outcome				
Glasgow outcome scale extended	35/33/30	2.34 (0.873)	1.21 (0.545)	1.13 (0.346)
Peds QL total score				
Child	8/8/7	80.13	90.71	94.25 (9.98)
Teen	24/26/24	75.11	91.21	93.12 (8.52)
Peds Fatigue (Child and teen)	32/34/31	68.20 (21.28)	83.13 (16.03)	86.65 (13.07)
Returned to school, %	34/34/33	88.2	97.1	90.9
Pre-injury leisure activity level, yes	33/35/33	12.1	88.6	90.9
Pre-injury level of sport, yes	33/35/33	12.1	74.3	90.9

PCSI: post-concussion symptom inventory; SCAT: sport-concussion assessment tool; DHI: dizziness handicap inventory; Peds QL: pediatric quality of life inventory; Peds Fatigue: pediatric quality of life multidisciplinary fatigue scale; ROM: range of motion; BESS: balance error scoring system; FGA: functional gait assessment.

Table 11.4: *Mean symptom change, proportions above symptom cut-offs and proportions demonstrating abnormal performance*

	T1			T2			T3		
VOMS components tested	**Mean symptom provocation**	**Proportion >/= 2**	**Proportion Abnormal performance**	**Mean symptom provocation**	**Proportion >/= 2**	**Proportion Abnormal performance**	**Mean symptom provocation**	**Proportion >/= 2**	**Proportion Abnormal performance**
VOMS global symptom provocation	-	20.59	-	-	2.86	-	-	11.11	-
Smooth pursuit	0.091 (0.384)	3.03	-	0.171 (1.014)	2.86	-	0.083 (0.500)	2.78	-
Smooth pursuit horizontal	-	-	14.71	-	-	5.56	-	-	5.56
Smooth pursuit vertical	-	-	32.35	-	-	11.11	-	-	13.89
Horizontal saccade	0.25 (0.672)	6.25	20.59	0	0.0	8.33	0.086 (0.507)	2.86	0.00
Vertical saccade	0.219 (0.659)	6.25	41.18	0.171 (1.014)	2.86	11.11	0.086 (0.507)	2.86	11.43
Convergence	0.406 (0.946)	12.5	3.03	0.176 (1.029)	2.94	2.86	0.083 (0.500)	2.78	2.78
Horizontal VOR	0.758 (1.696)	15.15	0.00	0.257 (1.197)	2.86	5.56	0.278 (0.815)	11.11	2.78
Vertical VOR	0.667 (1.429)	12.12	0.00	0.228 (1.190)	2.86	2.78	0.083 (0.500)	2.78	0.00
VMS/VOR suppression	0.879 (1.816)	15.15	14.29	0.2 (1.023)	2.86	2.78	0.194 (0.822)	5.56	11.11

Additional OM/VOR tested	**Mean**	**Proportions abnormal**	**Mean**	**Proportions abnormal**	**Mean**	**Proportions abnormal**
Reflexive saccade ICS Impulse saccade latency	199.64 (32.39)	10.34	206.78 (33.42)	13.33	204.64 (25.13)	8.57
Convergence Near point of convergence	4.98 (4.06)	22.22	4.26 (6.66)	22.22	4.15 (6.34)	16.00
VOR gain ICS Impulse vHIT left ICS Impulse vHIT right	 0.99 (0.127) 0.92 (0.86)	 9.09 6.06	 1.07 (0.16) 0.94 (0.07)	 3.03 3.03	 1.04 (0.13) 0.95 (0.12)	 2.94 0.00
DVA InVision DVA LogMAR change left InVision DVA LogMAR change right	 0.29 (0.14) 0.31 (0.15)	 35.48 45.16	 0.27 (0.16) 0.26 (0.18)	 32.35 29.41	 0.29 (0.19) 0.30 (0.23)	 34.29 34.29

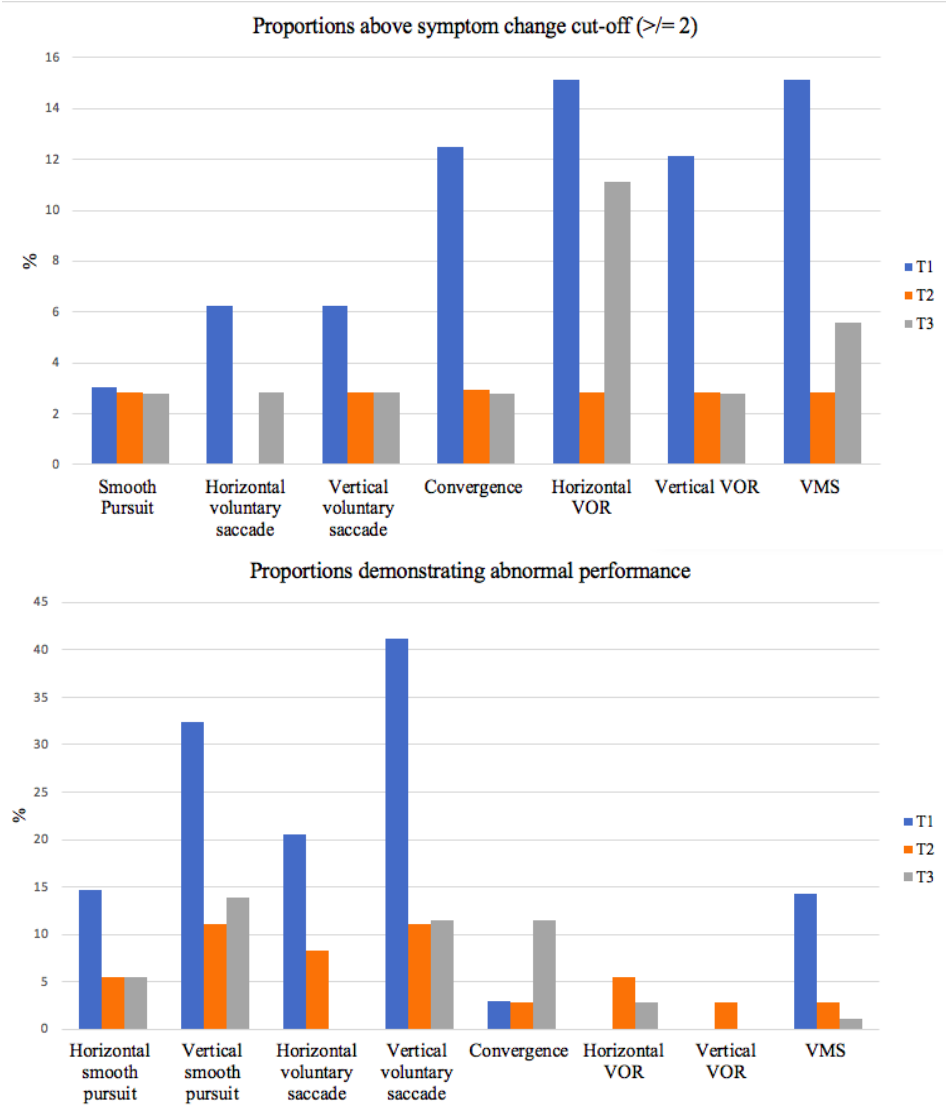
**N values for VOMS components presented ranged from N=32-36. Additional OM/VOR variables tested range from N=25-36. Exact N values can be found in Table A5.1 (Appendix 5). VOMS: vestibular/oculomotor screening tool; VOR: vestibulo-ocular reflex; DVA: dynamic visual acuity; LogMAR: logarithm of the minimum angle of resolution*

Table 11.5: *Change values over time Odd Ratio (Binary) and Parameter estimates (Continuous)*

Dichotomous variables				
Odds ratio	**T2 to T1 evaluation (range)**	**P-value**	**T3 to T1 evaluation (range)**	**P-value**
Global VOMS	9.90 (1.67-58.80)	0.01*	2.26 (0.69-7.41)	0.18
Horizontal SP performance	3.02 (0.50-18.12)	0.23	3.02 (0.49-18.52)	0.23
Vertical SP performance	4.04 (1.16-14.03)	0.03*	3.12 (1.05-9.26)	0.04*
Horizontal Voluntary saccade performance	3.08 (0.98-9.64)	0.05	N/A	
Vertical voluntary saccade performance	6.06 (1.73-21.21)	<0.01*	5.91 (1.56-22.31)	0.01*
Convergence performance	1.11 (0.07-17.94)	0.94	1.12 (0.07-19.12)	0.94
Horizontal VOR performance	N/A	-	N/A	-
Vertical VOR performance	N/A	-	N/A	-
VOR suppression performance	6.43 (0.56-74.31)	0.14	1.35 (0.40-4.58)	0.63
Continuous variables				
Parameter estimate of change	**T2 to T1 evaluation (SE, 95% CI)**	**P-value**	**T3 to T1 evaluation (SE, 95% CI)**	**P-value**
Reflexive saccades	6.20 (5.52, -4.62 to 17.01)	0.26	4.23 (5.98, -7.50 to 15.96)	0.48
Convergence	-0.52 (1.05, -2.59 to 1.54)	0.62	-0.64 (0.99, -2.58 to 1.30)	0.62
vHIT left	0.02 (0.02, -0.01 to 0.05)	0.31	0.03 (0.02, -0.02 to 0.07)	0.24
vHIT right	0.07 (0.03, 0.01 to 0.12)	0.01*	0.05 (0.03, -0.01 to 0.10)	0.08
DVA left	-0.03 (0.02, -0.07 to 0.02)	0.27	-0.01 (0.03, -0.06 to 0.05)	0.78
DVA right	-0.05 (0.03, -0.10 to 0.00)	0.06	-0.01 (0.03, -0.07 to 0.06)	0.79

SP: smooth pursuit; VOR: vestibulo-ocular reflex; vHIT: video head impulse test; N/A: not applicable as there were no observed abnormalities at initial evaluation

Figure 11.1: *Abnormal performance and symptom provocation proportions over time*



This figure outlines the proportions of our sample demonstrating symptom provocation of 2 or more (top) and abnormal performance (bottom) on each VOMS component. VOR: vestibulo-ocular reflex, VMS: visual motion sensitivity, T: timepoint

Discussion

Identifying impairments and understanding the mechanisms that contribute to persistent symptoms following pediatric mTBI can be challenging. In the past, measures using symptom reporting have been most common as they are generally easy to administer, quick and easy to interpret. However, they do not provide precision and objectiveness. Moreover, in pediatric populations, concussion-related symptom reporting has been found to be inconsistent (35, 36). Specific to VOR and OM

symptom provocation, 3-21% of athletes reported symptom improvement (rather than provocation) in the VOMS while completing testing (24) reinforcing certain challenges with such measures within this age group.

This study included more objective measures of VOR function and supporting eye movements to elucidate whether changes or compromises to specific subcomponents of VOR function may persist over time beyond symptom resolution. As such, the study included symptom-based measures and objective measures of VOR responses and OM eye movements contributing to overall VOR function. Outcomes were analyzed by subcomponents in order to determine the effect of mTBI on each in this pediatric sample.

The primary objective of this study was to determine the extent to which performance on clinical and computerized tests of VOR function and of its supportive OM system vary over time in children and adolescents at 21 days, 3 months, and 6 months after a mTBI. Our study demonstrated statistically significant change over time from T1 to T2 and T3 in vertical smooth pursuit performance, vertical voluntary saccades performance, and from T1 to T2 in right VOR function (right gain, vHIT) and VOMS global symptom provocation (VOMS).

The secondary objective of this study was to determine the proportion of children with mTBI presenting with abnormal scores on VOR and OM tests at each timepoint. In terms of performance, our findings demonstrated that vertical smooth pursuits and vertical voluntary saccade performance displayed the greatest abnormal proportions. In terms of symptom provocation induced, when considering both the mean symptom provocation and the proportions with a symptom increase ≥ 2, horizontal VOR, vertical VOR and VMS symptom provocation displayed the highest means and proportions. While convergence demonstrated elevated proportions with a symptom increase ≥ 2, the mean symptom provocation (and thus symptom severity) driving these proportions was not as high as the vestibular VOMS variables.

<u>VOMS global symptom provocation change over time</u>

VOMS global symptom provocation demonstrated significant change over time ($p=0.01$). More specifically, the horizontal VOR, vertical VOR and VMS components of the VOMS contributed

most to global symptom provocation at T1 (Table 11.4). These findings are consistent with previous pediatric mTBI literature that has demonstrated a high prevalence of vestibulo-ocular dysfunctions (28.6-62.5%) (12, 37) and has demonstrated scores on the VMS and VOR components of the VOMS to be predictive of concussion diagnosis (27). To better understand why these 3 subcomponents may be driving symptoms, it is important to consider the specific function assessed. First, the VOR task targeted gaze stabilization (with active head motion). Second, the VMS task targeted VOR suppression through gaze pursuits while performing full-body rotations (active standing position). The symptom provocation induced may be representative of a sensory conflict between the visual and vestibular systems during the tasks (38). More specifically, this sensory conflict may stem from an impairment at some point along the vestibular pathways mediating the VOR response to stabilize gaze or the inhibition required to generate the appropriate gaze pursuit response in the relevant testing conditions. In order to maintain a stable gaze it is crucial to have a fully functional VOR and intact VOR pathway (39). In order to inhibit the VOR's response to allow for gaze pursuit in this instance, neurons involved in the VOR's motor response must be attenuated/inhibited (39-41). Predictive pursuit commands contributing to VOR suppression may also play a role (42, 43). While outlining the specific neural pathways involved with the VOR and VOR suppression is beyond the scope of this paper, an in-depth understanding can be gained in Cullen & Roy (2004), Cullen (2012), Roy & Cullen (2002) and Belton & McCrea (2000) (39-42). Future research with more precise measures could explore these findings to understand the physiological mechanisms that underly the symptoms provoked.

Right VOR change over time

In our study a significant change over time was observed in right VOR gain ($p=0.01$) as measured by the vHIT. While not significant, a similar trend was also identified in right DVA LogMAR change values ($p=0.06$). The sample size and type of outcome measures used do not allow us to draw conclusions as to why this may be. However previous studies outlining hemispheric asymmetries and lateralized activation patterns influenced by handedness could provide potential explanations as our sample contained mostly right-handed individuals (89%).

The role of handedness, has been linked to different activation patterns in the brain (44), with right-handed individuals demonstrating pronounced contributions from the right hemisphere when

undergoing vestibular stimulation (45). This phenomenon highlights a preference to the non-dominant hemisphere when considering vestibular function (46), consistent with findings by Bronstein et al. (2015) and Arshad et al. (2013) who demonstrated VOR-specific modulation dependent on their subject's handedness (47, 48).

While this theory is exploratory in the context of our study, the handedness of our sample, could potentially contribute to the asymmetrical finding of change over time in right VOR variables. It would be interesting for future literature to specifically explore the role of handedness in relation to the reflexive control of eye movements. Investigating the control of the VOR specifically at the brainstem/cerebellar versus the cortical/subcortical levels would be informative as these regions are responsible for the reflexive control of gaze/head/body and self-motion/voluntary movement/balance respectively (49).

Change over time in vertical versions:

Our findings show significant change over time in vertical version performance. These findings indicate the potential value of adding performance quantifiers when using the VOMS to assess the functioning of VOR or OM subcomponents. At the present time, there are few reliable and validated clinical measures that demonstrate the ability to quantify VOR and OM performance improvements over time following mTBI. While a previous study by Anzalone et al. (2017) included additional performance quantifiers to the VOMS, it did not separate abnormal symptom provocation from abnormal clinical-observation (19). In our study, having both symptom provocation and clinician observation allowed the significant changes over time in vertical SP performance ($p=0.03$, T2 and 0.04, T3) and vertical voluntary saccade performance ($p=<0.01$, T2 and 0.01, T3) to be detected while also allowing us to identify the VOR contributions (previously outlined) driving symptom provocation. Had performance quantifiers not been included, the changes in version performance would have been overlooked.

In addition, these findings support the neurophysiological contributions to saccades and smooth pursuits in the horizontal versus vertical directions which are not the same. With regards to saccades, directional differences were extensively explored in the work of Irving & Lillakas (2019) (50). Four important differences were outlined: i) the pulse innervation from the excitatory burst

neurons for horizontal saccades originates from the paramedian pontine reticular formation for the horizontal direction, while this innervation originates in the rostral interstitial nucleus of the medial longitudinal fasciculus for saccades in the vertical direction (51); ii) the neural integrator differs when considering the horizontal and vertical directions; iii) while only two extraocular muscles are responsible for moving the eyes horizontally, four extraocular muscles must work in an integrated manner to produce vertical eye movements; and iv) when considering the work of Foulsham et al. (2011), which demonstrated greater horizontal saccade use when navigating our environments, it outlines that it would be plausible to infer an increased efficiency of the horizontal saccade pathway (50).

With regards to smooth pursuits, while the pathways share similarities, the pathway for vertical SP includes the rostral nucleus reticularis tegmenti pontis (rather than the dorsolateral pontine nuclei in the horizontal direction), involves the y-group nucleus (rather than the medial vestibular nucleus) and involves the dentate nucleus (52). Moreover, in a study by Ingster-Moati et al. (2009) maturational differences were demonstrated, highlighting later maturation of the brain networks associated with vertical smooth pursuits (11 years old compared to 8 years old in the horizontal direction) (53).

These directional differences are of importance when measuring OM eye movements and interpreting results as positive findings could hold different meanings depending on directionality. In the context of this study, as these eye movements support VOR function, it would be important to further understand if, and specifically how, positive findings in each direction may influence characteristics of the VOR response in order to inform and refine rehabilitation strategies.

<u>Significant covariates and notable observations:</u>

All models in this study included sex, age and time since injury as potential covariates. Our findings demonstrated increased odds of normal VMS with increasing age in a pediatric mTBI population. This would suggest improvements in VMS as one matures through adolescence and approaches adulthood. Such findings align with literature indicating higher rates of motion sensitivity in children, with peak incidence rates at pre-adolescence (54), and then decreasing into adulthood (55).

With regards to sex, our findings indicate increased odds of abnormal NPC in children and adolescents with mTBI identifying as female, and support similar findings by Gray et al. (2020) (13). While these findings cannot be conclusively explained at this time, further research should explore potential associations between the neural pathways associated with convergence and the structural and functional differences between male and female brains highlighted in the context of concussion by Solomito et al. (2018) (56).

Of note in this study, the high abnormal proportions for the DVA variables may underline a need to further investigate the reliability of the InVision DVA test and/or the cut-off values used.

Limitations

Individuals recruited from the concussion clinic may have represented a population experiencing a more complicated recovery, and two outliers beyond the 21-day evaluation period were included due to scheduling difficulties. Additionally, six individuals included in this study were seen by a physiotherapist prior to their initial evaluation. While their values do not demonstrate obvious differences from the sample, this could lead to overestimating the effect of time on recovery.
With regards to our data, three participants, two at T1 and one at T2 demonstrated symptom improvement. These values were removed from symptom provocation calculations as there is no physiological explanation for negative symptom reports (24) thus these would be considered to be inconsistent and unreliable (35). Further, three individuals demonstrated elevated perception times thus, according to software specifications, the validity of their LogMAR values is questionable. Finally, as this study consisted of a modest sample size, a type I error may have occurred where a difference was identified but may have been due to chance. Further literature is needed to confirm our findings.

Conclusion

With increasing literature focused on VOR function following pediatric mTBI, it is becoming evident that impairments to VOR function and its supporting eye movements may often present in a portion of this population and could influence the recovery process. This is supported by the

clinical profile perspective of Kontos et al. (2019), which has identified the vestibular and ocular profiles as two of the five distinct clinical trajectories following sport-related concussion (57). While impairments found within these profiles are now often guiding physical therapy interventions in mTBI settings, the evolution and precise mechanisms underlying these impairments are poorly understood. It is thus challenging to speak conclusively to the pathophysiology associated with negative prognosis. Continuing to adapt clinical assessments to include more objective rather than uniquely symptom-based measures will help to address this. Ensuring such assessments beyond medical clearance in order to monitor VOR function will be equally important in order to understand whether recovery of these functions is maintained.

This study identified significant changes over time in VOMS global symptom provocation (driven by the VOR components), vertical voluntary saccade performance, vertical smooth pursuit performance and right VOR gain. The subcomponents with the largest proportions of abnormal performance-based results were vertical voluntary saccade and vertical smooth pursuit performance. The subcomponents with the largest proportions of abnormal symptom-based results were the VOR, VOR cancellation and convergence subcomponents. Furthermore, males had higher odds of having normal NPC, and older children and adolescents had higher odds of having normal VMS performance.

The findings according to subcomponents of VOR function in our study highlight certain important observations. With regards to the VOMS, our findings demonstrate: i) the potential value of further exploring the underlying mechanisms of VOR components that seem to drive global symptom provocation on the VOMS; ii) the value of including objective performance quantifiers to the VOMS in order to capture functional abnormalities that may be overlooked if solely relying on symptom provocation; and iii) the value of including vertical and horizontal components when assessing SPs and saccades. With regards to the asymmetrical findings for VOR gain change, our findings uncover the potential contribution of handedness on VOR gain.

Future directions

Research exploring specific variables within each subcomponent outlined in this study, using computerized measures to increase the granularity of findings, and with a much larger pediatric mTBI sample would bring valuable insight to help understand the mechanisms underlying impairments to VOR function in this population. Precise findings in specific variables may then encourage future studies to draw links with associated brain regions and neural circuits.

References

1. Karlin AM. Concussion in the pediatric and adolescent population:“different population, different concerns”. PM&R. 2011;3(10):S369-S79.
2. Meehan WP, Taylor AM, Proctor M. The pediatric athlete: younger athletes with sport-related concussion. J Clin Sports Med. 2011;30(1):133-44.
3. Bryan MA, Rowhani-Rahbar A, Comstock RD, Rivara F. Sports-and recreation-related concussions in US youth. Pediatrics. 2016;138(1).
4. Cook RS, Schweer L, Shebesta KF, Hartjes K, Falcone RA, Jr. Mild traumatic brain injury in children: Just another bump on the head? J Trauma Nurs. 2006;13(2):58-65.
5. Buzzini SR, Guskiewicz KM. Sport-related concussion in the young athlete. Curr Opin Pediatr. 2006;18(4):376-82.
6. Ommaya, Goldsmith, Thibault. Biomechanics and neuropathology of adult and paediatric head injury. Br J Neurosurg. 2002;16(3):220-42.
7. Lannsjo M, af Geijerstam JL, Johansson U, Bring J, Borg J. Prevalence and structure of symptoms at 3 months after mild traumatic brain injury in a national cohort. Brain Inj. 2009;23(3):213-9.
8. Rutherford WH, Merrett JD, McDonald JR. Symptoms at one year following concussion from minor head injuries. Injury. 1979;10(3):225-30.
9. Oldenburg C, Lundin A, Edman G, Deboussard CN, Bartfai A. Emotional reserve and prolonged post-concussive symptoms and disability: a Swedish prospective 1-year mild traumatic brain injury cohort study. BMJ Open [Internet]. 2018; 8(7).
10. Corwin DJ, Wiebe DJ, Zonfrillo MR, Grady MF, Robinson RL, Goodman AM, et al. Vestibular Deficits following Youth Concussion. J Pediatr. 2015;166(5):1221-5.
11. Master CL, Master SR, Wiebe DJ, Storey EP, Lockyer JE, Podolak OE, et al. Vision and vestibular system dysfunction predicts prolonged concussion recovery in children. Clin J Sport Med. 2018;28(2):139-45.
12. Ellis MJ, Cordingley D, Vis S, Reimer K, Leiter J, Russell K. Vestibulo-ocular dysfunction in pediatric sports-related concussion. J Neurosurg Pediatr. 2015;16(3):248-55.

13. Gray M, Wilson JC, Potter M, Provance AJ, Howell DR. Female adolescents demonstrate greater oculomotor and vestibular dysfunction than male adolescents following concussion. Phys Ther Sport. 2020;42:68-74.
14. Master CL, Scheiman M, Gallaway M, Goodman A, Robinson RL, Master SR, et al. Vision diagnoses are common after concussion in adolescents. Clin Pediatr (Phila). 2016;55(3):260-7.
15. Storey EP, Master SR, Lockyer JE, Podolak OE, Grady MF, Master CL. Near point of convergence after concussion in children. Optom Vis Sci. 2017;94(1):96-100.
16. Cross E, Podolak OE, Lockyer J, Corwin DJ, Storey EP, Grady MF, et al. Prevalence of vestibular and vision problems following concussion in children under 12. Am Acad Pediatrics; 2018.
17. Reneker JC, Cheruvu VK, Yang J, James MA, Cook CE. Physical examination of dizziness in athletes after a concussion: A descriptive study. Musculoskelet Sci Prac. 2018;34:8-13.
18. Pillai C, Gittinger JW, Jr. Vision testing in the evaluation of concussion. Semin Ophthalmol. 2017;32(1):144-52.
19. Anzalone AJ, Blueitt D, Case T, McGuffin T, Pollard K, Garrison JC, et al. A positive vestibular/ocular motor screening (VOMS) is associated with increased recovery time after sports-related concussion in youth and adolescent athletes. Am J Sports Med. 2017;45(2):474-9.
20. Hoffer ME, Balaban C, Szczupak M, Buskirk J, Snapp H, Crawford J, et al. The use of oculomotor, vestibular, and reaction time tests to assess mild traumatic brain injury (mTBI) over time. Laryngoscope Investig Otolaryngol. 2017;2(4):157-65.
21. Cheever KM, McDevitt J, Tierney R, Wright WG. Concussion recovery phase affects vestibular and oculomotor symptom provocation. Int J Sports Med. 2018;39(2):141-7.
22. Desai N, Wiebe DJ, Corwin DJ, Lockyer JE, Grady MF, Master CL. Factors Affecting Recovery Trajectories in Pediatric Female Concussion. Clin J Sports Med. 2019;29(5):361-7.
23. Sinnott AM, Elbin RJ, Collins MW, Reeves VL, Holl CL, Kontos AP. Persistent vestibular-ocular impairment following concussion in adolescents. J Sci Med Sport. 2019;22(12):1292-7.

24. Elbin RJ, Sufrinko A, Anderson MN, Mohler S, Schatz P, Covassin T, et al. Prospective changes in vestibular and ocular motor impairment after concussion. J Neurol Phys Ther. 2018;42(3):142-8.
25. Zaslow T, Mueske NM, Yu GJ, Conrad-Forrest A, Edison B, Wren TA. Oculomotor function in adolescent athletes following concussion. Orthop J Sports Med. 2020;8(4_suppl3):2325967120S0015.
26. Alsalaheen BA, Mucha A, Morris LO, Whitney SL, Furman JM, Camiolo-Reddy CE, et al. Vestibular rehabilitation for dizziness and balance disorders after concussion. J Neurol Phys Ther. 2010;34(2):87-93.
27. Mucha A, Collins MW, Elbin RJ, Furman JM, Troutman-Enseki C, DeWolf RM, et al. A brief vestibular/ocular motor screening (VOMS) assessment to evaluate concussions: preliminary findings. Am J Sports Med. 2014;42(10):2479-86.
28. Graham R, Rivara FP, Ford MA, Spicer CM, National Research Council, Committee on sports-related concussions in youth. Sports-related concussions in youth: improving the science, changing the culture. Washington, D.C.: National Academies Press; 2014.
29. Carroll L, Cassidy JD, Holm L, Kraus J, Coronado V. Methodological issues and research recommendations for mild traumatic brain injury: the who collaborating centre task force on mild traumatic brain injury. J Rehabil Med. 2004;36(0):113-25.
30. Trauma, Montreal Children's Hospital. Understanding and managing concussion in youth 2018. Montréal, Canada: MCH Trauma. 3.
31. Kontos AP, Sufrinko A, Elbin RJ, Puskar A, Collins MW. Reliability and associated risk factors for performance on the vestibular/ocular motor screening (VOMS) tool in healthy collegiate athletes. Am J Sports Med. 2016;44(6):1400-6.
32. Otometrics. ICS impulse manual USB. GN Otometrics; 2015.
33. McGarvie LA, MacDougall HG, Halmagyi GM, Burgess AM, Weber KP, Curthoys IS. The video head impulse test (vHIT) of semicircular canal function - age-dependent normative values of VOR gain in healthy subjects. Front Neurol. 2015;6:154.
34. NeuroCom International I. Clinical Integration Manual- Invision System. Clackamas, OR: NeuroCom International, Inc. ; 2008.

35. Iverson GL, Silverberg ND, Mannix R, Maxwell BA, Atkins JE, Zafonte R, et al. Factors associated with concussion-like symptom reporting in high school athletes. JAMA Pediatr. 2015;169(12):1132-40.
36. Asken BM, Snyder AR, Smith MS, Zaremski JL, Bauer RM. Concussion-like symptom reporting in non-concussed adolescent athletes. Clin Neuropsychol. 2017;31(1):138-53.
37. Ellis MJ, Cordingley DM, Vis S, Reimer KM, Leiter J, Russell K. Clinical predictors of vestibulo-ocular dysfunction in pediatric sports-related concussion. J Neurosurg Pediatr. 2017;19(1):38-45.
38. Zhang LL, Wang JQ, Qi RR, Pan LL, Li M, Cai YL. Motion sickness: Current knowledge and recent advance. CNS Neurosci Ther. 2016;22(1):15-24.
39. Cullen KE, Roy JE. Signal processing in the vestibular system during active versus passive head movements. J Neurophysiol. 2004;91:1919-33.
40. Cullen KE. The vestibular system: multimodal integration and encoding of self-motion for motor control. Trends Neurosci. 2012;35(3):185-96.
41. Roy JE, Cullen KE. Vestibuloocular reflex signal modulation during voluntary and passive head movement. J Neurophysiol. 2002;87:2337-57.
42. Belton T, McCrea RA. Role of the cerebellar flocculus region in Cancellation of the VOR during passive whole body rotation. J Neurophysiol. 2000;84:1599-613.
43. Barnes GR. Visual-vestibular interaction in the control of head and eye movement: the role of visual feedback and predictive mechanisms. Prog Neurobiol. 1993;41:435-72.
44. Li M, Chen H, Wang J, Liu F, Long Z, Wang Y, et al. Handedness- and hemisphere-related differences in small-world brain networks: a diffusion tensor imaging tractography study. Brain Connect. 2014;4(2):145-56.
45. Dieterich M, Bense S, Lutz S, Drzezga A, Stephan T, Bartenstein P, et al. Dominance for vesitbular cortical function in the non-dominant hemisphere. Cerebral Cortex. 2003;13:994-1007.
46. Arshad Q, Siddiqui S, Ramachandran S, Goga U, Bonsu A, Patel M, et al. Right hemisphere dominance directly predicts both baseline V1 cortical excitability and the degree of top-down modulation exerted over low-level brain structures. Neuroscience. 2015;311:484-9.
47. Bronstein AM, Patel M, Arshad Q. A brief review of the clinical anatomy of the vestibular-ocular connections-how much do we know? Eye (Lond). 2015;29(2):163-70.

48. Arshad Q, Nigmatullina Y, Bronstein AM. Handedness-related cortical modulation of the vestibular-ocular reflex. J Neurosci. 2013;33(7):3221-7.
49. Dieterich M, Kirsch V, Brandt T. Right-sided dominance of the bilateral vestibular system in the upper brainstem and thalamus. J Neurol. 2017;264(Suppl 1):55-62.
50. Irving EL, Lillakas L. Difference between vertical and horizontal saccades across the human lifespan. Exp Eye Res. 2019;183:38-45.
51. Hunfalvay M, Roberts CM, Murray NP, Tyagi A, Kelly H, Bolte T. Horizontal and vertical self-paced saccades as a diagnostic marker of traumatic brain injury. Concussion. 2019;4(1).
52. Wong AMF. Eye movement disorders. Oxford: Oxford University Press; 2008.
53. Ingster-Moati I, Vaivre-Douret L, Bui Quoc E, Albuisson E, Dufier JL, Golse B. Vertical and horizontal smooth pursuit eye movements in children: a neuro-developmental study. Eur J Paediatr Neurol. 2009;13(4):362-6.
54. Graudins L. Preventing motion sickness in children Australian Prescriber. 2009;32(3):61-3.
55. Huppert D, Grill E, Brandt T. Survey of motion sickness susceptibility in children and adolescents aged 3 months to 18 years. J Neurol. 2019;266(Suppl 1):65-73.
56. Solomito MJ, Reuman H, Wang DH. Sex differences in concussion: a review of brain anatomy, function, and biomechanical response to impact. Brain Inj. 2019;33(2):105-10.
57. Kontos A, Sufrinko A, Sandel N, Emami K, Collins MW. Sport related concussion clinical profiles: clinical characteristics, targeted treatments, and preliminary evidence. Curr Sports Med Rep. 2019;18(3):82-92.

Chapter 12: Discussion

The overarching goal of our work was to characterize VOR function following mTBI in children and adolescents, with a special focus on its assessment, using patient-reported and clinician administered measures. Our first line of inquiry *(assessment of VOR function)* identified and described the tests administered, and tools used to measure VOR function, highlighting important characteristics and uses for each (Study 1, Manuscript 1). In order to synthesize these findings in a manner that was both easy to interpret and useful to clinical practice, our work identified three main categories among the outcome measures used to assess VOR function. It also found a low level of agreement between commonly used measures spanning all three categories and underlined the possible contribution of coexisting cervical injuries to symptom-based findings when assessing VOR function (Study 2, Manuscript 2). Together, the findings from this line of inquiry support the need for a battery of tests when assessing VOR function and may help to inform the choice of tests that would assess complementary elements of VOR function. From our findings, key considerations when developing best practice recommendations for a battery of tests would be to ensure it is: 1) efficient, accessible and affordable for clinicians who most often work with pediatric mTBI; 2) reliable and valid within this population; and 3) includes both symptom and performance-based measures of VOR function.

Strengths and limitations

A strength of Study 1 was its emphasis on thoroughly describing how each test and tool included was administered and used, respectively, as this allowed for important differences to be outlined between similar tests and between similar tools. As a result, the pressing need to develop best practice recommendations and standardized protocols when assessing VOR function following TBI was strongly underlined. Limitations to this review were certain iterative steps required during the screening and selection of studies.

A strength of Study 2 was its originality, as no previous study of agreement between these commonly used measures of VOR function has been performed to date. Additionally, identifying the possibility that cervical injuries may contribute to the symptoms reported and/or induced in this population is highly pertinent, as it supports recent research published in this promising new

field (157, 158). A limitation to this study was the lack of control group and a sample size too small to make our findings conclusive. While both a control group and larger sample size were originally planned, the COVID-19 pandemic rendered further evaluation of control participants impossible.

Our second line of inquiry *(relationship between measures of VOR function and patient-reported outcome)* has demonstrated a relationship between measures of symptom-provocation induced by VOR and/or VOR suppression tasks and patient-reported outcome as well as between symptom provocation induced by certain OM tasks and patient-reported outcome (Study 3, Manuscript 3). This work may assist clinicians in interpreting clinical findings on symptom-based assessments, and in understanding the difficulties and/or disabling sensations imposed by symptoms on a child or adolescent's daily function and activities. Moreover, the lack of relationship between performance-based measures of VOR function and patient-reported measures speaks to the value of including performance-based outcome measures in assessments of VOR function as relevant abnormalities may otherwise not be captured. Such an oversight could result in a child or adolescent returning to activity or sports with compromised VOR functioning, potentially putting them at a higher risk of re-injury.

Strengths and limitations

A strength of Study 3 is the relationship that was demonstrated between the symptom-based measures included and patient-reported outcome *specific* to dizziness and vision (respectively). As there is very scarce literature that has explored the relationship between measured VOR and OM function and *construct specific* patient-reported outcome, the relationship demonstrated may provide clinicians with unprecedented insight when interpreting clinical findings obtained using these measures. As the DHI and the VOMS tool in particular are widely used clinical measures in mTBI populations, findings from this study have high clinical relevance. A limitation of this study is the presence of missing values within our data. In order to minimize the impact of this limitation, the Markov chain Monte Carlo technique for multiple imputation was used in the analysis which replaces each missing value with a random sample from the joint distribution based on the observed data and reflects the uncertainty due to missing values.

Our third line of inquiry *(VOR function over time)* demonstrated changes over time in measures of specific subcomponents of VOR function (Study 4, Manuscript 4). These findings may contribute to developing more targeted treatment recommendations in children and adolescents following mTBI. More specifically, this work provides insight on certain pathophysiological mechanisms that could contribute to impairments and symptoms in this population. The changes over time demonstrated in our findings indicate likely sensory conflict, as well as potential vulnerability in the neural pathways known to differ according to handedness, and in those responsible for vertical saccades and vertical smooth pursuits following mTBI. From an assessment perspective, as eye movements supporting VOR function are more frequently assessed in the horizontal direction in pediatric mTBI populations, our findings underline the importance of encouraging their assessment in the vertical direction as well in order to ensure associated impairments are not overlooked.

Strengths and limitations

A strength of Study 4 was the use of three timepoints *unguided by markers of recovery*. This allowed for a unique and more specific representation of changes to VOR function over time, beyond the timeframe most often included in previous studies. The descriptive characteristics of VOMS subcomponents provide novel insight and important support towards a more widespread use of added performance quantifiers with the VOMS tool. An important limitation of this study is the small sample size affecting the power of our findings. Further research is thus warranted to more conclusively speak to the changes over time identified in this study and to potentially inform targeted treatment approaches. While a much larger sample was recruited and included in the study, the COVID-19 pandemic resulted in substantial loss to follow-up when country-wide research was halted.

*Additional limitation in studies #2, 3 and 4: a small number of participants (n=4, 4 and 3, respectively) were evaluated outside of the 21-day window due to scheduling complications. Due to the loss of participants from the pandemic, these participants were retained in our analysis.

Implications for future research

Findings from our three lines of inquiry have allowed specific directions for future research to be identified within each manuscript. Together our findings first support the need for further research in order to develop standardized recommendations that may support a more homogeneous approach to the assessment of VOR function in both research and clinical settings. Second, the relationship identified between symptom-provocation and patient-reported outcome should now be further explored with more specific subcomponents of VOR and OM function and according to symptom-type in order to more precisely explain this relationship. Third, in order to attach further meaning to the changes over time identified in our longitudinal study, these subcomponents should now be assessed when compared to an uninjured control group and in a larger sample.

Finally, as recent literature has underlined associations between symptoms and cervical findings in mTBI populations, and our findings have characterized a similar trend, there would be value to more fully exploring this relationship in order to further understand the causal or contributing mechanisms. A collaborative approach to address the research avenues outlined, including integrated research teams composed of clinicians, researchers and measurement experts would ensure these recommendations be most efficiently addressed.

Implication for clinical practice

When considering the clinical management of children and adolescents with mTBI, our work provides valuable insight with regards to both administering and interpreting assessments of VOR function. Our findings highlight important considerations that may support a more comprehensive clinical assessment of VOR function in this young population. Of note, we emphasize the importance of including measures of symptom provocation and of performance when evaluating VOR function following pediatric mTBI as each provides unique information to the overall assessment.

When specifically considering performance-based measures, our work highlights that it would be of value to further emphasize the assessment of eye movements that support VOR function in both

the horizontal and vertical directions as the neural pathways for each differ. As commonly used tests evaluating VOR function and the supporting OM system often favor the horizontal direction, this suggestion would ensure a more comprehensive assessment, yet would add little time to the overall clinical assessment. From a broader lens, the regular use of performance-based measures when assessing VOR function and the OM system will continue to increase the overall understanding among clinicians of how specific eye movement characteristics could potentially act as a biomarker (55, 159, 160) to diagnosing, directing treatment, evaluating recovery and/or determining prognosis following pediatric mTBI.

Furthermore, as treatment approaches for cervical impairments exist, our findings support the value of incorporating cervical assessments when providing clinical care for pediatric mTBI populations. Assessing these structures at initial evaluation would assist clinicians in identifying co-existing injuries that can be addressed with existing treatment strategies. While certain specialized clinics have recently incorporated such assessments in their evaluation of mTBI patients, this is not the case in more general clinical care settings.

Finally, the relationship we have demonstrated between symptom-provocation induced by VOR and OM tasks and patient-reported outcome may provide clinicians with information regarding the construct-specific day-to-day challenges experienced by patients as a result of symptoms. This can support clinicians in developing treatment plans that are realistic for each young patient in order to optimize their adherence.

Chapter 13: Conclusion

The field of study focusing on VOR function following pediatric mTBI is one that demonstrates important potential both from an assessment and treatment perspective. This thesis and the three lines of inquiry upon which it is built sought to address important assessment gaps, in order to support the development of future targeted treatment approaches.

From an assessment perspective, our work supports the need to develop recommendations for an accessible and affordable battery of tests, in order to provide a reliable and more comprehensive means of assessing VOR function in the pediatric mTBI population. We have identified key considerations to account for during such assessments, highlighting the importance of selecting tests that will assess complementary elements of VOR function and providing direction for this selection. In addition, we have identified three distinct categories of outcome measures that assess VOR function, demonstrated the level at which those commonly used may agree with one another, and identified important relationships that will assist clinicians in interpreting positive clinical findings. Furthermore, our work has identified symptom-based and performance-based abnormalities relating to VOR function, as well as changes over time in specific subcomponents. As such, this work contributes to a more precise understanding of VOR function following pediatric mTBI. As extensive research has mapped the neural pathways involved with specific eye movements, this work represents another step towards understanding the pathophysiological mechanisms associated with compromised VOR function in this population.

From a treatment perspective, our work demonstrates that together the three categories of measures assessing VOR function (including both symptom and performance-based measures), will provide valuable person-centered and function-centered information to clinicians in order to assist them when developing a strategy to best support a child or adolescent's physiological recovery, while minimizing the day-to-day environmental burdens experienced following mTBI. Additionally, the potential co-existing injuries to address, and the changes in VOR function following injury that we have identified may support the refinement of targeted treatment approaches.

As a whole, this work has contributed to more fully understanding how VOR function has been assessed in the past, how it may more optimally be assessed in the present, and recommendations for improvements in the future. We have identified important characteristics of VOR function and its supporting OM eye movements in children and adolescents who have experienced a mTBI. Importantly many of the findings in this work are of high clinical relevance as they speak to results obtained by, or pertaining to, outcome measures commonly used in clinical practice with pediatric mTBI populations.

References

1. Bryan MA, Rowhani-Rahbar A, Comstock RD, Rivara F, Seattle Sports Concussion Research C. Sports-and recreation-related concussions in US youth. Pediatrics. 2016;138(1).
2. Barlow KM, Crawford S, Stevenson A, Sandhu SS, Belanger F, Dewey D. Epidemiology of postconcussion syndrome in pediatric mild traumatic brain injury. Pediatrics. 2010;126(2):e374-81.
3. Kontos AP, Sufrinko A, el N, Emami K, Collins MW. Sport-related concussion clinical profiles: Clinical characteristics, targeted treatments, and preliminary evidence. J Curr Sports Med Rep. 2019;18(3):82-92.
4. Master CL, Scheiman M, Gallaway M, Goodman A, Robinson RL, Master SR, et al. Vision diagnoses are common after concussion in adolescents. Clin Pediatr (Phila). 2016;55(3):260-7.
5. Storey EP, Master SR, Lockyer JE, Podolak OE, Grady MF, Master CL. Near Point of Convergence after Concussion in Children. Opt Vis Sci. 2017;94(1):96-100.
6. Cross E, Podolak OE, Lockyer J, Corwin DJ, Storey EP, Grady MF, et al. Prevalence of vestibular and vision problems following concussion in children under 12. Am Acad Pediatrics; 2018.
7. Reneker JC, Cheruvu VK, Yang J, James MA, Cook CE. Physical examination of dizziness in athletes after a concussion: A descriptive study. Musculoskelet Sci Prac. 2018;34:8-13.
8. Corwin DJ, Wiebe DJ, Zonfrillo MR, Grady MF, Robinson RL, Goodman AM, et al. Vestibular Deficits following Youth Concussion. J Ped. 2015;166(5):1221-5.
9. Master CL, Master SR, Wiebe DJ, Storey EP, Lockyer JE, Podolak OE, et al. Vision and vestibular system dysfunction predicts prolonged concussion recovery in children. Clin J Sports Med. 2018;28(2):139-45.
10. Anzalone AJ, Blueitt D, Case T, McGuffin T, Pollard K, Garrison JC, et al. A positive vestibular/ocular motor screening (VOMS) is associated with increased recovery time after sports-related concussion in youth and adolescent athletes. Am J Sports Med. 2017;45(2):474-9.
11. Dewan MC, Rattani A, Gupta S, Baticulon RE, Hung YC, Punchak M, et al. Estimating the global incidence of traumatic brain injury. J Neurosurg. 2018;2018:1-18.

12. Menon DK, Schwab K, Wright DW, Maas AI, et al. Position statement: definition of traumatic brain injury. Arch Phys Med Rehabil. 2010;91(11):1637-40.
13. Langlois JA, Rutland-Brown W.; Wald, MM. The epidemiology and impact of traumatic brain injury. J Head Trauma Rehabil. 2006;21(5):375-8.
14. Pillai C, Gittinger JW, Jr. Vision testing in the evaluation of concussion. Semin Ophthalmol. 2017;32(1):144-52.
15. Goodrich GL, Flyg HM, Kirby JE, Chang C-H, Martinsen GL. Mechanisms of TBI and visual consequences in military and veteran populations. Optom Vis Sci. 2013;90(2):105-12.
16. Ruff RM. Mild traumatic brain injury and neural recovery: rethinking the debate. Neurosurgery. 2011;57:300-6.
17. Lewin JD. Structural and functional brain imaging in mTBI. In: Zollman FS, editor. Manual of Traumatic Brain Injury: Assessment and Management 2nd ed. New York, NY: Demos Medical Publishing 2016. p. 90-100.
18. Sheedy JH, E.; Faux, S.; Geffen, G. Emergency department assessment of Mild Traumatic Brain Injury and the Prediction of Postconcussive Symptoms: A 3-Month Prospective Study. J Head Trauma Rehabil. 2009;24(5):333-43.
19. Iverson GL, Brooks BL, Collins MW, Lovell MR. Tracking neuropsychological recovery following concussion in sport. Brain Inj. 2006;20(3):245-52.
20. Zemek RL, Grool AM, Rodriguez Duque D, DeMatteo C, Rothman L, Benchimol EI, et al. Annual and Seasonal Trends in Ambulatory Visits for Pediatric Concussion in Ontario between 2003 and 2013. J Pediatr. 2017;181:222-8 e2.
21. Carroll L, Cassidy JD, Holm L, Kraus J, Coronado V. Methodological issues and research recommendations for mild traumatic brain injury: the who collaborating centre task force on mild traumatic brain injury. J Rehabil Med. 2004;36(0):113-25.
22. McCrory P, Meeuwisse W, Aubry M, Cantu B, Dvorak J, Echemendia R, et al. Consensus statement on Concussion in Sport - The 4th International Conference on Concussion in Sport held in Zurich, November 2012. Phys Ther Sport. 2013;14(2):e1-e13.
23. Szymanowicz D, Ciuffreda KJ, Thiagarajan P, Ludlam DP, Green W, Kapoor N. Vergence in mild traumatic brain injury: A pilot study. J Rehabil Res Dev. 2012;49(7).
24. Rutherford WH, Merrett JD, McDonald JR. Symptoms at one year following concussion from minor head injuries. Injury. 1979;10(3):225-30.

25. Oldenburg C, Lundin A, Edman G, Deboussard CN, Bartfai A. Emotional reserve and prolonged post-concussive symptoms and disability: a Swedish prospective 1-year mild traumatic brain injury cohort study. BMJ Open [Internet]. 2018; 8(7).
26. Lannsjo M, af Geijerstam JL, Johansson U, Bring J, Borg J. Prevalence and structure of symptoms at 3 months after mild traumatic brain injury in a national cohort. Brain Inj. 2009;23(3):213-9.
27. Yarnell PR, Rossie GV. Minor whiplash head injury with major debilitation. Brain Inj. 2009;2(3):255-8.
28. Leininger BEG, S. E.; Farrell, A. D.; Kreutzer, J. S.; Peck, E. E. Neuropsychological deficits in symptomatic minor head injury patients after concussion and mild concussion. J Neurol Neurosurg Psychiatry. 1990;53:293-6.
29. McCarthy MT, Kosofsky BE. Clinical features and biomarkers of concussion and mild traumatic brain injury in pediatric patients. Ann N Y Acad Sci. 2015;1345(1):89-98.
30. Bandak FA, Ling G, Bandak A, De Lanerolle NC. Chapter 6 - Injury biomechanics, neuropathology, and simplified physics of explosive blast and impact mild traumatic brain injury. In: Grafman J, Salazar AM, editors. Handbook of Clinical Neurology. 127: Elsevier; 2015. p. 89-104.
31. Guskiewicz KM, Broglio SP. Chapter 10 - Acute sports-related traumatic brain injury and repetitive concussion. In: Grafman J, Salazar AM, editors. Handbook of Clinical Neurology. 127: Elsevier; 2015. p. 157-72.
32. Katz DI, Cohen SI, Alexander MP. Chapter 9 - Mild traumatic brain injury. In: Grafman J, Salazar AM, editors. Handbook of Clinical Neurology. 127: Elsevier; 2015. p. 131-56.
33. Barkhoudarian G, Hovda DA, Giza CC. The molecular pathophysiology of concussive brain injury. Clin Sports Med. 2011;30(1):33-48, vii-iii.
34. Giza CC, Hovda DA. The Neurometabolic Cascade of Concussion. J Ath Train. 2001;36(3):228-35.
35. Johansson J, Nygren de Boussard C, Oqvist Seimyr G, Pansell T. The effect of spectacle treatment in patients with mild traumatic brain injury: a pilot study. J Clin & Exp Optom. 2017;100(3):234-42.
36. Alhilali LM, Yaeger K, Collins M, Fakhran S. Detection of central white matter injury underlying vestibulopathy after mild traumatic brain injury. Radiology. 2014;272(1):224-32.

37. Thiagarajan P, Ciuffreda KJ, Capo-Aponte JE, Ludlam DP, Kapoor N. Oculomotor neurorehabilitation for reading in mild traumatic brain injury (mTBI): an integrative approach. NeuroRehabilitation. 2014;34(1):129-46.
38. Rosenbaum SB, Lipton ML. Embracing chaos: the scope and importance of clinical and pathological heterogeneity in mTBI. Brain Imaging Behav. 2012;6(2):255-82.
39. Smith C. Neuropathology. Textbook of Traumatic Brain Injury: American Psychiatric Publishing; 2011.
40. Konrad C, Geburek AJ, Rist F, Blumenroth H, Fischer B, Husstedt I, et al. Long-term cognitive and emotional consequences of mild traumatic brain injury. Psychol Med. 2011;41(6):1197-211.
41. Duhaime A-C, Rindler RS. Chapter 15 - Special considerations in infants and children. In: Grafman J, Salazar AM, editors. Handbook of Clinical Neurology. 127: Elsevier; 2015. p. 219-42.
42. Miller JH, McKinstry RC, Philip JV, Mukherjee P, Neil JJ. Diffusion-tensor MR imaging of normal brain maturation: a guide to structural development and myelination. Am J Roentgenol. 2003;180(3):851-9.
43. McKeever CK, Schatz P. Current issues in the identification, assessment, and management of concussions in sports-related injuries. Appl Neuropsychol. 2003;10(1):4-11.
44. Niogi SN, Mukherjee P. Diffusion tensor imaging of mild traumatic brain injury. J Head Trauma Rehabil. 2010;25(4):241-55.
45. Pinto PS, Meoded A, Poretti A, Tekes A, Huisman TAGM. The unique features of traumatic brain injury in children. Review of the characteristics of the pediatric skull and brain, mechanisms of trauma, patterns of injury, complications, and their imaging findings-Part 2. J Neuroimaging. 2012;22(2):e18-e41.
46. Chiron C, Raynaud C, Mazière B, Zilbovicius M, Laflamme L, Masure M-C, et al. Changes in regional cerebral blood flow during brain maturation in children and adolescents. J Nucl Med. 1992;33(5):696-703.
47. Giza CC, Mink RB, Madikians A. Pediatric traumatic brain injury: not just little adults. Curr Opin Crit Care. 2007;13(2):143-52.

48. Stuart S, Parrington L, Martini D, Peterka R, Chesnutt J, King L. The measurement of eye movements in mild traumatic brain injury: A structured review of an emerging area. Front Sports Act Living. 2020;2.
49. Ventura RE, Balcer LJ, Galetta SL. The neuro-ophthalmology of head trauma. Lancet Neurol. 2014;13(10):1006-16.
50. Kontos AP, Elbin R, Schatz P, Covassin T, Henry L, Pardini J, et al. A revised factor structure for the post-concussion symptom scale: baseline and postconcussion factors. Am J Sports Med. 2012;40(10):2375-84.
51. Ellis MJ, Cordingley D, Vis S, Reimer K, Leiter J, Russell K. Vestibulo-ocular dysfunction in pediatric sports-related concussion. J Neurosurg Pediatr. 2015;16(3):248-55.
52. Ellis MJ, Cordingley D, Vis S, Reimer K, Leiter J, Russell K. Clinical predictors of vestibulo-ocular dysfunction in pediatric sports-related concussion. J Neurosurg Pediatr. 2017;19(1):38-45.
53. Whitney SL, Sparto PJ. Eye movements, dizziness, and mild traumatic brain injury (mTBI): A topical review of emerging evidence and screening measures. J Neurol Phys Ther. 2019;43:International Conference on Vestibular Rehabilitation:S31-S6.
54. DiCesare CA, Kiefer AW, Nalepka P, Myer GD. Quantification and analysis of saccadic and smooth pursuit eye movements and fixations to detect oculomotor deficits. Behav Res Methods. 2017;49(1):258-66.
55. Cochrane GD, Gould SJ, Sheehan N, Busettini C, Christy JB, Weise KK, et al. Saccadic intrusions in paediatric concussion. Clin Exp Optom. 2020.
56. Schneider KJ, Emery CA, Black A, Yeates KO, Debert CT, Lun V, et al. Adapting the dynamic, recursive model of sport injury to concussion: an individualized approach to concussion prevention, detection, assessment, and treatment. J Orthop Sports Phys Ther. 2019;49(11):799-810.
57. Drachman DA. A 69-year-old man with chronic dizziness. JAMA. 1998;280(24):2111-8.
58. Hain TC, Helminski JO. Anatomy and physiology of the normal vestibular system. Vestibular rehabilitation. 2007;11:2-18.
59. Cioni G, Favilla M, Ghelarducci B, La Noce A. Development of the dynamic characteristics of the horizontal vestibulo-ocular reflex in infancy. Neuropediatrics. 1984;15(03):125-30.

60. Slavik B, Kitsuwa-Lowe J, Danner P, Green J, Ayres A. Vestibular stimulation and eye contact in autistic children. Neuropediatrics. 1984;15(01):33-6.
61. bon Hofsten C, Rosander K. The development of gaze control and predictive tracking in young infants. Vision Research. 1996;36(1):81-96.
62. Braswell J, Rine RM. Evidence that vestibular hypofunction affects reading acuity in children. Int J Pediatr Otorhinolaryngol. 2006;70(11):1957-65.
63. Montgomery PC. Assessment of Vestibular Function in Children. Phys Occup Ther Pediatr. 2009;5(2-3):33-55.
64. Mehta Z, Stakiw D. Childhood Vestibular Disorders. Commun Disord Q. 2004;26(1):5-16.
65. Nandi R, Luxon LM. Development and assessment of the vestibular system. Int J Audiol. 2008;47(9):566-77.
66. Agrawal Y, Carey JP, Della Santina CC, Schubert MC, Minor LB. Disorders of balance and vestibular function in US adults: data from the National Health and Nutrition Examination Survey, 2001-2004. Arch Intern Med. 2009;169(10):938-44.
67. Graham V. Differential Diagnosis and Treatment of Balance Disorders: The interaction of visual, vestibular and somatosensory systems. 2010 April 2010.
68. Suvundra P, Luxon LM. The physiology of equilibrium and its application to the dizzy patient. In. Michael gleeson. Scott-Browns otolaryngology Vol I,6th edn. Oxford: Butter worth-Heinemann; 1997.
69. O'Reilly R, Grindle C, Zwicky EF, Morlet T. Development of the vestibular system and balance function: Differential diagnosis in the pediatric population. Otolaryngol Clin North Am. 2011;44(2):251-71.
70. Uemura T. Neuro-otological Examination: With special reference to equilibrium function tests: University Park Press; 1977.
71. Keshner EA, AK G. Postural abnormalities in vestibular disorders. Vestibular rehabilitation Philadelphia: FA Davis Co. 1994:47-67.
72. Weiss AH, Phillips JO. Congenital and compensated vestibular dysfunction in childhood: An overlooked entity Journal of Child Neurology 2006;21(7):572-9.
73. Herdman S. Vestibular rehabilitation. 3rd ed. ed. Philadelphia: F.A. Davis; 2007.

74. Verbecque E, Marijnissen T, De Belder N, Van Rompaey V, Boudewyns A, Van de Heyning P, et al. Vestibular (dys)function in children with sensorineural hearing loss: a systematic review. Int J Audiol. 2017;56(6):361-81.
75. Gray M, Wilson JC, Potter M, Provance AJ, Howell DR. Female adolescents demonstrate greater oculomotor and vestibular dysfunction than male adolescents following concussion. Phys Ther Sport. 2020;42:68-74.
76. Diaz DS. Management of athletes with postconcussion syndrome. Semin Speech Lang. 2014;35(3):204-10.
77. Akin FW, Murnane OD, Hall CD, Riska KM. Vestibular consequences of mild traumatic brain injury and blast exposure: a review. Brain Injury. 2017;31(9):1188-94.
78. Hoffer ME, Balaban CD, Gottshall K. Vestibular rehabilitation after mild traumatic brain injury with vestibular pathology. Neurorehabilitation. 2011;29(2):167-71.
79. Buch VN. Relationship between presence of clinical oculomotor and vestibular impairments to functional mobility in children and adolescents in the sub-acute stage following mild Traumatic Brain Injury [Masters]. Montréal, Québec, Canada: McGill University 2014.
80. Herishanu YO. Abnormal cancellation of the vestibulo-ocular reflex (VOR) after mild head and/or neck trauma. Neuro-Opthalmology. 1992;12(4):237-40.
81. Master CL, Curry AE, Pfeiffer MR, Metzger KB, Kessler RS, Haarbauer-Krupa J, et al. Characteristics of concussion in elementary school-aged children: Implications for clinical management. J Pediatr. 2020;223:128-35.
82. Chamelian L, Feinstein A. Outcome after mild to moderate traumatic brain injury: The role of dizziness. Arch Phys Med Rehabil. 2004;85(10):1662-6.
83. Maskell F, Chiarelli P, Isles R. Dizziness after traumatic brain injury: results from an interview study. Brain Inj. 2007;21(7):741-52.
84. Ellis MJ, Leddy JJ, Willer B. Physiological, vestibulo-ocular and cervicogenic post-concussion disorders: an evidence-based classification system with directions for treatment. Brain Inj. 2015;29(2):238-48
85. Morris L, Gottshall K. Physical therapy management of the patient with vestibular dysfunction from head trauma. In: R.A HSJC, editor. Vestibular Rehabilitation. Philadelphia F.A. Davis Company 2014. p. 504-29.

86. Balaban CDJ, R. G.; Furman, J. M. Neurologic bases for comorbidity of balance disorders, anxiety disorders and migraine: neurotherapeutic implications. Expert Rev Neurother. 2011;11(3):379-94.
87. Fife TD, Kalra D. Persistent vertigo and dizziness after mild traumatic brain injury. Ann N Y Acad Sci. 2015;1343:97-105.
88. Danna-Dos-Santos A, Mohapatra S, Santos M, Degani AM. Long-term effects of mild traumatic brain injuries to oculomotor tracking performances and reaction times to simple environmental stimuli. J Sci Rep. 2018;8(1):4583.
89. Balaban C, Hoffer ME, Szczupak M, Snapp H, Crawford J, Murphy S, et al. Oculomotor, vestibular, and reaction time tests in mild traumatic brain injury. PLos One. 2016;11(9):e0162168.
90. Bin Zahid A, Hubbard ME, Lockyer J, Podolak O, Dammavalam VM, Grady M, et al. Eye tracking as a biomarker for concussion in children. Clin J Sport Med. 2018;8:08.
91. Ciuffreda KJ, Kapoor N. Oculomotor dysfunctions, their remediation, and reading-related problems in mild traumatic brain injury. J Behav Optom. 2007;18(3):72-7.
92. Ciuffreda KJ, Rutner D, Kapoor N, Suchoff IB, Craig S, Han ME. Vision therapy for oculomotor dysfunctions in acquired brain injury: a retrospective analysis. Optometry. 2008;79(1):18-22.
93. Strupp M, Kremmyda O, Adamczyk C, Bottcher N, Muth C, Yip CW, et al. Central ocular motor disorders, including gaze palsy and nystagmus. J Neurol. 2014;261 Suppl 2:S542-58.
94. Orban de Xivry J-J, Lefèvre P. Saccades and pursuit: two outcomes of a single sensorimotor process. J Physiol. 2007;584(1):11-23.
95. Liversedge SP, Gilchrist ID, Everling S. The Oxford handbook of eye movements. Oxford: Oxford University Press; 2011.
96. Ventura RE, Balcer LJ, Galetta SL. The neuro-ophthalmology of head trauma. Lancet Neurol. 2014;13(10):1006-16.
97. Ventura RE, Balcer LJ, Galetta SL, Rucker JC. Ocular motor assessment in concussion: Current status and future directions. J Neurol Sci. 2016;361:79-86.
98. Pierrot-Deseilligny C, Milea D, Muri RM. Eye movement control by the cerebral cortex. Curr Opin Neurol. 2004;17:17-25.

99. Morton RL. Visual dysfunction following traumatic brain injury. 2010. In: Traumatic Brain Injury - Rehabilitation, treatment, case management [Internet]. Boca Raton, FL: CRC Press, Taylor & Francis Group 3rd. [255-80].
100. Johnson B, Zhang K, Hallett M, Slobounov S. Functional neuroimaging of acute oculomotor deficits in concussed athletes. Brain Imaging Behav. 2015;9(3):564-73.
101. Kapoor N, Ciuffreda KJ, Han Y. Oculomotor rehabilitation in acquired brain injury: A case series. Arch Phys Med Rehabil. 2004;85(10):1667-78.
102. Ciuffreda KJ, Han Y, Kapoor N, Ficarra AP. Oculomotor rehabilitation for reading in acquired brain injury. NeuroRehabilitation. 2006;21:9-21.
103. Ciuffreda K, Kapoor N, Han Y. Reading-related ocular motor deficits in traumatic brain injury. Brain Injury Professional. 2005;2:16-21.
104. Williams IM, Ponsford JL, Gibson KL, Mulhall LE, Curran CA, Abel LA. Cerebral control of saccades and neuropsychological test results after head injury. J ClinNeurosci. 1997;4(2):186-96.
105. DeHaan A, Halterman C, Langan J, Drew AS, Osternig LR, Chou L-S, et al. Cancelling planned actions following mild traumatic brain injury. Neuropsychologia. 2007;45(2):406-11.
106. Maruta J, Suh M, Niogi SN, Mukherjee P, Ghajar J. Visual tracking synchronization as a metric for concussion screening. J Head Trauma Rehabil. 2010;25(4):293-305.
107. Pierrot-Deseilligny C, Müri RM, Ploner CJ, Gaymard B, Demeret S, Rivaud-Pechoux S. Decisional role of the dorsolateral prefrontal cortex in ocular motor behaviour. Brain. 2003;126(6):1460-73.
108. Greenwald BD, Kapoor N, Singh AD. Visual impairments in the first year after traumatic brain injury. Brain Inj. 2012;26(11):1338-59.
109. Heitger MH, Anderson TJ, Jones RD, Dalrymple-Alford JC, Frampton CM, Ardagh MW. Eye movement and visuomotor arm movement deficits following mild closed head injury. Brain. 2004;127(Pt 3):575-90.
110. Paus T, Petrides M, Evans AC, Meyer E. Role of the human anterior cingulate cortex in the control of oculomotor, manual, and speech responses: a positron emission tomography study. J Neurophysiol. 1993;70(2):453-69.

111. Fukushima K, Yamanobe T, Shinmei Y, Fukushima J, Kurkin S, Peterson BW. Coding of smooth eye movements in three-dimensional space by frontal cortex. Nature. 2002;419(6903):157.
112. Averbuch-Heller L, Leigh RJ. Eye movements. Curr Opin Neurol. 1996;9(1):26.
113. Liu GT, Volpe NJ, Galetta S. Neuro-ophthalmology: diagnosis and management. 2nd ed. ed. [Philadelphia]: Saunders Elsevier; 2010.
114. Suh M, Kolster R, Sarkar R, McCandliss B, Ghajar J, Cognitive, et al. Deficits in predictive smooth pursuit after mild traumatic brain injury. Neuroscience letters. 2006;401(1-2):108-13.
115. Suh M, Basu S, Kolster R, Sarkar R, McCandliss B, Ghajar J, et al. Increased oculomotor deficits during target blanking as an indicator of mild traumatic brain injury. Neuroscience letters. 2006;410(3):203-7.
116. Hunt AW, Mah K, Reed N, Engel L, Keightley M. Oculomotor-based vision assessment in mild traumatic brain injury: A systematic review. J Head Trauma Rehabil. 2016;31(4):252-61.
117. Ventura RE, Jancuska JM, Balcer LJ, Galetta SL. Diagnostic tests for concussion: is vision part of the puzzle? J Neuroophthalmol. 2015;35(1):73-81.
118. Ciuffreda KJ, Ludlam DP, Kapoor N. Clinical oculomotor training in traumatic brain injury. Optom Vis Dev. 2009;40(1):16-23.
119. Zee D, Yamazaki A, Butler PH, Gucer G. Effects of ablation of flocculus and paraflocculus of eye movements in primate. J Neurophysiol. 1981;46(4):878-99.
120. Ciuffreda KJ, Kapoor N, Rutner D, Suchoff IB, Han ME, Craig S. Occurrence of oculomotor dysfunctions in acquired brain injury: a retrospective analysis. Optometry. 2007;78(4):155-61.
121. Dursteler M, Wurtz RH. Pursuit and optokinetic deficits following chemical lesions of cortical areas MT and MST. J Neurophysiol. 1988;60(3):940-65.
122. Kelly KM, Kiderman A, Akhavan S, Quigley MR, Snell ED, Happ E, et al. Oculomotor, vestibular, and reaction time effects of sports-related concussion: Video-oculography in assessing sports-related concussion. J Head Trauma Rehabil. 2019;34(3):176-88.
123. Mucha A, Collins MW, Elbin RJ, Furman JM, Troutman-Enseki C, DeWolf RM, et al. A brief vestibular/ocular motor screening (VOMS) assessment to evaluate concussions: Preliminary findings. Am J Sports Med. 2014;42(10):2479-86.

124. Singman EL. Automating the assessment of visual dysfunction after traumatic brain injury. Med Instrum. 2013;1(1).
125. Suter PS. Rehabilitation and management of visual dysfunction following Traumatic Brain Injury. 2010 In: Traumatic Brain Injury - Rehabilitation, treatment, case management [Internet]. Boca Ranton, FL CRC Press, Taylor & Francis Group 3rd. [307-55].
126. Tove MJ. An Introduction to the Visual System. Leiden: Cambridge University Press; 2008.
127. Mays LE, Porter JD, Gamlin PD, Tello CA. Neural control of vergence eye movements: neurons encoding vergence velocity. J Neurophysiol. 1986;56(4):1007-21.
128. Thiagarajan P, Ciuffreda KJ, Ludlam DP. Vergence dysfunction in mild traumatic brain injury (mTBI): a review. Ophthalmic Physiol Opt. 2011;31(5):456-68.
129. Scheiman M, Gallaway M. Vision therapy to treat binocular vision disorders after acquired brain injury: Factors affecting prognosis. Visual and vestibular consequences of acquired brain injuries, Santa Ana, CA: Optometric Extension Program Foundation. 2001:439-48.
130. Cohen M, Groswasser Z, Barchadski R, Appel A. Convergence insufficiency in brain-injured patients. Brain Inj. 1989;3(2):187-91.
131. Hellerstein LF, Scheiman M. Visual Problems Associated with Acquired Brain Injury 2011. In: Understanding and managing vision deficits: A guide for occupational therapists [Internet]. Thorofare, NJ: Slack Incorporated. 3rd. [189-201].
132. Ciuffreda K. Components of clinical near vergence testing. J Behav Optom. 1992;3(1):3-13.
133. Ciuffreda KJ, Tannen B. Eye movement basics for the clinician: Mosby Incorporated; 1995.
134. Ciuffreda K, Han Y, Kapoor N, Suchoff I. Oculomotor consequences of acquired brain injury. Visual and vestibular consequences of acquired brain injury Santa Ana, CA: OEP Foundation. 2001:77-88.
135. Ciuffreda KJ, Kapoor N. Oculomotor dysfunctions, their remediation, and reading-related problems in mild traumatic brain injury. J Behav Optom. 2007;18(3):72.

136. Cifu DX, Wares JR, Hoke KW, Wetzel PA, Gitchel G, Carne W. Differential Eye Movements in Mild Traumatic Brain Injury Versus Normal Controls. J Head Trauma Rehabil. 2015;30(1):21-8.
137. Heitger MH, Jones RD, Macleod AD, Snell DL, Frampton CM, Anderson TJ. Impaired eye movements in post-concussion syndrome indicate suboptimal brain function beyond the influence of depression, malingering or intellectual ability. J Brain Injury. 2009;132:2850-70.
138. Scheiman M. Understanding and managing vision deficits: A guide for occupational therapists: Slack Incorporated; 2011.
139. Kapoor N, Ciuffreda KJ. Vision disturbances following Traumatic Brain Injury. Curr Treat Options Neurol. 2002;4:271-80.
140. Berger S, Kaldenberg J, Selmane R, Carlo S. Effectiveness of interventions to address visual and visual-perceptual impairments to improve occupational performance in adults with traumatic brain injury: A systematic review. Am J Occup Ther. 2016;70(3):7003180010p1-7.
141. Valente LM. Assessment techniques for vestibular evaluation in pediatric patients. Otolaryngol Clin North Am. 2011;44(2):273-90.
142. Philips JO, Backous DD. Evaluation of vestibular function in young children. Otolaryngol Clin North Am. 2002;35:765-90.
143. Fife TD, Tusa RJ, Furman JM, Zee DS, Frohman E, Baloh RW, et al. Assessment: Vestibular testing techniques in adult and children. Neurology. 2000;55(10):1431-41.
144. Wallace B, Lifshitz J. Traumatic brain injury and vestibulo-ocular function: Current challenges and future prospects. Eye Brain. 2016;8:153-64.
145. Zhou G, Brodsky JR. Objective vestibular testing of children with dizziness and balance complaints following sports-related concussions. Otolaryngol Head Neck Surg. 2015;152(6):1133-9.
146. Hamilton SS, Zhou G, Brodsky JR. Video head impulse testing (VHIT) in the pediatric population. Int J Pediatr Otorhinolaryngol. 2015;79(8):1283-7.
147. Lei-Rivera L, Sutera J, Galatioto JA, Hujsak BD, Gurley JM. Special tools for the assessment of balance and dizziness in individuals with mild traumatic brain injury. NeuroRehabilitation. 2013;32(3):463-72.
148. Goebel JA, Tungsiripat N, Sinks B, Carmody J. Gaze stabilization test: A new clinical test of unilateral vestibular dysfunction. Otol Neurotol. 2007;28(1):68-73.

149. Cheever KM, McDevitt J, Tierney R, Wright WG. Concussion recovery phase affects vestibular and oculomotor symptom provocation. Int J Sports Med. 2018;39(2):141-7.
150. Snegireva N, Derman W, Patricios J, Welman KE. Eye tracking technology in sports-related concussion: a systematic review and meta-analysis. Physiol Meas. 2018;39(12):12TR01.
151. Gottshall K, Drake A, Gray N, McDonald E, Hoffer ME. Objective vestibular tests as outcome measures in head injury patients. Laryngoscope. 2003;113(10):1746-50.
152. Zhou G, Brodsky JR. Objective vestibular testing of children with dizziness and balance complaints following sports-related concussions. Otolaryngol Head Neck Surg. 2015;152(6):1133-9.
153. Schneider KJ, Meeuwisse WH, Palacios-Derflingher L, Emery CA. Changes in measures of cervical spine, vestibulo-ocular reflex, dynamic balance and divided attention following sport-related concussion in elite youth ice hockey players. J Orthop Sports Phys Ther. 2018:1-29.
154. Chinn RN, Wang A, Brodsky JR, Raghuram A. Vergence and accommodation in children and adolescent patients with vestibular diagnoses. Investig Ophthalmol Vis Sci. 2020;61(7):1719-1719.
155. Zaslow T, Mueske NM, Yu GJ, Conrad-Forrest A, Edison B, Wren TAL. Oculomotor function in adolescent athletes following concussion. Orthop J Sports Med. 2020;8(4_suppl3):2325967120S0015.
156. McCrory P, Meeuwisse W, Dvorak J, Aubry M, Bailes J, Broglio S, et al. Consensus statement on concussion in sport-the 5(th) international conference on concussion in sport held in Berlin, October 2016. Br J Sports Med. 2017;51(11):838-47.
157. Schneider KJ. Cervicovestibular rehabilitation therapy in sport-related concussion: a randomised controlled trial. Br J Sports Med. 2014;48(17):1294-8.
158. Kennedy E, Quinn D, Chapple C, Tumilty S. Can the neck contribute to persistent symptoms post concussion? A prospective descriptive case series. J Orthop Sports Phys Ther. 2019;49(11):845-54.
159. Taghdiri F, Varriano B, Tartaglia MC. Assessment of Oculomotor Function in Patients With Postconcussion Syndrome: A Systematic Review. J Head Trauma Rehabil. 2017;32(5):E55-E67.

160. Elbin RJ, Sufrinko A, Anderson MN, Mohler S, Schatz P, Covassin T, et al. Prospective Changes in Vestibular and Ocular Motor Impairment After Concussion. J Neurol Phys Ther. 2018;42(3):142-8.
161. Sady MD, Vaughan CG, Gioia GA. Psychometric characteristics of the postconcussion symptom inventory in children and adolescents. Arch Clin Neuropsychol. 2014;29(4):348-63.
162. Davis GA, Purcell L, Schneider KJ, Yeates KO, Gioia GA, Anderson V, et al. The child sport concussion assessment tool 5th edition (child SCAT5): background and rationale. 2017;51(11):859-61.
163. Treleaven J. Dizziness handicap inventory (DHI). Austr J Physiother. 2006;52(1):67.
164. Khadka J, Ryan B, Margrain TH, Court H, Woodhouse JM. Development of the 25-item Cardiff visual ability questionnaire for children (CVAQC). Br J Ophthalmol. 2010;94(6):730-5.
165. Varni JW, Limbers CA, Burwinkle TM. Parent proxy-report of their children's health-related quality of life: an analysis of 13,878 parents' reliability and validity across age subgroups using the PedsQL 4.0 Generic Core Scales. Health Qual Life Outcomes. 2007;5:2.
166. Varni JW. The PedsQL Measurement model for the pediatric quality of life inventory 1998.
167. Varni JW, Seid M, Kurtin PS. PedsQL 4.0: Reliability and validity of the pediatric quality of life inventory version 4.0 generic core scales in healthy and patient populations. 2001; 39(8):800-812.
168. Varni JW, Burwinkle TM, Szer IS. The PedsQL Multidimensional fatigue scale in pediatric rheumatology: reliability and validity. Journal Rheumatol. 2004;31(12):2494-500.
169. Beers SR, Wisniewski SR, Garcia-Filion P, Tian Y, Hahner T, Berger RP, et al. Validity of a pediatric version of the Glasgow Outcome Scale-Extended. J Neurotrauma. 2012;29(6):1126-39.
170. Howell DR, Brilliant AN, Meehan III WP. Tandem gait test-retest reliability among healthy child and adolescent athletes. J Athl Train. 2019;54(12):1254-9.
171. Finnoff JT, Peterson VJ, Hollman JH, Smith JJP. Intrarater and interrater reliability of the Balance Error Scoring System (BESS). 2009;1(1):50-4.

Appendices

Appendix 1.

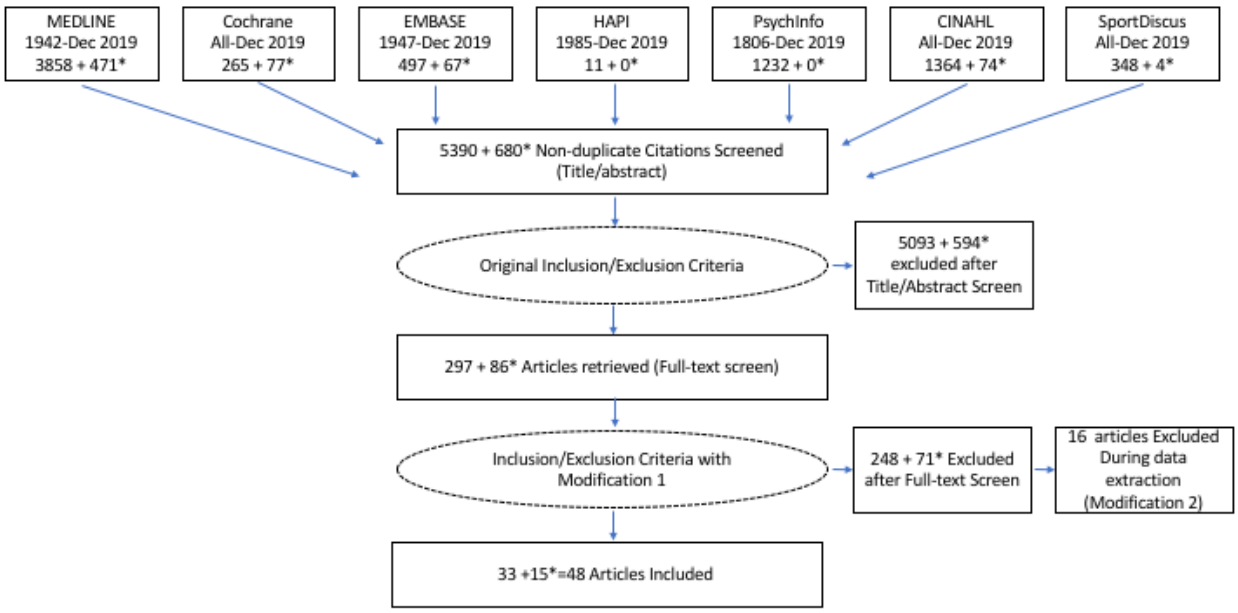
Figure A1.1: Original scoping review search strategy (Ovid Medline)

Database(s): **Ovid MEDLINE(R) ALL** 1946 to November 12, 2019

Search Strategy:

#	Searches
1	Vision Disorders/
2	(vision adj2 disorder*).ti,ab,kf.
3	Eye Movements/
4	Vision, Ocular/
5	visuomotor.ti,ab,kf.
6	Oculomotor Muscles/
7	ocular motility.ti,ab,kf.
8	Oculomotor.ti,ab,kf.
9	eye movement*.ti,ab,kf.
10	Vestibular Diseases/
11	DIZZINESS/
12	Vertigo/
13	Reflex, Vestibulo-Ocular/
14	VOR.ti,ab,kf.
15	vestibular.ti,ab,kf.
16	dizziness.ti,ab,kf.
17	balance.ti,ab,kf.
18	vertigo.ti,ab,kf.
19	vestibulo-ocular.ti,ab,kf.
20	oculo-vestibular.ti,ab,kf.
21	exp Brain Injuries/
22	traumatic brain injur*.ti,ab,kf.
23	brain injur*.ti,ab,kf.
24	head trauma.ti,ab,kf.
25	Head Injuries, Closed/
26	Brain Concussion/
27	concussion.ti,ab,kf.
28	ABI.ti,ab,kf.
29	TBI.ti,ab,kf.
30	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9
31	10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20
32	21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29
33	30 or 31
34	32 and 33

Figure A1.2: PRISMA flow chart.



*Note: *Represents articles included when original search strategy was re-run from November 2018-November 2019*

Appendix 2.

Table A2.1: Description of patient-reported, cervical and balance measures

Outcome measure	Definition
PCSI total	Total score on Post Concussion Symptom Inventory. Developmentally appropriate and bilingual versions were used according to age. Used as a marker of recovery post-concussion (161).
SCAT 5 total	Sport Concussion Assessment Tool 5 total score (162).
Dizziness present on PCSI	Patient-reported dizziness on PCSI. Prompted additional details as to what type of dizziness was present.
DHI total score	Total score on Dizziness Handicap Inventory (163). Developmentally appropriate and bilingual versions were used according to age.
Cardiff total score	Total score on Cardiff Visual Acuity Questionnaire (measured in Logits) (164).
Returned to school	Patient has returned to school
Level of leisure	Self-reported level at which participant is currently participating in leisure activities.
Level of sport	Self-reported level at which participant is currently participating in school
Peds QL total score	Total score on Pediatric Quality of Life Inventory. Brings together generic core scales to measure core health dimensions outlined by the world health organization in youth (165, 166, 167).
Peds Fatigue	Total score on Pediatric Quality of Life Multidimensional Fatigue Scale measuring general fatigue, sleep/rest, and cognitive fatigue (168). Developmentally appropriate versions were used according to age.
Glasgow outcome scale extended	Score on the pediatric version of the Glasgow Outcome Scale measuring overall functional outcome (169).
Neck ROM normal	Normal neck range of motion as measured by passive head rotation, side-flexion, flexion and extension.
Neck pain present	Presence of pain on any of the movements assessing neck ROM.
Cervical flexion endurance	Length of time participant can maintain cervical flexion while lying, knees bent, hands resting on their abdomen. Participant is required to move their chin in the maximally tucked position and then lift their head approximately 2.5cm.
Normal cervical flexion rotation	Measures C1-C2 joint. Tested with patient in the supine position. No firm resistance encountered as examiner fully flexes the cervical spine, then rotates to the right and left with the occiput resting against the examiner's abdomen. Examiner measures disparity between right and left rotation.
Tandem best score	Participant's best time (seconds) on the tandem gait test performed by walking heel to toe along a 3-meter long, 38mm wide line walking forward, turning around and coming back (170).
BESS score	Score on Balance Error Scoring System Assessment. This test is a balance assessment protocol developed specifically for assessing concussion (171).
FGA total	Functional Gait Assessment test and used to assess dynamic balance.

Appendix 3.

Table A3.1: Possible confounders and variables found to be significant in non-imputed models

Variable	Estimate (SE)	P-value
CVAQ		
Age	0.079 (0.049)	0.112
Sex	0.145 (0.226)	0.524
Time since injury	-0.037 (0.017)	0.0390
Version symptom provocation	0.606 (0.323)	0.065
Convergence function	0.747 (0.361)	0.042
DHI		
Age	1.451 (0.744)	0.057
Sex	-1.394 (3.760)	0.712
VO symptom provocation	14.168 (4.064)	0.001
VOR gain left	35.87 (16.689)	0.036
DVA LogMAR left	-35.460	0.005

CVAQ: cardiff visual acuity questionnaire for children; DHI: dizziness handicap inventory; VO: vestibulo-ocular; VOR: vestibulo-ocular reflex; DVA: dynamic visual acuity

Appendix 4.

Figure A4.1: Subgroups grouped by symptom provocation and abnormal function

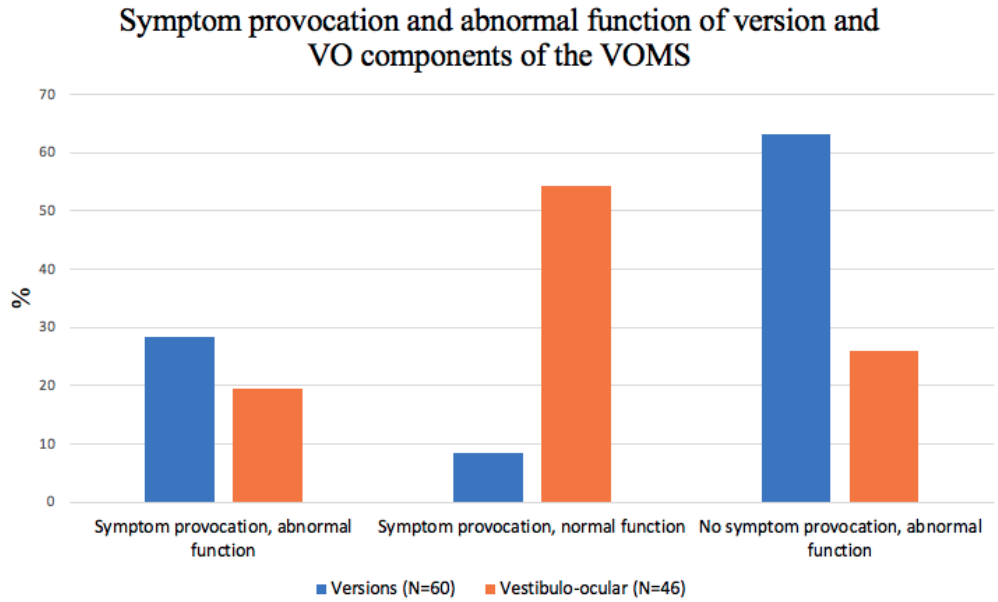


Figure A4.1: Proportions of each sub-group demonstrating their respective positive findings. Symptom provocation is defined as >/= 2 symptoms provoked

Figure A4.2: Characteristics of version subgroups

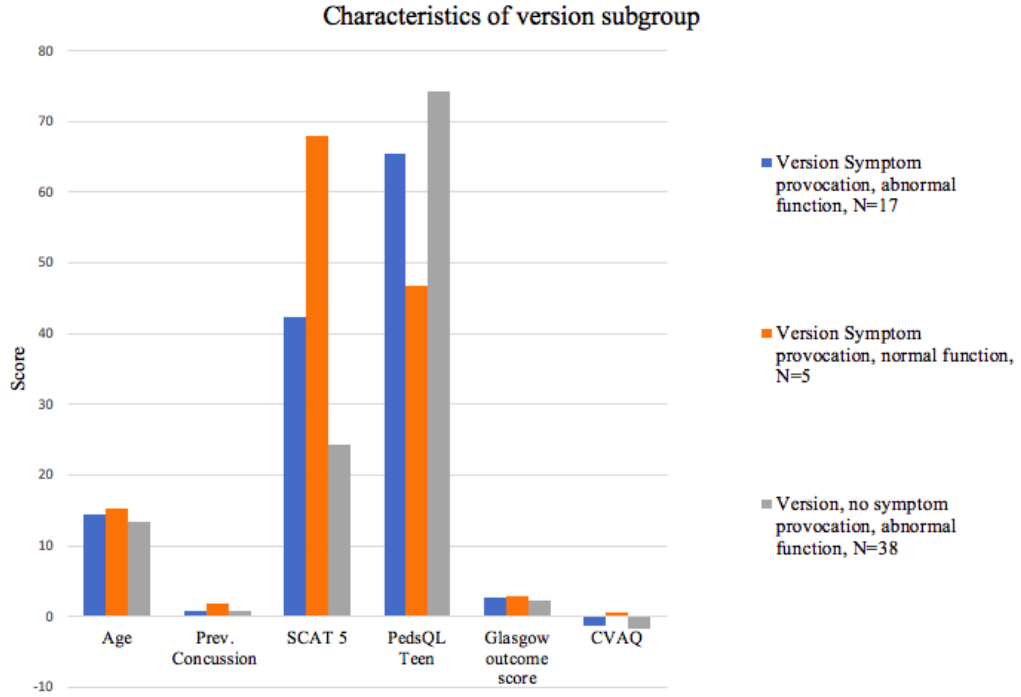


Figure A4.2: General characteristics of sub-groups demonstrating version findings and scores on selected measures. SCAT-5: Sport concussion assessment tool-5; CVAQ: Cardiff visual ability questionnaire

Figure A4.3: Characteristics of VOR subgroups

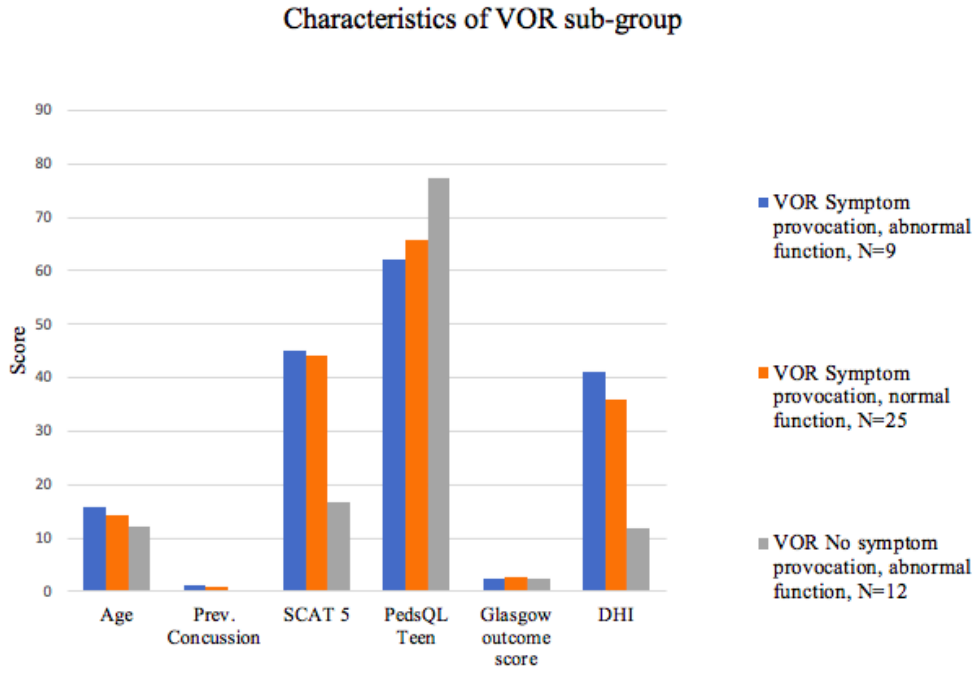


Figure A4.3: General characteristics of sub-groups demonstrating version findings and scores on selected measures. SCAT-5: Sport concussion assessment tool, DHI: Dizziness handicap inventory, VOR: vestibulo-ocular reflex

Appendix 5.

Table A5.1: N values for table 11.4, Study 4 (Manuscript 4)

	T1			T2			T3		
VOMS components tested	**Mean symptom change**	**Proportion >/= 2**	**Proportion Abnormal performance**	**Mean symptom change**	**Proportion >/= 2**	**Proportion Abnormal performance**	**Mean symptom change**	**Proportion >/= 2**	**Proportion Abnormal performance**
Global VOMS symptom provocation	-	34	-	-	35	-	-	36	-
Smooth pursuit	33	33	-	35	35	-	36	36	-
SP horizontal	-	-	34	-	-	36	-	-	36
SP vertical	-	-	34	-	-	36	-	-	36
Horizontal saccade	32	32	34	35	35	36	35	35	35
Vertical saccade	32	32	34	35	35	36	35	35	35
Convergence	32	32	33	35	34	35	36	36	36
Horizontal VOR	33	33	35	35	35	35	36	36	35
Vertical VOR	33	33	35	35	35	36	36	36	36
VMS	33	33	35	35	35	36	36	36	36

Additional OM/VOR tested	**Mean**	**Proportions abnormal**	**Mean**	**Proportions abnormal**	**Mean**	**Proportions abnormal**
Reflexive saccade ICS Impulse saccade latency	29	29	30	30	35	35
Convergence Near point of convergence	27	27	27	27	25	25
VOR gain ICS Impulse vHIT right ICS Impulse vHIT left	 33 33	 33 33	 33 33	 33 33	 33 34	 33 34
DVA InVision DVA LogMAR change left InVision DVA LogMAR change right	 31 31	 31 31	 34 34	 34 34	 35 35	 35 35

N values for associated table in Study 4 (Manuscript 4). As certain data was missing for different outcomes, this table provide the appropriate N values for each. VOMS: vestibular/oculomotor screening tool; VOR: vestibulo-ocular reflex; DVA: dynamic visual acuity; LogMAR: logarithm of the minimum angle of resolution