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NEW NEUROPHYSIOLOGICAL AND IMAGING METHODS FOR DETECTION OF MICROSTRUCTURAL CHANGES IN MILD TRAUMATIC BRAIN INJURY

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ABSTRACT

Mild traumatic brain injury is a very common health problem. Although outcome is generally good, a significant proportion of patients have persistent symptoms or an incomplete functional recovery. The mechanisms of this are incompletely understood, but believed to include microstructural injuries that may be undetectable by presently used diagnostic tests. This thesis aims at exploring new diagnostic methods that could be utilised in examining mild traumatic brain injury.

I study tested transcranial magnetic stimulation defined motor thresholds in a sample of chronic phase mild traumatic brain injury patients. Elevated motor thresholds were found compared to healthy controls, associated with altered excitability of the corticospinal tract.

II study used transcranial magnetic stimulation combined with electroencephalography to probe responses of frontal brain regions. The employed method is reported to be sensitive to changes in excitability and connectivity of the brain. Differences were found between samples of fully recovered and persistently symptomatic patients with mild traumatic brain injury and healthy controls. On basis of this, transcranial magnetic stimulation and electroencephalography could be used to detect functional changes that are not paralleled by lesions on routine magnetic resonance imaging.

III study compared diffusion tensor imaging based deterministic tractography and a newer method, based on constrained spherical deconvolution, automatic, deep learning based segmentation and probabilistic tractography. Participants were patients with symptomatic mild traumatic brain injury and healthy controls. The newer approach was able to find differences between the groups, while diffusion tensor method was not. This suggests the new approach may be more sensitive in detecting microstructural changes related to mild traumatic brain injury.

These results show that mild traumatic brain injury can be associated with functional and structural changes in the absence of trauma-related findings on routine MRI. The methods evaluated may provide new ways to detect these changes.

KEYWORDS: Traumatic brain injury, transcranial magnetic stimulation, diffusion weighted imaging, tractography

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TIIVISTELMÄ

Lievä aivovamma on erittäin tavallinen. Toipuminen on yleensä hyvää, mutta osalle potilaista jää pitkäkestoisia oireita tai toimintakyvyn vajavuutta. Näiden syntymekanismia ei täysin ymmärretä, mutta ajatellaan sen voivan liittyä aivojen mikrorakenteellisiin muutoksiin, joiden toteamiseen nykyiset diagnostiset testit voivat olla riittämättömiä. Tämä väitöstutkimus selvittää uusia keinoja, joita voitaisiin hyödyntää lievän aivovamman arvioinnissa.

I osatyössä tutkittiin transkraniaalisen magneettistimulaation avulla motorisia kynnyksiä. Tutkimusjoukkona oli lievän aivovamman saaneita, kroonisen vaiheen potilaita. Potilasjoukolla todettiin terveisiin verrokkeihin nähden korkeampia motorisia kynnyksiä, joka liittyy muutoksiin kortikospinaaliradan ärtyvyydessä.

II osatyö hyödynsi transkraniaalista magneettistimulaatiota ja elektroenkefalografiaa frontaalisten aivoalueiden vasteiden tutkimisessa. Aiempien julkaisujen perusteella menetelmä on herkkä aivojen ärtyvyyden ja aivoalueiden välisten yhteyksien muutosten toteamisessa. Menetelmällä löydettiin eroja lievästä aivovammasta oireettomiksi toipuneista, pitkäkestoisesti oireilevista ja terveistä verrokeista koostuneiden osallistujajoukkojen välillä. Transkraniaalisen magneettistimulaation ja elektroenkefalografian yhdistelmällä saatetaan siten havaita toiminnallisia muutoksia, joille ei ole vastinetta tavallisissa magneettikuvissa.

III osatyössä verrattiin diffuusiotensorikuvantamista ja determinististä traktografiaa uudempaan menetelmään, joka perustui constrained spherical deconvolution -laskentaan, automaattiseen, syväoppimiseen perustuvaan segmentaatioon ja probabilistiseen traktografiaan. Tutkimusjoukkona oli lievän aivovamman saaneita, oireisia potilaita ja terveitä verrokkeja. Uudella menetelmällä löydettiin eroja ryhmien välillä, mutta vertailumenetelmällä eroja ei havaittu. Tällä perusteella uusi menetelmä vaikuttaa herkemmältä aivovammaan liittyvien mikrorakenteellisten muutosten toteamisessa.

Tulokset osoittavat, että lievään aivovammaan voi liittyä toiminnallisia ja rakenteellisia muutoksia, vaikka tavanomaisen magneettikuvauksen löydös olisi normaali. Näiden muutosten toteaminen voi olla mahdollista arvioiduilla menetelmillä.

AVAINSANAT: Aivovamma, transkraniaalinen magneettistimulaatio, diffuusiokuvantaminen, traktografia.

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Abbreviations

ADC	Apparent diffusion coefficient
ANOVA	Analysis of variance
ANCOVA	Analysis of covariance
CMCT	Central motor conduction time
CSD	Constrained spherical deconvolution
CSP	Cortical silent period
CT	Computed tomography
DAI	Diffuse axonal injury
DLPFC	Dorsolateral prefrontal cortex
DTI	Diffusion tensor imaging
DWI	Diffusion weighted imaging
EEG	Electroencephalography
EMG	Electromyography
ERP	Event-related potential
FA	Fractional anisotropy
fMRI	Functional magnetic resonance imaging
GABA	Gamma-aminobutyric acid
GCS	Glasgow coma scale
GOSE	Glasgow outcome scale, extended
LDA	Linear discriminant analysis
M1	Primary motor cortex
MD	Mean diffusivity
MEP	Motor evoked potential
MTBI	Mild traumatic brain injury
MRI	Magnetic resonance imaging
PTA	Posttraumatic amnesia
RMT	Resting motor threshold
rmANOVA	Repeated measures analysis of variance
ROI	Region of interest
TMS	Transcranial magnetic stimulation
TBI	Traumatic brain injury
WHO	World health organization

List of Original Publications

This thesis is based on the following original publications, which are referred to in the text by Roman numerals I–III.

I Tallus J, Lioumis P, Hämäläinen H, Kähkönen S, Tenovuo O. Long-lasting TMS motor threshold elevation in mild traumatic brain injury. *Acta Neurologica Scandinavica*, 2012; 126: 178−182.

II Tallus J, Lioumis P, Hämäläinen H, Kähkönen S, Tenovuo O. Transcranial magnetic stimulation-electroencephalography responses in recovered and symptomatic mild traumatic brain injury. *Journal of Neurotrauma*, 2013; 30: 1270−1277.

III Tallus J, Mohammadian M, Kurki T, Roine T, Posti JP, Tenovuo O. A comparison of diffusion tensor imaging tractography and constrained spherical deconvolution with automatic segmentation in traumatic brain injury. *NeuroImage: Clinical,* 2023; 37.

1 Introduction

Traumatic brain injury is a major public health problem, most commonly caused by falls and traffic accidents. Mild traumatic brain injury represents almost 90% of traumatic brain injuries. Although outcome after mild traumatic brain injury is commonly good, a proportion of patients have persistent symptoms and incomplete functional recovery. The mechanisms of these are incompletely understood. It is also known, for example, that repetitive mild traumatic brain injury is a risk factor for later neurodegenerative diseases. Such long-term sequelae of mild traumatic brain injury present a diagnostic challenge, as many patients do not have objective trauma-related findings in routinely used diagnostic tests, such as structural magnetic resonance imaging.

The aim of this thesis is to explore new neurophysiological and imaging tools that could be applied to mild traumatic brain injury. It is believed that mild traumatic brain injury causes microstructural changes in the brain that can be difficult to detect with routinely used imaging methods. New methods that have thus far seen little to no clinical application in mild traumatic brain injury are studied. These include transcranial magnetic stimulation coupled with motor evoked potential and electroencephalographic measurements, and a new white matter tractography approach using constrained spherical deconvolution and deep learning based automatic tract segmentation method. These tools allow us to probe the consequences of mild traumatic brain injury from a functional and structural viewpoint and possibly highlight new diagnostic options for future development and adoption.

2 Review of Literature

2.1 Definition of traumatic brain injury

What is generally meant by traumatic brain injury (TBI) is an injury to the brain caused by an external force. It can be caused by a direct impact or rapid acceleration forces affecting the head, or a blast (explosion). Penetrating brain injuries fall to the same broad category but are often considered separately because of distinct clinical needs and prognosis (Takahashi et al., 2021).

Rapid acceleration forces and impacts to the head are commonly encountered in for example sports, but do not always lead to TBI. An influential consensus statement (Menon et al., 2010) has defined TBI to be present, if there is an alteration in brain function, or other evidence of brain pathology, caused by the external force. Alterations of brain function consistent with TBI include loss or decrease of consciousness, amnesia related to the time of injury, neurological deficits (loss of balance, dyspraxia, changes in vision etc.) and other co-occurring alterations in mental state (e.g. disorientation). What is meant by other evidence of brain pathology can be neuroimaging findings or possible other biomarkers related to brain trauma (Menon et al., 2010). These definitions form the foundation of the clinical diagnostics of TBI.

To establish a causal relation of the external force to the alterations in brain function, other possible causes for the observed symptoms and signs must be considered and excluded with reasonable certainty. This is not always straightforward. Acute symptoms may be confounded by the presence of for example pain, intoxication, shock, or other injuries that mimic neurological deficits. Diagnostic challenges may also be related to injuries that lack imaging findings, injured patients presenting to healthcare after some delay, or lack of accurate (outsider witness) account of the injury events. Some neuropsychiatric symptoms (e.g. impulsivity or apathy) may also be detected only later, and their causal relation to the injury difficult to prove. In such conditions a definitive diagnosis of TBI may be impossible to establish, although it could still be considered a possible cause for symptoms in the presence of an appropriate history (Menon et al., 2010).

2.2 Severity stratification

The Glasgow coma scale (GCS) was published in 1974 (Teasdale and Jennett, 1974) and is widely used in the evaluation of deteriorated consciousness and disorientation. It is based on quantification of motor response, verbal response, and eye opening. The GCS is a central tool in initial clinical severity assessment of TBI. GCS 13−15 has commonly been defined as mild (MTBI), 9−12 moderate and 3−8 severe TBI (Rimel et al., 1981, 1982). The rationale for acute phase injury severity classification is that it guides the selection of further diagnostic tools (e.g. imaging), treatment and follow-up, and helps in outcome prediction.

Although GCS is strongly associated with outcome across the entire severity spectrum of TBI (Teasdale et al., 2014), relatively high rates of longer-term morbidity are associated even with GCS-defined mild injuries (Rimel et al., 1981). On the other hand, Grote et al. (2011) found that almost one half of multitrauma patients with severe TBI based on the Abbreviated Injury Scale score had initial GCS > 8. Therefore sensitivity of GCS for severe TBI may also be lacking. More refined stratification systems have been developed, which, in addition to GCS, now typically include posttraumatic amnesia (PTA) duration, assessment of the duration of loss of consciousness, neuroimaging, and possibly the presence and duration of other neurological symptoms (Carroll et al., 2004a; Holm et al., 2005; Vos et al., 2012).

As MTBI is often more of a diagnostic problem than more severe injuries, several guidelines have been developed especially for it (Carroll et al., 2004a; Head et al., 1993; The Management of Concussion-mild Traumatic Brain Injury Working Group, 2016; Vos et al., 2012). One of the most used criteria for MTBI are those by the World Health Organization (WHO) Collaborating Centre for Neurotrauma Task Force (Carroll et al., 2004a). With external force to the head assumed to be the causative factor, WHO taskforce definition of MTBI is based on the following criteria:

1. One or more present: confusion or disorientation, loss of consciousness ≤ 30 minutes, PTA < 24 hours, other transient neurological abnormalities such as focal signs, seizure, and intracranial lesion not requiring surgery;

2. GCS score of 13–15 after 30 minutes post-injury or later upon presentation for healthcare;

3. Signs and symptoms of TBI are not due to intoxication, other injuries or other problems and are not caused by a penetrating craniocerebral injury.

Other diagnostic guidelines for MTBI follow similar lines. MTBI defined in this way is a narrower category than just GCS 13–15, as for example according to

the WHO criteria PTA ≥ 24 hours or loss of consciousness > 30 minutes will imply at least a moderate TBI. It should also be noted that diagnostic guidelines may be designed with different aims, e.g. some more focused on outcome prediction and some (like the Scandinavian Neurotrauma Committee guideline; Undén et al., 2013) meant primarily to guide initial management.

Trauma-related findings in computed tomography (CT) or structural magnetic resonance imaging (MRI) are typical in more severe TBIs, but depending on diagnostic guideline used can be considered incompatible with MTBI (The Management of Concussion-mild Traumatic Brain Injury Working Group, 2016; Vos et al., 2012) or permissible with possibly some limitations (e.g. they should not require surgery) (Carroll et al., 2004a; Head et al., 1993). The term "complicated MTBI" is sometimes used for MTBI with neuroradiological findings.

The term "concussion" is often used, especially in the context of sports. Exact definitions differ, but it is often considered interchangeable with MTBI, possibly with the exclusion of more severe or complicated end of the MTBI spectrum (Mccrory et al., 2017). Proposals have been made to avoid the term concussion, as it is not clearly defined and is not pathophysiologically distinct from MTBI. Also, in the sense normally used, concussion downplays the actual risk for long-term adverse effects (Sharp and Jenkins, 2015). On the contrary, some have also advocated the term in patient communication for partially the same reasons, to avoid the stigma of brain injury and emphasise the generally good prognosis of mild injuries ("VA/DoD Clinical Practice Guideline for Management of Concussion/Mild Traumatic Brain Injury.," 2009).

2.3 Epidemiology

Globally 64–74 million individuals are estimated to suffer a TBI of some severity yearly (Dewan et al., 2018). Generally, trauma causes 10% of deaths globally, with brain and spinal cord trauma estimated to be the most common causes of trauma-related mortality and disability (Rubiano et al., 2015).

Based on a meta-analysis, in Europe the yearly incidence of TBI treated in healthcare is 262 / 100 000 (Peeters et al., 2015). Comparable incidence estimates of TBI treated in healthcare have been reported from Finland, e.g. 221 / 100 000 from Numminen (2011). This rate would translate to roughly 12 000 TBIs per year presenting to healthcare in Finland. However, all TBIs do not present to healthcare, and true incidence of all severity TBIs in Europe has been estimated to be close to 1000 / 100 000 (Dewan et al., 2018).

The most common causes of TBIs are falls and road traffic accidents. TBI incidence has a bimodal distribution, being most common in the age groups < 25 years and > 75 years. Men are more commonly affected (Peeters et al., 2015).

A trend of increasing mean age of individuals experiencing TBI has been observed, and falls have become a more common cause than traffic accidents especially in high-income countries (in Finland falls exceed traffic accidents by a clear margin) (Koskinen and Alaranta, 2008; Roozenbeek et al., 2013). In low-income and middle-income countries at the same time TBI incidence has increased because of increased traffic-related injuries (Roozenbeek et al., 2013).

86% of TBI is mild based on a recent international meta-analysis, with the rest being about ⅔ moderate and ⅓ severe (Nguyen et al., 2016). A large part of MTBI is not treated at institutional healthcare. Based on population surveys of self-reported head injury, true rates of MTBI have been estimated to be above 600 / 100 000 (Holm et al., 2005), possibly almost twice the number in Europe and North America (Dewan et al., 2018). This would mean that MTBI outside institutional settings is much more common than all severities of TBI presenting to healthcare taken together.

The difference between incidence at healthcare and true incidence is one of the problems in epidemiological studies of MTBI. Another is the variation in definitions and case ascertainment. For example, Numminen (2011) found that adopting a more stringent, EFNS MTBI criteria-based approach to case ascertainment, instead of relying only on the diagnostic code assigned in healthcare, reduced their estimated incidence of TBI in healthcare from 221 to 137 / 100 000. Based on the reported figures, TBI is without doubt a major worldwide health problem, and its significance has probably been underestimated previously. Still the exact incidence of TBI can be debated, as there is some variation in diagnostic definitions, and a large part of the injuries (mostly mild) do not present at healthcare and are not documented.

2.4 Pathophysiology

TBI encompasses multiple histological types of injury to the brain. The basic common mechanisms of closed-head injury (non-penetrating) TBI are 1) the brain impacting against the inner surface of the skull, causing mechanical deformation, and 2) shearing forces affecting the brain tissue as a result of rapid movement that contains some rotational component. The injuries caused are dependent on multiple event-related and subject-related factors, such as head position, magnitude and duration of forces, use of protective equipment and individual anatomy (Taber and Hurley, 2013).

Common concepts that are helpful in understanding the different pathophysiological injury types are focal and diffuse injury, and primary and secondary injury. These are not exclusive types but are commonly seen together in varying proportions (Povlishock and Katz, 2005).

Primary injury is the combination of injuries that occur as a direct result of physical forces affecting the brain. This includes contusions and intracranial haemorrhages (primary focal injury) and diffuse axonal injury (DAI, a type of primary diffuse injury). Secondary injuries have a more multifactorial aetiology, involving complex cellular level mechanisms, and develop over an extended time period (McGinn and Povlishock, 2016).

Focal injuries are common in moderate and severe TBIs, while diffuse injuries are important in TBIs of all severities. The concepts of primary−secondary and focal−diffuse, along with their major manifestations are outlined in Table 1, which is modified and expanded from Povlishock and Katz (2005). Penetrating brain injuries will be outside of the scope of this review.

Table 1. Pathophysiological concepts in TBI and examples of injury types (modified and expanded from Povlishock & Katz, 2005).

	Primary injury *Caused by physical forces near the time of injury*	**Secondary injury** *Multifactorial, develops over an extended time period*
Focal *Typically manifested in more severe injuries*	Epidural haematoma Subdural haematoma Subarachnoid haemorrhage Cerebral contusion	Delayed neuronal injury Microvascular injury and blood brain barrier disruption Focal hypoxic-ischaemic injury Herniation Regional metabolic changes
Diffuse *Occurs in both mild and moderate-to-severe injuries*	Diffuse axonal injury Microhaemorrhages	Delayed neuronal injury Microvascular injury and blood brain barrier disruption Diffuse hypoxic-ischaemic injury Diffuse metabolic changes Inflammation Neurodegeneration

DAI was initially detected in neuropathological specimens and used to be considered a rapid event, where shear and tensile forces had torn the axons (Adams et al., 1989, 1977). This mechanism is now thought to be a feature of only the most severe injuries. More commonly DAI is caused by a cascade of events starting with mechanical disruption of axonal membrane and resultant disruption in ionic homeostasis (Povlishock and Katz, 2005). Taber and Hurley (2013) outline a process, where a focal influx of Ca^{2+} and Na^{+} ions causes hyperpolarisation and disruption of axonal cytoskeleton, which leads to disrupted fast axonal transport

and axon swelling, possibly progressing to axotomy. This may take hours to days in humans. After an axon is severed, degenerative changes in downstream nerve terminals may already manifest at 1-2 days. The detached distal axon and possibly also myelin sheath will then break down over months (Povlishock and Katz, 2005). Axotomy or an injury cascade triggered by injury to other parts of neuron membrane can result in death of the whole cell (delayed neuronal injury), although some injured neurons also have a prolonged survival and may recover (Greer et al., 2011; Singleton and Povlishock, 2004). Regarding clinical outcome, DAI has been thought to be a central cause of morbidity in TBI of all severities, and often outweighs the importance of focal lesions as a determinant of outcome even in moderate and severe TBI, with brainstem DAI being especially significant (McGinn and Povlishock, 2016; Povlishock and Katz, 2005; Tjerkaski et al., 2022).

Along with the above-described cascade of events that may lead to delayed axotomy and necrotic neuron death, a key factor of secondary injury is the brief increase in extracellular glutamate and other neurometabolic consequences (McGinn and Povlishock, 2016). Glutamate is an excitatory neurotransmitter, and its concentrations increase dramatically within minutes following insult to the brain. Excessive glutamate receptor stimulation (excitotoxicity) leads to disturbed ionic homeostasis, which in turn can induce cellular damage and apoptosis (Povlishock and Katz, 2005). The cells will attempt to restore homeostasis by energy-dependent ion pumps, possibly contributing in turn to a metabolic crisis. Excitotoxicity is part of the early response to injury, which may underlie the acute clinical manifestations of TBI and is also associated with patient outcome. However, clinical trials with glutamate antagonists have been disappointing, possibly because the neurometabolic cascade of TBI involves other transmitters, and countering glutamate effects may not be sufficient to prevent secondary injury development (Povlishock and Katz, 2005).

Posttraumatic metabolic changes have been detected in studies on humans as cortical regional hyperglycolysis and elevated lactate during first days after injury, which then changes to a more long lasting global hypometabolism (based on animal studies this is thought to persist until recovery, i.e. weeks to months) (McGinn and Povlishock, 2016; Povlishock and Katz, 2005). Also decreased N-acetyl aspartate is seen, which has been suggested to reflect impaired mitochondrial function (Povlishock and Katz, 2005). Markers of brain energy metabolism, such as the lactate-pyryvate-ratio, can be measured in neurointensive care environment using microdialysis. Elevated ratio is often interpreted as a sign of ischaemia and mitochondrial dysfunction (Larach et al., 2011).

With sufficient strain at the time of injury, there will be small vessel vascular injuries in the brain parenchyma, leading to punctate foci of haemorrhage, called microhaemorrhages (Bigler and Maxwell, 2012; Taber and Hurley, 2013). The

same injury mechanism causes DAI. Thus, in diagnostic imaging the more easily detectable microhaemorrhages are commonly considered an indirect sign of DAI, but it has been noted that vascular and axonal injuries are only partially co-localised (Andreasen et al., 2020; Orrison et al., 2009).

Microvascular dysfunction, including altered blood flow, microthrombosis, and blood-brain barrier disruption is also seen across the spectrum of TBI, even when the primary injury is not severe enough to tear the vessels (Sandsmark et al., 2019). Vasospasms, widespread hypoperfusion and increased intracranial pressure are features of moderate or severe TBI (Dixon, 2017).

Inflammatory response to TBI encompasses activation of brain's resident microglia immune cells and arrival of peripheral neutrophil and monocyte/macrophage immune cells to the brain through the disturbed blood-brain barrier. The inflammatory cells clear injury related debris, form gliosis and mediate and uphold inflammation. The inflammatory response, along with blood-brain barrier disruption, contributes to cerebral oedema, which may become maladaptive. It has also been hypothesised that prolonged inflammation, along with functional vascular changes may have some role in the increased vulnerability to subsequent insults and later neurodegeneration (Dinet et al., 2019; McGinn and Povlishock, 2016).

Focal contusions and haematomas may cause secondary injuries to surrounding brain parenchyma by ischaemic damage, haemorrhagic progression and oedema. Mechanisms of delayed ischaemic damage and haemorrhagic progression may involve microvascular failure and possibly also systemic coagulopathy (Fujisawa et al., 1994; Kurland et al., 2012). Large focal lesions may cause progressive surrounding oedema, which may eventually lead to brain tissue herniation, widespread secondary brain damage and death. The secondary injuries may be aggravated (typically in moderate or severe TBI) by episodes of increased intracranial pressure, decreased systemic blood pressure, or hypoxia (Povlishock and Katz, 2005).

Alongside these mostly structural injuries, TBI has been linked to functional changes in seemingly structurally intact tissue. These include impaired vascular autoregulation and vasoreactivity, and changes in the functioning of the brain's excitatory and inhibitory networks (McGinn and Povlishock, 2016).

2.5 Outcome

2.5.1 Outcome measures

Outcome in TBI can be measured from several aspects, including but not limited to functional and cognitive recovery. The current gold-standard of functional outcome

assessment is the extended version of the Glasgow outcome scale (GOSE) (Jennett et al., 1981; Ranson et al., 2019; Teasdale et al., 1998). GOSE is scored on an ordinal scale, with values ranging from 1 (death) to 8 (upper good recovery). The score assigned is mostly dependent on the ability to take care of oneself, return to work or other previous activities, and function socially. The GOSE has been criticised for insensitivity to mild impairment, with most of its structured interview items relating to more severe deficits (McMillan et al., 2016; Ranson et al., 2019).

While more severe TBI often leads also to motor and other somatic symptoms (e.g. epilepsy, neuroendocrine dysregulation, sexual dysfunction, bladder and bowel incontinence, metabolic dysregulation (Masel and DeWitt, 2010)), in MTBI more commonly complaints are related to cognitive and emotional domains. Commonly reported after MTBI are headache, dizziness, fatigue, irritability, sleep disturbances, challenges in attention, memory, and emotion regulation, and poor stress and alcohol tolerance.

A postconcussional syndrome or disorder, constituted from such symptoms was a part of the widely used ICD-10 and DSM-IV diagnostic classifications, and has often been used as an outcome measure in research (Boake et al., 2005). However, it was eliminated and substituted by other terminology in present editions of the classifications (ICD-11 and DSM-V). The validity of postconcussional syndrome was questioned in part because it does not form a constellation specific to TBI. Comparable symptoms are common in patients with e.g. depression or chronic pain (Iverson, 2006; Iverson and McCracken, 2009), history of other injury (Boake et al., 2005; Meares et al., 2011), and even in healthy controls (Asken et al., 2017; Lagarde et al., 2014). Additionally, studies looking into the risk factors for persistent symptoms have found relatively poor correlation between apparent injury severity and the syndrome, and suggested other explanatory factors, for which reason the term postconcussional syndrome may have conferred a simplistic and misrepresentative view of the aetiology of the condition (Carroll et al., 2004b). On the other hand, removing this TBI-specific diagnostic category has been criticised for the potential to lead to undertreatment (although no specific treatment is available) and worse medicolegal outcomes for patients involved in litigation (McIntyre et al., 2021).

Other instruments for assessing outcome after TBI have been created, of which the Rivermead Post Concussion Symptoms Questionnaire (RPQ, King et al., 1995) and the Quality of Life after Brain Injury (QOLIBRI) scale (Von Steinbüchel et al., 2010) are mentioned. The RPQ is a short, 16 item questionnaire that allows for numeric quantification of typical symptoms experienced after MTBI (Balalla et al., 2020). The QOLIBRI assesses health-related quality of life after TBI (Von Steinbüchel et al., 2010, Gorbunova et al., 2020).

Besides instruments developed especially for TBI, several other measures may be appropriate when assessing outcome. These may include neuropsychological tests, tests designed to evaluate for psychiatric disorders and substance use disorders, and different general symptom questionnaires.

2.5.2 Outcome in MTBI

MTBI generally has a good prognosis, with most patients making a full clinical recovery. A large 2004 review (Carroll et al., 2004b) concluded that children, if symptomatic, usually recover fully by 2 weeks to 3 months, with most studies not reporting cognitive or behavioural deficits afterwards. Adults commonly experience cognitive deficits and other symptoms (most commonly headache) in the first weeks, but for most the symptoms resolve by about 3 months. However, many studies included in the review were noted to have methodological weaknesses, especially in control group selection. The control groups were often matched for certain demographic variables (such as age and sex), but not for history of trauma. This leaves uncontrolled the general effects related to trauma, such as pain, loss of function and emotional distress. Sometimes no control group was used, and preinjury status was estimated from the participants' retrospective reports. This approach is vulnerable to the documented tendency to underestimate preinjury symptoms (Ferguson et al., 1999; Iverson et al., 2010).

Symptoms persisting for a longer time after MTBI are a well-known problem. Estimates of the prevalence of persistent symptoms depend (among other factors) on the time from injury and what is considered a significant symptom burden, as there is no consensus on the proper criterion for the latter (Boake et al., 2005; Dwyer and Katz, 2018). Widely varying estimates of the prevalence of persistent symptoms or incomplete functional recovery have been published. At 6−12 months, reported rates of incomplete functional recovery or persistent symptoms range from 0.9−65% (e.g. Åhman et al., 2013; Hossain et al., 2020; McMahon et al., 2014; Nelson et al., 2019; Spinos et al., 2010; Van Der Naalt et al., 2017).

Recently, two large multicenter studies, TRACK-TBI and CENTER-TBI, have assessed also outcome. In TRACK-TBI 53% of MTBI patients, compared to 38% of orthopaedic injury controls had some level of functional impairment based on GOSE at 12 months (Nelson et al., 2019). In CENTER-TBI 53% of patients were impaired at 3 months and 49% at 6 months (Voormolen et al., 2020). These figures however are based on a panel of seven separate questionnaire instruments, and reaching a defined cut-off score on any of these was defined as impairment. The authors also reported impairment based on GOSE alone (allowing for a more direct comparison with the cited TRACK-TBI results), which was 23% at 3 months and 16% at 6 months. Both studies included uncomplicated MTBI (normal head CT)

and complicated MTBI (trauma-related findings in head CT), and noted, that outcome was worse in complicated MTBI.

On population level, the prevalence of most MTBI related symptoms seems to decline until at least 1 year after the injury, with most recovery seen until 3−6 months (Carroll et al., 2020; McMahon et al., 2014; Polinder et al., 2018; Theadom et al., 2016). Some patients continue to have debilitating symptoms for a far longer time, even several years (Åhman et al., 2013).

Neuropsychological testing may show some form of persistent cognitive impairment in roughly half of MTBI patients at 3 months or later, according to a recent review (McInnes et al., 2017). Abnormalities have been detected in executive functions, learning or memory, attention, processing speed, and language functions.

Factors that have been reported to be associated with the risk of persistent symptoms or otherwise incomplete recovery after MTBI (not in order of importance) include higher age at injury (Jacobs et al., 2010), lower GCS at admission (Hsiang et al., 1997; Van Der Naalt et al., 2017), acute phase symptoms such as dizziness and headache (Savola and Hillbom, 2003), pre-injury mental health disorders and post-traumatic stress disorder (Meares et al., 2011; Van Der Naalt et al., 2017), pain (Meares et al., 2011; Van Der Naalt et al., 2017), involvement in compensation seeking or litigation (review by Carroll et al., 2004b), imaging evidence of micro- or macrostructural injury (Oehr and Anderson, 2017; Puig et al., 2020; Voormolen et al., 2020), and elevated TBI-related blood based biomarkers (S100B and tau; (Hossain et al., 2020; Savola and Hillbom, 2003). In one large study, emotional distress and coping style (assessed at 2 weeks after injury), were found to predict functional outcome (Van Der Naalt et al., 2017). Outcome studies can be riddled by complex confounding factors. For example, McMahon et al. (2014) reported that patients with pathologic imaging findings actually reported less symptoms at 6 and 12 months than those with normal imaging, but this difference disappeared when patients with previous neurological or psychiatric morbidity were excluded from the analysis.

Sex probably has some role in TBI outcome, but research data regarding this is complex and at times contradictory. Many human studies have reported worse outcomes for females, but this is not a universal pattern. The relation between sex and outcome is probably not simple but may consist of multiple factors interacting with sex (e.g. injury severity, genetic factors, age) that can be difficult to control for (review by Gupte et al., 2019).

The biological basis of symptoms beyond acute phase in MTBI has been suggested to include DAI, microstructural white matter injury, neuroinflammation, and altered cerebral blood flow (Barlow et al., 2017; Filley and Kelly, 2018; Irvine and David Clark, 2018; Reuben et al., 2014). Altered structural and functional

connectivity has been postulated as a mechanism for cognitive decline after MTBI. This is supported by studies that have found correlations with diffusion-tensor imaging measures (implying microstructural white matter injury) and cognitive functioning (e.g. Oehr and Anderson, 2017; Puig et al., 2020). It remains a matter of some controversy to what extent neural injury and other factors explain the persistent symptoms seen after MTBI (Polinder et al., 2018), and with presently available clinical diagnostic tools, significance of the aforementioned brain pathologies is often impossible to ascertain in individual patients.

In conclusion, although for most patients the prognosis of MTBI is favourable, a sizeable minority experiences persistent symptoms or does not make a complete functional recovery. The widely varying estimates of incomplete recovery highlight methodological challenges in this research field. Methods of outcome and symptom estimation have been varied, as has utilisation of control groups. Secondly, the aetiology of long-term symptoms has been debated, with both biological and psychosocial factors relating to risk of symptom development. The correlation of blood-based and imaging biomarkers to outcome seems to suggest that MTBI contains a spectrum of severities that may not be adequately captured by the basic clinical severity stratification. It has also been argued that TBI (especially more severe cases) should be viewed as a disease process with lifelong consequences rather than an isolated injury (Masel and DeWitt, 2010).

2.5.3 Neurodegeneration after TBI

In long term, TBI has been associated with earlier onset and increased risk of dementia and Alzheimer's disease type pathology (Abner et al., 2014), risk of Parkinson's disease (Goldman et al., 2006) and chronic traumatic encephalopathy (Katz et al., 2021; VanItallie, 2019). The latter is a disease uniquely associated with a history of repetitive, often relatively mild TBIs or even repeated head impacts without a clinical TBI, and has been studied especially in the context of professional contact sports. Neuropathologically the hallmark of chronic traumatic encephalopathy is accumulation of hyperphosphorylated tau protein in neurons and astrocytes around small cortical blood vessels (McKee et al., 2015; VanItallie, 2019). It is a tauopathy, and shares histopathological and clinical features with Alzheimer's disease and frontotemporal degeneration, but there are also significant differences that have justified considering it a separate disease entity (Abner et al., 2014; VanItallie, 2019). Factors that have been associated with either increased risk, earlier onset or greater severity of a dementing neurodegenerative disease (such as Alzheimer's disease or chronic traumatic encephalopathy) after TBI are: greater severity of a single moderate-to-severe TBI, repetitive MTBI, decreased

cognitive or neuronal reserves or older age at the time of TBI, and the presence of apolipoprotein E ε4 gene alleles (Mendez, 2017).

2.6 Imaging TBI

2.6.1 CT

The primary imaging modality of TBI in the emergency department setting is usually noncontrast-enhanced CT scan of the head (Schweitzer et al., 2019). The availability of CT is better and price lower than that of MRI. CT is faster to acquire, which can be a decisive advantage with agitated and confused or critically injured patients. Disadvantages of CT include exposure to ionising radiation (being of concern particularly in children; (Abalo et al., 2021) and inferior soft tissue contrast compared to MRI. The main rationale for CT imaging in the acute setting is to detect intracranial lesions that might require prompt treatment or closer monitoring and follow-up than otherwise necessary (e.g. haemorrhage or brain oedema; Schweitzer et al., 2019).

CT is usually considered superior to MRI for detecting fractures of the skull (Lindberg et al., 2019; Schweitzer et al., 2019), although advances in MRI technique are closing this gap (Dremmen et al., 2017; Kralik et al., 2019). CT is good for detecting many types of intracranial haemorrhages, but MRI is considered more sensitive for very small epidural and subdural haematomas, non-haemorrhagic contusions, brainstem injuries and haemorrhagic (microhaemorrhages) and nonhaemorrhagic DAI (Schweitzer et al., 2019).

Several guidelines have been published to help decide who should get an emergent CT. The aim of these is to reduce superfluous imaging, while selecting for imaging with high sensitivity those who will have a lesion requiring treatment. According to guidelines of the Scandinavian Neurotrauma Committee (Undén et al., 2013) and national Finnish guidelines (Traumatic brain injury: Current Care Guidelines, 2021, www.kaypahoito.fi) urgent head CT in acute adult TBI is indicated in all but the mildest, low risk MTBIs. The requirements for not recommending a head CT in MTBI (in other words, criteria for recognising very low risk patients) are summarised in table 2.

Table 2. The requirements for not recommending a head CT in acute adult MTBI.

	Finnish Current Care Guidelines	**Scandinavian Neurotrauma Committee Guidelines**
GCS	Never < 13 in the emergency department Normalised to 15 within two hours	Never < 15*
Loss of consciousness	Conditional − Does not necessitate CT if all the following are true: • Age < 65 • No coagulation disorder • No high-risk injury mechanism • Retrograde amnesia ≤ 30 min	No*
Anticoagulant therapy	No	No, also no coagulation disorders
Suspected fractures	No	No
Other risk factors	No seizure No focal neurological deficit No repeated vomiting	No seizure No focal neurological deficit No repeated vomiting*

* Exception may apply if S100B sampled < 6 hours from injury is normal (see text).

In contrast to Finnish national guidelines, the Scandinavian Neurotrauma Committee guidelines utilise S100B blood sampling as a strategy to identify very low risk patients. According to the Scandinavian guidelines, some criteria in Table 2 can be violated to a certain extent, if all others are met and the S100B level, sampled less than 6 hours from injury, is normal. The scenarios where a normal S100B can remove the need for CT are: a) GCS 14 with no other risk factors, b) loss of consciousness with later GCS 15 and no other risk factors and c) repeated vomiting with no other risk factors.

Several acute CT finding scoring systems have been developed for outcome prediction, i.e. Marshall CT classification (Marshall et al., 1992), Rotterdam CT score (Maas et al., 2005), Helsinki CT score (Raj et al., 2014) and Stockholm CT score (Nelson et al., 2010). Outcome prediction is possible to some extent in all severity TBIs using these classifications (Posti et al., 2020; Summaka et al., 2020; Thelin et al., 2017). A recent large cohort of patients demonstrated a negative impact on outcome for several intracranial haemorrhage types also in MTBI (Yuh et al., 2021). However, CT is of limited utility as an outcome prediction tool in

unselected MTBI patients, because most will not have any relevant abnormalities. Generally, only 9% of imaged TBI patients have had trauma-related abnormalities detected in CT, even when considering all severities (Korley et al., 2016).

2.6.2 MRI

MRI is the mainstay of neuroradiology. Resources permitting, it can also be used as a first line imaging modality in the emergency department for sufficiently cooperative and stable patients. This is especially worth consideration in paediatric patients, who have greater sensitivity for adverse effects from ionising radiation (Kutanzi et al., 2016; Lindberg et al., 2019). More commonly, however MRI is reserved for later stages and patients with a clinical suspicion of a significant TBI, but normal CT, or relatively mild CT findings that do not explain a more severe clinical presentation. Typically recommended basic brain MRI sequences in TBI are 3D T1, T2, T2 fluid-attenuated inversion recovery (FLAIR), susceptibility weighted imaging (SWI) and diffusion weighted imaging (DWI) (Mutch et al., 2016; Traumatic brain injury: Current Care Guidelines, 2021, www.kaypahoito.fi).

MRI is more sensitive than CT in detecting very small intra and extra-axial haemorrhages, haemorrhagic and nonhaemorrhagic lesions related to DAI and small or nonhaemorrhagic contusions (Beauchamp et al., 2011; Orrison et al., 1991; Paterakis et al., 2000; Yuh et al., 2014). Lesion localisation also matters, as CT images suffer near bony anatomy from beam-hardening artefacts, which can be especially troublesome in the posterior fossa (Hwang et al., 2012), increasing the superiority of MRI in these areas.

A study by Yuh et al. (2014) reported that 28% of MTBI patients with normal head CT had trauma-related abnormalities in MRI. The most common additional findings in CT-negative patients' MRIs were petechial haemorrhages that are commonly associated with DAI (in 23% of CT-negative patients' MRIs), with a few brain contusions and extra-axial haematomas also detected. A study by Kara et al. (2008) reported a series of patients with clinically severe TBI and normal CT. In total, 91% of these had significant pathology at MRI, most commonly (in 60%) evidence of shear injuries. These results highlight the fact that even severe pathology can be nonvisualised at CT, especially diffuse white matter injuries. At the same time, it should be noted that approximately ¾ of MTBI patients with a normal CT will not have abnormalities even at clinical MRI (Yue et al., 2019; Yuh et al., 2014).

Animal and human studies have shown that in MTBI only a small percentage of axons in any given area are typically injured, which means the injuries may be below the resolution of MRI (Bigler and Maxwell, 2012; Farkas and Povlishock, 2007; Taber and Hurley, 2013). Given the relatively high prevalence of functional impairment and symptoms even at 12 months after MTBI (Nelson et al., 2019), it

seems plausible that some significant microstructural injuries may not be detected by routine clinical MRI.

2.6.3 DWI

Diffusion represents the random thermal movement of particles in a medium, such as a liquid. Diffusion depends on the particles studied, the medium and presence of structures that limit diffusion, and the temperature of the studied system (Huisman, 2010). In humans DWI primarily quantifies the movement of water molecules, and the measured signal is emitted by the protons (hydrogen nuclei) in water.

Diffusion in tissues is limited by the local microstructure. In areas with little cell membranes or other diffusion-limiting structures (e.g. the cerebrospinal fluid in ventricles of the brain), diffusion is relatively unrestricted. In areas with densely packed cells and little interstitial (between cells) fluid, and cells with a high nucleus to cytoplasm ratio, diffusion is relatively restricted (Lin et al., 2010). Examples of tissues with relatively restricted diffusion are cellular neoplasms (e.g. lymphoma) and ischaemic or otherwise damaged brain tissue that is exhibiting cytotoxic oedema. In cytotoxic oedema the damaged cells take in water and become bloated, and the fraction of interstitial fluid is reduced. This is in contrast with vasogenic oedema (such as in blood-brain barrier disruption), where the opposite happens and mean diffusion is increased (Schaefer et al., 1997).

The principle of nuclear magnetic resonance-based diffusion measurement was experimentally verified and described in 1965 (Stejskal and Tanner, 1965) and clinical applications of the technique in MRI began in the 1980's (Le Bihan et al., 1986). Since then, DWI has become a common and important part of clinical MRI. It is used for example in the early detection of ischaemia and differential diagnostics of neoplasms and inflammatory processes in multiple organs.

Generally, the signal intensity of an imaged voxel in MRI is dependent on the number of protons that are excited and become uniformly oriented or acquire phase synchronisation in the course of imaging (Mangrum et al., 2012). In DWI two motion probing magnetic gradient pulses are applied with a certain interval of time between them. The first gradient pulse is called a dephasing and the second a rephasing pulse. In the absence of motion, the phase shift caused to the proton spins by the first gradient is cancelled by the second gradient and a relatively strong signal can be measured. If protons have displaced during the time interval between the motion probing gradient pulses, the rephasing by the second gradient pulse will be imperfect, resulting in signal loss (Chilla et al., 2015; Higaki et al., 2018). Therefore, more stationary protons result in more signal, but more diffusion reduces the signal.

A central parameter in DWI is the b-value, which reflects the amount of diffusion weighting in an imaging sequence. The b-value depends on the magnitude, duration

and time interval of the motion probing gradient pulses (Koh and Padhani, 2006). Increasing b-value leads to increased sensitivity for slower diffusion and greater diffusion weighting, i.e. greater proportion of diffusion-related contrast in the generated images (Higaki et al., 2018). However, higher b-value leads to lower absolute signal intensity and a decreasing signal-to-noise ratio. Therefore, it is more demanding to generate good quality images with a higher b-value. The relationship of b-value and signal intensity can be expressed by the equation (2.1):

$$S_{bi} = S_{b0} \exp(-b_i D), \tag{2.1}$$

where S_{bi} is signal intensity with b-value i, S_{b0} represents signal intensity without diffusion weighting, and b_i is the b-value (Higaki et al., 2018). D is the diffusion coefficient, which is a property of a certain type of diffusing particle in a certain medium. Measured D in biological tissue is called the apparent diffusion coefficient (ADC). D can be solved from equation (2.1) and specified, if two diffusion measurements done with different b-values are available. Commonly, one of the used b-values is b = 0 s/mm^2, i.e. no diffusion weighting, and the other is obtained with values close to 1000 s/mm^2. Equation (2.1) is an idealised monoexponential model of diffusion. However, the relationship of b-value and signal is not linear across all b-values. Diffusion on especially low (approximately < 200 s/mm^2) and high (approximately > 2000 s/mm^2) b-values does not conform to a monoexponential model generated from the typically used b-values. More complex models have therefore been developed, which estimate diffusion with more accuracy, but require measurements with multiple b-values (known as multi-shell acquisition) (Higaki et al., 2018).

2.6.3.1 Diffusion tensor imaging

In biological tissues the magnitude of diffusion is often dependent on direction. White matter tracts, for example contain many parallel axons and fascicles (the term fibre is commonly used to refer to one or many axons grouped together), and diffusion occurs predominantly in the direction of the tract (Douek et al., 1991). Note however, that high (> 1000 s/mm^2) b-values are required to measure the actual slow diffusion occurring inside axons, while the faster effects that can be measured with lower b-values reflect the diffusion in extracellular space between axons (Jones et al., 2013). The property of diffusion occurring predominantly in some directions is called anisotropy, which conceptually is a negation of isotropy. Diffusion is isotropic if it occurs in the same magnitude in all directions.

Minimum requirement for DWI is to measure diffusion in three orthogonal directions. Many common clinical applications of DWI, however, require only mean diffusivity data, which is calculated by combining the values of different

directions. Analyses that utilise directionality data will profit from image acquisition with more diffusion encoding directions. Defining the diffusion tensor requires at least six directions (Alexander et al., 2007), whereas a minimum of 45 directions have been recommended for so-called high angular resolution diffusion weighted imaging (Tournier et al., 2013).

Diffusion tensor imaging (DTI, Basser et al., 1994) can be used to characterise the three-dimensional diffusion properties of the brain. In DTI the diffusion of each voxel is broken down to three orthogonal components, that define the diffusion tensor. The diffusion tensor describes the magnitude, degree of anisotropy, and orientation of the anisotropy of diffusion (Alexander et al., 2007). Diffusion tensor can be described graphically as a three-dimensional ellipsoid, with the long axis oriented along the principal direction of diffusion, and the amount of diffusion anisotropy represented by the shape (more oblate or prolate vs. spherical) of the ellipsoid (Huisman, 2010) (see Figure 1).

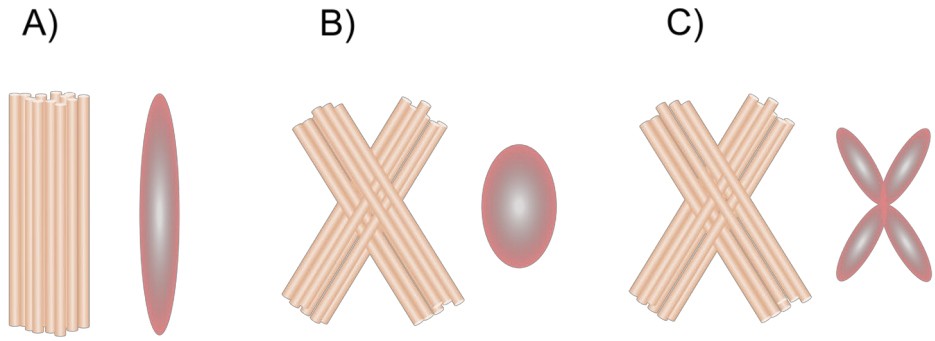

Figure 1. Schematic representation of diffusion modelling in voxels of cerebral white matter, with axonal fibres represented by narrow cylinders and diffusion tensor or fibre orientation distribution function (in C) by ellipsoids. A) A voxel with relatively anisotropic diffusion, with fibres running parallel and closely packed, resulting in a diffusion tensor with one clearly dominant direction (corresponding to the long axis of the ellipsoid). B) A voxel with crossing fibres. The diffusion tensor is unable to model such fibre architecture accurately but displays a relative decrease in fractional anisotropy and less obvious principal direction of diffusion. C) An example of a more advanced method of modelling fibre orientations, that represents the crossing fibres more accurately.

Meaningfully measuring and interpreting a three-dimensional image stack composed of diffusion tensors would be impractical without some simplification (Alexander et al., 2007). Common practical measures derived from DTI are axial diffusivity, radial diffusivity, mean diffusivity (MD), and fractional anisotropy (FA). Axial diffusivity represents the magnitude of diffusion along the principal diffusion direction. Radial diffusivity represents mean diffusion perpendicular to the principal direction. MD is the diffusivity average of all diffusion components of the tensor. MD is closely related to the concept of ADC, and the terms are

sometimes used interchangeably. FA describes the ratio of the diffusion components of a tensor. FA can have values from 0 − 1, with 0 representing perfectly isotropic diffusion and 1 perfectly anisotropic diffusion.

Besides measuring these parameters from any selected region, another approach to analysing DTI data is tractography. As mentioned, white matter tracts contain many parallel axons or fibres, and the principal direction (i.e. highest eigenvalue) of the diffusion tensor is presumed to align with the tangent of the fibres (Jones et al., 2013). Based on this assumption, it is possible to track white matter fibres and reconstruct anatomical white matter tracts in three-dimensional space. Additional conditions for anatomically plausible tractography may include minimum FA limit and maximum curvature limit of the tracked fibres, and predefined anatomical regions that should or should not be included in the tract reconstruction (Domin et al., 2014).

Three-dimensional visualisation of white matter tracts provided by tractography may by itself be valuable in e.g. presurgical planning (Henderson et al., 2020). Quantitative analysis and comparison of tracts between individuals and groups of individuals is possible also. Once a three-dimensional tract is reconstructed, for example the volume, length, mean FA and mean MD of the entire tract can be calculated (e.g. Brandstack et al., 2013; Sydnor et al., 2018).

2.6.3.2 DTI in MTBI

DTI and related methods that quantify directional diffusion are among the most promising developments in MTBI imaging, offering the prospect of quantifying white matter injuries that are not detectable at routine MRI (Taber and Hurley, 2013). Research in DTI and brain injury has been active in the past two decades (see reviews by Hulkower et al., 2013; Hunter et al., 2019). Most commonly reported metrics in these studies have been FA and MD. Typically in TBI decreased FA and increased MD of white matter tracts are reported, but this is not a universal pattern, and may depend on at least the time from injury (Lipton et al., 2012; Mayer et al., 2010). Histological mechanisms for these changes are not fully understood or obvious, but (depending on the time from injury) are thought to include damage to myelin or axon membranes, reduced number of axons, reduced axon coherence, and oedema (Borja et al., 2018; Lin et al., 2016; Nolan et al., 2021). It has also been suggested that abnormally high FA sometimes detected soon after the injury may reflect compensatory processes and relate to a better outcome (Strauss et al., 2016).

The macroanatomical structure that is most commonly reported to have evidence of injury is the corpus callosum (especially genu) (Hulkower et al., 2013; Hunter et al., 2019). As many studies have opted to have preselected regions of interest (ROIs) for analysis and the corpus callosum is relatively easy to define

anatomically, there may be some selection bias in the literature. Whole brain analysis approaches have equally often detected abnormalities in the superior and inferior longitudinal fascicles, with abnormalities slightly less frequently reported in many other structures (Hulkower et al., 2013; Hunter et al., 2019).

Several studies have found that parameters (especially FA) derived from DTI and related methods, measured within one month from injury had value in predicting the outcome of MTBI (Bazarian et al., 2007; Meier et al., 2016; Messé et al., 2012; Strauss et al., 2016; Veeramuthu et al., 2015; Yuh et al., 2014). Later measurements have also been found to correlate with outcome (Mohammadian et al., 2020; Niogi et al., 2008). However, it is also quite common to not find a significant correlation between DTI metrics and outcome (Churchill et al., 2017; Studerus-Germann et al., 2018; Wäljas et al., 2015, 2014). One of the possible reasons for this is lack of sensitivity. For example, a study by Palacios et al. (2020) found that while DTI metrics did not predict outcome in their sample, a newer method called neurite orientation dispersion and density imaging did.

Diffusion changes, such as reduced white matter FA, are not specific to TBI. Similar changes have been reported in psychiatric disorders such as depression and post-traumatic stress disorder, substance abuse, chronic pain, and transient or chronic sleep deprivation (Davenport et al., 2016; Elvsåshagen et al., 2015; Frøkjær et al., 2011; Grumbach et al., 2020; Hampton et al., 2019; Jak et al., 2020; Jiang et al., 2017). Some interindividual variation in DTI measures is also related to cognitive capacity (Dizaji et al., 2021). With many potential confounding factors, establishing a causal link from injury to microstructural characteristics in imaging is not straightforward. For concerns about standardisation and comparability of different DTI methodologies, lack of appropriate reference standards, and lack of specificity, the role of DTI in contemporary clinical and medicolegal practice is not well established (Shenton et al., 2018).

2.6.3.3 Constrained spherical deconvolution

The diffusion tensor model estimates a single maximum for diffusion orientation in each voxel. There is evidence that majority of white matter voxels contain multiple fibre orientations, that cannot be distinguished by a diffusion tensor (Jeurissen et al., 2013). Another limitation is, that DTI assumes the diffusion process to have a Gaussian distribution, which is only strictly true of free diffusion and not of the restricted diffusion in tissues (Assaf et al., 2004). Therefore, DTI greatly simplifies actual brain microstructure, which may lead to problems in areas with more complex fibre architecture. When white matter tracts cross, bend sharply, or come to proximity, but continue in different directions, measures derived from DTI may be unreliable (Basser et al., 2000; Basser and Pierpaoli, 1996). For example, the FA

measurements may be confounded in voxels with crossing fibres, as a reduction in the FA of one crossing fibre population may lead to a paradoxical increase in FA of the whole voxel (Tuch, 2004) or vice versa (cf. Figure 1 in section 2.6.3.1). In such circumstances DTI based tractography may also not be able to track the relevant fibres or may return false positive fibres that belong to an unrelated tract.

To overcome these limitations, several alternative mathematical frameworks for relating DWI data to the underlying diffusion process have been proposed (Assaf et al., 2004; Jensen et al., 2005; Tuch, 2004; Wedeen et al., 2005; Zhang et al., 2012). Constrained spherical deconvolution (CSD) (Jeurissen et al., 2011; Tournier et al., 2007) is one of these. In it, the mathematical operation of spherical deconvolution is used to estimate the distribution of white matter fibres' orientation (known as the fibre orientation distribution function), which can have multiple peaks per voxel. Compared to DTI, CSD does not assume unimodal Gaussian diffusion and allows for more accurate reconstruction of complex fibre structure in the brain, including crossing fibres.

CSD is less demanding in terms of image acquisition and computational resources than some of the alternative models like the composite hindered and restricted model for diffusion, q-ball imaging, or diffusion spectrum imaging (Tournier et al., 2007). It is developed for a single-shell (i.e. single b-value), high angular resolution MRI acquisition with ideally b = 2500−3000 s/mm^2, but has been successfully used with b ~ 1000 s/mm^2 data (Calamuneri et al., 2018; Tournier et al., 2007). This relatively low demand on data gives it wider applicability for routine clinical use. To date, there is evidence of CSD-based tractography correlating better than DTI with memory function in Alzheimer's disease (Reijmer et al., 2012) and motor function after stroke (Auriat et al., 2015), and depicting relevant white matter tracts in more detail before glioma surgery (Becker et al., 2020; Mormina et al., 2016).

2.6.3.4 Tractography and tract segmentation methods

After estimating the diffusion characteristics of each voxel, several methods are available for tracking fibres and delineating the anatomical tracts of interest (Jbabdi and Johansen-Berg, 2011). Deterministic streamline tractography is a category that covers the methods where local tract direction is defined from the local principal diffusion direction, and streamlines (essentially corresponding to fibres) are tracked by interpolating between neighbouring voxels with a similar principal diffusion direction. Adding anatomical constraints to this by selecting regions that should or should not be included in the tract ("virtual dissection") constitutes probably the most widely used approach to tractography presently (Jeurissen et al., 2019; Rheault et al., 2020).

Alternative approaches, grouped under probabilistic tractography, assess the probability of connection between a certain voxel and a given starting point.

Probabilistic tractography is superior to the deterministic approach in the sense that tracts can be propagated through regions of relative uncertainty without terminating (less stringent termination criteria are required), and the methods handle noise more robustly (Jeurissen et al., 2019). A general downside compared to deterministic tracking is the greater propensity for false positive fibres.

A third group of tractography approaches are the global methods. These approaches seek the configuration that optimises overall diffusion in the data, potentially also being less sensitive to local ambiguities (Jeurissen et al., 2019).

It is not obvious what approach works best in any given scenario, with each having certain weaknesses and strengths. One very common problem with modern tractography methods are false positive fibres, affecting especially probabilistic methods (Maier-Hein et al., 2017; Sarwar et al., 2019). False positives can be reduced manually by the virtual dissection approach, but this requires considerable amounts of human work and expertise, also implying operator dependency.

Automatic tract segmentation methods have been developed to address the issues of human workload and reproducibility. They can be grouped to ROI-based, clustering based, and direct segmentation (Wasserthal et al., 2018b). ROI-based segmentation methods rely on a pre-existing common atlas that contains information on the location and morphology of tracts. Individual subjects' data is registered to this atlas to help locate the tracts in individual subject space. Clustering based segmentation groups tracked fibres into clusters based on their location or relation to other anatomy. The clusters are then assigned (automatically or manually) to suitable anatomical tracts. Direct segmentation approaches are distinct from ROI and clustering based approaches in that they do not require streamline generation prior to tract segmentation, which makes them simpler and computationally less demanding. There are various methods for segmenting tracts directly from the input images prior to streamline generation, one of them being TractSeg (Wasserthal et al., 2018a). TractSeg is based on a fully convolutional neural network, that has been trained to segment white matter tracts directly from fibre orientation distribution function peaks. Examples of other semi-automated tools for tract segmentation include AFQ/pyAFQ (Kruper et al., 2021; Yeatman et al., 2012), and WMA segmentation (Bullock et al., 2019).

2.7 Transcranial magnetic stimulation and TBI

2.7.1 Transcranial magnetic stimulation

Transcranial magnetic stimulation (TMS) is a non-invasive method for inducing small electric currents to the brain (Barker et al., 1985). It is based on the phenomenon of electromagnetic induction. An electric current pulse in a coil

produces a transient magnetic field pulse. In accordance with Faraday's law of induction, this magnetic field pulse induces an electric field in a nearby conductor (Rossi et al., 2009). In TMS a rapidly changing magnetic field in the order of 1−2.5 T is generated with a coil held against the head. The generated magnetic pulse is relatively unattenuated by the skull, and can induce focal, brief electric currents near the surface of the brain (see Figure 2). Because the magnetic field decays proportional to the distance squared, conventional stimulator and coil setups are able to achieve immediate biological effects only on the cortex and nearby subcortical white matter (Paulus et al., 2013).

The effects of TMS may vary based on several parameters. These include stimulated brain region, individual anatomy and sensitivity to stimulation, coil design, stimulation intensity, pulse direction and possibly other pulse parameters (shape and duration of the pulse) (Paulus et al., 2013). In case of repetitive TMS, the frequency and duration of the pulse train are also very important. Different stimulation coil types are available, with the figure-of-eight coil being one of the most frequently used. It is composed of two circular coil elements placed side by side, which allows focusing stimulation with more anatomical precision compared to, for example a single circular coil.

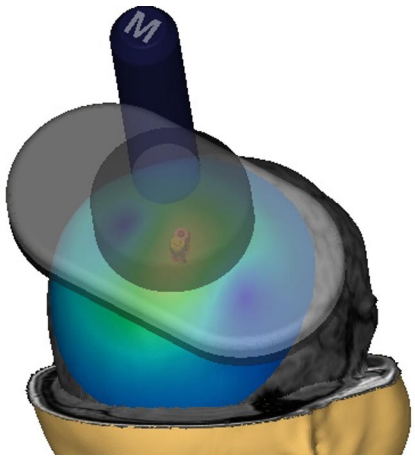

Figure 2. An example of a graphical TMS navigation aid (from the eXimia NBS system by Nexstim, Helsinki, Finland), displaying the stimulation coil held against the head, underlying individual brain anatomy, and modelled distribution of the induced electric field.

Neurons are most sensitive to stimulation at axonal bends and axonal terminations, where TMS can depolarise neurons and initiate action potentials and lead to inhibitory and excitatory postsynaptic potentials (Hill et al., 2016; Salvador et al., 2011). At the level of cortical neural circuits, TMS can have both excitatory

and inhibitory effects, as shown especially by studies involving motor cortical areas (Berardelli et al., 2008; de Goede et al., 2016; Malcolm and Paxton, 2015).

Effects of TMS on non-motor areas have been more challenging to measure. More direct approaches to measuring non-motor effects have involved combining TMS with methods such as electroencephalography (Komssi and Kähkönen, 2006), positron emission tomography (Paus et al., 1997) and functional MRI (fMRI, De Weijer et al., 2014). Each of these requires specially developed equipment and measurement paradigms, due to the capacity of the magnetic pulses to disturb nearby electronic devices. Non-motor effects of TMS can also be measured in a neurocognitive framework, utilising behavioural responses (reaction times, measures of perceptual accuracy etc.).

While the effects of single pulse and comparable (e.g. paired-pulse) TMS paradigms are considered transient, repetitive TMS under certain conditions can have more long term effects. Repetitive TMS has been studied and used as a therapy in e.g. neuropathic pain, depression, and post-stroke motor deficits (Lefaucheur et al., 2020). In such applications, typically hundreds or thousands of pulses are administered per session and treatment consists of several sessions that typically spread over several days or weeks.

Safety of TMS is dependent on pulse intensity, pulse train length and frequency, and individual risk factors. Single pulse TMS and low frequency ($\leq$ 1 Hz) repetitive TMS with pulse intensities close to the motor threshold are considered safe in most instances (Rossi et al., 2021, 2009; Wassermann, 1998). The most severe adverse effect associated with TMS is the induction of an epileptic seizure, which has been described mostly in relation to high frequency repetitive TMS and in individuals with prior risk factors for seizures (e.g. known epilepsy, medications that increase seizure risk, or a history of stroke or other potentially epileptogenic brain lesions) (Rossi et al., 2021, 2009; Wassermann, 1998). The most common and less severe adverse effect of TMS is mild local pain. This is usually due to inadvertent stimulation of peripheral nerves or muscles near the intended stimulation focus.

Implants and other magnetising objects and electronic devices near the stimulation coil are a potential contraindication to TMS, as they may malfunction, heat, or mechanically shift because of the magnetic pulse (Rossi et al., 2009). Laboratory equipment that is used in proximity to the stimulation coil, such as measurement electrodes and amplifiers, must be specially constructed to avoid heating, skin burns and malfunction of the device itself.

Defining the proper stimulation site used to be based on external anatomical landmarks (e.g. utilising the EEG 10−20 electrode placement system) and monitoring of behavioural or electrophysiological responses (e.g. hand muscle responses). More recently, stereotactic navigation based on individual cerebral

anatomy, as depicted on previously acquired MRIs has become common. This allows for the selection of stimulation targets based on individual brain anatomy (instead of approximating it based on external anatomy) and more detailed modelling of the magnitude and distribution of the induced electric field in the brain (Ruohonen and Karhu, 2010).

2.7.2 TMS-evoked motor potentials in TBI

Motor evoked potentials (MEPs) are electrical signals measured from peripheral nerves or muscles in response to stimulation. Muscle electrical activity and evoked potentials can be measured by electromyography, where measurement electrodes are placed either on the skin surface above a muscle or within the muscle (needle electrodes). Peripheral muscle MEPs generated by TMS are affected by the excitability of the primary motor cortex and the integrity of the corticospinal tract. However, motor cortex excitability by TMS is also a complex phenomenon, that is thought to be modulated by inputs from functionally distinct but interconnected brain areas, and contributions from presynaptic intracortical modulation, and postsynaptic cortical excitability (Bestmann and Krakauer, 2015). Specialised test protocols, including paired pulse, and specific measures of the motor output curve have been developed. These aim to discern some of the aforementioned contributions to MEPs more specifically and have been used in studies of TBI also. Table 3 summarises results from studies of motor cortical excitability after MTBI.

Table 3. Summary of studies of motor cortical excitability after mostly mild adult TBI (definitions of severity vary and some studies include patients with more severe TBI according to for example the WHO criteria).

	Participants	**Results (in comparison to control group)**
CHISTYAKOV ET AL., 1998	39 MTBI at 2 weeks, follow-up 15 MTBI at 3 months, 21 controls	higher RMT, partially normalised to follow-up, with correlation to symptom resolution, normal CMCT
CHISTYAKOV ET AL., 2001	38 TBI of varying severity, some with structural lesions on imaging, 20 controls	higher RMT, prolonged CSP and longer CMCT in more severe range of included injuries, difference of concussion group to controls nonsignificant
DE BEAUMONT ET AL., 2007	30 athletes with concussion at ≥ 9 months, 14 controls	prolonged CSP in subgroup with history of multiple concussions, no difference in RMT, SICI, ICF
DE BEAUMONT ET AL., 2009	19 retired athletes with history of 1−5 concussions, at 30+ years after, 21 controls	prolonged CSP, no difference in RMT, SICI, ICF

	Participants	Results (in comparison to control group)
NARDONE ET AL., 2011	44 MTBI or moderate TBI with posttraumatic sleep disturbance at 3 months, 14 controls	higher RMT and more pronounced SICI in patients with objective excessive daytime sleepiness (N=12), other patients not significantly different from controls
TREMBLAY ET AL., 2011	12 asymptomatic, multiply concussed athletes at > 12 months and 14 controls	prolonged CSP and increased LICI
DE BEAUMONT ET AL., 2012	13 athletes with repeated concussions at ≥ 9 months and 19 controls	increased LICI; no difference in CSP or RMT
MILLER ET AL., 2014	15 MTBI at 3 days and 1, 2, 4 and 8 weeks, 15 controls	prolonged CSP throughout the testing period; no difference in RMT
PEARCE ET AL., 2014	40 athletes with multiple concussions several years before, 20 controls	reduced CSP, SICI and LICI, with correlations to motor control test results
TREMBLAY ET AL., 2015	5 MTBI at 2 weeks, no controls	continuous theta-burst stimulation failed to elicit the usual suppression of MEPs
PEARCE ET AL., 2015	8 athletes tested before and at 2, 4 and 10 days after concussion, 15 controls	prolonged CSP at 2 and 4 days, correlating with performance in visuomotor and attention tests; other tests including AMT, RMT and SICI normal
DAVIDSON AND TREMBLAY, 2016	16 asymptomatic, concussed at ≥ 6 months to several years before, 16 controls	abnormalities in measures derived from ISP; other measures such as RMT and CSP normal
EDWARDS AND CHRISTIE, 2017	9 concussed, assessed repeatedly from 3 days to 2 months, 14 controls	lower RMT, higher resting MEP and prolonged CSP; no significant evolution in results during follow-up

* Abbreviations: AMT (active motor threshold), CMCT (central motor conduction time), CSP (cortical silent period), ICF (intracortical facilitation), ISP (ipsilateral silent period), LICI (long-interval intracortical inhibition), MEP (motor evoked potential), RMT (resting motor threshold), SICI (short-interval intracortical inhibition).

As the data in table 3 and the reviews by Major et al. (2015) and Lefebvre et al. (2015) confirm, changes in motor cortical excitability occur in MTBI. Signs related to increased intracortical inhibition have been most commonly detected (e.g. prolonged CSP), but there is much inconsistency in the results. Negative and

sometimes even opposite findings (increased excitability) are also common. Interpretation of the literature is complicated by varying times from injury to testing, dissimilar study populations and often small sample sizes.

Based on pharmacological studies, the synaptic mechanisms of intracortical inhibition and facilitation are mainly related to gamma-aminobutyric acid (GABA) and glutamatergic signalling (Kähkönen and Ilmoniemi, 2004; Paulus et al., 2008a). Glutamate is considered an excitatory transmitter and GABA inhibitory, but their contributions and interactions at neural level are complex. Studied with MR spectroscopy, motor cortex glutamate/glutamine concentrations have been found to correlate with CSP duration, but correlations with GABA are not reliably found. The latter is possibly because MR spectroscopy measurements depend mainly on metabolic and ambient extracellular GABA levels and do not accurately represent synaptic GABA (De Beaumont et al., 2012; Dyke et al., 2017; Tremblay et al., 2013).

Studies of paediatric MTBI and TMS evoked motor potentials have led to somewhat contrasting results, with signs of decreased intracortical inhibition (King et al., 2019; Seeger et al., 2017) and increased intracortical facilitation (King et al., 2019) reported in children who remained symptomatic after MTBI. Although paediatric MTBI is outside of the scope of this thesis, the results serve to highlight the potential complexities of cortical excitability changes after MTBI. TMS evoked motor potentials have also been studied in severe TBI, where both intracortical inhibition and facilitation have been found to be decreased and MTs elevated (Bagnato et al., 2012; Bernabeu et al., 2009).

2.7.3 TMS and electroencephalography

Electroencephalography (EEG; Berger, 1929) signal recorded with scalp electrodes is generated by extracellular, postsynaptic electric potentials of cortical neurons. Signal can be generated by both inhibitory and excitatory postsynaptic potentials, but neuronal action potentials notably are not a significant contributor to EEG signal. For signal to be measurable, synchronised activity of a large number of neurons is required (Beniczky and Schomer, 2020). It has for example been estimated that about 10 cm^2 of synchronised cortical activity is usually required to generate a detectable epileptiform spike discharge in clinical EEG (Tao et al., 2005). In addition, localising slower potential generators can be ambiguous due to volume conduction effects and typically a relatively distant reference electrode (Burle et al., 2015). Thus, besides being limited to measuring cortical potentials, EEG lacks anatomical precision compared to neuroimaging tools like CT or MRI. Temporal resolution on the other hand is considered excellent, being in the order of milliseconds, although volume conduction issues affect this to some extent also

(Burle et al., 2015). Methods such as current source analysis have been developed to improve the spatial resolution of EEG (Burle et al., 2015; Kamarajan et al., 2015).

In clinical use, analysis of raw EEG waveform can be used for e.g. identification of epileptiform activity (Slimen et al., 2020). In scientific context, more complex preprocessing is typically needed to demonstrate a link between brain's electrical activity and certain sensory or cognitive processes. A common approach is analysing event-related potentials (ERPs), which are negative or positive potentials (i.e. deflections above or below the baseline of the EEG waveform) associated and time-locked to a certain stimulus or an event. ERP analysis typically involves averaging the EEG across multiple trials that include the same stimulus, to enable detection of ERPs from background (spontaneous) electrical activity. EEG data can also be broken down to frequency bands to measure the power and coherence of oscillatory electric activity at specific frequencies. These two approaches can also be combined as in event-related oscillation analysis (Kamarajan et al., 2015).

Combining TMS and EEG (TMS-EEG) allows direct measurement of brain electrophysiological responses to magnetic stimulation. TMS has the potential to cause electrode heating and displacement and induce artefactual current in the electrodes, resulting in safety issues and amplifier saturation with immense artefacts. Therefore, TMS-EEG requires a specifically built EEG apparatus to minimise these effects (Ilmoniemi et al., 1997; Virtanen et al., 1999). With optimal instrumentation, physiological electrical activity can be measured at earliest 10−12 ms after the TMS pulse (Tremblay et al., 2019). Besides these direct effects of TMS on EEG instrumentation, the auditory and somatosensory evoked potentials related to the sound and somatosensory effects of TMS are also a potential confounder, and various approaches to minimising them have been proposed (Tremblay et al., 2019).

Navigated TMS-evoked EEG responses of primary motor cortex (M1) and dorsolateral prefrontal cortex (DLPFC) stimulation have shown high intraindividual test-retest reproducibility (Kerwin et al., 2018; Lioumis et al., 2009). Conditions that on a group or individual level may affect TMS-EEG responses are however many, including psychiatric disorders, Alzheimer's disease, antiepileptics and other drugs, ethanol intake, repetitive TMS therapy, and neurocognitive states such as performing some predefined cognitive or manual task (Cao et al., 2021; Darmani et al., 2019; Kähkönen et al., 2001; Kičić et al., 2008; Koivisto et al., 2017; Nardone et al., 2021). TMS-EEG thus seems to have both a high test-retest reliability and high sensitivity for probing the state of the brain, but the significance and neurophysiological mechanisms of the measured data in a given clinical context are variably understood.

EEG signal elicited by TMS is considered to reflect both cortical reactivity and spread of activation to other brain areas, making it a potential tool for studying functional connectivity of the brain (Cracco et al., 1989; Ilmoniemi et al., 1997). Notably, connectivity in MTBI has also been studied using fMRI, with multiple studies finding abnormalities especially in frontal areas being associated with symptoms (reviewed in Coyle et al., 2018). Unlike EMG based measurements, TMS-EEG is not limited to the study of the motor system, but most cortical brain areas can be studied. Compared to other non-invasive neuroimaging methods (e.g. fMRI or positron emission tomography), TMS-EEG offers superior temporal resolution and allows relatively direct causal inferences to be made from the stimulus to resultant activity. The usual evoked potentials by TMS include N15, P30, N45, P55, N100, P180 and N280 after M1 stimulation and P25, N40, P60, N100 and P185 after DLPFC stimulation (Kähkönen et al., 2005a; Kähkönen et al., 2005b; Lioumis et al., 2009). In M1 the early N15-P30 peaks likely reflect cortical excitatory activity and N45-N100 inhibitory activity (Tremblay et al., 2019). Physiological significance of evoked potentials on non-motor areas remains less well described.

TMS-EEG has seen scant application in TBI. Bashir et al. (2012) published a case study of one previously healthy patient with normal clinical MRI and DTI findings, tested at 2 and 6 weeks post MTBI and compared to a control group. They found more widespread activity at 50 ms on topographical maps, compared to controls, at both time points. Response to continuous theta burst stimulation was abnormal at 2 weeks but normalised by 6 weeks. This stimulation paradigm normally evokes inhibition, but opposite was observed in the MTBI patient (cf. Tremblay et al., 2015, results summarised in section 2.7.2, Table 3). Levy-Lamdan et al. (2020) studied TBI patients with structural signs of injury in MRI and stroke patients in chronic phase using TMS-EEG and so-called direct electrophysiological imaging (DELPHI). DELPHI software automatically extracts certain parameters of the TMS-evoked EEG response, and among other things can compare the TMS-EEG waveform's global adherence to age-matched healthy controls' data. Using this approach, the investigators found the TBI groups waveform deviated significantly from healthy controls on all examined brain regions, and the slope of the early part of the response (60−100 ms) deviated on left temporal and parietal areas (close to the stimulation site).

To some extent, TMS has also been evaluated as a tool for mitigation of MTBI related symptoms (e.g. depression and neurocognitive symptoms). A recent review (Oberman et al., 2020), based on nine original studies concludes that repetitive TMS has been safely applied also in this patient group, but there is no conclusive evidence of its efficacy. Generally, the studies suffer from small sample sizes and heterogeneity of applied TMS methodology, and results are mixed.

3 Aims

The aim of this thesis is to study potential new methods for the detection of MTBI related microstructural cerebral injuries, with emphasis on long-term sequelae of MTBI. We hypothesised that changes in cortical excitability and cerebral connectivity are related to symptoms of MTBI and could be uncovered with the tested new methods. Included studies were designed to probe the sequelae of MTBI from both a functional and a structural connectivity perspective. Specific aims of included studies were:

I Using TMS and EMG, to test whether elevated motor threshold (a marker of cortical excitability) could be found in chronic stage MTBI, and whether it is related to residual symptoms.

II To evaluate the capacity of navigated TMS evoked EEG responses of M1 and DLPFC to differentiate groups of fully recovered and persistently symptomatic patients with chronic stage MTBI from healthy controls.

III To compare DTI based deterministic tractography to CSD based probabilistic tractography and TractSeg automatic tract segmentation in chronically symptomatic TBI. It was hypothesised that CSD based tractography could be more sensitive in detecting microstructural changes related to TBI.

4 Materials and Methods

4.1 Participants

All participants gave their written informed consent before participation. All studies were accepted by the Ethical Committee of the Hospital District of Southwest Finland and carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki). All participants with a history of TBI were recruited at the TBI outpatient department of Turku University Hospital, from patients previously treated or evaluated there.

4.1.1 TMS-MEP and TMS-EEG study (I−II)

Symptomatic and recovered participants with a history of MTBI (N = 19) were tested and compared to healthy controls (N = 9). Inclusion criteria for patients were 1) age 18−65 years, 2) a history of a MTBI according to GCS 13–15 at admission to emergency department, 3) either full recovery (return to normal activities of work or studies, without any subjective symptoms or reports of problems by near ones) or chronic sequels fulfilling the ICD-10 criteria of postconcussional syndrome, and 4) normal findings in 3T routine clinical brain MRI, as evaluated by a neuroradiologist. MRI was performed at earliest 6 months after the injury and in most participants more than 1 year after the injury. At the least 3D T1, T2 and FLAIR sequences were available for all.

Exclusion criteria were clinically uncertain diagnosis, psychiatric or neurological comorbidities (excluding migraine), use of centrally acting drugs, or evidence of nervous injuries affecting limb functions.

Controls were 18−65-year-old healthy volunteers with no history of TBI and otherwise fulfilling the same criteria.

In the acute stage, all MTBI participants had had a variety of typical TBI symptoms, including fatigue, attention deficit, poor memory, and loss of initiation. Participants in the recovered group were clinically asymptomatic at the time of testing. Recovery was ascertained with a detailed interview with the relatives, neuropsychological examination, or both. Participants in the symptomatic group presented with a similar range of symptoms as in the acute stage and had received a

diagnosis of postconcussional syndrome. Diagnosis was based on careful evaluation of present symptoms, pre-injury health and function (both subjective report and report obtained from near ones), neuropsychological examination, structural brain MRI, evaluation of the injury mechanism and symptoms during the acute phase, and exclusion of other likely explanations for the symptoms. Patient evaluation was performed by a neurologist experienced in TBI evaluation.

4.1.2 DWI study (III)

Participants were 37 symptomatic patients with a history of TBI and 41 age and sex matched healthy controls. Patients were considered for inclusion if following criteria were met: 1) age 18−65 years during the injury and inclusion to the study, 2) no neurological comorbidities besides possible migraine, 3) no psychiatric comorbidities requiring treatment (a history of mild depression or anxiety disorder was permitted, if no medication or other treatment was presently required), 4) a history of non-penetrating TBI with the lowest acutely documented GCS of 13−15, 5) besides possible microhaemorrhages, no evidence of trauma or other neurological disease in routine clinical MRI evaluation (e.g., no mass lesions), 6) Glasgow outcome scale extended available, evaluated 6 months after injury earliest by an experienced neurologist, and scored < 8, indicating incomplete recovery, 7) presence of residual symptoms clinically related to TBI.

All patients had clinically obvious sequels from their TBI based on standard clinical evaluation. This was carefully assessed based on a detailed history of the injury event and symptom evolution, neuropsychological evaluation, and absence of other possible causes for the symptoms. The clinical variables GCS, GOSE, PTA duration, and time from injury to imaging were extracted from the patient records. Controls were healthy 18−65-year-old volunteers with no history of TBI and otherwise fulfilling the same criteria.

4.2 Navigated TMS (I−II)

A Magstim 200 stimulator (The Magstim Company Ltd., Whitland, UK) with a 70 mm figure-of-eight coil (P/N9925) was used with eXimia NBS navigation system (Nexstim Ltd., Helsinki, Finland). 3D T1-weighted MRIs were used for TMS navigation. Stimulation targets were the left M1 hand motor area (“motor knob”) and left DLPFC. These were individually located on brain MRIs, and with help of the navigation system the stimulation coil was manoeuvred to the optimal location for stimulating these targets, and then fixated in a coil holder. For M1, the same coil position and orientation was used as in RMT determination. For DLPFC, the coil was oriented perpendicular to the middle frontal gyrus. During the experiment,

the participants were comfortably seated in a chair, with head against the headrest, keeping their eyes open and fixated. Earplugs were used to minimize the auditory effect of the coil click.

4.3 EMG and EEG recordings (I−II)

EMG was recorded with a Keypoint electromyograph (Medtronic Inc., MN, USA), with measurement electrodes over the right abductor pollicis brevis muscle. Using suprathreshold pulses, the optimal coil location and orientation for eliciting a muscle contraction from the abductor pollicis brevis was first determined. RMT was defined as the minimum intensity evoking a > 50 μV EMG response from the target muscle, at least 5 times out of 10 stimuli (cf. Rossini ym., 1994).

EEG was recorded with a 60 channel eXimia EEG system (Nexstim Ltd., Helsinki, Finland). Reference electrode was on the right mastoid process, and ground on the right zygomatic bone. Eye movements were recorded (electrooculogram) during the entire session to be able to later eliminate epochs contaminated by eye movements or blinks. During TMS pulses, the amplifier was gated by a sample-and-hold circuit for 2 ms to remove most of the TMS-induced artefact.

During EEG, left M1 and left DLPFC were stimulated, and coil position was monitored in real time using the eXimia navigation system. One hundred single pulses were delivered at 90, 100 and 110% of RMT to each stimulation target. Stimulation frequency was 0.3 Hz. The combinations of different stimulation intensities and targets resulted in six stimulation blocks, which were administered in a randomized order. There were short breaks in the order of few minutes maximum between stimulation blocks, during which the stimulator and recording equipment were managed and the coil repositioned if necessary.

4.4 EEG analysis (II)

EEG data was imported into BrainVision Analyzer 2 (Brain Products GmbH, Gilching, Germany). Data was segmented into epochs of -100 to +500 ms relative to the TMS pulse. Epochs with artifacts from eye movements, muscle activity, or mechanical disturbances were removed from the raw data. A 45 Hz low-pass filter was applied. Remaining epochs were averaged separately for each stimulation intensity (90, 100 or 110% RMT) and stimulation target (M1 or DLPFC). Baseline correction was applied based on -100 to -20 ms prestimulus interval. Electrodes were pooled to form four ROIs (see Figure 3). Evoked potentials were measured from the stimulated ROI and the homologous ROI in the contralateral hemisphere.

Amplitudes and latencies of four peaks (local maxima; P30, N45, P60, N100, P200) were semi-automatically identified in all participants' data.

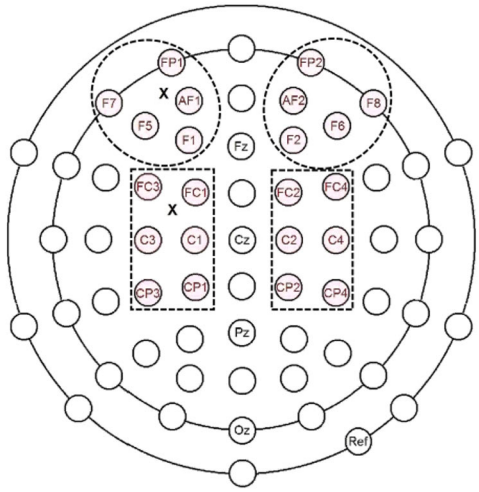

Figure 3. EEG electrode ROIs (in the EEG 10−20 system). Four electrode pools were averaged: left DLPFC (FP1, F7, AF1, F5, F1), right DLPFC (FP2, AF2, F8, F2, F6), left M1 (FC3, FC1, C3, C1, CP3, CP1), and right M1 (FC2, FC4, C2, C4, CP2, CP4). Stimulation was always targeted to the left hemisphere and approximate DLPFC and M1 stimulation foci relative to the electrodes are represented by Xs.

4.5 MRI acquisition (III)

A 3.0 T MRI scanner (Achieva, Philips Medical Systems, Best, Netherlands) was used with an eight-channel sensitivity encoding transmit-receive head coil. DWI was performed in transverse plane with echo-planar sequence (TR 5877 ms, TE 62 ms, 60 2.0 mm slices with no gap, 112 × 128 reconstructed matrix, turbo factor 59, echo-planar imaging factor 59, FOV rectangular 224 mm, two signals acquired). We acquired a b = 0 s/mm^2 image and b = 800 s/mm^2 images with 15 different gradient-encoding directions. Images with isotropic 2 mm voxel size were obtained. Besides DWI, routine T1, T2, fluid-attenuated inversion recovery and susceptibility weighted images were acquired. All images were analysed by a neuroradiologist to ascertain that inclusion criteria were fulfilled.

4.6 DWI analysis (III)

4.6.1 DTI based approach

Images were postprocessed to remove distortions due to shear, eddy currents, and motion using Diffusion Registration Tool (Philips Medical Systems). Deterministic DTI tractography was done using the FiberTrak software (Philips Medical Systems).

Analysed tracts were corpus callosum, left and right cingulum, left and right uncinate fascicle, and left and right superior longitudinal fascicle. Each was defined by two freehand inclusion ROIs and possible one exclusion ROI. ROIs were drawn based on individual anatomy, as depicted in overlaid colour coded DWI and T1 images. The ROIs were generated by a radiologist and inspected by a neuroradiologist. The tracts were defined in the following way: 1) The corpus callosum was defined by two inclusion ROIs drawn on sagittal images at the level of the left and right cingulate gyrus and including the corpus callosum. 2) The cingulum was defined by two inclusion ROIs drawn around the cingulum on coronal images at the level of the upper part of the aqueduct and at the level of the mamillary bodies. Also, an exclusion ROI was drawn around the corpus callosum on a midline sagittal image. 3) The superior longitudinal fascicle was defined by two ROIs drawn around the fascicle on coronal images at the level of the upper part of the aqueduct and at the level of the mamillary bodies. 4) The uncinated fascicle was defined by two ROIs drawn on a single coronal image, one surrounding the most anterior part of the fascicle that could be seen traversing in anteroposterior direction in the basal frontal lobe, and the other ROI surrounding the entire anterior temporal lobe at the same level.

For tract termination a minimum FA limit 0.5 was used for corpus callosum and 0.3 for the other tracts, and a maximum angle limit of 27°. Minimum track length was set at 10 mm. These criteria were used to reconstruct each tract volume, from which average FA and MD values were calculated by the FiberTrak software.

4.6.2 CSD based approach

For the CSD based tractography, DWI images were denoised (Veraart et al., 2016), corrected for Gibbs ringing artefacts (Kellner et al., 2016), eddy currents and head motion (Andersson and Sotiropoulos, 2016), and bias field (Tustison et al., 2010). MRtrix3 (Tournier et al., 2019) was used to generate fibre orientation distribution function (fODF) peaks, using the Tournier et al. (2013) iterative algorithm. Spherical harmonics up to order four were used to estimate the fODF. The fODF peaks were used as input for TractSeg to reconstruct fibre bundles, using

probabilistic tract orientation mapping tractography (Wasserthal et al., 2019, 2018b).

To evaluate the effect of the more advanced preprocessing methods available in the CSD analysis pipeline, compared to the DTI pipeline, an alternative CSD and TractSeg based analysis was calculated, with only motion and eddy current correction preprocessing steps. These results are reported separately. From both CSD and DTI based tractography the mean FA and MD values of selected tracts were extracted for statistical analysis.

4.7 Statistical analyses

4.7.1 TMS-MEP and TMS-EEG data (I−II)

Participant characteristics variables were compared between the groups using one-way analysis of variance (ANOVA), χ^2 test and independent samples t-test. RMTs were compared using one-way ANOVA with Tamhane's T2 post hoc tests.

The EEG data were analysed with repeated measures analyses of covariances (ANCOVAs) with stimulation intensity (90 / 100 / 110% RMT) × hemisphere (left / right, according to measured ROI's side) design, with participant group (symptomatic / recovered / control) as a between subjects factor, and RMT as a covariate. The analysis was focused on effects involving the factor participant group. Separate ANCOVAs were computed for amplitude and latency data of each peak and stimulation site (M1 / DLPFC). Partial eta squared estimates of effect size (η^2_p) were calculated. For post hoc comparisons, t tests were used. Greenhouse-Geisser and Bonferroni corrections were applied when appropriate. Stepwise linear discriminant analysis (LDA) with Wilks' Λ method and criteria $F = 2.5$ to enter or remove a variable were used to find a subset of variables that best distinguished between the groups. In LDA the variables were included where statistically significant differences were found between the participant groups in the main analysis. Statistical analyses were performed with IBM SPSS version 19 (IBM, Armonk, NY, USA).

4.7.2 DWI data (III)

Repeated measures analysis of variance (rmANOVA) was conducted, with analysis method (CSD based or DTI based) and tract (corpus callosum, and separately for each hemisphere the uncinate fascicle, cingulum, and superior longitudinal fascicle) as within-subjects variables and group (controls or TBI) as a between-subjects factor. Greenhouse-Geisser correction was applied where sphericity assumption was violated. Partial eta squared effect size estimates (η^2_p) were

calculated. Independent or paired samples t-tests and Mann-Whitney U-tests with Bonferroni corrections were used for post-hoc comparisons and χ^2 test for sex distribution. Spearman rank-order correlation coefficients were calculated to evaluate the relation of clinical variables (GCS, GOSE, PTA and time from injury) to tractography statistics. Pearson correlation coefficients were calculated to compare the FA and MD produced by each tractography method for every tract, and also for a calculated grand mean FA and MD, including data from all the tracts. All analyses were performed separately for the FA and MD values. Statistical analyses on DWI data were done using IBM SPSS Statistics version 25 (IBM corp., Armonk, NY, USA) and Matlab R2021a (The MathWorks, Natick, MA, USA).

5 Results

5.1 Participant characteristics (I−III)

5.1.1 TMS-MEP and TMS-EEG study (I−II)

Participant characteristics are outlined in Table 4.

Table 4. Participant characteristics (I−II).

	Symptomatic *(N = 11)*	**Recovered** *(N = 8)*	**Control** *(N = 9)*
Sex *(male / female)*	4 / 7	4 / 4	6 / 3
Age *(years, mean ± SD)*	43.7 ± 11.6	35.9 ± 15.9	33.6 ± 13.2
Age range *(years)*	30−61	19−56	23−59
Time from injury to testing *(years, mean ± SD)*	6.0 ± 5.4	3.8 ± 1.1	
N of participants with ≥ 24 h PTA	4	1	

The TBI had been sustained on average 5 years earlier. PTA duration varied from none to 2.5 weeks, with five participants (four in the symptomatic and one in the recovered group) having more than 24 h PTA, so their injury would not be classified as mild based on the WHO criteria. The differences in age ($p = 0.222$), PTA duration ($p = 0.579$), time from injury to testing ($p = 0.267$) and sex ($p = 0.403$) between the groups were not statistically significant. Two participants were left-handed (one in the control group and one in the recovered group), others were right-handed.

5.1.2 DWI study (III)

Characteristics of the participant sample are presented in Table 5.

Table 5. Participant characteristics (III). For sex and age, p-values (χ^2 test for sex and independent-samples t-test for age) of between groups comparisons are reported.

	TBI *(N = 37)*	**Control** *(N = 41)*	**p-value**
Sex *(female / male)*	15 / 22	17 / 24	0.934
Age *(years, mean ± SD)*	37.2 ± 11.4	36.4 ± 11.9	0.777
Age range *(years)*	19−60	18−57	
Time from injury to MRI *(years, mean ± SD (range))*	1.2 ± 2.1 (0.04−9.9)		
GCS *(score, (range))*	14.7 ± 0.6 (13−15)		
PTA *(hours, (range))*	76 ± 23.0 (0−504)		
GOSE *(score, (range))*	5.6 ± 1.1 (4−7)		
Microhaemorrhages	11 patients (29.7%)		

On average, the participants with TBI had sustained the injury 1.2 years before MRI, with shortest interval being 2 weeks and longest 9.9 years. All TBIs were sustained in civilian settings, with most common mechanisms being traffic accidents and falls, and some cases of assault also included. No penetrating or blast induced TBIs were included. All participants' TBI had been initially evaluated as mild based on GCS 13−15. However, 40.5% of patients were found to have a PTA ≤ 24 hours and 59.5% had a PTA > 24 hours, and 11 TBI participants (29.7%) had microhaemorrhages detected in clinical MRI. Depending on classification used, these features may imply a complicated mild or moderate TBI, despite initial mild level GCS. All TBI participants had incomplete functional recovery (GOSE < 8). The clinical neurological and neuropsychological evaluation results were studied from patient records and revealed common TBI related symptoms (e.g., fatigue, memory and emotional problems, minor motor symptoms).

5.2 TMS studies (I−II)

5.2.1 Motor thresholds (I)

RMTs differed among the groups ($F_{2,25} = 4.89$, $p = 0.016$, $\eta^2_p = 0.28$). The control group's mean RMT ± SD was 43.0 ± 0.8% of the maximum stimulator output, which was lower than in the symptomatic (52.5 ± 3.1%, $p = 0.036$) or the recovered (54.6 ± 3.4%, $p = 0.033$) group. Difference between the symptomatic and recovered group was non-significant. The results are presented in Figure 4 (note also relatively large variability in MTBI groups).

Excluding the five participants with PTA > 24 h from the analysis, there was still a statistically significant difference among the groups in RMT ($p = 0.008$), but in post hoc comparisons only the symptomatic group now differed from the controls ($p = 0.041$). No correlation was found between PTA and RMT.

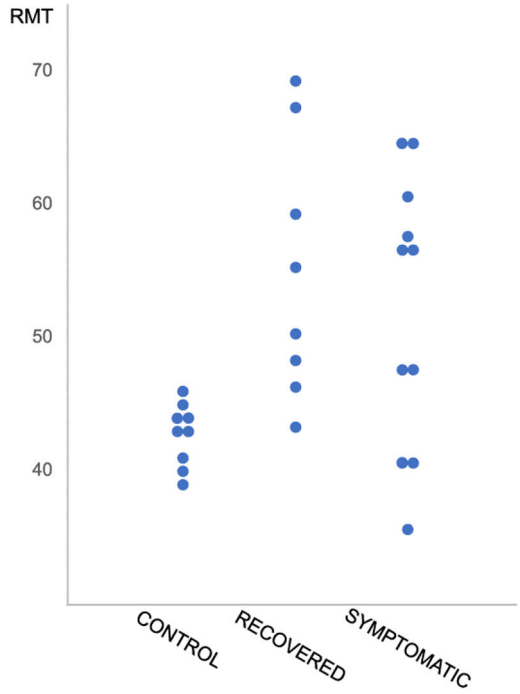

Figure 4. Individual participants' RMTs as % of maximum stimulator output, plotted separately for each group.

5.2.2 DLPFC evoked potentials (II)

Results of evoked potential analysis will be reported in the order in which the peaks temporally occur, i.e. first the results concerning P30, then N45, P60, N100 and P200. Average DLPFC stimulation evoked potential waveforms are presented in Figure 5.

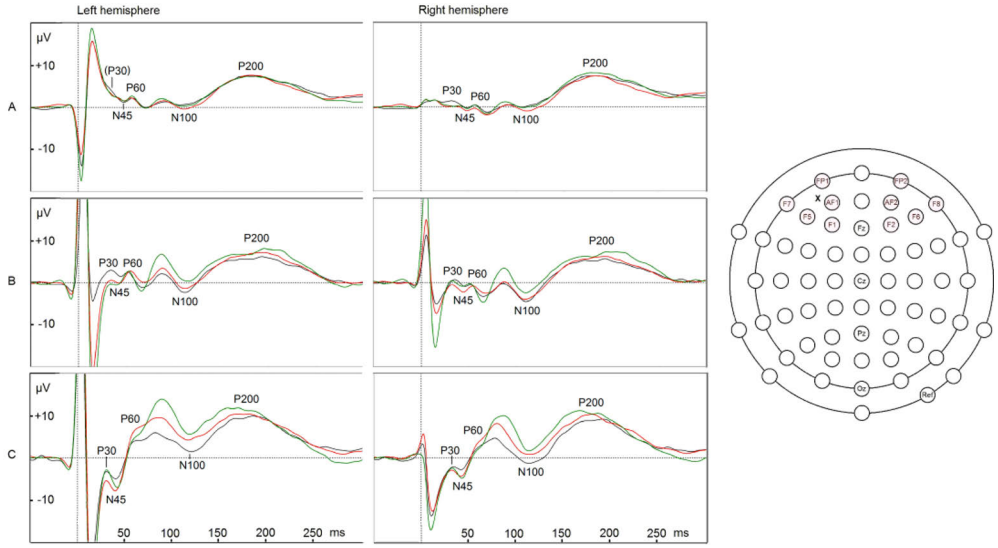

Figure 5. DLPFC evoked potentials, separately from the left (ipsilateral to stimulation) and right DLPFC ROI. Separate plots are presented of each participant group (A = control, B = symptomatic, C = recovered). Separate lines are drawn of each stimulation intensity (90% = black, 100% = red, 110% = green). Approximate stimulation site is marked with an "x" in the electrode map.

Summary of statistically significant effects is presented in Table 6, and more detailed description of the analyses in text below.

Table 6. Summary of statistically significant effects of the main analysis of DLPFC amplitude and latency data and indented the most likely explanations for these according to follow-up analyses. P-values are corrected for multiple comparisons. Ns = nonsignificant. Further details in text.

DLPFC stimulation	Amplitudes	Latencies
P30	ns	intensity × hemisphere × group ($p = 0.044$, $\eta^2_p = 0.18$) - left hemisphere at 90%, longer latencies in the symptomatic group vs. controls
N45	ns	hemisphere × group ($p = 0.040$, $\eta^2_p = 0.24$) - right hemisphere, longer latencies in the symptomatic group vs. recovered
P60	ns	ns
N100	main effect of group ($p = 0.044$, $\eta^2_p = 0.23$) - higher amplitudes in the symptomatic group vs. recovered	ns
P200	ns	main effect of group ($p = 0.043$, $\eta^2_p = 0.23$) - shorter latencies in the recovered group vs. other groups?

For P30 latencies, an intensity × hemisphere × group interaction was found ($p = 0.044$, $\eta^2_p = 0.18$). Follow-up ANCOVAs separately for each hemisphere showed an intensity × group interaction only on the ipsilateral (left) hemisphere ($p = 0.004$, $\eta^2_p = 0.19$), where on further examination, a statistically significant difference between the groups was found at 90% stimulation intensity ($p = 0.021$, $\eta^2_p = 0.28$), because of longer ipsilateral P30 latencies in the symptomatic group (39 ± 11 ms), compared to the control group (26 ± 11 ms, $p = 0.028$). No significant differences between the groups were found at 100% or 110% stimulation intensities.

For N45 latencies, a hemisphere × group interaction was found ($p = 0.040$, $\eta^2_p = 0.24$). On follow-up ANCOVAs separately for each hemisphere, the groups differed statistically significantly only on the contralateral (right) hemisphere latencies ($p = 0.030$, $\eta^2_p = 0.25$), because of longer latencies in the symptomatic group (54 ± 9 ms), compared with the recovered group (44 ± 8 ms; $p = 0.05$). Control groups' latencies were intermediate (49 ± 6 ms), not differing statistically significantly from the other groups. Ipsilateral hemisphere latencies (control: 50 ± 7 ms; symptomatic: 51 ± 9 ms; recovered: 45 ± 9 ms) did not differ statistically significantly between the groups.

No statistically significant differences were found for P60.

For N100 amplitudes, a main effect of group was found ($p = 0.044$, $\eta^2_p = 0.23$), because of higher N100 amplitudes in the symptomatic group (-4.6 ± 4.4 µV), compared with the recovered group (1.1 ± 4.2 µV; $p = 0.033$). The control group's amplitudes (-2.7 ± 4.6 µV) were intermediate, not differing statistically significantly from the other groups. Based on Figure 5 there seems to be a slower positive shift in recovered groups' amplitudes from approximately 60–100 ms, but statistically significant differences could only be demonstrated for N100 in this time range.

For P200 latencies, a main effect of group was also found ($p = 0.043$, $\eta^2_p = 0.23$). This is because of shorter latencies in the recovered group (167 ± 14 ms) compared with either the control group (183 ± 11 ms, $p = 0.028$, uncorrected), or the symptomatic group (183 ± 18 ms, $p = 0.027$, uncorrected), although the differences were not statistically significant after significance level correction.

5.2.3 M1 evoked potentials (II)

Average evoked potential waveforms for M1 stimulation are presented in Figure 6.

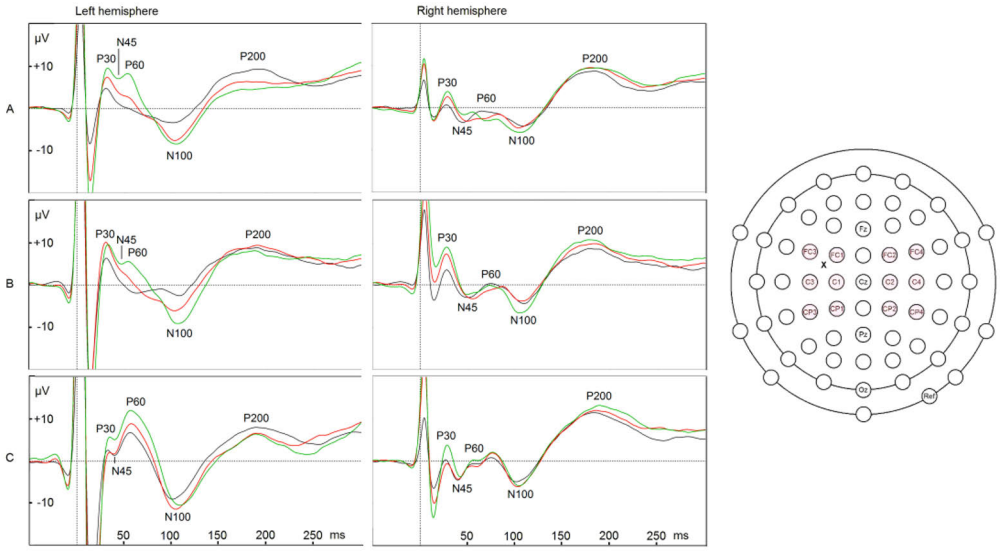

Figure 6. M1 evoked potentials, separately from the left and right hemisphere M1 ROI, and each participant group (A = control, B = symptomatic, C = recovered). Separate lines are drawn of each stimulation intensity (90% = black, 100% = red, 110% = green). Approximate stimulation site is marked with an "x" in the electrode map.

Summary of statistically significant effects is presented in Table 7, and more detailed description of the analyses in text below.

Table 7. Summary of statistically significant effects of the main analysis of M1 amplitude and latency data and indented the most likely explanations for these according to follow-up analyses. P-values are corrected for multiple comparisons. Ns = nonsignificant. Refer to text for further details.

M1 stimulation	Amplitudes	Latencies
P30	intensity × group ($p = 0.048$, $\eta^2_p = 0.18$) - increasing stimulation intensity progressively increases peak amplitude in controls, not in MTBI groups	ns
N45	intensity × group ($p = 0.023$, $\eta^2_p = 0.21$) - amplitude changes with changing stimulation intensity in controls, not as clearly in others?	ns
P60	hemisphere × group ($p = 0.032$, $\eta^2_p = 0.25$) - interhemispheric amplitude difference smaller in symptomatic group compared to recovered?	intensity × hemisphere × group ($p = 0.027$, $\eta^2_p = 0.20$) - at 110% intensity, statistically significant interhemispheric latency difference in the symptomatic group, not found in others
N100	ns	ns
P200	ns	ns

For P30 amplitudes, an intensity × group interaction was found ($p = 0.048$, $\eta^2_p = 0.18$). Post-hoc tests showed a progressive P30 amplitude increase with increasing stimulation intensity in the control group (90/100%: $p = 0.060$; 100/110%: $p = 0.030$), while in the recovered (90/100%: $p = .156$; 100/110%: $p = 1.00$) and symptomatic (90/100%: $p = 1.00$; 100/110%: $p = 0.186$) group, the relation of stimulation intensity and P30 amplitude was weaker, with no statistically significant effects being found in these groups.

For N45 amplitudes, an intensity × group interaction was also found ($p = 0.023$, $\eta^2_p = 0.21$). In post-hoc comparisons, however, no effects remained statistically significant. Closest to significance came the control group's decrease in N45

amplitude while stimulation intensity increased from 100% to 110% ($p = 0.108$). No similar relation between stimulation intensity and N45 amplitude was found in the other groups, probably explaining the interaction.

For P60 latencies, an intensity × hemisphere × group interaction was found ($p = 0.027$, $\eta^2_p = 0.20$). Post-hoc tests showed that in the symptomatic group, there was a statistically significant interhemispheric latency difference at 110% stimulation intensity ($p = 0.009$), while in other groups or other stimulation intensities no statistically significant interhemispheric latency differences were found. On P60 amplitudes, a hemisphere × group interaction was found ($p = 0.032$, $\eta^2_p = 0.25$). All groups had higher amplitudes on the ipsilateral side. Descriptive statistics and post-hoc tests suggest that the amplitude difference was smaller in the symptomatic group compared with recovered, although the difference was non-significant after significance level correction ($p = 0.054$).

5.2.4 Additional analyses (II)

LDA was used in an explorative analysis to test the possibility of grouping the participants correctly on basis of the ERP measures and RMT. Candidate variables for LDA were selected on basis of the statistically significant group-related effects found in the previous analyses and fulfilment of the normal distribution assumption (Shapiro-Wilk test $p > 0.05$). To capture some of the interactions found in the previous analyses, new subtraction variables were formed to reflect the changes observed between different stimulation intensity conditions and the amplitude and latency differences between hemispheres. The resultant model included two variables, RMT and a variable reflecting M1 P60 interhemispheric latency difference change from 90 to 110% stimulation intensity. Figure 7 displays participant classification based on this model. In leave-one-out cross-validation this model classified correctly 55% of symptomatic, 75% of recovered, and 56% of control group participants, with total cross-validated accuracy of 61%.

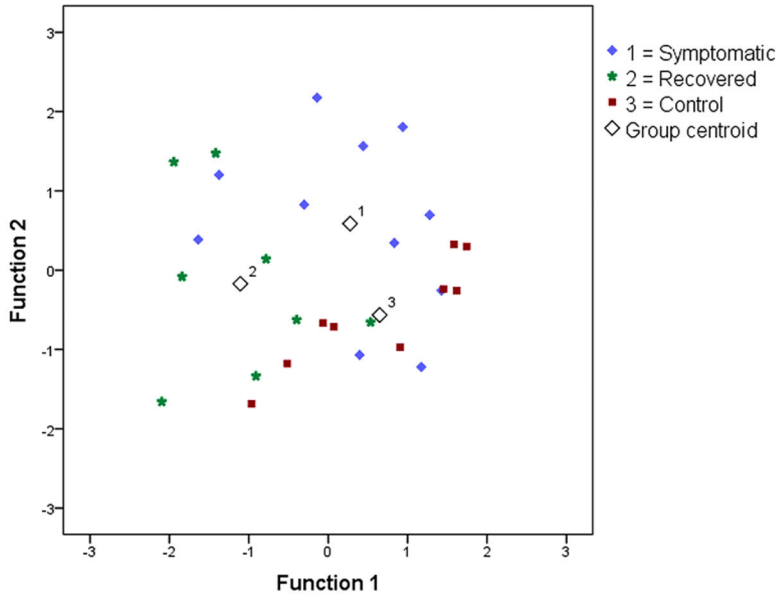

Figure 7. LDA based classification of participants. Standardized coefficients of each variable for functions 1 and 2 respectively are: RMT (- .575, .820) and M1 P60 interhemispheric latency difference change from 90% to 110% stimulation intensity (.786, .620).

The sample included five participants with PTA > 24 h (thus not MTBI on the WHO criteria). To evaluate for the effect of these to the results, the main ERP analyses were repeated leaving these participants out. This resulted in some statistically significant group related effects being lost and some new ones gained, with overall outcome substantially the same. This analysis is reported in more detail in original publication II.

5.3 Analysis of DWI data (III)

5.3.1 Analysis of FA and MD values (III)

Sample tractograms are presented in Figure 8.

As could be expected, different FA and MD values were found for different tracts (FA $p < 0.001$, MD $p < 0.001$). CSD and TractSeg tractography resulted in generally lower FA ($p < 0.001$) and lower MD ($p < 0.001$) values than DTI tractography.

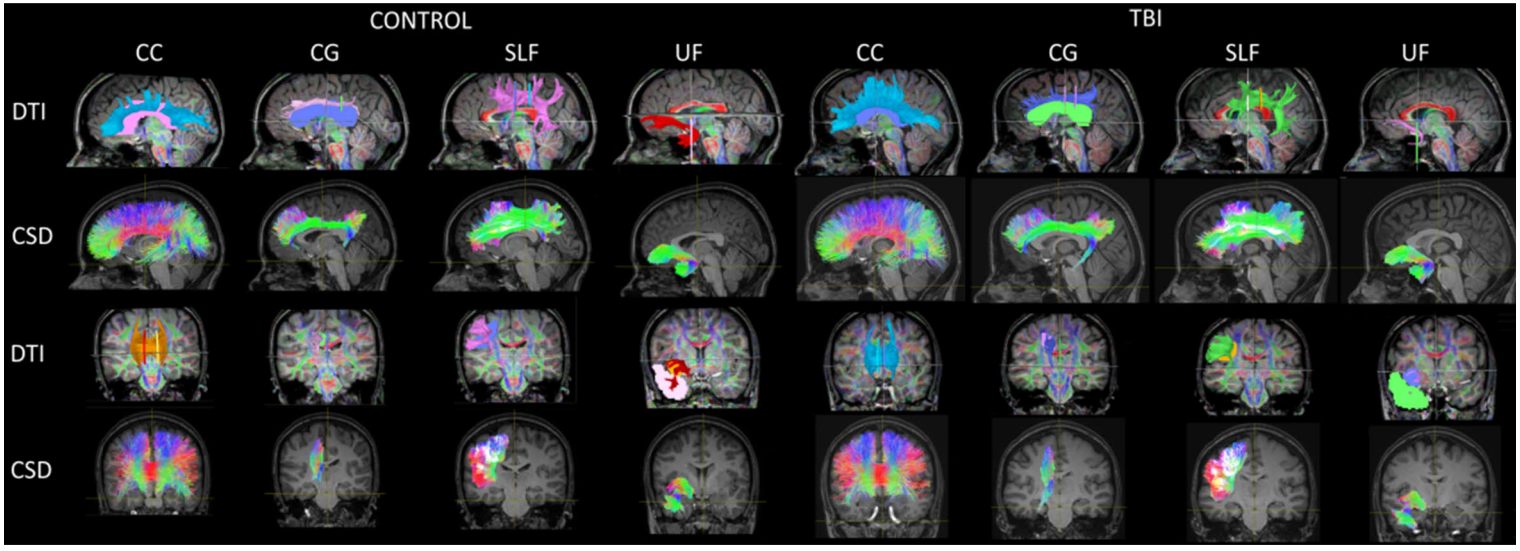

Figure 8. Sample tractograms from DTI and CSD based tractographies. On the left a sample patient's data from the control group and on the right from the TBI group. Data from different tractography methods is organised in rows, with sagittal images in two upper rows and coronal images in the lower rows. Tractograms are overlaid on T1 weighted images. For DTI, the ROIs on which the tractograms are based on are also demonstrated. CC, corpus callosum; CG, cingulum; UF, uncinated fasciculus; SLF, superior longitudinal fasciculus.

An interaction was found between tractography method and tract studied ($p < 0.001$ and $\eta^2_p = 0.969$ for FA values and $p < 0.001$ and $\eta^2_p = 0.770$ for MD values). Based on descriptive statistics (not shown) and Figure 9 this is due to CSD and DTI approaches resulting in different relative FA and MD values for different tracts. For example, with CSD and TractSeg the highest FA values were found in the superior longitudinal fascicles, but with DTI the highest FA was found in the corpus callosum (Figure 9).

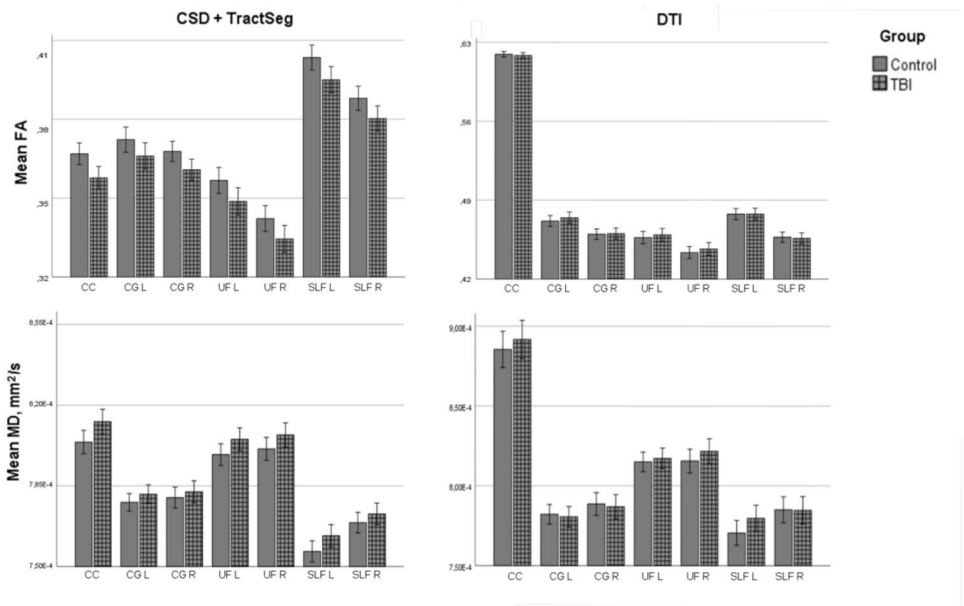

Figure 9. Mean values ± 95% confidence intervals of mean for each tract, separately for each group. Upper row, FA values; lower row, MD values. Left column, CSD and TractSeg; right column, DTI. CC, corpus callosum; CG, cingulum; UF, uncinated fasciculus; SLF, superior longitudinal fasciculus; L, left; R, right.

There was an interaction between the participant group and tractography method on FA values ($p < 0.001$, $\eta^2_p = 0.217$) and with a smaller effect size on MD values ($p = 0.007$, $\eta^2_p = 0.092$). To explain this, separate rmANOVAs were calculated for each tractography method. CSD based approach resulted in lower FA values ($p = 0.009$, $\eta^2_p = 0.086$) in the TBI group compared to the control group, while FA values derived from the DTI approach did not differ statistically significantly between the groups ($p = 0.772$, $\eta^2_p = 0.006$). Thus, the CSD based approach was able to differentiate the patient group from controls based on FA, but the same was not found for DTI.

For the MD values, follow-up rmANOVA did not reveal statistically significant effect of group on either the CSD based ($p = 0.059$, $\eta^2_p = 0.046$) or DTI

based values ($p = 0.322$, $\eta^2_p = 0.015$). Thus, the weaker group × method interaction for MD values is not conclusively explained. Based on descriptives and Figure 9 it may, however, be related to the higher MD values in TBI group compared to controls in CSD based tractography, while the difference between groups seems smaller in DTI tractography.

Correlation analyses did not reveal correlations between the recorded background variables (GCS, GOSE, PTA and time interval from injury to imaging) and tractography results.

5.3.2 Correlation between DTI and CSD based analysis methods (III)

Correlation coefficients were calculated for each tract's CSD and DTI tractography derived values. The results of the different tractography methods were positively correlated in every tract. Strong correlations were generally found for MD values. Most FA values were moderately or strongly correlated between the methods, with the strongest correlations found in the superior longitudinal fasciculi, and only a weak (but statistically significant) correlation in the left uncinate fascicle (Table 8).

Table 8. Pearson correlations of the different tractography methods for each tract. Correlations of both FA and MD values are indicated. CC, corpus callosum; CG, cingulum; UF, uncinated fasciculus; SLF, superior longitudinal fasciculus; L, left; R, right. Pearson correlation coefficients and p-values are reported.

	CC	**CG L**	**CG R**	**UF L**	**UF R**	**SLF L**	**SLF R**
FA	0.588 p < 0.001	0.532 p < 0.001	0.547 p < 0.001	0.387 p < 0.001	0.546 p < 0.001	0.686 p < 0.001	0.784 p < 0.001
MD	0.825 p < 0.001	0.828 p < 0.001	0.855 p < 0.001	0.762 p < 0.001	0.832 p < 0.001	0.876 p < 0.001	0.852 p < 0.001

As the correlation properties of each tract were very similar, mean FA and MD values across all tracts were also calculated by adding all individual tract results and dividing by the number of tracts. This was done to allow simpler presentations of the distribution and correlation of FA and MD values between DTI and CSD based tractography. The distributions of these compound mean FA and mean MD values are displayed in Figure 10. It is noteworthy that the distributions of control and TBI groups' values overlap in large part, but in CSD and TractSeg derived FA values, there is a longer tail of small FA values, representing a minority of TBI patients with more deviant values.

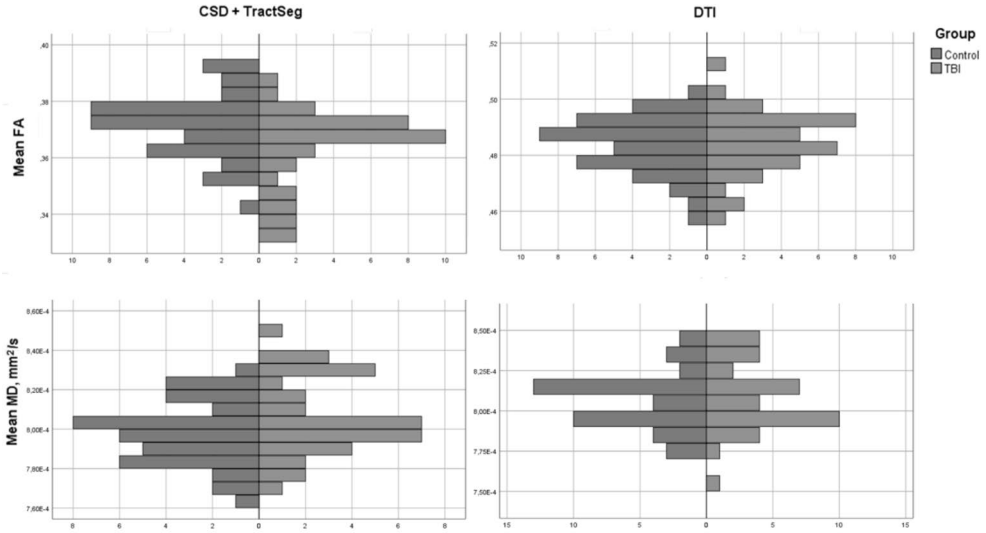

Figure 10. Pyramid plots of the distribution of mean MD and mean FA. Upper row, FA values; lower row, MD values. Left column, CSD; right column, DTI. On X axis is frequency (n of participants). Left side of each pyramid plot represents the controls and right side TBI group.

The mean FA values measured by DTI and CSD based tractography were moderately strongly correlated ($r = 0.710$, $p < 0.001$). The mean MD values were strongly correlated ($r = 0.911$, $p < 0.001$). Figure 11 visualises these correlations.

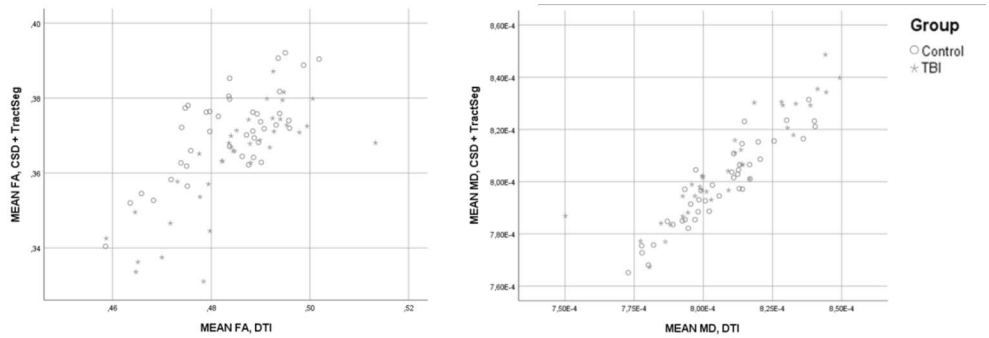

Figure 11. Scatter plots of mean FA and MD values. X axis represents values derived from DTI tractography and Y axis values from CSD tractography. Control group participants are represented by circles and TBI group participants by asterisks.

5.3.3 Alternative preprocessing approach (III)

To test for the effects of different preprocessing methods in DWI analyses, CSD and TractSeg tractography was done using only motion and eddy current correction, leaving the other previously mentioned preprocessing stages out to yield a preprocessing pipeline more similar to what was employed in the DTI based analysis. Using this preprocessing, we repeated the rest of the analysis and the rmANOVAs described in section 5.3.1. Mostly corresponding results were found, including the interaction of participant group × tractography method on FA values ($p < 0.001$). Changes brought by the alternative preprocessing include for FA values loss of the statistical significance of the previous tract × age interaction and for MD values loss of the interactions method × group and tract × method × age. At the same time new effects that gained statistical significance included interactions of method × age for both FA ($p < 0.001$) and MD values ($p = 0.027$).

6 Discussion

6.1 Elevated RMT in chronic MTBI (I)

Elevated RMT was found in a sample of chronic MTBI patients years after injury. It was not related to symptomatic recovery in this data. Greater variation was found in the MTBI group compared to controls, and many MTBI participants' RMTs were in the normal range. It is believed that clinical recovery in TBI is achieved to some extent by recruitment of reserve capacity or compensatory mechanisms, as neural tissue has little capacity for regeneration (Bigler and Stern, 2015; Turner et al., 2011). This could potentially explain why altered neurophysiological results were obtained even in the symptomatically recovered patients, although more direct support for this notion is not available from the present data.

RMT is considered to reflect the excitability of the motor cortex and the entire corticospinal tract (Bestmann and Krakauer, 2015). It is thus a relatively global and imprecise measure of the functionality of the motor system. Although there is other evidence from TMS studies for increased intracortical inhibition in MTBI (Lefebvre et al., 2015; Major et al., 2015), this is not necessarily the mechanism for elevated RMT based on pharmacological studies. RMT has been shown to be unaffected by gabaergic agents that increase intracortical inhibition and decrease facilitation (Kähkönen and Ilmoniemi, 2004; Paulus et al., 2008b). On the other hand, RMT elevation is caused by Na^+ channel blockers (e.g. some common anticonvulsants), that presumably do this by decreasing axonal excitability (Paulus et al., 2008b).

The mechanism for abnormal RMT in this study cannot be concluded, but hypothetically it could be related to diffuse microstructural brain injury and resultant less efficient conduction of the descending corticospinal volleys. Besides the general notion of white matter tract injuries in MTBI, this hypothesis is made more plausible by the observation that central motor conduction time and RMT are correlated in patients with mild-to-moderate TBI and structural lesions in MRI (Chistyakov et al., 2001). Spinal injury could also cause elevated RMT but is unlikely in our patients with MTBI and no motor symptoms.

Several earlier studies (reviewed in section 2.7.2) have found abnormalities in TMS-evoked motor potentials after MTBI, most commonly signs of increased

intracortical inhibition. Elevated RMTs specifically have been reported by Chistyakov et al. (1998, 2001) and Nardone et al. (2011), while not found by Davidson and Tremblay (2016), De Beaumont et al. (2007, 2009, 2012), Miller et al. (2014), and Pearce et al. (2015). The opposite, i.e. lower RMT was reported in relatively acute phase of MTBI by Edwards and Christie (2017). The timing of measurements in studies reporting elevated RMT has been from a few days to few months and studies reporting no difference have been done from few days to several years after the injury. Thus, the literature is inconsistent in terms of RMT behaviour after MTBI, but most studies have reported no difference. Some abnormalities in motor cortical excitability seems to occur in MTBI, with impaired inhibition having been most commonly detected and also reported to correlate with symptomatic recovery (review Lefebvre et al., 2015). What the present study may add to the above is the observation that elevated RMT may be a feature of chronic TBI even years after the injury, while most studies have focused on more acute phases.

Unlike the present study, many studies of motor cortical excitability after MTBI have been done in young adults (often athletes) in their twenties (e.g. of the studies reporting no difference in RMT reviewed here: Davidson and Tremblay (2016), De Beaumont et al. (2007, 2012), and Pearce et al. (2015). While this approach offers benefits, it does not necessarily represent what happens in MTBI in general. The concepts of reserve capacity (structural and cognitive) and compensatory mechanisms (Bigler and Stern, 2015) are used to explain why, after similar injury, some individuals progress to good recovery and others remain symptomatic. Neural tissue per se has a very limited capacity for regeneration, but young adults may be able to cope with brain injury better, because of higher reserve capacity. This idea is supported by studies where higher age at time of injury has been shown to negatively affect prognosis (Jacobs et al., 2010). The variables of age and preinjury health should be considered and may explain some of the discrepancies seen in studies of motor cortical excitability after MTBI.

In conclusion RMT may have some value in the evaluation of cortical and corticospinal excitability after MTBI, but as most studies to date have reported it not being altered in MTBI, and the mechanisms underlying possible changes remaining somewhat obscure, it cannot presently be recommended for clinical application. Future studies of cortical excitability and motor evoked potentials in MTBI should ideally include a more comprehensive measurement design (e.g. CSP, CMCT and others), to include parameters that have more commonly been reported as deviant. This would also better support inferences to be made about the neurophysiological mechanisms of possible alterations. Correlating the results to behavioural tests of reaction times, dexterity etc. would also be of interest.

6.2 TMS-EEG as a potential diagnostic tool in chronic MTBI (II)

Chronic MTBI was associated with functional, electrophysiological changes in the brain that could be detected using the combination of TMS and EEG. Participants were either healthy controls, fully recovered MTBI patients or persistently symptomatic MTBI patients. None of them had trauma-related findings in routine brain MRI. TMS-EEG seems to be a promising method for detecting subtle functional changes in the brain, that were not associated with signs of injury in routine imaging.

Differences in the amplitudes and latencies of TMS-EEG potentials were variably seen between the controls and either the symptomatic or the recovered group, and also between the two MTBI groups. As in I study, aberrant responses (compared to controls) in the fully recovered group may indicate a subclinical, compensated injury even in these participants (cf. Bigler & Stern, 2015), although this is mere speculation on the basis of this relatively small dataset.

From a neurophysiological perspective the observed differences between groups are hard to interpret, as there is little comparable research done in TBI. M1 responses have been best characterised in earlier studies, due to readily available motor measures that can be used to provide correlation. According to these, earliest part of the EEG response (until P30) is considered to predominantly reflect excitatory processes and the N45−N100 time range inhibition (Tremblay et al., 2019). Examples of findings supportive of this general frame include: P30 amplitude has been decreased by the inhibitory LICI (Premoli et al., 2014) and continuous theta-burst (Vernet et al., 2013) stimulation paradigms. N45 amplitude has been decreased and N100 increased by inhibitory repetitive stimulation (Casula et al., 2014; Van Der Werf and Paus, 2006), and N100 amplitude is positively correlated with $GABA_B$ mediated inhibition based on pharmacological studies (Tremblay et al., 2019). Somewhat at odds with this rough time-based interpretation, P60 amplitude is decreased by the inhibitory SICI and increased by the facilitatory ICF paradigm on both M1 and DLPFC (Cash et al., 2016; Ferreri et al., 2011). Additionally, studies localising EEG activity have found the initial EEG activity to be over the stimulated area but starting from 30−45 ms on M1 or 40−60 ms on DLPFC, the activity spreads to central and contralateral sites (Tremblay et al., 2019). This spread of activation reflects the functional connectivity of the stimulated site.

In II study group differences were found mainly from P30−N100 time range and additionally, after DLPFC stimulation, in the P200 time range. Based on literature cited above, neural mechanisms at play are uncertain, but disturbed balance of inhibitory and facilitatory mechanisms and altered functional connectivity are generally possible explanations for any of the observed

differences. Previous studies involving MTBI have found evidence of aberrant inhibitory response from TMS-evoked motor potentials (Bashir et al., 2012; Lefebvre et al., 2015; Major et al., 2015). Studies using TMS-EEG, although not many, have reported aberrant responses in time ranges 50−100 ms (Bashir et al., 2012; Levy-Lamdan et al., 2020), mostly consistent with our findings.

A methodological issue worth discussing in this study is related to determining the stimulation intensities based on RMTs. Because the MTBI groups had higher RMTs than the controls, their stimulation intensities were also higher, which could confound the data. TMS-evoked peak amplitudes correlate with stimulation intensity, but this is seen when stimulation intensity is varied for a single subject (Kähkönen et al., 2005; Komssi and Kähkönen, 2006; Paus et al., 2001). However, we defined stimulation intensity based on individual RMT precisely with the aim of reducing the contribution of interindividual cortical excitability differences to the TMS-evoked potentials. In statistical analyses, we also did not find the RMT to be correlated with any of the deflections where significant group effects were found. Additional factor making it unlikely that RMT as a confounding variable would explain a large part of our results is, that the stimulation intensities in the symptomatic and recovered groups did not differ significantly, but their EEG responses were different.

The LDA analysis included in II study shows how TMS-evoked motor and EEG responses might be used to classify patients. To be considered of practical value, this would obviously need far bigger data and independent validation.

In conclusion, TMS-EEG is a promising tool for probing functional changes associated with MTBI. However, the findings reported here are based on a small sample of patients and must be considered as preliminary. Replication on a larger sample and preferably at different time points relative to injury, involving also acute phase measurements would be useful. This way it could be found out, what features of the TMS-evoked EEG response are most reliably connected with MTBI or correlate with other signs and symptoms of injury. MRI tractography analysis (cf. III study) of the same patients could help in anchoring the neurophysiological data to certain structural alterations. Also, EEG generates abundant data that could be analysed in different ways. The presently used ERP approach is only one, and not necessarily the best approach, and tools like source localisation would be interesting to apply. A more general ongoing challenge is also to better characterise the neurophysiological foundations of TMS-EEG.

6.3 Comparison of CSD and TractSeg and DTI based tractography (III)

CSD and automated TractSeg based tractography were able to differentiate the TBI group from a group of healthy controls, while DTI based tractography was not. This suggests that CSD and TractSeg are more sensitive at detecting microstructural injuries associated with TBI than DTI based analysis. CSD and TractSeg might lead to clinically significant findings in patients for whom more traditional tractography might appear normal.

The groups differed mainly on FA (measured from the corpus callosum and three bilateral association tracts). The TBI group had lower FA, which is consistent with previous studies and has been interpreted as a sign of microstructural white matter injury (Borja et al., 2018; Eierud et al., 2014). There was also an interaction of tractography method and participant group on MD values in the main analysis (although in the alternative analysis with more limited preprocessing this effect was lost). Higher MD values of the TBI group compared to the control group in CSD and TractSeg tractography possibly underlie this weaker interaction but could not be conclusively demonstrated.

Using more advanced DWI processing methods such as CSD does not necessarily require newest high-end image acquisition but can be feasible with b = 800 s/mm^2 and 15 gradient directions data, if combined with appropriate tract reconstruction methods. However, higher b-value and gradient number imaging is recommended, if available, as the ability to resolve crossing fibres with CSD is better with higher b-values (Tournier et al., 2008). Based on our results, TractSeg is a feasible method for reconstructing TBI patients' tracts. Once the analysis pipeline is established, it can be faster than reconstructing the same tracts based on manual ROI definitions and reduces reliance on subjective judgement and neuroanatomical expertise. Thus, we demonstrate a method with the potential to both increase the sensitivity and reliability of tract analysis and reduce human labour requirement.

The values acquired by DTI and CSD-based tractography methods were generally moderately to strongly correlated. The distributions of FA and MD values were similar and largely overlapping between the groups, but CSD specifically seemed to find relatively low FA values in more participants of the TBI group than DTI did. This suggests a minority of the TBI participants with more pronounced microstructural injuries, that were better identified by the CSD and TractSeg approach, although a causal link between these findings and the initial injury cannot be established by this cross-sectional study.

Correlations were not found between GCS, GOSE, and PTA and the tractography results. There are mixed reports of tractography statistics correlating (Kraus et al., 2007; Kumar et al., 2009; Lipton et al., 2009; Mohammadian et al.,

2020, 2017; Niogi et al., 2008) or not correlating (Churchill et al., 2017; Studerus-Germann et al., 2018; Wäljas et al., 2015, 2014) with clinical variables. Although by far not a unique feature of our study, the lack of correlation might be considered to cast doubt on the clinical validity of the results. Several explanations for this shortcoming may be considered, namely challenges related to TBI severity stratification and outcome evaluation, multifactorial aetiology of long-term symptoms, and methodological issues generally related to tractography studies.

In our sample all TBI participants had an injury initially diagnosed as MTBI based on GCS, and majority had a GCS of 15. Therefore, GCS variability was low, and this may explain its lack of correlation. With regards to GOSE, all patients in the TBI sample showed incomplete recovery (GOSE < 8). Thus, patients with complete recovery were not in the analysis, and this might hamper finding correlations with tractography in the patient group. While GOSE is widely used and validated as a tool for measuring functional outcome, it has also been criticised for lacking inter-rater reliability and sensitivity, especially in grading long-term symptoms related to MTBI (McMillan et al., 2016). Addition of separate measures of cognitive outcome to TBI studies has been advocated (Bagiella et al., 2010) and could be especially helpful in studies of MTBI, as well as broader symptom questionnaires (cf. Voormolen et al., 2020).

Post-TBI symptoms are thought to represent the outcome of complex biopsychosocial interactions, where also other factors besides white matter injury may contribute. These may include e.g. post-traumatic stress disorder, prior physical and mental health, extracranial injuries, pain, and emotional distress (Carroll et al., 2004c; Iverson, 2006; Iverson and Lange, 2003; Iverson and McCracken, 2009; Van Der Naalt et al., 2017; Wäljas et al., 2015). Therefore, although we expected microstructural white matter injury to correlate with long-term symptoms, this may have been obscured by other factors.

On the other hand, we may still be unable to detect some significant injuries with the present techniques, and thus unable to account for injury-related symptoms by imaging. Improvements in imaging technique may help, but inherent limitations to diagnostic accuracy are posed by the sizeable inter-individual other cause variation in the studied structures. TBI-associated tractography findings are not disease-specific, and similar changes have been reported in e.g. psychiatric conditions, substance use, and sleep deprivation, with baseline cognitive capacity also potentially modifying the results (Dizaji et al., 2021; Elvsåshagen et al., 2015; Hampton et al., 2019; Jiang et al., 2017; Lipton et al., 2012).

Additionally, we found that FA and MD values calculated from DTI and CSD based tractography were generally different. CSD and TractSeg resulted in lower FA and MD than DTI. Also, the relative values of different tracts were different,

with e.g., the corpus callosum having the highest FA in the DTI analysis, but superior longitudinal fasciculi having the highest FA in CSD.

On a general level, these reflect the methodological differences between the tractography methods. Tracts reconstructed by such different methods cannot be expected to be directly comparable, as there are fundamental differences in how they are defined (Schilling et al., 2021). As demonstrated in Figure 8, CSD and TractSeg resulted in tracts with higher volume and extension closer to the cortical interface. This can explain why average FA was lower in CSD-based analysis. In deterministic DTI tractography the fibres were terminated if FA fell below the predefined limit. A sufficiently strict FA limit is required to prevent tracking of fibres that are not anatomically related to the target tract. In TractSeg, fibres with lower FA but still actually related to the target tract may be found, as tracts are directly segmented from the fODF, utilising a pretrained convolutional neural network. These differences do not automatically mean that one of the methods is always better than the other, as there is a trade-off between sensitivity and false positive rate. Based on the present results, however and the study by Ressel et al. (2018), inclusion of such fibres may improve clinical accuracy.

Seemingly small changes in tractography parameters can also result in substantial differences in the results, as exemplified here by the relatively high FA of corpus callosum in DTI tractography. This is related to the fact that we chose a tract termination minimum FA limit of 0.5 for the corpus callosum (to avoid excessive propagation), but 0.3 for other tracts. These findings do not pose a problem for our analysis, as the TBI and control group were analysed identically, but serve to highlight some of the potential challenges in generating normative data for clinical tractography (cf. Jones et al., 2013). Different relative FA and MD values may also be a reflection of how the tractography methods handle crossing fibres. The corpus callosum has highly parallel fibres, while association tracts have more crossing fibres, which results in lower DTI-based FA. Crossing fibres should be better addressed by CSD, possibly explaining the relatively high FA derived from e.g. the superior longitudinal fasciculi with CSD and TractSeg.

Besides different diffusion model and tractography method, different preprocessing steps in the CSD and DTI based analysis pipelines might have influenced our results (Maximov et al., 2019; Oldham et al., 2020). In this study, DTI preprocessing utilised an older, commercial preprocessing tool compatible with the tractography software, while preprocessing pipeline for CSD data was more modern. To control for possible effects, we did an alternative analysis with more limited preprocessing. This gave mostly equivalent results. As problems in signal-to-noise-ratio are more prevalent in higher b-value imaging (Maximov et al., 2019), it may be that our results are not particularly strongly affected by preprocessing approaches such as denoising. Still, some differences were also

observed, highlighting the importance of considering preprocessing when evaluating diffusion MRI studies.

6.4 Limitations

All included studies were cross-sectional, which limits causal inferences. TBI is a complex injury, where many biological and psychosocial variables may have effects. Great care was taken to control for confounding factors not related to the injury, but obviously they cannot be ruled out.

I−II studies had quite small sample sizes, which limits the generalizability of the results. Based on later reports, study I especially could have benefitted from more comprehensive testing of the participants' motor system, from both a neurophysiological and a behavioural perspective. Combining the methods used in study III to the same sample could have been of value when interpreting the results of studies I-II.

III study sought to demonstrate the superiority of CSD and TractSeg tractography compared to deterministic DTI based tractography. While we argue this was achieved, it is not possible to pinpoint the most crucial technical difference between the chosen approaches. Differences in preprocessing pipelines were tested and did not seem to have a substantial impact. The ability of CSD to discern complex fibre architecture or the more voluminous and "complete" tracts generated by TractSeg compared to deterministic tractography are both potential reasons for the superiority of the CSD and TractSeg analysis approach.

It could also be argued that study III was limited by the relatively modest DWI acquisition as this limits tractography quality. However, comparison of tractography methods was fair and an essential outcome of the study was that CSD based tractography could be accomplished from such acquisition, which is representative of many clinically used imaging setups.

Our samples did not include patients with focal brain lesions. While CSD and TractSeg worked robustly here, applicability in such circumstances was not tested.

In each study, we included a relatively large number of patients with a suboptimal outcome, although epidemiologically most MTBI patients make a full symptomatic recovery. This is especially true of the III study, where all MTBI participants had some persistent symptoms. While this was an intentional feature of study design, it should be remembered when interpreting the results, that they represent a select group and not the typical outcome of MTBI. Also based on the WHO criteria, all patients would not have been classified as MTBI, because PTA > 24 h was common.

Time from injury to testing was quite variable, which may add unwanted variance in our results. Statistically we were unable to show this would have had some systematic effect on the results.

We used GOSE and clinical evaluation (including interviews with the patient and close ones) to determine outcome. Neuropsychological testing was utilised, but not in a uniform manner that could have been included in statistical analyses. Addition of standardised, quantitative tests of cognitive function and more elaborate numerical operationalisation of residual symptoms or functional impairment would have been an interesting addition to correlate with our data. As such, we are limited to demonstrating differences between patient groups and healthy controls, while correlations to other clinical variables could not be shown. This weakens the inferences that can be made about the clinical utility and validity of the tested methods.

Finally, as a control group we used healthy controls, as has been customary in many comparable studies. It can be argued that general trauma patients without TBI would make a better control group (Carroll et al., 2004c), as they would better control for the risk factors associated with being injured and non-specific injury related effects (such as pain, emotional distress, and loss of function). Such factors may have some nonspecific effects on sensitive measures of the structure and function of the brain.

7 Conclusions

Chronic MTBI can be associated with functional and structural changes in the absence of trauma-related findings on routine MRI. This thesis sought to explore new methods for detecting these changes.

In I study a sample of persistently symptomatic and recovered MTBI patients and healthy controls were tested for RMT using TMS. Elevated RMTs were found in the patient groups, indicative of altered excitability of the corticospinal system. Considering literature utilising similar methodology, however it seems that this is an inconsistent finding and variability in reports of TMS-evoked motor potentials in MTBI is generally large.

In II study a sample of persistently symptomatic and recovered MTBI patients and healthy controls were tested using the combination of TMS and EEG. Differences were found between the groups, notably not only compared to controls, but also between the symptomatic and recovered MTBI groups. TMS-EEG seems to be a sensitive and thus promising method for probing subtle functional changes associated with MTBI, but the results must be considered preliminary due to the small sample and unclear underlying neurophysiological mechanisms.

In III study a sample of persistently symptomatic MTBI patients and healthy controls underwent DWI. A new tractography approach was used, consisting of CSD, automatic tract segmentation using TractSeg and probabilistic tractography. In contrast to a more established DTI methodology, the new approach could find differences between the tested groups and thus seems more sensitive in detecting microstructural injuries probably related to MTBI.

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I first got involved in research as an undergraduate at the Department of Psychology of the University of Turku. For some time I was working on a PhD there. Prof. Heikki Hämäläinen agreed to being my supervisor and helped me through my first publications, focused on the cognitive and neuropsychological mechanisms of spatial attention. I am very grateful for him for giving me the opportunity and believing in me, even though I did not finish this PhD project. Early on I learned that experimental research is not only theoretical pondering, but hands-on work, and can be fun. Prof. Hämäläinen was always available when needed and enabled me to focus on my work.

Eventually, I also got involved in brain trauma research, with prof. Olli Tenovuo becoming my supervisor. After transferring to do my degree at the Faculty of Medicine, I thought it more synergistic to focus on this. Prof. Tenovuo was inspirational to me, having combined careers as an accomplished researcher and one of the foremost clinical experts in his field, while still being a friendly, approachable person. I thought of it a great honor to get to work with him. He has also supported me with patience and never made me think of quitting, although some years passed with quite little research related accomplishment.

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References

Abalo, K.D., Rage, E., Leuraud, K., Richardson, D.B., Le Pointe, H.D., Laurier, D., Bernier, M.O., 2021. Early life ionizing radiation exposure and cancer risks: systematic review and meta-analysis. Pediatr Radiol 51, 45–56. https://doi.org/10.1007/S00247-020-04803-0/FIGURES/5

Abner, E.L., Nelson, P.T., Schmitt, F.A., Browning, S.R., Fardo, D.W., Wan, L., Jicha, G.A., Cooper, G.E., Smith, C.D., Caban-Holt, A.M., Van Eldik, L.J., Kryscio, R.J., 2014. Self-Reported Head Injury and Risk of Late-Life Impairment and AD Pathology in an AD Center Cohort. Original Research Article Dement Geriatr Cogn Disord 37, 294–306. https://doi.org/10.1159/000355478

Adams, J.H., Doyle, D., Ford, I., Gennarelli, T.A., Graham, D.I., Mclellan, D.R., 1989. Diffuse axonal injury in head injury: Definition, diagnosis and grading. Histopathology 15, 49–59. https://doi.org/10.1111/J.1365-2559.1989.TB03040.X

Adams, J.H., Mitchell, D.E., Graham, D.I., Doyle, D., 1977. Diffuse brain damage of immediate impact type. Its relationship to "primary brain-stem damage" in head injury. Brain 100, 489–502. https://doi.org/10.1093/BRAIN/100.3.489

Åhman, S., Saveman, B.I., Styrke, J., Björnstig, U., Stålnacke, B.M., 2013. Long-term follow-up of patients with mild traumatic brain injury: A mixed-methods study. J Rehabil Med 45, 758–764. https://doi.org/10.2340/16501977-1182

Alexander, A.L., Lee, J.E., Lazar, M., Field, A.S., 2007. Diffusion Tensor Imaging of the Brain. Neurotherapeutics 4, 316–329. https://doi.org/10.1016/j.nurt.2007.05.011

Andersson, J.L.R., Sotiropoulos, S.N., 2016. An integrated approach to correction for off-resonance effects and subject movement in diffusion MR imaging. Neuroimage 125, 1063–1078. https://doi.org/10.1016/J.NEUROIMAGE.2015.10.019

Andreasen, S.H., Andersen, K.W., Conde, V., Dyrby, T.B., Puonti, O., Kammersgaard, L.P., Madsen, C.G., Madsen, K.H., Poulsen, I., Siebner, H.R., 2020. Limited Colocalization of Microbleeds and Microstructural Changes after Severe Traumatic Brain Injury. J Neurotrauma 37, 581–592. https://doi.org/10.1089/NEU.2019.6608/FORMAT/EPUB

Asken, B.M., Snyder, A.R., Smith, M.S., Zaremski, J.L., Bauer, R.M., 2017. Concussion-like symptom reporting in non-concussed adolescent athletes. Clin Neuropsychol 31, 138–153. https://doi.org/10.1080/13854046.2016.1246672

Assaf, Y., Freidlin, R.Z., Rohde, G.K., Basser, P.J., 2004. New modeling and experimental framework to characterize hindered and restricted water diffusion in brain white matter. Magn Reson Med 52, 965–978. https://doi.org/10.1002/MRM.20274

Auriat, A.M., Borich, M.R., Snow, N.J., Wadden, K.P., Boyd, L.A., 2015. Comparing a diffusion tensor and non-tensor approach to white matter fiber tractography in chronic stroke. Neuroimage Clin 7, 771–781. https://doi.org/10.1016/j.nicl.2015.03.007

Bagiella, E., Novack, T.A., Ansel, B., Diaz-Arrastia, R., Dikmen, S., Hart, T., Temkin, N., 2010. Measuring outcome in traumatic brain injury treatment trials: Recommendations from the traumatic brain injury clinical trials network. Journal of Head Trauma Rehabilitation 25, 375–382. https://doi.org/10.1097/HTR.0b013e3181d27fe3

Bagnato, S., Boccagni, C., Sant'Angelo, A., Prestandrea, C., Rizzo, S., Galardi, G., 2012. Patients in a vegetative state following traumatic brain injury display a reduced intracortical modulation. Clinical Neurophysiology 123, 1937–1941. https://doi.org/10.1016/j.clinph.2012.03.014

Balalla, S., Krägeloh, C., Medvedev, O., Siegert, R., 2020. Is the Rivermead Post-Concussion Symptoms Questionnaire a Reliable and Valid Measure to Assess Long-Term Symptoms in Traumatic Brain Injury and Orthopedic Injury Patients? A Novel Investigation Using Rasch Analysis. Neurotrauma Rep 1, 63–72. https://doi.org/10.1089/NEUR.2020.0017

Barker, A.T., Jalinous, R., Freeston, I.L., 1985. Non-invasive magnetic stimulation of human motor cortex. Lancet 1, 1106–1107. https://doi.org/10.1016/S0140-6736(85)92413-4

Barlow, K.M., Marcil, L.D., Dewey, D., Carlson, H.L., Macmaster, F.P., Brooks, B.L., Lebel, R.M., 2017. Cerebral Perfusion Changes in Post-Concussion Syndrome: A Prospective Controlled Cohort Study. J Neurotrauma 34, 996–1004. https://doi.org/10.1089/NEU.2016.4634/ASSET/IMAGES/LARGE/FIGURE5.JPEG

Bashir, S., Yoo, W.K., Mizrahi, I., Theoret, H., Pascual-Leone, A., 2012. Changes in cortical plasticity after mild traumatic brain injury. Restor Neurol Neurosci 30, 277–282. https://doi.org/10.3233/RNN-2012-110207

Basser, P.J., Mattiello, J., LeBihan, D., 1994. MR diffusion tensor spectroscopy and imaging. Biophys J 66, 259. https://doi.org/10.1016/S0006-3495(94)80775-1

Basser, P.J., Pajevic, S., Pierpaoli, C., Duda, J., Aldroubi, A., 2000. In vivo fiber tractography using DT-MRI data. Magn Reson Med 44, 625–632. https://doi.org/10.1002/1522-2594(200010)44:4<625::AID-MRM17>3.0.CO;2-O

Basser, P.J., Pierpaoli, C., 1996. Microstructural and physiological features of tissues elucidated by quantitative-diffusion-tensor MRI. J Magn Reson B 111, 209–219. https://doi.org/10.1006/JMRB.1996.0086

Bazarian, J.J., Zhong, J., Blyth, B., Zhu, T., Kavcic, V., Peterson, D., 2007. Diffusion Tensor Imaging Detects Clinically Important Axonal Damage after Mild Traumatic Brain Injury: A Pilot Study. J Neurotrauma 24, 1447–1459. https://doi.org/10.1089/neu.2007.0241

Beauchamp, M.H., Ditchfield, M., Babl, F.E., Kean, M., Catroppa, C., Yeates, K.O., Anderson, V., 2011. Detecting traumatic brain lesions in children: CT versus MRI versus susceptibility weighted imaging (SWI). J Neurotrauma 28, 915–927. https://doi.org/10.1089/NEU.2010.1712/ASSET/IMAGES/LARGE/FIGURE1.JPEG

Becker, D., Scherer, M., Neher, P., Jungk, C., Jesser, J., Pflüger, I., Brinster, R., Bendszus, M., Bruckner, T., Maier-Hein, K., Unterberg, A., 2020. Going Beyond Diffusion Tensor Imaging Tractography in Eloquent Glioma Surgery–High-Resolution Fiber Tractography: Q-Ball or Constrained Spherical Deconvolution? World Neurosurg 134, e596–e609. https://doi.org/10.1016/j.wneu.2019.10.138

Beniczky, S., Schomer, D.L., 2020. Electroencephalography: basic biophysical and technological aspects important for clinical applications. Epileptic Disord 22, 697–715. https://doi.org/10.1684/EPD.2020.1217

Berardelli, A., Abbruzzese, G., Chen, R., Orth, M., Ridding, M.C., Stinear, C., Suppa, A., Trompetto, C., Thompson, P.D., 2008. Consensus paper on short-interval intracortical inhibition and other transcranial magnetic stimulation intracortical paradigms in movement disorders. Brain Stimul. https://doi.org/10.1016/j.brs.2008.06.005

Berger, H., 1929. Uber das Elektrenkephalogramm des Menschen, Archiv für Psychiatrie.

Bernabeu, M., Demirtas-Tatlidede, A., Opisso, E., Lopez, R., Tormos, J.M., Pascual-Leone, A., 2009. Abnormal corticospinal excitability in traumatic diffuse axonal brain injury. J Neurotrauma 26, 2185–2193. https://doi.org/10.1089/neu.2008.0859

Bestmann, S., Krakauer, J.W., 2015. The uses and interpretations of the motor-evoked potential for understanding behaviour. Exp Brain Res 233, 679–689. https://doi.org/10.1007/S00221-014-4183-7

Bigler, E.D., Maxwell, W.L., 2012. Neuropathology of mild traumatic brain injury: relationship to neuroimaging findings. Brain Imaging Behav 6, 108–136. https://doi.org/10.1007/S11682-011-9145-0

Bigler, E.D., Stern, Y., 2015. Traumatic brain injury and reserve, in: Handbook of Clinical Neurology. Elsevier, pp. 691–710. https://doi.org/10.1016/B978-0-444-63521-1.00043-1

Boake, C., McCauley, S.R., Levin, H.S., Pedroza, C., Contant, C.F., Song, J.X., Brown, S.A., Goodman, H., Brundage, S.I., Diaz-Marchan, P.J., 2005. Diagnostic criteria for postconcussional syndrome after mild to moderate traumatic brain injury. Journal of Neuropsychiatry and Clinical Neurosciences 17, 350–356. https://doi.org/10.1176/JNP.17.3.350/ASSET/IMAGES/LARGE/RK04914T4.JPEG

Borja, M.J., Chung, S., Lui, Y.W., 2018. Diffusion MR Imaging in Mild Traumatic Brain Injury. Neuroimaging Clin N Am. https://doi.org/10.1016/j.nic.2017.09.009

Brandstack, N., Kurki, T., Tenovuo, O., 2013. Quantitative Diffusion-Tensor Tractography of long association Tracts in Patients with Traumatic Brain injury without associated Findings at routine Mr imaging 1. Radiology 267. https://doi.org/10.1148/radiol.12112570/-/DC1

Bullock, D., Takemura, H., Caiafa, C.F., Kitchell, L., McPherson, B., Caron, B., Pestilli, F., 2019. Associative white matter connecting the dorsal and ventral posterior human cortex. Brain Struct Funct 224, 2631–2660. https://doi.org/10.1007/s00429-019-01907-8

Burle, B., Spieser, L., Roger, C., Casini, L., Hasbroucq, T., Vidal, F., 2015. Spatial and temporal resolutions of EEG: Is it really black and white? A scalp current density view. International Journal of Psychophysiology 97, 210–220. https://doi.org/10.1016/J.IJPSYCHO.2015.05.004

Calamuneri, A., Arrigo, A., Mormina, E., Milardi, D., Cacciola, A., Chillemi, G., Marino, S., Gaeta, M., Quartarone, A., 2018. White matter tissue quantification at Low b-values within constrained spherical deconvolution framework. Front Neurol 9, 1–14. https://doi.org/10.3389/fneur.2018.00716

Cao, K.X., Ma, M.L., Wang, C.Z., Iqbal, J., Si, J.J., Xue, Y.X., Yang, J.L., 2021. TMS-EEG: An emerging tool to study the neurophysiologic biomarkers of psychiatric disorders. Neuropharmacology. https://doi.org/10.1016/j.neuropharm.2021.108574

Carroll, E.L., Outtrim, J.G., Forsyth, F., Manktelow, A.E., Hutchinson, P.J.A., Tenovuo, O., Posti, J.P., Wilson, L., Sahakian, B.J., Menon, D.K., Newcombe, V.F.J., 2020. Mild traumatic brain injury recovery: a growth curve modelling analysis over 2 years. J Neurol 267, 3223–3234. https://doi.org/10.1007/S00415-020-09979-X/TABLES/2

Carroll, L.J., Cassidy, J.D., Holm, L., Kraus, J., Coronado, V.G., 2004a. Methodological issues and research recommendations for mild traumatic brain injury: The WHO Collaborating Centre Task Force on Mild Traumatic Brain Injury. J Rehabil Med Suppl 113–125. https://doi.org/10.1080/16501960410023877

Carroll, L.J., Cassidy, J.D., Peloso, P.M., Borg, J., von Holst, H., Holm, L., Paniak, C., Pépin, M., 2004b. Prognosis for mild traumatic brain injury: Results of the WHO Collaborating Centre Task Force on Mild Traumatic Brain Injury. J Rehabil Med Suppl 84–105. https://doi.org/10.1080/16501960410023859

Carroll, L.J., Cassidy, J.D., Peloso, P.M., Borg, J., von Holst, H., Holm, L., Paniak, C., Pépin, M., 2004c. Prognosis for mild traumatic brain injury: Results of the WHO Collaborating Centre Task Force on Mild Traumatic Brain Injury. J Rehabil Med Suppl 84–105. https://doi.org/10.1080/16501960410023859

Cash, R.F., Noda, Y., Zomorrodi, R., Radhu, N., Farzan, F., Rajji, T.K., Fitzgerald, P.B., Chen, R., Daskalakis, Z.J., Blumberger, D.M., 2016. Characterization of Glutamatergic and GABAA-Mediated Neurotransmission in Motor and Dorsolateral Prefrontal Cortex Using Paired-Pulse TMS–EEG. Neuropsychopharmacology 42, 502–511. https://doi.org/10.1038/npp.2016.133

Casula, E.P., Tarantino, V., Basso, D., Arcara, G., Marino, G., Toffolo, G.M., Rothwell, J.C., Bisiacchi, P.S., 2014. Low-frequency rTMS inhibitory effects in the primary motor cortex:

Insights from TMS-evoked potentials. Neuroimage 98, 225–232. https://doi.org/10.1016/j.neuroimage.2014.04.065

Chilla, G.S., Tan, C.H., Xu, C., Poh, C.L., 2015. Diffusion weighted magnetic resonance imaging and its recent trend—a survey. Quant Imaging Med Surg 5, 407. https://doi.org/10.3978/J.ISSN.2223-4292.2015.03.01

Chistyakov, A. V, Soustiel, J.F., Hafner, H., Elron, M., Feinsod, M., 1998. Altered excitability of the motor cortex after minor head injury revealed by transcranial magnetic stimulation. Acta Neurochir (Wien) 140, 467–472. https://doi.org/10.1007/s007010050126

Chistyakov, A. V, Soustiel, J.F., Hafner, H., Trubnik, M., Levy, G., Feinsod, M., 2001. Excitatory and inhibitory corticospinal responses to transcranial magnetic stimulation in patients with minor to moderate head injury. J Neurol Neurosurg Psychiatry 70, 580–587. https://doi.org/10.1136/jnnp.70.5.580

Churchill, N.W., Hutchison, M.G., Richards, D., Leung, G., Graham, S.J., Schweizer, T.A., 2017. Neuroimaging of sport concussion: persistent alterations in brain structure and function at medical clearance. Sci Rep 7. https://doi.org/10.1038/S41598-017-07742-3

Coyle, H.L., Ponsford, J., Hoy, K.E., 2018. Understanding individual variability in symptoms and recovery following mTBI: A role for TMS-EEG? Neurosci Biobehav Rev. https://doi.org/10.1016/j.neubiorev.2018.05.027

Cracco, R.Q., Amassian, V.E., Maccabee, P.J., Cracco, J.B., 1989. Comparison of human transcallosal responses evoked by magnetic coil and electrical stimulation. Electroencephalogr Clin Neurophysiol 74, 417–424. https://doi.org/10.1016/0168-5597(89)90030-0

Darmani, G., Bergmann, T.O., Zipser, C., Baur, D., Müller-Dahlhaus, F., Ziemann, U., 2019. Effects of antiepileptic drugs on cortical excitability in humans: A TMS-EMG and TMS-EEG study. Hum Brain Mapp 40, 1276–1289. https://doi.org/10.1002/hbm.24448

Davenport, N.D., Lamberty, G.J., Nelson, N.W., Lim, K.O., Armstrong, M.T., Sponheim, S.R., 2016. PTSD confounds detection of compromised cerebral white matter integrity in military veterans reporting a history of mild traumatic brain injury. Brain Inj 30, 1491–1500. https://doi.org/10.1080/02699052.2016.1219057

Davidson, T.W., Tremblay, F., 2016. Evidence of alterations in transcallosal motor inhibition as a possible long-term consequence of concussions in sports: A transcranial magnetic stimulation study. Clinical Neurophysiology 127, 3364–3375. https://doi.org/10.1016/j.clinph.2016.07.012

De Beaumont, L., Lassonde, M., Leclerc, S., Théoret, H., 2007a. Long-term and cumulative effects of sports concussion on motor cortex inhibition. Neurosurgery 61, 329–336. https://doi.org/10.1227/01.NEU.0000280000.03578.B6

De Beaumont, L., Lassonde, M., Leclerc, S., Théoret, H., 2007b. Long-term and cumulative effects of sports concussion on motor cortex inhibition. Neurosurgery 61, 329–336. https://doi.org/10.1227/01.NEU.0000280000.03578.B6

De Beaumont, L., Thoret, H., Mongeon, D., Messier, J., Leclerc, S., Tremblay, S., Ellemberg, D., Lassonde, M., 2009. Brain function decline in healthy retired athletes who sustained their last sports concussion in early adulthood. Brain 132, 695–708. https://doi.org/10.1093/brain/awn347

De Beaumont, L., Tremblay, S., Poirier, J., Lassonde, M., Théoret, H., 2012. Altered bidirectional plasticity and reduced implicit motor learning in concussed athletes. Cerebral Cortex 22, 112–121. https://doi.org/10.1093/cercor/bhr096

de Goede, A.A., ter Braack, E.M., van Putten, M.J.A.M., 2016. Single and paired pulse transcranial magnetic stimulation in drug naïve epilepsy. Clinical Neurophysiology. https://doi.org/10.1016/j.clinph.2016.06.025

De Weijer, A.D., Sommer, I.E.C., Bakker, E.J., Bloemendaal, M., Bakker, C.J.G., Klomp, D.W.J., Bestmann, S., Neggers, S.F.W., 2014. A setup for administering TMS to Medial and lateral cortical areas during whole-brain fMRI recording. Journal of Clinical Neurophysiology 31, 474–487. https://doi.org/10.1097/WNP.0000000000000075

Dewan, M.C., Rattani, A., Gupta, S., Baticulon, R.E., Hung, Y.C., Punchak, M., Agrawal, A., Adeleye, A.O., Shrime, M.G., Rubiano, A.M., Rosenfeld, J. V., Park, K.B., 2018. Estimating the global incidence of traumatic brain injury. J Neurosurg 130, 1080–1097. https://doi.org/10.3171/2017.10.JNS17352

Dinet, V., Petry, K.G., Badaut, J., 2019. Brain–Immune Interactions and Neuroinflammation After Traumatic Brain Injury. Front Neurosci 13, 1178. https://doi.org/10.3389/FNINS.2019.01178/BIBTEX

Dixon, K.J., 2017. Pathophysiology of Traumatic Brain Injury Traumatic brain injury TBI Pathophysiology Symptoms Mild TBI Concussion Blast TBI KEY POINTS. Phys Med Rehabil Clin N Am 28, 215–225. https://doi.org/10.1016/j.pmr.2016.12.001

Dizaji, A.S., Vieira, B.H., Khodaei, M.R., Ashrafi, M., Parham, E., Hosseinzadeh, G.A., Salmon, C.E.G., Soltanianzadeh, H., 2021. Linking brain biology to intellectual endowment: A review on the associations of human intelligence with neuroimaging data. Basic Clin Neurosci. https://doi.org/10.32598/bcn.12.1.574.1

Domin, M., Langner, S., Hosten, N., Lotze, M., 2014. Comparison of parameter threshold combinations for diffusion tensor tractography in chronic stroke patients and healthy subjects. PLoS One 9. https://doi.org/10.1371/journal.pone.0098211

Douek, P., Turner, R., Pekar, J., Patronas, N., Le Bihan, D., 1991. MR color mapping of myelin fiber orientation. J Comput Assist Tomogr 15, 923–929. https://doi.org/10.1097/00004728-199111000-00003

Dremmen, M.H.G., Wagner, M.W., Bosemani, T., Tekes, A., Agostino, D., Day, E., Soares, B.P., Huisman, T.A.G.M., 2017. Does the Addition of a "Black Bone" Sequence to a Fast Multisequence Trauma MR Protocol Allow MRI to Replace CT after Traumatic Brain Injury in Children? American Journal of Neuroradiology 38, 2187–2192. https://doi.org/10.3174/AJNR.A5405

Dwyer, B., Katz, D.I., 2018. Postconcussion syndrome, in: Handbook of Clinical Neurology. pp. 163–178. https://doi.org/10.1016/B978-0-444-63954-7.00017-3

Dyke, K., Pépés, S.E., Chen, C., Kim, S., Sigurdsson, H.P., Draper, A., Husain, M., Nachev, P., Gowland, P.A., Morris, P.G., Jackson, S.R., 2017. Comparing GABA-dependent physiological measures of inhibition with proton magnetic resonance spectroscopy measurement of GABA using ultra-high-field MRI. Neuroimage 152, 360–370. https://doi.org/10.1016/J.NEUROIMAGE.2017.03.011

Edwards, E.K., Christie, A.D., 2017. Assessment of motor cortex excitability and inhibition during a cognitive task in individuals with concussion. http://dx.doi.org.ezproxy.utu.fi/10.1080/02699052.2017.1327671 31, 1348–1355. https://doi.org/10.1080/02699052.2017.1327671

Eierud, C., Craddock, R.C., Fletcher, S., Aulakh, M., King-Casas, B., Kuehl, D., Laconte, S.M., 2014. Neuroimaging after mild traumatic brain injury: Review and meta-analysis. Neuroimage Clin 4, 283–294. https://doi.org/10.1016/j.nicl.2013.12.009

Elvsåshagen, T., Norbom, L.B., Pedersen, P.Ø., Quraishi, S.H., Bjørnerud, A., Malt, U.F., Groote, I.R., Westlye, L.T., 2015. Widespread Changes in White Matter Microstructure after a Day of Waking and Sleep Deprivation. PLoS One 10, e0127351. https://doi.org/10.1371/JOURNAL.PONE.0127351

Farkas, O., Povlishock, J.T., 2007. Cellular and subcellular change evoked by diffuse traumatic brain injury: a complex web of change extending far beyond focal damage. Prog Brain Res 161, 43–59. https://doi.org/10.1016/S0079-6123(06)61004-2

Ferguson, R.J., Mittenberg, W., Barone, D.F., Schneider, B., 1999. Postconcussion syndrome following sports-related head injury: Expectation as etiology. Neuropsychology 13, 582–589. https://doi.org/10.1037/0894-4105.13.4.582

Ferreri, F., Pasqualetti, P., Määttä, S., Ponzo, D., Ferrarelli, F., Tononi, G., Mervaala, E., Miniussi, C., Rossini, P.M., 2011. Human brain connectivity during single and paired pulse transcranial magnetic stimulation. Neuroimage 54, 90–102. https://doi.org/10.1016/j.neuroimage.2010.07.056

Filley, C.M., Kelly, J.P., 2018. White Matter and Cognition in Traumatic Brain Injury. J Alzheimers Dis. https://doi.org/10.3233/JAD-180287

Frøkjær, J.B., Olesen, S.S., Gram, M., Yavarian, Y., Bouwense, S.A.W., Wilder-Smith, O.H.G., Drewes, A.M., 2011. Altered brain microstructure assessed by diffusion tensor imaging in patients with chronic pancreatitis. Gut 60, 1554–1562. https://doi.org/10.1136/gut.2010.236620

Fujisawa, H., Maxwell, W.L., Graham, D.I., Reasdale, G.M., Bullock, R., 1994. Focal Microvascular Occlusion After Acute Subdural Haematoma in the Rat: a Mechanism for Ischaemic Damage and Brain Swelling? Acta Neurochir Suppl (Wien) 60, 193–196. https://doi.org/10.1007/978-3-7091-9334-1_52

Goldman, S.M., Tanner, C.M., Oakes, D., Bhudhikanok, G.S., Gupta, A., Langston, J.W., 2006. Head injury and Parkinson's disease risk in twins. Ann Neurol 60, 65–72. https://doi.org/10.1002/ANA.20882

Gorbunova, A., Zeldovich, M., Voormolen, D.C., Krenz, U., Polinder, S., Haagsma, J.A., Hagmayer, Y., Covic, A., Real, R.G.L., Asendorf, T., von Steinbuechel, N., 2020. Reference Values of the QOLIBRI from General Population Samples in the United Kingdom and The Netherlands. Journal of Clinical Medicine 2020, Vol. 9, Page 2100 9, 2100. https://doi.org/10.3390/JCM9072100

Greer, J.E., McGinn, M.J., Povlishock, J.T., 2011. Diffuse Traumatic Axonal Injury in the Mouse Induces Atrophy, c-Jun Activation, and Axonal Outgrowth in the Axotomized Neuronal Population. Journal of Neuroscience 31, 5089–5105. https://doi.org/10.1523/JNEUROSCI.5103-10.2011

Grote, S., Böcker, W., Mutschler, W., Bouillon, B., Lefering, R., 2011. Diagnostic value of the glasgow coma scale for traumatic brain injury in 18,002 patients with severe multiple injuries. J Neurotrauma 28, 527–534. https://doi.org/10.1089/NEU.2010.1433/FORMAT/EPUB

Grumbach, P., Opel, N., Martin, S., Meinert, S., Leehr, E.J., Redlich, R., Enneking, V., Goltermann, J., Baune, B.T., Dannlowski, U., Repple, J., 2020. Sleep duration is associated with white matter microstructure and cognitive performance in healthy adults. Hum Brain Mapp 41, 4397–4405. https://doi.org/10.1002/HBM.25132

Gupte, R., Brooks, W., Vukas, R., Pierce, J., Harris, J., 2019. Sex Differences in Traumatic Brain Injury: What We Know and What We Should Know. J Neurotrauma 36, 3063–3091. https://doi.org/10.1089/NEU.2018.6171/ASSET/IMAGES/LARGE/FIGURE6.JPEG

Hampton, W.H., Hanik, I.M., Olson, I.R., 2019. Substance abuse and white matter: Findings, limitations, and future of diffusion tensor imaging research. Drug Alcohol Depend. https://doi.org/10.1016/j.drugalcdep.2019.02.005

Head, J., Kay, T., Harrington, D.E., Adams, R., Anderson, T., Berrol, S., Cicerone, K., Dahlberg, C., Gerber, D., Goka, R., Harley, P., Hilt, J., Horn, L., Lehmkuhl, D., Malec, J., 1993. Definition of mild traumatic brain injury, Journal of Head Trauma Rehabilitation.

Henderson, F., Abdullah, K.G., Verma, R., Brem, S., 2020. Tractography and the connectome in neurosurgical treatment of gliomas: the premise, the progress, and the potential. Neurosurg Focus 48, E6. https://doi.org/10.3171/2019.11.FOCUS19785

Higaki, T., Nakamura, Y., Tatsugami, F., Kaichi, Y., Akagi, M., Akiyama, Y., Baba, Y., Iida, M., Awai, K., 2018. Introduction to the technical aspects of computed diffusion-weighted imaging for radiologists. Radiographics 38, 1131–1144. https://doi.org/10.1148/RG.2018170115/ASSET/IMAGES/LARGE/RG.2018170115.FIG15C.JPEG

Hill, A.T., Rogasch, N.C., Fitzgerald, P.B., Hoy, K.E., 2016. TMS-EEG: A window into the neurophysiological effects of transcranial electrical stimulation in non-motor brain regions. Neurosci Biobehav Rev 64, 175–184. https://doi.org/10.1016/j.neubiorev.2016.03.006

Holm, L., Cassidy, J.D., Carroll, L.J., Borg, J., 2005. Summary of the WHO Collaborating Centre for Neurotrauma Task Force on Mild Traumatic Brain Injury. J Rehabil Med 37, 137–141. https://doi.org/10.1080/16501970510027321

Hossain, I., Mohammadian, M., Takala, R.S.K., Tenovuo, O., Azurmendi Gil, L., Frantzén, J., van Gils, M., Hutchinson, P.J., Katila, A.J., Maanpää, H.R., Menon, D.K., Newcombe, V.F., Tallus, J., Hrusovsky, K., Wilson, D.H., Gill, J., Blennow, K., Sanchez, J.C., Zetterberg, H., Posti, J.P., 2020. Admission Levels of Total Tau and β-Amyloid Isoforms 1–40 and 1–42 in Predicting the Outcome of Mild Traumatic Brain Injury. Front Neurol 11, 325. https://doi.org/10.3389/FNEUR.2020.00325/BIBTEX

Hsiang, J.N.K., Yeung, T., Yu, A.L.M., Poon, W.S., 1997. High-risk mild head injury. J Neurosurg 87, 234–238. https://doi.org/10.3171/jns.1997.87.2.0234

Huisman, T.A.G.M., 2010. Diffusion-weighted and diffusion tensor imaging of the brain, made easy. Cancer Imaging 10, S163. https://doi.org/10.1102/1470-7330.2010.9023

Hulkower, M.B., Poliak, D.B., Rosenbaum, S.B., Zimmerman, M.E., Lipton, M.L., 2013. A Decade of DTI in Traumatic Brain Injury: 10 Years and 100 Articles Later. American Journal of Neuroradiology 34, 2064–2074. https://doi.org/10.3174/AJNR.A3395

Hunter, L.E., Lubin, N., Glassman, N.R., Xue, X., Spira, M., Lipton, M.L., 2019. Comparing Region of Interest versus Voxel-Wise Diffusion Tensor Imaging Analytic Methods in Mild and Moderate Traumatic Brain Injury: A Systematic Review and Meta-Analysis. J Neurotrauma 36, 1222–1230. https://doi.org/10.1089/neu.2018.5838

Hwang, D.Y., Silva, G.S., Furie, K.L., Greer, D.M., 2012. Comparative Sensitivity of Computed Tomography vs. Magnetic Resonance Imaging for Detecting Acute Posterior Fossa Infarct. J Emerg Med 42, 559–565. https://doi.org/10.1016/J.JEMERMED.2011.05.101

Ilmoniemi, R.J., Virtanen, J., Ruohonen, J., Karhu, J., Aronen, H.J., Näätänen, R., Katila, T., 1997. Neuronal responses to magnetic stimulation reveal cortical reactivity and connectivity. Neuroreport 8, 3537–3540. https://doi.org/10.1097/00001756-199711100-00024

Irvine, K.A., David Clark, J., 2018. Chronic pain after traumatic brain injury: Pathophysiology and pain mechanisms. Pain Medicine (United States) 19, 1315–1333. https://doi.org/10.1093/pm/pnx153

Iverson, G.L., 2006. Misdiagnosis of the persistent postconcussion syndrome in patients with depression. Arch Clin Neuropsychol 21, 303–310. https://doi.org/10.1016/J.ACN.2005.12.008

Iverson, G.L., Lange, R.T., 2003. Examination of "postconcussion-like" symptoms in a healthy sample. Appl Neuropsychol 10, 137–144. https://doi.org/10.1207/S15324826AN1003_02

Iverson, G.L., Lange, R.T., Brooks, B.L., Rennison, V.L.A., 2010. "Good Old Days" Bias Following Mild Traumatic Brain Injury. Clinical Neuropsychologist 24, 17–37. https://doi.org/10.1080/13854040903190797

Iverson, G.L., McCracken, L.M., 2009. 'Postconcussive' symptoms in persons with chronic pain. http://dx.doi.org.ezproxy.utu.fi/10.1080/026990597122990 11, 783–790. https://doi.org/10.1080/026990597122990

Jacobs, B., Beems, T., Stulemeijer, M., Van Vugt, A.B., Van Der Vliet, T.M., Borm, G.F., Vos, P.E., 2010. Outcome prediction in mild traumatic brain injury: Age and clinical variables are stronger predictors than CT abnormalities. J Neurotrauma 27, 655–668. https://doi.org/10.1089/NEU.2009.1059/ASSET/IMAGES/LARGE/FIG-2.JPEG

Jak, A.J., Jurick, S., Hoffman, S., Evangelista, N.D., Deford, N., Keller, A., Merritt, V.C., Sanderson-Cimino, M., Sorg, S., Delano-Wood, L., Bangen, K.J., 2020. PTSD, but not history of mTBI, is associated with altered myelin in combat-exposed Iraq and Afghanistan Veterans. Clin Neuropsychol 34, 1070–1087. https://doi.org/10.1080/13854046.2020.1730975

Jbabdi, S., Johansen-Berg, H., 2011. Tractography: Where Do We Go from Here? Brain Connect 1, 169. https://doi.org/10.1089/BRAIN.2011.0033

Jennett, B., Snoek, J., Bond, M.R., Brooks, N., 1981. Disability after severe head injury: observations on the use of the Glasgow Outcome Scale. J Neurol Neurosurg Psychiatry 44, 285–293. https://doi.org/10.1136/JNNP.44.4.285

Jensen, J.H., Helpern, J.A., Ramani, A., Lu, H., Kaczynski, K., 2005. Diffusional kurtosis imaging: The quantification of non-gaussian water diffusion by means of magnetic resonance imaging. Magn Reson Med 53, 1432–1440. https://doi.org/10.1002/MRM.20508

Jeurissen, B., Descoteaux, M., Mori, S., Leemans, A., 2019. Diffusion MRI fiber tractography of the brain. NMR Biomed. https://doi.org/10.1002/nbm.3785

Jeurissen, B., Leemans, A., Jones, D.K., Tournier, J.D., Sijbers, J., 2011. Probabilistic fiber tracking using the residual bootstrap with constrained spherical deconvolution. Hum Brain Mapp 32, 461–479. https://doi.org/10.1002/HBM.21032/FORMAT/PDF

Jeurissen, B., Leemans, A., Tournier, J.D., Jones, D.K., Sijbers, J., 2013. Investigating the prevalence of complex fiber configurations in white matter tissue with diffusion magnetic resonance imaging. Hum Brain Mapp 34, 2747–2766. https://doi.org/10.1002/HBM.22099

Jiang, J., Zhao, J., Hu, X.-Y., Du, M.-Y., Chen, Z.-Q., Wu, M., Li, K.-M., Zhu, H.-Y., Kumar, P., Gong, Q.-Y., 2017. Microstructural brain abnormalities in medication-free patients with major depressive disorder: a systematic review and meta-analysis of diffusion tensor imaging. J Psychiatry Neurosci 42. https://doi.org/10.1503/jpn.150341

Jones, D.K., Knösche, T.R., Turner, R., 2013. White matter integrity, fiber count, and other fallacies: The do's and don'ts of diffusion MRI. Neuroimage. https://doi.org/10.1016/j.neuroimage.2012.06.081

Kähkönen, S., Ilmoniemi, R.J., 2004. Transcranial magnetic stimulation: Applications for neuropsychopharmacology. Journal of Psychopharmacology 18, 257–261. https://doi.org/10.1177/0269881104042631

Kähkönen, S., Kesäniemi, M., Nikouline, V. V., Karhu, J., Ollikainen, M., Holi, M., Ilmoniemi, R.J., 2001. Ethanol modulates cortical activity: Direct evidence with combined TMS and EEG. Neuroimage 14, 322–328. https://doi.org/10.1006/nimg.2001.0849

Kähkönen, S., Komssi, S., Wilenius, J., Ilmoniemi, R.J., 2005. Prefrontal TMS produces smaller EEG responses than motor-cortex TMS: Implications for rTMS treatment in depression. Psychopharmacology (Berl) 181, 16–20. https://doi.org/10.1007/s00213-005-2197-3

Kähkönen, S., Komssi, S., Wilenius, J., Ilmoniemi, R.J., 2005. Prefrontal transcranial magnetic stimulation produces intensity-dependent EEG responses in humans. Neuroimage 24, 955–960. https://doi.org/10.1016/j.neuroimage.2004.09.048

Kähkönen, S, Komssi, S., Wilenius, J., Ilmoniemi, R.J., 2005. Prefrontal transcranial magnetic stimulation produces intensity-dependent EEG responses in humans. Neuroimage 24, 955–960. https://doi.org/10.1016/j.neuroimage.2004.09.048

Kamarajan, C., Pandey, A.K., Chorlian, D.B., Porjesz, B., Begleiter, H., 2015. The use of current source density as electrophysiological correlates in neuropsychiatric disorders: a review of human studies HHS Public Access. Int J Psychophysiol 97, 310–322. https://doi.org/10.1016/j.ijpsycho.2014.10.013

Kara, A., Celik, S.E., Dalbayrak, S., Yilmaz, M., Akansel, G., Tireli, G., 2008. Magnetic Resonance Imaging Finding in Severe Head Injury Patients with Normal Computerized Tomography. Turk Neurosurg 18, 1–9.

Katz, D.I., Bernick, C., Dodick, D.W., Mez, J., Mariani, M.L., Adler, C.H., Alosco, M.L., Balcer, L.J., Banks, S.J., Barr, W.B., Brody, D.L., Cantu, R.C., Dams-O'Connor, K., Geda, Y.E., Jordan, B.D., McAllister, T.W., Peskind, E.R., Petersen, R.C., Wethe, J. V., Zafonte, R.D., Foley, É.M., Babcock, D.J., Koroshetz, W.J., Tripodis, Y., McKee, A.C., Shenton, M.E., Cummings, J.L., Reiman, E.M., Stern, R.A., 2021. National Institute of Neurological Disorders and Stroke Consensus Diagnostic Criteria for Traumatic Encephalopathy Syndrome. Neurology 96, 848–863. https://doi.org/10.1212/WNL.0000000000011850

Kellner, E., Dhital, B., Kiselev, V.G., Reisert, M., 2016. Gibbs-ringing artifact removal based on local subvoxel-shifts. Magn Reson Med 76, 1574–1581. https://doi.org/10.1002/MRM.26054

Kerwin, L.J., Keller, C.J., Wu, W., Narayan, M., Etkin, A., 2018. Test-retest reliability of transcranial magnetic stimulation EEG evoked potentials. Brain Stimul 11, 536–544. https://doi.org/10.1016/j.brs.2017.12.010

Kičić, D., Lioumis, P., Ilmoniemi, R.J., Nikulin, V. V, 2008. Bilateral changes in excitability of sensorimotor cortices during unilateral movement: Combined electroencephalographic and transcranial magnetic stimulation study. Neuroscience 152, 1119–1129. https://doi.org/10.1016/j.neuroscience.2008.01.043

King, N.S., Crawford, S., Wenden, F.J., Moss, N.E.G., Wade, D.T., 1995. The Rivermead Post Concussion Symptoms Questionnaire: a measure of symptoms commonly experienced after head injury and its reliability. J Neurol 242, 587–592. https://doi.org/10.1007/BF00868811

King, R., Kirton, A., Zewdie, E., Seeger, T.A., Ciechanski, P., Barlow, K.M., 2019. Longitudinal assessment of cortical excitability in children and adolescents with mild traumatic brain injury and persistent post-concussive symptoms. Front Neurol 10, 451. https://doi.org/10.3389/fneur.2019.00451

Koh, D.M., Padhani, A.R., 2006. Diffussion-weighted MRI: A new functional clinical technique for tumour imaging. British Journal of Radiology 79, 633–635. https://doi.org/10.1259/BJR/29739265

Koivisto, M., Grassini, S., Hurme, M., Salminen-Vaparanta, N., Railo, H., Vorobyev, V., Tallus, J., Paavilainen, T., Revonsuo, A., 2017. TMS-EEG reveals hemispheric asymmetries in top-down influences of posterior intraparietal cortex on behavior and visual event-related potentials. Neuropsychologia 107, 94–101. https://doi.org/10.1016/j.neuropsychologia.2017.11.012

Komssi, S., Kähkönen, S., 2006. The novelty value of the combined use of electroencephalography and transcranial magnetic stimulation for neuroscience research. Brain Res Rev 52, 183–192. https://doi.org/10.1016/j.brainresrev.2006.01.008

Korley, F.K., Kelen, G.D., Jones, C.M., Diaz-Arrastia, R., 2016. Emergency department evaluation of traumatic brain injury in the United States, 2009-2010. Journal of Head Trauma Rehabilitation 31, 379–387. https://doi.org/10.1097/HTR.0000000000000187

Koskinen, S., Alaranta, H., 2008. Brain Injury Traumatic brain injury in Finland 1991-2005: A nationwide register study of hospitalized and fatal TBI Traumatic brain injury in Finland 1991-2005: A nationwide register study of hospitalized and fatal TBI. Brain Inj 22, 205–214. https://doi.org/10.1080/02699050801938975

Kralik, S.F., Supakul, N., Wu, I.C., Delso, G., Radhakrishnan, R., Ho, C.Y., Eley, K.A., 2019. Black bone MRI with 3D reconstruction for the detection of skull fractures in children with suspected abusive head trauma. Neuroradiology 61, 81–87. https://doi.org/10.1007/S00234-018-2127-9/FIGURES/3

Kraus, M.F., Susmaras, T., Caughlin, B.P., Walker, C.J., Sweeney, J.A., Little, D.M., 2007. White matter integrity and cognition in chronic traumatic brain injury: a diffusion tensor imaging study. Brain 130, 2508–2519. https://doi.org/10.1093/brain/awm216

Kruper, J., Yeatman, J.D., Richie-Halford, A., Bloom, D., Grotheer, M., Caffarra, S., Kiar, G., Karipidis, I.I., Roy, E., Chandio, B.Q., Garyfallidis, E., Rokem, A., 2021. Evaluating the Reliability of Human Brain White Matter Tractometry. Aperture Neuro 2021, 2021–2022. https://doi.org/10.52294/e6198273-b8e3-4b63-babb-6e6b0da10669

Kumar, R., Gupta, R.K., Husain, M., Chaudhry, C., Srivastava, A., Saksena, S., Rathore, R.K.S., 2009. Brain Injury Comparative evaluation of corpus callosum DTI metrics in acute mild and moderate traumatic brain injury: Its correlation with neuropsychometric tests Comparative evaluation of corpus callosum DTI metrics in acute mild and moderate traumatic brain injury: Its correlation with neuropsychometric tests. Brain Inj 23, 675–685. https://doi.org/10.1080/02699050903014915

Kurland, D., Hong, C., Aarabi, B., Gerzanich, V., Simard, J.M., 2012. Hemorrhagic progression of a contusion after traumatic brain injury: A review. J Neurotrauma 29, 19–31. https://doi.org/10.1089/NEU.2011.2122

Kutanzi, K.R., Lumen, A., Koturbash, I., Miousse, I.R., 2016. Pediatric Exposures to Ionizing Radiation: Carcinogenic Considerations. International Journal of Environmental Research and Public Health 2016, Vol. 13, Page 1057 13, 1057. https://doi.org/10.3390/IJERPH13111057

Lagarde, E., Salmi, L.R., Holm, L.W., Contrand, B., Masson, F., Ribéreau-Gayon, R., Laborey, M., Cassidy, J.D., 2014. Association of Symptoms Following Mild Traumatic Brain Injury With Posttraumatic Stress Disorder vs Postconcussion Syndrome. JAMA Psychiatry 71, 1032–1040. https://doi.org/10.1001/JAMAPSYCHIATRY.2014.666

Larach, D.B., Kofke, W.A., Le Roux, P., 2011. Potential non-hypoxic/ischemic causes of increased cerebral interstitial fluid lactate/pyruvate ratio: a review of available literature. Neurocrit Care 15, 609–622. https://doi.org/10.1007/S12028-011-9517-8

Le Bihan, D., Breton, E., Lallemand, D., Grenier, P., Cabanis, E., Laval-Jeantet, M., 1986. MR imaging of intravoxel incoherent motions: application to diffusion and perfusion in neurologic disorders. https://doi-org.ezproxy.utu.fi/10.1148/radiology.161.2.3763909 161, 401–407. https://doi.org/10.1148/RADIOLOGY.161.2.3763909

Lefaucheur, J.P., Aleman, A., Baeken, C., Benninger, D.H., Brunelin, J., Di Lazzaro, V., Filipović, S.R., Grefkes, C., Hasan, A., Hummel, F.C., Jääskeläinen, S.K., Langguth, B., Leocani, L., Londero, A., Nardone, R., Nguyen, J.P., Nyffeler, T., Oliveira-Maia, A.J., Oliviero, A., Padberg, F., Palm, U., Paulus, W., Poulet, E., Quartarone, A., Rachid, F., Rektorová, I., Rossi, S., Sahlsten, H., Schecklmann, M., Szekely, D., Ziemann, U., 2020. Evidence-based guidelines on the therapeutic use of repetitive transcranial magnetic stimulation (rTMS): An update (2014-2018). Clin Neurophysiol 131, 474–528. https://doi.org/10.1016/J.CLINPH.2019.11.002

Lefebvre, G., Tremblay, S., Théoret, H., 2015. Probing the effects of mild traumatic brain injury with transcranial magnetic stimulation of the primary motor cortex. https://doi-org.ezproxy.utu.fi/10.3109/02699052.2015.1028447 29, 1032–1043. https://doi.org/10.3109/02699052.2015.1028447

Levy-Lamdan, O., Zifman, N., Sasson, E., Efrati, S., Hack, D.C., Tanne, D., Dolev, I., Fogel, H., 2020. Evaluation of White Matter Integrity Utilizing the DELPHI (TMS-EEG) System. Front Neurosci 14. https://doi.org/10.3389/FNINS.2020.589107

Lin, C., Itti, E., Luciani, A., Haioun, C., Meignan, M., Rahmouni, A., 2010. Whole-body diffusion-weighted imaging in lymphoma. Cancer Imaging 10, S172. https://doi.org/10.1102/1470-7330.2010.9029

Lin, M., He, H., Schifitto, G., Zhong, J., 2016. Simulation of changes in diffusion related to different pathologies at cellular level after traumatic brain injury. Magn Reson Med 76, 290–300. https://doi.org/10.1002/MRM.25816/FORMAT/PDF

Lindberg, D.M., Stence, N. V., Grubenhoff, J.A., Lewis, T., Mirsky, D.M., Miller, A.L., O'Neill, B.R., Grice, K., Mourani, P.M., Runyan, D.K., 2019. Feasibility and accuracy of fast MRI versus CT for traumatic brain injury in young children. Pediatrics 144. https://doi.org/10.1542/PEDS.2019-0419/38445

Lioumis, P., Kičić, D., Savolainen, P., Mäkelä, J.P., Kähkönen, S., 2009. Reproducibility of TMS - Evoked EEG responses. Hum Brain Mapp 30, 1387–1396. https://doi.org/10.1002/hbm.20608

Lipton, M.L., Gulko, E., Zimmerman, M.E., Friedman, B.W., Kim, M., Gellella, E., Gold, T., Shifteh, K., Ardekani, B.A., Branch, C.A., 2009. Diffusion-tensor imaging implicates prefrontal axonal injury in executive function impairment following very mild traumatic brain injury. Radiology 252, 816–824. https://doi.org/10.1148/radiol.2523081584

Lipton, M.L., Kim, N., Park, Y.K., Hulkower, M.B., Gardin, T.M., Shifteh, K., Kim, M., Zimmerman, M.E., Lipton, R.B., Branch, C.A., 2012. Robust detection of traumatic axonal injury in individual mild traumatic brain injury patients: intersubject variation, change over time

and bidirectional changes in anisotropy. Brain Imaging Behav 6, 329–342. https://doi.org/10.1007/S11682-012-9175-2

Maas, A.I.R., Hukkelhoven, C.W.P.M., Marshall, L.F., Steyerberg, E.W., 2005. Prediction of outcome in traumatic brain injury with computed tomographic characteristics: A comparison between the computed tomographic classification and combinations of computed tomographic predictors. Neurosurgery 57, 1173–1181. https://doi.org/10.1227/01.NEU.0000186013.63046.6B

Maier-Hein, K.H., Neher, P.F., Houde, J.C., Côté, M.A., Garyfallidis, E., Zhong, J., Chamberland, M., Yeh, F.C., Lin, Y.C., Ji, Q., Reddick, W.E., Glass, J.O., Chen, D.Q., Feng, Y., Gao, C., Wu, Y., Ma, J., Renjie, H., Li, Q., Westin, C.F., Deslauriers-Gauthier, S., González, J.O.O., Paquette, M., St-Jean, S., Girard, G., Rheault, F., Sidhu, J., Tax, C.M.W., Guo, F., Mesri, H.Y., Dávid, S., Froeling, M., Heemskerk, A.M., Leemans, A., Boré, A., Pinsard, B., Bedetti, C., Desrosiers, M., Brambati, S., Doyon, J., Sarica, A., Vasta, R., Cerasa, A., Quattrone, A., Yeatman, J., Khan, A.R., Hodges, W., Alexander, S., Romascano, D., Barakovic, M., Auría, A., Esteban, O., Lemkaddem, A., Thiran, J.P., Cetingul, H.E., Odry, B.L., Mailhe, B., Nadar, M.S., Pizzagalli, F., Prasad, G., Villalon-Reina, J.E., Galvis, J., Thompson, P.M., Requejo, F.D.S., Laguna, P.L., Lacerda, L.M., Barrett, R., Dell'Acqua, F., Catani, M., Petit, L., Caruyer, E., Daducci, A., Dyrby, T.B., Holland-Letz, T., Hilgetag, C.C., Stieltjes, B., Descoteaux, M., 2017. The challenge of mapping the human connectome based on diffusion tractography. Nature Communications 2017 8:1 8, 1–13. https://doi.org/10.1038/s41467-017-01285-x

Major, B.P., Rogers, M.A., Pearce, A.J., 2015. Using transcranial magnetic stimulation to quantify electrophysiological changes following concussive brain injury: A systematic review. Clin Exp Pharmacol Physiol 42, 394–405. https://doi.org/10.1111/1440-1681.12363

Malcolm, M.P., Paxton, R.J., 2015. High-Frequency Repetitive Transcranial Magnetic Stimulation Effects on Motor Intracortical Neurophysiology: A Sham-Controlled Investigation HHS Public Access. J Clin Neurophysiol 32, 428–433. https://doi.org/10.1097/WNP.0000000000000203

Mangrum, W., Christianson, K., Duncan, S., Hoang, P., Song, A.W., Merkle, E., 2012. Duke Review of MRI Principles: Case Review Series. Elsevier/Mosby. https://doi.org/10.1016/j.acra.2013.04.017

Marshall, L., Marshall, S.B., Klauber, M., Clark, M.V.B., Eisenberg, H., Jane, J., Luerssen, T., Marmarou, A., Foulkes, M., 1992. The diagnosis of head injury requires a classification based on computed axial tomography. J Neurotrauma.

Masel, B.E., DeWitt, D.S., 2010. Traumatic brain injury: A disease process, not an event. J Neurotrauma 27, 1529–1540. https://doi.org/10.1089/NEU.2010.1358/FORMAT/EPUB

Maximov, I.I., Alnæs, D., Westlye, L.T., 2019. Towards an optimised processing pipeline for diffusion magnetic resonance imaging data: Effects of artefact corrections on diffusion metrics and their age associations in UK Biobank. Hum Brain Mapp 40, 4146–4162. https://doi.org/10.1002/HBM.24691

Mayer, A.R., Ling, J., Mannell, M. V., Gasparovic, C., Phillips, J.P., Doezema, D., Reichard, R., Yeo, R.A., 2010. A prospective diffusion tensor imaging study in mild traumatic brain injury. Neurology 74, 643–650. https://doi.org/10.1212/WNL.0b013e3181d0ccdd

Mccrory, P., Feddermann-Demont, N., Dvořák, J., Cassidy, J.D., Mcintosh, A., Vos, P.E., Echemendia, R.J., Meeuwisse, W., Tarnutzer, A.A., 2017. What is the definition of sports-related concussion: a systematic review. Br J Sports Med 51, 877–887. https://doi.org/10.1136/bjsports-2016-097393

McGinn, M.J., Povlishock, J.T., 2016. Pathophysiology of Traumatic Brain Injury. Neurosurg Clin N Am. https://doi.org/10.1016/j.nec.2016.06.002

McInnes, K., Friesen, C.L., MacKenzie, D.E., Westwood, D.A., Boe, S.G., 2017. Mild Traumatic Brain Injury (mTBI) and chronic cognitive impairment: A scoping review. PLoS One. https://doi.org/10.1371/journal.pone.0174847

McIntyre, M., Amiri, M., Kumbhare, D., 2021. Postconcussion Syndrome: A Diagnosis of Past Diagnostic and Statistical Manual of Mental Disorders. Am J Phys Med Rehabil 100, 193–195. https://doi.org/10.1097/PHM.0000000000001586

McKee, A.C., Stein, T.D., Kiernan, P.T., Alvarez, V.E., 2015. The neuropathology of chronic traumatic encephalopathy. Brain Pathol 25, 350–364. https://doi.org/10.1111/BPA.12248

McMahon, P., Hricik, A., Yue, J.K., Puccio, A.M., Inoue, T., Lingsma, H.F., Beers, S.R., Gordon, W.A., Valadka, A.B., Manley, G.T., Okonkwo, D.O., Casey, S.S., Cooper, S.R., Dams-O'Connor, K., Menon, D.K., Sorani, M.D., Yuh, E.L., Mukherjee, P., Schnyer, D.M., Vassar, M.J., 2014. Symptomatology and functional outcome in mild traumatic brain injury: results from the prospective TRACK-TBI study. J Neurotrauma 31, 26–33. https://doi.org/10.1089/NEU.2013.2984

McMillan, T., Wilson, L., Ponsford, J., Levin, H., Teasdale, G., Bond, M., 2016. The Glasgow Outcome Scale — 40 years of application and refinement. Nature Publishing Group 12. https://doi.org/10.1038/nrneurol.2016.89

Meares, S., Shores, E.A., Taylor, A.J., Batchelor, J., Bryant, R.A., Baguley, I.J., Chapman, J., Gurka, J., Marosszeky, J.E., 2011. The Prospective Course of Postconcussion Syndrome: The Role of Mild Traumatic Brain Injury. Neuropsychology 25, 454–465. https://doi.org/10.1037/A0022580

Meier, T.B., Bergamino, M., Bellgowan, P.S.F., Teague, T.K., Ling, J.M., Jeromin, A., Mayer, A.R., 2016. Longitudinal assessment of white matter abnormalities following sports-related concussion. Hum Brain Mapp 37, 833–845. https://doi.org/10.1002/HBM.23072

Mendez, M.F., 2017. What is the Relationship of Traumatic Brain Injury to Dementia? J Alzheimers Dis 57, 667–681. https://doi.org/10.3233/JAD-161002

Menon, D.K., Schwab, K., Wright, D.W., Maas, A.I., 2010. Position statement: Definition of traumatic brain injury. Arch Phys Med Rehabil. https://doi.org/10.1016/j.apmr.2010.05.017

Messé, A., Caplain, S., Pélégrini-Issac, M., Blancho, S., Montreuil, M., Lévy, R., Lehéricy, S., Benali, H., 2012. Structural integrity and postconcussion syndrome in mild traumatic brain injury patients. Brain Imaging Behav 6, 283–292. https://doi.org/10.1007/S11682-012-9159-2

Miller, N.R., Yasen, A.L., Maynard, L.F., Chou, L.S., Howell, D.R., Christie, A.D., 2014. Acute and longitudinal changes in motor cortex function following mild traumatic brain injury. http://dx.doi.org.ezproxy.utu.fi/10.3109/02699052.2014.915987 28, 1270–1276. https://doi.org/10.3109/02699052.2014.915987

Mohammadian, M., Roine, T., Hirvonen, J., Kurki, T., Ala-Seppälä, H., Frantzén, J., Katila, A., Kyllönen, A., Maanpää, H.R., Posti, J., Takala, R., Tallus, J., Tenovuo, O., 2017. High angular resolution diffusion-weighted imaging in mild traumatic brain injury. Neuroimage Clin 13, 174–180. https://doi.org/10.1016/j.nicl.2016.11.016

Mohammadian, M., Roine, T., Hirvonen, J., Kurki, T., Posti, J.P., Katila, A.J., Takala, R.S.K., Tallus, J., Maanpää, H.R., Frantzén, J., Hutchinson, P.J., Newcombe, V.F., Menon, D.K., Tenovuo, O., 2020. Alterations in Microstructure and Local Fiber Orientation of White Matter Are Associated with Outcome after Mild Traumatic Brain Injury. J Neurotrauma 37, 2616–2623. https://doi.org/10.1089/NEU.2020.7081/FORMAT/EPUB

Mormina, E., Arrigo, A., Calamuneri, A., Alafaci, C., Tomasello, F., Morabito, R., Marino, S., Longo, M., Vinci, S.L., Granata, F., 2016. Optic radiations evaluation in patients affected by high-grade gliomas: a side-by-side constrained spherical deconvolution and diffusion tensor imaging study. Neuroradiology 58, 1067–1075. https://doi.org/10.1007/s00234-016-1732-8

Mutch, C.A., Talbott, J.F., Gean, A., 2016. Imaging Evaluation of Acute Traumatic Brain Injury. Neurosurg Clin N Am. https://doi.org/10.1016/j.nec.2016.05.011

Nardone, R., Bergmann, J., Kunz, A., Caleri, F., Seidl, M., Tezzon, F., Gerstenbrand, F., Trinka, E., Golaszewski, S., 2011. Cortical excitability changes in patients with sleep-wake disturbances after traumatic brain injury. J Neurotrauma 28, 1165–1171. https://doi.org/10.1089/NEU.2010.1748/ASSET/IMAGES/LARGE/FIGURE2.JPEG

Nardone, R., Sebastianelli, L., Versace, V., Ferrazzoli, D., Saltuari, L., Trinka, E., 2021. TMS-EEG Co-Registration in Patients with Mild Cognitive Impairment, Alzheimer's Disease and Other Dementias: A Systematic Review. Brain Sci 11, 1–16. https://doi.org/10.3390/BRAINSCI11030303

Nelson, D.W., Nyström, H., MacCallum, R.M., Thornquist, B., Lilja, A., Bellander, B.M., Rudehill, A., Wanecek, M., Weitzberg, E., 2010. Extended analysis of early computed tomography scans of traumatic brain injured patients and relations to outcome. J Neurotrauma 27, 51–64. https://doi.org/10.1089/NEU.2009.0986

Nelson, L.D., Temkin, N.R., Dikmen, S., Barber, J., Giacino, J.T., Yuh, E., Levin, H.S., McCrea, M.A., Stein, M.B., Mukherjee, P., Okonkwo, D.O., Diaz-Arrastia, R., Manley, G.T., Adeoye, O., Badjatia, N., Boase, K., Bodien, Y., Bullock, M.R., Chesnut, R., Corrigan, J.D., Crawford, K., Duhaime, A.C., Ellenbogen, R., Feeser, V.R., Ferguson, A., Foreman, B., Gardner, R., Gaudette, E., Gonzalez, L., Gopinath, S., Gullapalli, R., Hemphill, J.C., Hotz, G., Jain, S., Korley, F., Kramer, J., Kreitzer, N., Lindsell, C., MacHamer, J., Madden, C., Martin, A., McAllister, T., Merchant, R., Noel, F., Palacios, E., Perl, D., Puccio, A., Rabinowitz, M., Robertson, C.S., Rosand, J., Sander, A., Satris, G., Schnyer, D., Seabury, S., Sherer, M., Taylor, S., Toga, A., Valadka, A., Vassar, M.J., Vespa, P., Wang, K., Yue, J.K., Zafonte, R., 2019. Recovery After Mild Traumatic Brain Injury in Patients Presenting to US Level I Trauma Centers: A Transforming Research and Clinical Knowledge in Traumatic Brain Injury (TRACK-TBI) Study. JAMA Neurol 76, 1049–1059. https://doi.org/10.1001/JAMANEUROL.2019.1313

Nguyen, R., Fiest, K.M., McChesney, J., Kwon, C.S., Jette, N., Frolkis, A.D., Atta, C., Mah, S., Dhaliwal, H., Reid, A., Pringsheim, T., Dykeman, J., Gallagher, C., 2016. The International Incidence of Traumatic Brain Injury: A Systematic Review and Meta-Analysis. Can J Neurol Sci 43, 774–785. https://doi.org/10.1017/CJN.2016.290

Niogi, S.N., Mukherjee, P., Ghajar, J., Johnson, C., Kolster, R.A., Sarkar, R., Lee, H., Meeker, M., Zimmerman, R.D., Manley, G.T., McCandliss, B.D., 2008. Extent of microstructural white matter injury in postconcussive syndrome correlates with impaired cognitive reaction time: A 3T diffusion tensor imaging study of mild traumatic brain injury, in: American Journal of Neuroradiology. pp. 967–973. https://doi.org/10.3174/ajnr.A0970

Nolan, A.L., Petersen, C., Iacono, D., Mac Donald, C.L., Mukherjee, P., van der Kouwe, A., Jain, S., Stevens, A., Diamond, B.R., Wang, R., Markowitz, A.J., Fischl, B., Perl, D.P., Manley, G.T., Dirk Keene, C., Diaz-Arrastia, R., Edlow, B.L., 2021. Tractography-pathology correlations in traumatic brain injury: A TRACK-TBI study. J Neurotrauma 38, 1662–1669. https://doi.org/10.1089/NEU.2020.7373/SUPPL_FILE/SUPP_TABLES4.PDF

Numminen, H.J., 2011. The incidence of traumatic brain injury in an adult population - how to classify mild cases? Eur J Neurol 18, 460–464. https://doi.org/10.1111/J.1468-1331.2010.03179.X/FORMAT/PDF

Oberman, L.M., Exley, S., Philip, N.S., Siddiqi, S.H., Adamson, M.M., Brody, D.L., 2020. Use of repetitive transcranial magnetic stimulation in the treatment of neuropsychiatric and neurocognitive symptoms associated with concussion in military populations. Journal of Head Trauma Rehabilitation 35, 388–400. https://doi.org/10.1097/HTR.0000000000000628

Oehr, L., Anderson, J., 2017. Diffusion-Tensor Imaging Findings and Cognitive Function Following Hospitalized Mixed-Mechanism Mild Traumatic Brain Injury: A Systematic Review and Meta-Analysis. Arch Phys Med Rehabil 98, 2308–2319. https://doi.org/10.1016/J.APMR.2017.03.019

Oldham, S., Arnatkevičiūtė, A., Smith, R.E., Tiego, J., Bellgrove, M.A., Fornito, A., 2020. The efficacy of different preprocessing steps in reducing motion-related confounds in diffusion MRI connectomics. Neuroimage 222. https://doi.org/10.1016/J.NEUROIMAGE.2020.117252

Orrison, W.W., Hanson, E.H., Alamo, T., Watson, D., Sharma, M., Perkins, T.G., Tandy, R.D., 2009. Traumatic brain injury: A review and high-field MRI findings in 100 unarmed combatants using a literature-based checklist approach. J Neurotrauma 26, 689–701. https://doi.org/10.1089/NEU.2008.0636

Orrison, W.W., Stimac, G.K., Stevens, E.A., LaMasters, D.L., Espinosa, M.C., Cobb, L., Mettler, F.A., 1991. Comparison of CT, low-field-strength MR imaging, and high-field-strength MR imaging. Work in progress, in: Radiology. pp. 121–127. https://doi.org/10.1148/radiology.181.1.1887020

Palacios, E.M., Owen, J.P., Yuh, E.L., Wang, M.B., Vassar, M.J., Ferguson, A.R., Diaz-Arrastia, R., Giacino, J.T., Okonkwo, D.O., Robertson, C.S., Stein, M.B., Temkin, N., Jain, S., McCrea, M., MacDonald, C.L., Levin, H.S., Manley, G.T., Mukherjee, P., 2020. The evolution of white matter microstructural changes after mild traumatic brain injury: A longitudinal DTI and NODDI study. Sci Adv 6. https://doi.org/10.1126/SCIADV.AAZ6892

Paterakis, K., Karantanas, A.H., Komnos, A., Volikas, Z., 2000. Outcome of patients with diffuse axonal injury: The significance and prognostic value of MRI in the acute phase. Journal of Trauma - Injury, Infection and Critical Care 49, 1071–1075. https://doi.org/10.1097/00005373-200012000-00016

Paulus, W., Classen, J., Cohen, L.G., Large, C.H., Di Lazzaro, V., Nitsche, M., Pascual-Leone, A., Rosenow, F., Rothwell, J.C., Ziemann, U., 2008a. State of the art: Pharmacologic effects on cortical excitability measures tested by transcranial magnetic stimulation. Brain Stimul 1, 151–163. https://doi.org/10.1016/j.brs.2008.06.002

Paulus, W., Classen, J., Cohen, L.G., Large, C.H., Di Lazzaro, V., Nitsche, M., Pascual-Leone, A., Rosenow, F., Rothwell, J.C., Ziemann, U., 2008b. State of the art: Pharmacologic effects on cortical excitability measures tested by transcranial magnetic stimulation. Brain Stimul. https://doi.org/10.1016/j.brs.2008.06.002

Paulus, W., Peterchev, A. V, Ridding, M., 2013. Transcranial electric and magnetic stimulation: Technique and paradigms, in: Handbook of Clinical Neurology. pp. 329–342. https://doi.org/10.1016/B978-0-444-53497-2.00027-9

Paus, T., Jech, R., Thompson, C.J., Comeau, R., Peters, T., Evans, A.C., 1997. Transcranial magnetic stimulation during positron emission tomography: A new method for studying connectivity of the human cerebral cortex. Neuroimage 5.

Paus, T., Sipila, P.K., Strafella, A.P., 2001. Synchronization of neuronal activity in the human primary motor cortex by transcranial magnetic stimulation: An EEG study. J Neurophysiol 86, 1983–1990. https://doi.org/10.1152/jn.2001.86.4.1983

Pearce, A.J., Hoy, K., Rogers, M.A., Corp, D.T., Davies, C.B., Maller, J.J., Fitzgerald, P.B., 2015. Acute motor, neurocognitive and neurophysiological change following concussion injury in Australian amateur football. A prospective multimodal investigation. J Sci Med Sport 18, 500–506. https://doi.org/10.1016/j.jsams.2014.07.010

Pearce, A.J., Hoy, K., Rogers, M.A., Corp, D.T., Maller, J.J., Drury, H.G.K., Fitzgerald, P.B., 2014. The long-term effects of sports concussion on retired Australian football players: A study using transcranial magnetic stimulation. J Neurotrauma 31, 1139–1145. https://doi.org/10.1089/NEU.2013.3219/ASSET/IMAGES/LARGE/FIGURE2.JPEG

Peeters, W., van den Brande, R., Polinder, S., Brazinova, A., Steyerberg, E.W., Lingsma, H.F., Maas, A.I.R., 2015. Epidemiology of traumatic brain injury in Europe. Acta Neurochir (Wien) 157, 1683–1696. https://doi.org/10.1007/S00701-015-2512-7/TABLES/5

Polinder, S., Cnossen, M.C., Real, R.G.L., Covic, A., Gorbunova, A., Voormolen, D.C., Master, C.L., Haagsma, J.A., Diaz-Arrastia, R., Von Steinbuechel, N., 2018. A Multidimensional Approach to Post-concussion Symptoms in Mild Traumatic Brain Injury. Front Neurol 9. https://doi.org/10.3389/FNEUR.2018.01113/FULL

Posti, J.P., Takala, R.S.K., Raj, R., Luoto, T.M., Azurmendi, L., Lagerstedt, L., Mohammadian, M., Hossain, I., Gill, J., Frantzén, J., van Gils, M., Hutchinson, P.J., Katila, A.J., Koivikko, P., Maanpää, H.R., Menon, D.K., Newcombe, V.F., Tallus, J., Blennow, K., Tenovuo, O., Zetterberg, H., Sanchez, J.C., 2020. Admission Levels of Interleukin 10 and Amyloid β 1–40 Improve the Outcome Prediction Performance of the Helsinki Computed Tomography Score in Traumatic Brain Injury. Front Neurol 11. https://doi.org/10.3389/FNEUR.2020.549527/FULL

Povlishock, J.T., Katz, D.I., 2005. Update of neuropathology and neurological recovery after traumatic brain injury. Journal of Head Trauma Rehabilitation 20, 76–94. https://doi.org/10.1097/00001199-200501000-00008

Premoli, I., Rivolta, D., Espenhahn, S., Castellanos, N., Belardinelli, P., Ziemann, U., Müller-Dahlhaus, F., 2014. Characterization of GABAB-receptor mediated neurotransmission in the human cortex by paired-pulse TMS-EEG. Neuroimage 103, 152–162. https://doi.org/10.1016/j.neuroimage.2014.09.028

Puig, J., Ellis, M.J., Kornelsen, J., Figley, T.D., Figley, C.R., Daunis-I-Estadella, P., Mutch, W.A.C., Essig, M., 2020. Magnetic Resonance Imaging Biomarkers of Brain Connectivity in Predicting Outcome after Mild Traumatic Brain Injury: A Systematic Review. J Neurotrauma 37, 1761–1776. https://doi.org/10.1089/NEU.2019.6623/ASSET/IMAGES/LARGE/NEU.2019.6623_FIGURE1.JPEG

Raj, R., Siironen, J., Skrifvars, M.B., Hernesniemi, J., Kivisaari, R., 2014. Predicting Outcome in Traumatic Brain InjuryDevelopment of a Novel Computerized Tomography Classification System (Helsinki Computerized Tomography Score). Neurosurgery 75, 632–647. https://doi.org/10.1227/NEU.0000000000000533

Ranson, J., Magnus, B.E., Temkin, N., Dikmen, S., Giacino, J.T., Okonkwo, D.O., Valadka, A.B., Manley, G.T., Nelson, L.D., 2019. Diagnosing the GOSE: Structural and Psychometric Properties Using Item Response Theory, a TRACK-TBI Pilot Study. J Neurotrauma 36, 2493–2505. https://doi.org/10.1089/NEU.2018.5998/ASSET/IMAGES/LARGE/FIGURE3.JPEG

Reijmer, Y.D., Leemans, A., Heringa, S.M., Wielaard, I., Jeurissen, B., 2012. Improved Sensitivity to Cerebral White Matter Abnormalities in Alzheimer's Disease with Spherical Deconvolution Based Tractography. PLoS One 7, 44074. https://doi.org/10.1371/journal.pone.0044074

Ressel, V., van Hedel, H.J.A., Scheer, I., O'Gorman Tuura, R., 2018. Comparison of DTI analysis methods for clinical research: influence of pre-processing and tract selection methods. Eur Radiol Exp 2. https://doi.org/10.1186/S41747-018-0066-1

Reuben, A., Sampson, P., Harris, A.R., Williams, H., Yates, P., 2014. Postconcussion syndrome (PCS) in the emergency department: predicting and pre-empting persistent symptoms following a mild traumatic brain injury. Emergency Medicine Journal 31, 72–77. https://doi.org/10.1136/EMERMED-2012-201667

Rheault, F., De Benedictis, A., Daducci, A., Maffei, C., W Tax, C.M., Romascano, D., Caverzasi, E., Morency, F.C., Corrivetti, F., Pestilli, F., Girard, G., Theaud, G., Zemmoura, I., Hau, J., Glavin, K., Jordan, K.M., Pomiecko, K., Chamberland, M., Barakovic, M., Goyette, N., Poulin, P., Chenot, Q., Panesar, S.S., Sarubbo, S., Petit, L., Descoteaux, M., 2020. Tractostorm: The what, why, and how of tractography dissection reproducibility. Hum Brain Mapp 41, 1859–1874. https://doi.org/10.1002/hbm.24917

Rimel, R., Giordani, B., Barth, J., Boll, T., Jane, J., 1981. Disability Caused by Minor Head Injury. : Neurosurgery. Neurosurgery.

Rimel, R.W., Giordani, B., Barth, J.T., Jane, J.A., 1982. Moderate head injury: Completing the clinical spectrum of brain trauma. Neurosurgery 11, 344–351. https://doi.org/10.1227/00006123-198209000-00002

Roozenbeek, B., Maas, A.I.R., Menon, D.K., 2013. Changing patterns in the epidemiology of traumatic brain injury. Nat Rev Neurol 9, 231–236. https://doi.org/10.1038/nrneurol.2013.22

Rossi, S., Antal, A., Bestmann, S., Bikson, M., Brewer, C., Brockmöller, J., Carpenter, L.L., Cincotta, M., Chen, R., Daskalakis, J.D., Di Lazzaro, V., Fox, M.D., George, M.S., Gilbert, D., Kimiskidis, V.K., Koch, G., Ilmoniemi, R.J., Pascal Lefaucheur, J., Leocani, L., Lisanby, S.H., Miniussi, C., Padberg, F., Pascual-Leone, A., Paulus, W., Peterchev, A. V, Quartarone, A., Rotenberg, A., Rothwell, J., Rossini, P.M., Santarnecchi, E., Shafi, M.M., Siebner, H.R., Ugawa, Y., Wassermann, E.M., Zangen, A., Ziemann, U., Hallett, M., 2021. Safety and recommendations for TMS use in healthy subjects and patient populations, with updates on

training, ethical and regulatory issues: Expert Guidelines. Clinical Neurophysiology. https://doi.org/10.1016/j.clinph.2020.10.003

Rossi, S., Hallett, M., Rossini, P.M., Pascual-Leone, A., Avanzini, G., Bestmann, S., Berardelli, A., Brewer, C., Canli, T., Cantello, R., Chen, R., Classen, J., Demitrack, M., Di Lazzaro, V., Epstein, C.M., George, M.S., Fregni, F., Ilmoniemi, R., Jalinous, R., Karp, B., Lefaucheur, J.P., Lisanby, S., Meunier, S., Miniussi, C., Miranda, P., Padberg, F., Paulus, W., Peterchev, A., Porteri, C., Provost, M., Quartarone, A., Rotenberg, A., Rothwell, J., Ruohonen, J., Siebner, H., Thut, G., Valls-Solè, J., Walsh, V., Ugawa, Y., Zangen, A., Ziemann, U., 2009. Safety, ethical considerations, and application guidelines for the use of transcranial magnetic stimulation in clinical practice and research. Clinical Neurophysiology 120, 2008–2039. https://doi.org/10.1016/j.clinph.2009.08.016

Rubiano, A.M., Carney, N., Chesnut, R., Puyana, J.C., 2015. Global neurotrauma research challenges and opportunities. Nature 527, S193–S197. https://doi.org/10.1038/nature16035

Ruohonen, J., Karhu, J., 2010. Navigated transcranial magnetic stimulation. Neurophysiologie Clinique 40, 7–17. https://doi.org/10.1016/j.neucli.2010.01.006

Salvador, R., Silva, S., Basser, P.J., Miranda, P.C., 2011. Determining which mechanisms lead to activation in the motor cortex: a modeling study of transcranial magnetic stimulation using realistic stimulus waveforms and sulcal geometry 1. Clin Neurophysiol 122, 748–758. https://doi.org/10.1016/j.clinph.2010.09.022

Sandsmark, D.K., Bashir, A., Wellington, C.L., Diaz-Arrastia, R., 2019. Cerebral microvascular injury: a potentially treatable endophenotype of traumatic brain injury-induced neurodegeneration HHS Public Access. Neuron 103, 367–379. https://doi.org/10.1016/j.neuron.2019.06.002

Sarwar, T., Ramamohanarao, K., Zalesky, A., 2019. Mapping connectomes with diffusion MRI: deterministic or probabilistic tractography? Magn Reson Med 81, 1368–1384. https://doi.org/10.1002/MRM.27471

Savola, O., Hillbom, M., 2003. Early predictors of post-concussion symptoms in patients with mild head injury. Eur J Neurol 10, 175–181. https://doi.org/10.1046/j.1468-1331.2003.00552.x

Schaefer, P.W., Buonanno, F.S., Gonzalez, R.G., Schwamm, L.H., 1997. Diffusion-weighted imaging discriminates between cytotoxic and vasogenic edema in a patient with eclampsia. Stroke 28, 1082–1085. https://doi.org/10.1161/01.STR.28.5.1082

Schilling, K.G., Rheault, F., Petit, L., Hansen, C.B., Nath, V., Yeh, F.C., Girard, G., Barakovic, M., Rafael-Patino, J., Yu, T., Fischi-Gomez, E., Pizzolato, M., Ocampo-Pineda, M., Schiavi, S., Canales-Rodríguez, E.J., Daducci, A., Granziera, C., Innocenti, G., Thiran, J.P., Mancini, L., Wastling, S., Cocozza, S., Petracca, M., Pontillo, G., Mancini, M., Vos, S.B., Vakharia, V.N., Duncan, J.S., Melero, H., Manzanedo, L., Sanz-Morales, E., Peña-Melián, Á., Calamante, F., Attyé, A., Cabeen, R.P., Korobova, L., Toga, A.W., Vijayakumari, A.A., Parker, D., Verma, R., Radwan, A., Sunaert, S., Emsell, L., De Luca, A., Leemans, A., Bajada, C.J., Haroon, H., Azadbakht, H., Chamberland, M., Genc, S., Tax, C.M.W., Yeh, P.H., Srikanchana, R., Mcknight, C.D., Yang, J.Y.M., Chen, J., Kelly, C.E., Yeh, C.H., Cochereau, J., Maller, J.J., Welton, T., Almairac, F., Seunarine, K.K., Clark, C.A., Zhang, F., Makris, N., Golby, A., Rathi, Y., O'Donnell, L.J., Xia, Y., Aydogan, D.B., Shi, Y., Fernandes, F.G., Raemaekers, M., Warrington, S., Michielse, S., Ramírez-Manzanares, A., Concha, L., Aranda, R., Meraz, M.R., Lerma-Usabiaga, G., Roitman, L., Fekonja, L.S., Calarco, N., Joseph, M., Nakua, H., Voineskos, A.N., Karan, P., Grenier, G., Legarreta, J.H., Adluru, N., Nair, V.A., Prabhakaran, V., Alexander, A.L., Kamagata, K., Saito, Y., Uchida, W., Andica, C., Abe, M., Bayrak, R.G., Wheeler-Kingshott, C.A.M.G., D'Angelo, E., Palesi, F., Savini, G., Rolandi, N., Guevara, P., Houenou, J., López-López, N., Mangin, J.F., Poupon, C., Román, C., Vázquez, A., Maffei, C., Arantes, M., Andrade, J.P., Silva, S.M., Calhoun, V.D., Caverzasi, E., Sacco, S., Lauricella, M., Pestilli, F., Bullock, D., Zhan, Y., Brignoni-Perez, E., Lebel, C., Reynolds, J.E., Nestrasil, I., Labounek, R., Lenglet, C., Paulson, A., Aulicka, S., Heilbronner, S.R., Heuer, K., Chandio, B.Q., Guaje, J., Tang, W.,

Garyfallidis, E., Raja, R., Anderson, A.W., Landman, B.A., Descoteaux, M., 2021. Tractography dissection variability: What happens when 42 groups dissect 14 white matter bundles on the same dataset? Neuroimage 243, 118502. https://doi.org/10.1016/j.neuroimage.2021.118502

Schweitzer, A.D., Niogi, S.N., Whitlow, C.T., Tsiouris, A.J., 2019. Traumatic brain injury: Imaging patterns and complications. Radiographics 39, 1571–1595. https://doi.org/10.1148/RG.2019190076/ASSET/IMAGES/LARGE/RG.2019190076.FIG11F.JPEG

Seeger, T.A., Kirton, A., Esser, M.J., Gallagher, C., Dunn, J., Zewdie, E., Damji, O., Ciechanski, P., Barlow, K.M., 2017. Cortical excitability after pediatric mild traumatic brain injury. Brain Stimul 10, 305–314. https://doi.org/10.1016/j.brs.2016.11.011

Sharp, D.J., Jenkins, P.O., 2015. Concussion is confusing us all. Pract Neurol. https://doi.org/10.1136/practneurol-2015-001087

Shenton, M.E., Price, B.H., Levin, L., Edersheim, J.G., 2018. Mild traumatic brain injury: Is DTI ready for the courtroom? Int J Law Psychiatry 61, 50–63. https://doi.org/10.1016/j.ijlp.2018.09.002

Singleton, R.H., Povlishock, J.T., 2004. Identification and Characterization of Heterogeneous Neuronal Injury and Death in Regions of Diffuse Brain Injury: Evidence for Multiple Independent Injury Phenotypes. Journal of Neuroscience 24, 3543–3553. https://doi.org/10.1523/JNEUROSCI.5048-03.2004

Slimen, I. Ben, Boubchir, L., Seddik, H., 2020. Epileptic seizure prediction based on EEG spikes detection of ictal-preictal states. J Biomed Res 34, 162–169. https://doi.org/10.7555/JBR.34.20190097

Spinos, P., Sakellaropoulos, G., Georgiopoulos, M., Stavridi, K., Apostolopoulou, K., Ellul, J., Constantoyannis, C., 2010. Postconcussion syndrome after mild traumatic brain injury in Western Greece. Journal of Trauma - Injury, Infection and Critical Care 69, 789–793. https://doi.org/10.1097/TA.0B013E3181EDEA67

Stejskal, E.O., Tanner, J.E., 1965. Spin Diffusion Measurements: Spin Echoes in the Presence of a Time Dependent Field Gradient. Citation: J. Chem. Phys 42, 288. https://doi.org/10.1063/1.1695690

Strauss, S.B., Kim, N., Branch, C.A., Kahn, M.E., Kim, M., Lipton, R.B., Provataris, J.M., Scholl, H.F., Zimmerman, M.E., Lipton, M.L., 2016. Bidirectional changes in anisotropy are associated with outcomes in mild traumatic brain injury. American Journal of Neuroradiology 37, 1983–1991. https://doi.org/10.3174/ajnr.A4851

Studerus-Germann, A.M., Gautschi, O.P., Bontempi, P., Thiran, J.P., Daducci, A., Romascano, D., von Ow, D., Hildebrandt, G., von Hessling, A., Engel, D.C., 2018. Central nervous system microbleeds in the acute phase are associated with structural integrity by DTI one year after mild traumatic brain injury: A longitudinal study. Neurol Neurochir Pol 52, 710–719. https://doi.org/10.1016/J.PJNNS.2018.08.011

Summaka, M., Zein, H., Elias, E., Naim, I., Fares, Y., Nasser, Z., 2020. Prediction of quality of life by Helsinki computed tomography scoring system in patients with traumatic brain injury. Brain Inj 34, 1229–1236. https://doi.org/10.1080/02699052.2020.1799435

Sydnor, V.J., Rivas-Grajales, A.M., Lyall, A.E., Zhang, F., Bouix, S., Karmacharya, S., Shenton, M.E., Westin, C.F., Makris, N., Wassermann, D., O'Donnell, L.J., Kubicki, M., 2018. A comparison of three fiber tract delineation methods and their impact on white matter analysis. Neuroimage 178, 318–331. https://doi.org/10.1016/j.neuroimage.2018.05.044

Taber, K.H., Hurley, R.A., 2013. Update on mild traumatic brain injury: Neuropathology and structural imaging. Journal of Neuropsychiatry and Clinical Neurosciences 25, 1–5. https://doi.org/10.1176/appi.neuropsych.12120401

Takahashi, C.E., Virmani, D., Chung, D.Y., Ong, C., Cervantes-Arslanian, A.M., 2021. Blunt and Penetrating Severe Traumatic Brain Injury. Neurol Clin. https://doi.org/10.1016/j.ncl.2021.02.009

Tao, J.X., Ray, A., Hawes-Ebersole, S., Ebersole, J.S., 2005. Intracranial EEG substrates of scalp EEG interictal spikes. Epilepsia 46, 669–676. https://doi.org/10.1111/J.1528-1167.2005.11404.X

Teasdale, G., Jennett, B., 1974. ASSESSMENT OF COMA AND IMPAIRED CONSCIOUSNESS: A Practical Scale. The Lancet 304, 81–84. https://doi.org/10.1016/S0140-6736(74)91639-0

Teasdale, G., Maas, A., Lecky, F., Manley, G., Stocchetti, N., Murray, G., 2014. The Glasgow Coma Scale at 40 years: Standing the test of time. Lancet Neurol. https://doi.org/10.1016/S1474-4422(14)70120-6

Teasdale, G.M., Pettigrew, L.E.L., Wilson, J.T.L., Murray, G., Jennett, B., 1998. Analyzing outcome of treatment of severe head injury: A review and update on advancing the use of the Glasgow outcome scale. J Neurotrauma 15, 587–597. https://doi.org/10.1089/NEU.1998.15.587

The Management of Concussion-mild Traumatic Brain Injury Working Group, 2016. VA/DoD Clinical Practice Guideline for the Management of Concussion-mild Traumatic Brain Injury The Management of Concussion-mild Traumatic Brain Injury Working Group The Office of Quality, Safety and Value, VA, Washington, DC & Office of Evidence Bas 1–133.

Theadom, A., Parag, V., Dowell, T., McPherson, K., Starkey, N., Barker-Collo, S., Jones, K., Ameratunga, S., Feigin, V.L., 2016. Persistent problems 1 year after mild traumatic brain injury: A longitudinal population study in New Zealand. British Journal of General Practice 66, e16–e23. https://doi.org/10.3399/bjgp16X683161

Thelin, E.P., Nelson, D.W., Vehviläinen, J., Nyström, H., Kivisaari, R., Siironen, J., Svensson, M., Skrifvars, M.B., Bellander, B.M., Raj, R., 2017. Evaluation of novel computerized tomography scoring systems in human traumatic brain injury: An observational, multicenter study. PLoS Med 14. https://doi.org/10.1371/JOURNAL.PMED.1002368

Tjerkaski, J., Nyström, H., Raj, R., Lindblad, C., Bellander, B.M., Nelson, D.W., Thelin, E.P., 2022. Extended Analysis of Axonal Injuries Detected Using Magnetic Resonance Imaging in Critically Ill Traumatic Brain Injury Patients. J Neurotrauma 39, 58–66. https://doi.org/10.1089/NEU.2021.0159/SUPPL_FILE/SUPP_DATAS1.DOCX

Tournier, J.D., Calamante, F., Connelly, A., 2013. Determination of the appropriate b value and number of gradient directions for high-angular-resolution diffusion-weighted imaging. NMR Biomed 26, 1775–1786. https://doi.org/10.1002/nbm.3017

Tournier, J.D., Calamante, F., Connelly, A., 2007. Robust determination of the fibre orientation distribution in diffusion MRI: Non-negativity constrained super-resolved spherical deconvolution. Neuroimage 35, 1459–1472. https://doi.org/10.1016/j.neuroimage.2007.02.016

Tournier, J.D., Smith, R., Raffelt, D., Tabbara, R., Dhollander, T., Pietsch, M., Christiaens, D., Jeurissen, B., Yeh, C.H., Connelly, A., 2019. MRtrix3: A fast, flexible and open software framework for medical image processing and visualisation. Neuroimage. https://doi.org/10.1016/j.neuroimage.2019.116137

Tournier, J.D., Yeh, C.H., Calamante, F., Cho, K.H., Connelly, A., Lin, C.P., 2008. Resolving crossing fibres using constrained spherical deconvolution: Validation using diffusion-weighted imaging phantom data. Neuroimage 42, 617–625. https://doi.org/10.1016/j.neuroimage.2008.05.002

Tremblay, S., Beaulé, V., Proulx, S., de Beaumont, L., Marjańska, M., Doyon, J., Pascual-Leone, A., Lassonde, M., Théoret, H., 2013. Relationship between transcranial magnetic stimulation measures of intracortical inhibition and spectroscopy measures of GABA and glutamate+glutamine. J Neurophysiol 109, 1343. https://doi.org/10.1152/JN.00704.2012

Tremblay, S., De Beaumont, L., Lassonde, M., Théoret, H., 2011. Evidence for the specificity of intracortical inhibitory dysfunction in asymptomatic concussed athletes. J Neurotrauma 28, 493–502. https://doi.org/10.1089/NEU.2010.1615/ASSET/IMAGES/LARGE/FIGURE1.JPEG

Tremblay, S., Rogasch, N.C., Premoli, I., Blumberger, D.M., Casarotto, S., Chen, R., Lazzaro, V. Di, Farzan, F., Ferrarelli, F., Fitzgerald, P.B., Hui, J., Ilmoniemi, R.J., Kimiskidis, V.K., Kugiumtzis, D., Lioumis, P., Pascual-Leone, A., Pellicciari, M.C., Rajji, T., Thut, G., Zomorrodi, R.,

Ziemann, U., Daskalakis, Z.J., 2019. Clinical utility and prospective of TMS-EEG. Clinical Neurophysiology 130, 802–844. https://doi.org/10.1016/j.clinph.2019.01.001

Tremblay, S., Vernet, M., Bashir, S., Pascual-Leone, A., Théoret, H., 2015. Theta burst stimulation to characterize changes in brain plasticity following mild traumatic brain injury: A proof-of-principle study. Restor Neurol Neurosci 33, 611–620. https://doi.org/10.3233/RNN-140459

Tuch, D.S., 2004. Q-ball imaging. Magn Reson Med 52, 1358–1372. https://doi.org/10.1002/MRM.20279

Turner, G.R., McIntosh, A.R., Levine, B., 2011. Prefrontal Compensatory Engagement in TBI is due to Altered Functional Engagement Of Existing Networks and not Functional Reorganization. Front Syst Neurosci 5. https://doi.org/10.3389/FNSYS.2011.00009

Tustison, N.J., Avants, B.B., Cook, P.A., Zheng, Y., Egan, A., Yushkevich, P.A., Gee, J.C., 2010. N4ITK: Improved N3 bias correction. IEEE Trans Med Imaging 29, 1310–1320. https://doi.org/10.1109/TMI.2010.2046908

Undén, J., Ingebrigtsen, T., Romner, B., 2013. Scandinavian guidelines for initial management of minimal, mild and moderate head injuries in adults: An evidence and consensus-based update. BMC Med 11, 1–14. https://doi.org/10.1186/1741-7015-11-50/TABLES/4

VA/DoD Clinical Practice Guideline for Management of Concussion/Mild Traumatic Brain Injury., 2009. . J Rehabil Res Dev 46. https://doi.org/10.1682/JRRD.2009.06.0076

Van Der Naalt, (J, De Koning Bsc, M.E., Van Der Horn, H.J., Jacobs, B., Spikman, J.M., Timmerman, E., Van Der Naalt, J., 2017. Early predictors of outcome after mild traumatic brain injury (UPFRONT): an observational cohort study. Articles Lancet Neurol 16, 532–572.

Van Der Werf, Y.D., Paus, T., 2006. The neural response to transcranial magnetic stimulation of the human motor cortex. I. Intracortical and cortico-cortical contributions. Exp Brain Res 175, 231–245. https://doi.org/10.1007/S00221-006-0551-2/FIGURES/13

VanItallie, T.B., 2019. Traumatic brain injury (TBI) in collision sports: Possible mechanisms of transformation into chronic traumatic encephalopathy (CTE). Metabolism 100S. https://doi.org/10.1016/J.METABOL.2019.07.007

Veeramuthu, V., Narayanan, V., Kuo, T.L., Delano-Wood, L., Chinna, K., Bondi, M.W., Waran, V., Ganesan, D., Ramli, N., 2015. Diffusion Tensor Imaging Parameters in Mild Traumatic Brain Injury and Its Correlation with Early Neuropsychological Impairment: A Longitudinal Study. J Neurotrauma 32, 1497–1509. https://doi.org/10.1089/NEU.2014.3750

Veraart, J., Novikov, D.S., Christiaens, D., Ades-aron, B., Sijbers, J., Fieremans, E., 2016. Denoising of diffusion MRI using random matrix theory. Neuroimage 142, 394–406. https://doi.org/10.1016/j.neuroimage.2016.08.016

Vernet, M., Bashir, S., Yoo, W.K., Perez, J.M., Najib, U., Pascual-Leone, A., 2013. Insights on the neural basis of motor plasticity induced by theta burst stimulation from TMS-EEG. European Journal of Neuroscience 37, 598–606. https://doi.org/10.1111/EJN.12069

Virtanen, J., Ruohonen, J., Näätänen, R., Ilmoniemi, R.J., 1999. Instrumentation for the measurement of electric brain responses to transcranial magnetic stimulation. Med Biol Eng Comput 37, 322–326. https://doi.org/10.1007/BF02513307

Von Steinbüchel, N., Wilson, L., Gibbons, H., Hawthorne, G., Höfer, S., Schmidt, S., Bullinger, M., Maas, A., Neugebauer, E., Powell, J., Von Wild, K., Zitnay, G., Bakx, W., Christensen, A.L., Koskinen, S., Sarajuuri, J., Formisano, R., Sasse, N., Truelle, J.L., 2010. Quality of Life after Brain Injury (QOLIBRI): Scale Development and Metric Properties. https://home.liebertpub.com/neu 27, 1167–1185. https://doi.org/10.1089/NEU.2009.1076

Voormolen, D.C., Zeldovich, M., Haagsma, J.A., Polinder, S., Friedrich, S., Maas, A.I.R., Wilson, L., Steyerberg, E.W., Covic, A., Andelic, N., Plass, A.M., Wu, Y.J., Asendorf, T., von Steinbüechel, N., 2020. Outcomes After Complicated and Uncomplicated Mild Traumatic Brain Injury at Three- and Six-Months Post-Injury: Results from the CENTER-TBI Study. J Clin Med 9. https://doi.org/10.3390/JCM9051525

Vos, P.E., Alekseenko, Y., Battistin, L., Ehler, E., Gerstenbrand, F., Muresanu, D.F., Potapov, A., Stepan, C.A., Traubner, P., Vecsei, L., von Wild, K., 2012. Mild traumatic brain injury. Eur J Neurol 19, 191–198. https://doi.org/10.1111/J.1468-1331.2011.03581.X/FORMAT/PDF

Wäljas, M., Iverson, G.L., Lange, R.T., Hakulinen, U., Dastidar, P., Huhtala, H., Liimatainen, S., Hartikainen, K., Öhman, J., 2015. A prospective biopsychosocial study of the persistent post-concussion symptoms following mild traumatic brain injury. J Neurotrauma 32, 534–547. https://doi.org/10.1089/NEU.2014.3339

Wäljas, M., Lange, R.T., Hakulinen, U., Huhtala, H., Dastidar, P., Hartikainen, K., Öhman, J., Iverson, G.L., 2014. Biopsychosocial outcome after uncomplicated mild traumatic brain injury. J Neurotrauma 31, 108–124. https://doi.org/10.1089/NEU.2013.2941

Wassermann, E.M., 1998. Risk and safety of repetitive transcranial magnetic stimulation: Report and suggested guidelines from the International Workshop on the Safety of Repetitive Transcranial Magnetic Stimulation, June 5-7, 1996. Electroencephalography and Clinical Neurophysiology - Evoked Potentials 108, 1–16. https://doi.org/10.1016/S0168-5597(97)00096-8

Wasserthal, J., Neher, P., Maier-Hein, K.H., 2018a. TractSeg - Fast and accurate white matter tract segmentation. Neuroimage 183, 239–253. https://doi.org/10.1016/J.NEUROIMAGE.2018.07.070

Wasserthal, J., Neher, P.F., Hirjak, D., Maier-Hein, K.H., 2019. Combined tract segmentation and orientation mapping for bundle-specific tractography. Med Image Anal 58. https://doi.org/10.1016/j.media.2019.101559

Wasserthal, J., Neher, P.F., Maier-Hein, K.H., 2018b. Tract orientation mapping for bundle-specific tractography, in: Lecture Notes in Computer Science (Including Subseries Lecture Notes in Artificial Intelligence and Lecture Notes in Bioinformatics). pp. 36–44. https://doi.org/10.1007/978-3-030-00931-1_5

Wedeen, V.J., Hagmann, P., Tseng, W.Y.I., Reese, T.G., Weisskoff, R.M., 2005. Mapping complex tissue architecture with diffusion spectrum magnetic resonance imaging. Magn Reson Med 54, 1377–1386. https://doi.org/10.1002/MRM.20642

Yeatman, J.D., Dougherty, R.F., Myall, N.J., Wandell, B.A., Feldman, H.M., 2012. Tract Profiles of White Matter Properties: Automating Fiber-Tract Quantification. PLoS One 7, 49790. https://doi.org/10.1371/journal.pone.0049790

Yue, J.K., Yuh, E.L., Korley, F.K., Winkler, E.A., Sun, X., Puffer, R.C., Deng, H., Choy, W., Chandra, A., Taylor, S.R., Ferguson, A.R., Huie, J.R., Rabinowitz, M., Puccio, A.M., Mukherjee, P., Vassar, M.J., Wang, K.K.W., Diaz-Arrastia, R., Okonkwo, D.O., Jain, S., Manley, G.T., Adeoye, O.M., Badjatia, N., Boase, K., Bodien, Y.G., Bullock, M.R., Chesnut, R.M., Corrigan, J.D., Crawford, K., Dikmen, S.S., Duhaime, A.C., Ellenbogen, R.G., Feeser, V., Foreman, B., Gardner, R.C., Gaudette, E., Giacino, J.T., Goldman, D.P., Gonzalez, L., Gopinath, S., Gullapalli, R., Hemphill, J.C., Hotz, G., Kramer, J.H., Kreitzer, N.P., Levin, H.S., Lindsell, C.J., Machamer, J., Madden, C.J., Martin, A.J., McAllister, T.W., McCrea, M., Merchant, R., Nelson, L.D., Noel, F., Palacios, E.M., Perl, D.P., Robertson, C.S., Rosand, J., Sander, A.M., Satris, G.G., Schnyer, D.M., Seabury, S.A., Sherer, M., Stein, M.B., Temkin, N.R., Toga, A.W., Valadka, A.B., Vespa, P.M., Zafonte, R., 2019. Association between plasma GFAP concentrations and MRI abnormalities in patients with CT-negative traumatic brain injury in the TRACK-TBI cohort: a prospective multicentre study. Lancet Neurol 18, 953–961. https://doi.org/10.1016/S1474-4422(19)30282-0

Yuh, E.L., Cooper, S.R., Mukherjee, P., Yue, J.K., Lingsma, H.F., Gordon, W.A., Valadka, A.B., Okonkwo, D.O., Schnyer, D.M., Vassar, M.J., Maas, A.I.R., Manley, G.T., Casey, S.S., Cheong, M., Dams-O'Connor, K., Hricik, A.J., Inoue, T., Menon, D.K., Morabito, D.J., Pacheco, J.L., Puccio, A.M., Sinha, T.K., 2014. Diffusion tensor imaging for outcome prediction in mild traumatic brain injury: a TRACK-TBI study. J Neurotrauma 31, 1457–1477. https://doi.org/10.1089/NEU.2013.3171/ASSET/IMAGES/LARGE/FIGURE4.JPEG

Yuh, E.L., Jain, S., Sun, X., Pisică, D., Harris, M.H., Taylor, S.R., Markowitz, A.J., Mukherjee, P., Verheyden, J., Giacino, J.T., Levin, H.S., McCrea, M., Stein, M.B., Temkin, N.R., Diaz-Arrastia, R., Robertson, C.S., Lingsma, H.F., Okonkwo, D.O., Maas, A.I.R., Manley, G.T., Adeoye, O., Badjatia, N., Boase, K., Bodien, Y., Corrigan, J.D., Crawford, K., Dikmen, S., Duhaime, A.C., Ellenbogen, R., Feeser, V.R., Ferguson, A.R., Foreman, B., Gardner, R., Gaudette, E., Gonzalez, L., Gopinath, S., Gullapalli, R., Hemphill, J.C., Hotz, G., Keene, C.D., Kramer, J., Kreitzer, N., Lindsell, C., MacHamer, J., Madden, C., Martin, A., McAllister, T., Merchant, R., Nelson, L., Ngwenya, L.B., Noel, F., Nolan, A., Palacios, E., Perl, D., Rabinowitz, M., Rosand, J., Sander, A., Satris, G., Schnyer, D., Seabury, S., Toga, A., Valadka, A., Vassar, M., Zafonte, R., 2021. Pathological Computed Tomography Features Associated With Adverse Outcomes After Mild Traumatic Brain Injury: A TRACK-TBI Study With External Validation in CENTER-TBI. JAMA Neurol 78, 1. https://doi.org/10.1001/JAMANEUROL.2021.2120

Zhang, H., Schneider, T., Wheeler-Kingshott, C.A., Alexander, D.C., 2012. NODDI: Practical in vivo neurite orientation dispersion and density imaging of the human brain. Neuroimage 61, 1000–1016. https://doi.org/10.1016/j.neuroimage.2012.03.072

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