High-level mobility in chronic traumatic brain injury

A case-control study

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Prologue and acknowledgements

Tigger: Come on, Rabbit. Let's you and me bounce, huh?
Rabbit: Good heavens! M-m-m-me bounce?
Tigger: Why, certainly! And look, you've got the feet for it.
Rabbit: I have?
Tigger: Sure! Come on, try it! It makes ya feel just grrreat!

From the motion picture "Winnie the Pooh and Tigger Too" (1974)

Simplified in A.A. Milnes epic storyline from the Hundred Acre Wood the essence of high-level mobility has been captured. It is all about making use of what you've got! With this thesis I aim to add some new insights on high-level mobility in chronic TBI. Hopefully it also can inspire more physiotherapists to focus on advanced gross motor skills in both TBI and other neurological patients –helping more people to **"feel just grrreat…"**

I wish to thank all participants in this study. Their participation is invaluable and impressive, as the gross motor testing was just a small part of all the investigations they undertook.

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Contents

Avansert grovmotorikk hos personer med kronisk traumatisk hodeskade. En case-control studie

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Sammendrag

Formål: Denne studien sammenligner forekomst av problemer med avansert grovmotorikk hos personer med kronisk moderat og alvorlig traumatisk hodeskade (TBI) med matchede kontroller.
Design: Case-control studie.
Måling av endepunkt: High-level mobility assessment tool (HiMAT) ble brukt som måleinstrument for å kartlegge avansert grovmotorikk.
Metode: Vi rekrutterte 69 personer med kronisk TBI i alderen 16 til 65 år fra en kohort bestående av moderate og alvorlige TBI-pasienter fra helseregion Midt-Norge. Pasientene ble innlagt på sykehus i perioden oktober 2004 til juli 2008. Kontrollgruppen besto av 76 personer fra samme geografiske region, matchet på alder, kjønn og utdanning. Alle deltakere ble inkludert og undersøkt i perioden mai 2009 til september 2010. Kjønnsspesifikke normscorer for unge voksne i alderen 18 til 25 år ble benyttet som sammenligningsgrunnlag. Som indikator for problemer med avansert grovmotorikk benyttet vi 5 persentilen.
Resultat: Personer med kronisk TBI hadde signifikant lavere mean HiMAT score (42.5 poeng; 95% CI: 39.9-45.1) sammenlignet med kontroller (47.4 poeng; 95% CI: 45.4-49.3). I TBI-gruppen presterte 51 personer (76.1%) innenfor 5 persentilen, sammenlignet med 32 personer (43.8%) i kontrollgruppen. Odds ratio (OR) for å ha problemer med avansert grovmotorikk var 4.1 (95% CI: 2.0-8.5) i TBI-gruppen sammenlignet med kontrollgruppen. Justert for treningsaktiviteter, smerte og bruk av medikamenter ble OR redusert til 3.1 (95% CI: 1.4-6.8) i TBI-gruppen sammenlignet med kontrollgruppen.
Konklusjon: I denne studien ble det funnet høy forekomst av problemer med avansert grovmotorikk blant personer med kronisk moderat og alvorlig TBI, identifisert hos mer enn tre fjerdedeler av deltakerne i TBI-gruppen. Det er behov for videre utvikling av aldersspesifikke normverdier for at HiMAT skal kunne gi et bedre sammenligningsgrunnlag og være retningsgivende for rehabiliteringsinnsats.

Nøkkelord: Avansert grovmotorikk. High-level mobility assessment tool. Traumatisk hodeskade.

High-level mobility in chronic traumatic brain injury – a case-control study

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Abstract

Objective: This study investigated the prevalence of high-level mobility problems in subjects with chronic moderate and severe traumatic brain injury (TBI) compared to matched controls.

Design: A case-control study.

Main Outcome Measures: Primary outcome measure was the high-level mobility assessment tool (HiMAT).

Methods: We recruited 69 subjects with chronic TBI (range 16-65 years), from a cohort of moderate and severe TBI patients from the Mid-Norway health region, admitted to hospital between October 2004 and July 2008. The control group consisted of 76 subjects from the same geographic region, matched on age, sex and education. All participants were included and tested during follow-up from May 2009 to September 2010. Sex specific normative scores for young adults aged 18-25 years were used as comparison, and the 5th percentile was set as an indicator for problems with high-level mobility.

Results: Subjects with chronic TBI had significantly lower mean HiMAT scores (42.5 points; 95% CI: 39.9-45.1) than controls (47.4 points; 95% CI: 45.4-49.3). In the TBI group 51 (76.1%) subjects performed at or below the 5th percentile compared with 32 (43.8%) subjects in the control group. Odds ratio for having problems with high-level mobility was 4.1 (95% CI: 2.0-8.5) in the TBI group compared to controls. Odds ratio adjusted for exercise activities, pain and use of medication was 3.1 (95% CI: 1.4-6.8) for the TBI group compared to controls.

Conclusions: High-level mobility problems are highly prevalent in chronic moderate and severe TBI, and were found in more than three-quarters of subjects. There is a need for further development of age appropriate normative scores on the HiMAT to aid comparability and direct rehabilitation efforts.

Key Words: High-level mobility. High-level mobility assessment tool. Traumatic brain injury.

Abbreviations

CI	Confidence interval
CNS	Central nervous system
DAI	Diffuse axonal injury
GCS	Glascow Coma Scale
GOSE	Glascow Outcome Score Extended
HiMAT	High-level Mobility Assessment Tool
HISS	Head Injury Severity Scale
ICC	Intraclass correlation coefficient
MRI	Magnetic resonance imaging
OR	Odds ratio
PTA	Post traumatic amnesia
r_s	Spearman's rho
SD	Standard deviation
TBI	Traumatic brain injury

Definitions

- Traumatic brain injury

  'an alteration in brain function, or other evidence of brain pathology, caused by an external force'

- High-level mobility

  'gross motor abilities important for everyday life and leisure activities, like running, jumping, hopping, and walking over obstacles'

- Motor control

  'the ability to regulate or direct the mechanisms essential to movement'

- Plasticity

  'the ability of the nervous system to respond to stimuli through change of structure and function'

- Being physically active

  'committing planned, structured, repetitive exercise aiming to improve or maintain physical fitness'

1.0 Introduction and background

Traumatic brain injury (TBI) is defined as *'an alteration in brain function, or other evidence of brain pathology, caused by an external force'* [1]. In Norway, recent findings suggest an annual incidence of 4100 hospitalized TBI [2]. There are no estimates of prevalence in Norway or Scandinavia. However, as many types of sequelae are common in survivors of TBI, it clearly provides many challenges to a vast number of people, whether being motor, psychiatric, behavioural or cognitive [3-5]. Incidence of TBI is high in young adults, leading to a potentially large prevalence in people of working age [5].

High-level mobility refers to gross motor abilities important for everyday life and leisure activities, like running, jumping, hopping and skipping [6]. An increasing body of evidence exists on good motor recovery in chronic phase after TBI, but there is a paucity of research on the recovery of high-level mobility. Physiotherapists and other clinicians have longstanding empirical evidence of traumatic brain injuries affecting motor skills and mobility. However, no previous studies have investigated the prevalence of high-level mobility in this population. Therefore, we still do not know to what extent TBI influence on advanced gross motor skills in the chronic phase. And until recently there were also no valid or reliable way of addressing this issue. Several norm-referenced tests assessing gross motor skills exists for children [7-10], but are scarce for adult populations. Gavin Williams and colleagues have developed a useful tool for testing high-level mobility in the TBI population, namely the High-level Mobility Assessment Tool (HiMAT) [11]. Adding to the clinical usefulness normative values for the age group 18 to 25 years have been published [12], producing a framework for interpretation of results. Development of the HiMAT and further publications from this research group, have pinpointed the importance of reacquisition of high-level mobility in chronic TBI patients. Regaining high-level mobility has the potential to increase level of participation in many important arenas, like return to work, sports and leisure activities.

This thesis concerns the quantitative properties of high-level mobility performance of subjects with chronic moderate or severe TBI. Quantitative research methods have many strengths enabling measure of differences between groups. However, this approach needs to be supported by valid, reliable and sensitive instruments in order to present meaningful

results, and the results must then be interpreted within a larger context. It is well established that by choosing to quantify human movements important information on quality and movement strategies is lost. Movement quality and strategies are an integral focus of physiotherapists working with neurological patients [13-15]. Additionally, quantitative methods might not be able to capture motivation and goals governing movements. Physiotherapy, both as a profession and as an instrument, must rely on several different theoretical and philosophical paradigms in order to adjust to the complexity of practice [16]. Results from a quantitative study must therefore be integrated with qualitative information and empirical knowledge to ensure optimal clinical impact.

1.1 Description and structure of the thesis

This thesis investigates high-level mobility in chronic moderate and severe TBI. The findings are presented in the paper 'High-level mobility in chronic traumatic brain injury – a case-control study', which is found in the last section of the thesis. The aim is to submit this paper to the journal 'Brain Injury'. Therefore, the paper has been written in accordance with the journal's guidelines (Appendix 1). It is recommended to read the paper first to get an overview of the study and its findings.

In the following text, the term 'TBI' will be used to describe both moderate and severe TBI. Specification of severity will be presented when justified. The first part of this thesis concerns the theoretical background of high-level mobility and TBI. Previous research is used to both present the current knowledge in the field and to identify knowledge gaps. The next section concerns the methodological composition of the study and expands on the methodological and analytical choices made during this research. Then, a summary of the main results will be presented before a discussion is given on both methodological issues and the findings of the study. A conclusion and thoughts for further research ends this part of the thesis.

2.0 Central theory and theoretical anchoring of the study

This section describes vital aspects of advanced gross motor mobility, motor control and motor learning. A presentation of important characteristics of the injury mechanisms and the neurobiology follows, with implications of injury on neuroplasticity. Finally, the current body of evidence on possibilities and limitations of high-level mobility in the TBI population is presented.

2.1 High-level mobility, motor control and motor learning

Understanding how human movements are controlled is very important to physiotherapists as they aim to help patients regain skilled movements after injuries. Motor control is defined as *'the ability to regulate or direct the mechanisms essential to movement'* [17]. To date no single theory has been able to account for the complete concept of motor control.

2.1.1 High-level mobility

High-level motor skills are usually developed during childhood and consolidated throughout adolescence [18]. To some extent flexible gross motor skills are taken for granted after adolescence. However, a plethora of factors can negatively affect these abilities in adults, ranging from stress, pain, injury and overweight to lack of motivation or interests in physical activity.

High-level mobility describes a large group of locomotor strategies. Each strategy has different requirements on the basic skills needed for success. Walking and running display very similar movement patterns, but running demands increased strength and balance [17, 19]. Bounding and hopping requires enough strength and flexibility to be able to jump off one leg into a flight phase, as well as demanding increased balance and coordination levels [17]. Additionally, bouncing movements like bounding, hopping and running requires a complex and coordinated spring system, consisting of muscles, tendons, ligaments and connective tissue in the lower extremities [20]. Skipping combines two different patterns. It entails a step-hop combination, first on one leg, then moving onto the other, repeating the

pattern. This challenges both flexibility, balance and coordination [17]. In addition, it has been found that attentional demand increases when the skill requires a high level of postural and balance activity [21].

Basic gait patterns can be made from central pattern generators in the spinal cord [22]. However, it has been recognized that higher level movement patterns like hopping, bounding and skipping must have higher level nervous system involvement [19]. Several different motor control theories exist on how this control is effectuated.

2.1.2 Motor control and motor learning

Motor control theories range from reflex driven control, hierarchical and schema theories to dynamic systems approaches [17]. The main objective has been to understand how the human body can control movement in a cost efficient way. Nicolai Bernstein [23] identified control of the redundant degrees of freedom as the main challenge. The sum of possible movements per joint involved in a motion is the possible degrees of freedom for the task. For each task there are more possible degrees of freedom than needed for each solution [23]. Bernstein's findings have led to a central question: 'How does the body choose the best movement strategy'?

Two main directions in motor control theories are motor schema theory and dynamic systems theory. Common for both theories is that the central nervous system (CNS) is the main controller of movements, but how the CNS actually does this is not clearly stated. In motor schema theory, it is suggested that a mental blueprint of the movement, or movement sequences needed to complete the task, is stored in memory [19]. A blueprint for any task possible is or can be developed and stored for future use. These blueprints are called generalized motor programs, and can be modified and altered by motor schemas enabling use in a variety of conditions. Schemas are developed and altered through motor learning [24]. However, how this learning occurs is unaccounted for. Coordinated movements are due to generalized motor programs and schemas, which can act with or without feedback. This is how schema theory overcomes the redundancy problem [19]. Schmidt [24] has also stressed the fact that this theory was developed to explain quick and discrete movements,

and therefore might not be the best theoretical basis for understanding continuous and long lasting movements.

Dynamic systems theory has evolved more directly from Bernstein's recognition of seeing the human body as a mechanical system that in itself must influence the number of possible movements [17]. The redundant degrees of freedom can be controlled by organizing muscles in synergies, making these synergies the smallest working unit [23]. This theory pinpoints variability of movements as the essential factor for adapting and consolidating new movement patterns. However, as soon as new movements are being learned they must be modulated within the systems in order to be fluent, efficient and precise [25]. The theory also suggests that variability is necessary in adjusting movements to different environmental challenges [17]. According to Schmidt [24], the dynamic systems theory has an advantage in explaining control of long lasting motor activities, as it unifies sensory information with action.

Hierarchical control of movement is still considered a useful way of understanding motor control, as different strategies are controlled at different levels. One example of this is reflexive movements giving the fastest motor response via the spinal cord, whilst somewhat slower, but more flexible actions, are controlled via the cortical motor and sensory areas [26]. However, Turvey and Fonseca [27] propose that a heterarchical control best describes the concept of motor control within the CNS, as it is not clear that it is a top-down or bottom-up process, but rather several levels of interconnectivity collaborating to control movements ranging from discrete motion to complex combined and simultaneous movement patterns.

Motor learning theories are concerned with the acquisition and adjustment of motion in healthy individuals, whereas motor relearning or recovery of function focuses on the reaquisition of movement altered by injury or illness [17]. The role of motor learning after brain injury has been debated. Krakauer [28] claims that recovery from brain injury rely on motor learning, both to enhance spontaneous recovery processes and compensational strategies. In contrast, Gentile [29] argues that the patient is not an initial learner and that the problem lies within the ability to control and coordinate motor activity. Although

Gentile points at an important factor, it is also true that the situation after an injury is new to the patient. Alterations of the ability to control and coordinate the body imply that learning must occur within new structural frames, thereby mimicking novel learning. Novel learners typically have variable performance and imprecise movements [19]. This makes it difficult to identify whether such performance reflects initial motor learning or problems with motor control.

2.2 Mechanisms and location of injury

2.2.1 Focal injuries

Focal injuries in TBI consists of contusions and heamorrhage [30]. Focal injuries are often seen in the limbic system as well as the frontal and temporal lobes [30, 31]. Also, in focal injuries there is a clear connection between injury localisation in the CNS and observed problems in cognition, motor function and behaviour [30].

The frontal lobe contains areas concerning planning, execution of motor output and evaluation [32]. A focal traumatic injury to the primary motor area can cause contralateral hemiparesis, similar to what is seen in stroke. Both the temporal lobes and the limbic system are engaged in memory functions. Additionally, the limbic system is important for learning and interpretation of emotions [22]. Emotional impact is especially important in the formation of memories [32]. Injuries to these areas may therefore impact both executive and adaptive properties of motor abilities. Evidence also exist on the importance of the cortico-striatal and cortico-cerebellar networks in motor learning and skill acquisition [33], indicating that injuries to the cortex can hamper the reacquisition of high-level mobility.

2.2.2 Diffuse axonal injuries

Motor vehicle accidents and falls are among the most frequent causes of TBI [34, 35], commonly causing diffuse axonal injuries (DAI) in the central nervous system. Diffuse injuries consist of axonal stretching, disruption and separation of nerve fibres, usually seen in the parasagittal white matter of the cerebral cortex, corpus callosum and brain stem [30,

36-38]. An additional threat to connectivity and white matter after TBI is secondary injuries causing Wallerian degeneration - which can lead to long term alterations of white matter and cause additional axonal injury [39-41].

The regions most susceptible to diffuse axonal injury following a TBI are very important for motor function, thus underpinning the potential devastating effect of DAI. The corpus callosum interconnects the two hemispheres [22], and new research suggest that white matter lesions in corpus callosum are associated with gait problems in elderly subjects [42, 43]. Information from cortical motor areas is sent through the corticospinal tract, enabling precise and skilled movements [22]. The tract passes through the brain stem before making synaptic connections with alpha motor neurons in the spinal cord. In the brain stem, premotor networks are involved with activation and coordination of muscular activity [22]. These are all important factors for gross motor skills [17]. Additionally, several tracts send and receive information from the cerebellum, a structure highly concerned with coordination, balance and muscle tone [22]. Among these, tracts within the superior cerebellar peduncles are especially vulnerable to DAI [44]. Recent publications have shown that diffuse axonal injury in the brain stem is associated with poor outcome [45-47]. There is also increasing evidence of the co-existence of focal injuries and DAI in TBI [30, 36, 45], possibly increasing the complexity of symptoms and motor problems.

2.3 Neuroplasticity

The current understanding of factors affecting outcome after TBI is complex and incomplete. Adding to the challenge, the TBI population is heterogeneous, and there is a broad variety and complexity in type of injury [35]. After an injury to the brain there will be spontaneous recovery, even in the absence of formal rehabilitation. Nonetheless, rehabilitation will have positive effect causing an increased level of recovery [48]. Plasticity is the ability of the nervous system to respond to stimuli through change of structure and function [22], and is a prerequisite to adaptation and learning [33, 49]. Evidence suggest that neuroplasticity can occur within a very long time frame [50]. However, the impact of

these plastic changes may recede with time, indicating that rehabilitation efforts have best effect if timed correctly.

Restitution after damage in the central nervous system has two main mechanisms. In *substitution,* unharmed neurones take over the function of injured neurones, whereas *compensation* occurs when surviving structures alter their function. Both mechanisms are due to the construction of new synapses or increased efficiency of existing synapses [22]. Increasing evidence suggests that development of new neurons occurs in the adult human brain and that this process might even be set off by the injury itself [50-52]. However, what impact neurogenesis has on restitution remains uncertain.

In addition to synaptic communication, a non-synaptic neurotransmission called volume transmission exists. In this process neurotransmitters like norepinephrine, dopamine and serotonin diffuse through the extra cellular fluid. They connect to receptors on the cell membrane, not on the actual nerve terminal [22, 48]. This way, the neurotransmitters function more closely to local hormones than the classical synaptic transference [22]. This mechanism can be essential for modulating processes like arousal and motivation, which are pivotal factors for the rehabilitation process. Many complex functions are dependent on both synaptic and non-synaptic transmission, and plastic changes of receptors in both systems may be important contributors to recovery after brain injury [48]. New insights in the reorganization of functional brain networks suggest that recovery is closely related to a balanced use of energy in restoring or building new connections [53]. This mimics plastic reorganization in motor skill learning, where sleep or passage of time is a driving force of functional plasticity and motor adaptation [33].

2.4 Previous research in traumatic brain injury and high-level mobility

2.4.1 Activities and participation after traumatic brain injury

Participation in different activities and on various arenas is an important aspect of life, and equally an important focus for rehabilitation. In Sweden, 91% were living independently and 60% were working 6-15 years after TBI [5]. People with mild TBI were significantly

more vocationally active than people with higher severities of TBI [5]. These findings are supported by an Australian study, which found 62% to be working or studying [4]. Equivalently, a Norwegian research group [54] found 45% to be working full time, and 13% working part time 10 years post injury. Of those who worked full time, 69% had moderate and 20% had severe TBI.

More than 90% of TBI patients decrease participation in leisure activities after injury, in which motor challenges contribute heavily [55]. One year after injury, many have difficulties in performing leisure activities, or require assistance. As a consequence, the majority of patients cease to participate in some or almost all pre-injury leisure activities [56]. This has been found also in well-recovered patients [57]. Even though many patients significantly alter participation levels, some chronic moderate to severe TBI patients continue to participate even in extreme sports, indicating that high-level mobility skills are utilized [56].

2.4.2 Recovery of high-level mobility

A clear timeframe has not been identified for the recovery of motor function after TBI, but it can be a lingering process [30]. It has been proposed that the majority of recovery happens within the first six months after injury [58]. A study on patients with severe TBI found that over 70% gained independent gait within five months [59]. Of these, 94% had achieved walking function within the first three months. Recovery of motor skills may happen in a variety of tempo and sequence, but there is a tendency towards patients regaining simpler skills like sitting balance and gait earlier than higher level mobility skills [60]. Patients with DAI have less predictable and more unique combinations of motor problems, than patients with focal pathology [30]. Some evidence suggests a better prognosis of motor recovery after DAI than in focal injuries, but with a prolonged time perspective [30, 59]. However, the underlying mechanisms are not fully understood.

There is a definite shortage of research on high-level mobility in neurological patients. However, a few case reports have focused on high-level mobility in TBI and other neurological populations [61-65]. I have been able to identify four published studies

investigating high-level mobility in a group of TBI patients using HiMAT [66-69]. McCulloch and colleagues [66] presented a study sample of 24 subjects with chronic TBI. They investigated the relationship between balance, attention and dual-task performance and related their findings with falls history. Williams and Morris [67] presented a small cohort study following patients with chronic TBI and other neurological diagnosis. They found significantly increased high-level mobility after participation in a three month training programme. Additionally, Williams and colleagues [68, 69] have investigated gait in two samples of chronic TBI samples, and presented HiMAT results for these samples. However, none of these studies have compared subjects with chronic TBI to healthy controls.

Only a limited number of studies have compared high-level mobility in chronic TBI with healthy controls. Most of the studies that exist have small sample sizes and have focused on gait. Findings prove reduced gait speed in patients with chronic TBI compared to healthy controls [68-73]. Subjects with chronic TBI have also been found to be slower and perform with less precision than controls in tasks like walking over an obstacle [70, 71] or multitasking during walking [73]. These studies have only investigated a very narrow range of high-level mobility skills. In clinically deemed well-recovered men, coordination, balance, agility and rhythmical skills have been found reduced compared to controls [57]. These skills are all prerequisites for high-level mobility.

To my knowledge, no previous studies have used HiMAT to compare high-level mobility in persons with moderate and severe chronic TBI to healthy controls.

3.0 The aim of the study

The aim of this study is to investigate the prevalence of high-level mobility problems in patients with moderate and severe TBI in chronic phase compared to healthy controls. Based on empirical evidence and previous research, it was assumed that people who have survived a moderate or severe traumatic brain injury would present more motor problems on advanced gross motor testing than matched healthy controls.

4.0 Materials and methods

This part of the thesis concentrates on the methodological choices of the study. It underlines and broadens upon the information given in the paper concerning the assessments and the design of the study.

4.1 Study design

This study has a case-control design comparing patients with TBI to healthy controls. It is part of the project 'Advanced MRI for diagnosis and outcome assessment in patients with traumatic brain injury (TBI)'. The project is a follow-up study of a cohort sample thoroughly presented in the paper. Of admitted patients 97% consented to registration, and less than 2% has been lost to follow up.

4.2 Study population

4.2.1 TBI group

Patients registered in a database, hospitalized at St. Olavs Hospital, Trondheim, in the period of October 2004 to July 2008, were contacted by phone if they were at least one year post-injury and fulfilled the inclusion criteria. A total of 69 patients agreed to participate and were included in this study. Data from time of injury and from follow-up during the period of May 2009 to September 2010, has been used in this study.

Glascow Outcome Scale Extended (GOSE) [74], measuring global outcome, was administered 12 months post injury with structured interviews. These results were used as indication of ability to cooperate during functional magnetic resonance imaging (fMRI).

4.2.2 Control group

Controls were strategically recruited and matched by sex, age and education. Age was matched within 5 years intervals. Highest completed education levels were chosen to

control for socioeconomic status. Matching was done as precisely as possible to both years of education and type of profession. In the control group, 76 subjects from the Mid-Norway region were recruited and examined during the same period as the TBI group. There were no significant differences between the groups on the matched variables (Sex: p=0.89. Age: p=0.15. Education: p=0.97), indicating that the matching was successful.

4.2.3 Exclusion from analysis

Participants who could not be tested or failed to complete the HiMAT were excluded from analysis (n=5). The exclusion of two cases and three controls did not lead to altered group differences on the matching criteria (Sex: p=0.63. Age: p=0.21. Education: p=0.74), suggesting that matching was still successful after exclusion.

4.2.4 Non-participants

A total of 38 (35.5%) people did not consent to participation in the follow-up project. These were significantly older at time of injury than those who did agree to partake in the study. There were no other significant differences between participants and non-participants on measures of injury severity.

4.3 Method

4.3.1 Background variables

Age, sex and highest completed education were registered for all participants. The ˈAchenbach System of Empirically Based Assessment – Adult self-report ˈ was part of the assessment in the main project, and from this information on highest completed education, marital status and current work or education was made available (Appendix 2). Current physical activity levels, and any illness or injury possibly affecting motor performance during testing, were mapped out during an interview (Appendix 3). Participants were weighed on an electronic scale to the nearest 10 grams, and self-reported height was registered. From this body mass index (kg/m^2) was calculated.

4.3.2 Measurements of injury severity

Glascow Coma Scale (GCS) [75] was used as an assessment of injury severity at hospital admission. The GCS is an ordinal scale, consisting of three parts: opening the eyes, motor response and verbal response [75]. The GCS is reliable, and has a high degree of accuracy when scored by experienced testers [76]. 13-15 points are considered mild, 9-12 points moderate and 3-8 points severe TBI [77].

Duration of post traumatic amnesia (PTA) was registered during hospitalization, defined as the interval from injury to return of orientation [78]. Duration of PTA has a high degree of validity as a measure of TBI severity [79]. Classification of severity after TBI through registration of PTA duration is divided into mild, moderate and severe [77]. PTA up to one day is classified as mild, less than seven days moderate, and more than seven days severe TBI [77]. Based on this, PTA > 7 days was defined as long PTA in this study.

The GCS and duration of PTA are the most common tools for classifying degree of severity in acute TBI [77]. Both measurements are recommended as a part of standard examination of TBI in research [80].

Inclusion in the database was based on HISS criteria, as described in the paper. In addition to the GCS score loss of consciousness at time of injury and reduced levels of consciousness at hospital admission are incorporated in the HISS score. Based on HISS scores, subjects scoring both 14 and 13 points on the GCS were included in the moderate group. Reliability and validity of HISS scores are not accounted for in the literature [81, 82].

Presence or absence of DAI and contusions was identified based on magnetic resonance imaging (MRI), conducted within 4 weeks of admittance. Description of the MRI interpretation is given in details elsewhere [45].

Age and cause of injury were registered at time of injury or hospital admission. Length of hospital stay was also registered.

4.3.3 High-level mobility

High-level motor function was examined using the HiMAT (Appendix 4). The scale is ordinal, and examines a variety of walking skills including negotiating stairs, running, skipping, hopping and bounding [11, 83]. Items are measured in seconds and centimetres, and transformed to item scores. All items are scored on a scale from 0 to 4 points, except two stair walking items where scores range from 0 to 5 points. Total score ranges from 0 to 54 points, with higher scores suggesting better motor performance [11].

HiMAT is developed for and validated in a TBI population [11]. It is sensitive [84], and can be used in patients with substantial cognitive challenges [11]. High degree of interrater reliability for item scores (ICC .99) and total score (ICC .99) has been demonstrated on subjects with TBI [85]. High test-retest reliability was also found when testing healthy young adults (ICC=0.88, 95% CI: 0.82-0.92) [12]. Normative values for healthy young adults aged 18-25 have found median scores of 54/54 points for men and 51/54 points for women. For the same age group 5^{th} percentile scores are 50/54 points for men and 44/54 points for women. A substantial ceiling effect is present in healthy young men, but not in women [12].

The HiMAT was recently translated to Norwegian by me and my colleague Ingerid Kleffelgård [86]. The translation process has followed international guidelines with cross-translations and expert reviews [87]. The Norwegian translation was used during testing.

In 2010, a reanalysis of the data used in developing the HiMAT concluded that the original test was multidimensional. By removing the stair items and the item `bound affected leg´, the scale showed a good unidimensional model-fit in a revised version of 8 items. Maximal total score on the revised HiMAT is 32 points [88]. Normative scores have not been published on the revised test.

4.3.4 Examiners

In the current study, examiners were trained by an experienced physiotherapist with thorough knowledge of the HiMAT, prior to the data collection process. Three examiners

conducted the tests and interviews. They were blinded to group assignment. The HiMAT requires information on most and least affected leg on three different items. In order to maintain blinding of examiners, all participants were asked what leg they considered their best leg. For those who did not know which leg was the better, a single leg stance was performed and the chosen leg to stand on was considered the better leg.

4.4 Ethics

This study is part of a large project: 'Advanced MRI for diagnosis and outcome assessment in patients with traumatic brain injury (TBI) ', which is approved by the Regional Committee for Medical Research Ethics in Health Region IV (REK number 4.2009.1019).

Participants gave their informed consent after receiving a written invitation letter informing about the study (Appendix 5 for cases and appendix 6 for controls), and additional oral information at attendance. For participants under the age of 18 years, a parent or legal guardian had to co-sign the consent form.

The tests are non-invasive, used in daily clinical practice, and are considered safe for participants. All participants were informed they could refuse items on the HiMAT if they considered it to be unsafe or too difficult to perform the task in question.

4.5 Analysis of the data

Statistical Package for Social Sciences (SPSS) for Windows, version 19.0 (SPSS Inc., Chicago, IL) was used for statistical analysis of the data. Two sided p-values <0.05 were considered statistical significant for all tests.

4.5.1 Preparation of the SPSS file and preliminary analyses

All collected data were defined and labelled when entered into the SPSS file. Entries were double checked in order to avoid errors before preliminary analyses were conducted.

Preliminary analyses were initiated with an additional error check with descriptive statistics. Data were also visually inspected and checked for outliers using histograms, bar graphs and boxplots. During this process, several missing data were identified, some outliers and a few non-viable variables. Correct variables were entered into the SPSS file after consulting the safely stored records for each ID number in question. None of the outliers were incorrect entries; therefore, the outliers were included in the material for analysis. However, some missing data did occur. Reasons for this were incomplete records from time of injury, two TBI participants could not be investigated with MRI within four weeks after injury, and some participants did not answer all questions during the interview. Several items on the HiMAT were scored as 0, due to refusal or inability to perform the item, according to the manual [86]. After correcting errors, descriptive statistics were performed on background characteristics of the participants. Categorical data was investigated using frequencies and for continuous variables mean, standard deviation, minimum and maximum scores were investigated [89].

4.5.2 Normality and presentation of data

Normality of data was assessed by using the Kolmogorov-Smirnov test [89]. Body weight and BMI was the only variables normally distributed (p=0.2 for both variables).

The HiMAT produces ordinal data, but mean and 95% confidence intervals (CI) are presented in the article and the tables, as median values did not give a good description of the difference between groups. Additionally, mean HiMAT scores have been published in all studies using HiMAT as assessment of high-level mobility so far [12, 61, 65-69]. Using mean scores therefore aids comparability between studies. These studies have also presented standard deviation as measure of variability. However, in this study, confidence intervals are presented to improve the interpretation of the significance levels.

Confidence intervals describe the degree of certainty of findings containing the value in question. A 95% CI is analogous to saying that there is a 5% chance that the value is not within the proposed interval [90].

4.5.3 Analysis of parametric data

Student's t-test for independent groups was used to analyse differences between groups for parametric data. Parametric data rely on three assumptions: Data must be normally distributed within random samples, sample variances must be equal and data must be from ratio or interval scales [90]. In a matched case-control study randomization is not possible, and equal sample variances can not be assumed.

The t-test is a robust test, not massively weakened by unequal variances in samples if sample sizes are of similar size [90]. In this study, the difference between sample sizes is minute, n=67 versus n=73. Additionally, according to the central limit theorem sample means will be normally distributed if the sample size is large enough [91], therefore the choice was made to apply this test on all continuous variables.

4.5.4 Analysis of non-parametric data

Non-parametric tests have less assumptions on population data and can be used when data do not meet the parametric test criteria [90]. They are also created to handle data from nominal and ordinal scales [90]. Apart from age at injury, duration of hospital stay, and current pain measured with visual analogue scale – all outcome measures in this study were either ordinal or categorical (nominal). Group comparisons on non-parametric data were performed using Mann-Whitney U test. The Mann-Whitney U test is the non-parametric equivalent to the parametric t-test [91].

Williams and colleagues have used parametric t-tests to compare total HiMAT scores between two groups [67] or within group [84]. However, the same research group has also used Mann-Whitney U test for comparisons of total HiMAT scores between two groups [12]. Choosing the parametric option would potentially gain a more powerful analysis [90]. However, Bjørndal and Hofoss [92] claim that the use of t-test on ordinal data is an unreasonable praxis, as it is very likely that the two groups represent totally different populations, thus comparing groups of unequal variety [92]. In the current study, the HiMAT data met the two assumptions for choosing a non-parametric test over a parametric

test. First, data were ordinal, and secondly, the Kolmogorov-Smirnov test was significant ($p<0.001$) (data not shown), suggesting that the assumption of normality in the total HiMAT scores was violated [90]. Thus, the Mann-Whitney U test was chosen to compare scores of the HiMAT between cases and controls.

Chi-square test was used to examine differences in proportions on categorical data. This test examines the existence of an association or lack thereof. It is important to acknowledge the fact that the chi-square test cannot produce information on the strength of the association. It only identifies whether the association is significant or not [90].

4.5.5 Logistic regression analysis, crude and adjusted odds ratio

Odds are the probability of a given event occurring divided by the likelihood of this event not occurring. The odds ratio (OR) depicts the relationship between two odds [92]. In this study, crude OR estimates the relationship between the odds of the cases presenting poor high-level mobility versus the odds of the controls performing poorly, if all other factors are equal [89]. This provides a measure of the prevalence of high-level mobility problems in chronic TBI compared to controls. The OR is provided with a 95% confidence interval.

In order to perform these analyses, a cut-off value must be present. Normative 5^{th} percentile scores specific for both sexes have been published by Williams and colleagues [12] for subjects between 18-25 years of age. This is a much narrower age range than what was included in this study. Therefore, it could be interesting to apply sex appropriate 5^{th} percentile scores based on the results of the control group participants calculated from the data material of this study. However, the sample size was too small, and would give very uncertain results if applied. Additionally, the 5^{th} percentile from the control group may not be representative as the participants were strategically chosen. Therefore, the decision was made to apply the normative scores given by Williams and his research team [12]. A thorough discussion on the use of the normative scores has been presented in the article.

Logistic regression analyses were also used to investigate effect of background variables on HiMAT results. Variables correlated with group and/or the outcome, in this case the total

score of HiMAT, were identified using Spearman's rho (r_s). This test is the non-parametric alternative to the parametric Pearson's correlation coefficient. The correlation coefficient ranges between -1.0 to 1.0, with 0 indicating absolutely no correlation and ±1.0 indicate a perfect correlation. A positive number indicates that the two variables are associated in the same direction, either increasing or decreasing. On the other hand, a negative number depicts a negative direction of the relationship, where an increase in one variable is associated with a decrease in the other variable [90]. Correlation coefficients are vulnerable to non-linear relationships between variables. The Spearman's rho is not able to precisely describe a curvilinear relationship. Therefore, if such a relationship is present, the use of Spearman's rho might give a correlation coefficient close to zero even if there is a true relationship between two variables [90]. In this study, age is a variable that possibly can have a curvilinear relationship with high-level mobility. However, as participants were matched on this variable, a possible curvilinear relationship would not impact on the results.

Several variables were correlated with HiMAT, but only two variables were correlated with both HiMAT and group. This was `number of exercise activities´ ($r_s$= 0.29 for HiMAT and $r_s$= -0.19 for group) and `pain´ (r_s= -0.22 for HiMAT and r_s= 0.20 for group). However, even though these correlations were statistically significant, they represented only minimal or to the best a weak relationship [90], and may potentially not be of clinical value. As 'number of exercise activities ' also had been found significantly larger within the control group compared to the TBI group (p=0.03, Mann-Whitney U test), this variable was identified as a potential confounder.

Inclusion of independent variables in the logistical regression analysis can be used to control for potential confounders creating an adjusted OR [90]. A 10% alteration of the OR was considered a significant contribution. 'Number of exercise activities ' reduced the OR with 14.6%, and explained a large part of variability. 'Pain ' did not contribute significantly to the model when entered on its own. Notwithstanding, as this variable had been found correlated with both HiMAT score and group, it was kept in the model as a potential confounder. Inclusion of the 'pain ' variable into the model together with 'number of exercise activities ' reduced the OR further, and explained a larger part of the variability than either variable alone. The pain variable did still not significantly contribute to the model.

Additionally, 'use of medication' was significantly correlated with HiMAT. Entered alone in the model, it contributed with a 9.8% reduction of the OR. Adding 'use of medication' together with the other two variables slightly reduced the risk estimate further, and gave the best explanation of the variability indicated through a reduction of the 95% confidence interval.

5.0 Summary of results

This section of the thesis presents a short summary of the most important findings. For a thorough presentation of results readers are referred to the paper.

This study found that suffering a moderate or severe TBI can severely impede high-level mobility even in the chronic phase compared to healthy controls. Only three items on the HiMAT did not show significant differences between the groups. Apart from the item 'walk down stairs independent', all stair items showed non-significant differences between the groups.

A total of 51 (76.1%) subjects in the TBI group performed within the 5th percentile, according to values given by Williams and colleagues [12], compared to 32 (43.8%) controls ($p<0.001$). Being in the TBI group showed a fourfold increased risk of having problems with high-level mobility compared to controls. Committing more physical activities, having little pain and not using any medication were associated with higher HiMAT scores. Controlling for these factors lowered the risk of high-level mobility problems in the TBI group to three times compared to controls.

As norm values are produced for the age band 18-25 years [12], a subgroup analysis for participants ≤25 years was performed. The OR of those participating in the TBI group ≤25 years having high-level motor problems was similar to the OR for the whole TBI group, indicating the use of published norms on the older participants in this study was justified.

6.0 Discussion

A thorough discussion on the findings in this study has been presented in the paper. This section broadens on some of the aspects mentioned in the paper and introduces additional critical points and arguments.

6.1 Method discussion

6.1.1 Controlling for confounding

Case-control studies are susceptible to several threats to internal validity. *'A confounder is associated with the predictor variable, but may also be a risk factor for the outcome variable'* [90]. Confounding occurs when other factors than those proposed examined in a study, affects the results. Confounding was controlled for with three different strategies: Matching, logistic regression analysis and exclusion.

6.1.2 Selection of matching criteria

Age was chosen as matching variable due to higher incidence of TBI in young males 15-24 years [93-95], and in adults older than 65 years [95]. Higher age is also correlated with poorer outcome [96-98]. There is also a natural decline in speed and balance with increasing age [17], possibly affecting motor performance.

The effect of sex on outcome after TBI is uncertain, therefore subjects were matched by sex. Several studies report that women have worse outcome than men following TBI [94, 99, 100], others have found the opposite [101-103] or no difference at all [104]. Additionally, the HiMAT discriminates between sexes, with males performing at higher levels than women [12].

Socioeconomic status is a possible confounder of physical activity levels, with higher education associated with better functional outcome in chronic TBI [4]. Higher education is also associated with higher levels of physical activity [105-107]. The subjects were therefore matched on education.

The matching procedure averts the ability to evaluate the effect of the matched variables on the risk of disease, possible inter-relationship among the matching variables and the exposure factors [108]. Thus, if the matched variables are not true confounders, statistical analysis cannot make use of these variables. Done correctly, matching can augment the accuracy of the odds ratio estimate [108], as the matching aids a more specific analysis of the investigated variable [109].

6.1.3 Multivariate analyses

The effect of confounding variables can also be managed through statistical analyses, either via logistic regression models or stratification [110]. Possible confounders can only be controlled for if they are predicted before data collection, so that necessary information is collected [111]. In this study, three variables were identified as potential confounders and entered into a logistic regression model. This has been thoroughly discussed in the paper.

6.1.4 Exclusion

Exclusion criteria were prior neurological or psychiatric diagnosis. Several psychiatric disorders have strong associations with physical inactivity [112, 113], and most neurological illnesses can lead to alterations in motor performance either temporarily or permanently. Both factors can potentially mask the consequences of TBI, and persons with such diagnoses were therefore excluded.

Fluency in Norwegian was an inclusion criterion set to make sure that language barriers could not impact the results. Also, the age limits of the inclusion criteria were chosen to avoid interference from developmental processes in the CNS in children [114] and the aging effects of CNS in the elderly [115], potentially impacting on motor recovery and high-level mobility after TBI.

Exclusion of people scoring <5 on GOSE might have skewed the TBI sample towards better motor recovery, potentially explaining the large differences in performance between our sample and previous research. However, the GOSE mainly concerns

cognitive and emotional challenges [74]. Thus choosing a lower cut-off as exclusion score may potentially not impact motor function levels.

6.1.5 Selection bias

The selection of participants is a crucial element to the validity of the study. Controls need to be from the same population as the cases in order to be comparable [110, 111, 116, 117]. In this study participants are selected from Mid-Norway, a defined geographic and administrative health region, thus securing that both cases and controls origins from the same population.

Selection bias can occur in selection of both cases and controls. HISS criteria were applied to identify true moderate and severe TBI in subjects asked to participate in the database. This gave a precise definition of diagnosis criteria [118], enabling reproduction of this study and avoiding inclusion of false positives, potentially affecting the results.

In this study, friends and family members of the cases were recruited as controls. This can in itself control for potential confounders, as they are likely to share ethnical, environmental and socioeconomic characteristics [90, 119]. On the other hand, it can also potentially bias the results, due to a halo effect [119]. When cases nominate controls a tendency has been found of introducing friends slightly more respectable than themselves – for example with somewhat higher education levels [116, 119]. However, cases and controls were matched on education, so this should not affect the results. Also, there is a potential for overmatching, which is discussed in the article. The recruitment of controls was a complex procedure in order to match on all three chosen variables. Therefore, controls were also included from other sources, minimizing the effect of potential bias due to close relationships and socioeconomic characteristics.

According to Sackett [120], non-participant bias may be present in all research, as it always will be uncertain whether those who did not respond or refused participation would perform within the same levels as those who did participate. It is also important to compare participants to non-participants on background variables, to check for potential differences

explaining why the non-respondents did not participate in the study [120]. In this study, 38 eligible participants did not consent to participation. The only significant difference was that these were older at time of injury than those who consented. One possible reason for not participating is that the main project required participants to undertake several time consuming investigations, which could be considered too demanding for participants of higher age.

6.1.6 Information bias

Information bias occurs if information is gathered differently between cases and controls [111], as in examiners consciously or unconsciously preferring a response over another between cases and controls, influencing the scores [121]. To control for information bias, examiners were blinded to group assignment. A discussion of the effect of the blinding is presented in the paper.

Cognitive challenges are frequent in TBI patients, and can include impaired memory. This can lead to potential recall bias for the background variables collected by self-report. However, one inclusion criterion was GOSE ≥5, suggesting at least a moderate cognitive function [74].

As a 14 step staircase was unavailable during testing, time to complete the stair items had to be calculated. This may have impacted the results slightly. However, since the procedure was equal for all participants, it could not have introduced any bias.

6.1.7 Chance

In any research results can occur by chance. The p-value indicates the likelihood of obtaining an observed difference in the study sample when there is no true difference between groups [91]. The highly significant results in this study indicates that it is unlikely that findings are due to chance, but rather indicates a true association between living with a chronic traumatic brain injury and having problems with high-level mobility. When the significance level is set to 0.05, this reflects a 5% risk of results being due to chance or other

factors than those investigated. A 5% risk has been identified as acceptable in most clinical research where consequences of being wrong do not lead to severe complications or fatality.

Controls performed better than cases on the HiMAT on all but three items. The stair items were all non-significantly different between groups apart from the item 'walking down stairs independent' (p=0.04). Reasons for this might be that walking down a set of stairs without external support imposes higher demands on both balance and eccentric muscle activity [17]. However, inspection of the 95% CI in table 3 (shown in the paper) shows an overlap between groups. Therefore it is possible that the observed p-value is incidental.

6.1.8 Subgroup analysis

A subgroup analysis for participants ≤ 25 years of age was performed in this study. This can be warranted if the subgroup in question has well-established or pathological characteristics as well as a large enough sample size [109]. The argument for performing such an analysis was to perform a valid comparison between the findings of this study to the normative 5th percentile scores. The subgroup analysis yielded practically the same OR as for the entire study sample and the confidence intervals overlapped, suggesting that there is no significant difference between the two different samples. However, the chosen subgroup sample was small, thereby introducing a power problem to the analysis. This was evident as the range of the confidence interval increased compared to the confidence interval seen in the whole sample analysis [91]. Small power gives a risk of committing a Type II error, where a non-significant finding occurs even if there is a true difference between groups.

6.2 High-level mobility in chronic traumatic brain injury

This is the first investigation of the prevalence of high-level mobility problems in subjects with chronic moderate and severe TBI, compared to healthy controls, using HiMAT. Additionally, to my knowledge this is the largest case-control study investigating the difference in a range of high-level mobility skills in both sexes for this population.

Performance on the HiMAT was significantly poorer for cases than controls. This can easily be interpreted as a result purely due to neurological motor impairments after TBI. Both brain contusions and DAI were highly prevalent in our study sample, indicating that motor problems should be expected. However, the impact of these findings is unclear. Conflicting evidence exist concerning the association between DAI and motor outcome [30, 46, 59, 122]. Recent findings suggest that injuries to the brainstem impact negatively on outcome [45-47]. It is also plausible that other injury related factors can affect high-level mobility. Fractures and soft tissue injuries in the extremities are common in TBI, due to motor vehicle accidents and falls [123]. Additionally, complications like contractures [124, 125] can further impact negatively on advanced gross motor abilities. Unfortunately, information on other injury related factors were not available for this study. The study design is limited in that it cannot identify cause or etiology of motor problems. Further research is needed in order to determine the etiology of high-level mobility in chronic TBI.

Another potential cause of the difference in performance between groups is that cases are less confident in their motor skills than ablebodied controls. In support of this, it is noteworthy that a small practice effect of 1 point has been found in repeated measures for subjects with TBI [85], but not for healthy young adults [12]. Lack of confidence may also origin from minimal practise of high-level motor skills. McCulloch and colleagues [66] found that adding HiMAT to the assessment made several participants discover unknown high-level abilities. Participants had not been challenged on these skills neither in rehabilitation nor usual routines. This suggests that high-level mobility is underemphasized during the course of rehabilitation for moderate and severe TBI.

A statistical significant result does not equal a clinical important finding [91], therefore it is crucial that results are interpreted and discussed within theoretical, methodical and practical paradigms. The results found in this study both support and expand on the findings of previous research. Additionally, the findings of this study support the empirical knowledge of physiotherapists and other professionals in the field of TBI rehabilitation, thereby indicating that the statistical significance found in this study is clinically relevant.

7.0 Conclusion

This study has identified that high-level mobility problems are prevalent in more than 75% of chronic moderate and severe TBI patients. Additionally, a four times higher risk of having high-level motor problems was found in TBI subjects compared to healthy matched controls. Adjusted for activities, pain levels and use of medication the risk estimate was three times higher compared to controls. This study is the first to report the prevalence of high-level mobility problems in this population investigated with HiMAT, giving evidence based support to clinicians' empirical knowledge.

8.0 Further research

The chosen research design of this study cannot identify cause-effect relationships. Further research is needed to examine etiology of high-level motor problems in chronic moderate and severe TBI patients. Knowledge of factors impacting or causing problems with high-level mobility will aid clinical decision making and help guide rehabilitation efforts. It will also be of great interest to identify training programmes and treatment approaches best suited to improve high-level mobility in this population.

9.0 References

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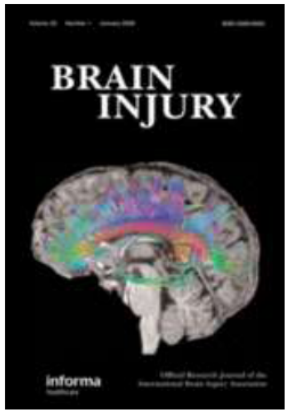
Appendix 1

Brain Injury

Instructions for Authors



Brain Injury publishes critical information relating to research and clinical practice, adult and pediatric populations. The Journal covers a full range of relevant topics relating to clinical, translational, and basic science research. Manuscripts address emergency and acute medical care, acute and post-acute rehabilitation, family and vocational issues, and long-term supports. Coverage includes assessment and interventions for functional, communication, neurological, and psychological disorders.

Manuscript Preparation

Authors should prepare and upload two versions of their manuscript. One should be a complete text, while in the second all document information identifying the author(s) should be removed from files to allow them to be sent anonymously to referees. When uploading files authors will then be able to define the non-anonymous version as "File not for review".

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General Guidelines

Please write clearly and concisely, stating your objectives clearly and defining your terms. Your arguments should be substantiated with well reasoned supporting evidence.

In writing your paper, you are encouraged to review articles in the area you are addressing which have been previously published in the Journal, and where you feel appropriate, to reference them. This will enhance context, coherence, and continuity for our readers.

For all manuscripts, gender-, race-, and creed-inclusive language is mandatory.

Use person-first language throughout the manuscript (i.e., persons with brain injury rather than brain injured persons).

Ethics of Experimentation: Contributors are required to follow the procedures in force in their countries which govern the ethics of work done with human subjects. The Code of Ethics of the World Medical Association (Declaration of Helsinki) represents a minimal requirement.

Abstracts are required for all papers submitted, they should not exceed 200 words and should precede the text of a paper. See below for further information.

Authors should include telephone and fax numbers as well as e-mail addresses on the cover page of manuscripts.

File preparation and types

Manuscripts are preferred in Microsoft Word format (.doc files). Documents must be double-spaced, with margins of one inch on all sides. Tables and figures should not appear in the main text, but should be uploaded as separate files and designated with the appropriate file type upon submission. References should be given in Council of Science Editors (CSE) Citation & Sequence format (see References section for examples).

Manuscripts should be compiled in the following order: title page; abstract; main text; acknowledgments; Declaration of Interest statement; appendices (as appropriate); references; tables with captions (on separate pages); figures; figure captions (as a list).

Title Page

A title page should be provided comprising the manuscript title plus the full names and affiliations of all authors involved in the preparation of the manuscript. One author should be clearly designated as the corresponding author and full contact information, including phone number and email address, provided for this person. Keywords that are not in the title should also be included on the title page. The keywords will assist indexers in cross indexing your article. The title page should be uploaded separately to the main manuscript and designated as “title page – not for review” on ScholarOne Manuscripts.

Abstract

Structured abstracts are required for all papers, and should be submitted as detailed below, following the title and author's name and address, preceding the main text.

For papers reporting original research, state the primary objective and any hypothesis tested; describe the research design and your reasons for adopting that methodology; state the methods and procedures employed, including where appropriate tools, hardware, software, the selection and number of study areas/subjects, and the central experimental interventions; state the main outcomes and results, including relevant data; and state the conclusions that might be drawn from these data and results, including their implications for further research or application/practice.

For review essays, state the primary objective of the review; the reasoning behind your literature selection; and the way you critically analyse the literature; state the main outcomes and results of your review; and state the conclusions that might be drawn, including their implications for further research or application/practice.

The abstract should not exceed 200 words.

Tables, figures and illustrations

The same data should not be reproduced in both tables and figures. The usual statistical conventions should be used: a value written 10.0 ± 0.25 indicates the estimate for a statistic (e.g. a mean) followed by its standard error. A mean with an estimate of the standard deviation will be written 10.0 SD 2.65. Contributors reporting ages of subjects should specify carefully the age groupings: a group of children of ages e.g. 4.0 to 4.99 years may be designated 4 +; a group aged 3.50 to 4.49 years 4 ± and a group all precisely 4.0 years, 4.0.

Tables and figures should be referred to in text as follows: figure 1, table 1, i.e. lower case. 'As seen in table [or figure] 1 ...' (not Tab., fig. or Fig).

The place at which a table or figure is to be inserted in the printed text should be indicated clearly on a manuscript:

Insert table 2 about here

Each table and/or figure must have a title that explains its purpose without reference to the text. Tables and/or figure captions must be saved separately, as part of the file containing the complete text of the paper, and numbered correspondingly. The filename for the tables and/or figures should be descriptive of the graphic, e.g. table 1, figure 2a.

Tables

Tables should be used only when they can present information more efficiently than running text. Care should be taken to avoid any arrangement that unduly increases the depth of a table, and the column heads should be made as brief as possible, using abbreviations liberally. Lines of data should not be numbered nor run numbers given unless those numbers are needed for reference in the text. Columns should not contain only one or two entries, nor should the same entry be repeated numerous times consecutively. Tables should be grouped at the end of the manuscript on uploaded separately to the main body of the text.

Figures and illustrations

Figures must be uploaded separately and not embedded in the text. Avoid the use of colour and tints for purely aesthetic reasons. Figures should be produced as near to the finished size as possible. Files should be saved as one of the following formats: TIFF (tagged image file format), PostScript or EPS (encapsulated PostScript), and should contain all the necessary font information and the source file of the application (e.g. CorelDraw/Mac, CorelDraw/PC). All files must be 300 dpi or higher.

Please note that it is in the author's interest to provide the highest quality figure format possible. Please do not hesitate to contact our Production Department if you have any queries.

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Letters to the Editor will be considered for publication subject to editor approval and provided that they either relate to content previously published in the Journal or address any item that is felt to be of interest to the readership. Letters relating to articles previously published in the Journal should be received no more than three months after publication of the original work. Pending editor approval, letters may be submitted to the author of the original paper in order that a reply be published simultaneously.

Letters to the Editor can be signed by a maximum of three authors, should be between 750 and 1,250 words, may contain one table/figure and may cite a maximum of five references. All Letters should be submitted via ScholarOne Manuscripts and should contain a Declaration of Interest statement.

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All authors are asked to take account of the diverse audience of ***Brain Injury***. Clearly explain or avoid the use of terms that might be meaningful only to a local or national audience.

Some specific points of style for the text of original papers, reviews, and case studies follow:

- ***Brain Injury*** prefers US to 'American', USA to 'United States', and UK to 'United Kingdom'.
- ***Brain Injury*** uses conservative British, not US, spelling, i.e. colour not color; behaviour (behavioural) not behavior; [school] programme not program; [he] practises not practices; centre not center; organization not organisation; analyse not analyze, etc.
- Single 'quotes' are used for quotations rather than double "quotes", unless the 'quote is "within" another quote'.

- Punctuation should follow the British style, e.g. 'quotes precede punctuation'.
- Punctuation of common abbreviations should follow the following conventions: e.g. i.e. cf. Note that such abbreviations are not followed by a comma or a (double) point/period.
- Dashes (M-dash) should be clearly indicated in manuscripts by way of either a clear dash (-) or a double hyphen (- -).
- ***Brain Injury*** is sparing in its use of the upper case in headings and references, e.g. only the first word in paper titles and all subheads is in upper case; titles of papers from journals in the references and other places are not in upper case.
- Apostrophes should be used sparingly. Thus, decades should be referred to as follows: 'The 1980s [not the 1980's] saw ...'. Possessives associated with acronyms (e.g. APU), should be written as follows: 'The APU's findings that ...', but, NB, the plural is APUs.
- All acronyms for national agencies, examinations, etc., should be spelled out the first time they are introduced in text or references. Thereafter the acronym can be used if appropriate, e.g. 'The work of the Assessment of Performance Unit (APU) in the early 1980s ...'. Subsequently, 'The APU studies of achievement ...', in a reference ... (Department of Education and Science [DES] 1989a).
- Brief biographical details of significant national figures should be outlined in the text unless it is quite clear that the person concerned would be known internationally. Some suggested editorial emendations to a typical text are indicated in the following with square brackets: 'From the time of H. E. Armstrong [in the 19th century] to the curriculum development work associated with the Nuffield Foundation [in the 1960s], there has been a shift from heurism to constructivism in the design of [British] science courses'.
- The preferred local (national) usage for ethnic and other minorities should be used in all papers. For the USA, African-American, Hispanic, and Native American are used, e.g. 'The African American presidential candidate, Jesse Jackson...' For the UK, African-Caribbean (not 'West Indian'), etc.
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- n (not N), % (not per cent) should be used in typescripts.
- Numbers in text should take the following forms: 300, 3000, 30 000. Spell out numbers under 10 unless used with a unit of measure, e.g. nine pupils but 9 mm (do not introduce periods with measure). For decimals, use the form 0.05 (not .05).

Acknowledgments and Declaration of Interest sections

Acknowledgments and Declaration of interest sections are different, and each has a specific purpose. The Acknowledgments section details special thanks, personal assistance, and dedications. Contributions from individuals who do not qualify for authorship should also be acknowledged here. Declarations of interest, however, refer to statements of financial support and/or statements of potential conflict of interest. Within this section also belongs disclosure of scientific writing assistance (use of an agency or agency/ freelance writer), grant support and numbers, and statements of employment, if applicable.

Acknowledgments section

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Declaration of Interest section

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Examples are provided as follows:

Journal article: [1] Steiner U, Klein J, Eiser E, Budkowski A, Fetters LJ. Complete wetting from polymer mixtures. Science 1992;258:1122-9.

Book chapter: [2] Kuret JA, Murad F. Adenohypophyseal hormones and related substances. In: Gilman AG, Rall TW, Nies AS, Taylor P, editors. The pharmacological basis of therapeutics. 8th ed. New York: Pergamon; 1990. p 1334-60.

Conference proceedings: [3] Irvin AD, Cunningham MP, Young AS, editors. Advances in the control of Theileriosis. International Conference held at the International Laboratory for Research on Animal Diseases; 1981 Feb 9-13; Nairobi. Boston: Martinus Nijhoff Publishers; 1981. 427 p.

Dissertations or Thesis: [4] Mangie ED. A comparative study of the perceptions of illness in New Kingdom Egypt and Mesopotamia of the early first millennium [dissertation]. Akron (OH): University of Akron; 1991. 160 p. Available from: University Microfilms, Ann Arbor MI; AAG9203425.

Journal article on internet: [5] De Guise E, Leblanc J, Dagher J, Lamoureux J, Jishi A, Maleki M, Marcoux J, Feyz M. 2009. Early outcome in patients with traumatic brain injury, pre-injury alcohol abuse and intoxication at time of injury. Brain Injury 23(11):853-865. http://www.informaworld.com/10.1080/02699050903283221. Accessed 2009 Oct 06

Webpage: [6] British Medical Journal [Internet]. Stanford, CA: Stanford Univ; 2004 July 10 - [cited 2004 Aug 12]; Available from: http://bmj.bmjjournals.com

Internet databases: [7] Prevention News Update Database [Internet]. Rockville (MD): Centers for Disease Control and Prevention (US), National Prevention Information Network. 1988 Jun - [cited 2001 Apr 12]. Available from: http://www.cdcnpin.org/

Appendix 2

SPØRSMÅL HENTET FRA SELV-RAPPORT FOR VOKSNE I ALDEREN 18-59 ÅR

(Achenbach System of Empirically Based Assessment – Adult self-report)

FULLFØRT UTDANNELSE

☐ 1. Barneskole (1.-7. klasse)

☐ 2. Ungdomsskole (8.-10. klasse)

☐ 3. Videregående skole, allmennfaglig (gymnas)

☐ 4. Videregående skole, yrkesfaglig (yrkesskole)

☐ 5. Fagopplæring innen håndverk, industri, landbruk e.l.

☐ 6. 3-årig høyskole (lærer, sykepleier, distriktshøyskole e.l.)

☐ 7. Universitet eller annen langvarig utdannelse, lavere grad

☐ 8. Hovedfag/mastergrad

☐ 9. Doktorgrad eller embetsstudie

☐ 10. Annet (beskriv) …….

EKTEFELLE ELLER SAMBOER

☐ Aldri vært gift/samboer ☐ Separert

☐ Gift/samboer ☐ Skilt

☐ Enke/enkemann ☐ Annet (vennligst beskriv) …….

ARBEID

Har du hatt betalt arbeid i løpet av de siste 6 månedene? (Ta også med virksomhet som selvstendig næringsdrivende og militærtjeneste)

☐ Nei

☐ Ja – beskriv hvilke(n) jobb(er) du har hatt: …….

UTDANNELSE

Har du vært under utdannelse i løpet av de siste 6 månedene?

☐ Nei

☐ Ja – angi type utdanning: …….

Hvilken eksamen eller grad tar du sikte på? …… Hovedfag? ……

Når venter du å være ferdig? ……

Appendix 3

Generelt skjema	Dato:
	Id. nr:

Navn: _____

Fødselsdato: _____

Høyde: _____ **Vekt:** _____ **Hodeomkrets:** _____

Trener du? **JA** **NEI**

Evt. hva? _____

Hvor ofte? (pr. uke) _____

Hvor lenge? (pr. gang) _____

Har du alltid trent like mye/lite?

_____

Er du/har du vært syk i det siste som du tror vil påvirke din fysiske prestasjon:

_____

Evt. medikamenter: _____

Har du skader i det siste som du tror vil påvirke din fysiske prestasjon:

Hvor: _____

Skadetidspunkt: _____

Smerter (VAS):

0 _____ 10

Appendix 4

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.

HiMAT er oversatt til norsk av Kine Therese Moen og Ingerid Kleffelgård.
For spørsmål, kommentarer og informasjon kontakt: kine.therese.moen@gmail.com eller ingerid.kleffelgard@ulleval.no

Meld fra til Gavin Williams på e-postadressen gavin@neuro-solutions.net eller gavin.williams@epworth.org.au slik at bruken av HiMAT kan spores.

Appendix 5

Det medisinske fakultet
Institutt for sirkulasjon og bildediagnostikk

FORESPØRSEL OM Å DELTA I VITENSKAPELIG UNDERSØKELSE:

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Den nye studien skal undersøke om nye og mer avanserte MR- og EEG-metoder kan finne ut mer om årsakene til problemer som personer kan få etter hodeskade. Slik håper vi å finne ut hvordan vi best kan hjelpe pasienter i framtiden. Dette delprosjektet ledes av lege og førsteamanuensis Asta Håberg.

Sammen med resultat fra de tidligere undersøkelsene vil denne studien kunne gi ny kunnskap om hodeskader. Din deltakelse vil være særdeles verdifull. Gjennom å delta vil du være med på å gi et viktig bidrag til viten om hodeskader.

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Med vennlig hilsen

Alexander Olsen
Institutt for sirkulasjon og bildediagnostikk, NTNU.
E-post alexander.olsen@ntnu.no
Telefon: 90259147

Asta Håberg
Institutt for sirkulasjon og bildediagnostikk, NTNU.
E-post: asta.haberg@ntnu.no
Telefon: 91722824

Toril Skandsen
Munkvoll rehabiliteringssenter, St. Olavs Hospital/Institutt for nevromedisin, NTNU.
E-post: toril.skandsen@ntnu.no
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1. Bakgrunn og målsetting for studien
Vi ønsker å finne ut om nye MR- og EEG-metoder kan bidra til klinisk nyttig informasjon hos pasienter med hodeskader. Dette vil i neste omgang kunne føre til bedre diagnostisering og dermed bedre behandling og rehabilitering av hodeskadde. Vi vil for eksempel kunne studere årsakene til oppmerksomhetsproblemer. Vi vil også kunne analysere hvilke av de aktuelle metodene som best kartlegger omfanget av hodeskader, og eventuelt kan forutsi grad av problemer i dagliglivet som pasienter kan ha etter hodeskade.

2. Hva er MR?
Vi vil i denne studien bruke følgende MR-metoder: 1. Funksjonell MRI (fMRI) er en metode som kan vise de ulike hjerneområdene som en person bruker for å gjøre en oppgave. 2. Diffusjon tensor bildedannelse (DTI) er en MR-metode som avdekker endringer i strukturen av hjernebanene, d.v.s. de nervetrådene som binder ulike områder av hjernen sammen. Ved å kombinere fMRI og DTI kan man finne ut hvordan hjernecellene bearbeider informasjon. Man kan også studere hvordan forbindelsene mellom de ulike hjerneområdene som skal samarbeide fungerer.

3. Hva er EEG?
EEG er en metode som måler hjernecellenes elektriske aktivitet ved hjelp av elektroder festet til hodebunnen.

4. Hvilke undersøkelser skal gjøres?
EEG og MR- undersøkelsene tar ca. 60 minutter hver, og vil foregå på Nevrosenteret (Nevro Vest), St. Olavs Hospital. I tillegg vil du samme dag fylle ut noen spørreskjema sammen med en av forskerne, og gjennomføre noen tester av håndfunksjon. Vi er opptatt av at hver enkelt får gjort det så godt som mulig på oppgavene. Det vil derfor bli flere pauser underveis. Det er planlagt en lengre pause mellom MR og EEG- delen slik at du får mulighet til å slappe av. Du må derfor sette av mye av dagen for å delta på testingen.

EEG
Før eksperimentet begynner vil du få påsatt en hette med elektroder på hodet. Prosjektmedarbeideren vil sørge for god kontakt mellom elektrodene og hodebunnen din ved å sprøyte inn en ufarlig gelé mellom den spesiallagede hetten og hodebunnen. Dette er viktig for å kunne måle hjerneaktiviteten på best mulig måte og tar ca. 5-10 minutter. Under eksperimentet får du få ulike oppgaver som du skal svare på ved å trykke inn bestemte knapper. Du vil også bli bedt om å sitte helt i ro og slappe av. Undersøkelsen varer i ca 60 minutter.

MR undersøkelsen
Du blir lagt på et bord som skyves et stykke inn i MR-maskinen. Maskinen er en slags tunnel som er åpen i begge ender. Under eksperimentet får du se bokstaver som du skal svare på ved å

trykke inn en knapp. Vi vil også ta noen MR-bilder der du skal ligge helt i ro og slappe av. Eksperimentet varer i ca 60 minutter.

Spørreskjema
Spørreskjemaene skal gi oss informasjon om din kognitive funksjon, livskvalitet og psykiske helse. Spørsmålene består for eksempel av en liste med en rekke vanlige plager og problemer som alle av og til har, og du skal krysse av for hva som passer best for deg. Vi legger også vekt på hvordan de nærmeste vurderer situasjonen etter skaden. Derfor vil vi også be deg om tillatelse om å spørre en av dine nærmeste pårørende om å fylle ut spørreskjema som handler om din kognitive funksjon og psykiske helse. Dersom du ikke ønsker at vi kontakter dine pårørende kan du allikevel delta i studien (se alternativ på siste side i dette dokumentet).

Undersøkelse av motorisk funksjon
Denne undersøkelsen vil kartlegge motorisk funksjon, som tempo og koordinasjon i finmotoriske oppgaver samt grovmotoriske oppgaver, som blant annet balanse. Undersøkelsen varer i ca 30-40 min.

6. Hvem kan delta?
Forsøkspersonene er kvinner og menn i alderen 16-65 år. Forsøkspersonene rekrutteres fra "Hodeskadeprosjektet" ved NTNU/St. Olavs Hospital. Både pasienter og de som deltar i kontrollgruppen inviteres til å delta. Deltagelse er ikke mulig dersom du er gravid eller har metalliske fremmedlegemer i kroppen (f.eks. pacemaker, metallsplinter, innoperert metall i hjernen eller indre øret).

6. Risiko/ubehag
Det er ingen kjent risiko knyttet til bruken av MR. Det er imidlertid noe støy fra maskinen under bildeopptakene. Det er heller ingen kjent risiko knyttet til bruken av EEG.

7. Hva skjer dersom vi finner noe uvanlig på MR-bildene eller EEG-opptakene?
EEG-opptakene og MR-bildene vil ikke granskes spesielt for å avdekke annen sykdom Det *kan* likevel forekomme at vi finner tegn på ny sykdom. Hvis vi finner slike endringer, vil du bli henvist av prosjekt- ansvarlig til oppfølging ved St. Olavs Hospital.

8. Frivillighet
Du oppfordres til å delta i forskningsstudien, men du må huske at dette er frivillig og at du kan trekke tilbake ditt samtykke på et hvilket som helst tidspunkt uten å måtte begrunne dette nærmere.

9. Tidsramme
Undersøkelsen vil gjennomføres i løpet av 2009-2010.

10. Databehandling og taushetsplikt
Alle data vil bli behandlet konfidensielt og alle som behandler data er underlagt taushetsplikt i henhold til Forvaltningsloven §13 og Helsepersonellslovens §21. Dataene blir anonymisert og skal kun brukes i forskningsøyemed. Alle data vil bli oppbevart på en betryggende måte i 10 år (jf. Nylenna utvalget).

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Prosjektet omfattes av Norsk pasientskadeerstatning.

12. Økonomi
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13. Etisk vurdering
Prosjektet er godkjent av Regional komité for medisinsk forskningsetikk og meldt til Personvernombudet for forskning, Norsk samfunnsvitenskapelig datatjeneste A/S.

SAMTYKKEERKLÆRING

Navn:_____

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Kontaktopplysninger for aktuelle pårørende:

Navn:

Adresse:

Telefonnummer:

E-post:

Mine kontaktopplysninger:

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Dato:_____

Underskrift:_____

Appendix 6

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Fødselsdato:_____

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Telefonnummer:

E-post:

Dato:_____

Underskrift:_____

10. Paper

High-level mobility in chronic traumatic brain injury – a case-control study.

Kine Therese Moen

Stiftelsen CatoSenteret, Department of Medical Rehabilitation Services,
Son, Norway

Corresponding author: Kine Therese Moen, Stiftelsen CatoSenteret, Department of Medical Rehabilitation Services, Son, Norway.
E-mail: kine.therese.moen@catosenteret.no

Abstract

Objective: To investigate the prevalence of high-level mobility problems in subjects with chronic moderate and severe traumatic brain injury (TBI) compared to healthy controls.
Design: Case-control study.
Main Outcome Measure: High-level mobility assessment tool (HiMAT).
Methods: A total of 69 subjects with chronic TBI (age 16-65 years) were recruited from a cohort of moderate and severe TBI patients from Mid-Norway. Patients were admitted to hospital between October 2004 and July 2008. Additionally, 76 age, sex and education matched controls were recruited from the same geographic region. Inclusion and testing took place from May 2009 to September 2010.
Results: Subjects with chronic TBI had significantly lower mean HiMAT scores (42.5 points; 95% CI: 39.9-45.1) than controls (47.4 points; 95% CI: 45.4-49.3). The 5th percentile based on normative scores for adults aged 18-25 years was used to indicate high-level mobility problems. The TBI group had a fourfold increased risk of having high-level mobility problems compared with controls (OR: 4.1; 95% CI: 2.0-8.5). Adjusting for exercise activities, pain and medication reduced the odds to 3.1 (95% CI: 1.4-6.8).
Conclusions: High-level mobility problems are highly prevalent in subjects with chronic moderate and severe TBI.

Keywords: *High-level mobility, high-level mobility assessment tool, traumatic brain injury*

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Introduction

High-level mobility depicts gross motor abilities important for everyday life and leisure activities, like running, jumping, hopping, and walking over obstacles [1]. Traumatic brain injury (TBI) can entail motor, psychiatric, behavioural or cognitive problems even in the chronic phase [2-4], defined as more than one year post injury [5]. Problems in any of these areas can affect quality of life and participation in social activities, sports, studies or work [3, 6]. Traditionally, main goals of physical therapy and rehabilitation have focused on acquiring independence in gait and daily activities [7, 8]. However, in the chronic phase aims often shift towards resuming vocational and leisure activities. High-level mobility can be essential in obtaining these goals [8-10].

Traumatic brain injuries are costly on society. A current estimate of the total European annual incidence of TBI is 235 cases pr 100 000 population, including non-hospitalized subjects [11]. A recent Norwegian study found an annual incidence of 83 hospitalized TBI patients pr 100 000 inhabitants in Oslo [12]. In year 2000 total costs of dead, hospitalized and medically treated TBI in the USA was estimated to 60.4 billion dollars. Loss of productivity alone cost 51.2 billion dollars [13].

Several studies report good motor recovery in the chronic phase after TBI [4, 8, 14-16]. The majority has used outcome measures with high degree of ceiling effects, too insensitive to measure high-level mobility. The ability to conduct advanced gross motor skills after TBI is not well established as few studies have focused on high-level mobility in chronic TBI [10, 17-21]. Studies have investigated small sample sizes. Only one study have compared chronic male TBI patients to controls [18]. Findings included reduced gait speed, as well as significantly lower balance, coordination, agility and rhythmical skills in men with chronic TBI compared to healthy controls [18].

High-level Mobility Assessment Tool (HiMAT) is currently the best tool to quantify high-level mobility after TBI [10, 22]. Normative values for healthy young adults have been presented for HiMAT, as well as sex specific 5^{th} percentile scores [23]. To our knowledge there are no published studies comparing high-level mobility, measured with

HiMAT, in subjects with moderate and severe chronic TBI to healthy sex, age and education matched controls.

The aim of this study was to investigate the prevalence of high-level mobility problems in persons with chronic moderate and severe traumatic brain injury compared to healthy controls.

Materials and methods

Participants

The current study reports findings from a large follow-up study using advanced MRI for diagnosis and outcome assessment in TBI patients. All patients with moderate and severe TBI based on Head Injury Severity Scale (HISS) criteria [24], admitted to the department of Neurosurgery at St.Olavs Hospital, Trondheim University Hospital, Norway, in the period of October 2004 to August 2008, were asked to participate in a database. During this period, 231 patients were included in the database. The only exclusion criteria for this database were being deemed clinically unsalvageable on admission or death due to other injuries during the initial 24 hours after injury [25]. St.Olavs Hospital is the only centralized level 1 trauma centre in the Mid-Norway health authority, a health region with approximately 660 000 inhabitants. The database thus consists of a representative cohort of moderate and severe TBI patients in this region.

TBI group

Subjects from the above-mentioned database were contacted by phone if they were more than one year post-injury and fulfilled the inclusion criteria for the follow-up study: Between 16 and 65 years old, no prior psychiatric or neurological illnesses, fluent in oral and written Norwegian, and able to cooperate during functional magnetic resonance imaging (fMRI) defined as Glascow Outcome Score Extended (GOSE) ≥5.

Of the 231 patients in the database, 50 died before follow up, 33 were above or below the given age limit and 28 patients had premorbid illness. Three patients were not fluent in

Norwegian and 10 had GOSE scores <5. This left 107 participants eligible for this study, whereof 38 did not consent to participation. Hence, 69 participants were included. Participants were assessed at hospital admission and at follow-up in the period of May 2009 to September 2010. Two subjects could not perform the HiMAT, and were therefore excluded from analysis. One of these was wheelchair dependant and not eligible for the HiMAT, and the other refrained from testing due to headache. This left 67 subjects available for analysis.

Control group

Participants in the control group were from the Mid-Norway region, and chosen through a strategic sampling from the patients' families and social networks, hospital employees and recruitment through advertisement at different workplaces in Trondheim, in order to match on sex, age and education. The control group fulfilled the same inclusion criteria as the TBI group, but ability to cooperate on functional magnetic resonance imaging was determined as the ability to give an informed consent. Controls were examined during the same time period as the follow-up of the TBI group. Three subjects were unable to complete the HiMAT and excluded from analysis. One subject injured a thigh muscle during testing. Additionally, time constraints due to unforeseen external factors hindered two subjects from completion of testing. This left 73 subjects available for analysis in the control group.

Non-participants

The subjects with TBI who did not consent to participation were significantly older at time of injury than those who did agree to partake in the study. Mean age was 38.0 (SD 21.9) years for non-participants and 28.6 (SD 13.9) years for all included participants ($p=0.02$). There were no significant differences in injury mechanisms, Glascow Coma Scale (GCS) score, duration of post traumatic amnesia (PTA), location of diffuse axonal injury (DAI), presence of DAI, presence of focal injury, bilateral brain stem injury or GOSE score at 12 months post injury between participants and non-participants ($p \geq 0.3$).

Background characteristics

Participants were matched on sex, age and education. Information on marital status, current physical activity levels, illness, injury, pain or use of medication was collected through interview. Being physically active was defined as committing planned, structured, repetitive exercise aiming to improve or maintain physical fitness [26]. Body mass index (kg/m^2) was calculated from self-reported height and weight was measured to the nearest 10 g.

Injury specific variables

Cause of injury and age were registered at hospital admission. GCS [27] was examined at or after hospital admission, or before intubation during prehospital intubation. The GCS ranges from 3-15 points, and scores were categorized into mild (15-13), moderate (9-12) and severe TBI (3-8 points). Length of stay in acute hospital and duration of post traumatic amnesia were also registered. PTA was dichotomized into short and long PTA, with long PTA defined as more than seven days [13]. MRI scans were conducted within 4 weeks of admittance, identifying presence or absence of DAI, contusions and bilateral brain stem injury.

High-level mobility

High-level mobility was examined in both groups using HiMAT [28]. This is an ordinal scale, consisting of 13 items examining a variety of walking skills including negotiating stairs, running, skipping, hopping and bounding [1, 28]. Item scores are summed to a total of 54 points, with higher scores indicating better motor function [28]. Participants were tested on their best leg on items examining the least affected side. If uncertain the leg chosen to perform a single leg stance was identified as best. The test requires a 14 step staircase. This was unavailable at the testing site, and participants were tested in a 12 step staircase. Measured time x 14/12 was used to calculate time on the stair items. Performances at or below the normative 5^{th} percentile scores given by Williams and colleagues [23], were chosen to signify problems with high-level mobility.

A revised version of the HiMAT was developed in 2010 [29]. Application of a new rasch analysis on the original material identified that the stair items added heterogeneity to the

test. Removal of these and one bound item secured a unidimensional test consisting of eight items, with maximum total score of 32 points.

Examiners

Interviews and assessments were performed by three different examiners (two physiotherapists, one bachelor of sports). The examiners were not informed of participants' group assignment.

Statistical analysis

Data analyses were performed using IBM SPSS 19.0. A two sided p-value <0.05 was considered statistical significant. Differences between groups on parametric data were analysed with student's t-test for independent groups. Mann-Whitney U test was used for non-parametric data or data not normally distributed. Chi-square test was used to examine differences in proportions. Correlation analyses between background variables and group and/or outcome were performed using Spearman rho (r_s).

We calculated the odds ratios (OR) for high-level mobility problems by use of logistic regression analysis with adjustments for potential confounders. Variables correlated with outcome measure and/or group were included in the model one by one. If the variable changed the OR by >10%, it was considered as a potential confounder for the relationship and included in the full model. A subgroup analysis was performed for those aged ≤ 25 years, as this age group is comparable to the sample from which the normative scores of Williams and colleagues were derived from [23].

Ethics

This study is part of a large project approved by the Regional Committee for Medical Research Ethics in Mid-Norway. Written and oral informed consent was given by all participants.

Results

Background characteristics of both groups are presented in table 1. The male:female ratio was 2.7:1 in the TBI group and 3.3:1 in the control group. The only significant difference between groups was that participants in the control group engaged in more exercise activities than participants in the TBI group. There were no significant differences on the matched variables age (p=0.21), sex (p=0.63) and education (p=0.74), indicating that matching was successful, even after exclusion of five participants. Marital status, presence of resent illness or injury, use of medication and being defined as physically active did not differ between groups either (data not shown).

Mean age at injury was 29.2 (SD 13.9) years (range 13.1-63.3). Mean time since injury was 2.83 (SD 1.0) years (range 1.5-5.4) and mean length of hospital stay was 12.7 (SD 13.5) days (range 1-93). Motor vehicle accidents and falls were the most common causes of TBI. Injury specific variables for the TBI subjects are presented in table 2. The majority (53.1%) had short PTA (≤ seven days). Scores on GCS ranged from 3 to 14 points, and 50 (74.6%) subjects were defined as moderate or severe TBI with GCS. MRI showed DAI in 47 (72.3%) of cases and focal injuries to the cerebral cortex were present in 45 (68.5%). Bilateral brain stem injuries were present in four subjects (6.2%).

HiMAT item scores and total scores are presented in table 3. Mean total score was higher in the control group than the TBI group (p=0.001). Ten item scores differed significantly between the groups (table 3). Only one of the stair items was significantly different between the groups, this was the 'walking down stairs independent' item (p=0.04). Calculation of the revised eight-item HiMAT scores showed a mean total score in the TBI group of 24.1 points (95% CI: 22.3-25.9) compared to 27.9 points (95% CI: 26.6-29.2) in the control group (p<0.001).

A total of 51 (76.1%) subjects in the TBI group performed ≤ 5th percentile of normative HiMAT scores, compared to 32 (43.8%) controls (p<0.001). The odds of performing ≤ 5th percentile were four times higher in the TBI group compared to the control group (table 4). Two variables correlated with both group and outcome: 'Number of exercise

activities '(r_s= 0.29 for HiMAT and r_s= -0.19 for group) and 'pain ' (r_s= -0.22 for HiMAT and r_s= 0.20 for group). Additionally, 'use of medication ' correlated with HiMAT (r_s= -0.28). Engaging in more activities, less pain and medications were associated with higher HiMAT scores. Adjusting for 'number of exercise activities ' reduced the OR (table 4). Including 'pain ' and 'use of medication ' in the logistic regression model slightly reduced the risk estimate further (table 4).

A subgroup analysis was performed on participants ranging from 16-25 years of age. This subgroup consisted of 54 participants, 29 TBI subjects and 25 controls. Mean total HiMAT scores were 47.2 (95% CI 44.5-49.9) in the TBI group compared to 51.2 (95% CI 49.9-52.5) in the control group (p=0.01). Seventeen (58.6%) TBI participants performed within the 5th percentile compared to six (24.0%) controls. The TBI subgroup had 4.5 times higher risk of performing ≤ 5th percentile on HiMAT compared to the control subgroup (table 4). Adjustment for potential confounders reduced the OR slightly (table 4).

Discussion

The present study shows that the control group performed better than the TBI group on all items on the HiMAT apart from the stair items. Calculation of the revised eight-item HiMAT score, where stair items and bound on the most affected leg are removed, did not alter the results. We also showed that persons with moderate and severe TBI have a fourfold higher risk of high-level mobility problems compared to controls.

This is the first study to investigate the prevalence of high-level mobility problems in subjects with chronic moderate and severe TBI compared to healthy controls using HiMAT. Also, to our knowledge this is the largest case-control study investigating the difference in a range of high-level mobility skills for both sexes in this population.
In contrast to most publications on TBI, we have used HISS criteria to define moderate and severe injury. HISS is the recommended severity score in Scandinavia [30]. Patients scoring 13 points on the GCS display findings more associated with the moderate group

than patients with higher scores, which has been integrated in HISS criteria [30, 31]. Additional strengths to this study are blinding of examiners to group assignment and good attendance levels. Of eligible patients from the cohort 64.5% consented to participation.

Blinding of examiners reduce the risk of information bias [32]. But the possibility of examiners being able to identify cases based on clinical experience can not be excluded. However, as the item measures are objective measures of time and length, we consider chances for information bias slim.

Non-participants were significantly older than participants. This could bias the results as older age is associated with lower gait speed and balance [33]. If this were the case, our result would underestimate the prevalence of high-level mobility problems. However, as age was a matching criterion, this should not affect the results.

Strategic sampling of controls was necessary to meet matching criteria, but could also lead to bias. Use of friends and family as controls can cause overmatching, as they may be too similar to cases on other important variables than those controlled for, thereby reducing the OR [32]. To reduce this risk we also recruited controls from other sources.

This study showed highly significant differences between groups. Therefore, it is unlikely that results are due to chance, i.e. does not reflect true differences between cases and controls [34]. Given the tendency of the biases to reduce the difference between groups, if any bias were to remain in our data despite our efforts to control for them, the OR should be even larger than what we found in this study.

Results were similar comparing cases and controls both on the original and the revised HiMAT. This suggests that the two versions are alike in discrimination between high and low levels of advanced mobility. The revised version takes less time to complete and does not require a staircase, making it more available to various clinical settings. Unfortunately, there are currently no normative scores developed for the revised version, making scores less available for interpretation.

We used the normative 5th percentile HiMAT scores given by Williams and colleagues [23] as the cut-off limit for high-level mobility problems. This cut-off may seem arbitrary. However, it is of great clinical value to be able to identify those who perform the worst. This is a known procedure in norm-referenced gross motor tests used in children and adolescents [35, 36]. Normative scores for additional age groups are warranted as this might help clinicians decide level of treatment goals, potential and need for rehabilitation. Further research is needed to investigate whether the 5th percentile is the best cut-off to identify problems with high-level mobility.

It is noteworthy that norm values were derived from university students recruited from physiotherapy, occupational therapy and rehabilitation studies [23]. The normative scores may thus be well optimistic as higher education is correlated with higher levels of physical activity [37-39]. Also, people choosing this type of education may have a healthier lifestyle. This could potentially underestimate the performance of participants in this study, resulting in larger estimates of problems with high-level mobility than reality. However, the OR between groups would most likely be unaffected.

It is important to recognize that HiMAT discriminates between sex as well as age. Normative sex specific values exist for the age band 18-25 years, enabling clinically valuable comparisons between subjects with TBI and controls. Using the norm values can downgrade the performance of older participants, as motor function declines with increasing age [40]. This will in turn affect the risk estimate by increasing the OR. We ran a subgroup analysis to investigate if results differed when analysing age appropriate subjects to the norm scores. The OR was essentially the same as for the entire sample in total, identified by overlapping confidence intervals. This suggests that use of the normative scores was not a major problem in our study. Notwithstanding, sex specific normative values for additional age bands would improve the external validity of comparisons.

Number of exercise activities was identified as one potential confounder in this study. Engaging in multiple exercise activities suggests an active lifestyle, increasing the

likelihood of being challenged on high-level mobility skills, thereby improving proficiency. However, it is possible that number of activities is not a confounder, but merely a result of having better high-level mobility. Controlling for those who were most active reduced the OR, but the risk estimate was still significant. Pain and use of medication were also included in the logistic regression model as these variables were associated with HiMAT. Chronic pain is present in the majority of the TBI population, but is more prevalent in mild TBI [41, 42]. Pain can influence high-level mobility as it is associated with reduced muscle strength [43] and fear avoidance behaviour [44, 45]. Medications can both enable and hamper physical activity. However, neither pain nor use of medication differed significantly between groups, and may therefore not be considered confounders of the association between group and outcome in this study.

All correlations with both group and outcome were weak, suggesting low clinical value. However, for very complex phenomena a low correlation may be of clinical importance as a piece of the puzzle for understanding the phenomenon [46]. This may potentially be the case when investigating high-level mobility, as it is unlikely that one or two variables are able to provide a complete understanding of the concept. Further research is needed to investigate if those variables found in this study truly are related to problems with high-level mobility.

Performance on the HiMAT was significantly poorer for cases than controls in this study. This can easily be interpreted as a result purely due to neurological motor impairments after TBI. However, additional injury related factors can affect high-level mobility. Fractures and soft-tissue injuries of the extremities are common, as injury mechanisms most often are motor vehicle accidents and falls [47]. Such injuries can also lead to contractures [48, 49], further impacting negatively on advanced gross motor abilities. Unfortunately, such information was not available to this study. Further research is needed to determine the impact of additional injuries to TBI on high-level mobility.

It is difficult to compare our results to previous findings, since this is the first study to investigate high-level mobility using HiMAT in chronic TBI compared to controls. A few studies have presented HiMAT results from chronic TBI group samples. McCulloch and

colleagues [20] investigated high-level performance related to balance, attention and multitasking in 24 subjects with chronic TBI. They presented a mean HiMAT score of 20.3 points, whereas we found a mean score of 42.5 points. Participants were older and tested at longer time since injury than our sample. Severity of brain injury was unaccounted for, and subjects were recruited from inpatient rehabilitation and a care facility. This implies that samples may not be comparable. Williams and Morris [10] investigated the effect of a three month exercise programme aiming to increase high-level mobility in a sample of 16 subjects with TBI, similar to ours in age and chronicity. Initial mean HiMAT score was 19.9 points, increasing to 27.8 points at follow-up. Even with significant improvement after following an exercise programme these participants performed at lower levels than our findings. Williams and colleagues have also used HiMAT in studies investigating gait in chronic TBI [50, 51]. Mean HiMAT scores are similar to the other studies; 22.7 [50] and 21.2 points [51]. In the three latter studies, the majority of participants had PTA lasting > 28 days, suggesting higher injury severity than our sample.

A Finnish case-control study investigated clinically well-recovered men with TBI. They found that gait speed, coordination, balance and agility were reduced compared to controls [18]. These qualities are all prerequisites for advanced gross motor skills. However, as this study did not use HiMAT, had a small sample size and only investigated young men, comparability of findings is limited.

This study is the largest case-control study to date investigating a range of high-level mobility skills, and the first to present a representative range of HiMAT scores in this population. Our results suggest better high-level mobility in chronic moderate and severe TBI than previous findings. However, comparability is low as inclusion and diagnostic criteria differ widely between studies.

Conclusion

Persons with chronic moderate and severe TBI have a fourfold increased risk of having problems with high-level mobility compared to healthy controls. Increased risk was evident also after controlling for exercise activities, pain and medication. With this study we have confirmed clinical knowledge and the findings of previous studies, indicating that high-level mobility is problematic for the vast majority of subjects with chronic TBI. The HiMAT is currently the best measure of high-level mobility in the TBI population. However, normative reference scores are needed for additional age bands in order to produce valid comparisons for people older than 25 years.

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Table 1. Background characteristics of the traumatic brain injury (TBI) group and the control group.

Variable	**n**	**TBI (n=67)**		**Control (n=73)**		***p***
		Mean	(SD)	Mean	(SD)	
Age (years)	140	32.1	(13.8)	35.0	(14.1)	0.21
Education (years)	140	12.0	(2.2)	12.1	(2.1)	0.74
Height (cm)	138	178.7	(9.0)	179.2	(7.9)	0.72
Weight (kg)	138	79.7	(15.3)	83.3	(13.5)	0.15
Body mass index (kg/m^2)	137	24.8	(3.7)	25.9	(4.0)	0.09
Current pain (visual analogue scale, cm)	139	1.2	(2.0)	0.7	(1.8)	0.14
Exercise (times pr week)	139	2.6	(2.8)	2.9	(2.8)	0.43
Exercise length pr time (min)	136	57.9	(64.6)	68.6	(53.9)	0.24
Exercise activities (number)	139	1.3	(1.2)	1.8	(1.4)	0.03

Table 2. Injury specific characteristics of the traumatic brain injury group.

Variable	Value	n (%)
Duration of post traumatic amnesia (n=64)	Long (>7 days)	30 (46.9)
Glascow Coma Scale category (n=67)	Mild (13-15 points)	17 (25.4)
	Moderate (9-12 points)	21 (31.3)
	Severe (3-8 points)	29 (43.3)
Injury mechanism (n=67)	Motor vehicle accident	32 (47.8)
	Falls	26 (38.8)
	Other	9 (13.4)
Diffuse axonal injury (DAI) (n=65)	DAI only	16 (24.6)
	DAI + other	31 (47.7)
Contusions (n=65)	Unilateral	17 (25.4)
	Bilateral	28 (43.1)
Bilateral brain stem injury (n=65)	Yes	4 (6.2)

Table 3. Mean item and total points with 95% confidence intervals (95% CI) on High level Mobility Assessment Tool (HiMAT) for the traumatic brain injury (TBI) group and the control group.

Items	**TBI (n=67)**		**Control (n=73)**		
	Mean points	(95% CI)	Mean points	(95% CI)	***p***
Walk	3.4	(3.2-3.6)	3.7	(3.6-3.8)	<0.01
Walk backwards	3.6	(3.4-3.7)	3.8	(3.7-3.9)	<0.01
Walk on toes	3.4	(3.2-3.6)	3.8	(3.7-3.9)	<0.01
Walk over obstacle	3.2	(3.0-3.4)	3.6	(3.5-3.8)	<0.01
Run	2.5	(2.2-2.8)	3.1	(2.9-3.4)	<0.01
Skip	2.3	(2.0-2.7)	2.9	(2.6-3.3)	0.02
Hop forward (most affected/non-dominant leg)	2.7	(2.3-3.0)	3.3	(3.0-3.5)	<0.01
Bound (most affected/non-dominant leg)	3.0	(2.6-3.4)	3.5	(3.3-3.8)	0.02
Bound (least affected/dominant leg)	3.1	(2.7-3.4)	3.6	(3.4-3.9)	<0.01
Up stairs dependent	4.8	(4.7-5.0)	4.8	(4.7-5.0)	0.95
Up stairs independent	3.0	(2.6-3.3)	3.0	(2.7-3.3)	0.72
Down stairs dependent	4.8	(4.6-4.9)	4.9	(4.7-5.0)	0.16
Down stairs independent	2.8	(2.5-3.2)	3.3	(3.0-3.6)	0.04
Total HiMAT score	**42.5**	**(39.9-45.1)**	**47.4**	**(45.4-49.3)**	**<0.01**

Table 4. Odds ratio (OR) for high-level mobility problems in the traumatic brain injury (TBI) group compared to the control group, and a subgroup analysis of participants ≤ 25 years old.

	≤ 5th percentile (n)	**Crude OR** (95% CI)	**Adjusted OR*** (95% CI)	**Adjusted OR**** (95% CI)
All participants:				
Control n = 73	32	1.0	1.0	1.0
TBI n = 67	52	4.1 (2.0 to 8.5)	3.5 (1.6 to 7.6)	3.1 (1.4 to 6.8)
Participants ≤ 25 years:				
Control n = 25	6	1.0	1.0	1.0
TBI n = 29	18	4.5 (1.4 to 14.6)	3.6 (1.1 to 12.3)	3.3 (1.0 to 11.5)

CI = Confidence interval.

* adjusted for no. exercise activities. ** adjusted for no. exercise activities, pain and use of medication