Perceptual-cognitive training after pediatric mild traumatic brain injury: Towards a sensitive marker of recovery

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For Sylvie & Kenneth, my greatest collaborators

For Émy, may auntie's work have a positive impact on your generation

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Abstract

Background Pediatric mild traumatic brain injury (mTBI) awareness and care seeking has drastically increased over the past years, so much that this condition is now recognized as a public health concern. This condition can present itself through various forms rendering its diagnosis and management difficult for clinicians working with its population. MTBI usually lead to symptoms of physical, cognitive, emotional and sleep-related natures. While most cases recuperate over two to four weeks, about a third of children who sustain an mTBI will experience delayed recovery (having symptoms for over four weeks), and could benefit from rehabilitation interventions. Even after recovery is complete, when children go back to their normal life activities (school, physical, leisure), they are at higher risk of sustaining a second injury than others without a history of such an injury, perhaps because we fail to fully identify subtle deficits. MTBI management comes with its own challenges. First, it is important to identify children that may be at risk of prolonged recovery in order to offer interventions that could aid in rehabilitative processes. Second, there is a need for interventions that are ecological, as most emphasis is currently placed on physical rather than cognitive rehabilitation. Third, there is a need for clinical markers of mTBI recovery to ensure that children going back to activities do not see their risk of re-injury increase.

Objective The overarching goal of this work was to address current research gaps in the clinical management of pediatric mTBI, by following three lines of inquiry. The first line of inquiry consisted of identifying predicting factors of delayed recovery in a clinical outpatient pediatric mTBI population (manuscript I). The second line of inquiry aimed to explore the use of three-dimensional multiple object tracking (3D-MOT) as an intervention for children who experience delayed recovery after mTBI (manuscript II & III). Finally, the use of 3D-MOT was explored as a mean to detect clinical recovery in pediatric mTBI (manuscript IV & V).

Methods and results The first study consisted of identifying predictors of delayed recovery in children who sought care in a specialized mTBI outpatient clinic (manuscript I). Factors such as post-concussion symptom scores, gender, age, history of mTBI, sleep disturbances, anxiety, learning disabilities, attention problems and depression were analyzed through logistic regression on 213 children presenting themselves at the clinic within 10 days of their injury. Results showed that total post-concussion symptom score at their initial visit was a predictor of delayed recovery.

Manuscript II aimed to look at theoretical foundations for the use of 3D-MOT, a perceptual-cognitive training paradigm, to alleviate symptom presentation in pediatric mTBI. The second study used these theoretical foundations (manuscript II) with a study (manuscript III) aiming to explore the tolerability and safety of six 3D-MOT training sessions in symptomatic children after mTBI (n=10). To investigate tolerability, protocol adherence and deviations were recorded; safety was evaluated through symptom presentation at each training session. In addition, clinical measures pertinent to mTBI management were collected. It was demonstrated that minimal protocol deviations (<1%) were performed and that adherence to the training regimen was predominantly maintained (91%). In addition, no adverse effects from training were reported during or after training, allowing us to conclude that 3D-MOT training could be tolerated and be safe in symptomatic pediatric mTBI.

The third study (manuscript IV) explored differences in 3D-MOT training trajectories between children post-mTBI (n=20) and healthy control children (n=14). This study aimed to explore if learning on this training task occurred similarly across groups. Results demonstrated that both groups improved their task performance over time, however, the gains from initial trainings visits occurred more slowly for the mTBI group.

The fourth study (experiment 1: manuscript V) compared 3D-MOT training gains in children that had been followed in a specialized mTBI outpatient clinic and had been clinically cleared for return to activities (clinically recovered n=10) to those of healthy controls (n=10). In addition, clinical measures, such as balance, coordination, speed of processing, quality of life and self-efficacy, pertinent to mTBI recovery were collected. Results demonstrated that clinically recovered individuals performed similarly to controls on 3D-MOT over time and on clinical measures, hence corroborating the hypothesis children identified as clinically recovered using multimodal evaluations such as those delivered in a specialized mTBI program have indeed completed their healing and that their learning occurs similarly to that of healthy controls.

The fifth study (experiment 2: manuscript V) compared 3D-MOT training gains in children who had been followed in a specialized mTBI clinic and had been clinically cleared for return to activities (clinically recovered n=10) to those of children with recent history of mTBI and being in various phases of recovery (n=12) recruited through community partnerships. Significant group differences were found in initial training sessions where children with a history of mTBI exhibit lower training gains than clinically recovered children on 3D-MOT. Results suggest the need for further investigation for the use of 3D-MOT as a clinical marker of mTBI recovery as it was able to highlight training differences across two groups of children with a recent history of mTBI.

Conclusions This work suggested that it is possible to predict which children will be more likely to experience delayed recovery after a mTBI, within an outpatient clinical setting. It also demonstrated that perceptual-cognitive training through the use of 3D-MOT was a potentially safe and tolerated intervention for children who experience persisting symptoms. Last, it demonstrated that training differences can be perceived in 3D-MOT across groups of individuals, and that this training task can identify differences between healthy controls and children having a history of mTBI.

This work showed promising use of 3D-MOT in the management of mTBI and sets ground for future studies using this training paradigm.

Abrégé

Contexte L'incidence des traumatismes craniocérébraux légers (TCCl) a grandement augmenté au cours des dernières années, à un point tel que cette condition médicale est maintenant reconnue comme un souci de santé publique. Cette condition peut se présenter sous plusieurs formes, rendant ainsi son diagnostic et sa gestion difficiles pour les cliniciens travaillant avec cette population. Le traumatisme craniocérébral léger se présente sous des symptômes de nature physique, cognitive, émotionnelle ou reliée au sommeil. Alors que la plupart des cas récupèrent à l'intérieur de deux à quatre semaines; il est estimé qu'un tiers des enfants auront une récupération lente (avoir des symptômes plus que quatre semaines). Ces enfants pourraient bénéficier de stratégies d'interventions afin d'encourager leur récupération. Une fois récupérés et quand les enfants reprennent leurs activités (école, loisirs, sports), ils sont à risque de subir une seconde blessure. Ainsi la gestion des traumatismes craniocérébraux légers soulève plusieurs défis. Premièrement, il est important de pouvoir identifier les enfants à risque de récupération lente afin de leur proposer rapidement des stratégies d'intervention. Deuxièmement, il est nécessaire de pouvoir offrir des interventions qui sont écologiques, puisqu'actuellement l'emphase est placée sur la réadaptation physique plutôt que cognitive. Troisièmement, il y a un grand besoin de trouver un marqueur de récupération clinique afin d'éviter les risques de blessures subséquentes.

Objectif L'objectif général de cet ouvrage est d'adresser les besoins de recherche actuels en lien avec la gestion des TCCl, le tout en suivant trois lignes d'investigation. La première ligne d'investigation consiste à établir des facteurs de prédiction de récupération lente chez une population pédiatrique de TCCl en milieu clinique (manuscrit 1). La seconde ligne vise à explorer l'utilisation de *three-dimensional multiple object tracking (3D-MOT)* comme une intervention pour les enfants démontrant une récupération lente (manuscrits II & III). La troisième ligne explore

l'utilisation du 3D-MOT comme moyen de détection de récupération clinique suite à un TCCl (manuscrits IV & V).

Méthodes et résultats La première étude consiste à identifier des marqueurs de récupération lente chez des enfants qui reçoivent des soins dans une clinique externe spécialisée en gestion de TCCL (manuscrit I). Des marqueurs tels que le score total de symptômes, le genre, l'âge, l'historique de TCCL, de troubles du sommeil, d'anxiété, de difficultés d'apprentissage et de dépression ont été analysés à l'aide de régression sur 213 enfants se présentant à l'intérieur de 10 jours suivant leur blessure. Les résultats ont démontré que le score total de symptômes était un marqueur de récupération lente.

Le second manuscrit explore les fondations théoriques du 3D-MOT, un paradigme d'entrainement de perceptivo-cognition, dans le but de réduire la présentation de symptômes suite à un TCCL. Ainsi, la deuxième étude utilise ses fondations (manuscrit II) afin d'explorer la sécurité ainsi que la tolérabilité d'un protocole de 6 visites (n=10). La tolérabilité est investiguée sous forme d'adhérence et de déviations au protocole. La sécurité est évaluée selon la présence des symptômes à chaque visite. Des mesures cliniques sont également collectées. Il est démontré que des déviations mineures de protocoles ont été présentes et que l'adhérence au programme a été maintenue. De plus, les symptômes n'ont pas augmenté, démontrant ainsi la sécurité du paradigme.

La troisième étude (manuscrit IV) a exploré les différences lors d'un paradigme d'entrainement au 3D-MOT chez des enfants en phase post-TCCl (n=20) et des sujets sains (n=14). Cette étude avait pour but d'explorer et de comparer l'apprentissage lors de cette tâche. Les résultats démontrent que malgré le fait que les enfants post-TCCL peuvent améliorer leur performance, leurs gains sont significativement différents que les sujets sains.

La quatrième étude (expérience 1: manuscrit V) compare l'entrainement au 3D-MOT chez des enfants ayant été suivi dans une clinique spécialisée de gestion des TCCl et ayant obtenu leur congé de traitement (TCCl récupéré n=10), à celui de sujets sains (n=10). Les résultats démontrent que les TCCl récupérés performent similairement au sujets sains. Ainsi nous supposons que leur cerveau apprend cette tâche d'une façon similaire à des sujets sains.

La cinquième étude (expérience 2: manuscrit V) compare les gains à l'entrainement d'enfants ayant été suivi en clinique (TCCl récupéré n=10) à ceux d'enfants avec un historique de TCCl et étant dans diverses phases de récupération (n=12). Des différences dans l'entrainement sont notées lors des premiers entrainements, alors que les enfants avec un historique de mTBI démontrent moins de gains d'entrainement que les enfants avec un TCCl récupéré. Les résultats suggèrent l'investigation du 3D-MOT en tant que marqueur de récupération clinique suite à un TCCl.

Conclusions Cet ouvrage révèle qu'il est possible de prédire quels enfants seront plus à risque d'une récupération lente dans un contexte clinique. Il est également démontré que 3D-MOT peut servir comme intervention potentielle, tolérable et sécuritaire, lors de symptômes persistants. Finalement, il a été démontré que le 3D-MOT peut percevoir des différences chez des groupes d'individus ayant un historique de TCCl. Cet ouvrage contribue à la recherche future sur les interventions et les marqueurs de récupération possible suite à un TCCl pédiatrique.

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Preface

Statement of originality

This thesis solely contains original work designed and conducted by the doctoral student with hopes to contribute in addressing the limitations and gaps currently identified in the literature. Except where specified, material of this work has never been published elsewhere. Studies presented in chapters of this work aim to contribute to the existing body of literature addressing management of pediatric mild traumatic brain injury (mTBI). Original scholarship in this thesis includes;

1) Establishing predictors of delayed recovery in pediatric mTBI individuals seeking outpatient care;
2) Establishing theoretical foundations for the use of perceptual-cognitive training in the management of delayed recovery in the pediatric mTBI population;
3) Exploring the use of perceptual-cognitive training through 3D-MOT in the pediatric mTBI population & contributing to the first known scientific literature using 3D-MOT in this patient population;
4) Exploring the tolerability and safety of a novel perceptual-cognitive training intervention in children experiencing delayed recovery after an mTBI;
5) Exploring the use of perceptual-cognitive training as a marker of recovery in pediatric mTBI.

The results of this PhD will contribute to 1) better understand predictors of delayed recovery in children after mTBI, 2) suggest a potential intervention strategy to assist in recovery and 3) propose a potential detection tool of clinical recovery of these individuals.

Contribution of authors

This thesis is presented in a manuscript format, including a total of five distinct manuscripts. Of these five manuscripts, two are already published in peer-reviewed journals. These manuscripts are the work of Laurie-Ann Corbin-Berrigan under the supervision of Isabelle Gagnon and Jocelyn Faubert, as well as guidance from the supervisory committee. Laurie-Ann Corbin-Berrigan is responsible for research design, data collection, analyses and writing of manuscripts.

Manuscript I: Co-Author Isabelle Gagnon

Study design, data analyses and manuscript preparation were done by Laurie-Ann Corbin-Berrigan. Data collection had previously been conducted as part of the Montreal's Children Hospital's Trauma Program Concussion Clinic's research database, which gathers demographic information as well as care and visits outcomes on individuals followed at the clinic. Isabelle Gagnon assisted through all the steps involved in the preparation of this manuscript and reviewed the final manuscript.

Manuscript II: Co-Authors Jocelyn Faubert & Isabelle Gagnon

Laurie-Ann Corbin-Berrigan, with guidance from Isabelle Gagnon developed the theoretical question to be answered by this theoretical manuscript. Theoretical foundations of 3D-MOT were provided by Jocelyn Faubert. Laurie-Ann Corbin-Berrigan was responsible for proposing the use of this paradigm as an intervention for children with persisting post-concussive symptoms by linking theory provided by Jocelyn Faubert to factors contributing to persistent symptoms. All authors reviewed the manuscript and approved the final manuscript.

Manuscript III: Co-Authors Jocelyn Faubert & Isabelle Gagnon

Study design, data collection, data analyses and manuscript preparation were done by Laurie-Ann Corbin-Berrigan. Isabelle Gagnon assisted through all the steps involved in the preparation of this manuscript and reviewed the final manuscript. Jocelyn Faubert was involved in designing the intervention, reviewed and approved the final manuscript.

Manuscript IV & V: Co-Authors Kristina Kowalski, Jocelyn Faubert, Brian Christie & Isabelle Gagnon

Study design, data collection (Montreal site), data analyses and manuscript preparation were done by Laurie-Ann Corbin-Berrigan. Kristina Kowalski assisted in data collection (Victoria, British Columbia site), as well as helped design the study in order to align procedures at both sites. Jocelyn Faubert and Brian Christie were involved in designing the intervention, reviewed and approved the final manuscript. Isabelle Gagnon assisted through all the steps involved in the preparation of this manuscript and reviewed the final manuscript.

Chapter 1: Introduction

It is estimated that about a third of children sustaining a mTBI will experience delayed recovery as observed through persisting symptoms [1], making them unable to resume meaningful activities (school, leisure, sport) as quickly as they would like. When a child sustains an mTBI, proper management is required to ensure safe and efficient return to activities upon resolution of the injury. While more and more interventions are proposed to facilitate recovery, most continue to focus on the physical aspect of recovery [2-6] although many cognitive or perceptual deficits are often reported. Finally, because research has proposed that physiological recovery could continue beyond clinical return to baseline, there is a need for additional objective clinical markers of mTBI recovery once children report that they are ready to resume activities, to ensure that their return is safe and adequate.

The overarching goal of our work was to explore novel ways to detect who, among children with mTBI, would go on to present with persisting symptoms (beyond 4 weeks) and require additional interventions, as well as to contribute some evidence about an innovative cognitive training strategy which could promote recovery in this population. Specifically, we wanted to explore three lines of inquiries which would target current gaps in the literature on the clinical management of pediatric mTBI; 1) gain better insight on the prediction of which children are most at risk of delayed recovery, 2) propose an intervention to encourage recovery and finally, 3) suggest a performance-based marker of recovery (detection) to assist clinicians in determining when complete recovery occurs.

This thesis is organized in three main sections. First, a general literature review section (Chapter 2) about pediatric mTBI, will be presented covering clinical presentation, management and current rehabilitation approaches as well as some background information about an innovative perceptual-cognitive training paradigm, proposed as a potential intervention and detection tool to assist clinicians. Our experimental work will then be presented in the form of 5 manuscripts as per the table below (chapters 5,7,9,11 & 13). Finally, the last section of the thesis will consist in a general discussion also covering the limitations of our research and future avenues for investigation (chapters 14 & 15).

Manuscript	Title	Page
I	Postconcussion symptoms as a marker of delayed recovery in children and youth who recently sustained a concussion: a brief report	21
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Note: Terms *concussion* and *mild traumatic brain injury* are often used interchangeably within the scientific literature.

Chapter 2: Background

Mild Traumatic Brain Injury

Definition

A mild traumatic brain injury (mTBI), also commonly referred to as a concussion, is defined as a brain injury induced by biomechanical forces that cause the brain to accelerate, decelerate or collide inside of the cranium, potentially occasioning shearing of brain matter [7]. This condition is typically described as a " […] rapid onset of short-lived impairment of neurological function […]" that " […] may result in neuropathological changes, but the acute clinical signs and symptoms largely reflect a functional disturbance rather than a structural injury and, as such, no abnormality is seen on standard structural neuroimaging studies" and which " […] results in a range of clinical signs and symptoms that may or may not involve loss of consciousness. Resolution of the clinical and cognitive features typically follows a sequential course. However, in some cases symptoms may be prolonged." [7]

Incidence

MTBI is often referred to as a silent epidemic due to its dramatically increasing rates [8]. Worldwide, it is estimated that its incidence of hospital visits for mTBI ranges between 100 and 300 cases per 100 000 people [9]. Since underreporting is a common phenomenon when it comes to the pediatric mTBI population [10-13], it is believed that an incidence over 600 cases per 100 000 people would be more accurate [9]. It is suggested that the pediatric population is at greater risk of sustaining this injury [14] and that approximately 1 in 5 children will withstand a head injury before the age of 10 [15]. The commonness of this injury has had health authorities refer to mTBI as a public health priority [16].

Clinical Presentation of mTBI

Self-reported symptoms, referred to as post-concussion symptoms (PCS), play an important role in injury recognition and management. Symptoms associated with an mTBI can be categorized into four main clusters: physical, emotional, cognitive and sleep-related [17]. Physiological [18-20], psychological [19-21] and environmental [20] factors are believed to be responsible for symptom etiology. PCS are prominent in the initial days following the injury and slowly resolve over a predictable period of up to 4 weeks in children [7, 22-25] and 2-3 weeks in adults [7, 26]. However, in some cases they persist in time, and this is referred to as atypical, slow or delayed recovery. It is suggested that symptoms of a physical nature appear acutely after the onset of the injury due to physiological factors from the trauma that disrupt cortical processes [18-20]. Cognitive, sleep-related and emotional symptoms are more likely linked to psychological [19-21, 27] and environmental [20] factors and tend to appear in the more sub-acute to chronic phases for both adult and children populations [28, 29] (Refer to Appendix 1 for hypothesized mechanisms of lasting symptom presentation).

Physical and cognitive presentation of mTBI

Although self-reported symptoms play an important role in the recognition and management of mTBI, identifiable impairments of physical (including visual and vestibular) and cognitive nature are also important to consider. These deficits can be present from the time of injury to weeks following [26], with the most common presentations being: altered balance [7 30], decreased cognitive performance and memory [31,32], increased reaction time [32], decreased visuomotor performance [33] and longer speed of processing [32].

Pathophysiology

Initial self-reported symptoms, as well as physical and cognitive deficits are partially explained by brain physiological mechanisms occurring from the onset of the injury [18-20]. Animal studies have greatly contributed to our increased understanding of mTBI, by providing explanations of the effect of the injury at the cellular level. It is thus suggested that, in the minutes to days following the injury, a complex neurophysiological phenomenon known as the *Neurometabolic Cascade of Concussion* [34] takes place where a complex cascade of metabolic and ionic chain reactions occurs [34]. It is believed that the biomechanical impact causing the mTBI disrupts neurological functions, within less than a second after impact [35]. The injured brain then reacts to this disruption by drastically shifting cellular physiology [34-36]. These changes give rise to post-concussive symptoms as well as physical and cognitive deficits that are believed to remain until the return of homeostasis within cerebral matter [26, 31, 35, 37-39], which can take up to a few weeks [36]. In addition, it is suggested that the mechanical trauma associated with mTBI can cause stretching of neurons and axons, a mechanism recognized as cerebral strain or diffuse axonal injury, which could also contribute to symptom and deficits noted after the injury [40].

Potential lasting deficits of mTBI and their clinical implication

Regardless of recovery status, the literature suggests that children who sustain a head injury are at greater risk of sustaining a second head injury in the months following their initial trauma [41]. It is speculated that subtle persisting cognitive and physical impairments after sustaining a mTBI could potentially be responsible for increased reoccurrence of injury [41-44] due to deficits that can persist even upon symptom resolution [39, 45, 46]. Research has shown that navigation [47-49], motor planning and execution [50], visuo-motor response [33, 50] and visual processing [51] deficits can outlast self-reported symptom recovery. These perceptual and cognitive skills are highly solicited in sport participation and everyday activities [47, 48]. Hence, it is suggested that routine mTBI-specific clinical measures may fail to identify subtle deficits which outlast symptoms [52]. Although mechanisms responsible for these deficits remain unclear, it is suggested that residual impairments in vestibular and visual systems [31, 33, 53] as well as altered neuronal integrity may be partially responsible [54]. Experimental imaging studies have shown that neurometabolic integrity of the brain after mTBI could take weeks to recuperate, therefore potentially explaining the latency in functional recovery [55],

MTBI markers of recovery

The mTBI literature lacks a clinical gold standard to determine what the right time is to return individuals to activities after sustaining a head injury [56, 57]. Many efforts have been deployed in the past decade to find real-time markers of mTBI recovery to assist clinical decision-making when working with that population. Many avenues have been explored such as neuroimaging [58-61] and blood biomarkers [62], however, their clinical utility remains inconclusive.

Hence, despite many efforts made by the scientific community, a clinical marker of recovery that is safe, easy to administer, sensitive, non-expensive, which is as ecological as possible when it comes to determining readiness for safe return to activities (sports, leisure, school) has yet to be identified.

MTBI recovery in the pediatric population

From a clinical standpoint, it is suggested that a large majority of children recuperate from their injury within 4 weeks [7, 22-25]. Clinical recovery is currently ascertained through the resolution of self-reported symptoms, injury-associated psychosocial factors and through the return to baseline of physical and cognitive functioning [7, 63, 64].

It is estimated that up to 30% cases of pediatric mTBI will exhibit delayed recovery with symptoms persisting beyond 4 weeks [65]. This phenomenon is referred to as chronic phases of mTBI or suffering from post-concussion syndrome as per the 10th revision of the International Statistical Classification of Diseases and Related Health Problems (ICD-10) diagnostic criteria [66]. It is recognized that delayed recovery can have detrimental effects on children when it comes to participating in meaningful activities such as school, sport and leisure [7]. For this reason, much emphasis has been placed on identifying factors that could predict delayed recovery so that clinical management could be initiated earlier in order to promote recovery. [67]. Currently available studies suggest that increased initial symptom burden [1, 7, 67-69], being of female sex [1], of teenage age [1], and having pre-morbid factors such as history of migraine [1], and history of previous mTBI [70] with delayed recovery [1] are strong predictors of persistent symptoms presentation [71]. To date, more advanced measures such as neuroimaging and neurocognitive performance have failed to predict delayed recovery when used on their own [72, 73]. Most studies looking at poorer outcome prediction focus on pre-injury factors and presentation at the time of, or in the few hours following the injury. Although these studies have greatly contributed to the identification of children with potential delayed recovery, they are not as helpful for the significant number of individuals (estimated about 800 000 cases yearly in the United States) who seek care later on, in specialized clinical settings [74]. In the adult population, only two studies reported using symptoms as predictors of delayed recovery at 1 week following the injury [75, 76], reinforcing the need for more clinically relevant studies.

Clinical Management of MTBI

Historically, the appropriate management of concussion or mTBI in physically active individuals was to recommend physical and mental rest until symptoms resolution [77]. Once symptoms had resolved for a minimum of 24 hours, a stepwise approach to return to physical activity was recommended. In the case of children, expert consensus recommended an even more conservative approach suggesting a prolonged symptom-free period [77], constraining individuals to remain inactive and away from their meaningful activities for extended periods.

Fortunately, studies on the adverse effects of prolonged rest [78-80] helped remove such an emphasis on rest, and allow light physical activity in the early period post-injury [7]. In fact, the last published Consensus Statement on Concussion in Sports [7], which represents world leading experts recommendations on the management of sport-related concussions, now advocates the use of rest solely in the first 48 hours following the injury. Individuals are now encouraged to gradually incorporate some level of activities in their daily routine, if no symptoms are triggered or exacerbated, and subsequently engage in a stepwise approach for return to full activities once symptoms have resolved [7]. In cases where symptoms persist, current expert recommendations promote the use of active rehabilitation approaches [7]. Active rehabilitation, in the context of mTBI is referred to as the use of light physical activity as well as other focused therapies to alleviate symptoms.

Interventions for delayed recovery

The concept of active rehabilitation has been introduced over the past decade [2, 3, 5, 6, 81-84] and is now being endorsed by world leading experts in the field [7]. In the pediatric population, Gagnon and colleagues demonstrated that youth who presented with atypical recovery, could benefit from a rehabilitation program consisting of aerobic and coordination exercises as well as visualization and education [5, 6]. In the adult population, various rehabilitation approaches such as education, cognitive behavioral therapy and aerobic exercise have demonstrated benefits on mTBI recovery [2, 3, 85, 86]. There is also an increasing trend in the literature to support the implementation of rehabilitation programs that are multidimensional, through exploration of cognitive, vestibular, and psychological therapies [87, 88]. Other researchers and experts in the field have also supported this approach, and have suggested that rehabilitation strategies involving perception and cognition be explored [89]. It is believed that symptoms may be diminished by facilitating brain plasticity [90]. To this day, little evidence on the effectiveness of cognitive rehabilitation programs after an mTBI can be found, especially in the pediatric population.

Proposed suggestions with regards to mTBI clinical recovery

On one hand we know, from previous sections of this work, that current management strategies for clearance of return to activities after mTBI may be flawed. Self-reported symptoms are often underreported and there are known persisting deficits of mTBI that are unrecognized by routine measures. Guskiewicz and colleagues [91] stated that the ideal sport concussion assessment battery should include measures that are objective, reliable, valid, easy to administer and time efficient. MTBI measures need to be ecological and representative of challenges faced by individuals when returning to their activities. In order to facilitate return to activities and diminish risk of re-injury, children need to be physically and cognitively ready. As presented, many efforts are placed on physical abilities post-mTBI, and less is known about the cognitive skills that are required to engaged back in activities [7]. For example, it is believed that children's perceptual-cognition is highly stressed upon when returning to sports or engaging back into social scenes [92]; requiring children to quickly and adequately perceive complex visual scenes. This area of research would be pertinent to investigate in order to reduce risk or re-injury when reintegrating activities.

On the other hand there is a clear need expressed by experts in the field of mTBI management to incorporate cognitive rehabilitation strategies to promote recovery [7]. From available literature, we also know that perceptual-cognition can too be trained over time [93-96]. Hence, perceptual-cognition, a yet explored avenue in mTBI research, offers promising grounds for intervention and detection measures when it comes to mTBI clinical management.

Perceptual-Cognitive training

Perceptual-Cognition

Perceptual-cognition, refers to experience-induced cognitive learning [97, 98]. It is believed that perceptual-cognition is deeply embedded into our interactions with the world and that perception through our senses can contribute to acquire knowledge [97]. Most commonly, research involving perceptual-cognition focuses on the role of the visual perception [97, 99, 100]. Visual perceptual-cognition is highly solicited on a daily basis whether we are learning new skills through visual cues, participating in sport activities or just browsing through visual scenes. Visual perceptual-cognition is believed to be a trainable skill anchored in brain plasticity [101].

Targeting brain plasticity

Cerebral plasticity refers to the brain's ability to modify its connections and wiring [102] in response to experiences and stimuli of various nature [103]. Plasticity plays an important role in human development. Plastic abilities of the brain are known to be augmented in childhood [104, 105], only reaching adult-like learning abilities by the end of teenage years, with periods of maximal learning capacities until the age of 10 [105]. Lifelong plasticity is believed to be trainable, resulting in improved cognitive functioning [106, 107]. At the brain cellular level, enhanced plasticity can be explained through brain-derived neurotrophic factor (BDNF); a crucial component of synaptic regulation [108]. Increases in BDNF expression, from physical and cognitive training, can lead to increased synaptic efficacy [109], which is highly linked to learning and memory [108].

In the field of rehabilitation, it is widely accepted that the damaged or injured brain can benefit from plasticity-focused intervention strategies, of which the main purpose is to restitute functions of altered brain circuitry [110, 111]. Many studies confirm the positive effects of such rehabilitation regimens on various populations suffering from cerebral lesions [112-121]. Visually-guided plasticity-related strategies are easily used, non-invasive methods involving binocular vision, with examples such as: Exploration training [122, 123], Optokinetic stimulation [124, 125] and Multiple object tracking [126].

Multiple object tracking

Multiple object tracking (MOT) has initially been studied and advertised through Pylyshyn's FINST (FINgers of INSTantiation)'s theory [127]. The FINST theory suggested that indexation of visual objects within a visual scene was an automatic process [128]. Groundwork was based on the hypothesis of a primitive visual system. This system would allow the eyes to attend to broad scenes with focal attention tracking moving stimuli, hence targeting visual recognition and discrimination [129]. Through the years, visual theories based on Pylyshyn's work have evolved and are now translated into currently available perceptual-cognitive training strategies.

Multiple object tracking consists of tracking multiple moving objects (MOT) in a virtual setting [129]. MOT, a dynamic paradigm, requires an individual to split attention between a limited number of moving objects, through the ability to discriminate between targets and distractors [130]. It harnesses three main components of attention: 1) Selectivity, 2) Capacity, and 3) Effort [131, 132]. It is hypothesized that MOT targets visuospatial short-term memory as well as working memory [133], in both the adult [134] and the pediatric populations [135]. MOT, an active task, mimics demands of everyday living, where attention needs to be separated between multiple visual information sources [136, 137]. It is broadly recognized and highlighted in the literature that one can benefit from training in a MOT paradigm

[132, 136, 138]. Training using MOT can be quantified through maximum speed at which targets can be tracked amongst distractors, and this is referred to as *speed thresholds* [92, 139]. *In the case of MOT, speed thresholds represent a value reflecting overall task performance, where higher speed thresholds are a synonym of increased speed at which the brain can process visual scenes.*

Multiple object tracking in the pediatric population

The literature suggests that children can perform MOT-based tasks [130, 140, 141]. It was also noted that children who engage in sports activities and videogames will most likely exhibit greater tracking performance in the amounts of targets they can follow [130]. This finding supports the theory that perceptual-cognition is a skill that can be trained [92]; hence suggesting that children could benefit from exposure to MOT training [142-144]. When considering screening abilities of MOT, research suggests that performance on this paradigm could also be sensitive to altered brain development [145], in population such as children suffering from Turner's Syndrome [145] and William's Syndrome [146].

Perceptual-Cognitive training through Three-Dimensional Multiple Object tracking

An emerging methodology based on the concepts of MOT has recently gained popularity in the athletic world, and is now the object of increasing research. Its popularity rests in its ability to combine virtual reality, sports science and neurophysics [147]. This methodology is delivered through the NeuroTracker platform (CogniSens, Montréal, Qc) [147]. This task relies on MOT, in a three-dimensional virtual reality setting (3D-MOT), using a large visual field, and at individualized optimal speed thresholds. *Since the NeuroTracker was the first and currently is the only patented platform delivering 3D-MOT, both terms can be use interchangeably in the context of our work.*

The task consists of following (tracking) a predetermined number of spheres, out of others acting as distractors, that move, bounce, and randomly spread through a large visual field, and properly identify these spheres upon their immobilization [147]. The spheres are all identical in shape and color. Before each trial, some spheres are highlighted, and then returned to their original color. Participants are asked to track those spheres for the duration of the trial. The main task starts at a given speed, and speed from one trial to another is adjusted based on the performance of the participant. For example, if the participant can correctly identify all spheres that were identified as targets, the speed of the next trial will increase, if the participant fails to identify correctly all spheres previously identified, the speed of the following trial will be decreased [92]. Thus creating an individualized training regimen for participants, requiring them to work their perceptual cognitive skills at their outmost limits [92]. Each training session provides a speed of processing value, referred to as speed threshold. This training may be repeated in time in order to improve speed thresholds [92]. *Methodological considerations and procedures involved in 3D-MOT will be discussed in later chapters of this work.*

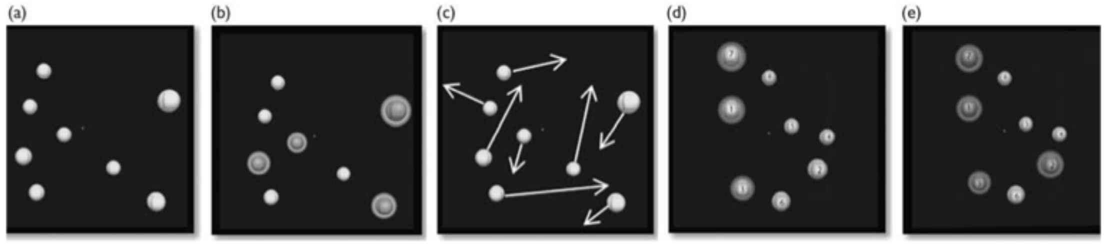

Illustration of the five critical phases: (a) presentation of randomly positioned spheres in a virtual volumetric space, (b) identification of the spheres to track during the trial, (c) removal of identification and movement of all spheres with dynamic interactions, (d) stoppage and observer's response by identifying the spheres, (e) feedback is given to the observers.

Reproduced with permission[148]

Figure 1 Representation of a 3D-MOT training trial

Success of this training methodology resides on its four main characteristics, 1) MOT, 2) Large visual field, 3) Speed thresholds, 4) Stereoscopy [149], which allow for this training paradigm to stand out compared to other available options. First, the use of MOT has been widely studied in improving cognitive processes through repetitive exposure or training [132, 136, 138]. Second, the literature suggests that regular training of visual field may lead to improvement in overall vision [150-152], even in brain injured individuals [153]. Third, using speed thresholds [154, 155], or optimal individualized training speed [92] have shown to be efficient ways to improve cognitive performance[156] as more attentional resources are required at increased speeds [156, 157]. Improvements in speed thresholds can be translated into improvements in visual speed of processing and allow to quantify task-specific effects over time. Lastly, stereoscopy or the use of a three-dimensional environment, although understudied, has demonstrated beneficial cognitive effects [158], and serves as a more ecological approach to cognitive training, representing stresses pertinent to activities of daily living [92, 159].

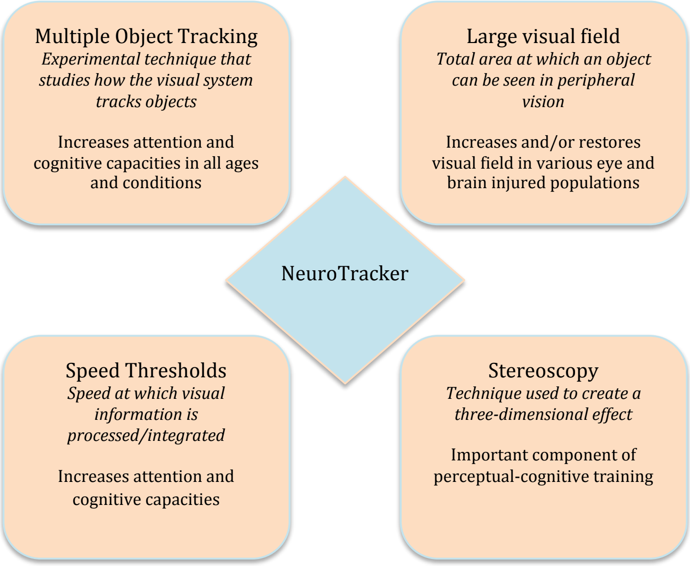

Figure 2 Underlying mechanisms behind each of the four components of the NeuroTracker and their individual training benefits

For reasons stated above, the NeuroTracker has been widely studied to improve attention-related measures in various populations including the military [160], elderly [148, 161], athletes [92, 159, 162, 163], and more recently children with developmental conditions [142-144]. Studies involving the use of 3D-MOT in athletes support the trainable, task-specific effects of 3D-MOT [164] with significant speed threshold increases over the course of training [92, 159, 162, 165]. Work with other populations has shown similar benefits of training as well. For example, the elderly population has shown to have improved speed thresholds over a training period [166]. In fact, it was even possible in an elderly population to improve their performance, through enhanced plasticity, up to the point when their perceptual-cognitive abilities matched those of healthy young adults who had not been trained with 3D-MOT [138]. Beauchamp & Faubert (2001) suggest that in the initial hour of training, an improvement in reaction time of 50% can be noted [167] .

Improvements in 3D-MOT performance over a training period can be observed and quantified through speed threshold gains over time or learning curves. Across studies, it was suggested that despite different initial performance, learning abilities of various populations follow a predictable and stable path [92, 161, 162], regardless of age and level of athletic abilities (ex: professional athletes versus non-athletes; elderly versus young adults). The characteristic learning trajectory (through repetitive speed threshold calculations) observed during training with 3D-MOT potentially allows it to be used as a proxy for brain function.

Aside for task-specific improvements, it is suggested that training on this platform can also transfer to other cognitive measures of cognitive performance. For example, after training, athletes seem to perform better in sport-specific evaluations [92 159], elderly show improved biological motion perception [148] and children with neurodevelopmental conditions exhibit improved overall attention in various situations [144]. A recent study by Parsons and colleagues [168] demonstrated quantifiable changes in brain electrophysiological activity after training. Authors suggest that 3D-MOT has a robust potential for transferability of training gains to other tasks through neural re-organization [168]. Repetitive 3D-MOT training was associated with improvements in attention, working memory and visual speed of processing [168], and these improvements were supported by notable changes in brain function [168], thus reinforcing the theory that 3D-MOT has a direct impact on brain plasticity.

3D-Multiple object tracking as a detection tool

Although widely recognized as a training paradigm, the NeuroTracker was furthermore found useful as an assessment tool of specific attention skills in different populations [143, 169, 170]. In the athletic population, it was shown that basketball players exhibiting greater performance on initial 3D-MOT speed threshold calculation, were most likely to demonstrate better sport-specific measures of performance [169]. Similar measures have also been used as a way to quantify laparoscopic surgical skills on medical students [170], demonstrating the potential uses for this measure outside of the athletic world. In the pediatric population, it was shown that initial performance of children with developmental disorders on this task correlated to higher performance on tests specific to attention [142]. Lastly, recent findings suggest that speed thresholds are indicators of attentional resources capability of individuals being trained on the task [157].

3D-Multiple object tracking in the pediatric population

To date, little evidence is available on the use of the NeuroTracker in the pediatric population. Tullo and colleagues (2016; 2017) [142, 143] studied the use of 3D-MOT in children with developmental conditions such as autism spectrum disorder (ASD), attention deficit with hyperactivity disorder (ADHD) and intellectual disability. These studies demonstrated that children with developmental disorders can improve their performance on the NeuroTracker through repeated trainings [142, 143]. Moreover, it was also suggested that, although non-significant, training with the use of 3D-MOT improved overall performance on a variety of attention tests [143]. Unfortunately studies by Tullo and colleagues (2016; 2017) [142, 143] constitute the only available information on the use of the NeuroTracker in the pediatric population. Since the NeuroTracker has been shown feasible and has had training benefits on other brain conditions such as ASD and ADHD, it would be interesting to study the impact of this type of training in the pediatric mTBI population. *To our knowledge, studies presented in the following chapters of this work are the first to be studying pediatric mTBI population with the use of 3D-MOT.*

Chapter 3: Rationale and Objectives

Our review of the literature has established that recovery from mTBI in the pediatric population can be broadly categorized into typical recovery, with symptom resolving within days to weeks of the injury, and delayed or atypical recovery, where symptoms persist over 4 weeks, thus preventing complete return to activities. Despite available rehabilitation interventions, there is a highlighted need to involve more cognitive processes in the active rehabilitation protocols that are currently available. Last, it was also demonstrated that despite available resources, clinical markers of recovery after mTBI are still required to ensure safe and effective return to activities.

Despite efforts by many to fill the gaps in evidence in the field of pediatric mTBI, it remains difficult for clinicians to 1) predict how children will evolve and who will go on to have persisting symptoms; 2) know what to offer to this group of children in order to promote their recovery, and 3) determine when kids are healed and ready to return to the activities they love to do. This doctoral work will contribute to the body of evidence by pursuing those three lines of inquiry.

1- To identify predictors of delayed recovery in children and youth who sustained an mTBI and sought care in a pediatric, hospital-based, mTBI program.

This line of inquiry was undertaken to facilitate clinicians' efforts to identify children with delayed recovery, in order to better plan and provide active rehabilitation interventions that could aid in the healing processes.

2- To explore the contribution of a perceptual-cognitive training paradigm as an intervention for children who present with persistent symptoms after mTBI

The main purpose of this second line of inquiry was to generate knowledge about an addition to current management options for this population. First by examining the theoretical foundations of 3D-MOT performed with the NeuroTracker and how those can be linked to mTBI recovery. Second by exploring the tolerability and safety of a training regimen using the NeuroTracker in a population of symptomatic mTBI youth as a mean of active rehabilitation. This general objective addressed what is referred to as the 'training' capacity of 3D-MOT, and was separated into the following specific aims.

a. **To establish theoretical foundations for the use of 3D-MOT as a mean of active rehabilitation in children and adolescents who are experiencing delayed recovery after an mTBI.**

b. **To explore the tolerability and safety of a 6 training sessions of 3D-MOT as a mean of active rehabilitation in children that are experiencing delayed recovery after an mTBI.**

3. To explore the use of 3D-MOT as a clinical marker of normal cerebral function, after sustaining an mTBI

This line of inquiry was undertaken to explore the potential of 3D-MOT as a clinical marker of recovery. What is here referred to as the <u>detection</u> capacity of this training paradigm has been studied in various populations, by examining learning curves on the task, which are usually found to be both stable and predictable. Specific aims for this objective are therefore:

a) **To compare 3D-MOT learning gains in the post-acute phases of mTBI to those of healthy controls.**
b) **To explore discriminant abilities of 3D-MOT as a marker of clinical recovery by comparing 3D-MOT learning gains in children that are discharged from an mTBI clinic to those of those of children in post-acute phases of mTBI and healthy controls.**

Chapter 4: Introduction to the 1st manuscript

Previous sections of this work have illustrated that the pediatric mTBI population is one of complex nature, with symptoms that can either be transient in nature or that can persist for weeks. Hence it was well established that although each and every mTBI case is different, type of recovery could be seen within two major categories 1) typical and 2) atypical or delayed.

Unfortunately, when facing mTBI cases, it is very difficult for clinicians to determine into which category a patient will fall, as limited prediction factors and rules are currently available. It was however shown within the first sections of this work that more and more focus is placed on the importance of identifying children that will be at risk of experiencing delayed recovery in the hopes of improving patient care by partaking in rehabilitation interventions sooner. This has resulted in an increase in information available on prediction rules and factors of delayed recovery, at the time of injury or in the hours following the injury. Although these studies may be quite enlightening, there is still a gap in the literature when it comes to typical cases a clinician will face within an outpatient context. Better identification of these potential cases could tremendously contribute to provide rapid and more comprehensive rehabilitation interventions that are tailored for this specific population.

Thus the initial study (manuscript I) of this work targeted to assess this gap by *identifying predictors of delayed recovery in children and youth who sustained an mTBI and sought care in a pediatric, hospital-based, mTBI clinic* (objective 1 of this doctoral work).

Chapter 5: Manuscript I

Post-concussion symptoms as a marker of delayed recovery in children and youth who recently sustained a concussion: A brief report

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Short title: Markers of delayed recovery in pediatric concussion

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Abstract

Objective: Identify predictors of delayed recovery in children who sustained a mTBI and sought care in a pediatric hospital.

Design: Retrospective cohort study design.

Setting: Montreal Children's Hospital Concussion Clinic's database

Patients: Children who sustained a concussion and sought care within 10 days of the injury, with complete medical history and Post-Concussion Symptoms Scale (PCSS) score available.

Independent Variables: Total symptom score on the PCSS, gender, age, history of concussion, sleep disturbances, anxiety, learning disabilities, attention problems, depression.

Main Outcome Measure: Delayed recovery (28 days or more).

Results: 213 children (F=76, M=138) with a mean age of 13.89±2,55 years were included. Only total PCSS score at 10 days post-injury was identified as a significant predictor of delayed recovery (OR: 1.019 p=0.01).

Conclusions: This study demonstrates the potential for clinicians to identify, with the sole use of the PCSS, children at risk of experiencing symptoms for longer periods of time.

Keywords: Concussion; mild traumatic brain injury; children; paediatrics; post-concussion symptoms; delayed recovery; slow to recover.

Introduction

Clinicians working with the pediatric concussed population rely mostly on symptom resolution to ascertain recovery post-injury, as advocated by current expert consensus on the management of concussions[1]. Rest is the primary treatment strategy for concussion in the acute phase of recovery; literature suggests that children and adolescents should abstain from physical and cognitive activities until complete symptom resolution [1]. This strategy works for most children with many of them recovering in the first month [2]. However, 10-20% of children and adolescents sustaining a concussion will experience symptoms beyond 4 weeks (28 days) [1, 3], classifying them as being *slow to recover, or suffering from post-concussion syndrome as per ICD-10 diagnostic criteria*[4]. Delayed or slow recovery affects participation in every day activities such as school and sports. There is an increasing need for clinicians to identify children at risk of requiring more healthcare intervention for their atypical recovery, with approaches such as active rehabilitation [1].

Current literature focuses on prediction of recovery from reported symptoms experienced at the time of injury [5-7]. Other reports suggest that the majority of mild head injury cases are not immediately reported to health care professionals [8], causing children to seek medical care days after the injury, when initial symptoms cannot easily be recalled, in settings such as hospital-based concussion rehabilitation programs.

The identification of markers of delayed recovery could help guide clinicians in choosing appropriate rehabilitation strategies, as early as their initial consultation with this population. *The aim of this study was to identify predictors of delayed recovery in children and youth who sustained a concussion and sought care in a pediatric, hospital-based, concussion clinic.*

Methods

A retrospective cohort study design, based on The Montreal Children's Hospital Concussion Clinic's clinical database was used. This clinic mainly offers services to physically active children (ages 5-18), wishing to obtain clearance to return to activities, or begin a rehabilitation program for their persisting symptoms.

Participants were included if they had sustained a concussion, as per World Health Organization's definition [9], and were seen by professionals of the Concussion Clinic between April 1 2012 and March 31 2013. Participants whose Post-Concussion Symptoms Scale (PCSS) score was obtained within 10 days of the injury (initial visit to clinic), and who had a complete medical history, were included. Total symptom score on the PCSS, gender, age, history of concussion, of sleep disturbances, of anxiety, of learning disabilities, of attention problems and of depression were used in order to find the best predictive model of delayed recovery.

Total PCSS was gathered from the Sport Concussion Assessment Tool 2 (SCAT-2) symptom evaluation [10]. This symptom evaluation checklist assesses the presence and severity of 22 common symptoms on a scale of 0 (none) to 6 (severe).
Children were identified with delayed or slow recovery if they experienced symptoms for more than 28 days while being followed at Concussion Clinic, whereas children symptom-free as per clinical assessment and discharged from the clinic in less than 28 days post-injury were identified as normal recovery. Children were continuously seen at the concussion clinic until either discharged to return to activities, referred to other health care professional or voluntarily dropped out of the clinic's program. Ethical approval was obtained from the Montreal Children's Hospital Research Ethics Board.

Statistical analyses

Binary logistic regression was used to identify markers (PCSS, gender, age, history of concussion, sleep disturbances, anxiety, learning disabilities, attention problems and depression) of delayed recovery in children who had recently sustained a concussion, with a significance level set at <0.05. Ad Hoc analyses were performed on each category of the Post-Concussion Symptom Scale (physical, cognitive, emotional, sleep). Due to the uneven amount of symptoms per category, data analysis included percentage of total possible score with respect to each category. Ad Hoc analyses were also performed to assess prediction abilities of individual post-concussion symptoms.

Results

A total of 213 children (F=76, M=138) with a mean age of 13.89±2,55 years were included (Table 1). Of the total, 113 participants met the criteria for delayed recovery. Study groups demonstrated no significant differences with regards to age, gender, number of days post-injury, history of sleep disorder, anxiety, depression, learning and attention problems as well as number of previous concussions.

Total PCSS score at 10 days post-injury was identified as a significant predictor of delayed recovery (OR: 1.019 p=0.01) (Table 2). Post-concussion symptoms were separated into 4 major categories (physical, cognitive, emotional, sleep disturbances); which were separately analyzed. The *Emotional* category showed a strong tendency toward significance for predicting delayed recovery (OR: 7.287 p=0.05), when looking at percentage of total score for this category. In addition, when looking at individual symptoms, *Irritability* demonstrated a tendency (p=0.07) when predicting slow recovery.

Table 1 Patients' characteristics and Post-Concussion Symptom Scale score at initial visit presented for overall group and sub-groups (Slow versus Normal recovery)

	Overall	Slow Recovery	Normal Recovery
N	213	100	113
Gender			
Male	138 (65%)	66	71
Female	76 (35%)	47	29
Age	13.89±2.55	14.11±2.48	13.64±2.64
Days after injury	5.54±2.52	5.67±2.48	5.44±2.54
# of previous concussions	0.63±0.81	0.67±0.78	0.57±0.83
Concussion Hx	101 (47%)	58	43
Sleep Disorder Hx	32 (15%)	18	14
Anxiety Disorder Hx	46 (22%)	25	21
Depression Hx	5 (2%)	2	3
Learning Disability Hx	10 (15%)	4	6
Attention Problems Hx	16 (18%)	10	6
PCSS Total*	26.80±19.92	30.14±19.72	23.09±19.67
PCSS % Physical	22.65±16.31	25.05±16.29	20.06±16.03
PCSS % Cognitive	21.57±19.80	23.70±19.74	19.08±19.76
PCSS % Emotional*	13.03±18.63	15.97±20.44	9.83±15.88
PCSS % Sleep	18.07±26.45	17.99±24.92	18.33±28.28

* Where significant ($p<0.05$) independent t-tests differences where found between Slow and Normal recovery sub-groups

Table 2 Odds Ratio for prediction of Slow recovery based on Post-Concussion Symptom Score, and its associated categories

Category	Symptom	Odds Ratio	Significance
Physical		11.93	0.13
	Headache	0.90	0.46
	Pressure in head	1.13	0.45
	Neck pain	1.08	0.50
	Nausea	0.98	0.88
	Dizziness	0.83	0.19
	Blurred vision	1.17	0.40
	Balance difficulty	1.13	0.46
	Sensitivity to light	0.97	0.82
	Sensitivity to noise	1.18	0.25
Cognitive		0.44	0.53
	Feeling slowed down	1.04	0.81
	Feeling in a fog	0.98	0.93
	Don't feel right	0.93	0.64
	Difficulty concentrating	0.99	0.94
	Difficulty remembering	1.08	0.62
	Fatigue	1.22	0.14
	Confusion	0.73	0.11
Emotional**		7.29	0.05
	Emotional	1.25	0.27
	Irritability	1.29	0.07
	Sadness	0.86	0.48
	Nervousness	1.11	0.55
Sleep		0.81	0.72
	Drowsiness	0.98	0.89
	Difficulty falling asleep	0.85	0.21
PCSS Total*		1.02	0.01

* Where significance was reached ($p<0.05$)

**Where a strong trend toward significance was noted

Discussion

This study demonstrates the potential for clinicians to identify, with the use of the PCSS, children at risk of experiencing symptoms for longer periods of time after a concussion. Indeed, self-reported symptoms (PCSS total and Emotional category) within 10 days of injury, in a hospital-based, clinical rehabilitation setting, predict delayed recovery, in the youth and adolescent population. Other factors such as age, gender, history of concussion, number of previous concussion, history of anxiety, depression, learning disability, attention problems, and sleep disturbances do not appear to be predictors of delayed recovery in the pediatric population.

Results support those of previous studies [7] [11], where delayed recovery in the pediatric population was associated with higher PCSS score at the time of injury, regardless of other factors such as age, gender, medical history, etc. Results as such [7] [11] demonstrate that, in a clinical setting, self-reported symptoms may be used as a predictor of delayed recovery in the youth and adolescent population after suffering a concussion, whether they are assessed at the moment of the injury, or more importantly a few days later.

Special attention in future researches should focus on presentation of symptoms from PCSS categories (physical, cognitive, emotional, sleep). In this study, *Emotional* category symptom percentage score seemed to represent a prediction factor for delayed recovery. These results support a study by Cunningham and colleagues [12], where, in individuals aged 14 and higher, seeking hospital care, somatic symptoms tended to decrease in time, whereas symptoms of cognitive and emotional nature tended to persist. Hence, future research should focus on presentation of persisting symptoms, especially those of emotional nature.

A limitation of this study was the number of participants involved in the statistical analysis. A greater number of children could have brought more power to the analyses, and potentially solidify results when it comes to post-concussion symptoms.

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Chapter 6: Integration of manuscript I and II

Our first study (manuscript I) identified markers of delayed recovery in the pediatric mTBI population and will contribute to provide a better understanding of the clinical presentation of this population. This research differed from previously published work, as it evaluated children who did not seek care immediately following their injury, which is more representative of the reality faced by most rehabilitation clinicians working with this population. The results suggested that it is possible, through the use of symptom reporting, to identify children who are more at risk of experiencing delayed recovery from mTBI. Being able to identify children at risk in a clinical context can contribute to identifying more comprehensive and earlier rehabilitation strategies that can assist in faster symptom alleviation and overall injury recovery.

In the next study (manuscript II) we introduce our second line of inquiry by exploring the theory behind the intervention that will be proposed in the context of the rest of our work: 3D-MOT. This paradigm is included in the NeuroTracker platform. We aimed to link the theoretical foundations of 3D-MOT to its potential effects on symptom presentation. This manuscript provides the theoretical background necessary to validate the use of the 3D-MOT as a potential mean to assist clinicians in the overall management of mTBI.

Chapter 7: Manuscript II

Enhancing brain plasticity through perceptual cognitive training: Three dimensional multiple object tracking and its potential role in post-concussion symptom resolution in the pediatric population

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Abstract

Cognitive interventions for the management of persistent symptoms in pediatric mild traumatic brain injury (mTBI) are advocated for despite mechanisms responsible for symptom presentation being incompletely understood. These mechanisms should be better understood in order to properly prescribe intervention strategies to enhance symptom recovery from a physiological perspective. In addition, to this date, most literature focuses on the effects of physical interventions on symptoms presentation, whereas limited information is available on the effects of cognitive interventions. This theoretical article articulates the current hypotheses regarding the underlying mechanisms of mild traumatic brain injury related symptoms from a broad physiological view. This article introduces a type of cognitive intervention involving visual perception that could tackle these mechanisms. Hence, a strategy using multiple object tracking for enhancing brain plasticity is presented within the context of symptomatic mTBI management. This training paradigm has been widely studied in athletes and elderly and seems to have all necessary components for rehabilitation of symptomatic mTBI. It proposes that large visual field, speed thresholds, stereoscopy and the use of multiple object tracking embedded in its training would promote brain plasticity in healthy, aging and injured brains. Its theoretical framework supports its use as a mean to alleviate symptom presentation.

Keywords: concussion, mTBI, symptoms, NeuroTracker, perceptual cognitive training, 3D-MOT

Introduction

Mild traumatic brain injury (mTBI), is induced by traumatic biomechanical forces affecting the brain [1]. This condition creates complex pathophysiological processes which result in a graded set of clinical symptoms from the initial time of the injury to days, and sometimes weeks, following [1, 2]. This condition is fairly common in physically active populations, especially in children and adolescents [3]. Typically, symptoms present following the injury will resolve within two to four weeks [4] in the pediatric population, with children most likely experiencing symptoms such as, but not limited to, headache, fatigue, sleep disturbances and dizziness [1, 2, 5]. Unfortunately, it is estimated that up to 30% of pediatric mTBI cases will suffer from post-concussive symptoms (PCS), lasting over four weeks [1, 6]. These children are referred to as exhibiting slow or delayed recovery after mTBI. Current standard of care in the pediatric mTBI population is to allow for a few days of physical and cognitive rest, and then promote light activities such as walking until symptom resolution, and gradual re-integration of school, physical and leisure activities [1]. However, research has recently shown that removing children and adolescents from their meaningful activities, such as sports, leisure and school could in fact have adverse effects on recovery causing increased symptom scores as well as cognitive and physical deconditioning [7, 8]. Many efforts have been deployed to find active rehabilitation strategies that could help children in their recovery process by diminishing symptom presentation, and allowing them to resume their meaningful activities sooner. These strategies have mainly emphasized the paradigms that use light physical activity, oculomotor and vestibular therapies [1, 9, 10], with the most popular being sub-symptom threshold physical activity [11, 12]. Most of the ground work supporting the use of exercise in alleviating symptoms resides in exercise-induced improvement in overall brain plasticity [11, 12], which could also be obtained with cognitive rehabilitation approaches. For this reason, expert recommendations advocate the addition of cognitive rehabilitation to current strategies for symptom management [1, 10, 13-15]. To date, little is known about the effects of cognitive rehabilitation on symptom presentation and recovery after pediatric mTBI. This article aims to provide a theoretical rationale for the use of cognitive rehabilitation in the pediatric mTBI population, based on brain physiological processes occurring as a result of this injury. Therefore, we are proposing an innovative cognitive management strategy to reduce symptoms based on these cortical mechanisms.

Underlying brain mechanisms of active rehabilitation after mTBI

Active rehabilitation after mTBI is believed to have numerous potential beneficial effects on individuals, including improved mood, self-esteem, cognitive functioning and most importantly reducing symptom burden [11]. Its theoretical foundation is mainly anchored in physical activity-induced plasticity changes in the brain [11]. Indeed, it is well established that physical activity can have a direct impact on brain plasticity [16] by encouraging neurogenesis [16] [11, 17]. Brain derived neurotrophic factor (BDNF), a type of growth factor, is known to be responsible for this phenomenon, through its increased cortical concentration upon exercise [16-18]. BDNF is believed to be essential for successful brain functioning and networking [19]; facilitating cellular metabolism and vascularization [19]. In the context of active rehabilitation, it is suggested that BDNF could assist in maintaining, as well as encouraging, the growth of new neural pathways after a brain injury. Studies have also endorsed the role of BDNF in improving cognitive processes in various populations [20-23], hence supporting the use cognition-based intervention strategies for mTBI rehabilitation.

Cognitive rehabilitation is an abundant field of research in the management of brain injuries [24-27]. Many studies have shown increased brain plasticity as a result of cognitive training [28-31]. Studies in healthy aging [32-34] and brain injuries [35-37] have successfully demonstrated that through enhanced plasticity, notable changes after cognitive training were noted in improved executive function [34] such as working memory [33, 38], vision [35-37], and attention [33]. Meta-analyses on the topic demonstrate the potential of cognitive rehabilitation to benefit individuals with acquired brain injuries [25, 39] and moderate to severe traumatic brain injuries [40]. Only a few studies are available in individuals who recently sustained an mTBI, and those are focused on the adult population. However, these studies encourage the use of cognitive rehabilitation mainly to improve cognitive processes after injury [41, 42]. It is believed that enhancing brain plasticity through cognitive rehabilitation could encourage neurogenesis, and could speed the consolidation of new/modified networks [35, 43]. However, limited evidence is available on the potential of this rehabilitation strategy for its beneficial effects on symptom presentation after mTBI, despite expert recommendations. Before investigating the use of cognition-based rehabilitation strategies for persistent symptoms, it is important to highlight causes of said symptoms, such as injury-related physiological changes. Hence, when deciding upon which rehabilitation methodology to use, one must consider how this methodology can affect potential physiological mechanisms that may be responsible for prolonged symptom presentation.

Potential causes of Post-Concussive Symptoms

Factors associated with cortical changes in the brain after an mTBI are referred to as physiological type factors [44-46], and for the purpose of this work, can further be categorized into neurometabolic and diffuse axonal injury (DAI).

Neurometabolic injury

When the brain sustains an injury such as mTBI, a complex cascade of metabolic and ionic chain reactions occurs [47] with the biomechanical impact of mTBI disrupting neurological functions in the brain [48]. It is suggested that within seconds of the injury, the brain reacts to this disruption by radically shifting cellular physiology [48]. This shift in cellular physiology results in a chain effect of alterations of ionic concentrations [47-49]. It is estimated from animal models that these alterations last for weeks [49]. This phenomenon is recognized as a neurometabolic cascade, which results in an accumulation of calcium in the brain [47]. It is believed that impaired neural connectivity [47], irritated vasculature of meninges [48], diminished cerebral blood flow [50] and mitochondrial respiration dysfunctions [50] may occur as a reaction to the neurometabolic cascade. When brain physiology is changed by an insult to its structure, either directly or indirectly, plasticity is greatly affected through altered neurogenesis [43, 47, 50]. Once brain homeostasis is returned, damaged networks can remodel and consolidation of these new neural networks can occur [43, 48, 51]. It is suggested that changes in homeostasis could be at the root of symptoms appearance from an physiological neurometabolic standpoint [47].

Functional magnetic resonance imaging (fMRI) research supports this hypothesis and has shown that after injury, the brain's ability to allocate attention and to adapt to change can be reflected in working memory alterations [52-54]. Research has told us that alterations in working memory can initially give rise to symptoms of cognitive complaints and later on translate into physical, emotional and sleep-related types of symptoms [44, 55, 56]. In addition, the visual system also demonstrates accommodative dysfunctions due to neuronal changes in the brain. Hence visual complaints, which are quite common after sustaining a mTBI could possibly be explained by this phenomenon [57].

Diffuse axonal injury

The mechanical trauma associated with mTBI can cause disruptive stretching of neurons and axons, a mechanism that can also recognized as a cerebral strain. DAI can arise from acceleration shear, pressure gradients/skull distortion, and cervical spine stretch [58]. The shearing force associated with DAI can cause disturbances of neural networks, alteration of neural excitability, and inability to properly propagate action potentials [58] hence altering plastic abilities of the brain [58]. It is believed that DAI also affects working memory, which can cause posttraumatic amnesia and difficulties with short-term memory, and cognitive fatigue [54, 55, 58]. Diffuse axonal injury can create posttraumatic changes in physical systems (vestibular, visual and postural reflexes), causing changes in visual and auditory processing such as visual deficits and blurred vision[59, 60], tinnitus [61], hyperacusis [61], dizziness and balance deficits [62, 63].

For the brain to heal after a brain insult, it first needs to remodel and consolidate newly created networks [43]. Hence, the ideal cognitive rehabilitation strategy should exhibit potential in generating new networks and should demonstrate transferability of training intervention to activities of daily living. The following section of this work will aim to propose an innovative perceptual cognitive methodology for treatment of symptoms following mTBI. Its components will be presented, and its potential as a mean to alleviate symptoms presentation through enhanced plasticity will be discussed.

An innovative research/training method: Three Dimensional Multiple Object Tracking

The NeuroTracker technology (CogniSens Industries, Montreal, Qc, Canada), is a perceptual-cognitive training platform relying on three dimensional multiple object tracking (3D-MOT). This technology first emerged from combining virtual reality, sports sciences, and neurophysics [64]. Perceptual-cognitive training on this platform consists of tracking moving objects amongst distractors in a 3D virtual reality setting. Training is achieved by modifying the speed at which tracking is being performed [64].

Originally, the NeuroTracker's main focus was to train athletes to recognize and process complex movements. This type of training is known to enable athletes to distribute attentional resources at optimal speed of processing speeds throughout the visual field; ultimately enhancing their performance in sports settings [64]. In recent years, a number of studies hypothesized that repeated training on 3D-MOT could have a direct role on improving brain plasticity [65-67] by generating brain networks [66]. This assumption was confirmed by Parsons et al., (2016) where quantifiable changes in electroencephalography (qEEG) were demonstrated through repeated training on 3D-MOT[66]. In addition, when comparing cognitive measures performance, pre- and post-training, to those of healthy controls, it was demonstrated that individuals who received training improved their performance on measures of cognitive function [66]. Altogether, these results permitted to conclude that benefits of training on 3D-MOT could be transferred to activities of daily life [66], rendering this training methodology even more interesting for clinical use. Furthermore, these results suggest that this methodology could have an impact on generating brain networks, hence directly tapping into plastic abilities of the brain. Emerging transferability studies can support this theory, where training gains on 3D-MOT were transferred to real-life situations [68, 69].

From a clinical standpoint, the use of 3D-MOT as a rehabilitation strategy for persistent symptoms in pediatric mTBI is interesting. First, it is readily available: it is currently widely used in the sports industry, with more and more teams and clinics having access to the NeuroTracker platform. Second, it has been used in children before and has demonstrated that the pediatric population can train under this paradigm and exhibit training gains that transfer to improvements in cognitive measures [70, 71]. Third, it directly targets the plastic abilities of the brain, as demonstrated through qEEG and transferability studies [66, 68-71] thus making it an ideal strategy in the management of pediatric mTBI.

It is advocated that the success of this training paradigm resides in its global approach to perceptual-training; it is comprised of four main characteristics thought to be essential in making it different from other perceptual-cognitive methods [72]: 1) Multiple object tracking, 2) Large visual field, 3) Speed thresholds, 4) Stereoscopy [72].

Active components of the NeuroTracker platform

Multiple objects tracking (MOT)

Multiple object tracking (MOT) is based on a theory of primitive mechanisms being responsible in tracking moving visual features. It consists of tracking multiple objects that are moving, bouncing and colliding, within a visual scene [73]. MOT is a dynamic paradigm, requiring individuals under training to split attention between a limited number of moving objects [74, 75]. It is hypothesized that MOT targets visuo-spatial short-term memory as well as working memory [76], in both the adult [77] and the pediatric populations [78]. A number of studies have highlighted the potential for paradigms involving MOT to improve plasticity [66, 69, 79, 80], and how this acquisition of new knowledge could benefit various populations [75, 81].

Visual field

Visual field, also known as field of vision, refers to the range into which the immobile eye can perceive objects. The literature suggests that regular training of visual field may lead to improvement in overall vision in healthy [82-84] and brain injured individuals [85]. Performing tasks that require the implication of both eyes is believed to aid in the process of recovery, creating a reorganization of cortical synaptic connections [84]. Damage to the visual field can be a consequence of an injury from cortical damage, which, for example and as previously described, can occur following a TBI [86]. It is believed that field of view training can induce visual improvement that go beyond simply visual field improvement [85], and that these enhancements in vision can be transferred through a generalization effect to visually guided activities of daily living [84].

Speed thresholds

Studies demonstrate that the speed at which we perceive and process visual cues can be improved through training [87, 88], with the use of perceptual learning tasks increasing in stimulation velocity [87, 89], such as MOT. Although the literature on the precise mechanisms behind speed threshold improvements is currently incomplete, some researches shed light on some possibilities. For example, a study on monkeys has demonstrated that speed perception is directly linked to temporal neurons [90], which are linked to visual and auditory sensory inputs, as well as object and space relationships [91]. It is also suggested that perceptual learning occurs through improved plasticity induced by retinal inputs, most likely in the primary visual cortex [92]. Although these mechanisms remain under study, it is possible to suggest that brain plasticity may be a contributor for such improvements. More importantly, to strengthen the hypothesis that neural plasticity is responsible for training gains, various studies have shown that speed threshold training is transferable to other cognitive tasks [88, 89, 93, 94] and activities of daily living [88, 89, 93]. In fact, studies related to transferability provide a strong argument on the implication of neural plasticity, suggesting that neural pathways become more efficient over time and eventually can transfer to other activities.

Stereoscopy

Stereoscopy refers to the ability to make the viewing of objects in a three-dimensional fashion. Little evidence is available on the effects of repetitive training under a stereoscopic paradigm. However, Wittenberg et al., (1969) illustrated that stereoscopic acuity can in fact be trained, and beneficial to subjects undergoing training [95]. Authors suggest that training in three-dimension could boost brain plasticity through neural re-organization from binocular processing of stereoscopic cues [95].

Perceptual learning and Plasticity

The preceding section demonstrated potential effects of perceptual learning beyond perception itself. Indeed, changes in visual areas, beyond visual cortex, can occur through visual perceptual learning [96]. It is also suggested that perceptual training is also beneficial on working memory [97, 98]. Where training of working memory not only activates related areas, but spreads the activation to areas close-by [99], hence, directly tapping into brain plasticity and neurogenesis. These assumptions render this methodology very interesting in the management of PCS in the MTBI population.

Discussion

How 3D-MOT administered through the NeuroTracker platform could help alleviate PCS

The theoretical framework of the NeuroTracker platform (MOT, visual field, speed threshold and stereoscopy) targets mechanisms that would principally affect symptoms related to physiological sources. Indeed, the literature on MOT, visual field and speed thresholds demonstrate that brain plasticity can be improved through repetitive training. Moreover, all four components of the NeuroTracker, have the potential to increase neural processing relative to vision [82, 100, 101]. It has been demonstrated multiple times that when these four components are brought together through the NeuroTracker platform, training gains can be transferred to improved working memory, attention, processing speed and even activities of daily living (ADL) [66, 68, 69, 102]. It is suggested in the field of cognitive training that transfer effects to non-trained tasks occurs through training-induced plasticity [103]. The fact that training gains on 3D-MOT can transfer to aspects non-related to training itself (eg. ADL) demonstrates the more global effect that this task offers on enhancing overall brain plasticity and function, and that these effects could persist in time. These results have been supported by quantifiable brain imaging changes upon repetitive training, where resting state neuroelectric function of the brain was increased upon repetitive training and linked to overall improvements in cognition [66]. Legault and Faubert (2012) showed that transferable training gains of 3D-MOT were still present beyond training itself in elderly individuals [81], supporting the idea that cortical changes induced by training can persist in time and assist in non-specific task performance. Indeed, elderly individuals, were able to improve their cognitive capacities, which allowed for transferability to better interpret biological movements, a socially relevant task in this age group [81]. Although Legault and Faubert's study focused on older individuals, it has recently been shown that age is not a factor for functional visual rehabilitation outcome in mTBI [104].

3D-MOT as a piece of the puzzle

Similarly to light physical activity, the use of a cognitive paradigm for rehabilitation in persistent PCS, can be supported by its ability to enhance plasticity. We believe that 3D-MOT delivered through the NeuroTracker platform, through its main components could be used as a rehabilitation strategy by facilitating symptom recovery and potentially improving clinical outcomes after a mTBI [72]. More and more emphasis is placed on active rehabilitation as a mean to manage PCS in the mTBI population [1]; this work sets grounds for the use of the 3D-MOT as a complement to current management strategies, through cognitive training.

Initially, the NeuroTracker was created to improve skills of athletes performing sports under high perceptual cognitive stresses [105]. Training has shown to transfer to sports performance [69, 105], and biological motion in elderly [68]. Hence, it is possible that training benefits under this paradigm could go beyond symptom management in the pediatric mTBI population and could assist children in regaining skills that are necessary to return to their meaningful activities, such as sports, and reduce the risk of re-injury or premature return.

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Chapter 8: Integration of manuscripts II and III

In the previous chapter (manuscript II) we discussed the theoretical foundations of 3D-MOT, explained its active ingredients, and how they could help provide new ways of treating persisting symptoms in the pediatric mTBI population. This chapter set grounds for the intervention line of inquiry of this doctoral work. It was argued that 3D-MOT delivered by the NeuroTracker platform has the ability to impact brain plasticity by improving neural networks in the healthy brain and we proposed that this characteristic could promote the resolution of pediatric mTBI symptoms. To date no known studies have looked at this training paradigm as an intervention in persistent mTBI symptoms and limited information is available on the tolerability and safety of 3D-MOT in the pediatric symptomatic mTBI population.

To follow this line of inquiry, our next study proposes to introduce this methodology in a clinical perspective, exploring its potential as an aid to the rehabilitation of persistent symptoms in MTBI. Study 3 (manuscript III) therefore will explore the tolerability and safety of using the NeuroTracker in a case series of children with mTBI experiencing delayed recovery and persistent post-concussion symptoms.

Chapter 9: Manuscript III

The use of three-dimensional multiple object tracking as a mean of active rehabilitation in children who are experiencing prolonged recovery after mild traumatic brain injury: a tolerability and safety study.

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Abstract

Introduction: Mild traumatic brain injury (mTBI) has a high incidence in physically active youth. While many recover within two to four weeks, 30% of individuals will continue to experience symptoms beyond 4weeks (delayed recovery). Relative rest is predominantly used as a management strategy for these individuals after sustaining this type of injury. However, recent studies demonstrate that prolonged rest might potentially be responsible for adverse effects on youth as they are removed from meaningful activities. For these reasons world leading experts in the field recommend providing rehabilitation strategies that could assist mTBI recovery in youth when symptoms persist, such as active rehabilitation measures (both physical and cognitive). Recent studies suggest that light physical activity could aid in symptom presentation and ultimately recovery. Nevertheless, very little is known on the feasibility and effects of cognitive rehabilitation in a symptomatic pediatric mTBI population. Faubert et al. recently introduced Three-Dimensional Multiple Object Tracking (3D-MOT) in various populations as a mean of training cognition, and have demonstrated that cognitive gains achieved through training are predictable and can transfer to real-life activities by stimulating brain plasticity. **Objective:** To determine the tolerability and safety of using 3D-MOT with children who experience delayed recovery post-concussion, as well as to explore its impact on symptom resolution. **Participants:** 9 youth aged 12 to 17 years old (mean age =14.61 years), followed for delayed recovery at the Montreal Children's Hospital's Trauma Center Concussion Clinic. **Methods:** Children were trained over 6 visits using 3D-MOT, every 2 to 7 days. Each visit consisted of 3 reaction time calculations on the task, as well as symptom reporting. In addition, at visit 1 and 6, clinical measures including balance, coordination, quality of life, self-efficacy and mTBI-specific cognitive test battery (ImPACT) were administered. **Results:** All participants were able to complete the visits and tolerated the task with no adverse events reported. Tendency for symptom reduction and improved fatigue levels through the course of training were noted. **Conclusion and Discussion:** This first of a kind, exploratory study sets the stage to study the impact of using 3D-MOT training in pediatric symptomatic mTBI patients. Results demonstrate that children can perform the task safely and tolerate the training regimen. In addition, symptomatic children can be trained and improve their task-specific reaction time trough repetitive trainings using 3D-MOT. This allows us to conclude that training on 3D-MOT is safe and tolerable in this population and although additional studies are required, this paradigm could potentially aid in mTBI recovery from a clinical standpoint.

Key words: mild traumatic brain injury, symptoms, intervention, 3D-MOT, perceptual cognitive training, NeuroTracker

Introduction

Mild traumatic brain injury (mTBI), also referred to as concussion in the athletic domain, is a condition with growing incidence in physically active youth [1]. In Canada, it is estimated that about 40% of children and adolescents presenting themselves to emergency departments for a sport-related head injury will be diagnosed with a concussion [2]. Diagnosis and management of mTBI greatly rely on clinical presentation in the form of self-reported symptoms [3, 4]. A wide array of symptoms can result from this injury with the most common being headache, fatigue, sleep disturbances and dizziness [5, 6]. Studies have demonstrated that for the majority of individuals, symptoms resolve within two weeks [7].

It is estimated that up to 30% of pediatric mTBI cases will experienced delayed/atypical recovery [5, 8, 9], exhibiting symptoms for longer than 4 weeks [10]. The most common persisting symptoms are fatigue, headache, dizziness, memory issues, irritability, and sleep disturbances [11-13]. Currently, mTBI management is largely symptom-limited, meaning that proposed recommendations suggest that individuals do not resume complete physical and cognitive activities (such as sport, leisure, school, work) while still experiencing symptoms. In children, management is suggested to be more conservative, due to the potential risks of catastrophic second impacts that are specific to that age group [14]. This translates into prolonged asymptomatic days before the initiation of a stepwise approach to return to physical/sport activity [3] and other risk-taking behaviours, which is initiated only once a complete return to school activities without accommodations is achieved. [3]. Management strategies need to balance the need for initial activity restrictions in the days following the injury and potential rehabilitation strategies offered to individuals with PCS. Keeping children away from their meaningful activities can have adverse effects on physical and psychological aspects, leading to even more delayed recovery [15].

Hence, there is a need for rehabilitation strategies that can encourage recovery when it comes to persisting symptoms in the pediatric mTBI population. Studies have shown that children who are slow to recover can benefit from active rehabilitation paradigms. For example, low level evidence studies report that after entering a physical activity rehabilitation program consisting of light physical activity and visualization, individuals achieved clinical recovery from their mTBI within two to twelve weeks [16, 17]. Further recommendations for pediatric mTBI management suggest to implement multidisciplinary rehabilitation programs that comprise cognitive, vestibular, and psychological therapies in addition to low-intensity aerobic activity [18].

To this day, little evidence is available for the effectiveness of cognitive rehabilitation programs after an mTBI, especially in the pediatric and adolescent population. However, the use of cognitive training has shown positive outcomes in adults having sustained a TBI [19] [20] and children with acquired moderate to severe brain injuries [21-23]. For these reasons, we believe there is a need to explore the possibility of using cognitive activities with children who are slow to recover after an mTBI, in order to facilitate the recovery process, improve clinical outcomes and ensure a safe return to activities.

One of the most common types of cognitive training specifically targeting perception and attention is known as Multiple Object Tracking (MOT) and it has been used as basis for cognitive training regimens for decades [24-28]. MOT, a dynamic training paradigm repeated over time, is believed to tap into selectivity, capacity and effort, three crucial components of attention [29, 30]. This paradigm requires individuals to split their visual attention between a number of targets and distractors that are in motion within the visual field [27]. Training under a MOT paradigm is believed to improve visuo-spatial short-term memory as well as working memory [31-33]. A recent training paradigm using the foundations of MOT within a three-dimensional context is gaining in popularity, especially in the sports performance world. This paradigm is referred to as Three-Dimensional Multiple Object Tracking (3D-MOT) and is delivered through the NeuroTracker platform (CogniSens Industries, Montréal, Qc, Canada). This training paradigm was initially created to improve perceptual skills of athletes, and ultimately improve their performance in sports. 3D-MOT is now widely used in research contexts where dynamic visual attention is trained in various populations (elderly, military personnel, healthy controls, children with autism spectrum disorder) [34-38].

Perceptual-cognitive training is supported by theoretical principles that degraded cognitive performance can be trained by enhancing brain plasticity [39]. Elderly individuals who exhibited lower perceptual skills than younger adults managed to improve their perceptual skill performance to the level of young adults only after a few 3D-MOT training sessions [40]. Children with neurodevelopmental disorder improved their performance on the task and other related clinical measures of cognition [41]. As previously mentioned, there is a great need for interventions of cognitive nature in the management of pediatric mTBI [3]. Based on available knowledge, 3D-MOT could be a suitable candidate to add to current active rehabilitation protocols in order to enhance recovery after an mTBI. Moreover, it is suggested that 3D-MOT training could decrease anticipatory response time in play actions, boost confidence and increase abilities in physically active individuals when returning to activities after an injury [39], components that are crucial for participation.

To our knowledge, this is the first study examining the safety and tolerability of 3D-MOT in children who are experiencing delayed recovery after an mTBI. Hence the aim of this study is to explore the tolerability and safety of a 6-training visits with a 3D-MOT paradigm in children who are experiencing delayed recovery after a mTBI. We hypothesized that 3D-MOT would be well tolerated and safe to use as a potential means of cognitive rehabilitation in children with persisting symptoms, and favor clinical recovery.

Methods

Participants

A sample of 9 children and adolescents aged 12 to 17 years old with persistent post-concussive symptoms were enrolled in the study. Enrolled participants sought care at the Montreal Children's Hospital's Trauma Center Concussion Clinic as part of the McGill University Health Center (MUHC) between April 2014 and September 2017. They were considered to be symptomatic if they still experienced a minimum of 1 symptom with affected normal functioning at 4 weeks post-injury. All participants spoke French or English and had been screened by clinic coordinators and followed by treating physical therapist. Children were excluded if they had a diagnosis of learning disability and attention disorder, neurological condition, orthopedic injury that could affect balance, uncorrected abnormal vision, a history of mTBI in the previous year, skull fracture or prolonged loss of consciousness upon injury (> 30 minutes). At the time that the participants initiated active rehabilitation for persisting symptoms as per standard of care in the Concussion Clinic [16] , they were recruited to participate in the 3D-MOT training regimen. Standard of care at this establishment includes light aerobic activity within sub-symptom thresholds, coordination exercises as well a visualization, to be performed daily at home and guided by the physical therapist's recommendations. Approval from the MUHC Pediatric Research Ethics Board was obtained. Written parent consent and patient assent were obtained.

Measures

Since this study is the first to look at the use of 3D-MOT in a symptomatic pediatric mTBI population, it was necessary to closely monitor safety of this training paradigm. Consequently, safety of 3D-MOT in symptomatic pediatric mTBI was measured through the presence of adverse events, which prompted discontinuation ("stopping rule") of the study. An adverse event was defined as an increase in symptom score on the Post-Concussion Symptom Inventory (PCSI), a well-validated measure of post-mTBI symptoms [42]. This measure offers age-specific versions (4), scores for individual symptoms, including somatic, emotional sleep-related and cognitive, are added to provide a total symptom score. Scores were collected before and after each 3D-MOT training visits and were used to derive a stopping rule for our study, meaning that if training on the task increased symptom scale score by two points or more on the PCSI scale for 12-18 years old, training would be stopped on that visit and training was resumed at the following visit. In the case that symptoms were increased for participants on two consecutive visits, participants were withdrawn from the study

Tolerability of the training protocol was assessed through report of adverse events, reasons for discontinuing the study and completion of all training sessions at each visit (total of 18 sessions over the course of the study), and requesting training protocol deviations. Deviations were defined as any modifications to 3D-MOT study procedures presented below.

Secondary outcomes: Symptoms and clinical measures

Symptoms

Symptom scores of participants were ascertained at the beginning of each visit and scored using the The Post-Concussion Symptom Inventory (PCSI) [42]. Symptoms are scored on an age-adapted Likert scale, scores for individual symptoms are added to provide a total symptom score. Participants filled out the PCSI the beginning of each visit, and were asked to report symptoms they were currently experiencing. This allowed us to get a total symptom score for each of the 6 visits included in the study protocol.

Clinical measures

Balance was assessed through the balance error scoring system (BESS) which consists of 3 different stances (double, single, tandem) that are performed on a firm surface and on a soft surface (foam). Participants are instructed to maintain the position, with their eyes closed and the number of errors in the stance position is recorded [43]. This measure has been shown to be highly valid and reliable [43]; mainly in detecting large differences in balance, including in mTBI populations [44]. In addition the Balance subtest of The Bruininks-Oseretsky Test of Motor Proficiency – second edition (BOT-2) was used as an adjunct to evaluate balance. This measure was developed to assess motor performance in children and adolescents aged 4 to 21 [45]. Balance assessment through this measure consists of items such as walking on a straight line and standing heel-to-toe on a balance beam. Coordination was also assessed using BOT-2 Coordination subtest. Bilateral coordination consists of items such as jumping jacks and tapping feet and fingers. Self-Efficacy was measured through an mTBI-specific scale derived from Bandura's framework of self-efficacy [46], where children were asked to report their confidence in performing tasks (total scores range from 10 to 100%) on athletic and mTBI related items. Fatigue and quality of life in children with mTBI were assessed through the Pediatric Quality of Life Inventory (Peds-QL) using age-specific scales. This questionnaire measures quality of life in children aged 2 to 18 years old, through self- or proxy-reports and has been proven to be both valid and reliable [47]. Cognitive functioning was assessed through The Immediate Post-Concussion Assessment and Cognitive Testing (ImPACT). ImPACT is a cognitive testing battery that has been created for individuals (aged 10 or more) after an mTBI. It consists of 6 subscales: symptom checklist, verbal memory, visual memory, reaction time, processing speed, and impulse control. This test is widely used and validated for the pediatric mTBI population [48]. All measures were administered individually in a quiet room and according to age-appropriate versions; as per administrative manual guidelines.

3D-MOT: NeuroTracker

3D-MOT training took place in a quiet and dark room where the stimuli were projected on a 60" 3D screen. For each of the 6 study visits, participants underwent training under the *CORE* program of the NeuroTracker platform, which consists of a total of 3 speed threshold calculations (3 *CORE* calculations). Throughout their study participation, a total of 18 *CORE* calculations were possible (3 calculations for 6 visits). One *CORE* calculation is computed trough 20 trials on the 3D-MOT task.

Trials on the 3D-MOT consist of five essential steps: First, the presentation phase, in which eight yellow spheres are presented for three seconds in a random position within the 3D virtual space presented on the screen (A). Second, the identification phase, in which four spheres out of eight will be temporarily highlighted by the NeuroTracker program and identified as the targets to follow for this trial (B). Third, the removal phase, where spheres return to their initial color and the eight spheres move for eight seconds (C). Fourth, the stoppage phase, in which participants have to identify the spheres they had previously identified as the targets (D). Last, the feedback phase, during which the participant is provided feedback about his answer. The main task starts at a given speed (in m/s), and speed from one trial to another is adjusted based on the performance of the participant. For example, if the participant can correctly identify the four spheres, the speed of the next trial will increase, if the participant fails to identify correctly all four spheres, the speed of the following trial will be decreased. These speeds at which participants can identify spheres are also known as speed thresholds (in m/s). Speed thresholds are calculated using a 1-up 1-down staircase procedure [49], that is, after a correct response, the speed is increased by 0.05 log and decreased by the same proportion after each incorrect response, resulting in a threshold criterion of 50%. The staircase is interrupted after 20 trials and the *CORE* threshold is calculated. Participants were given 2 to 5 minutes break time in between *CORE* calculations. Training on this task was performed every 3 to 7 days.

Figure 1 **Illustration of the 5 phases of 3D-MOT training, using the NeuroTracker**

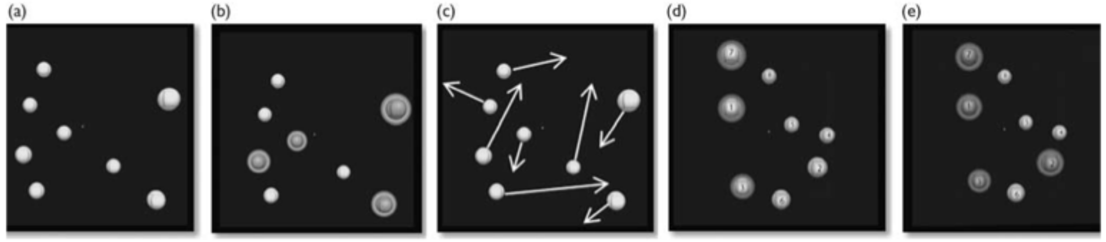

Illustration of the five critical phases: (a) presentation of randomly positioned spheres in a virtual volumetric space, (b) identification of the spheres to track during the trial, (c) removal of identification and movement of all spheres with dynamic interactions, (d) stoppage and observer's response by identifying the spheres, (e) feedback is given to the observers.

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Analysis

Descriptive analyses were calculated for primary outcomes and all other study variables. With regards to secondary outcome measures, visual inspection of *CORE* speed thresholds on the 3D-MOT and symptom presentation during each training visit was performed. Paired sample t-tests with significance set at $p<0.05$ allowed to identify changes between final (visit 6) and initial (visit 1) visits in speed thresholds as well as in symptom scores. Post- hoc paired sample t-tests with significance set at $p<0.05$ were performed in order to detect at which training visit(s) significant changes were noted for both measures. In addition, changes in clinical outcome measures from final and initial trainings were analyzed using paired samples t-tests, where significance was set at $p<0.05$. Statistical analyses were performed with the use of the Statistical Package for the Social Sciences (SPSS) version 20.

Results

Participation in the CORE sessions

Nine children aged 12 to 17 years old participated in the study. Participants (1 male: 8 females) had a mean age of 14.61years (SD=3.33) and had been symptomatic from the mTBI on average for 53.75 (SD=25.87) days before entering the study (See Table

1). No participants experienced adverse effects and therefore none had to be discontinued from the study. One participant discontinued the study after the initial visit as he reported feeling better and not seeing the need to pursue the study, thus participating in three *CORE* calculations out of a possible 18 as per study protocol. The remaining eight participants were able to complete the 6 visits 3D-MOT paradigm with three *CORE* calculations at each visit for the course of the study. Deviations to study adherence, hence, resulted in a total of 15 missed *CORE* calculations out of a possible 162 (9%). One participant required longer rest periods between calculations (more than 5 minutes) on three different occasions. Another participant asked to perform the task with the lights on during 3 *COREs*, due to symptoms of sensitivity to light and was bothered by the light contrast from the screen and the dark room. Hence protocol deviations were noted for 6 *COREs* (<5%).

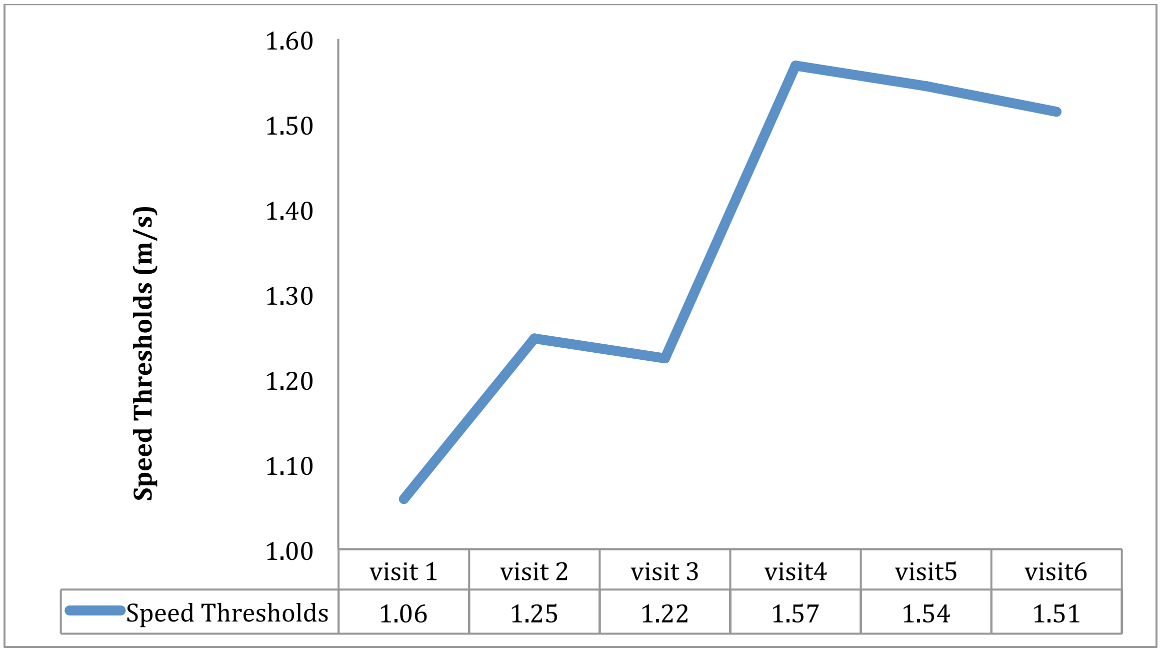
Table 1 **Participants' characteristics**

Age	Gender (n=9)	Time since injury (days)	Initial Symptom score	Final Symptom score
14.61±3.33years	1 male; 8 females	53.75±25.87	13.44±13.41	3.86±3.34

Speed Thresholds

Visual inspection of the learning curve over a 6-visit training on the 3D-MOT paradigm demonstrated that children who are still symptomatic after a mTBI can improve their speed thresholds on the task. In addition, paired sample t-tests revealed a significant increase in speed thresholds between training visits 3 and 4 (t=-3.464 p=0.013), visual inspection of the training curve illustrates that limited training gains are acquired until visit 3, and that the significant increase in training gains noticed at visit 4 is maintained until the 6th visit.

Figure 2 **Speed thresholds on 3D-MOT training paradigm over 6 visits**

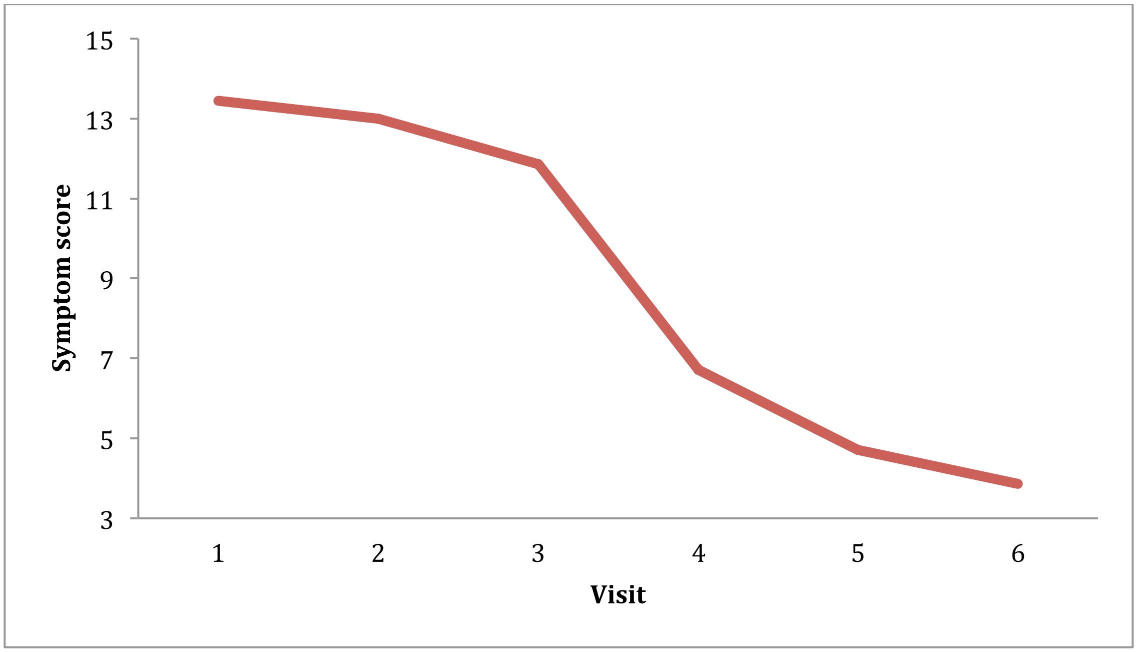


	visit 1	visit 2	visit 3	visit4	visit5	visit6
Speed Thresholds	1.06	1.25	1.22	1.57	1.54	1.51

Symptoms

Paired t-tests revealed a tendency for symptom reduction between training 1 and 6 (t=2.300 p=0.061) (See Figure 3 for symptom presentation). Visual inspection of symptom presentation, demonstrated that symptom presentation is notably decreased between training 3 and 4, which in addition, coincide with greater speed threshold gains.

Figure 3 **Total symptom score for each visit over the course of a 6 training 3D-MOT paradigm**



Clinical measures

Paired t-tests revealed a tendency towards improvement in overall self-reported fatigue level ($p=0.05$). In addition, a tendency towards significance was also reported in improvement of ImPACT performance where cognitive efficiency enhanced from 0.24 to 0.40 ($p=0.08$).

No significant differences were noted in measures of coordination, balance, self-efficacy, and parent reported quality of life. Refer to Table 2 for clinical measures values and associated statistical test report.

Table 2 **Clinical performance and associated statistical reports at visit 1 and 6**

		Visit 1	**Visit 6**	**t-test**	**p-value**
Balance	***BOT2 Scale Score***	14.33	14.83	-0.25	0.81
	BESS				
	Double Support Firm	0	0	n/a	n/a
	Single Support Firm	3.29	2.29	1.27	0.25
	Tandem Firm	0.29	1.43	-1.92	0.1
	Double Support Soft	0	0.14	-1	0.36
	Single Support Soft	5.57	4.57	1.11	0.31
	Tandem Soft	2.57	2.57	n/a	n/a
Coordination	*BOT2 Scale Score*	15.57	17.57	-1.87	0.11
Self-Efficacy	*Athletic Scale*	808.57	854.29	-1.15	0.29
	mTBI Scale	587.5	595	-0.08	0.94
Quality of Life	*PEDSQL - **Self-Reported***				
	Multidimensional fatigue	62.94	79.2	-2.24	0.05
	*PEDSQL - **Parent Reported***	62.31	80.78	-1.8	0.13
ImPACT	*Cognitive Efficiency*	0.24	0.4	-2.35	0.08

Discussion

Results from this study demonstrated that children who are still symptomatic after an mTBI can tolerate and safely undergo a 6 visits 3D-MOT training (primary objective). Participant did not have any symptom exacerbation, showed a high rate of completion of the cognitive rehabilitation training regimen, and had minimal protocol deviations. Children exhibited greater training gains on 3D-MOT between training visits 3 and 4, which also coincided with a greater symptom diminution. Regardless of statistical significance, visual inspection of training gains and symptom presentation curves suggest that the laps of time between these two visits is valuable although yet unexplained. Symptom presentation is a rather fundamental aspect of mTBI recovery, as most management strategies greatly rely on self-reported symptoms presentation. In children that are experiencing delayed recovery; the primary objective of clinicians working with this population is to reduce symptoms in the most efficient and rapid fashion. Results from this study suggest further investigation of the potential connection between perceptual – cognitive training gains and symptom presentation.

Clinical measures of mTBI recovery allow us to reinforce that a training regimen on 3D-MOT is safe for the symptomatic population and does not seem to interfere with current active rehabilitation protocols for prolonged symptoms established as per standard care in our clinical facility [16], as clinical measures did not worsen through the course of training. Contrarily, fatigue levels perceived by our participants showed a tendency towards improvement. This phenomenon could potentially be explained by improvement in executive function in children upon training, which would result in improved fatigue levels [50] [51].

A tendency towards improvement on the cognitive efficiency index of the ImPACT test battery was also noted; reinforcing findings that training on 3D-MOT is safe and tolerated. Participants improved their test values from 0.24 to 0.40. Cognitive efficiency within this test measures may vary from a score of zero to a maximum of 0.70. It is suggested that the average performance is positioned around 0.34. Moreover, a score of 0.20 or below is considered to display poor speed and memory performance [52]. In this current study, children initially exhibited a low score, being close to the 0.20 limit, and improved their test score over average upon completion of the training regimen. Further studies are necessary to draw conclusions on the link between improvements in cognitive processes and training on this paradigm.

Conclusion

This study demonstrates that it is possible to train children that are experiencing delayed recovery on 3D-MOT, and that this training paradigm is well tolerated, and safe for this particular population as it did not exacerbate symptom presentation and did not negatively affect clinical measures. This study if one of a kind when it comes to looking at perceptual cognitive training in children who experience delayed recovery from their mTBI, as most studies focus on physical rehabilitation. Results of tolerability through adherence and protocol deviations were supported by previously published work on cognitive rehabilitation interventions in other populations [53, 54]. In addition, adherence was within limits of what is currently being reported in the scientific literature when it comes to rehabilitation interventions in pediatric mTBI [16].

Even though this study was of exploratory nature, it leads us to question the possibility that a 3D-MOT training regimen in parallel to current active rehabilitation protocols [16] may actually have a beneficial effect on symptom presentation in children that are experiencing delayed recovery by enhancing brain plasticity. All together, this methodology could easily be implemented in mTBI follow-up clinics, assisting clinicians' efforts in facilitating recovery.

However, study limitations are present. First, children participating in the study also underwent active rehabilitation involving light physical activity, coordination and visualization; hence it is impossible to conclude that 3D-MOT is solely responsible for symptom and clinical improvements. In addition, the sample size was small and gender distribution was uneven, favoring girls, and no placebo intervention was available to compare overall clinical improvements. Hence, further studies, with wider age representation and larger groups, comparing the use of this methodology to a sham intervention would allow to better understand if 3D-MOT can indeed enhance recovery after sustaining an mTBI.

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Chapter 10: Integration of manuscripts III and IV

In the second study (manuscript III) we demonstrated that the theoretical framework previously established for the use of 3D-MOT as a mean of active rehabilitation (manuscript II) could be implemented in a small group of symptomatic pediatric mTBI patients. It was shown that it is feasible and safe to administer this training regimen as a mean of cognitive active rehabilitation in parallel to current standard care. In addition, it was suggested that such training regimen could potentially improve clinical presentation within this population, in reducing symptom presentation and improving fatigue levels, quality of life and cognitive abilities.

Moving onto the third line of inquiry of this doctoral work (detection) the next study (manuscript IV) explored the use of the 3D-MOT in the context of a broader mild traumatic brain injury population, in order to assess if this methodology could act as a potential marker of recovery once mTBI symptoms disappear. Since the NeuroTracker can be both used as a training paradigm (as seen in manuscript III) and as a mean to explore brain functioning (as presented in previous sections of this work), the following manuscript aims to explore the detection abilities of this said paradigm, through gains exhibited upon training. The initial step for exploring detection abilities of 3D-MOT was to explore if children who had sustained an mTBI performed similarly on this task when compared to healthy controls. Hence, a group of children with recent history of mTBI and a healthy control group underwent a repeated 3D-MOT protocol and were compared in terms of performance on the task.

Chapter 11: Manuscript IV

Three-dimensional multiple object tracking in the pediatric population: The NeuroTracker and its promising role in management of mild traumatic brain injury

Short title: NeuroTracker in pediatric mTBI

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Conflict of Interest:

JF is a Scientific Officer for CogniSens, Inc. the producer of the commercial version of the 3D-MOT system used in this study. In this capacity, he holds shares in the company.

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Abstract

Since mild traumatic brain injury (mTBI) affects hundreds of thousands of children and their families each year, investigating potential mTBI assessments and treatments is an important research target. Multiple object tracking (3D-MOT), where an individual must allocate attention to moving objects within 3-dimensional space, is one potentially promising assessment and treatment tool. To date, no research has looked at 3D-MOT in a pediatric mTBI population. Thus, the study aim was to examine 3D-MOT learning in children and youth with and without mTBI. Thirty-four participants (mean age=14.69±2.46), with and without mTBI, underwent 6 visits of 3D-MOT training. A two-way repeated measures ANOVA suggested a significant time effect, a non-significant group effect and non-significant group by time interaction on absolute speed thresholds. In contrast, significant group and time effects and a significant group by time interaction on normalized speed thresholds were found. Individuals with mTBI showed smaller training gains at visit 2 than healthy controls, but groups did not differ on the remaining visits. Although youth can significantly improve their 3D-MOT performance following mTBI, similarly to non-injured individuals, they demonstrate slower speed of processing in the first few training sessions. This preliminary work suggests that using a 3D-MOT paradigm to train visual perception after mTBI may be beneficial for both stimulating recovery and informing return to activity decisions.

Key Words: NeuroTracker; Perceptual-cognitive training; Three-dimensional multiple object tracking; Object tracking; Children; Pediatrics; Mild traumatic brain injury; Concussion; Return to activities

Introduction

Clinicians working with children and adolescents with mild traumatic brain injuries (mTBI) often face the challenge of determining when recovery is sufficient to clear them for safe return to activities (e.g., sport, school, leisure). Current literature on mTBI management prioritizes the assessment of self-reported post-concussive symptoms (PCS) when clearing children and adolescents for return to their activities [1]; however, this method can be prone to underreporting [2]. Moreover, recent studies have demonstrated that although children are cleared for return to activities upon resolution of their PCS, cognitive and motor deficits, unidentifiable through routine concussion testing, can persist for weeks [3-5]. This puts injured children and youth at risk for premature return to activities and risk of re-injury [5].

Current assessment measures have yielded inconsistent results when it comes to determining readiness to resume activities after mTBI. This lack of agreement thus encouraged researchers to look deeper into newly available measures such as, among others, fluid biomarkers[6, 7], and vision-related assessment[8, 9]. The latter (vison-based) area of research seems promising as it focuses on more ecological and cost-efficient methods for concussion tracking and recovery, mainly looking at oculomotor function. Since mTBI symptoms can be expressed through vision and neuro-ophtalmologic signs and symptoms vision-related assessments are an intriguing potential assessment tool. At this time, vision-based concussion diagnosis and management tools still require further investigation [8]. Although findings from vision based assessment can weigh in on the clinical management of pediatric mTBI, these assessments should not yet be relied upon solely when clearing children to return to activity [8, 9]. Hence, there is a need for clinicians working with the peadiatric mTBI population for a measure of recovery that involves ecological paradigms, and that could weigh in more significantly in granting readiness to go back to activities.

Faubert and colleagues, through their innovative work with elite sports teams, military personnel, and aging adults, have developed a 3-dimensional multiple object tracking (3D-MOT) tool, the NeuroTracker, that shows promise for both mTBI assessment and treatment [10-12]. In 3D-MOT, individuals must allocate their attention among multiple moving targets among distractors moving across the visual field. This 3D-MOT task involving speed of information processing, visual perception and dynamic visual processing, has shown its potential to promote brain plasticity, as well as cognitive function in adults [13], in addition to demonstrating a very clear and reproducible 3D-MOT learning curve across diverse populations (young adults, elderly, athletes) [10-12, 14]. In line with Faubert and Sidebottom's initial declaration[15], these studies have consistently shown that optimal training gains are reached within the first five training sessions on the NeuroTracker [14-19]. Moreover, this research has found that training gains stabilize over time and follow a predictable learning curve based on age group [15] and physical activity level [16, 17].

Faubert & Sidebottom (2012) hypothesized that 3D-MOT using the NeuroTracker could be a suitable candidate for management and return to play decisions, due to its controlled and accurate retest ability, its precise and consistent perceptual-cognitive training conditions and the presumption that this task provides mild cognitive stimulation, a concept that was previously suggested to improve recovery after mTBI [11]. However, to date there is no scientific data to support the use of 3D-MOT for either mTBI assessment or treatment. Hence, the aim of this study was to compare 3D-MOT learning gains in the post-acute phases of mTBI to those of healthy controls during NeuroTracker training.

Methods

Participants

Thirty-four physically active, English or French speaking participants aged 9-18 years (76% male, mean age: 14.69±2.46), were recruited for this study from the

Greater Montreal and Greater Victoria regions. Twenty control participants (93% male, mean age: 12.79±2.19) and 14 participants who had a recent history of mTBI and were symptom-free (63% male, mean age: 16.01±1.66) were included in this study (Table 1). Participants had normal or corrected to normal vision with no history of learning disability, attention deficit disorder with or without hyperactivity, cognitive disabilities, learning and or behavioral problems. Control participants had no history of mTBI in the previous year. Participants were recruited through word of mouth and advertisements in local sports organizations. Ethical approval was obtained from both the Montreal Children's Hospital and the Victoria University Human Research Ethics Board.

Table 1

Overall and subgroups (controls vs post-mTBI) participants' characteristics

	Overall	**Controls**	**Post-mTBI**
Age (years)	14.69±2.46	12.79±2.19	16.01±1.66
Gender			
Male(%)	26(76)	13(93)	13(63)
Female (%)	8(24)	1(7)	7(37)
Time since injury (months)			2.21±2.46

Study Procedures

Eligible and consenting individuals underwent cognitive perceptual training using the CORE mode of the NeuroTracker system (CogniSens, Montreal, Canada). Participants wore active stereoscopic glasses and were seated in a dark room 160 cm away from a 60 inch TV screen with eyes positioned at the center of the screen.

Although optimal training gains are achieved within the first 5 training sessions in adult populations [9-14], limited information is available on training gains within the population. Upon visual inspection of learning curves from pilot unpublished work done on pediatrics subjects in our labs, we opted for 6 training visits. At each visit, participants completed 3 blocks of 20 trials of 3D-MOT that took approximately 8 minutes and followed identical procedures, with a rest period from 2 to 5 minutes in between each blocks. A mean speed threshold, based on the average performance of the 3 blocks was calculated at each visit. Each appointment took about 30 minutes, and occurred every 3 to 7 days. First, the participant was presented with 8 identical yellow balls randomly placed on a television screen (presentation phase). Second, 4 of 8 balls turned red and were highlighted with a white halo for 2 seconds to identify the targets to track (identification phase). Third, the 4 target balls returned to yellow and all 8 balls moved and bounced around the screen for 8 seconds (removal phase). Fourth, the balls stopped moving and the participant was asked to name the target balls that were formerly identified (stoppage phase). Last, the participant was given feedback about the correct target balls for 3 seconds (See Figure 1). Speed thresholds, the outcome variable of interest, was calculated using a 1-up 1-down staircase procedure [20], such that after each correct response (i.e., 4 target balls identified accurately) the speed of the balls was increased by .05 log and after each incorrect response the speed of the balls was decreased by .05 log. The process resulted in a threshold criterion of 50%. After 20 trials, the speed threshold was calculated as the mean speed threshold (m/s) from the last 4 inversions.

Speed thresholds training gains on the 3D-MOT task were analyzed using both absolute (unprocessed speed thresholds) and normalized values (processed speed thresholds). The latter value represents performance relative to the mean of visit 1 rather than the actual speed threshold calculated at each visit. Hence, with regards to normalized gains, visit 1 is the zero value and gains/losses at subsequent visits vary based on the participants' performance on the initial visit.

Figure 1 **Illustration of the 5 phases of 3D-MOT training, using the NeuroTracker**

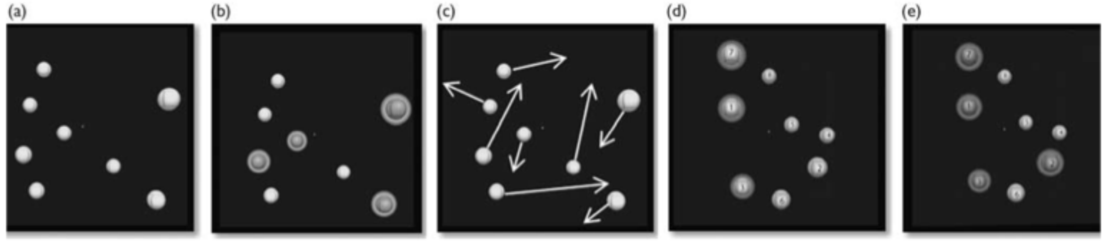


Illustration of the five critical phases: (a) presentation of randomly positioned spheres in a virtual volumetric space, (b) identification of the spheres to track during the trial, (c) removal of identification and movement of all spheres with dynamic interactions, (d) stoppage and observer's response by identifying the spheres, (e) feedback is given to the observers.

Reproduced with permission [14]

Analysis

Groups were significantly different with regards to age, with the post-mTBI group being slightly older than the control group. Unpublished work by Kowalski and colleagues [21] previously demonstrated that initial absolute speed thresholds tend to increase with age [21]. Since, although significant, the age differences between our both groups were fairly small, and number study participants were limited, we opted not to control for age. To establish whether training gains on the 3D-MOT task were different between the post-mTBI and control groups, a repeated measure ANOVA (time x group) was performed, with significance level set at p< .05. Post-hoc independent sample t-tests were conducted to look at the performance at each visit between the two study groups.

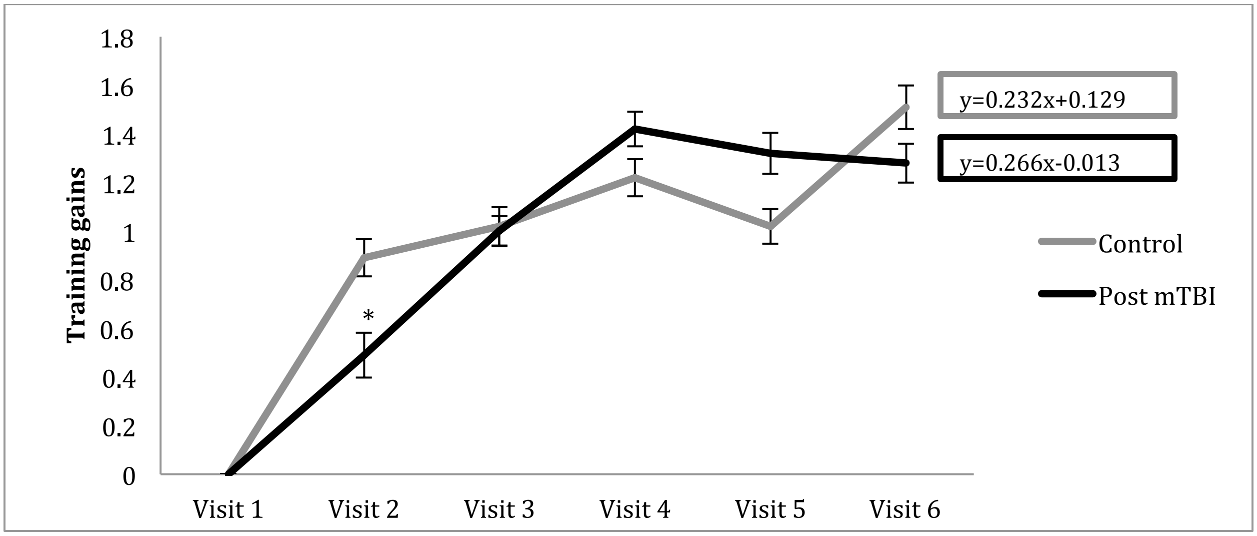
Results

A two-way repeated measure ANOVA with significance level set at p<.05 did not reveal significant differences between the two groups on absolute speed thresholds (F(1,32)=2.635, p=.114) nor a group by time interaction (F(1,32)= 0.044, p=.836) (See Figure 1). However, a significant time effect was observed (F(1,32)= 40.231, p<.001), revealing that both groups improved on the task over time. In contrast, when looking at normalized values of speed thresholds, a two-way repeated measure ANOVA revealed main effects of group (F(1, 32)=4.427, p=.043) and time (F(1,32)=37.589, p<.001) , and a significant group by time interaction(F(1,32)=6.307, p=.017); the mTBI group showed lower normalized speed thresholds over the course of training. Ad hoc independent t-tests revealed a significant group difference on absolute speed thresholds at the second visit only (t=2.622, p<.05) (See Table 2), with non-significant differences between groups at subsequent visits, and similar training gains slopes (See Figure 2).

Table 2 **Absolute and normalized speed thresholds for the course of a 6 visit training paradigm along with paired t-tests results for normalized speeds**

		1	**2**	**3**	**4**	**5**	**6**
Absolute	**Controls**	1.04	1.40	1.53	1.64	1.60	1.87
	Post-mTBI	0.94	1.01	1.26	1.39	1.5	1.57
		1	**2**	**3**	**4**	**5**	**6**
Normalized	**Controls**	0.00	0.35	0.49	0.60	0.56	0.79
	Post-mTBI	0.00	0.02	0.31	0.45	0.56	0.63
	t-tests	*t*	*6.62*	*1.78*	*1.35*	*-0.01*	*1.34*
		sig	*0.01*	*0.09*	*0.17*	*0.99*	*0.19*

Figure 2 **Normalized speed thresholds means and associated standard errors in m/s on a 6-visits training paradigm in healthy control children and children that recently sustained a mTBI**



* where significant group difference was noted

Discussion

Our results demonstrate that healthy youth and youth with mTBI can both benefit from 3D-MOT training, with significant time effects. Our findings also show that although youth can improve their 3D-MOT performance with repeated testing/training following mTBI, compared to non-injured youth, they show slower speed of processing in initial training sessions. Specifically, the control group demonstrated a 79% increase in speed thresholds over the course of 6 training appointments, whereas post-mTBI group improved by 66%. Within the first hour of training (2 visits), a 33% increase in speed threshold was observed in controls and 0.06% in participants who recently sustained a mTBI. In their 2011 study, Beauchamp and Faubert indicated that elite adult athletes improved by 50% within their first hour of training [22]. This difference could be explained by the age of our participants or differences in their participation in activities and sports requiring multiple object tracking.

Post-mTBI youth displayed similar training gains at visits 3, 4, 5 and 6 as non-injured controls. The significant difference on normalized speed threshold at the second visit is seen even though participants were in the post-acute phases of mTBI, suggesting a maintenance of training effects before the 3rd visit. Learning gains slopes were similar for both groups leading to believe that over the course of six 3D-MOT training sessions, post-mTBI participants can exhibit training patterns similar to healthy controls. However, since the post-mTBI group showed significantly lower speed thresholds at the second visit, we can conclude that their training gains pick up with repeated training and mimic those of non-injured individuals over time. This phenomenon could be due to natural recovery of mTBI, or could possibly be an effect of repeated training on the NeuroTracker : further work is necessary to explore the later hypothesis.

On average participants in the mTBI group had sustained their injury 2.21 ± 4.32 months prior to their participation. Knowing that the expected window of recovery post-mTBI is about 10 days [1], we can assume that most participants in this group were back to activities (sport, school, etc.) upon participation in this study. These results provide further support that cognitive deficits in youth post-mTBI may persist, even upon return to activities, and help stress the importance of developing assessment tools to better assess clinical recovery in pediatrics mTBI [3-5].

Study limitations included sample size, age differences between groups and a variable time since injury in mTBI participants. Further research with a larger sample, earlier in the recovery process, and less variable time since injury could help reinforce the present findings. In addition, on the basis of previously discussed work by K. Kowalski, H. Cullen, K. Oslund, L. Drabkin, A. Rodway, T. Christie, J. Faubert I. Gagnon B. Christie (unpublished data), older teenagers demonstrate higher initial speed thresholds than younger teenagers. In our study, the post-mTBI group was significantly older than the control groups, however, the latter still demonstrated higher training gains and speed thresholds in the initial visits. Hence, it is possible that the effect of age in this study may be masking an even greater effect of group on the 3D-MOT task. Despite these limitations, this preliminary work suggests that a brief 3D-MOT training paradigm may be beneficial for monitoring recovery following mTBI and warrants further investigation.

To our knowledge, this study is also the first to examine 3D-MOT through NeuroTracker in the population, demonstrating that it is possible to improve speed thresholds in both the healthy and post-injured brain. To establish 3D-MOT as a safe and effect treatment tool for pediatrics mTBI, future work will need to examine the effect of 3D-MOT training on symptom recovery and other outcomes following mTBI, including days to return to play, cognitive function and measures of brain plasticity. Work in healthy university students has demonstrated that 3D-MOT improves attention, working memory, visual processing speed, and produces changes in cerebral resting state brain function [23]. However, the effect of 3D-MOT on mTBI outcomes has not yet been explored. As is true of mTBI treatments in general [1, 24], a well-designed randomized control trial is necessary to establish 3D-MOT as a safe and effective treatment alternative to current best practice for pediatrics mTBI (i.e., rest and watchful waiting).

Conclusion

This promising preliminary work suggests that 1) 3D-MOT could serve as an inexpensive and easily accessible tracker of recover following pediatrics mTBI and 2) children may benefit from 3D-MOT training post-mTBI. 3D-MOT warrants further exploration as both an assessment and treatment tool for pediatrics mTBI.

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Chapter 12: Integration of manuscripts IV and V

In the third study (manuscript IV) we have established that children who recently sustained a mild traumatic brain injury (mTBI) can exhibit training gains when undergoing a 3D-MOT training regimen, but their training gains differed from those of healthy controls. Knowing that the 3D-MOT training with the NeuroTracker is known for demonstrating stable and predictable training gains across healthy populations of various ages; showing different learning gains can therefore be hypothesized to be an indicator of altered cognitive abilities. This manuscript thus set grounds for further investigation of the use of the NeuroTracker as a sensitive marker of recovery in the pediatric mTBI population.

In the fourth and fifth studies (manuscript V) we aimed to further investigate the use of 3D-MOT as a sensitive marker of recovery in the pediatric mTBI population. A group of children and adolescents who were considered clinically recovered from their injury after evaluation in a specialized clinic, were compared to two distinct groups of children: 1) healthy controls, and 2) children with recent history of mTBI. Comparing clinically recovered individuals to healthy controls and children in various phases of mTBI recovery allowed to gain better insight on the detection abilities of 3D-MOT with regards to pediatric mTBI recovery.

Chapter 13: Manuscript V

Could Three-Dimensional Multiple Object Tracking be used as a clinical marker of recovery after pediatric mild traumatic brain injury?

Short title: 3D-MOT as a marker of mTBI recovery

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Conflict of Interest:

JF is a Scientific Officer for CogniSens, Inc. the producer of the commercial version of the 3D-MOT system used in this study. In this capacity, he holds shares in the company.

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Abstract

Pediatric mild traumatic brain injury (mTBI) is a public health issue. Despite the availability of specialized clinics in the management of this condition, many cases are self-managed. In addition, it has been shown that lasting deficits of mTBI could possibly make return to activities risky. There is a need for a clinical marker of mTBI recovery that would contribute to ensure safe and efficient return to activities. Children often return to activities where perceptual-cognitive abilities are highly solicited. Multiple object tracking (3D-MOT), is a way to train perceptual-cognition, on which healthy populations of various ages have been shown to exhibit similar training gains. Thus this study aimed to explore the potential for 3D-MOT to be used as a marker of functional recovery after mTBI. Experiment 1 compared 3D-MOT performance between children and adolescents who had been cleared for return to activities to that of healthy controls. A two-way repeated measures ANOVA suggested no differences between the groups but a significant time effect. Experiment 2 compared children who have been cleared to return to activities by health care professionals in a specialized mTBI management clinic (same as experiment 1) after mTBI to a group of children with a recent history of mTBI recovery. A two-way repeated measures ANOVA suggested a significant training differences between these groups and a significant time effect. Results suggested that clinically recovered children and adolescents exhibit similar training abilities as controls on this task. In addition 3D-MOT performance varied within children and adolescents with a history of mTBI (clinically recovered vs post-acute). Results supported further investigation looking at the abilities of 3D-MOT to act as a marker of recovery.

Key Words: NeuroTracker; Perceptual-cognitive training; Three-dimensional multiple object tracking; Object tracking; Children; Pediatrics; Mild traumatic brain injury; Concussion; Return to activities

Introduction

The incidence of mild traumatic brain injury (mTBI) continues to increase within the pediatric population [1]. When children recover from their injury, they face many challenges returning to activities (school, sport, leisure) and proper management is incontestably essential [2]. In fact, the Canadian Ministry of Health has invested over 1 million $ of its 2016 budget towards developing strategies for return to activities post-injury in the pediatric population [3]. Since current management strategies mainly rely on symptom reporting [2], it is difficult for clinicians to determine if, when children return to activities, their brain is fully recovered. Research has shown that even when symptoms resolve, deficits can still be seen in various domains (cognition, balance, vision) [4-7]. As such, even when clinicians adhere to management recommendations, children may go back to their physical activities while still experiencing some subtle deficits despite not reporting symptoms. There is therefore an urgent need for markers of recovery to ensure proper and safe return to activities, as well as diminish risk of re-injury in the pediatric population.

The majority of pediatric patients who seek care after an mTBI do so in an Emergency Department (ED), and then proceed to self-manage their recovery (themselves or through proxies, such as a parent) with or without instructions received during their initial visit at the ED. Regrettably, the literature shows that a significant number of parents and children demonstrate a lack of knowledge about the proper course of mTBI recovery, as well as about management and return to activity recommendations [8-11]. Outpatient clinics specializing in the management of mTBI propose a more comprehensive follow-up to injured children and their families, from injury all the way to clearance for return to activities. Clinicians in these settings will often make return to activity decisions based on thorough physical evaluations, and exertion testing, hence reducing the risk of premature return and controlling for potential mTBI-related persisting deficits.

Despite proper clinical care, residual persistent physical and cognitive deficits linked to mTBI may still be present upon return to activities and difficultly measured by standard current clinical tools [4-7]. Thus, the scientific literature still lacks evidence of cost-efficient, easy to administer, and ecological clinical markers of recovery, that could be used within a clinical setting. Indeed, when returning to activities, children need to be able to perceive and integrate, complex, unpredictable moving patterns [12] in order to diminish the risk of re-injury. Cognitive perceptual skills are required to adapt to changes in the environment when returning to activities. It is believed that these skills can be trained and improved [13, 14] resulting in better processing of complex visual information [12].

The ability to track multiple objects, referred to as multiple object tracking, has been previously identified as an important factor in reacting swiftly and effectively in the context of sports [14]. Recently, three-dimensional multiple object tracking (3D-MOT) as been introduced in the field of performance sport to enhance perceptual skills of athletes [12]. Since then, studies have demonstrated that this training paradigm shows a great potential not only for training but also for providing quantifiable measures (screening) of perceptual-cognitive skills [15-19]. Previous studies have demonstrated that various populations can benefit from training with a 3D-MOT paradigm over repeated visits to improve task-specific skills such as biological motion perception [15] and sport-related skills [16]; and that the gains made can transfer to other measures involving cognition [15-19]. The advantage of this task as an evaluative tool dwells in the stability and predictability of the training curves, achieved through individual training gains at each session. It was shown in healthy adult and elderly populations that training curves are stable for age groups and level of athletic fitness [20, 21]. It is believed that 3D-MOT can also serve as a means to evaluate perceptual skills on sporadic (versus repeated trainings) evaluations, as shown in a study demonstrating that professional basketball players who had an increased performance on this measure also had better overall sport performance [22]. Our research group has found that despite similar 3D-MOT training curves, differences in training gains in the initial sessions were found when comparing performance between children post-mTBI and healthy controls [19]. It is hypothesized that looking at training gains rather than curves could allow for the detection of subtle differences in functional performances in the presence of brain pathology.

To explore the potential for 3D-MOT to act as a marker of functional recovery after mTBI, we first needed to confirm whether differences exist in performance between children without injury and those qualified as "recovered" with a multimodal assessment including exertion testing. We did this with distinct experiments. The objective of the first experiment was to compare 3D-MOT training gains in children who are determined as clinically recovered from a mTBI (mTBI-CR) to those of healthy controls; while the objective of the second experiment was to compare 3D-MOT training gains in mTBI-CR children to those with a recent history of mTBI.

EXPERIMENT 1

The current literature on markers of recovery in mTBI is blooming. While most studies involve biological markers of recovery (e.g. fluid, imaging), there is still a need for a readily available, inexpensive, and time efficient marker that clinicians working with the pediatric mTBI population could rely on when it comes to granting permission to return to activities. Literature has shown that children may be at risk of returning to activities prematurely while still exhibiting deficits related to their mTBI which are not detected by current clinical tools [4-7]. Being ecological in nature, by mimicking stresses placed upon individuals in their daily lives, the 3D-MOT task, delivered through the NeuroTracker platform (CogniSens Athletic Inc., Montreal, Qc, Canada) poses as a promising avenue for establishing differences in speed of processing differences across populations [19, 20, 22]. As previously stated, there is a significant increase in accessibility of outpatient clinics that propose management of mTBI and assist in the process of granting return to activities. This study serves as a channel to explore clinical recovery, with insights on how a clinically recovered brain behaves under perceptual-cognitive training. Hence, experiment 1 compared performance on 3D-MOT between mTBI-CR and healthy controls. In addition clinical measures specific to mTBI were compared amongst both groups to examine if training on 3D-MOT was related to overall clinical presentation.

Methods

Participants

Participants consisted of children and adolescents who sustained a mild traumatic brain injury between May 2014 and September 2017 and sought care from the Trauma Program Concussion Clinic at the Montreal Children's Hospital (McGill University Health Centre), and had obtained clearance for complete return to activities. Clinical recovery was determined by a multi-disciplinary team of experienced clinicians (nurses, physical therapists, neuropsychologists, physicians) based on a standardized evaluation of the following domains: 1) symptom resolution, 2) balance and agility testing, 3) complete return to cognitive activities (school), 4) exertion testing including tolerance to exercise. This group is referred to as 'Clinically recovered' or 'mTBI-CR'. To be eligible to participate in the study, mTBI-CR participants had to enter the study protocol within 10 days of being cleared for return from the Concussion Clinic. In addition, a healthy control group of children and youth who had not sustained a mTBI in the past 12 months was recruited for comparison. This group consisted of friends and siblings of mTBI-CR participants.

3D-MOT

The NeuroTracker platform offers a wide variety of training paradigms with most commonly studied being the *CORE* program using eight spheres (4 distractors; 4 targets). A *CORE* session consists in participants being first presented with eight identical yellow balls on a 3D television screen (presentation phase). Second, four of the eight spheres are highlighted and identified as targets to follow for the duration of the trial (about 8 seconds) (identification phase). Third, the highlighted spheres return to their original color and start moving within the 3D environment (removal phase). Fourth, the spheres are immobilized on the screen and participants identify which spheres they were required to track for the trial (stoppage phase). Last, participants are given feedback on the accuracy of their responses (feedback phase) (See Figure 1). Speed thresholds are calculated through a step up and down manner [23] where each correct/wrong answer during the stoppage phase increases/decreases the speed of the following trial. These steps are repeated for 20 trials, accounting for one training *CORE* session. A mean speed threshold calculation is provided at the end of the session. Each training visit consists of 3 *CORE* sessions/calculations. A six-visit 3D-MOT training protocol was administered to all study participants using the NeuroTracker (6 visits, 18 total *CORE* calculations). Visits were scheduled every 3 to 7 days.

Figure 1 **Illustration of the 5 phases of 3D-MOT training, using the NeuroTracker**

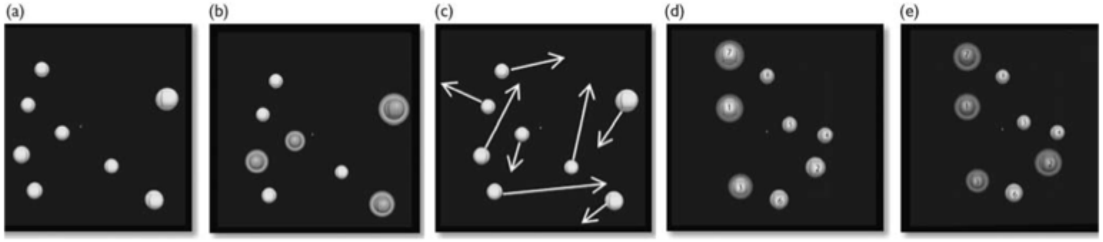

Illustration of the five critical phases: (a) presentation of randomly positioned spheres in a virtual volumetric space, (b) identification of the spheres to track during the trial, (c) removal of identification and movement of all spheres with dynamic interactions, (d) stoppage and observer's response by identifying the spheres, (e) feedback is given to the observers.

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For each visit, we compiled each *CORE* session's absolute threshold value and calculated normalized training thresholds values. The normalized value is obtained by subtracting the initial visit (first 3 *CORE* sessions) average speed threshold calculation from values from each subsequent visit. Hence, the value for the initial visit is set at 0, and succeeding values depend on the participants' performance relative to the initial visit. In previously published work in the pediatric mTBI population [19] it was demonstrated that normalized values (referring to training gains) identified differences in 3D-MOT training whereas absolute (nontransformed) values did not. For the purpose of this study, both normalized and absolute values will be analyzed.

Clinical measures

Clinical measures pertinent and validated for the mTBI population were administered to mTBI-CR and control participants in order to explore if 3D-MOT was related to clinical presentation. The test battery consisted of a Balance and coordination evaluation (Balance Error Scoring System [25]; Balance subtest of the Bruininks-Oseretsky test of Motor Proficiency, Second Edition [26]), Fatigue (Peds-QL multidimensional fatigue scale [27]), Parent-reported quality of life (Peds-QL [27]), Self-efficacy related to physical activity [28], and a computerized cognitive test battery (ImPACT [29]). Clinical measures were collected at the beginning of the initial and final 3D-MOT training visits. All testing was performed in a private room to minimize external distractions, and both testing and administration were based on published standardized procedures.

Statistical Analyses

Repeated measure ANOVA with significance set at $p<0.05$ were performed in order to compare absolute and normalized training gains between mTBI-CR individuals and healthy controls. Post-Hoc one-way ANOVAs were performed to highlight training differences at individual visits between the mTBI-CR and healthy groups, with significance set at $p<0.05$. Paired sample t-tests, with significance set at $p<0.05$ were performed to investigate differences between and within groups at initial and final training visits for clinical outcome measures. All analyses were performed with SPSS Statistics version 20.0

Results and discussion

A convenience sample of ten children and adolescents (5 males, mean age: 14.6 ± 1.50 years) who were clinically recovered by the Montreal Children's Hospital

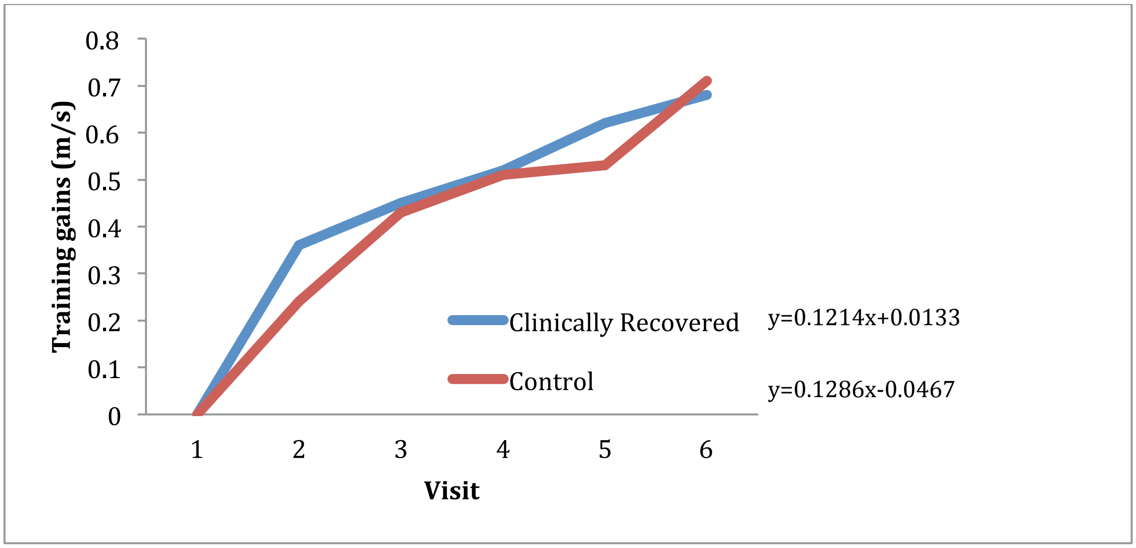
Trauma Program Concussion Clinic and ten children and adolescents (8 males: 13.12 ± 2.34 years) recruited as healthy controls were included in the primary analysis. See Table 2 for demographic information on participants.

Table 1 **Demographic characteristics of participants**

	Age (years)	N, Gender (% males)	Time since injury (days)
Clinically recovered	14.6±1.50	10, 50%	83.33±54.82
Controls	13.05±2.34	10, 80%	N/A

A repeated measure ANOVA (2 x 6) showed no significant between group effects ($F_{(1,10)}$= 0.005, p= 0.946, η^2_p< 0.001), a significant intercept ($F_{(1,10)}$= 310.709, p<0.001, η^2_p=0.969) and significant time effect ($F_{(5,50)}$= 21.737, p<0.001, η^2_p=0.685) when looking at absolute training values. A repeated measure ANOVA (2 x 6) looking at normalized training gains suggested no significant group effects ($F_{(1,10)}$= 0.023, p= 0.881, η^2_p= 0.002), a significant intercept ($F_{(1,10)}$= 104.035, p<0.001, η^2_p=0.912) and significant time effect ($F_{(5,50)}$= 21.737, p<0.001, η^2_p=0.685). Post-hoc one-way ANOVAs did not detect significant differences on normalized training values for each training visit. No significant differences in clinical measures were noted within and between groups for initial and final visits.

Figure 2 **Normalized training gains for clinically recovered individuals after a mTBI and healthy controls on a 6 visits 3D-MOT paradigm**



Children across both study groups exhibited no significant differences on clinical measures and overall training performance. Results suggest that children who receive clearance from a specialized mTBI clinic and are deemed clinically recovered exhibit 3D-MOT performance similar to that of healthy controls. The implications of these results are two-fold. First, a clinically recovered brain can learn over repeated training sessions on a perceptual-cognitive task similarly to a non-injured brain, as shown by significant time effect with large effect sized for both groups. Despite the need for studies with bigger sample sizes, this exploratory study suggests that multimodal evaluation in specialized clinics may truly allow for adequate brain recovery after mTBI and potentially diminish the risk of returning to activities prematurely with known mTBI deficits. Second 3D-MOT could have the potential to be used as a marker of recovery in mTBI if it can highlight contrasts in training when comparing various groups of children who recently sustained a mTBI (eg. Clinically recovered children vs children in various phases of mTBI recovery). The following experiment will focus on this question.

EXPERIMENT 2

In the second experiment, we wanted to determine if the 3D-MOT task performance was different between mTBI-CR children and children with a recent history of mTBI, at various stages of recovery (symptomatic or not) (post-mTBI). A previous publication by our group demonstrated that children in the post-acute recovery phase, performed differently in the initial 3D-MOT training sessions when compared to healthy controls [19]. These results contrast those presented in Experiment 1, leading us to postulate that differences found in training are not solely due to having a history of mTBI, but could rather be explained by other mTBI-related factors such as phase of recovery. In order to evaluate the potential use of 3D-MOT as a marker of recovery, it was necessary to compare the 3D-MOT performance of mTBI-CR children from Experiment 1 to a group of children sharing similar history of mTBI, but not necessarily clinically cleared using similar multimodal methods; similar to the ones studied by Corbin-Berrigan and colleagues (2018) [19].

Methods

Participants

Participants included in this experiment consisted of the same mTBI-CR participants presented in Experiment 1 and a sample of individuals who had sustained a recent mTBI in the greater Victoria region (British Columbia, Canada). Participants were in various phases of recovery (eg. Symptomatic, non-symptomatic). They were recruited through word of mouth and from community partnerships such a local schools. Hence, some participants may have been followed clinically whereas others may have self-managed, for these reasons, we believe this groups to be representative of post-acute mTBI recovery. (See Table 3 for participants' characteristics).

Table 2 **Demographic characteristics of participants**

	Age (years)	N, Gender (% males)	Time since injury (days)
Clinically recovered	14.6±1.50	10, 50%	83.33±54.82
Post-mTBI	16.25±1.00	12, 100%	42.09±73.19

Procedure:

3D-MOT

Similar procedures as Experiment 1 were performed for 3D-MOT training.

No clinical measures were administered for the purpose of this experiment.

Statistical analyses

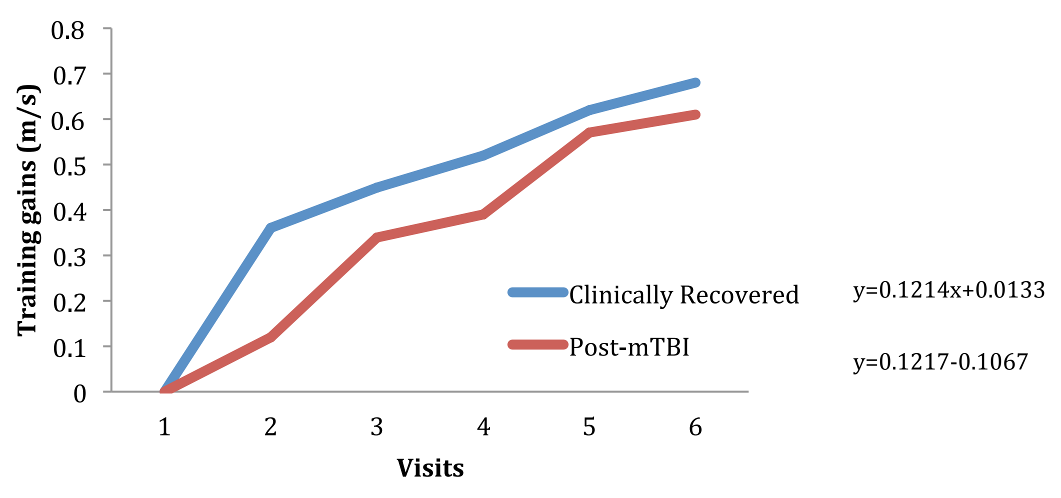
A repeated measure ANOVA with significance set at $p<0.05$ was performed in order to compare learning curves (absolute values) and gains (normalized values) between clinically recovered individuals and healthy controls. Post-hoc one-way ANOVAs were performed to highlight training differences between the clinically recovered and post-acute mTBI group, with significance set at $p<0.05$. All analyses were performed with SPSS Statistics version 20.0

Results and discussion

A convenience sample of twelve participants (all males, 16.25 ± 1.00 years) who had recently been diagnosed with a mTBI were recruited through the research programs at the University of Victoria. In contrast to mTBI-CR, these participants had been followed in diverse clinical settings, and were at various stages of their mTBI recovery. They underwent similar training procedures on the 3D-MOT as the clinically recovered group. Their training gains (absolute and normalized) were compared to those of clinically recovered children and adolescents presented in

Experiment 1. A repeated measure ANOVA (2 x 6) showed no significant between group effects ($F_{(1,13)}$= 0.1.486, p= 0.245, η^2_p= 0.103), a significant intercept ($F_{(1,13)}$= 137.029, p<0.001, η^2_p=0.103) and significant time effect ($F_{(5,65)}$= 43.156, p<0.001, η^2_p=0.769) when looking at absolute training values. A repeated measure ANOVA (2 x 6) looking at normalized training gains suggested a significant group effects ($F_{(1,13)}$= 46.822, p= 0.001, η^2_p= 0.783) with post-mTBI participants exhibiting lower training gains than clinically recovered, a non-significant intercept ($F_{(1,13)}$= 1.263, p=0.281, η^2_p=0.089) and significant time effect ($F_{(5,65)}$= 20.292, p<0.001, η^2_p=0.610) Ad hoc one-way ANOVAs suggested a significant normalized gain difference at visit 2 on 3D-MOT ($F_{(2,13)}$ 7.629; p=0.012), with the post-mTBI group showing less improvements. No other significant differences were found between other training visits.

Figure 3 **Normalized training gains for clinically recovered and post-mTBI individuals on a 6 visits 3D-MOT paradigm**



Results suggested that clinically recovered children significantly exhibited bigger training gains in the initial 3D-MOT visits when compared to children post-mTBI. Despite small sample sizes, large effect sizes were noted, suggesting 3D-MOT may be sensitive to recovery after mTBI. Differences in training gains support the work of Corbin-Berrigan and colleagues [19], where lesser training gains were exhibited in the initial training session, in a similar post-acute mTBI group of individuals when compared to controls. It has recently been suggested that 3D-MOT could serve has a window to explore brain functions as a measure of attention resource capacity [30]. Results from this study suggest that performance in 3D-MOT can differ in a broad group of children with a recent history of mTBI, and such differences could potentially be explained by stages of recovery. Results from Experiment 2 further support the need to explore in greater depth the potential of 3D-MOT in marking delayed recovery after sustaining an mTBI. In addition, this experiment reinforces the validity of specialized mTBI clinic when it comes to evaluating readiness to engage back in activities when recovering from an mTBI.

General Discussion

These two experiments contribute to the body of literature about the use of perceptual-cognitive training in a context of recovery after sustaining an mTBI. Originally this training paradigm, through the use of 3D-MOT, had been created to improve visual performance of athletes while performing sports [21] and has now been made available worldwide to the athletic community. Despite theoretical suggestions that it could play a positive role in injury management [31], there was no clear scientific evidence supporting the use of repetitive perceptual-cognitive training in children and mTBI. Recently, it was suggested that this training paradigm could isolate differences in training gains in children in post-acute phases of their mTBI [19]. This current study provides valuable information with regards to the detection potential of 3D-MOT.

Children who have been granted return to activities after completing a thorough clinical evaluation upon symptom resolution of mTBI exhibit similar training gains on a 3D-MOT training regimen than healthy controls. In addition, both clinically recovered and control individuals did not differ in clinical measure upon initial and final evaluations, meaning that clinically recovered participants presented similarly to controls when it comes to balance, coordination, fatigue, quality of life and cognitive measures. Results from the clinical evaluation reinforce the hypothesis that children successfully undergoing thorough physical examination and exertion testing in a clinical setting in order to get medically cleared to go back to activities after a mTBI could safely go back to activities, as their brain learns a new task similarly to non-injured children.

Unfortunately, literature has highlighted that despite increase in mTBI awareness efforts, most cases are not managed within a clinical setting. A recent study that looked at pediatric medical records in the United States showed that only 4% of mTBI cases are being managed through outpatient clinics [1]. Furthermore, a study by Swaine and colleagues identified that children who recently sustained a mTBI were at greater risk of re-injury within the first 6-12 months following the initial injury [32]. Hence, it is reasonable to believe that the risk of re-injury seen in the literature could be linked to improper or lack thereof management after such injury, and that better consensus on granting return to activities should be seeked upon. It is possible that children managed in specialized clinics may exhibit favorable outcomes of recovery when compared to children that self-managed. Further validation studies will be necessary to evaluate this affirmation. However, the fact that brain-training differences were noted between both mTBI groups raised awareness on the importance of proper and thorough clinical management of mTBI, from the onset of injury, to discharge and clearance to go back to activities.

Due to the exploratory nature of these experiments, small sample sizes were used. Despite large effects sizes supporting significant statistical differences, additional studies are required with larger sample size and even gender distribution, to be able to implement 3D-MOT as a strategy to assess clinical recovery after an mTBI. In addition, it would be interesting to evaluate 3D-MOT's role as a mean to assist mTBI recovery. It would be interesting to evaluate the role 3D-MOT can play in aiding return to activities for children undergoing a stepwise approach. A recent study by Tullo and colleagues [33] demonstrated that children with neurodevelopmental conditions can benefit from 3D-MOT training to increase their attentional abilities. Hence, it would be valuable to explore the clinical utility of 3D-MOT as a rehabilitative measure in addition to being a clinical marker of recovery.

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Chapter 14: Discussion

The overarching aim of this work was to contribute evidence towards the clinical management of pediatric mild traumatic brain injury through three distinct lines of inquiries.

The first line of inquiry (prediction) (study 1; manuscript I) allowed us to identify factors that could contribute to delayed recovery in children who seek care in an outpatient-based clinic. To date, much of the emphasis on prediction has been based on factors present within initial hours of the injury. Our work is different in that it managed to identify factors that are relevant to clinicians working in outpatient clinics, who will only see patients a few days after their injury. Our work highlighted that symptom presentation within 10 days of the injury can contribute to identify children who will be a risk of delayed recovery.

The second line of inquiry (intervention), first established the theoretical foundations for a perceptual-cognitive intervention (manuscript II), and then explored the tolerability and safety of the intervention as a mean to alleviate symptoms (study 2; manuscript III). This line of inquiry was anchored in current expert recommendations and provided evidence of a perceptual-cognitive intervention for the management of persistent symptoms after mTBI. This line of inquiry was grounded within the theoretical roots for symptom presentation and perceptual-cognition. This was the first known work looking 3D-MOT in mTBI. Results demonstrated that children can tolerate 3D-MOT and that this training regimen is safe.

The third line of inquiry (detection) (studies 3, 4 ,5; manuscripts IV & V) demonstrated that differences in perceptual-cognitive training can be found between healthy controls and children in various stages of mTBI recovery. Many prior studies have suggested that through the hallmark training gains observed over time in various populations, 3D-MOT could act as a marker of brain function [92] [157].

Hence manuscript IV allowed to demonstrate that 3D-MOT could pick up differences in training gains between healthy controls and children in post-acute phases of mTBI. Results suggested that training gains obtained on the task from initial sessions may contribute to the detection of normal brain functioning after mTBI. Furthermore, these results highlighted the need for further studies looking at brain function in post-acute phases of mTBI. Manuscript V revealed that children who are being thoroughly followed and granted recovery in a specialized mTBI clinic exhibit similar training gains as healthy control (thus differ from post-acute mTBI). This line of inquiry supports the importance of proper clinical management and suggests that 3D-MOT may be sensitive to stages of recovery after mTBI.

Strengths and limitations of the thesis

Prediction

The study presented within this line of inquiry was different from most emergency room studies as it looked at predictors of delayed recovery beyond the first few hours post-injury and is more representative of population that will seek care in outpatient follow-up clinics. Since presentation of mTBI evolves over time, it was pertinent to examine if prediction factors highlighted in emergency room studies also progressed over time. The greatest strength of this line of inquiry was to establish that it is possible to predict who is more likely to experience delayed recovery even when not managed from the initial moment of the injury. This provides significant new information to the literature. If we make a parallel to general medicine; when someone shows up to the emergency room with a disease/condition/injury, the initial steps are to identify the main complaint and establish risk factors at the time of the injury (eg. imaging, blood test). Then subsequent outpatient visits will allow to track recovery, evaluate risk factors that have been missed or have evolved, etc. MTBI management should be tackled in a similar fashion. Where emergency room visits and outpatient visits both serve different purposes, and are accompanied by different measures, tests, procedures.

Yet, to date, and despite the increase in accessibility to outpatient clinics, there are limited resources for prediction rules in this type of setting.

Limitations within this line of inquiry include the need for bigger sample. Our work suggested that gender was not a contributor to delayed recovery, whereas most prediction studies states that gender is in fact a serious predictor [1, 7]. Differences between our study and others could reside in the kind of sample of individuals we collected. There is a need to establish first if our sample is representative of most outpatient clinic users before we can further investigate the predictive role of gender in a clinical setting. In addition, a bigger sample could also contribute to shedding light on tendencies that were found within the emotional category.

Intervention

The greatest strength of this line of inquiry lies in the fact that 3D-MOT was studied for the first time in the context of mTBI, and more specifically pediatric mTBI. The study presented grounded itself in the theoretical foundations of 3D-MOT to support its use as an intervention. It demonstrated that this intervention is tolerated and safe in symptomatic mTBI patients, and that it does not interfere with current standard care involving active rehabilitation. In addition to tolerating the 3D-MOT intervention, children also improved their performance on the task, hence they could benefit from training itself; as seen in other populations.

Limitations reside in the small sample size of participants, and the lack of control or placebo intervention. Results show that at the same time that children experience less symptoms, performance on 3D-MOT improves, this warrants further investigation to establish what truly happens during this time period. Could symptoms and performance be linked? Are they completely independent? These questions will need to be addressed before 3D-MOT can be recommended as a mean to symptoms alleviation post-mTBI.

Detection

The biggest strength of this line of inquiry (and associated 3 studies) is exhibiting the potential of 3D-MOT to serve as a clinical marker of pediatric mTBI recovery. Much emphasis has been placed in the preceding chapters of this work on the utility and importance of providing access to a clinical marker of recovery in the mTBI population. Studies presented in manuscripts of this work are the first known studies looking at learning on 3D-MOT as a mean to reflect brain functions through training performance in mTBI. These studies have demonstrated that the way the brain learns a new task can differ between children with mTBI and controls. Another strength of this work was reinforcing the importance of outpatient clinics specialized in management of mTBI. Although not an initial objective of this doctoral work, our studies provided more insight on the importance of clinical recovery before returning to activities.

Limitations for this line of inquiry include small sample groups, and age differences between compared samples. Unpublished work by another research group have suggested that initial speed thresholds on 3D-MOT increase with age in pediatrics (K. Kowalski, H. Cullen, K. Oslund, L. Drabkin, A. Rodway, T. Christie, J. Faubert I. Gagnon B. Christie). We believe that we have dealt with age distribution by looking at normalized training gains rather than absolute gains. However, it would be valuable to study age-comparable groups in order to get a bigger picture on the absolute gains these populations undergo on the task. When comparing different stages of mTBI recovery for differences in 3D-MOT performance, we were limited in the group variations we could study. Lastly, since the NeuroTracker is recognized for the predictability of its training curves, it would be valuable to inquire if larger samples could detect differences in overall training curves, and not solely in individual normalized training gains. This would reinforce the use of this training paradigm to as a proxy to brain performance and recovery after mTBI.

Implication for clinical practice

This doctoral work provides much information for clinical management of mTBI. First, it contributes to increased knowledge on symptoms presentation after mTBI, from a prediction view but also from theoretical mechanisms. This work also brings valuable knowledge on a training paradigm that is already available and used in many sports and clinical settings. 3D-MOT seems to be safe to use under our research parameters in post-acute phases of mTBI, even when symptoms are present. Results from 3D-MOT studies contribute to the body of literature that recommends cognitive strategies for persistent symptom management, and could be added to current clinical management strategies that mainly focus on physical rehabilitation. In addition, it is more than plausible that 3D-MOT could contribute to increased perceptual cognitive skills after mTBI, which are skills that are highly stressed upon when returning to activities. Last, 3D-MOT is a training strategy that highly engages individuals to participate in their training, and this point alone could positively contribute to psychological factors surrounding mTBI recovery.

Implication for future research

From a prediction perspective, this work suggests that emotional symptoms could be important players in causing persistent symptoms. This work sets grounds, but further studies are necessary. Next steps would be to look at psychological (including emotional) and environmental factors contributing to persisting symptoms, and explore if these factors can be controlled with early intervention.

From an intervention perspective, the next step would be to reproduce a similar study, but with a sham intervention. This would allow to better understand what happens mid-training, were symptoms diminish and training improves. Is this due to natural recovery? Or is there an underlying cortical mechanism responsible for this? Can measures of cortical activity (eg. EEG) detect changes in training? It would also be interesting to further study the weight of individual symptoms in the context of this intervention. For example, we know from previous studies that sleep contributes to cognitive consolidation [171, 172], we also known that sleep-related symptoms can be present after mTBI [173]. Hence it would be valuable to explore the interaction between these two concepts through repetitive cognitive training. A bigger sample could help solidify results, allow to look at independent *CORE* calculations and provide more power when looking at changes in clinical measures. This doctoral work set grounds for the use of 3D-MOT as an intervention, and a current randomized control trial is currently underway at our research institute.

Similar implications from a detection perspective are noted. Studies in this doctoral work showed that children in post-acute phases of mTBI showed different training gains than controls and clinically recovered children. Next study steps would be to compare 3D-MOT performance to a sham intervention. In addition, before we can suggest that this training regimen is indeed a marker of recovery, we need to further study sub-groups within the mTBI population (eg. Self-managed versus clinical recovery, symptomatic versus asymptomatic, asymptomatic versus clinically recovered). This work sets grounds for much larger validation studies. It would too be highly valuable to study cortical mechanisms responsible for between groups differences in training. Results from this doctoral work represent preliminary tests on 3D-MOT, they do not represent sensitivity, or validation of the tool as a marker of recovery.

Chapter 15: Conclusions

This thesis was constructed over areas of the mTBI pediatric literature that needed the most looking into from a clinical standpoint. From its three lines of inquiry (prediction, intervention and detection), it aimed to address gaps in the literature that had been identified by world leading experts. In parallel to contributing to a much needed body of evidence from these three lines of inquiry, this doctoral work also allowed to gain more insight on a perceptual-cognitive training platform and contribute to its associated literature.

We believe the preceding chapters of this work have managed to highlight the potential that 3D-MOT trough the NeuroTracker platform poses as a management strategy in the pediatric mTBI population. When looking at the pediatric mTBI population, it was shown to be tolerable and safe when used in parallel to current standard care. Despite the need for further studies, based on previous work, we can suppose that repeated training using the paradigm could enhance recovery after mTBI, from enhanced plasticity and generation of brain networks. In addition, it contributes to bridging gaps that were identified in the mTBI literature by world leading experts, where the need for cognitive rehabilitation strategies was stressed [7].

As presented in the background chapter of this work, important players in the field of mTBI management suggest that the ideal mTBI assessment tool should be objective, reliable, easily and quickly administered [91]. 3D-MOT administered through the NeuroTracker platform fits all of these requirements. First, it provides, upon training, a quantifiable and objective value of performance (speed threshold). This value allows to track learning on the task over time, which is believed to be a marker of overall brain function [157]. Second, its use has been validated on many populations and has demonstrated transferability potential. Third, this training regimen is easy and fast to administer (not more than 30 minutes for 3 *CORE* calculations). The work presented in this thesis demonstrates the incredible potential the NeuroTracker can serve within a clinical mTBI context.

Perceptual-cognitive training after pediatric mild traumatic brain injury, the title of this work, clearly illustrates the path that this doctoral work undertook by proposing a novel training strategy with the potential to contribute to clinical management of mTBI. This linear work, contributed *towards* better prediction of delayed recovery from a clinical setting perspective, *towards* a perceptual-cognitive avenue for intervention within the context of mTBI and *towards* ecological detection of recovery (marker of recovery).

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Appendix

Appendix 1: Possible sources, factors and mechanisms of Post-Concussive Symptoms after sustaining a mTBI

SOURCE	FACTORS	MECHANISM		ASSOCIATED SYMPTOMS**
ORGANIC[18-20]	Damage to organic structures [40]	Injury to head and neck	Pain [174, 175]	Headache [176]
		Pre-existing chronic injury [175]	Discomfort	Sleep disturbances [177]
		Injury to inner ear	Labyrinthine concussion [178]	Tinnitus [179] Dizziness[178, 180] Balance [181]
	Stretch injury to cerebral matter [40]	Disturbance of neural networks	Altered plasticity [34, 40, 182] Altered working memory [183] Increased awareness to environmental factors Impaired visual system Impaired central auditory processing Disruption of vestibular and postural reflexes	Dizziness [178, 180] Balance [181] Amnesia [183] Difficulty concentrating [176] Feeling slowed down [176, 183] Cognitive fatigue [176, 183] Decreased visual field [184, 185] Blurred vision [184-186] Sleep disturbances [177] Depressive mood [18]
		Diffuse axonal injury		
	Neurometabolic cascade *Drastic changes in cortical cellular physiology* [34-36]	Disturbances of neural networks - Ionic shift - Altered perfusion/metabolism		
Psychological[19-21]	Pre-existing psychological factors [187] *Mental health*		Depressive mood [18, 188-190] Anxiety [188, 189] Stress	Can be linked to any symptom [174] Most commonly: Sleep disturbances [27] Fatigue Headache
	Neurosis [191]	Fright of the accident	Stress Anxiety	Symptoms of organic matter [191]
	Malingering [192]	Refusal to admit improvement		Can be linked to any symptom
Environmental[20]	Personal [20]	Awareness of injury [193, 194]		Can be linked to any symptom
	External [174]	Impaired neural networks	Increased awareness to environmental factors [18] Altered resilience and inhibitions	Mostly cognitive fatigue Can be linked to any symptom
		Social support		Can be linked to any symptom