Vestibular rehabilitation for dizziness and balance problems after mild-to-moderate traumatic brain injury

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Abbreviations

AUC	Area under the receiver operating characteristic curve (ROC)
BPPV	Benign paroxysmal positional vertigo
BESS	Balance error scoring system
CI	Confidence interval
CNS	Central nervous system
CONSORT	Consolidated Standards for Reporting Trials
CT	Computer Tomography
CTr	Control group
DHI	Dizziness Handicap Inventory
DSM	Diagnostic and Statistical Manual of Mental Disorders
GCS	Glasgow Coma Scale
GOSE	Glasgow Outcome Scale Extended
HADS	Hospital Anxiety and Depression Scale
HADS-A	Hospital Anxiety and Depression Scale- anxiety subscale
HADS-D	Hospital Anxiety and Depression Scale-depression subscale
HEP	Home Exercise Program
HiMAT	High-Level Mobility Assessment Tool for Traumatic Brain Injury
HRQoL	Health related quality of life
ICC	Intra Class Correlation
ICD	International Classification of Diseases
ICVD	International Classification of Vestibular Disorders
ICF	International Classification of Function
IQR	Interquartile range
IT	Intervention group
ITT	Intention-to-treat
LOC	Loss of Consciousness
MDC	Minimal Detectable Change
MIC	Minimal Important Change
MRI	Magnetic Resonance Imaging
OUH	Oslo University Hospital
OAUC	Oslo and Akershus University College
PCS	Post-concussion syndrome
PPPD	Persistent Postural-Perceptual Dizziness
PT	Physical therapist
PTA	Post Traumatic Amnesia
QOLIBRI	Quality of Life after Brain Injury
RCT	Randomized controlled trial
ROC curve	Receiver Operator Characteristic curve
RPQ	Rivermead Post-Concussion Symptoms Questionnaire
SEM	Standard error of measurement
SDD	Smallest detectable difference
SD	Standard deviation
SPSS	Statistical Package for the Social Sciences
TBI	Traumatic Brain Injury

VCR	Vestibulo-collic reflex
VOR	Vestibulo-ocular reflex
VC	Vestibular Compensation
VR	Vestibular Rehabilitation
VSR	Vestibulo-spinal reflex
VSS-A	Vertigo Symptom scale-autonomic/anxiety sub-scale
VSS-sf	Vertigo Symptom Scale-short form
VSS-V	Vertigo Symptom Scale-vertigo/balance sub-scale
WHO	World Health Organisation

List of papers

Paper I

Kleffelgaard, I., Roe, C., Sandvik, Leiv., Hellstrøm, T., Soberg, HL. (2013). *Measurement Properties of the High-Level Mobility Assessment Tool for Mild Traumatic Brain Injury.* Physical Therapy. Volume 93: Number 7: p. 900-910.

Paper II

Kleffelgaard, I., Soberg HL., Bruusgaard KA., Tamber AL., Langhammer, B. (2016) *Vestibular rehabilitation after traumatic brain injury – a case series.* Physical Therapy. Volume 96: Number 6: p. 839-849.

Paper III

Kleffelgaard, I., Langhammer, B., Hellstrom, T., Sandhaug, M., Tamber, A.L., Soberg, H.L.

Dizziness-related disability following mild-to-moderate traumatic brain injury.

Accepted for publication in Brain Injury. In press.

Paper IV

Kleffelgaard, I., Soberg HL., Bruusgaard KA., Sandhaug, M., Tamber AL., Langhammer, B.

The Effect of Vestibular Rehabilitation Addressing Dizziness and Balance Problems in Patients after Traumatic Brain Injury: A Randomized Controlled Trial.

Submitted 08 July 2017 to Neurorehabilitation and Neural Repair.

Summary

Background: Traumatic brain injury (TBI) has become an important public health concern because it is one of the leading causes of long-term disability, even mild TBI. The consequences of mild-to-moderate TBI often include disabilities in the areas of physical, cognitive, behavioral and emotional functioning. Dizziness and balance problems are common and lead to physical disability and psychological stress, which contribute to reduced function and disability. Vestibular rehabilitation (VR) is an accepted and frequently used treatment for dizziness and balance problems. However, evidence regarding the effect of VR after TBI is scarce.

Aims: The first aim of this research project was to examine the measurement property of the High-Mobility Assessment Tool for Traumatic Brain Injury (HiMAT) for the mild TBI population. The second aim was to describe the dizziness-related disability and its associations with pre-injury and injury-related factors. The third aim was to describe and explore the effect of an individually modified, group-based VR intervention for patients with dizziness and balance problems after a mild-to-moderate TBI.

Methods: This thesis includes four papers that describe the results of one methodological study (paper I), one case series (paper II), one prospective study (paper III), and one randomized controlled trial (paper IV). All participants were recruited from the outpatient department of Physical Medicine and Rehabilitation at Oslo University Hospital (OUH). Paper I included 92 patients with mild TBI, paper II included four patients with mild TBI, and papers III and IV included 65 patients with mild-to-moderate TBI.

Measurements: Testing was conducted at baseline (papers I, II, III and IV), after the intervention (papers II and IV) and 6 (paper I) and 8 (paper IV) months after the injury.

Dizziness-related disability was assessed with the Dizziness Handicap Inventory (DHI), which was the main outcome measure in papers II-IV. Balance and mobility were measured with the HiMAT, which was the secondary outcome measure in papers II-IV. Several other self-report and performance-based outcome measures were used for post-concussion symptoms, symptoms of dizziness/vertigo, health-related quality of life, psychological distress, and balance.

Intervention: The participants in study IV were randomly assigned to intervention (IT) or control (CT) groups. The IT group received an individually modified group-based VR intervention twice per week for eight weeks, a home exercise program and an exercise diary. Both groups were offered multidisciplinary TBI rehabilitation at OUH.

Results: Paper I: The inter- and intrarater reliabilities for the HiMAT sum score were high (Interrater ICC = 0.99, intrarater ICC = 0.95). The criterion-related validity was

moderate ($r = -0.63$, $p < 0.001$). The responsiveness was good, and the HiMAT discriminated well between patients with self-perceived improved versus unchanged balance function (AUC = 0.86).

Paper III: Multivariate analyses showed that dizziness-related disability was predicted by pre-injury comorbidities ($p \leq 0.05$) and was associated with self-reported vertigo symptoms ($p < 0.001$), reduced performance-based balance ($p \leq 0.05$) and psychological distress ($p \leq 0.05$).

Papers II and IV: The intervention was feasible, and no adverse effects were reported. An intention-to-treat analysis identified a significant difference between the groups in favor of the intervention group immediately after the intervention with an adjusted mean difference between the groups of - 8.74 points (CI -16.56 - -0.93) on the DHI and 3.71 points (CI 1.38 - 6.04) on the HiMAT. However, there was no significant difference between the groups 8 months after the injury.

Conclusion: Paper I: The HiMAT demonstrated satisfactory measurement properties for patients with mild TBI, which indicates that the HiMAT may be used as an outcome measurement of balance and mobility problems in patients with mild TBI.

Paper III: Dizziness-related disability at 3 months after a mild-to-moderate TBI is significantly predicted by pre-injury comorbidities and is associated with concurrent symptoms of vertigo, reduced performance on balance tests and psychological distress. The results suggest that dizziness and balance problems after a mild-to-moderate TBI are complex phenomena that includes several aspects from a biopsychosocial perspective.

Papers II and IV: The individually modified group-based VR intervention appeared to be safe and beneficial and to accelerate recovery for patients with dizziness and balance problems after TBI. The results imply that it safely can be incorporated as a component of multidisciplinary rehabilitation. Further studies and high quality RCTs are needed to confirm the outcomes and examine the impact of the dose and progression of exercises on rehabilitation outcomes.

1 INTRODUCTION

This thesis focuses on patients with ongoing symptoms of dizziness and balance problems after mild-to-moderate traumatic brain injury (TBI). The current research project aims to explore different aspects of functioning related to dizziness and balance problems, and to increase the evidence-based knowledge regarding vestibular rehabilitation for patients with mild-to-moderate TBI.

The annual incidence of hospital-treated patients with TBI in Oslo, Norway, is reported to be 83.3/100,000 and represents an important public health concern because it is one of the leading causes of long-term disability (Andelic, Sigurdardottir, Brunborg, & Roe, 2008). Patients with mild-to-moderate TBI represent the largest group of patients with TBI, and typically account for 80-90% of the hospital-treated patients with TBI (Andelic et al., 2008).

Dizziness and balance problems are common after mild-to-moderate TBI with a prevalence of approximately 39% at 6 weeks after injury and 25% at 12 months after injury (Hartvigsen, Boyle, Cassidy, & Carroll, 2014). Dizziness and balance problems may remain disabling for several months post injury and are often combined with anxiety and depression (Chamelian & Feinstein, 2004; Lacour, Helmchen, & Vidal, 2016; Maskell, Chiarelli, & Isles, 2007). The physical disability and psychological distress in relation to dizziness and balance problems may contribute to reduced function and disability (Lacour et al., 2016).

Vestibular rehabilitation (VR) is an accepted and frequently used treatment for dizziness and balance problems (Whitney & Sparto, 2011). VR is a broad concept that includes compensation training after a vestibular lesion or disease and balance training and compensation in other causes of vertigo, dizziness and balance problems (Tjernstrom, Zur, & Jahn, 2016). VR was first described by Cooksey and Cawhtorne who developed and described a group exercise program designed to decrease dizziness in patients with vestibular dysfunction after concussion/head injuries (Cawthorne, 1944; Cooksey, 1946; Whitney & Furman, 2007). A more individualized, problem-oriented treatment approach based on a combination of exercises that includes components mainly addressing the patient impairments and activity limitations has been more frequently described in recent years (Hall et al., 2016; Herdman & Clendaniel, 2014).

Reports from studies applying principles of vestibular rehabilitation (VR) in patients with mild TBI indicate a reduction in dizziness and balance problems (Alsalaheen et al., 2010; K. Gottshall, 2011; Schneider et al., 2014). However, a review of the literature has indicated that there is a lack of evidence regarding the effect of VR for patients with dizziness and balance problems after mild-to-moderate TBI. Furthermore, modifications appear necessary to accommodate post-concussion symptoms and physical and cognitive problems (Alsalaheen et al., 2012; Gurley,

Hujsak, & Kelly, 2013; Shumway-Cook, 2007). The existing recommendations for VR after mild-to-moderate TBI are based on guidelines for the general dizzy population and reports predominately from sports and military-related TBI populations. Limited reports address the population targeted in this research project.

The current research project was performed because increased knowledge regarding dizziness and balance problems after mild-to-moderate TBI is needed. This knowledge is important for targeting rehabilitation interventions specifically for patients with dizziness and balance problems after mild-to-moderate TBI, and to better understand how these interventions may be included in a clinical setting to decrease disability and improve function and participation.

This thesis includes four papers. One paper describes a study (paper I) of the measurement properties of a patient specific balance and mobility outcome measure (HiMAT) used in all studies included in this thesis. The other three papers describe dizziness-related disability and its associations with pre-injury and injury-related factors and post-injury functioning in the TBI population (paper III), an individually modified group-based VR intervention (paper II), and the effects of this intervention among patients with dizziness and balance problems after a mild-to-moderate TBI (paper IV).

2 BACKGROUND

To enable the comprehension and evaluation of the research project, it is important to understand the theoretical foundation for the approach. The World Health Organization (WHO) International Classification of Functioning, Disability and Health (ICF) was selected as a framework for understanding the complex process that may lead to dizziness-related disability after TBI and is presented in chapter 2.1. The participants in this research project are predominantly patients with mild TBI; however, patients with mild complicated and moderate TBI are included. Thus, the topics of chapter 2.2 include the definitions, classification, pathophysiology and epidemiology of mild-to-moderate TBI. Chapter 2.3 reviews important aspects of dizziness and balance problems after TBI and defines the main terms. Vestibular rehabilitation is an accepted and effective means of treating dizziness and vestibular disorders and is increasingly used to treat dizziness and balance problems after TBI. Thus, a description of the main elements and mechanisms of vestibular compensation and rehabilitation is provided in chapter 2.4. The current evidence of the effect of VR on dizziness-related disability in patients with TBI and the individually modified group-based VR intervention explored in this research project is also provided in chapter 2.4.

2.1. Biopsychosocial perspective on functioning and disability

TBI leads to different impairments in body functions and structures that may affect the life of the patient, his or her family and ultimately the broader society (Laxe, Cieza, & Castano-Monsalve, 2015). The ICF is a potentially useful tool in the rehabilitation of patients with TBI that improves our understanding of the full burden of TBI (Laxe et al., 2015; Laxe et al., 2014; Laxe et al., 2013). The ICF is increasingly used in the research field of TBI and has previously been applied in the assessment of disability after TBI (Andelic et al., 2010; Sveen, Ostensjo, Laxe, & Soberg, 2013). The ICF is a universal classification of human functioning. The ICF views the functional consequences of a health condition in a multidimensional biopsychosocial perspective, in which functioning is considered to be complexly interrelated with biological, individual and social factors, as well as contextual factors of both the environment and the individual (WHO, 2001). The ICF is neutral in terms of etiology and provides an opportunity to determine the patient's need according to their functioning status and not only the etiological diagnosis. It thereby provides a more comprehensive view necessary for comprehensive rehabilitation of complex and chronic conditions, such as TBI (Laxe et al., 2015).

The ICF is divided into two parts, with two components each for the classification of health and health-related conditions: 1. Functioning and disability, and 2. Contextual factors. See Figure 1.

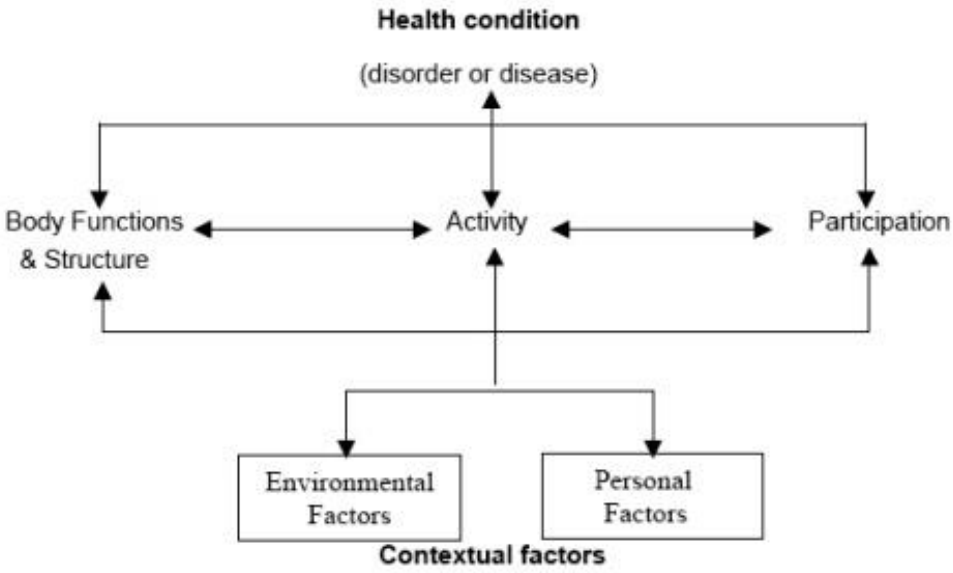

Figure 1: Illustration of interactions of the health components in the biopsychosocial ICF model (WHO 2001).

The ICF comprises three domains of functioning: body functions and structure, activities and participation. These aspects of functioning interact with the contextual factors of the individual and environment. The definitions of the concepts and components of the ICF are as follows (WHO, 2001):

- ***Health condition*** is an umbrella term for disease, disorder, injury or trauma.
- ***Functioning*** is an umbrella term that encompasses the first components of the model which are ***body functions***, ***body structures***, ***activities*** and ***participation***, whereas ***disability*** is an umbrella term for impairments, ***activity limitations*** and ***participation restrictions.***
- ***Body functions*** are the physiological functions of body systems (including psychological functions).
- ***Body structures*** are anatomical parts of the body such as organs, limbs and their components. Impairments are problems in body function or structure as a significant deviation or loss.
- ***Activity*** is the execution of a task by a life situation. Activity limitations are difficulties an individual may experience in involvement in life situations.
- ***Participation*** is involvement in a life situation. Participation restrictions are problems an individual may experience in involvement in life situations.

- ***Contextual factors*** comprise environmental and personal factors.
- ***Environmental factors*** comprise the physical, social and attitudinal environments in which individuals live and conduct their lives.
- ***Personal factors*** are the background of the individual's life and living and comprise features of the individual that are not part of a health condition or health status. Personal factors include age, gender, lifestyle, habits, coping strategies, fear-avoidance, self-efficacy beliefs and psychosocial factors.

Dizziness and balance problems after TBI represent health conditions that may have consequences for different aspects of functioning (Chamelian & Feinstein, 2004; Maskell et al., 2007). These issues are complex phenomena, and a biopsychosocial approach using the ICF framework may be useful to increase the knowledge and understanding (Laxe et al., 2015; Laxe et al., 2014). In this thesis, the ICF will be applied as a framework for exploring and describing different aspects of functioning in patients with dizziness and balance problems after TBI. The loss of body function or abnormality of a body part, difficulties in the ability to execute activities and problems with involvement in life situations, are functional states that may be positively or negatively influenced by contextual factors, which comprise both environmental and personal factors (WHO, 2001). The use of the ICF to explore these aspects of functioning may increase knowledge regarding dizziness and balance problems after TBI and may be beneficial for conceptualizing rehabilitation programs targeted toward improving disability (Laxe et al., 2014). Furthermore, the ICF was used as a framework for classifying the outcome measures that are used to explore different aspects of functioning in patients with dizziness and balance problems after TBI. See Table 4.

2.2 Traumatic brain injury (TBI)

2.2.1 Definition of TBI

Traumatic brain injury is defined as: "An alteration in brain function, or other evidence of brain pathology caused by an external force" (Menon, Schwab, Wright, & Maas, 2010, p. 1637). An alteration in brain function is defined as the appearance of one of the following clinical signs: a period of decreased or lost consciousness, loss of memory immediately before or after the injury, neurological deficits, such as weakness, loss of balance, sensory loss, change in visual, speech or language function or change in mental state, such as confusion, disorientation or slowed thinking (Menon et al., 2010).

2.2.2 Classification and pathophysiology of mild-to-moderate TBI

The TBI severity is most commonly measured by Glasgow Coma Scale (GCS) scores and is classified as mild, moderate or severe (Teasdale & Jennett, 1974). The presence of the loss of consciousness (LOC) and post-traumatic amnesia (PTA) are also accepted indices of TBI severity; see Table 1 for the most commonly described classification structure (Kristman et al., 2014; Morris & Gottshall, 2014).

Table 1: Severity classification for Traumatic Brain Injury.

	Mild	Moderate	Severe
GCS	13-15	9-12	3-8
LOC	0-30 minutes	> 30 minutes to < 24 hours	> 24 hours
PTA	< 1 day	> 1 day but < 7 days	> 7 days

GCS, Glasgow Coma Scale; LOC, Loss of consciousness; PTA, Post-traumatic amnesia.

As most patients described in this thesis have mild TBI, this will be the main focus in this section. Concussion and mild TBI are terms often used synonymously (Levin & Diaz-Arrastia, 2015). Concussions typically represent injuries in the milder end of the TBI spectrum and are often defined and described in relation to sports (McCrory et al., 2013). In this thesis, mild TBI is used, and we will not further define or describe concussion. The American Congress of Rehabilitation Medicine (ACRM) and the World Health Organization (WHO) Collaborating Centre Task Force on Mild TBI defined mild TBI as a GCS score from 13-15 at least 30 minutes after the injury examined by a qualified health care provider (American Congress of Rehabilitation Medicine (ACRM), 1993; Carroll, Cassidy, Holm, Kraus, & Coronado, 2004; Kristman et al., 2014).

Mild TBI manifests as one or more of the following symptoms: confusion or disorientation, loss of consciousness (LOC) for less than 30 minutes, post-traumatic amnesia (PTA) for less than 24 hours or transient neurological abnormalities (including seizures, intracranial lesions and neurological signs such as weakness, loss of balance, sensory loss, or changes in vision, speech or language) (Carroll et al., 2004; Kristman et al., 2014). Furthermore, mild TBI may be classified as complicated or uncomplicated based on whether there are positive findings on CT/MRI with respect to structural brain injury (Iverson, 2006; D. H. Williams, Levin, & Eisenberg, 1990). Most patients with mild TBI do not exhibit trauma-related abnormalities via neuroimaging. However, abnormalities are identified in 5-10% of emergency department patients (Smits et al., 2008). Rather than structural changes, mild TBI may result in neuropathologic changes with functional disturbances that affect the brain's processing ability (Bazarian, Blyth, & Cimpello, 2006; Giza & Hovda, 2014; Levin &

Diaz-Arrastia, 2015; Morris & Gottshall, 2014). Structural changes that may occur, particularly after mild complicated and moderate TBI, include diffuse axonal injury, diffuse microhemorrhages, focal contusions, traumatic subarachnoid hemorrhage, and extra-axial hematoma (Dixon, 2017; Levin & Diaz-Arrastia, 2015; Smits et al., 2008). Moderate TBI is defined as a GCS from 9-12, LOC for more than 30 minutes but less than 24 hours, and PTA for more than one day but less than one week (Dixon, 2017).

2.2.3 Epidemiology

The incidence of TBI varies in different epidemiological studies and is difficult to assess as a result of the different diagnostic criteria and different methods used to collect data, as well as variations in healthcare systems (Peeters et al., 2015). Furthermore, not all patients seek medical care, and registrations from primary health care may be difficult to obtain (Andelic, 2013; Andelic et al., 2008). The annual incidence of hospital-treated patients with TBI in Oslo, Norway, is reported to be 83.3/100,000, which is lower than many other reports from epidemiological studies (Andelic et al., 2008). A meta-analysis from 2015 reports an overall incidence rate of 262/100,000 for hospital-admitted patients with TBI in Europe (Peeters et al., 2015). In contrast, the TBI-related hospitalization rate in the US is reported to be 93.8/ 100,000 patients (Faul & Coronado, 2015). In studies that examine all TBI severities, the percentage of mild TBI varies from 71 – 97.5%, and the percentage of moderate TBI varies from 1 – 10% (Andelic et al., 2008; Peeters et al., 2015).

The mean age distribution in the TBI population varies from 22-49 years in different studies, which is most likely a result of the different inclusion criteria and case ascertainment (Peeters et al., 2015). Many studies only include adults in their studies. In the general TBI population, the prevalence is higher among children and adolescents aged under 25 and the elderly aged over 75 (Peeters et al., 2015; Taylor, Bell, Breiding, & Xu, 2017).

In Norway and Scandinavia, falls are the major cause of TBI (Andelic et al., 2008). There appears to be a change in the main cause of TBI from traffic accidents to falls. This change is thought to be a result of preventive efforts, such as better road standards, safer cars, and the use of helmets and safety belts (Andelic et al., 2008). However, in the young adult group, traffic accidents are the most frequent cause of TBI (Peeters et al., 2015). Falls are most common among children and the elderly (Peeters et al., 2015; Taylor et al., 2017).

A male predominance is present in most studies with male: female ratios that range from 1.2:1.0 to 4.6:1.0 (Andelic et al., 2008; Peeters et al., 2015; Taylor et al., 2017).

2.2.4 Post-concussion symptoms and post-concussion syndrome

The post-concussion symptoms that are commonly seen after mild-to-moderate TBI may be categorized as somatic (dizziness, balance problems, headaches, nausea, problems with vision, sensitivity to light and noise, neck pain and sleep disturbance), cognitive (concentration, attention, memory, cognitive endurance, and delayed processing), and emotional (anxiety, lability, depression, irritability, and frustration (King, Crawford, Wenden, Moss, & Wade, 1995; Morris & Gottshall, 2014; Sigurdardottir, Andelic, Roe, Jerstad, & Schanke, 2009). Symptoms that last 3 months or more have been defined as post-concussion syndrome (PCS) (Levin & Diaz-Arrastia, 2015; Morris & Gottshall, 2014).

The World Health Organization for the International Classification of Diseases (ICD-10) coding system: (F07.2) (World Health Organization, 2016) and the American Psychiatric Association for the DSM IV (American Psychiatric Association, 2013) further defined PCS as "A syndrome that occurs following head trauma (usually sufficiently severe to result in loss of consciousness) and includes a number of disparate symptoms such as headache, dizziness, fatigue, irritability, difficulty in concentration and performing mental tasks, impairment of memory, insomnia, and reduced tolerance to stress, emotional excitement, or alcohol" (American Psychiatric Association, 2013; World Health Organization, 2016). Both the DSM-IV and ICD-10 are consistent regarding a prerequisite history of brain trauma for the diagnosis of post-concussion syndrome with both focused on symptom presentation. However, the diagnostic criteria differ. The DSM-IV requires immediate symptom onset and persistence for at least three months in contrast to the ICD-10. In addition, the DSM-IV requires objective evidence of memory or attention deficits, whereas the ICD-10 explicitly precludes this evidence. In the most recent DSM-5 edition, PCS has been excluded. Instead, the DSM-5 includes mild neurocognitive disorder due to TBI, which strongly suggests performance-based, quantifiable evidence of acquired cognitive deficits after mild TBI, in which the most frequently reported post-concussion symptoms are reduced to the status of associated features (American Psychiatric Association, 2016). The variability in the terminology and associated criteria of the DSM-IV and ICD-10 hampers the accurate identification and diagnosis of patients with PCS. Different classifications may result in an overestimation or underestimation of symptoms, particularly when relying on a subjective endorsement of symptoms by patients (Boake et al., 2005; Yeates, 2010).

The Rivermead Post Concussion Symptoms Questionnaire (King et al., 1995) has been validated in Norway to generate the diagnoses of PCS using the ICD-10 (Ingebrigtsen, Waterloo, Marup-Jensen, Attner, & Romner, 1998). The interpretation of the ICD-10 of PCS applied at the Department of Physical Medicine and Rehabilitation at OUH is that patients should have at least one cognitive, one emotional and one somatic symptom rated as moderate or severe (scores 3 or 4) on the RPQ to be diagnosed with PCS (Sigurdardottir et al., 2009).

2.2.5 Recovery and prognostic factors of mild-to-moderate TBI

Most patients with uncomplicated mild TBI experience a relatively quick recovery from their injury. However, it is often estimated that in a significant minority (10-23%), symptoms persist, and patients develop PCS (Broshek, De Marco, & Freeman, 2015; Cassidy, Boyle, & Carroll, 2014; Levin & Diaz-Arrastia, 2015). There are indications that patients with complicated mild and moderate TBI recover more slowly; however, the literature is limited and somewhat mixed regarding outcomes (Iverson, 2006; Sigurdardottir et al., 2009).

Controversies exist regarding the mechanisms that cause the development of PCS. A mix of biopsychosocial factors, other than sustaining a TBI, such as older age, lower education, poor expectations for recovery, and depressive symptoms appear to be associated with prolonged recovery after mild TBI (Broshek et al., 2015; Cassidy et al., 2014; Ponsford et al., 2012; Wood, O'Hagan, Williams, McCabe, & Chadwick, 2014). Furthermore, pre-injury physical or psychiatric problems have been identified to be predictive of continuing post-concussion symptoms at 3 months with concurrent indicators, including anxiety, post-traumatic stress symptoms, other life stressors and pain (Broshek et al., 2015; Ponsford et al., 2012). Coping style, resilience, anxiety sensitivity, and alexithymia may also be associated with the persistence of post-concussive symptoms (Broshek et al., 2015; Sullivan, Kempe, Edmed, & Bonanno, 2016; Wood et al., 2014). Moreover, vestibular dysfunction and balance problems after TBI are significant contributors to anxiety/psychological distress post injury (Chamelian & Feinstein, 2004; Daneshvar et al., 2011; Lacour et al., 2016).

Overall, it has been hypothesized that both neurobiological and psychological factors have an influence on symptoms during the early stages of recovery, and psychological disturbances that contribute to the symptoms during the acute stages after mild TBI are stable and persistent in prolonged presentations of post-concussive symptoms and predictive of late outcomes of PCS (Broshek et al., 2015; Silverberg & Iverson, 2011; Yeates, 2010). Biopsychosocial models that include pre-injury factors represent frameworks that are likely to be constructive and appropriate in conceptualizing and explaining the complex and multifactorial etiology of persistent symptoms after mild-to-moderate TBI (Ruff, 2011; Snell, Macleod, & Anderson, 2016; Yeates, 2010).

2.3 Dizziness and balance problems

First the anatomy and physiology of the normal vestibular system including the central sensorimotor integration in the central nervous system related to TBI is presented. Further, definitions are provided, and the prevalence and common causes of dizziness and balance problems after TBI is presented.

2.3.1. Anatomy and physiology of the normal vestibular system

The etiology and rationale of dizziness and balance problems after TBI, treatment and rehabilitation are based primarily on the structures and function of the vestibular system (balance system). This system is complex and comprises a peripheral sensory apparatus, a central processor and a mechanism for motor output (Hain & Helminski, 2014). The peripheral apparatus consists of motion sensors ("vestibular", "proprioception", and "visual") that send information to the central nervous system (CNS) (vestibular nucleus complex and cerebellum) (Fife, 2010; Hain & Helminski, 2014). The CNS processes these signals and combines them with other sensory information to estimate the head and body position and motion (Hain, 2011). Motion inputs include vestibular signals from the inner ear, position sensation from the proprioceptive system, visual signals and intended movement ("motor commands"). The central processor (vestibular nuclear complex) integrates these inputs and generates motor commands to drive eye and body movements. The cerebellum monitors and readjusts the vestibular processes if necessary and is responsible for maintaining the accuracy of the vestibular system (Hain & Helminski, 2014), as illustrated in Figure 2.

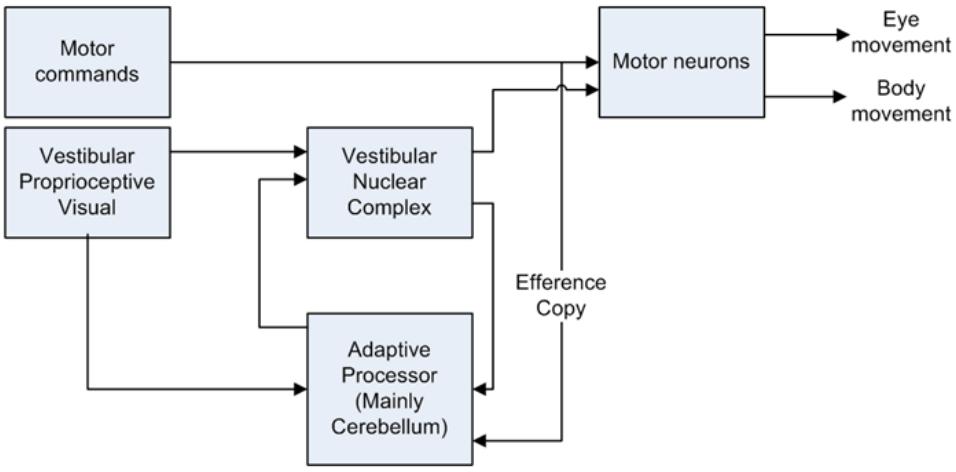

Figure 2: Block diagram illustrating the organization of the vestibular system. Reproduced from Timothy C. Hain with permission (Hain, 2011, Hain & Helminski, 2014).

The peripheral vestibular organs are located bilaterally in the inner ear. Each organ consists of 3 semicircular canals (SCC) and 2 otolith organs (utricle, saccule); see Figure 3 (Fife, 2010; Hain & Helminski, 2014). The SCCs provide the sensory inputs to the CNS regarding the angular velocity of head motion. The otolith organs provide sensory input regarding linear acceleration and respond to linear head motion and static tilt of the head with respect to gravity (Hain & Helminski, 2014).

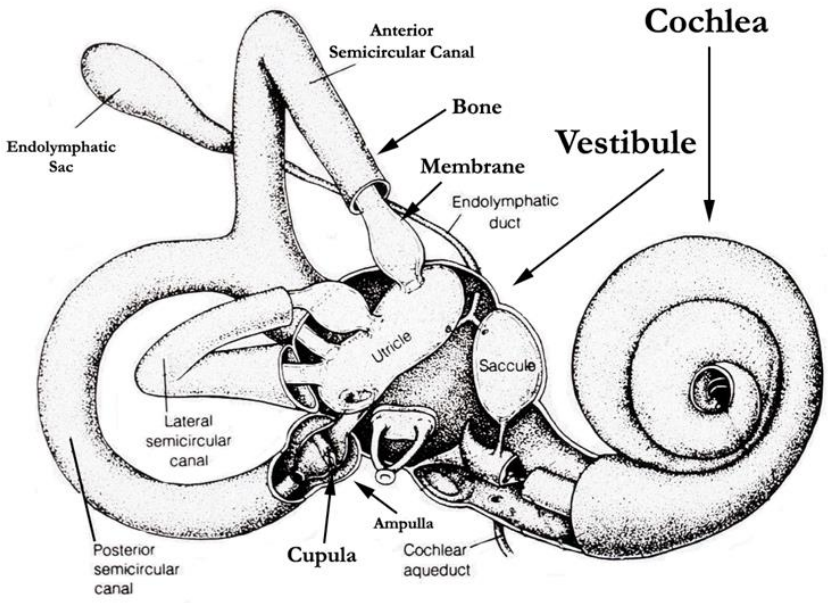

Figure 3: Illustration of the membranous and bony labyrinths with the semicircular canals and otolith organs. Reproduced from Timothy C. Hain with permission (Hain, 2011, Hain & Helminski, 2014).

The vestibular nerve transmits afferent signals from the semicircular canals and the otolith organs to the vestibular nuclear complex in the brainstem. The vestibular nuclear complex consists of four major nuclei. The superior and medial vestibular nuclei are relays for the vestibulo-ocular reflex (VOR). The lateral vestibular nucleus is the principal nucleus for the vestibulo-spinal reflex (VSR). The descending nucleus is connected to the other nuclei and the cerebellum. Commissures connect the vestibular nuclei on the two sides of the brainstem, and enable them to interact (Hain, 2011, Hain & Helminski, 2014). Connections between the vestibular nuclear complex, cerebellum, ocular motor nuclei and brainstem reticular activating systems are necessary to concurrently process the sensory information necessary to provide the

VOR and VSR effector organs with appropriately oriented and timed signals (Hain & Helminski, 2014). The cerebellum is not necessary for the vestibular reflexes; however, they may become ineffective and uncalibrated when there is a lesion in the cerebellum. The cerebellar flocculus is required to adapt the gain of the VOR. The cerebellar nodulus adjusts the duration of VOR responses and is involved in the processing of otholith input. Lesions of the anterior-superior vermis of the cerebellum affect the VSR and cause truncal instability and gait ataxia (Hain & Helminski, 2014).

In general, eye and body movements are described in terms of three reflexes, including the vestibulo-ocular reflex (VOR), the vestibulo-collic reflex (VCR) and the vestibule-spinal reflex (VSR). The VOR generates eye movements and enables clear vision during head movements. The VCR generates neck muscles responsible for stabilizing the head on the trunk. The VSR stabilizes the body and prevent falls (Fife, 2010; Hain & Helminski, 2014). Reflexes are sensory processors that rapidly convert sensory input to motor output. Higher-level/central vestibular processing of multiple sensory inputs require more processing and are slower than reflexes, but they are more accurate and are often partly consciously controlled (Hain, 2011).

Central sensorimotor integration is an important aspect of balance control that may underlie dysfunctions in static and dynamic balance after TBI (Fino et al., 2017; L. F. Lin et al., 2015). Central sensorimotor integration relies on the central nervous system to select the optimal combination of sensory sources for balance and to reweight the sensory contributions as sensory conditions change (Fino et al., 2017; Peterka, 2002; Peterka & Loughlin, 2004). Centrally mediated suboptimal weighing and /or reweighing of vestibular, visual and somatosensory information or abnormal sensory-to-motor transformations that inappropriately scale the magnitude of corrective motor actions may cause difficulties in static and/or dynamic balance tasks under challenging surface and/or visual conditions, even when the peripheral vestibular, visual and somatosensory systems are intact (Peterka, Statler, Wrisley, & Horak, 2011). In patients with sensory impairment, typically present in patients after TBI (Fino et al., 2017), reweighting is important because altered patterns of weighting are necessary to compensate for the sensory dysfunction. Some patterns of compensation may be more functional than other patterns, which suggest the important role of rehabilitation in supporting patients in their development of effective compensation strategies to improve the recovery of central sensorimotor integration and balance (Hain & Helminski, 2014). In general, the central sensorimotor, vestibular processing and integration processes are more modifiable than vestibular reflexes and are therefore particularly relevant to rehabilitation (Hain & Helminski, 2014). Vestibular rehabilitation is likely to improve the internal models that are used for central sensorimotor and vestibular processing and integration (Hain & Helminski, 2014; Whitney & Sparto, 2011).

2.3.2 Definitions

Definitions are important for professional communication in clinical work and research (A. R. Bisdorff, Staab, & Newman-Toker, 2015). Dizziness is often used as a non-specific term that includes vague symptoms of disorientation and lightheadedness, as well as more clear-cut symptoms of illusion of movement (vertigo) and balance problems (Maskell, Chiarelli, & Isles, 2006).

The Committee for the Classification of Vestibular Disorders of the Bárány Society has organized a systematic consensus process to build The International Classification of Vestibular Disorders (ICVD). The ICVD has provided primary vestibular symptom definitions that we relate to in the present work (A. R. Bisdorff et al., 2015, p. 543):

"*Dizziness* is the sensation of disturbed or impaired spatial orientation without a false or distorted sense of motion".

"*Vertigo* is the sensation of self-motion (of head/body) when no self-motion is occurring or the sensation of distorted self-motion during an otherwise normal head movement".

"*Postural symptoms* are balance symptoms related to maintenance of postural stability, occurring only while upright (seated, standing, or walking)".

In contrast to the subjective symptoms defined by the ICVD, balance problems and reduced mobility are often more observable (objective), assessable and may be analyzed to quantify post-injury functioning. There are several definitions of balance and many terms used to describe balance and balance problems. Terms such as postural control, equilibrium and posture are often used synonymously (Shumway-Cook & Woollacott, 2017). In this thesis, we use the term balance, based on the theoretical background of the Systems Framework for postural control described by Shumway-Cook and Wollacott (Shumway-Cook & Woollacott, 2017). According to this framework, *balance* is defined as: "A task that involves controlling the body's positions in space for a) stability, defined as controlling the center of body mass relative to the base of support, and b) orientation, defined as the ability to maintain an appropriate relationship between the body segments and between the body and the environment for a task" (Shumway-Cook & Woollacott, 2017, p. 154). *Mobility* is defined as: "the ability to independently and safely move from one place to another" (Shumway-Cook & Woollacott, 2017, p. 309).

2.3.3 Prevalence of dizziness and balance problems after TBI

Dizziness and balance problems are common symptoms after TBI, with the prevalence ranging from 24 to 81% of included patients (Basford et al., 2003; Bland, Zampieri, & Damiano, 2011; Campbell & Parry, 2005; Cassidy et al., 2014; L. F. Lin et al., 2015; Maskell et al., 2006; Morris & Gottshall, 2014). Different methods were used in these studies. Prevalence appears to depend on the severity of the injury, time since injury,

inclusion and exclusion criteria, and definition of dizziness (Berman & Fredrickson, 1978; Chamelian & Feinstein, 2004; Maskell et al., 2006). Dizziness and balance problems may remain disabling for several months post injury (Chamelian & Feinstein, 2004; Hartvigsen et al., 2014; Kleffelgaard, Roe, Soberg, & Bergland, 2012; Maskell et al., 2007). A large population-based cohort study by Hartvigsen et.al. identified a prevalence of dizziness in patients with mild TBI of 38.9% 6 at weeks after injury and 25.4% at 12 months after injury (Hartvigsen et al., 2014).

2.3.4 Common causes of dizziness and balance problems after TBI

Theoretically, a TBI may affect one or several bodily systems (the motor, sensory and/or cognitive systems) that interact to control balance (Shumway-Cook & Woollacott, 2017). TBI may lead to difficulties in detecting or interpreting various sensations, problems with the integration of sensations, problems of motor output, and/or disturbances in the recalibration systems that are important for adaptation to personal or environmental change (Campbell & Parry, 2005; Shumway-Cook, 2007; Shumway-Cook & Woollacott, 2017).

The diverse etiologies of dizziness and balance problems following TBI may be divided into peripheral vestibular disorders, central vestibular disorders and non-vestibular disorders. The exact cause of dizziness and balance problems may be unclear, and a combination of disorders is often present (Arshad et al., 2017; Ellis, Leddy, & Willer, 2015; Ernst et al., 2005; Fife & Giza, 2013).

Dizziness and balance problems that originate in the *peripheral vestibular system*, may include Benign Paroxysmal Positional Vertigo (BPPV), labyrinthine concussion, temporal bone fractures, unilateral vestibular nerve injury, damage to the utricle or saccule, perilymphatic fistula or traumatic endolymphatic hydrops (Basta, Todt, Scherer, Clarke, & Ernst, 2005; Fife & Giza, 2013; Morris & Gottshall, 2014).

Central vestibular system dysfunction may cause dizziness and balance problems after injury to the vestibular nuclei in the brainstem, thalamus or cerebellum (Cosetti & Lalwani, 2011; Fife & Giza, 2013; Grossman et al., 2012; V. E. Johnson, Stewart, & Smith, 2013; Maskell et al., 2006; Montgomery, Fenton, McClelland, MacFlynn, & Rutherford, 1991; Peskind et al., 2011).

Non-vestibular causes of dizziness and balance problems after TBI may be considered in relation to structural or microstructural central system injury and complicated interactions between migraine, anxiety, predisposing psychological distress, environmental and stress-related factors (Fife & Giza, 2013). Furthermore, concomitant injuries to the visual system with reduced function in smooth pursuit and saccadic eye movements or injuries that affect the range of motion, e.g., in the neck, may affect the ability of the vestibular systems to generate their output and thereby cause dizziness and balance problems (Campbell & Parry, 2005; Drew et al., 2007;

Fife & Kalra, 2015; Maskell et al., 2006; Morris & Gottshall, 2014; Peterson, 2010; Suh, Basu, et al., 2006; Suh, Kolster, Sarkar, McCandliss, & Ghajar, 2006).

The term post-concussion dizziness is sometimes used and implies that it is a component of the post-concussion syndrome. It is often characterized with a rocking or swaying sensation, floating lightheadedness, feeling of drunkenness or balance problems that often gets worse with head movements. The description is compatible with a wide variety of potential causes from microstructural changes of the brain, to post-traumatic migrainous vertigo, labyrinthine concussion, cervical vertigo, anxiety-related vertigo and some combination of these that is further aggravated by poor coping ability (Fife & Giza, 2013).

The most common causes of dizziness after TBI are elaborated below.

BPPV is often seen in addition to peripheral or central vestibular disorders and should be assessed with positional tests (Dix-Hallpike and roll test) (Ahn et al., 2011; Ernst et al., 2005). Head trauma, including relatively minor injuries (flexion-extension injuries to the neck) to more severe head trauma, is the second most common cause of BPPV (Herdman & Hoder, 2014). BPPV is a mechanical problem that occurs when otoconia become dislodged and move into the semicircular canals (Balatsouras et al., 2017; Herdman & Hoder, 2014). The incidence of post traumatic BPPV varies from 5% - 28% (Ahn et al., 2011; Morris & Gottshall, 2014). The variation in incidence rate in these patients might be due to the severity of their other injuries, length of time between trauma and assessment, or spontaneous resolution (Morris & Gottshall, 2014). Studies report a higher rate of horizontal and anterior semicircular canal involvement and a higher incidence of multiple and bilateral canal involvement in post-traumatic BPPV than ordinary BPPV (Ahn et al., 2011; Balatsouras et al., 2017). Post-traumatic BPPV appears to be more difficult to treat/requires more treatment sessions (Ahn et al., 2011; Balatsouras et al., 2017; Gordon, Levite, Joffe, & Gadoth, 2004). Several studies also report a higher recurrence rate (Balatsouras et al., 2017; Gordon et al., 2004).

Potential mechanism for unilateral vestibular loss after head trauma include traction or injury-induced demyelination of the vestibulocochlear nerve, ruptures of the membranous labyrinth due to shearing forces, trauma-related bleeding or micro-ischemic changes, temporal bone fractures that affect the bony labyrinth or vestibule, or direct trauma or injury to the labyrinth (Cosetti & Lalwani, 2011; Fife & Giza, 2013; Maskell et al., 2006). The term Labyrinthine concussion is often used to describe a non-specified injury to the membranous labyrinth that results from acceleration-deceleration forces on the bony labyrinth from head trauma (Fife & Giza, 2013). The term is used to define a syndrome and presumed cause rather than a well-defined injury (Fife & Giza, 2013).

TBI may lead to traction on or contusion of the vestibular nuclei in the brainstem, thalamus or cerebellum (Grossman et al., 2012; Montgomery et al., 1991). Diffuse

axonal injury (DAI) may be caused by TBI, which refers to an injury to axons within the white matter fiber tracts due to abrupt stretching, which damages the axonal cytoskeleton, reduces elasticity and impairs axoplasmic transport (Cosetti & Lalwani, 2011; V. E. Johnson et al., 2013). Any of these mechanisms may also disrupt vestibular and postural reflex pathways and consequently lead to dizziness and balance problems (Fife & Giza, 2013).

Non-vestibular dizziness after TBI may be related to visual and/or proprioceptive dysfunction. Visual vertigo or visual motion sensitivity are terms used to describe an increased sense of disorientation, dizziness or postural symptoms in situations with visual and vestibular conflict. These symptoms are assumed to arise from the inability of the CNS to effectively integrate sensory information, particularly vestibular information, which creates overreliance on vision (Broglio, Collins, Williams, Mucha, & Kontos, 2015; Maskell et al., 2007). In cervicogenic dizziness, pathology in the cervical spine is assumed to create abnormal muscular activity in the deep layers of the upper cervical spine, which normally provides proprioceptive input to the CNS (Broglio et al., 2015; Ellis et al., 2015). A mismatch between aberrant cervical proprioceptive information, vestibular and visual inputs is assumed to cause dizziness (Broglio et al., 2015).

Patients with mild-to-moderate TBI may also develop Persistent Postural-Perceptual Dizziness (PPPD), which is a diagnosis recently defined by the Bárány Society and the WHO (Dieterich & Staab, 2017). PPPD typically begins shortly after an event that causes acute vertigo, dizziness or balance problems, such as mild-to-moderate TBI. Diagnostic criteria have been developed and include symptoms of dizziness and balance problems present most days for 3 months or more, and that are present without specific provocation but exacerbated by upright posture, active or passive motion without regard to direction or position, and exposure to moving visual stimuli or complex visual patterns (Dieterich & Staab, 2017). Furthermore, the symptoms should cause “significant distress” or “functional impairment” and not be better attributed to another disease or disorder (Dieterich & Staab, 2017). PPPD may coexist with other vestibular disorders, which may confuse the diagnosis. Anxiety and depression may be present as comorbidities; however, they are not symptoms of PPPD. Nevertheless, anxiety and depression may increase the likelihood of developing PPPD (Staab, 2012).

2.4. Recovery and treatment of dizziness and balance problems

In this section, vestibular compensation (VC) and vestibular rehabilitation (VR) in general is presented. Furthermore, the evidence for the effect of VR for patients with TBI is provided. Finally, the individually modified group-based VR intervention explored in this research project, is presented.

2.4.1 Vestibular compensation

Vestibular compensation (VC) is the term used to describe the general recovery after unilateral vestibular loss or hypofunction of any cause, including trauma (Curthoys & Halmagyi, 2014). The spontaneous functional recovery after damage to the vestibular system constitutes neuronal and behavioral plasticity of the nervous system to reorganize and overcome the damages of the peripheral vestibular system (Lacour et al., 2016).

Unilateral vestibular loss results in static (present continuously) and dynamic symptoms (present during movement) with both sensory and motor components, like reduced balance, inadequate compensatory responses to head movement, and changes in the perception of body orientation and movement (Curthoys & Halmagyi, 2014). Static symptoms include spontaneous vestibular nystagmus, head and body tilt to the lesion side, ocular tilt, balance problems and altered vestibulo-ocular and spinal reflexes (Curthoys & Halmagyi, 2014; Herdman & Whitney, 2014; Lacour et al., 2016; Tjernstrom et al., 2016). Dynamic symptoms include visual blurring, balance problems and gait ataxia during head movement which are caused by the disruption/loss of the vestibular response to the dynamic portion of the vestibular system (Herdman & Whitney, 2014).

Compensation of the static symptoms is spontaneous and a result of cerebellar modulation or inhibition of the initial asymmetric activity of the vestibular nuclei (Tjernstrom et al., 2016). For most patients with unilateral hypofunction, the static symptoms decrease over the first few days and continue to progressively resolve over the first month (Curthoys & Halmagyi, 2014; Lacour et al., 2016). The dynamic symptoms improve more slowly and may never be fully compensated (Lacour et al., 2016). Compensation of the dynamic symptoms is a longer-term dynamic distributed learning process in which non-vestibular sensory input and cognitive-behavioral strategies probably plays a role (Curthoys & Halmagyi, 2014; Lacour et al., 2016). Recovery from the dynamic symptoms requires both visual inputs and active movement of the head and body (Herdman & Whitney, 2014). Vestibular rehabilitation may promote vestibular compensation via improving dynamic performance by systematically replacing some previously compensatory strategies with new, learned strategies that enhance functional recovery (Balaban, Hoffer, & Gottshall, 2012; Deveze, Bernard-Demanze, Xavier, Lavieille, & Elziere, 2014).

Patients may experience partial or complete relapse (decompensation) in the dynamic phase, with return of the acute symptoms (spontaneous nystagmus, sensations of vertigo and postural disequilibrium) (Curthoys & Halmagyi, 2014). Decompensation may be triggered by stressful events, and/or a reduction in cerebellar function (Curthoys & Halmagyi, 2014). Head injury may affect the compensation ability, modify the effect of VR and result in a negative outcome (Shepard, Telian, Smith-Wheelock, & Raj, 1993). Other factors that may negatively affect vestibular compensation and vestibular rehabilitation include migraine, anxiety, depression,

cerebellar dysfunction, visual impairments, medical co-morbidities, peripheral neuropathy, and physical restrictions of daily activities (Hall et al., 2016; Shepard et al., 1993; Whitney & Furman, 2007).

2.4.2 Vestibular rehabilitation (VR)

VR is a broad concept that incorporates compensation training after a vestibular lesion or disease, and balance training and compensation in other causes of vertigo, dizziness or balance problems (Deveze et al., 2014; Hansson, 2007; Tjernstrom et al., 2016; Whitney & Sparto, 2011). The aims of VR are to decrease dizziness and motion sensitivity and improve gaze stability and functional balance through exercises and activities that are designed to enhance central nervous system compensation to vestibular system dysfunction (Deveze et al., 2014; Herdman & Whitney, 2014). Furthermore, VR aims to improve the patients' general physical condition, normalize activity limitations and participation restrictions in society and reduce social isolation (Herdman & Whitney, 2014).

VR typically comprises information, guidance and support, and a combination of exercises that include different components to address the impairments and functional limitations identified during the assessment (Hall et al., 2016; Herdman & Whitney, 2014).

A brief presentation of the specific components in VR are provided as follows:

- Adaptation: Repetitive and provocative movements of the head and/or eyes are used to restore the vestibulo-ocular reflex (VOR) gain (Cabrera Kang & Tusa, 2013; McDonnell & Hillier, 2015; Whitney & Sparto, 2011) and improve the visual-vestibular interaction (adaptation) and eye/hand co-ordination. The primary signal for inducing vestibular adaptation is retinal slip (the movement of a visual image across the retina). This slip results in an error signal (dizziness, blurred vision) that the brain attempts to minimize by increasing the gain of the vestibular responses (Herdman & Whitney, 2014).
- Substitution: Awareness, cognition and stimulation of sensory inputs are used to promote the use of individual strategies or combinations of several sensory inputs, e.g., visual and/or somatosensory, instead of the dysfunctional vestibular input to strengthen the use of alternative strategies and promote central compensation (substitution) (Alrwaily & Whitney, 2011; Cabrera Kang & Tusa, 2013; McDonnell & Hillier, 2015). Substitution does not restore lost functions; it replaces them with new operating modes using either other sensory cues or newly elaborated motor strategies (Lacour et al., 2016).
- Habituation/compensation: Motion is used to reduce symptoms of dizziness by repetitive exposure to the movements that provoke the symptoms to habituate or reduce responsiveness to repetitive stimuli and re-balance tonic activity

within the vestibular nuclei (Cabrera Kang & Tusa, 2013; McDonnell & Hillier, 2015; Whitney & Sparto, 2011).

- Balance and gait exercises are used to enhance central sensorimotor and vestibular processing and integration by manipulating the visual, somatosensory, or vestibular sensory systems (Whitney & Sparto, 2011). Balance and gait exercises, reconditioning activities, and functional/occupational retraining are based on motor control theory and motor learning principles to change movement behavior and/or promote movement fitness (McDonnell & Hillier, 2015; Shumway-Cook & Woollacott, 2017).

In addition, repositioning maneuvers for benign paroxysmal positional vertigo are often included in VR (Cabrera Kang & Tusa, 2013; Hilton & Pinder, 2014; McDonnell & Hillier, 2015). The maneuvers are based on a mechanical rationale to remove/shift vestibular debris out of the affected semicircular canal(s) (e.g., Epley maneuver) (Hilton & Pinder, 2014; McDonnell & Hillier, 2015).

2.4.3 Evidence for the effect of VR after TBI

Vestibular rehabilitation for patients with TBI has been described; however, evidence for its effect is limited by a poor methodological quality. In this research project, a comprehensive literature search was performed. The goal of the search was to identify studies on vestibular rehabilitation that aimed to improve dizziness and balance problems in adults with TBI. Reference lists from retrieved articles and guideline documents were screened for additional relevant articles and publications.

The literature search was performed in the PubMed/Medline, Cochrane, Embase and PEDro databases using the following terms: Dizziness, vertigo, postural balance, balance, postural stability, mobility, vestibular rehabilitation, balance training, exercise, rehabilitation, physical therapy, concussion, traumatic brain injury, head injury-closed, head injury-penetrating, and head trauma.

The following criteria were applied to select relevant articles:

- The study design was preferably a randomized controlled trial; however, other relevant articles were included.
- The included patients had to represent the adult population with TBI and dizziness and balance problems. Studies that involved children were only included if they also included adults, and the adults comprised the majority of the study sample.
- Interventions should be vestibular rehabilitation (therapy) including balance training.

- Only studies that included outcome measures related to dizziness and balance were included. Dizziness Handicap Inventory (DHI) as an outcome measure was preferred; however, studies that employed other similar self-reported outcome measures were also included.
- Studies on sport-related concussion, acute and chronic TBI were included.
- Studies that involved other central nervous system populations, such as stroke, brain tumors and subarachnoid hemorrhage-SAH, were excluded.
- Studies on severe TBI, defined by no ability to ambulate or cooperate in therapy were excluded.
- Studies performed in a virtual reality environment or with virtual reality equipment, were excluded.
- Only studies published from 2000 were included.

The results of the literature search are presented in Table 2.

Table 2: Description of RCTs and other primary studies that evaluated the effect of VR on DHI/other main outcome measures among TBI patients. RCTs are presented first, followed by prospective and retrospective studies, cases series and case reports are presented last.

Author	Design	Study population Age, sex, N	Assessment/ Outcome measures	Intervention	Result (selected outcomes reported)
Schneider et al.2014 (Schneider et al., 2014)	RCT	Sports related concussion Age: 12-30, n = 31	Medical clearance to return to sport. Several secondary outcomes e.g., Numeric Pain Rating Scale score, ABC scale, DHI, SCAT 2, modified motion sensitivity test, FGA, DVAT.	Intervention group: Rest followed by graded exertion, vestibular rehabilitation and cervical spine physical therapy once weekly and HEP daily for 8 weeks Control group: Rest followed by graded exertion	Return to sport (%). 73.3% in the intervention group vs. 7.1% in the control group. OR 10.7, p = 0.001 for return to sports for the intervention group who completed the intervention Intention to treat analyses: OR 3.91, p=0.002 for the treatment group to be medically return to sport. compared with the control group.
Gottshall et al 2010 (K. R. Gottshall & Hoffer, 2010)	Observational prospective cohort	Soldiers with blast induced mild TBI n = 82	SOT, MCT, DGI Perception time, DVAT, GST	Vestibular physical therapy for one hour, twice weekly for 8-12 weeks and HEP	Meaningful improvement for target following and dynamic visual acuity after 8 weeks of treatment. DGI score increased from 21 to 23 points at week 8, max. scores 24/24 at 12 weeks ($p \leq 0.05$)
Hoffer et al 2007 (Hoffer, Balough, & Gottshall, 2007)	Observational prospective cohort	n = 77 58 mild, 10 moderate, 9 severe TBI	RTW and time to resolution of symptoms	Vestibular physical therapy	Improvement with respect to symptoms of dizziness, perception of balance function and measures of VOR function after 6-8 weeks
Hoffer et al 2004 (Hoffer, Gottshall, Moore, Balough, & Wester, 2004)	Prospective patient registry, characterization of diagnosis types, patient distribution by diagnosis type	Military personnel n = 58, mild TBI	Time to return to work and symptom remission. Vestibular assessments, DHI, ABC, Romberg, tandem Romberg, Fukuda step test	Vestibular physical therapy. Duration of the intervention varied per patient depending on diagnoses, RTW and symptom remission.	Diagnosis type: 41% Migraine related dizziness, 28% BPPV, 19% spatial disorientation, 12% not able to characterize Mean time to return to work: BPPV = < 1 week PTMAD = 3.8 weeks PTSD = > 3 months PTED = 4 weeks

Alsalaheen et al 2010 (Alsalaheen et al., 2010)	Retrospective Chart review	n = 114 with concussion 67 children 8-18 years	Self-report outcome measures: dizziness severity, DHI, ABC. Performance-based outcome measures: DGI, FGA, TUG, gait speed, SOT	VR: eye-head coordination exercises, habituation exercises, static and dynamic postural control training HEP daily	Significant improvement in subjective dizziness, gait and balance within 5 weeks Dizziness severity score: pre 21; post 12, $p < 0.001$ ABC: pre 64%, post 84%, $p < 0.001$ DHI: pre 49, post 30, $p < 0.001$ DGI: pre 20, post 23, $p < 0.001$ FGA: pre 22, post 28, $p < 0.001$ TUG (sec): pre 9.7 post 7.8 $p < 0.001$ Gait speed (m/s): pre 1.02, post 1.28 $p < 0.001$ SOT: pre 48/100, post 71/100, $p < 0.001$
Gurr and Moffat 2001 (Gurr & Moffat, 2001)	Observational prospective case series	Adult patients > 18 years old with mild-to moderate TBI n = 18	Vertigo coping questionnaire, vertigo symptom questionnaire-short version, vertigo handicap questionnaire, HADS	VR with a multidimensional psychological approach Six weekly, 1-hour treatment sessions	Significant improvement on scores on measures of vertigo symptoms, handicap, emotional distress, physical flexibility and postural stability
Brown et al 2006 (Brown, Whitney, Marchetti, Wrisley, & Furman, 2006)	Retrospective case series	Central vestibular dysfunction n =48 Posttraumatic n =5 Mean age: 63.9, female 31 (66%)	DHI, ABC, DGI, TUG	Custom designed PT program for a mean of 5 visits over an average of 5 months	Improvement in subjective and objective outcomes
Faltus 2014 (Faltus, 2014)	Case report	Concussion, sports related, n =1	DHI BESS	VR and HEP to be done daily	Improvements were noted across all outcome measures DHI: pre 38, post 14 BESS: pre 25, post 18
Peterson 2010 (Peterson, 2010)	Case report	Adult patients with moderate and severe TBI n = 2	Clinical tests and performance based tests on balance and mobility HiMAT	Visual and vestibular rehabilitation	Improvements on several outcome measures

Gottshall 2005 (K. Gottshall, Gray, & Drake, 2005)	Case report	Military personnel Mild TBI n = 1	FIM, DGI, ABC, Romberg, Dix-Hallpike	VR and walking program over 16 weeks	Full return to work and military duty FIM: pre 5, post 7/7 in all domains DGI: pre 21/24, post 24/24 ABC: pre 88%, post 100%

RCT, Randomized Controlled Trials; ABC, Activities-specific Balance Confidence; DHI, Dizziness Handicap Inventory; SCAT 2, Sport Concussion Assessment Tool; FGA, Functional Gait Assessment; DVAT, Dynamic Visual Acuity Test, HEP, Home Exercise Program; OR, Odds Ratio; TBI, Traumatic Brain Injury; SOT, Sensory Organization Test; MCT, Motor Control Test; DGI, Dynamic Gait Index; GST, Gaze Stabilization Test; RTW, return to work; VOR, Vestibulo-Ocular reflex; BPPV, Benign paroxysmal positional vertigo; PTMAD, post-traumatic migraine associated dizziness; PTSD, post-traumatic spatial disorientation; PTED, post-traumatic exercise-induced dizziness; TUG, Timed UP and Go; SOT, Sensory Organization Test; VR, Vestibular Rehabilitation; HADS, Hospital Anxiety and Depression questionnaire; PT, Physical Therapy; BESS, Balance Error Scoring System; HiMAT, High-level Mobility Assessment Tool; FIM, Functional Independence Measure

Three systematic reviews were found (Bland et al., 2011; Murray, Meldrum, & Lennon, 2017; Quatman-Yates et al., 2016) (not included in the table). They concluded that the current evidence for the optimal prescription and efficacy of Vestibular Rehabilitation exercises in patients with mild TBI is promising but limited (Murray et al., 2017; Quatman-Yates et al., 2016), and there is poor evidence for gait and balance interventions in patients with mild-to-moderate TBI (Bland et al., 2011).

Primary studies regarding vestibular rehabilitation for patients with TBI indicate generally favorable outcomes. Only one RCT was found (Schneider et al., 2014), in addition to prospective, retrospective and descriptive studies without control groups (Alsalaheen et al., 2010; Brown et al., 2006; K. R. Gottshall & Sessoms, 2015; Gurr & Moffat, 2001; Peterson, 2010). Moreover, many studies are of sport-related injuries and trauma in the military (K. R. Gottshall & Hoffer, 2010; Hoffer et al., 2007; Hoffer et al., 2004), which limits the generalizability of the studies.

Clinical evidence-based practice guidelines for concussion/mild traumatic injury and persistent symptoms have been developed (Marshall et al., 2015). The guidelines include recommendations for persistent vestibular (balance/dizziness) dysfunction. However, the guideline only vaguely discusses specific VR interventions. There are also several articles/reviews that describe VR exercises and assessments of dizziness and balance problems after TBI (Alsalaheen et al., 2012; Chandrasekhar, 2013; Lei-Rivera, Sutera, Galatioto, Hujsak, & Gurley, 2013; Maskell et al., 2006).

Finally, two updated Cochrane reviews confirm that there is moderate to strong evidence for VR and Epley repositioning maneuver being safe and effective management for unilateral peripheral vestibular dysfunction and BPPV (Hilton & Pinder, 2014; McDonnell & Hillier, 2015). The Cochrane reviews do not address subgroups, such as TBI; however, it appears reasonable to assume that patients with uncomplicated TBI and BPPV and/or vestibular hypofunction may benefit from VR and maneuver treatment.

In summary, benefits and no adverse effects of VR for patients with TBI/concussion and persistent vestibular and/or balance problems are suggested by existing studies (Murray et al., 2017). However, there is a lack of high-quality studies, and more research is warranted, particularly regarding the effect and ideal dosing parameters for VR after TBI (Bland et al., 2011; Hall et al., 2016; Murray et al., 2017; Quatman-Yates et al., 2016).

2.4.4 Individually modified group-based VR intervention for patients with TBI

Group-based VR was first described by Cooksey and Cawhtorne in the 1940s, who developed and described an exercise program designed to decrease dizziness in patients with vestibular dysfunction after concussion/head injuries (Cawthorne, 1944;

Cooksey, 1946; Whitney & Furman, 2007). A more individualized problem-oriented treatment approach that identifies impairments and functional limitations has subsequently been used (Herdman & Clendaniel, 2014). The advantages of both a group-based and individualized approach was combined to form the bases for the modified, group-based VR intervention explored in this research project.

The group-based VR intervention was derived from a VR group intervention program developed at the Outpatient Department at the Physiotherapy Program at Oslo and Akershus University College (Tamber, Bruusgaard, & Bruusgaard, 2014). It was based mainly on principles from motor control theory for improving balance and self-efficacy theory for coping with the symptom pressure and disease burden (Bandura, 1997). Elements from established VR programs were included and followed the principles of habituation, adaptation/gaze stability, substitution exercises and balance relearning (Herdman & Clendaniel, 2014). According to the motor learning principles, a gradual increase in the challenges of balance exercises that required integration of multiple sensory inputs was used (Shumway-Cook & Woollacott, 2012).

Individual modifications and adjustments that appeared necessary to accommodate post-concussion symptoms and physical and cognitive challenges that are typical after a mild and moderate TBI were considered (Alsalaheen et al., 2012; Morris & Gottshall, 2014; Shumway-Cook, 2007). The modifications included a follow-up twice weekly by two physical therapists experienced in vestibular and TBI rehabilitation. Furthermore, the groups were small, comprised of 2-5 patients, which made individual tailoring of exercises easier. The individual tailoring of exercises was based on symptoms, signs and functional challenges registered at each patient's baseline and on the tentative underlying cause(s) of their dizziness. A circle training design with stations enabled patients to work individually with the exercises, thus allowing them to skip stations they did not tolerate or did not need. Furthermore, an individually tailored home exercise program (HEP) was provided. The responses to the performed exercises and activities were monitored by exercise diaries.

In designing the intervention, steps that would facilitate a patient's self-efficacy were taken into account. Self-efficacy has been shown to predict physical activity participation in individuals with TBI (Reavenall & Blake, 2010). Self-efficacy is a concept that refers to an individual's sense of confidence in his/her ability to perform a given task and reach goals (Bandura, 1997). A central part of self-efficacy theory is that the stronger the individual's confidence in his/her ability to perform a set of actions, the more likely the individual will be to initiate and persist in a given activity (Bandura, 1997). Increased self-efficacy in the individually modified group-based VR intervention, was facilitated by focusing on positive experiences, gaining control by interpretation of physical and emotional symptoms, and strengthening the patients' beliefs in their own ability to reach their goals. Furthermore, the group-based approach facilitated interactive and social processes and provided the patients with opportunities for indirect learning and peer support, in addition to support, feedback and information

from the physical therapists (Bandura, 1986). The patients were also stimulated to explore ways of coping with their situation, and common challenges, such as TBI and dizziness, were used as stimuli to yield positive social relationships and increase motivation for physical activities (Bandura, 1986).

3 AIMS AND HYPOTHESIS

The first aim in this research project was to examine the measurement property of the High-Level Mobility Assessment Tool for Traumatic Brain Injury (HiMAT) for the mild TBI population. The second aim was to describe the dizziness-related disability and its associations with pre-injury and injury-related factors in the TBI population. The third aim was to describe and explore the effect of an individually modified, group-based vestibular rehabilitation intervention for patients with dizziness and balance problems after a mild-to-moderate TBI. We hypothesized that the individually modified group-based VR intervention would be safe and beneficial in that it would decrease dizziness-related disability and increase function among these patients. The specific aims for each paper are described below.

3.1 Paper I

Measurement Properties of the High-Level Mobility Assessment Tool for Traumatic Brain Injury

The aim was to examine the reliability, validity and responsiveness of the HiMAT in a mild TBI population.

3.2 Paper II

Vestibular Rehabilitation after Traumatic Brain Injury – A Case series

The aims were to describe the modified, group-based VR intervention and examine how the intervention may be beneficial in addressing dizziness and balance problems by describing changes in self-perceived dizziness, balance, and health-related quality of life (HRQoL) in four patients.

3.3 Paper III

Dizziness-related disability following mild-to-moderate traumatic brain injury

The aims were to describe dizziness-related disability after mild-to-moderate TBI and investigate the associations between dizziness-related disability after mild-to-moderate TBI and personal factors, injury-related factors and post-injury functioning using the International Classification of Functioning, Disability and Health (ICF) as a framework.

3.4 Paper IV

The Effect of Vestibular Rehabilitation Addressing Dizziness and Balance Problems in Patients after Traumatic Brain Injury: A Randomized Controlled Trial

The aim was to explore the effect of the modified, group-based VR intervention on patients with dizziness and balance problems 2-6 months after TBI. The hypothesis was that an individually modified group-based VR intervention would decrease dizziness-related disability and improve balance and mobility in patients with dizziness and balance problems after mild-to-moderate TBI.

4 MATERIALS AND METHODS

4.1 Research design

The studies included in this research project have four different designs. A methodological (test-retest) design was used to assess the measurement properties of the HiMAT (paper I). The study that described the intervention was designed as a case series (paper II). The study that assessed dizziness-related disability after TBI had a prospective design and included personal factors, injury-related variables and clinical assessments and outcome measures for patients at their inclusion in the RCT (paper III). The study that explored the effect of the individually modified group-based VR intervention was designed as a randomized controlled trial (RCT) with two follow-ups, including the first follow-up immediately after the intervention and the second follow-up eight months after the injury (paper IV). The RCT followed the criteria set out in the CONSORT (Consolidated Standards of Reporting Trials) Statement for reporting randomized trials, which is an evidence-based, minimum set of recommendations for reporting randomized trials consisting of a checklist and a flow diagram (Moher et al., 2012; Schulz, Altman, & Moher, 2010). The RCT has elements from pragmatic trials, patients were recruited from their usual care setting, the main outcome measure was a self-report measure of function, intention-to-treat analyses were employed, and flexibility in administering the intervention was allowed (Loudon et al., 2015; Thorpe et al., 2009).

4.2 Recruitment procedure and setting

Patients in all four studies were recruited from the outpatient department of Physical Medicine and Rehabilitation at OUH, which receives patients with mild and moderate TBI approximately two to six months after the injury. The patients were mainly referred from the Neurosurgical department at OUH, however, they also originated from other departments at OUH, other hospitals, or general practitioners in the Oslo and Akershus municipalities. The Physiatrist who was responsible for the routine follow-up, provided information regarding the studies and referred eligible patients to the physiotherapist (PT) who administered clinical assessments and included the patients in the respective studies.

In paper I, all assessments and retests were conducted at the outpatient department of the Department of Physical Medicine and Rehabilitation, OUH. The HiMAT was performed as a routine test for all patients, and eligible patients who met the inclusion criteria and agreed to participate in the study were included in the study. The patients were retested at 6 months after the injury. A subgroup of 25 patients were recruited for the inter- and intra-tester reliability. The same physiotherapist tested the participants at 3 and 6 months after the injury. Three experienced physical therapists performed the

inter- and intra-tester reliability. The recruitment period was from May 2008 to November 2010.

In papers II-IV, the assessments were conducted at the outpatient department of the Department of Physical Medicine and Rehabilitation, OUH, and at the Institute of Physiotherapy at Oslo and Akershus University College, OAUC. The intervention and control assessments were conducted at OAUC. After the routine follow-up with a physiatrist at OUH, eligible patients who met the inclusion criteria were assessed (clinical assessments) by the PT. Patients who did not meet the exclusion criteria were informed about the study and asked to participate. The patients who consented were assessed at the OAUC using the standardized self-report questionnaires and performance-based tests by the same PT, and for all patients included in study IV, this was performed prior to randomization. The four patients included in the case study (paper II) were recruited during the spring in 2012. The recruitment period for patients included in studies III and IV was from January 2013 to October 2015.

The follow-ups in papers II -IV were administered by the PT who also conducted the clinical assessments. The patients completed the self-report questionnaires before they were collected by the blinded assessor, who interviewed the patients for the GOSE and performed the BESS and HiMAT performance-based tests. The outcome assessor was blinded to the group allocation throughout the data collection period. The patients were instructed not to discuss their treatment with the blinded outcome assessor. The participants and the interventionists were aware of the allocation.

4.3 Participants

The participants included in papers I-IV were 16-67 years old, with mild and moderate TBI. They lived in Oslo and Akershus county and were admitted to the outpatient Department of Physical Medicine and Rehabilitation at OUH for a routine follow-up by a Physiatrist.

The inclusion and exclusion criteria for the studies are presented in Table 3.

Table 3: Inclusion and exclusion criteria:

Paper	Inclusion criteria	Exclusion criteria
I	• Age between 16 and 67 years • Mild TBI GCS 13-15	• Severe psychological disease reported in the medical record • Insufficient command of Norwegian • Injuries to the extremities that made testing difficult
II-IV	• TBI • Age between 16 and 60 years • Dizziness reported on the RPQ and/or a positive Romberg's test	• Severe psychological disease reported in the medical record • Substance abuse • Insufficient command of Norwegian • Cognitive dysfunction (unable to follow instructions and/or fill in forms) • Fractures or other co-morbidities affecting mobility and independent gait • < 15 on the DHI

TBI, Traumatic Brain Injury; GCS, Glasgow Coma Scale; RPQ, Rivermead Post-Concussion Symptoms Questionnaire; DHI, Dizziness Handicap Inventory.

Paper I - Measurement Properties of the High-Level Mobility Assessment Tool for Traumatic Brain Injury

One hundred twenty-eight patients were eligible for participation in paper I. Thirty-two patients were excluded from the study. These patients included 24 men and 8 women with a mean age of 41 years (SD 13). The main reason for exclusion was extremity injuries (n = 22). Four patients were excluded due to insufficient command of Norwegian, and six patients had other reasons for exclusion. In addition, four patients did not wish to participate, which resulted in 92 patients included in the study. They included 63 (69%) men, the mean age was 37.1 (SD 13.8) and the mean GCS was 14.7 (SD 0.7). Fifty-one patients were retested at 6 months. They included 30 (58.8%) men, the mean age was 41.4 (SD 13.2) years and the mean GCS was 14.8 (SD 0.4). The group that did not attend the 6-month control (n = 41) was significantly younger and consisted of significantly more men. However, the injury severity measured with the GCS was not significantly different from the group that attended the 6-month control.

Paper II - Vestibular Rehabilitation after Traumatic Brain Injury – A Case series

Four patients were recruited for participation in paper II, including two women and two men (age 24–45) with mild TBI, dizziness and balance problems.

Papers III – Dizziness-related disability following mild-to-moderate traumatic brain injury and IV- The Effect of Vestibular Rehabilitation Addressing Dizziness and Balance Problems in Patients after Traumatic Brain Injury: A Randomized Controlled Trial

One hundred sixty-one patients were assessed for eligibility. Twenty patients did not meet the inclusion criteria. Forty-four patients were excluded (reasons for exclusion: Insufficient command of Norwegian n = 8, psychological disease n = 6, fractures/comorbidities n = 5, < 15 on DHI n = 25. Thirty-two patients declined to participate, including one who withdrew after randomization and did not consent to the use of data from the baseline assessments. One patient was subject to an administrative error (received the psycho-educative group sessions prior to the group-based VR intervention) and was included in the baseline population (paper III), but excluded from the RCT (paper IV). The flowchart presents the included patients in papers III and IV. Figure 4.

There were no significant age or injury severity (GCS) differences between the study population and the non-participants. However, there were significantly more women among the included patients than in the group that did not participate in the study (Chi-Square = $p < 0.001$).

In the RCT, the patients were followed up immediately after the intervention (T1) and 8 months after the injury (T2). One individual was lost to follow-up in the intervention group at T1. No reason was provided. At T2, 8 individuals were lost to follow-up, including 5 in the intervention group and 3 in the control group (reasons for loss to follow-up: Intervention group: one individual underwent orthopedic surgery, one did not come due to a lengthy travel/vacation, and three did not wish to participate. Control group: one individual did not provide a reason, and two did not wish to participate).

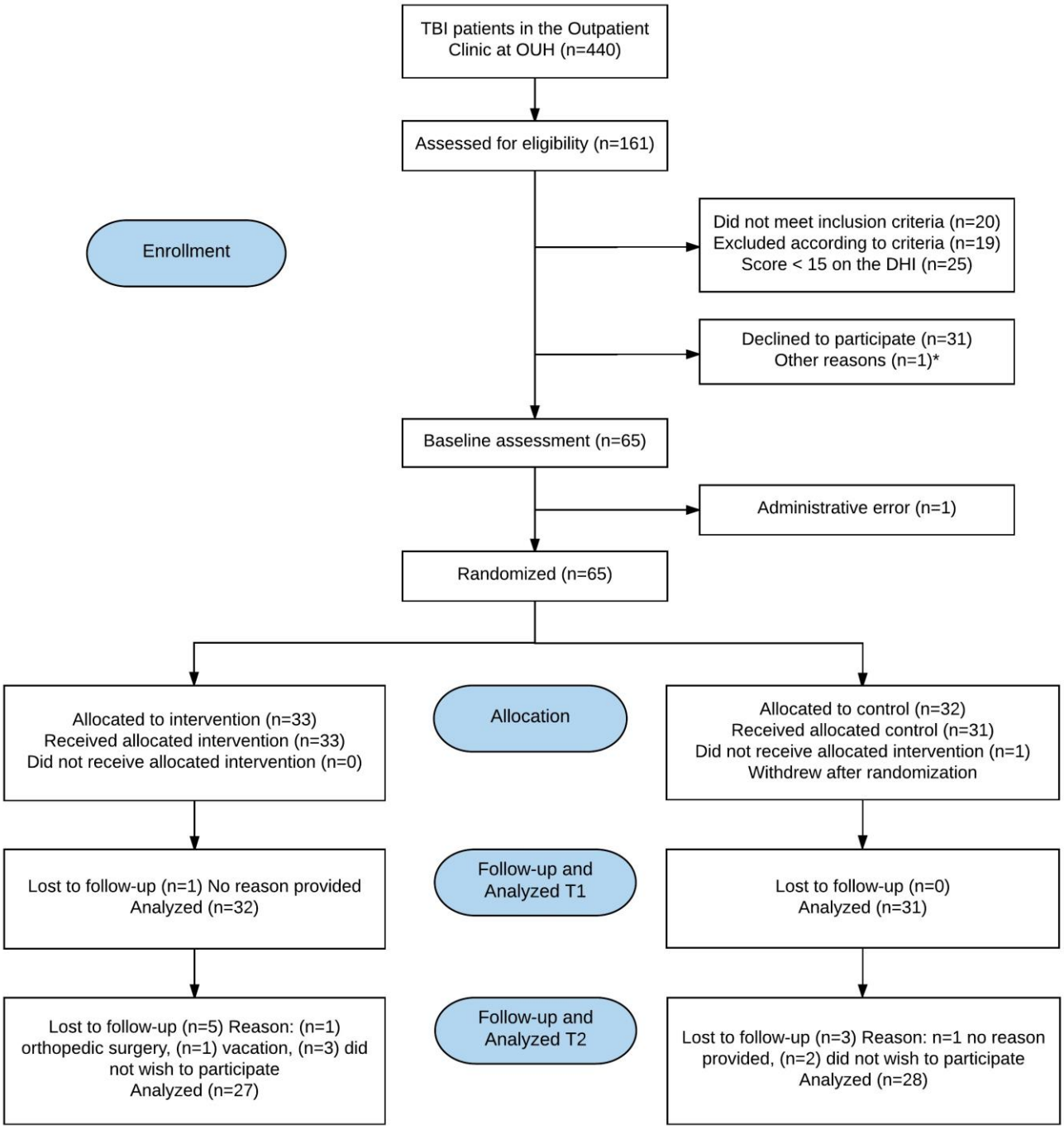

Figure 4: CONSORT flow chart of the included patients in studies III and IV.

* n = 1 withdrew after randomization and did not consent to the use data obtained from the baseline assessments. One patient was offered the psycho-educative group sessions prior to the VR rehabilitation, and was not randomized.

4.4 Data collection – clinical assessments and outcome measures

The data in this research project were collected from the patients' medical records and assessments. The assessments comprised clinical assessments and self-reported, clinician-rated and performance-based outcome measures. The clinical assessments and outcome measures were mapped to the main domains of functioning and disability in the ICF, Table 4. This approach was performed to place the assessment in the context of vestibular rehabilitation after TBI and provide an overview of the specific aspects of functioning and disability that were assessed in the TBI population included in this research project.

Demographic variables included age, gender, education, marital status, employment status, sick-leave, and pre-injury comorbidities. *Injury-related variables* were collected from the medical records and included the GCS score, loss of consciousness (LOC), post-traumatic amnesia (PTA), positive MRI/CT scans and skull fractures.

Clinical assessments comprised tests that are commonly applied in patients with dizziness (Herdman & Clendaniel, 2014; Morris & Gottshall, 2014). The vestibular and oculomotor systems were assessed with positional testing for Benign Paroxysmal Positional Vertigo – BPPV (Dix-Hallpike and Roll test), Head-Impulse Test, Clinical Test for Dynamic Visual Acuity, Oculomotor tests (smooth pursuit, saccadic eye movements and vergence). Auditive symptoms, such as tinnitus, were registered. Neck pain and restricted active range of movement in the neck were also registered. Romberg and sharpened Romberg were used for balance screening, and the Modified test for Sensory Interaction in Balance (mCTSIB) was used for the evaluation of sensory interaction (Herdman & Clendaniel, 2014). The clinical assessments were not used as outcome measures in this research project.

The *outcome measures* used in this research project are commonly employed in patients with dizziness, balance problems and TBI. The measurement of dizziness and balance problems after TBI is complex, and there is no adequate universal outcome measure (Lei-Rivera et al., 2013; Maskell et al., 2006; Morris & Gottshall, 2014). Because of the diffuse pathology seen in mild-to-moderate TBI, multiple tests are often used to determine the impairment and the impact on the patient's activity and participation level, as in this research project (Chandrasekhar, 2013; Lei-Rivera et al., 2013; Maskell et al., 2006). Several considerations were made in selecting the outcome measures used. Practical aspects, such as burden for the patients and raters and costs were considered. The outcome measures had to be available in preferably validated Norwegian versions. Quality aspects of the outcome measures were considered, and the validity, reliability and responsiveness were confirmed to enable us to rely on the results from the RCT and measure changes over time (Mokkink, Prinsen, Bouter, Vet, & Terwee, 2016). The main outcome measurement was the Dizziness Handicap Inventory (DHI). The secondary outcome measurement was the High-Mobility Assessment Tool for Traumatic Brain Injury (HiMAT). In addition,

several other self-reported, clinician-rated and performance-based outcome measures of dizziness, balance and psychological distress, were used. Descriptions of the outcome measures and their psychometric properties are presented in more detail in sections 4.4.1 and 4.4.2.

Table 4: Mapping of the clinical assessments and outcome measures to the main domains of functioning and disability in the ICF.

ICF domain	Measures and Instruments	Paper
Personal factors	Age	I - IV
	Gender	I - IV
	Social/marital status	III-IV
	Education level	II - IV
	Employment/study status pre-injury	II- IV
	Comorbidity pre-injury	II-IV
	Level of physical activity	I
Body functions and structures	Level of consciousness GCS	I - IV
	Loss of consciousness LOC	I - IV
	Post-traumatic amnesia PTA	I - IV
	MRI/CT scans	I - IV
	Post-concussion symptoms RPQ	I-IV
	Positional tests, Dix-Hallpike, Roll test	II-IV
	Head-impulse test	II-IV
	Dynamic visual acuity test	II-IV
	Smooth pursuit and saccadic eye movements, vergence	II-IV
	Auditive symptoms	II-IV
	Neck pain, active range of neck movement	II-IV
	Romberg, sharpened Romberg	II-IV
	Clinical test for sensory interaction in balance	II-IV
	Symptoms of vertigo VSS-sf	II-IV
	Psychological distress HADS	II-IV
	Balance BESS	II-IV
Activities and participation	Dizziness related disability DHI	II-IV
	Mobility HiMAT	I-IV
	Health related quality of life QOLIBRI	II
	Global outcome GOSE	II-III
Environmental factors	Sick leave	II-IV
	Multidisciplinary rehabilitation	III-IV
Other variables	Cause of injury	II-IV

GCS, Glasgow Coma Scale; LOC, Loss of Consciousness; PTA, Post Traumatic Amnesia; MRI, magnetic resonance imaging; CT, computer tomography; RPQ, Rivermead Post-Concussion Symptoms Questionnaire; VSS-sf, Vertigo Symptom Scale-short form; HADS,

Hospital Anxiety and Depression Scale; BESS, Balance Error Scoring System; DHI, Dizziness Handicap Inventory; HiMAT, High-Mobility Assessment Tool for Traumatic Brain Injury; QOLIBRI, Quality of Life after Brain Injury; GOSE, Glasgow Outcome Scale Extended.

4.4.1 Self-reported and clinician-rated outcome measures

Dizziness Handicap Inventory (DHI)

The main outcome measure was the Norwegian version of the Dizziness Handicap Inventory (DHI) (Tamber, Wilhelmsen, & Strand, 2009). The DHI quantifies the impact of dizziness on daily life by measuring self-perceived disability in activity and participation. The DHI is a 25 item self-report questionnaire with 3 response levels: yes = 4, sometimes = 2, and no = 0. The scores are transformed into a sum score of 0-100 points, in which a higher score indicates a worse handicap (Jacobson & Newman, 1990; Tamber et al., 2009). The Norwegian version of the DHI has demonstrated satisfactory reliability (ICC = 0.90) and internal consistency (Cronbach's alpha = 0.88 - 0.95) (Tamber et al., 2009). The Norwegian DHI has a minimal important change (MIC) of 11 points, and a smallest detectable difference (SDD) of 20 points (Tamber et al., 2009).

The DHI is one of the most commonly used self-report outcome measure of dizziness (Maskell et al., 2006). It is disease specific and multidimensional, and it provides information regarding the consequences of vestibular disorders on a wide spectrum of health- and functioning-related domains, as classified by the ICF. The DHI also refers to the relational aspects of functioning and the environment. The DHI was constructed to indicate a causal direction of the patient's perceived symptoms. It assesses the specific activities (ICF components activities and participation) that trigger dizziness or balance problems (ICF component body function), and the consequences of the symptoms on the degree of participation in social life and on emotion, respectively (ICF components activities and participation and body function) (Kurre et al., 2010).

The original subscale structure of the DHI, with physical, emotional and functional subscales, has not been demonstrated to be valid. Therefore, only the total scale is recommended for use as in this research project (Kurre et al., 2010). Kurre et al. conducted a study to investigate the internal validity of the subscale structure. They performed a factor analysis of the DHI and suggest a 3-factor solution, which appears to be reliable, clinically relevant and may partly be explained with the ICF (Kurre et al., 2010). Factor 1 assesses the impact of dizziness and unsteadiness on emotion and participation. Factor 2 assesses specific activities/movements of effort that provoke dizziness or unsteadiness. Factor 3 assesses the walking ability and the feeling of postural stability in relation to the environment factors (Kurre et al., 2010).

Rivermead Post Concussion symptoms questionnaire (RPQ)

Self-reported post-concussion symptoms (PCS) were measured by the RPQ. It is a 16-item standardized and validated questionnaire designed to measure the severity of PCS following TBI (King et al., 1995). The scale range is a five-point ordinal scale from 0 (no problem) to 4 (severe problem). The RPQ scores are the sum of symptoms scores excluding the ratings of 1 because this rating signifies a level that is the same as preinjury (King et al., 1995). The sum score ranges from 0-64, with higher scores indicating more symptoms and more severe symptoms. In this research project, we used the physical (RPQ 3: headaches, dizziness, and nausea), and psychological subscale (RPQ 13: noise sensitive, sleep disturbance, fatigue, irritable, depressed, frustrated, forgetfulness, poor concentration, longer to think, blurred vision, light sensitive, double vision, and restlessness) subscales as recommended by Eyres et al. (Eyres, Carey, Gilworth, Neumann, & Tennant, 2005). For the study described in paper I, a question about balance was added to the questionnaire. The question was: "Do you now suffer from balance problems?". The same ordinal scale was used for the response.

Vertigo Symptom Scale-Short form (VSS-sf)

The frequency and severity of dizziness symptoms were measured with the Norwegian, short version of the Vertigo Symptom Scale (VSS-sf) (Wilhelmsen, Strand, Nordahl, Eide, & Ljunggren, 2008). The scale consists of 15 items scored on a 5-point ordinal scale (range 0-4, best to worst). The sum score of the symptom severity ranges from 0-60, with higher scores indicating more severe problems. The clinical significant change is ≥ 3 points, and the cut-off for severe dizziness is set at ≥ 12 points (Yardley et al., 2004). The VSS-sf has two sub-scales, with 8 items related to vertigo-balance symptoms (VSS-V) (0-32) and 7 items related to autonomic-anxiety symptoms (VSS-A) (0-28). The Norwegian VSS-sf has demonstrated satisfactory reliability (ICC = 0.88) (Wilhelmsen et al., 2008). The VSS-sf has demonstrated the ability to discriminate between the dizzy and not dizzy patients with cut-off values of 6.5 on the VSS-sf, 2.5 on the VSS-V and 3.5 on the VSS-A (Wilhelmsen et al., 2008).

Quality of life after brain injury (Qolibri)

Health-related Quality of Life (HRQoL) was measured with the Quality of Life after Brain Injury (QOLIBRI) which is a self-report instrument that was specifically developed for patients with TBI. It has 37 questions distributed on six domains. These domains are cognition, self, daily life and autonomy, social relationships, emotions, and physical problems. Responses to each item is scored 1 (not at all) to 5 (very), and the sum of all items are converted arithmetically to a percentage scale, with 0 representing the lowest possible and 100 the best possible HRQoL (von Steinbuchel, Wilson, Gibbons, Hawthorne, Hofer, Schmidt, Bullinger, Maas, Neugebauer, Powell, von Wild, Zitnay, Bakx, Christensen, Koskinen, Sarajuuri, et al., 2010). The disease-specific questionnaire provides a profile of health-related quality of life and a total score, and it provides information that is particularly relevant in clinical settings

(Soberg, Roe, Brunborg, von Steinbuchel, & Andelic, 2017). The QOLIBRI has demonstrated satisfactory measurement properties (Hawthorne, Kaye, Gruen, Houseman, & Bauer, 2011). It has excellent test-retest reliability and internal consistency (von Steinbuchel, Wilson, Gibbons, Hawthorne, Hofer, Schmidt, Bullinger, Maas, Neugebauer, Powell, von Wild, Zitnay, Bakx, Christensen, Koskinen, Sarajuuri, et al., 2010). The QOLIBRI has demonstrated satisfactory construct and content validity (von Steinbuchel, Wilson, Gibbons, Hawthorne, Hofer, Schmidt, Bullinger, Maas, Neugebauer, Powell, von Wild, Zitnay, Bakx, Christensen, Koskinen, Formisano, et al., 2010). It has been translated to Norwegian, and the Norwegian version has demonstrated favorable psychometric properties (Soberg et al., 2017).

In this research project, we only analyzed the QOLIBRI scores in the study presented in paper II. However, there is a paucity of knowledge regarding the HRQoL status for patients with TBI with dizziness and unsteadiness, and we plan a separate publication for the QOLIBRI data as part of the dissemination from this study.

Hospital Anxiety and Depression Scale (HADS)

Psychological distress was assessed with the Hospital Anxiety and Depression Scale (HADS), which is validated, recommended and widely used in TBI research (Shukla, Devi, & Agrawal, 2011; Whelan-Goodinson, Ponsford, & Schonberger, 2009). The Hospital Anxiety and Depression Scale (HADS) is a self-report questionnaire that contains 14 items on two subscales (anxiety and depression). The total score is 42 points, with 21 points for each of the respective subscales (Zigmond & Snaith, 1983). The participants rate each item using a 4-point scale from no distress (0) to too much distress (3). Scores on the total HADS scale between 15-18 may be interpreted as potential cases of psychological distress, whereas scores ≥ 19 may be interpreted as significant psychological distress that requires treatment (Zigmond & Snaith, 1983). For each subscale, 8 was set as a cut-off for possible anxiety or depression, and 11 was set as a cut off for probable anxiety or depression (Bjelland, Dahl, Haug, & Neckelmann, 2002; Herrmann, 1997; Zigmond & Snaith, 1983). The HADS has demonstrated good concurrent validity and adequate to excellent internal consistency (Bjelland et al., 2002). The test-retest reliability has been reported to be adequate to excellent (Herrmann, 1997; Roberts, Bonnici, Mackinnon, & Worcester, 2001).

Glasgow Outcome Scale Extended (GOSE)

The GOSE was used to register global outcome. The GOSE has 19 questions that assess eight levels (minimum score 0, maximum score 8) of post-injury functioning within the areas of independence, work, social and leisure activities and participation in social life. The GOSE is divided into upper (8) and lower (7) levels of good recovery, upper (6) and lower (5) moderate disability, severe disability (3 and 4), vegetative state (2) and dead (1). The GOSE is extensively used; however, it has been criticized for ceiling effects and insufficient sensitivity to functional changes, particularly in patients with mild TBI (Shukla et al., 2011). A categorization in which

GOSE scores of 3-4 represent severe disability, 5-6, represent moderate disability, and 7-8 represent good recovery may be used to increase its sensitivity (Shukla et al., 2011). In this research project, this categorization was only used for the interpretation of the GOSE score. Good interrater reliability and content validity have been demonstrated for the GOSE (Levin et al., 2001; Wilson, Pettigrew, & Teasdale, 1998). The GOSE was administered as a structured face-to-face interview by the blinded outcome assessor.

4.4.2 Performance-based outcome measures

High-level mobility assessment tool for traumatic brain injury (HiMAT)

Mobility was measured with the High-level mobility assessment tool for traumatic brain injury (HiMAT). The HiMAT consists of 13 walking, running, skipping, hopping, bounding and stair items that are measured by a stopwatch or tape-measure. Raw scores measured in times and distances are noted and converted to a score on a 5-point scale from 0-4, except for the two dependent stair items that are rated on a 6-point scale from 0-5. A 0 corresponds to an inability to perform the item, and 1 -4/5 represents increasing levels of ability. The sum score range is 0-54 (worst-best) (G. Williams, Morris, Greenwood, Goldie, & Robertson, 2004; G. Williams, V. Robertson, K. Greenwood, P. Goldie, & M. E. Morris, 2005a; G. Williams, V. Robertson, K. M. Greenwood, P. A. Goldie, & M. E. Morris, 2005b). Normative scores have been developed for the HiMAT (G. Williams, Rosie, Denisenko, & Taylor, 2009).

The HiMAT has demonstrated very high internal consistency (Cronbach's alpha: 0.97), interrater (ICC = 0.99) and retest reliability (ICC = 0.99) (G. Williams, Greenwood, Robertson, Goldie, & Morris, 2006). The MDC of the HiMAT is an increase of 4 points or a decrease of 2 points (G. Williams, Greenwood, et al., 2006). Moderate concurrent validity for measuring high-level mobility and satisfactory responsiveness have been demonstrated (G. Williams, Robertson, Greenwood, Goldie, & Morris, 2006).

The psychometric properties of the HiMAT from a Norwegian mild TBI population are presented in paper I (Kleffelgaard, Roe, Sandvik, Hellstrom, & Soberg, 2013).

The HiMAT has been further developed to ensure a unidimensional scale (G. Williams, Pallant, & Greenwood, 2010). The stair items and one of the bound items were removed from the scale, creating a revised HiMAT with 8 items. The revised HiMAT has excellent internal consistency and is valid to use in rehabilitation and community settings with no access to stairs (G. Williams et al., 2010). The revised version was considered in the current research project, however we decided to use the original version to enable comparison of the results with previous studies.

Balance Error Scoring System (BESS)

Balance was assessed with the Balance Error Scoring System (BESS), which was developed for patients with mild TBI. The BESS consists of three 20 second, standardized stances with eyes closed (double leg stance, single-leg stance and tandem stance) initially tested on a firm surface, followed by a foam surface. Errors are counted during each 20-second trial (Bell, Guskiewicz, Clark, & Padua, 2011; Finnoff, Peterson, Hollman, & Smith, 2009). An error is defined as opening eyes, lifting hands off hips, stepping, stumbling or falling out of position, lifting the forefoot or heel, abducting the hip by more than 30˚, or failing to return to the test position in more than 5 seconds. Each committed error is assigned 1 point. If a subject commits multiple errors simultaneously, one error is recorded. The maximum total number of errors for a single condition is 10. Patients who are unable to maintain the testing procedure for a minimum of five seconds are assigned the highest possible score (10) for the testing condition. The maximum BESS score is 60 (range 0-60 best-worst) (Bell et al., 2011; BESS manual, 2014; Finnoff et al., 2009). The BESS has demonstrated variable but mostly satisfactory measurement properties with adequate test-retest reliability (ICC = 0.70) and adequate to excellent inter- and intrarater reliability (Bell et al., 2011; Finnoff et al., 2009; Susco, Valovich McLeod, Gansneder, & Shultz, 2004). The BESS has demonstrated adequate to excellent criterion validity (Barlow, Schlabach, Peiffer, & Cook, 2011; Bell et al., 2011; Susco et al., 2004). Age- related normative values have been developed (Iverson & Koehle, 2013a, 2013b).

Although the BESS is a frequently used clinical balance assessment tools after mild TBI (Fino et al., 2017), it suffers from a high degree of subjectivity. As its reliability has been shown to be variable, it is recommended researchers establish reliability before using it as an outcome measure (Bell et al., 2011). Related to our study, we performed a study of the measurement properties of the BESS in a motion analysis laboratory at OAUC. The results showed that the BESS demonstrated fair to good interrater reliability and criterion related validity below the recommended quality criteria, which limits the utility for both clinicians and researchers. Furthermore, the interrater MDC was 10.2 points, which indicates that the number of points required to represent a change in the subject's balance rather than a reflection of interrater scoring variability should be more than10 points (Kleffelgaard, Langhammer, Sandhaug, Pripp, & Soberg, 2017).

4.5 Translation of the HiMAT

The HiMAT was translated into Norwegian as part of the study presented in paper I. The translation was performed with permission from the developer of the HiMAT, Gavin Williams (P.T/PhD), and was conducted in collaboration with Physiotherapist Kine Therese Moen, who has also used the Norwegian version of the HiMAT (Moen et al., 2014).

The forward-backward translation method was used to produce the Norwegian version of the HiMAT (Beaton, Bombardier, Guillemin, & Ferraz, 2000; Y.-H. Lin, Chen, & Chiu, 2005). The translation procedure involved several steps. Step 1 was the translation of the original English version of the HiMAT into Norwegian. Two bilingual translators with Norwegian as their first language/mother tongue produced two independent translations. The translators had different backgrounds. One translator had a medical background as a physiotherapist and was aware of the concepts being tested in the HiMAT. The other translator had no medical background and was not aware or informed about the concepts being tested in the HiMAT. Step 2 was a synthesis of the two translations into a new Norwegian version of the HiMAT. Step 3 was a back translation of the new Norwegian version of the HiMAT into the original English language. This step was performed by a bilingual translator with English as the first language/mother tongue. The back-translator had medical background as a physician. Step 4 consisted of a comparison of the back translated version and the original version of the HiMAT. A new prefinal version of the HiMAT was created based on step 4 and step 2. This version was tested by several physiotherapists working in rehabilitation hospitals in Norway with TBI patients. Inconsistencies were resolved in consensus meetings, and a final version of the Norwegian HiMAT was deemed acceptable for use. See the appendix for the Norwegian version of the HiMAT.

4.6 Randomization

For paper IV, participants were randomly assigned with a 1:1 allocation to the intervention (IT) or control (CTr) groups. Allocation followed a computer-generated list of random numbers in blocks of four, prepared by a statistician not involved in the trial. The allocation sequence was concealed from the interventionist; an uninvolved research assistant stored the list and prepared sequentially numbered, opaque, sealed envelopes. The envelopes were kept in a locked drawer and consecutively drawn after the baseline assessments. The sealed envelopes were opened by the patients who subsequently were enrolled in the intervention or control group.

4.7 Ethical considerations

All participants received oral and written information regarding the studies. Written informed consent was provided by all participants. Age and gender were recorded for the patients who declined to participate in the study to document selection bias. The studies were conducted according to the Helsinki Declaration (World Medical Association, 2013). All participants underwent a medical exam prior to inclusion in the study. Special attention was given during testing and intervention to avoid falls and injuries. The studies were approved by The Regional Ethics Committee for Medical

Research in Norway (id #171.08) for paper I and (id #2012/195b 20120306 for papers II-IV) and the Data Inspectorate at OUH.

4.8 Intervention

This section provides a brief description of the intervention used in the case series and the RCT (Papers II and IV). A short description of the usual multidisciplinary TBI rehabilitation at OUH offered to all patients, is also included.

The individually modified group-based VR intervention consisted of guidance and individually tailored VR exercises (habituation, adaptation, substitution, and balance) offered twice weekly for eight weeks, a home exercise program (HEP) and an exercise diary. The HEP included 2 to 5 VR exercises to be performed daily and general physical activity. The exercise diary was used to enhance awareness and motivation and to register the performed exercises and activities and the responses to them. Two experienced PT's (interventionists) were responsible for the VR intervention. The background for the development of the intervention is described in section 2.4.4. The intervention is thoroughly described in Paper II (Kleffelgaard, Soberg, Bruusgaard, Tamber, & Langhammer, 2016).

All participants (IT and CTr groups) were offered the usual multidisciplinary TBI rehabilitation at OUH, which consist of clinical examinations by a physiatrist, multidisciplinary assessments, and recommendations for further treatment and rehabilitation, if needed. Treatment with a repositioning maneuver (Epley and Bar-B-Que Roll maneuvers) was performed by the interventionists in all patients who had a positive positioning test (Dix-Hallpike, roll test) (Hilton & Pinder, 2014). Not treating BPPV was considered to be in conflict with research ethics, because of the strong existing evidence (Hilton & Pinder, 2014), and knowledge-based practice of maneuver treatment.

After the 8-week intervention period, the participants in both IT and CTr groups in the RCT could participate in psycho-educative group sessions that address coping strategies to lessen their symptoms after the injury and return to work. Specific VR exercises was not included in these sessions, but the participants received some information about dizziness and balance problems and the importance of physical activity and balance training after TBI. The multidisciplinary team at OUH was responsible for these group sessions, which were held over four consecutive weeks. The psycho-educative group sessions are described and evaluated in another research project (Sveen et al., 2013; Vikane et al., 2017).

4.9 Statistics

The main statistical methods in all papers are subsequently presented. The statistical analyses were performed using the statistics program IBM Statistical Package for the Social Sciences (SPSS), versions 18.3 (paper I), and 23 (papers III and IV). A significance level of $p < 0.05$ was used for hypothesis testing.

All outcome measures included in the statistical analyses had fewer than 10% missing items. Missing items were imputed by averaging the available items on the scale or subscale.

An uninvolved research assistant entered the data from the RCT (paper IV) into the SPSS database. Furthermore, the interventionists were blinded for group allocation during the statistical analyses.

4.9.1 Sample size/power estimation

The sample size for study IV was based on the primary outcome measure (DHI). We used the result from a methodological study of the DHI performed in Norway in the power calculation (Tamber et al., 2009). With 80% power ($\beta = 0.8$), alpha (α) of 0.05, and standard deviation (δ) of 15, 60 patients, 30 patients per group, were needed. We expected that approximately 10% would be lost to follow-up and decided to include at least 35 patients in each group, with 70 patients in total. However, the study was terminated at 65 patients because of slow the rate of recruitment and the lack of time and economic resources.

4.9.2 Validity, responsiveness and reliability

In paper I, the criterion-related validity was assessed by Spearman Rho. The balance question added to the RPQ was dichotomized to no balance problems (score 0-1) and balance problems (score 2-4) and the score was used as a criterion in the validity analyses and as an anchor in the responsiveness analyses.

The responsiveness of the HiMAT was assessed by calculation of the proportions of patients who reported improvement in the balance score (RPQ) and had a change of at least the minimal detectable change (MDC) score on the HiMAT. The responsiveness was analyzed via ROC curve analyses and interpretation of the AUC.

The discriminant ability of the HiMAT, the ability to discriminate between participants with and without self-reported balance problems, was also assessed with receiver-operator characteristic (ROC) curve analyses and a cut-off point was set.

The inter- and intrarater reliabilities were assessed with the intraclass correlation coefficient (ICC) (Model: Two-way mixed, Type: Consistency).

The minimal detectable change (MDC) was calculated with the formula MDC = m +/- 1.96 x √2 x SEM, where m is the mean difference between the initial and retest scores in the intrarater test. The standard error of measurement (SEM) was calculated by the formula SEM = SD x √ 1- RC, where SD is the mean of the standard deviation for the first and second tests, and RC is the ICC reliability coefficient.

4.9.3 Comparing groups and exploring associations

In paper I, the associations between the HiMAT sum score and age, gender and physical activity at 3 months were analyzed with multiple linear regression analysis.

In paper III, the differences between the groups for the continuous variables were tested using the Student's t-test or Mann–Whitney U-test. The chi-square test was used to detect group differences for the categorical variables. Correlation analyses (Spearman's ρ) were performed to assess the strength of the associations between dizziness (on the DHI) and post-injury functioning measured with the secondary outcome measures. Furthermore, both simple/univariate and hierarchical multivariate regression analyses were used to evaluate the associations between the dependent variable, dizziness-related disability (DHI), and the independent variables, which were divided into four groups: personal factors, injury-related factors, clinical assessments and standardized outcome measures. To handle candidate variables in the multiple regression analyses, we initially performed separate block analyses for the self-reported and performance-based outcome measures. Variables in each block that qualified for further analyses ($p < 0.1$) were included in the final model.

In paper IV, between-group comparisons of the demographic and clinical data at each time point were performed using independent sample t-tests. The participants were assessed at three time points (baseline, T1 and T2). Paired sample t-tests were used to assess the changes from baseline to T1, and baseline to T2 for all patients. Intention-to-treat analyses were performed when comparing the IT group with the CTr group on the primary and secondary outcomes for all participants enrolled in the study, regardless of adherence to the VR intervention. To further evaluate the treatment effect, a linear mixed model analysis for repeated measurements with a random intercept was used to assess the between-group differences at the two follow-up time points, T1 and T2. As fixed effects, the statistical model included the baseline value of the outcome as a covariate, the main effects of treatment and follow-up, the interaction terms between treatment and follow-up, and the baseline value of the outcome and follow-up.

5 SUMMARIES OF PAPERS – MAIN RESULTS

This section presents the baseline characteristics of the participants included in paper III and IV and the main findings in the studies described in papers I -IV.

Baseline characteristics of the 65 participants described in papers III and IV:

Personal factors: The mean age was 39.2 years (SD 12.9), 71% were female, 74% were married or living together, 77% had more than 12 years of education, 92% were employed or students pre-injury, 43% had pre-injury comorbidity (musculoskeletal 18%, anxiety/depression 14%, migraine/epilepsy 11%) and 85% were on complete or partial sick-leave.

Injury-related factors: Injury mechanisms were: Falls 65%, traffic accidents 15%, violence 9%, other 11%. 42% of patients had positive MRI/CT scans and/or skull fractures, indicating complicated mild TBI. Based on their initial GCS scores, two of these patients had moderate TBI (GCS 11, 12) and one had severe TBI (GCS 7).

Post-injury functioning:

Clinical assessments and symptoms: Positive tests for BPPV in 32%, positive dynamic visual acuity test in 29%, positive oculomotor tests (smooth pursuit, saccadic eye movements, vergence) in 62%, auditory symptoms (including tinnitus) in 49% and neck pain in 37% of the patients.

Outcome-measures: The mean DHI score was 44.6 (SD 17.9), and 75% reported moderate to severe dizziness-related disability. The mean VSS-sf score was 18.6 (SD 9.8), and 80% had a score of 12 or more, which is considered severe dizziness (Wilhelmsen et al., 2008). The mean RPQ score was 31.6 (SD 10.4), with fatigue, dizziness, poor concentration, frustration and taking longer to think representing the most severe symptoms. The mean HADS score was 15.7 (SD 7.9) and 60 and 45% had scores above the cut-off of 8 points on HADS-A and HADS-D respectively (Zigmond & Snaith, 1983). The median GOSE score was 6 (IQR 5-6), and 91% scored moderate disability. The median HiMAT score was 42 (IQR 34.5-47.0) and the mean BESS score was 29.2 (SD 6.1), and over 75% of the patients scored below population norms (Iverson & Koehle, 2013a; G. Williams et al., 2009).

In paper IV, 64 patients from the population were included in the analyzes, giving slightly different scores.

5.1 Paper I

Measurement properties of the High-Level Mobility Assessment Tool for Traumatic Brain Injury

The HiMAT was translated into Norwegian according to the existing guidelines, described in section 4.5.

We aimed to examine the reliability, validity and responsiveness of the HiMAT in a mild TBI population because this had not been previously performed.

Ninety-two patients, 69% men, mean age 37.1 (SD 13.8) and Glasgow Coma Scale score 14.7 (SD 0.7), were included in the study and tested at 3 months' post-injury. Fifty-one patients were retested at 6-months. A subgroup of 25 patients was selected for the reliability testing. Balance function reported on the RPQ was selected as the criterion and anchor. The criterion-related validity was assessed with a correlation analysis.

The inter- and intrarater reliabilities for the HiMAT sum score were high (interrater ICC = 0.99, intrarater ICC = 0.95). The Minimal Detectable Change (MDC) was -3 to +4 points. The HiMAT had a ceiling effect of 22.8%. The correlation between the HiMAT and self-reported balance problems was good ($r = -0.63$, $p < 0.001$), which indicates a moderate criterion-related validity. The responsiveness of the HiMAT was good, and it discriminated well between patients with self-perceived improved versus unchanged balance function (Area under Curve (AUC) = 0.86).

In conclusion, the HiMAT demonstrated satisfactory measurement properties for patients with mild TBI, and the current results indicate that the HiMAT may be used as an outcome measurement of balance and mobility problems in patients with mild TBI.

5.2 Paper II

Vestibular Rehabilitation after Traumatic Brain Injury – A Case series

The purpose of the case series was to describe the individually modified group-based VR intervention and examine how this intervention may be beneficial in addressing dizziness and balance problems by describing changes in self-perceived dizziness, balance, and HRQoL. Two women and two men (aged 24–45) with mild TBI, dizziness and balance problems participated in the 8-week intervention, which comprised group sessions with guidance, individually modified VR exercises, a home exercise program and an exercise diary. Self-reported and performance-based outcome measures were applied to assess the impact of dizziness and balance problems on functions related to activity and participation.

The intervention did not cause adverse effects. Three of the four patients reported reduced self-perceived disability because of dizziness on the DHI, diminished

frequency and severity of dizziness symptoms, an improved HRQoL, reduced psychological distress, and improved performance-based balance and mobility. The change scores exceeded the minimal detectable change, which indicates a clinically significant change and/or improvement in the direction of normal age-related norms. The fourth patient did not change or improve on most outcome measures.

The individually modified group-based VR intervention was safe and appeared to be beneficial for addressing dizziness and balance problems and promoting overall function. However, concurrent physical and psychological symptoms, other neurological deficits and musculoskeletal problems may influence the course of central nervous system compensation and recovery. The effect of the intervention is explored in the RCT presented in paper IV in this thesis.

5.3 Paper III

Dizziness-related disability following mild-to-moderate traumatic brain injury

In Paper III, dizziness-related disability was investigated. The objective was to investigate the associations between dizziness-related disability after mild-to-moderate TBI and personal factors, injury-related factors and post-injury functioning using the International Classification of Functioning, Disability and Health (ICF) as a framework.

Baseline assessments were obtained for 65 patients, mean age was 39.2 years (SD 12.9). Seventy-one% were women) with TBI (median GCS score 15) who had dizziness and reduced balance 2–6 months after injury. The severity of the brain injury, physical and psychological self-reported symptoms and results of performance-based tests were analyzed to capture impairments and activity limitations. The main outcome variable, the Dizziness Handicap Inventory (DHI), also captured participation restrictions.

Multivariate analyses showed that dizziness-related disability was predicted by pre-injury comorbidities ($p \leq 0.05$) and was associated with self-reported vertigo symptoms ($p < 0.001$), reduced performance-based balance ($p \leq 0.05$) and psychological distress ($p \leq 0.05$). These factors accounted for 62% of the variance in the DHI.

The results in paper III indicate that dizziness and balance problems after mild-to-moderate TBI appear to be complex biopsychosocial phenomena. Assessments linked to the ICF domains of functioning may contribute to a broader understanding of the needs of these patients. Further prospective clinical studies with non-dizzy control groups are required to investigate dizziness-related disability after TBI.

5.4 Paper IV

The Effect of Vestibular Rehabilitation Addressing Dizziness and Balance Problems in Patients after Traumatic Brain Injury: A Randomized Controlled Trial

In paper IV, the effect of the individually modified group-based VR intervention with guidance and VR exercises was explored. Sixty-five patients with dizziness and balance problems after TBI were randomly assigned (1:1 allocation) to receive a group-based VR intervention (IT group) in addition to the usual multidisciplinary TBI rehabilitation (CTr group) at OUH. The main outcome measure was the DHI measured at baseline, immediately after the 8-week intervention period (T1), and 8 months after the injury (T2). The secondary outcome measure was the HiMAT. Both groups had improvements from baseline on both outcome measures. The intention-to-treat analysis showed that there was a significant difference between the groups in favor of the intervention group immediately after the intervention (T1), with an adjusted mean difference between the groups of - 8.74 points (CI -16.56 - - 0.93) on the DHI and 3.71 points (CI 1.38 - 6.04) on the HiMAT, after adjusting for baseline differences. However, there was no significant difference between the groups at approximately 8 months after the injury (T2).

In summary, this RCT showed that an additional 8-week individually modified, group-based VR intervention improved dizziness-related disability and mobility/dynamic balance in favor of the intervention group at postintervention follow-up. There were no significant between-group differences 8 months after the injury. These findings suggest that VR is a safe and beneficial intervention, which accelerates recovery for patients with dizziness and balance problems after TBI. The findings imply that VR safely can be included as a component of multidisciplinary rehabilitation. Further studies and high quality RCTs are needed to confirm the outcomes and examine the impact of the dose and progression of exercises on rehabilitation outcomes.

6 DISCUSSION

The discussion is divided into two main sections. The first section discusses methodological aspects with respect to the external and internal validity of the studies. The second section discusses the interpretation of the main results in light of current relevant publications.

6.1 Methodological aspects

6.1.1 External validity

External validity concerns the extent to which the results of the research project may be generalized or applied to patients outside the study population and to other circumstances and clinical practices (Green & Glasgow, 2006; Veierød, Lydersen, & Laake, 2012).

Oslo University Hospital (OUH) is a Regional Trauma Center that treats approximately 400 patients with TBI per year. The Department of Physical Medicine and Rehabilitation specializes in TBI rehabilitation. It is important to be aware that patients with TBI admitted to OUH differ from patients with TBI in primary care in that they are more severely injured and represent a patient population of more complicated mild TBI patients. In this respect, the results of this research project pertain to a select patient group and cannot be generalized to the larger, unselected mild TBI population. However, regarding hospital admitted TBI patients, the population is more representative.

The external validity is also influenced by the exclusion criteria. In the studies described in papers III and IV, 44 (31%) patients were excluded, and 25 of these patients were excluded because they scored 15 or less on the DHI at baseline. This exclusion criterion was applied because a score less than 15 on the DHI represent a dizziness-related disability that was considered too small to be addressed in the rather comprehensive intervention. An additional reason for this criterion was that potential improvement registered on the primary outcome measure (DHI) would not be hampered by floor-effects. The cut-off point at 15 points was selected because this score is the midpoint between the minimally important change (MIC) of 11 and the smallest detectable difference (SDD) of 20 (Tamber et al., 2009).

Patients with substance abuse and severe psychological disease, insufficient command of Norwegian and fractures/co-morbidities that affected mobility were also excluded, which limits the studies generalizability. However, the included patients represent a heterogeneous group of patients with variable pre-injury comorbidities, such as musculoskeletal conditions, anxiety/depression or migraine/epilepsy, and different injury severities and causes of dizziness.

Furthermore, 32 (23%) of the eligible patients were not willing to participate in the studies described in papers III and IV. There were no significant differences in the age or injury severity (GCS score) between the participants and non-participants in these studies; however, there were significantly more women among the included patients ($p < 0.001$). The gender distribution differed from epidemiological studies of patients with TBI, in which the incidence is typically highest among males (Andelic et al., 2008; Peeters et al., 2015). However, of the 141 eligible patients with dizziness and balance problems, the gender distribution was more equal with 53% women and 47% men, which is in accordance with the gender distribution in groups with prolonged symptomatology identified in a cohort by Hartvigsen et al. (Hartvigsen et al., 2014). This finding suggests that there are more female patients in the sub-chronic and chronic TBI populations which is in accordance with a study by Styrke et al. (Styrke, Sojka, Bjornstig, Bylund, & Stalnacke, 2013). Furthermore, in our study, there was an increase in the number of eligible women through the stages of the inclusion process, which resulted in significantly more women than men in the final study population (71% women). This was partly a result of the fact that fewer men wished to participate and more eligible men were excluded (fractures, co-morbidities, multitrauma, and insufficient command of Norwegian). In the general population, women report more vertigo, dizziness and balance problems than men (A. Bisdorff, Bosser, Gueguen, & Perrin, 2013). The results from the current studies indicate that after a TBI, dizziness may be reported to a higher degree by women than men.

Based on the inclusion and exclusion criteria, the study samples may be representative of an adult population with persistent dizziness and balance problems 2-6 months after a mild-to-moderate TBI, but without severe psychological disease, substance abuse, insufficient command of Norwegian, severe cognitive dysfunction or fractures/co-morbidities that affect mobility and independent gait.

6.1.2 Internal validity

Internal validity is related to methodological procedures and concerns potential biases in the way the data were collected, analyzed and interpreted (Veierød et al., 2012). Thus, internal validity is the degree to which a study is free of random or systematic errors (Aalen & Frigessi, 2006). Internal validity is considered a prerequisite for the external validity of the study; however, the study needs to have external validity to be clinically useful (Green & Glasgow, 2006; Veierød et al., 2012).

Designs

In this research project, different designs were used depending on the purpose of the four included studies.

The methodological design (test-retest design) in Paper I was considered appropriate to investigate the reliability, validity and responsiveness of the HiMAT. It enabled us to determine the extent to which the scores for patients who had not changed were the

same for repeated measurements under two conditions: by different raters on the same occasion - interrater reliability; or the same patients on different occasions - intrarater reliability (Mokkink et al., 2016). The test-retest design also enabled us to investigate the responsiveness of the HiMAT, which refers to the ability of an outcome measure to detect change over time in the construct measured (Mokkink et al., 2016). Criterion validity is the degree to which the scores of an outcome measure are an adequate reflection of a "gold standard". We recognize the weaknesses of using self-reported balance as a criterion and anchor in the validity and responsiveness analyses. However, measurements by self-report or performance are considered to reflect similar aspects of function as long as the constructs measured by the two methods are the same (Coman & Richardson, 2006).

In paper II, we used a prospective clinical case series to describe the intervention evaluated in this research project. Reports from RCTs are often criticized because the intervention is not sufficiently described to replicate the trial and to reliably implement interventions that are shown to be useful (Boutron, Altman, Moher, Schulz, & Ravaud, 2017; Hoffmann et al., 2014). Format and length limitations for journals often precludes inclusion of a thorough description of the evaluated intervention, hence a case series was used to describe the intervention in detail (Boutron et al., 2017; Hoffmann et al., 2014). Clinical case series can be used to explain, describe or explore interventions through analyses of clinical information from several cases (Crowe et al., 2011; Yin, 2014). Case series are also the simplest form of studies of the effects of interventions (Herbert et al., 2011).

The case series design was useful because it led to a thorough description of mode of delivery, essential processes and monitoring of the intervention. Furthermore, it described the clinical assessments and outcome measures. Also, key features like duration, dose and intensity was described, and this was considered important because these factors are likely to influence the effect and replicability of the intervention (Hoffmann et al., 2014). The TIDieR (template for intervention description and replication) checklist was used to guide and assist the description of the intervention in the current case series (Hoffmann et al., 2014), which increased the quality of the report of what was done and evaluated in this research project. The checklist was developed as an extension of the CONSORT statement, and aims at improving the completeness of reporting, and ultimately, the replicability of interventions (Hoffmann et al., 2014).

We are aware of the fact that a case series provide very weak evidence of the effects of an intervention due to extraneous factors that can masquerade the treatment effect (e.g. natural recovery, statistical regression, placebo effects and polite patients) (Herbert et al., 2011). Thus, the main focus of the case series in this research project was on the description of the intervention as the effect of the intervention was explored in paper IV.

A prospective cohort design was used in Paper III. The study reports on personal factors (pre-injury factors), injury-related variables and functioning measured by clinical assessments and outcome measures at inclusion in the RCT (baseline measures). As the collected data were from pre-injury, at the time of injury and at inclusion in the study 3 months post-injury (median, IQR 2-4), the groups of patients were followed forward in time (prospective) (Veierød et al., 2012). Several exposures and outcomes are typically assessed with a prospective design, and the design is often used to investigate exposure-outcome associations, such as in Paper III. Patients are never exposed to one factor alone; moreover, to estimate the association between exposures (TBI) and outcome (dizziness-related disability) in a prospective study, confounding variables must be adjusted for in analyses. Multivariate methods, such as linear regression, play an essential role in adjusting for confounders and was used in the study described in Paper III (Veierød et al., 2012). Data that originate from a RCT, such as in our study, may also be used to assess prognosis. However, prognostic models obtained from RCT data may have restricted generalizability because of the strict eligibility criteria for the trial, low recruitment levels, or large numbers refusing consent, which was the case in the study described in paper III (Moons, Royston, Vergouwe, Grobbee, & Altman, 2009).

A randomized controlled trial (RCT) design was used in paper IV. A RCT is considered the gold standard for the evaluation of health care interventions in clinical research (Veierød et al., 2012). RCTs are prospective and experimental. The "randomized" component of a RCT refers to random the allocation of participants to treatment and control groups (Jadad & Enkin, 2008). The most important advantage of randomization is to ensure that patients with different known and unknown prognostic factors are randomly distributed between or among interventions (Moher et al., 2012; Veierød et al., 2012). The randomization was considered successful in study IV because there were no major differences between the groups regarding registered baseline characteristics.

Evaluation of the RCT in a pragmatic-explanatory continuum

RCTs are often described as explanatory or pragmatic (Alford, 2007; Gaglio, Phillips, Heurtin-Roberts, Sanchez, & Glasgow, 2014; Loudon et al., 2015; Thorpe et al., 2009). Pragmatic trials are designed to determine the effects (effectiveness) of an intervention under the usual conditions in which it will be applied. It enables a more seamless application to clinical practice, and as such, it has increased external validity (Thorpe et al., 2009). Explanatory studies are designed to determine the effects of an intervention under ideal circumstances (efficacy) and enable a better understanding of the mechanisms for identified treatment effects. Explanatory studies have increased internal validity. It is difficult to maximize both external and internal validity in a RCT, and as study parameters are typically tightened to improve internal validity, some external validity will be lost and vice versa. Few trials are purely pragmatic or explanatory, which is the case for the RCT included in this thesis. Many aspects of a

RCT can be pragmatic or explanatory, thus representing a continuum rather than a dichotomy. This makes it challenging to evaluate a RCT's potential for translation into practice (Gaglio et al., 2014).

Thorpe et al introduced the pragmatic-explanatory continuum indicator summary (PRECIS) tool, which was used to evaluate the clinical trial described in paper IV. Domains that were evaluated to be more pragmatic included the *recruitment* and treatment of the participants in the usual care *setting* at OUH. Furthermore, *flexibility in administering* the intervention to adapt it to the individual needs and capabilities of each patient was allowed. We also accepted *flexibility in adherence* to the intervention, e.g., how many sessions they attended and how actively they used the HEP and the exercise diary. Furthermore, the *primary outcome*, the DHI, was a self-report outcome measure of function, which is considered more pragmatic. Finally, intention to treat *analyses* of the primary outcome (DHI) were performed. Thus, patients with low adherence were accepted and included as part of the population, which is also considered a more pragmatic approach.

Some domains were evaluated to be equally pragmatic and explanatory and included the *follow-ups* that were pre-specified and more frequent than what they typically would be outside the trial. Moreover, participants were contacted if they failed to keep trial appointments. Furthermore, more extensive data were collected, particularly intervention related data, which would not be typical outside the trial.

Domains that were evaluated to be more explanatory included the participant *eligibility* criteria and the *organization*. The included participants were selected from only one source (OUH), which decreases the variability in the sample and increases the internal validity. Furthermore, participants thought to be least likely to respond to the intervention and whose adherence might pose difficulties, such as substance abuse, were excluded. The expertise and resources needed to deliver the intervention, the organization, required additional training to increase the expertise of the healthcare professionals involved in the trial. Furthermore, the number of healthcare professionals available to deliver the intervention was more than available in usual care.

The overall evaluation of the RCT included in this thesis is that it appears, in some respects, to be a more pragmatic than explanatory clinical trial. This increases its external validity and together with the thorough description of the intervention in paper II, an application of the intervention to clinical settings should be possible.

Outcome measures

In papers II-IV, several different tests and outcome measures commonly used in the research fields of TBI and dizziness/balance problems were employed. The final selection of outcome measures was based on a literature review and research on outcome measures used at OUH, OAUC and other groups working with neurorehabilitation and/or dizziness in Norway. The outcome measures have acceptable psychometric properties for the TBI population and/or patients with

dizziness and are available in validated Norwegian versions (Bjelland et al., 2002; Ingebrigtsen et al., 1998; Kleffelgaard et al., 2013; Soberg et al., 2017; Tamber et al., 2009; Wilhelmsen et al., 2008).

Both performance-based and self-reported outcome measures were used in this research project, which may be considered a strength as they complement each other in terms of the measurement of patient functioning after the injury (Maskell et al., 2006). However, the rather comprehensive list of self-report outcome measures may have represented a burden for the included patients who were asked to complete several questionnaires with similar and somewhat overlapping contents (Mokkink et al., 2016). However, the performance-based measures of balance and mobility were easy and quick to administer, portable and cost-effective in that they did not require expensive equipment and personnel (Bell et al., 2011; G. Williams et al., 2005a).

The main outcome measure, the DHI, is one of the most commonly used self-reported outcome measures of dizziness (Maskell et al., 2006; Tamber et al., 2009). Despite its acceptable psychometric properties, it has several weaknesses. The wording of the scale is complex and assumes dizziness to be the primary symptom (Maskell et al., 2006). In the TBI population, dizziness is most likely not the primary or only symptom, and it may be difficult for patients to separate out the relative contribution of dizziness to the difficulties they experience (Maskell et al., 2006). However, the patients in the current research project were instructed to be aware of this issue.

The performance-based test was administered by different raters, which may have affected the test-retest reliability of the scores. The baseline assessments were performed by an experienced physiotherapist. The outcome assessor who performed the retesting was a physical educator with experience with TBI patients. To ensure test-retest reliability, the outcome assessor was trained prior to retesting. We also performed an interrater reliability study of the performance-based tests used in the studies/trials, which indicated excellent interrater reliability for the HiMAT (described in paper I), and acceptable but variable interrater reliability for the BESS (Kleffelgaard et al., 2017).

The outcome measures in this research project were mapped to the main domains of functioning and disability in the ICF. The analyses showed that dizziness-related disability was significantly associated with personal factors (comorbidities) and body function (symptoms of vertigo/dizziness, balance and psychological distress). The analyses did not include outcome measures on participation which is a limitation. Participation factors, such as return to work are known to be affected in patients with dizziness after TBI (Chamelian & Feinstein, 2004).

Randomization, drop outs, concealed allocation, and blinding

Selection bias and ascertainment bias are common systematic errors identified in clinical trials. The procedure of random group allocation in RCTs abolishes selection bias to a substantial degree. However, it is important that the randomization is

concealed, such as in our study (Jadad & Enkin, 2008; Schulz et al., 2010). To avoid imbalance in group size, we used blocked randomization with blocks of 4 in our RCT (paper IV). One limitation in this procedure is that it is slightly predictable. If the allocation of the first three patients is known, the investigator can predict the allocation of the fourth subject. A random variation of the block size between four and six, would have avoided this predictability (Schulz et al., 2010; Veierød et al., 2012).

The drop-out rate in the RCT described in paper IV was 3% at the first follow-up and 12% at the second follow-up, which yielded a completion rate of 85%. Attrition rates in longitudinal studies of TBI vary widely, and conservative estimates suggest that approximately one-third of participants with TBI are lost to follow-up during long-term outcome trials (Corrigan et al., 2003; Langley, Johnson, Slatyer, Skilbeck, & Thomas, 2010). Losses to follow-up may introduce important bias into the findings of a trial; however, a loss of follow-up of 15% is acceptable (Herbert et al., 2011), and there was no significant difference between the groups in the frequency or causes of drop-outs in the current RCT.

Ascertainment bias occurs in a RCT when knowledge regarding which intervention each participant is receiving systematically distorts the results or conclusions of the trial (Jadad & Enkin, 2008; Schulz, 2000). The bias may originate from the administrator, assessor or analyzer (investigators), or the participants (Schulz, 2000). The procedure of blinding can protect ascertainment bias (Schulz, 2000). It was not possible to blind the PT and the participants in the current study with respect to group allocation. Ideally, the interventionist should not be involved in the administration of the study, as in our study. Consciously or unconsciously, this may have affected the treatment and follow-ups in favour of the intervention group and thus lead to exaggerated effect estimates. Importantly, the outcome assessor was blinded to the group allocation, and the patients were instructed not to discuss their group allocation. Furthermore, an uninvolved research assistant entered the data into the SPSS database, and the interventionist was blinded for the group allocation during the statistical analyses, which reduces the possibility for bias in the current RCT.

Statistics

Power and sample size

Power and sample size estimations are used to determine how many subjects are needed to answer the research question (Veierød et al., 2012).

For papers I and III, no formal sample size calculations were performed. In paper I, the sample size was lower (n = 25) than the recommended 50 for the reliability analysis (Terwee et al., 2007). However, both the inter-and intrarater reliability coefficients (ICC) were 0.99 (CI 0.98 - 0.99) and 0.95 (CI 0.89 - 0.98) respectively, which is stronger than the recommended minimum standard of 0.70 for reliability (Terwee et al., 2007).

Paper III reports the baseline characteristics of the RCT (paper IV), which is the reason we did not calculate a sample size for this particular study, as power estimation had been performed for the RCT. There is no straightforward method of estimating sample size in multivariate prognostic research. When the number of predictors is substantially larger than the number of outcome events, such as in our study, there is a risk of overestimating the predictive performance of the model. However, we required at least 10 patients for each predictor assessed, as recommended in various studies (Kirkwood & Sterne, 2003; Moons, Altman, Vergouwe, & Royston, 2009; Moons, Royston, et al., 2009).

Regarding the RCT, the power of the study is the probability that it can detect a treatment effect, if it is present. Power calculations indicate the number of patients required to avoid a type I or a type II error (Veierød et al., 2012). Type I error occurs if we reject the null hypothesis incorrectly (detecting an effect that is not present) and report a difference between the two groups investigated. A type II error occurs when we accept the null hypothesis incorrectly (failing to detect an effect that is present) and report that there is no difference between the two groups. We used a significance level of 0.05, which indicates that the probability of a type I error, given that the null hypothesis is true, is 5% (Veierød et al., 2012). In paper IV, we did not reach the planned 70 patients for inclusion or the estimated 60 patients for the multivariate analysis. Thus, the study was subject to type II error. However, we identified significant differences between the IT and CTr groups on the primary and secondary outcome measures immediately after the eight-week intervention.

Statistical methods

In paper I, the ICC was used to calculate the reliability coefficient. The ICC is recommended for continuous measures and was considered suitable for evaluating the HiMAT scores (Koo & Li, 2016; Terwee et al., 2007). The ICC was calculated by using a two-way mixed model, consistency. This approach may provide a misleading high estimate of reliability compared with a two-way mixed model, agreement, because it concerns if the raters score to the same group of subjects are correlated in an additive manner and not if different raters assign the same score to the same subject (Koo & Li, 2016; Terwee et al., 2007).

Standard error of measurement (SEM) and the smallest/minimal detectable change (SDC/MDC) are the preferred statistics for measurement error, and the results from our study corresponded well with previous studies, thus indicating the number of points required to represent a change in the subject's mobility rather than a reflection of the interrater scoring variability. Receiver operating characteristics (ROC) curve analyses and the AUC are considered an adequate measure of responsiveness (Terwee et al., 2007).

In paper II, only descriptive data were presented. No statistical analyses were considered adequate because the design of the study was a case series with only four patients.

In paper III, hierarchical regression analyses were performed to investigate the associations between the dizziness-related disability on the DHI and the independent variables. The selection of candidate variables was based on the results from univariate analyses. The independent variables were divided into four ICF-related groups to reflect personal and injury-related factors, clinical assessments and outcome measures that represented the following domains of functioning: Body functions and structures, activities and participation. The chosen cut-off set at $p < 0.1$ in the univariate analyses may have had consequences for the inclusion of variables in the final model. The large number of explanatory variables may result in an overestimation of the associations between explanatory factors and outcome. This problem is greatest with small sample sizes and many explanatory variables, as in the study presented in paper III, and the results should thus be confirmed in other studies (Moons, Altman, et al., 2009). However, tests were performed to ensure that there was no violation of the assumptions for the statistical analyses.

We implemented a simple method of mean replacement when single values were missing. More complex and robust techniques are recommended (Veierød et al., 2012); however, there were so few missing items that it was unlikely that the chosen method have biased the results of the studies in this research project.

Intention to treat (ITT) analyses were applied in paper IV. ITT analyses aim to include all participants into a RCT, regardless of what subsequently occurred which preserves the huge benefit of randomization (Gupta, 2011; Schulz et al., 2010). We decided to perform ITT analyses because they are generally preferred for being unbiased and because they address a more pragmatic and clinically relevant question (Gupta, 2011; Higgins, Green, & Cochrane, 2011). The following principles of ITT analyses are described: 1) Keep participants in the intervention group to which they were randomized, regardless of the intervention received. 2) Measure outcome data on all participants. 3) Include all randomized participants in the analyses (Higgins et al., 2011; Schulz et al., 2010). The first principle was applied in the analyses in paper IV; all participants were included in the analysis according to the original group allocation, regardless of their adherence. As a result of participant's withdrawal, it was not possible to comply with the second criterion in paper IV, and a mixed model analysis was performed to address the missing values. One participant withdrew after randomization and did not consent to use the collected data. We had to remove him from the analyzes and this made it difficult to comply with the third principle. However, as this applied to only one subject, we assume that this did not bias the results of the analyses.

Analyzes of a justified subset of the population is called modified ITT concept (Gupta, 2011), and this may be a more correct description of the analyzes performed in the RCT described in Paper IV. However, the definition given to the modified ITT has been found to be irregular and arbitrary because of lack of consistent guidelines for its application (Gupta, 2011).

The alternative to an ITT analysis is a per protocol analysis, which is restricted to only participants who adhere to the protocol (Moher et al., 2012). This approach was considered; however, with consideration of the possibilities of flawed analyses and results, this was not performed (Moher et al., 2012; Schulz et al., 2010). Nevertheless, it is possible that ITT analyses may have underestimated the effect of the group-based VR intervention as a result of non-adherence (n = 2) and low adherence (n = 9) (Moher et al., 2012). ITT analyzes has been criticized for being too cautious and thus being more susceptible to type II error (Gupta, 2011).

The major advantage of the mixed model in our study was that it handles correlated data and unequal variances. Mixed methods also allow an unequal number of repetitions, which makes imputation of missing data unnecessary (Veierød et al., 2012). The mixed model was sufficiently robust to handle the different outcome measures included in the study, and the assumptions for the statistical procedure were met.

6.2 Main results

This section discusses the main results of this research project in view of other current evidence. Paper I showed that the measurement properties for the HiMAT were acceptable for the mild TBI population. Paper III showed that dizziness-related disability at 3 months after a mild-to-moderate TBI is significantly predicted by pre-injury comorbidities and associated with concurrent symptoms of vertigo, reduced performance on balance tests and psychological distress. Papers II and IV showed that participation in a modified, group-based VR intervention is safe, appears beneficial and accelerates recovery for patients with dizziness and balance problems after TBI.

6.2.1 Measurement properties of the HiMAT

In paper I, we concluded that the Norwegian version of the HiMAT showed adequate measurement properties (reliability, responsiveness and validity) to be used as an outcome measure in the mild TBI population. The establishment of measurement properties for the mild TBI population was considered important because most of our participants had mild TBI and because the HiMAT had not previously been validated for this patient group. Furthermore, there is a lack of balance and mobility measures suitable for the mild TBI population. The frequently used outcome measures have demonstrated substantial ceiling effects and are not considered feasible for patients

with mild TBI (Kleffelgaard et al., 2012; G. Williams, Robertson, et al., 2006). In our study, we also identified a relatively high ceiling effect on the HiMAT, particularly among men, the youngest age groups and the most physically active participants. This finding is in accordance with previous findings (G. Williams et al., 2009). Importantly, there was no ceiling effect among the patients who reported balance problems, which corresponds well with the results from the ROC curve analyses that showed the HiMAT discriminate well between patients with and without self-reported balance problems. The best cut off point for sensitivity/specificity on the HiMAT was ≤ 47 points (Kleffelgaard et al., 2013), which indicates that patients who score higher than this cut-off do not have a balance and mobility problem. This finding corresponds with the established norms for the HiMAT in a healthy population aged 18-25, which are 50-54 for men and 44-54 for women (G. Williams et al., 2009). In papers II -IV, only patients with dizziness and balance problems were included, and more women than men were included; thus, the ceiling effect was less of a problem. This is reflected in the baseline scores of the HiMAT in papers II-IV.

The reliability estimates from our study were excellent and corresponded well with the results from other reliability studies of the HiMAT (G. Williams, Greenwood, et al., 2006; G. Williams et al., 2009). The excellent interrater reliability was particularly important because the HiMAT was used by two different raters at baseline and the follow-ups in the RCT (paper IV).

The responsiveness of the HiMAT in our study was good, and this finding was in accordance with an Australian study on the responsiveness of the HiMAT (G. Williams, Robertson, et al., 2006). Our results indicate that HiMAT is a responsive instrument for the mild TBI population. Responsiveness, or the ability of an instrument to detect a clinically important change over time, even if the change is small, is crucial for an outcome measure, such as the HiMAT (Mokkink et al., 2016; Terwee et al., 2007). In papers II and IV, we experienced that HiMAT worked well and documented change over time. It also differentiated between the groups.

A minimal clinically important difference, defined as "the smallest difference in score in the domain of interest which patients perceive as beneficial and which would mandate, in the absence of troublesome side effects and excessive costs, a change in the patient's management" (Angst, Aeschlimann, & Angst, 2017), has not been established for the HiMAT, However, the minimal detectable change - MDC, which indicates the number of points required to represent a change in the subject's balance rather than a reflection of the interrater scoring variability, was established. The MDC was -3 to +4 points and corresponded well with the MDC reported for Williams study (G. Williams, Robertson, et al., 2006). This finding enabled us to establish that the change that was measured after the group-based VR intervention in papers II and IV exceeded measurement error, and was more likely a result of a true change in the patients' dynamic balance and mobility.

6.2.2 Factors associated with dizziness-related disability

To our knowledge, the study presented in paper III is the first investigation to examine the associations between dizziness-related disability and personal and injury-related factors and post injury functioning after TBI. An investigation of the factors associated with dizziness-related disability post TBI was thought to be important because dizziness, as one of the most common symptoms after TBI, is often analyzed as part of the post-concussion symptoms, which makes the contribution of dizziness to the patient's disability somewhat unclear (Chamelian & Feinstein, 2004; Maskell et al., 2006). Furthermore, the associations between dizziness and balance problems and other post-concussion symptoms with functioning remain poorly described and understood. As these issues are complex phenomena, a biopsychosocial approach using the International Classification of Functioning, Disability and Health (ICF) framework appeared useful. Thus, a biopsychosocial approach and different assessment tools linked to the ICF domains of functioning were used to increase the understanding of dizziness-related disability after TBI.

The study presented in paper III identified a statistically significant model that explained the impact of personal factors, impairments and activity limitations on dizziness-related disability. The model shows that the relationship between dizziness-related disability and post injury functioning is complex and cannot be explained by a single mechanism. Furthermore, dizziness-related disability measured with the DHI was predicted by pre-injury comorbidities and was associated with self-reported symptoms of vertigo (VSS-V), depressive symptoms (HADS-D) and performance-based tests of balance (BESS). Our findings are consistent with results from a cross-sectional study, which indicated that after a TBI, dizzy patients had significantly more somatic complaints, psychological distress and worse psychosocial functioning than patients without dizziness (Chamelian & Feinstein, 2004). These finding will be discussed in the following section.

Comorbidities

The finding that pre-injury comorbidities were a predictor of dizziness-related disability corresponds well with the results of other studies that indicated pre-morbid psychiatric and physical histories were predictive of post-concussive symptoms after TBI (Broshek et al., 2015; Ponsford et al., 2012; van der Naalt et al., 2017). Dizziness-related disability was measured with the main outcome measure, DHI. The dizziness-related disability was moderate for the majority of the sample, with a mean DHI score of 45 points (SD 18). This finding is similar to other reports of patients with persistent symptoms of dizziness and balance problems after mild TBI. Alsalaheen et al. reported DHI scores of 49 points (SD 21), whereas Schneider et al. found DHI scores of 42 points (range 6-84) and 46 points (range 6-84), respectively (Alsalaheen et al., 2010; Schneider et al., 2014).

The results from our study suggest that the pre-injury comorbidities in the included patients (musculoskeletal conditions, anxiety/depression or migraine/epilepsy) may

lead to increased vulnerability and a potentially higher self-perceived symptom load, including dizziness, and thus should be evaluated as part of the assessment protocol post injury. This finding supports the use of biopsychosocial models that include pre-injury factors to be constructive and appropriate frameworks to conceptualize and explain the complex and multifactorial etiology of persistent symptoms and dizziness related disability after mild-to-moderate TBI (Ruff, 2011; Snell et al., 2016; Yeates, 2010). Furthermore, factors that are known to negatively affect vestibular compensation and may lead to prolonged dizziness-related disability are migraine, anxiety, depression, medical co-morbidities and physical restrictions of daily activities (Hall et al., 2016; Shepard et al., 1993; Whitney & Furman, 2007). The pre-injury comorbidities may also have implications for the design and effect of VR programs/interventions, and these factors are further addressed in the discussion of the description and evaluation of the group-based VR intervention presented in papers II and IV.

Dizziness, vertigo and post-concussion symptoms

Regarding frequency and severity of dizziness symptoms, the majority of our study population reported severe dizziness according to the Vertigo symptom scale with a mean score of 18.4 points (SD 9.6) (Wilhelmsen et al., 2008). The self-reported dizziness symptoms were, not very surprising, the strongest contributors to the explained variance in the model that explained dizziness-related disability after injury. We considered it important to include frequency and severity of dizziness symptoms as an impairment because of its contribution to explaining dizziness-related disability as a phenomenon at the ICF activity and participation levels captured in the DHI (Kurre et al., 2010). Therefore, frequency and severity of dizziness symptoms are important when predicting and understanding dizziness-related disability. Importantly, concurrent self-reported symptoms of the vertigo subscale (VSS-V) were the strongest contributors to the variance in dizziness-related disability at baseline in our study, which indicates that the vertigo-balance dimension rather than the autonomic-anxiety dimension of the VSS-sf was most troublesome (Wilhelmsen et al., 2008). The participants also reported dizziness as one of the most bothersome symptoms on the RPQ, which is somewhat different from other comparable TBI populations in which the cognitive symptoms were more prominent than the physical symptoms 3 months after injury (Roe, Sveen, Alvsaker, & Bautz-Holter, 2009; Sigurdardottir et al., 2009). Furthermore, the frequency and severity of dizziness symptoms reported by the participants, correspond well to the clinical test results that confirmed that 30-60% of the included patients presented with a mix of clinical characteristics that may lead to dizziness and vertigo, such as BPPV, indications of reduced function of the VOR, indications of vestibular hypofunction, indications of visual and auditory dysfunction, and neck pain.

The participants in the current research project also reported a considerable burden of post-concussion symptoms (RPQ mean 32.9 points (SD 9.9)), which may be related to

the overall impact of the injury and not specifically to dizziness. However, the cognitive and emotional symptoms may have accentuated the dizziness experienced by the participants in our study. A reduced attentional capacity and slowed speed of information processing, which are common after TBI, may be responsible for some sensations described as dizziness (Maskell et al., 2007). The amount of attentional resources required for the processing of vestibular system inputs appears to be increased in patients with vertigo (Maskell et al., 2007). It is possible that patients may have to allocate a significant amount of their remaining attentional resources to maintain their balance (Maskell et al., 2007). Furthermore, emotional difficulties, such as irritability and frustration, may be related to certain activities being more challenging to perform than in the past as a result of the dizziness (Maskell et al., 2007).

Balance

The balance scores in the current study were below population norms (Iverson & Koehle, 2013a; G. Williams et al., 2009). Moreover, indications of reduced balance (below norms) and mobility were identified in more than 75% of the patients. Thus, the results confirm that balance problems are common after TBI and is in agreement with several other studies (Bland et al., 2011; Campbell & Parry, 2005; Fino et al., 2017; Kleffelgaard et al., 2012; Maskell et al., 2007). Performance based scores on balance (BESS) significantly contributed to the model that explained dizziness-related disability and confirms that balance performance is an important aspect of functioning post injury. These findings confirm that it is important to include balance assessment and training in rehabilitation programs after TBI, and the results from the RCT (paper IV) provides evidence for positive effects of balance training immediately after the intervention.

Balance problems in this population may be associated with multi-system dysfunction and require a comprehensive assessment (Campbell & Parry, 2005; Fino et al., 2017). The BESS assesses the relative contributions of the visual, vestibular and somatosensory systems to static, standing balance and challenges sensory interaction. However, the BESS provides only limited information regarding the balance control system and does not account for the complex integration of sensory and motor systems (Fino et al., 2017; Horak, Wrisley, & Frank, 2009). Sensory information from the vestibular, visual and somatosensory systems is integrated in the CNS to control static and dynamic balance. After TBI, one or several of these sensory systems may be affected, thus leading to reduced balance. Furthermore, it is hypothesized that a proportion of individuals with no prominent or measurable sensory deficits may have balance problems that may be attributable to an abnormal central control of balance (Fino et al., 2017). Proper central sensorimotor integration relies on the ability of the CNS to select the optimal combination of sensory sources for balance and to reweight the sensory contributions as sensory conditions change. Currently, there is a lack of knowledge regarding central sensorimotor integration following mild and moderate

TBI. However, future studies are planned to characterize balance deficits in patients with mild TBI with objective measures of central sensorimotor integration. Hopefully, this research will contribute to a better understanding of balance problems after mild and moderate TBI and subsequently lead to an improved rehabilitation of these patients (Fino et al., 2017).

Psychological distress

Psychological distress was reported by over 30% of the included patients, and the score was higher (worse) on anxiety than depression (HADS-A: 9.0 points (SD 5.0), HADS-D: 6.8 points (SD 4.6). However, the depressive symptoms contributed strongest to the dizziness-related disability in the model with 8% explained variance. Compared with other studies on the mild-to-moderate TBI population 3 months after injury, our population reports a higher level of psychological distress (Ponsford et al., 2012; Sigurdardottir et al., 2009). This finding is consistent with the study of Chamelian et al., who reported that patients with dizziness after mild-to-moderate TBI were significantly more anxious and depressed than were the non-dizzy controls (Chamelian & Feinstein, 2004). Because the methodology of the current study does not allow us to infer causal relationships, we do not know whether dizziness promoted psychological distress or vice versa.

Anxiety has been determined to predict post-concussion symptoms, including dizziness, in patients with mild TBI at 3 months post-injury (Ponsford et al., 2012; van der Naalt et al., 2017). Anxiety in patients with dizziness may be related to the perception of the balance being at risk and fear of falling (Maskell et al., 2007). Moreover, a heightened anxiety sensitivity described as a "fearful response associated with the individual's own bodily sensation that arises from the belief that these sensations are signs of harmful consequences" (Broshek et al., 2015), may exacerbate the symptom of dizziness after mild-to-moderate TBI and contribute to ongoing symptoms (Broshek et al., 2015). Furthermore, anxiety-related dizziness has been described following TBI (Balaban, Jacob, & Furman, 2011; Ellis et al., 2015; Fife & Kalra, 2015). However, secondary anxiety is common in patients with long-lasting dizziness of any cause (Staab & Ruckenstein, 2007). It is therefore important not to automatically assume that generalized anxiety is the cause of dizziness reported by patients with TBI (Fife & Kalra, 2015; Staab & Ruckenstein, 2007).

Kurre et al. found that patients with dizziness and depression felt significantly more disabled by dizziness and unsteadiness than dizzy patients without depression (Kurre, Straumann, van Gool, Gloor-Juzi, & Bastiaenen, 2012). This finding may be one reason for the significant contribution of the HADS-D to explaining dizziness-related disability in our study. Furthermore, Cassidy et al. also reported that baseline depressive symptoms were associated with poor recovery after mild TBI (Cassidy et al., 2014).

Anxiety and depression may also increase the likelihood of developing Persistent Postural-Perceptual Dizziness (PPPD), which includes symptoms of dizziness and balance problems present most days for 3 months or more (Dieterich & Staab, 2017; Staab, 2012). Many patients included in the current study described dizziness-related disability and dizziness symptoms consistent with a diagnosis of PPPD. The diagnostic criteria for PPPD (Dieterich & Staab, 2017) were not used in the current research project; however, they should be considered in future work.

In summary, the significant contribution of vertigo symptoms, pre-injury comorbidities, balance and psychological distress to the dizziness-related disability model confirm that dizziness is a multidimensional phenomenon. Thus, the use of the ICF to describe disability may increase our knowledge regarding dizziness after TBI. Moreover, it may be beneficial for conceptualizing rehabilitation programs targeted towards improving dizziness-related disability, such as the group-based VR intervention described and evaluated in papers II and IV.

6.2.3 Description and exploration of the group-based VR intervention

The description of the intervention in paper II makes it possible to replicate it for research purposes and apply it in clinical practice. As previously discussed, this increases the external validity of this study. Furthermore, the description provides information on how tailoring a VR intervention to each individual TBI patient may be feasible within a group-based approach. However, a case series does not allow us to determine whether the observed improvements in outcomes were direct results of the intervention or other factors, such as natural recovery, participation in other treatments, or the impact of greater attention from the therapists. As the effect of VR is not established for patients with TBI, the group-based VR intervention's short- and long-term effects were explored in a RCT (paper IV).

The results from the RCT presented in paper IV indicate that the participants in the intervention group had significantly better scores on dizziness-related disability (DHI) and balance/mobility (HiMAT) than the participants in the control group after the 8-week intervention. The effect of the intervention was maintained; however, there was no difference between the groups 8 months after the injury. These results provide evidence that a group-based VR intervention with guidance and individually adapted exercises based on the principles of habituation, adaptation (gaze stabilization), substitution and balance relearning accelerate the recovery for patients with dizziness and balance problems after TBI. Therapies that accelerate the rate of recovery can help the patients to return to activities, studies and work faster and thereby improve the efficiency of rehabilitation.

The effect of the group-based VR intervention

The results from the current study are supported by other studies that indicate that VR may be beneficial to target dizziness and balance problems after TBI, and have the potential to increase functioning and decrease dizziness-related disability (Alsalaheen et al., 2010; Brown et al., 2006; Godbout, 1997; Gurr & Moffat, 2001; Hoffer et al., 2007; Peterson, 2010; Schneider et al., 2014). However, the level of evidence in many of these studies is weak because of the lack of control groups. We have only found one recently published RCT performed by Schneider et al., who performed a trial of 31 patients with sports-related concussion aged 12-30 years. They combined vestibular and cervical physiotherapy and determined that 8 weeks of treatment decreased the time to medical clearance to return to sports (Schneider et al., 2014). Direct comparisons to our results are difficult because our population is older, more severely injured, not related to sport injuries, and the intervention was initiated later after injury. However, they had the same length of the intervention, and the patients who were cleared to return to sport in the intervention group had a greater improvement in the Dizziness Handicap Inventory than the other patients. This finding is in accordance with our results in that the intervention group had a significantly greater improvement in the DHI after the 8-week VR intervention.

Our result on the main outcome measure (DHI) in favor of the intervention group at the first follow-up indicates that the intervention had a positive effect on dizziness-related disability that was reflected in the different factors of functioning as covered in the DHI, such as "emotional functioning and participation in social life", "specific activities/movements that provoke dizziness and/or unsteadiness", and "self-perceived walking ability and the feeling of postural stability in relation to contextual factors" (Kurre et al., 2010). The reported improvements in favor of the intervention group on the DHI regarding aspects of balance/mobility were confirmed on the secondary outcome measure (HiMAT). The HiMAT and DHI factor "self-perceived walking ability and the feeling of postural stability in relation to contextual factors" may be understood as tapping on the same phenomenon, i.e., mobility. In contrast to the multidimensionality of the DHI, the HiMAT is a more unidimensional performance-based measure of mobility and dynamic balance that reflects the physical dimension of motor performance rather than the cognitive or behavioral dimension that may limit motor performance (G. Williams et al., 2005a). Thus, the intervention appeared to have a positive effect on motor performance and the perception of it.

It is difficult to determine whether a specific component of the group-based VR intervention in our study contributed to the improvements because it was designed as a package aimed at multiple domains of functioning and included a combination of guidance to facilitate self-efficacy and exercises mainly to address the impairments and activity limitations identified during the baseline evaluation. Furthermore, the inclusion criteria in the present RCT were mainly symptom-based and targeted deficits in function rather than specific vestibular diagnoses. Moreover, specific vestibular

diagnoses, except for those with positive test for BPPV, were not made because we did not have access to the clinical and computerized vestibular function testing performed by ear-nose-throat specialists. Specific diagnosis of underlying etiologies appears to be complicated after TBI and may, in addition to ear-nose-throat specialists, require specialists such as a neurologist or ophthalmologist (Elziere, Deveze, Bartoli, & Levy, 2017). However, the current research project confirms that BPPV is a common cause of dizziness after mild-to-moderate TBI and supports the importance of assessment and treatment of BPPV (Arshad et al., 2017; Elziere et al., 2017; Ernst et al., 2005). Moreover, based on the clinical assessments and the outcome measures, many participants had symptoms and signs that corresponded to multiple causes of dizziness, such as BPPV, alterations in vestibular function, visual function, somatosensory function and balance/mobility, all of which are commonly found in patients with TBI (Deveze et al., 2014; Ernst et al., 2005).

Hoffer et al. reported that the effectiveness of VR differed based on the type of post-traumatic dizziness. They categorized the etiology of the dizziness into four groups, including BPPV, migraine-related dizziness, spatial disorientation and exercise-induced dizziness, and determined that the resolution of symptoms differed from one week in the BPPV group to up to 39 weeks in the spatial disorientation group (Hoffer et al., 2007; Hoffer et al., 2004). It is not very surprising that the BPPV group had a faster resolution of symptoms, which is in accordance with an updated Cochrane review that have reported that the Epley repositioning maneuver is considered a safe and effective treatment for posterior canal BPPV (Hilton & Pinder, 2014). However, several studies report that post-traumatic BPPV appears to be more difficult to treat than ordinary BPPV (Ahn et al., 2011; Balatsouras et al., 2017; Gordon et al., 2004). Furthermore, after a TBI a combination of BPPV and other peripheral or central vestibular dysfunction, is often found (Arshad et al., 2017; Ellis et al., 2015; Ernst et al., 2005; Hoffer et al., 2007). Subgroup analyses were not performed in the current research project because the size of the groups was considered too small. However, the emerging evidence suggests that vestibular system examination and especially screening for BPPV needs to be included in medical consultations and rehabilitation after TBI (Balatsouras et al., 2017; Gordon et al., 2004; E. G. Johnson, 2009).

The constitution of unique clinical subtypes leading to dizziness and balance problems after TBI have also been suggested by other researchers (Broglio et al., 2015; Ellis et al., 2015; Hoffer et al., 2007). It is suggested that these clinical subtypes may occur concurrently or independently and require targeted therapies and treatments to be managed most effectively (Broglio et al., 2015). However, the complexity of dizziness and balance problems after TBI, makes it challenging to categorize patients in subgroups. Patients will overlap and may not fit into different subtypes in the categorisation. Moreover, the categorization does not currently direct patients towards evidence-based treatment options (Ellis et al., 2015). Even though an updated Cochrane review has established moderate to strong evidence for VR as a safe and

effective management for unilateral peripheral vestibular dysfunction, it does not address subgroups, such as TBI with unilateral peripheral vestibular dysfunction (McDonnell & Hillier, 2015). Furthermore, some would argue that it may be easier to provide more individual and targeted therapy in a one-to-one setting compared to a group setting. This may be preferred initially. However, a group setting can be stimulating for some patients because it may increase their motivation to continue with the VR exercises (Deveze et al., 2014). A combination of one-to-one setting with a group setting may be a preferred approach, and this should be addressed in future research.

The length of the intervention

Further research is required to explore whether the improvement in the intervention group was a result of natural recovery, which was accelerated by the intervention, or whether the improvement would have continued if the intervention lasted longer than 8 weeks compared with the control group. Gottshall et al. indicate that many patients with TBI respond to VR over a period of 8 weeks; however, some patients require longer time and continue to improve over an additional 4 to 8 weeks (K. Gottshall, 2011).

As already discussed, the time needed for different etiologies of post-traumatic dizziness to respond to the different components in VR interventions varies. There are also indications that patients with complicated mild and moderate TBI, which represented 42% of the included patients in paper IV, recover slower than mild TBI; however, the literature is limited and somewhat mixed regarding general outcomes (Iverson, 2006; Sigurdardottir et al., 2009). Post-concussion symptoms and concurrent physical, cognitive and emotional conditions are factors that may hamper the natural recovery and CNS compensation of vestibular dysfunction after TBI (Gurley et al., 2013). Furthermore, given that central vestibular plasticity is involved in vestibular compensation (Lacour et al., 2016), disruption of central vestibular pathways may theoretically hamper the recovery from both central and peripheral vestibular injury. This may render patients with TBI less liable to respond to VR (Arshad et al., 2017).

There is also evidence that anxiety/depression are associated with a poorer outcome, and in patients with psychological conditions, addressing the psychological needs as an adjunct to physical therapy may increase the success of the intervention (Hall et al., 2016). Furthermore, migraine is reported to have a negative effect on VR (Hall et al 2016). Despite the improvement identified in the current study, both groups continued to have mild-to-moderate dizziness-related disability (DHI) and severe dizziness symptoms on the VSS-sf after the intervention. This finding may be explained by the complex mix of pre-injury comorbidities, post-concussion symptoms and anxiety/depression present in the included population which is described in the study presented in paper III. Thus, it is possible that some of the patients included in this study would have profited on an intervention that lasted longer.

Clinical relevance of the results

Another aspect that should be discussed pertains to whether the statistically significant differences between the groups on the primary (DHI) and secondary (HiMAT) outcome measures at 8 weeks were also reflected in clinically important differences. The average magnitude of change was greater than the minimally important clinical difference MIC (11 points) for the DHI (Tamber et al., 2009) at both 8 weeks and 8 months for the intervention group, whereas it was smaller than the MIC at 8 weeks for the control group. However, for the control group, it approached the MIC at 8 months post injury. The same tendency was identified on the HiMAT with an improvement greater than the minimal detectable change MDC (4 points) (Kleffelgaard et al., 2013) at both 8 weeks and 8 months for the intervention group, but only at 6 months for the control group. The improvement in balance was confirmed on the test results for the BESS with a change greater than the interrater reliability MDC (9.4 points) (Finnoff et al., 2009), and the MDC of 10.2 (Kleffelgaard et al., 2017) at both time points in the control group, but not in the intervention group.

Adherence

Of interest for the interpretation of our results is the attendance in the intervention sessions. Adherence is an important outcome in clinical trials because if the participant does not adhere to the intervention, it will not be possible to determine whether the intervention is feasible or has an effect. Adherence may be measured in different ways (Picorelli, Pereira, Pereira, Felicio, & Sherrington, 2014). Adherence to center-based exercise programs is relatively easy to document by simple registration of the attendance. Overall, 67% of the intervention group attended more than 50% of the group sessions, which was defined as the minimum amount of the intervention. Twelve (37%) patients had over 80% adherence, and an additional 10 (30%) patients had greater than over 50% adherence. Nine patients (27%) attended between 1 and 7 sessions, and the remaining two (6%) patients did not attend at all. The attendance rate may have affected the outcome and with an attendance less than 50%, which occurred in 33% of the intervention group, it appears reasonable to expect a smaller effect. The adherence rate in our study may have contributed to a smaller difference between the IT and CTr groups. Adherence to the HEP was not analyzed because of incomplete quantitative data regarding the dose of the performed exercises. We have not found studies that report on factors that may influence adherence to VR interventions after TBI; however, fatigue, post-concussion symptoms, neck pain and exacerbation of dizziness during the first exercise sessions may affect adherence. Furhtermore, a lack of motivation, personal health and tiredness have been reported as important barriers to physical activity after TBI (Reavenall & Blake, 2010). Cognitive problems with memory and pain are known to be additional barriers (Reavenall & Blake, 2010).

There is also limited knowledge regarding the ways in which exercise dose (frequency and intensity) affects outcomes in patients with vestibular hypofunction in general (Hall et al., 2016), and this issue seems even more complicated in TBI patients. As

described in paper II, a conservative approach with careful gradual introduction to the exercises were practiced in the VR intervention explored in this research project. However, optimal exercise dose for TBI patients with dizziness and balance problems after TBI needs to be established through further research. As described in paper III, dizziness-related disability after TBI is a multidimensional phenomenon, and pre-injury and concurrent comorbidities along with post-injury functioning should be taken into consideration when studying the optimal dose for individually modified VR programs after TBI.

The multidisciplinary TBI rehabilitation

The usual multidisciplinary TBI rehabilitation that was provided at OUH for all participants in the current study likely contributed to the significant improvement seen in both groups on all outcome measures. The multidisciplinary TBI rehabilitation at OUH consists of clinical examination by a physiatrist, multidisciplinary assessment and recommendations for further treatment and rehabilitation, which is considerably more treatment than is typically provided for this group of patients in Norway. Furthermore, after the 8-week intervention period, both groups were offered attendance in the psycho-educative group sessions held by the multidisciplinary team at OUH over four consecutive weeks. Attendance in these groups could have contributed to a smaller difference between the IT and CTr groups at T2 8 months after injury. Although this intervention did not specifically address dizziness, they all received information on coping strategies to lessen their symptoms. They also received information regarding the importance of physical activity and how dizziness and balance problems affect daily living and participation (Vikane et al., 2017). Moreover, both groups received treatment for BPPV because it was considered unethical not to treat BPPV because of the strong existing evidence for the effect of maneuver treatment (Hilton & Pinder, 2014). However, these factors did not compromise the internal validity of the study because the attendance in the psycho-educative group sessions and the occurrence and treatment of BPPV were similar in both groups.

7 CONCLUSIONS AND IMPLICATIONS FOR PRACTICE

7.1 Conclusions

This thesis includes four papers with different aims and designs. Paper I is a methodological study in which the aim was to examine the measurement property of the High-Level Mobility Assessment Tool for Traumatic Brain Injury (HiMAT) for the mild TBI population. Paper II is a case series in which the aim was to describe the individually modified group-based VR intervention evaluated in this research project. Paper III has a prospective design that aims to describe dizziness-related disability and its associations with pre-injury and injury-related factors. Study IV is an RCT in which the aim was to explore the effect of an individually modified, group-based vestibular rehabilitation program for patients with dizziness and balance problems after a mild-to-moderate TBI. The conclusions from the four studies must be interpreted in light of the strengths and limitations previously discussed in this thesis and in each paper. The following conclusions can be drawn.

- The HiMAT demonstrated satisfactory measurement properties and can be used as an outcome measurement of balance and mobility in patients with mild TBI (paper I).
- The description of the individually modified group-based VR intervention may be useful for clinicians and researchers in tailoring VR interventions to TBI patients and makes it possible to replicate the trial and implement the intervention (paper II).
- Dizziness-related disability measured with the DHI at 3 months after a mild–moderate TBI was significantly predicted by pre-injury comorbidities and was associated with concurrent symptoms of vertigo, reduced performance on balance tests and psychological distress (paper III).
- The participants in the intervention group had significantly greater improvement in the dizziness-related disability on the DHI and mobility/dynamic balance on the HiMAT right after the 8-week intervention. There was, however, no significant difference between the groups 8 months after the injury (Paper IV).
- The individually modified group-based VR intervention appeared safe, beneficial and accelerated recovery for patients with dizziness and balance problems after TBI. No severe adverse events or effects were recorded (paper II and IV).

7.2 Implications for practice and future research

The main reasons for performing the studies presented in papers I-IV were to expand knowledge regarding the factors related to dizziness and balance problems in patients after TBI and explore the effect of an individually modified group-based VR intervention in this patient group. The current research project contributes to the evidence-based knowledge base regarding dizziness and balance problems after TBI, and to the scientifically documented recommendations for VR among patients with TBI.

The methodological study supports the use of the HiMAT as a balance and mobility outcome measure for patients with mild TBI. Furthermore, the results may represent a valuable contribution towards a standardization and consensus on valid and reliable outcome measures that should be used for the mild and moderate TBI population. This is important to be able to compare studies. The HiMAT is increasingly used as an outcome measure after TBI, and it is available on websites that describe outcome measures, such as the Rehabilitation Measures Database (Rehabilitaiton Measures Database, 2010) and the Center for Outcome Measures in TBI (COMBI) (The Center for Outcome Measurement in Brain Injury, 2006).

The results from the present research project supports the use of biopsychosocial models that include pre-injury factors to be constructive and appropriate frameworks to conceptualize and explain the complex and multifactorial etiology of persistent dizziness-related disability after mild-to-moderate TBI (Ruff, 2011; Snell et al., 2016; Yeates, 2010). However, to fully understand the impact of dizziness and balance problems after mild-to-moderate TBI, further prospective clinical studies with non-dizzy control groups are required.

Based on the results from the present research project, modified group-based VR can be recommended. The intervention is well described and provides a treatment option for physiotherapists who work with patients with mild-to-moderate TBI in hospitals and primary care settings. The treatment response may vary according to different subgroups with different etiologies of dizziness and balance problems. In future research, it should be evaluated how different subgroups respond to group-based VR to identify the optimal rehabilitation for the respective patients. However, this may be challenging because high-quality subgroup analyses require large study populations. Thus, multicentre studies may be the solution to this problem.

Our research project did not contribute evidence for the optimal dose of the VR exercises, timing or progression of the exercises. There is a general research recommendation that researchers should examine the impact of the frequency, intensity, time and type of exercises on rehabilitation outcomes (Hall et al., 2016). Furthermore, researchers should determine the difficulty of exercises and how to progress patients in a systematic manner (Hall et al., 2016; Morris & Gottshall, 2014).

In general, the design and standardization of treatment approaches are essential in future research to advance practice (Bland et al., 2011), and there is a need for more high-quality RCTs in this field. However, there is also an increased focus on more pragmatic trials with individually tailored interventions adapted to the needs of each individual patient. Our study complied with some of these notions.

Patients with TBI may suffer from significant disability as a result of dizziness and balance problems. However, post-concussion symptoms/syndrome also substantially contributes to their disability. Therefore, options for VR should be included in a comprehensive, multidisciplinary TBI program.

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Appendix

The Norwegian version of the High-level Mobility Tool for Traumatic Brain Injury.

HiMAT: HIGH-LEVEL MOBILITY ASSESSMENT TOOL

DATO.....
ULYKKESDATO.....
DIAGNOSE.....
AFFISERT SIDE VENSTRE/HØYRE

PASIENT ID

		SKÅR					
DELTEST	RESULTAT	0	1	2	3	4	5
GÅ	sek	X	> 6.6	5.4–6.6	4.3–5.3	< 4.3	X
GÅ BAKLENGS	sek		> 13.3	8.1–13.3	5.8–8.0	< 5.8	X
GÅ PÅ TÅ	sek		> 8.9	7.0–8.9	5.4–6.9	< 5.4	X
GÅ OVER HINDRING	sek		> 7.1	5.4–7.1	4.5–5.3	< 4.5	X
LØPE	sek		> 2.7	2.0–2.7	1.7–1.9	< 1.7	X
HINKEHOPP*	sek		> 4.0	3.5–4.0	3.0–3.4	< 3.0	X
HINKE (mest affisert ben)	sek		> 7.0	5.3–7.0	4.1–5.2	< 4.1	X
SPRANG** (mest affisert ben)	1) cm 2) 3)		< 80	80–103	104–132	> 132	X
SPRANG** (minst affisert ben)	1) cm 2) 3)		< 82	82–105	106–129	> 129	X
OPP TRAPP IKKE SELVSTENDIG (bruk av rekkverk **ELLER** ikke-resiprokt mønster***: hvis ikke skår 5 her og grader nedenfor)	sek		> 22.8	14.6–22.8	12.3–14.5	< 12.3	
OPP TRAPP SELVSTENDIG (uten rekkverk **OG** resiprokt mønster***: hvis ikke skår 0 her og grader ovenfor)	sek		> 9.1	7.6–9.1	6.8–7.5	< 6.8	X
NED TRAPP IKKE SELVSTENDIG (rekkverk **ELLER** ikke-resiprokt mønster***: hvis ikke skår 5 her og grader nedenfor)	sek		> 24.3	17.6–24.3	12.8–17.5	< 12.8	
NED TRAPP SELVSTENDIG (uten rekkverk **OG** resiprokt mønster***: hvis ikke skår 0 her og grader ovenfor)	sek		> 8.4	6.6–8.4	5.8–6.5	< 5.8	X
	DELSUM						

* Hinkehopp er å bevege seg fremover med et lite hink etter hvert steg/sprang.
** Et sprang er et hopp fra det ene benet til det andre med en svevefase.
*** Resiprokt mønster er å plassere en fot på hvert trinn vekselvis.

TOTAL HiMAT-SKÅR /54

HiMAT: High-level Mobility Assessment Tool

Instruksjoner

Egnethet: HiMAT egner seg til å vurdere balanse- og bevegelses problemer hos mennesker med et høyt funksjonsnivå. Minstekravet for testing er 20m selvstendig gangfunksjon uten ganghjelpemidler. Ortoser er tillatt.

Testing: Testingen tar 5–10 minutter. Pasientene tillates et prøveforsøk før hver deltest.

Instruksjoner: Pasientene blir bedt om å utføre deltestene så raskt som mulig, men i en hastighet som ikke går utover sikkerheten. Deltestene sprang- og trappegange er unntatt fra dette, se instruksjonsmanual.

Gå: Tiden pasientene bruker på de midterste 10m av 20m registreres (fra 5 til 15 m).

Gå bakover: Som for ”gå”.

Gå på tå: Som for ”gå”. Hvis hælen kommer i kontakt med bakken er deltesten ikke godkjent.

Gå over hindring: Som for ”gå”. En murstein plasseres på tvers midtveis i gangbanen (ved 10 m). Pasientene må gå over mursteinen uten å komme i kontakt med den. Deltesten er ikke godkjent hvis pasientene går rundt mursteinen eller kommer i kontakt med den.

Løpe: Tiden pasientene bruker på de midterste 10m av 20m registreres. Deltesten er ikke godkjent hvis pasientene ikke har sammenhengende svevefaser, ingen dobbel standfase gjennom hele deltesten.

Hinkehopp: Hinkehopp er å bevege seg fremover med et lite hink/etter hvert steg/sprang. Tiden pasientene bruker på de midterste 10m av 20m registreres. Deltesten er ikke godkjent hvis pasientene ikke har sammenhengende svevefaser, ingen dobbel standfase gjennom hele deltesten.

Hinke: Pasientene står på mest affisert ben og hinker fremover. Tiden pasientene bruker på å hinke 10m registreres.

Sprang (mest affisert) Et sprang er et hopp fra det ene benet til det andre med en svevefase. Pasientene står bak en strek på minst affisert ben, hendene på hoftene. Pasientene hopper fremover og **lander på mest affisert ben**. Hvert sprang måles (i cm) fra startstreken til hælen på benet pasientene lander på. Gjennomsnittet av tre forsøk registreres.

Sprang (minst affisert) Pasientene står bak en strek på mest affisert ben, hendene på hoftene. Pasientene hopper fremover og **lander på minst affisert ben**. Gjennomsnittet av tre forsøk registreres.

Opp trapp: Pasientene blir bedt om å gå opp en trapp med 14 trinn på samme måte som de vanligvis gjør i normalt gangtempo. Tiden fra pasientene starter til de står med begge benene på toppen av trappen registreres. For pasienter som bruker rekkverk og/eller et ikke-resiprokt mønster*, registreres resultatet i deltesten **Opp trapper ikke selvstendig**. For pasienter som går opp trappene med resiprokt mønster* uten rekkverk, registreres resultatet i deltesten **Opp trapper selvstendig**, og de får 5 tilleggspoeng i den siste kolonnen i Opp trapper ikke selvstendig.

*Resiprokt mønster: plassere en fot på hvert trinn vekselvis.

Ned trapp: Som for Opp trapper.

Nb! Der man ikke har en 14 trinns trapp beregnes skår ut fra registrert tid multiplisert med 14/antall trinn. For eksempel ved trapp med 12 trinn: registrert tid: 5,4 sek x 14/12

Skåring: Alle tidene og lengdene registreres i resultatkolonnen. Man setter ring rundt den tilsvarende skåren for hver deloppgave og finner delsummen av hver kolonne. Deltester som ikke godkjennes skåres 0. Deretter legger man sammen delsummene og beregner HiMAT-skåren.

Meld fra til Gavin Williams på e-postadressen gavinw@unimelb.edu.au slik at bruken av HiMAT kan spores.

Originalreferanser:
1. Williams G, Robertson V, Greenwood K, Morris ME. *The High-level mobility assessment tool (HiMAT) for traumatic brain injury. Part 1. Item generation.* Brain Inj. 2005;19:925-932.
2. Williams G, Robertson V, Greenwood K, Morris ME. *The High-level mobility assessment tool (HiMAT) for traumatic brain injury. Part 2. Content validity and discriminability.* Brain Inj 2005:19:833-843.
3. Williams GP, Greenwood, KM, Robertson VJ, Goldie, PA. Morris ME. *High-Level Mobility Assessment Tool (HiMAT): interrater reliability, retest reliability and internal consistency*. Phys Ther 2006;86:395-400.
4. Williams G, Robertson V, Greenwood K, Goldie P, Morris, ME. *The concurrent validity and responsiveness of the High-level mobility assessment tool for measuring mobility limitations of people with traumatic brain injury.* Arch Phys Med Rehabil 2006;87:437-442

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Errata

Page	Original text	Corrected text
Page x	a individually modified group-based VR program	an individually modified group-based VR intervention
Page 71	a individually modified group-based VR intervention	an individually modified group-based VR intervention
Page 71	Center For Outcome Measures in TBI	Center for Outcome Measures in TBI
Figures 1-4	Move the figure text from above the figures to below the figures	
Article III:		
Figure 1	Move the figure text from above the figure to below the figure	
Article IV:		
Page 9	DHI.[35] and had severe symptoms of dizziness according to the VSS-SF	DHI,[35] and severe symptoms of dizziness according to the VSS-SF
Table 2	HiMAT row, control group T1 column: corrected from n = 23 to n = 26	
Table 3	HiMAT row: The value should be 4.58, 95% CI 3.34-5.81 and 6.28, 95% CI 3.45-6.28, not -4.58 CI -5.81 to -3.34 and -6.28 CI -6.28 to -3.45	
Figures 1-2	Move the figure text from above the figures to below the figures	