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# THE EFFECT OF MILD TRAUMATIC BRAIN INJURY ON OSCILLATORY BRAIN ACTIVITY

Hanna Kaltiainen

ACADEMIC DISSERTATION

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*To my family*

# ABSTRACT

Mild traumatic brain injuries (mTBI) are common, and while most patients recover well, there is a minority of patients suffering from prolonged symptoms lasting over three months. Pathological processes provoke low-frequency (0.5 - 7 Hz) oscillatory brain activity, measurable with electroencephalography (EEG) and magnetoencephalography (MEG). After mTBI, low frequency activity (LFA) is hypothesized to arise from cortical neurons suffering from de-afferentation after traumatic axonal injury. The natural evolution and prognostic value of low-frequency activity (LFA) measured with MEG, however, is not yet firmly established and reliable biomarkers for cognitive complaints after mTBI are lacking.

The aim of this thesis was to examine the occurrence and natural evolution of low frequency activity (LFA) after mild traumatic brain injury (mTBI), and to assess its prognostic value in predicting those with prolonged symptoms. Additionally, we wanted to examine the effect of mTBI to brain oscillatory activity during cognitive tasks and find indicators for altered processing.

The existence of LFA in healthy subjects might, however, hamper its' diagnostic value. Therefore, in Study I we created a reference database of resting-state oscillatory brain activity and observed LFA in only 1,4% of healthy subjects' MEG recordings. The Study II assessed the occurrence and evolution of LFA in resting-state MEG recordings of mTBI patients. At a single-subject level, 7/26 patients presented aberrant 4–7 Hz (theta) band activity; 3/7 patients with abnormal theta activity were without any detectable lesions in MRI. Of the twelve patients with follow-up measurements, five showed abnormal theta activity in the first recording, but only two in the second measurement, implying the importance of early measurements in clinical settings. The presence of LFA was not, however, correlated with the prevalence of self-reported symptoms.

The Study III concentrated on the modulation of oscillatory activity during cognitive tasks, Paced Auditory Serial Addition Test (PASAT) and a vigilance test. Attenuation of cortical activity at alpha band (8 – 14 Hz) during PASAT compared with rest was stronger in patients than in controls ($p \leq 0.05$, corrected). Furthermore, the patients presented significant attenuation of oscillatory activity also in the left superior frontal gyrus and right prefrontal cortices which was not detected in controls. Spectral peak amplitudes of areal mean oscillatory activity at the alpha band were negatively correlated with the patients' neuropsychological performance ($p<0.01$, uncorrected). Areal alpha frequency modulation during PASAT compared with rest was altered in patients: While the alpha peak frequency increased occipitally and remained stable at other areas in controls, it was stable occipitally and decreased at other areas in mTBI patients ($p=0.012$).

According to our studies, LFA, especially theta-band oscillatory activity can provide an early objective sign of brain dysfunction after mTBI, and cortical oscillatory activity during a demanding cognitive task (PASAT) is altered after

mTBI. Our observations suggest that both aberrant theta-band activity and the altered alpha activity during cognitive tasks may offer clinically relevant indicators of changes in neural processing after mTBI.

# TIIVISTELMÄ

Lievät aivovammat ovat yleisiä, ja vaikka suurin osa loukkaantuneista toipuu hyvin, kärsii pieni vähemmistö yli kolme kuukautta kestävistä jälkioireista. Toipumista ennustavia tekijöitä ei juuri ole, mikä vaikeuttaa lievän vamman saaneiden potilaiden arviointia. Aivosairaudet, myös aivovammat, aiheuttavat matalataajuista rytmistä toimintaa (0.5 – 7 Hz), joka voidaan tunnistaa aivosähkökäyrän (EEG) tai magnetoenkefalografian (MEG) avulla. Aivovamman jälkeisen hidasaaltotoiminnan ajatellaan johtuvan hermosolujen viejähaarakkeiden vaurion aiheuttamasta hermosolujen poikkeavasta sähköisestä toiminnasta. Hidasaaltotoiminnan yhteys pitkittyneisiin oireisiin ja sen ennustearvo potilaiden toipumisen kannalta ei kuitenkaan ole vielä selvillä.

Selvitimme hidasaaltotoiminnan esiintyvyyttä ja ajallista käyttäytymistä lievän aivovamman jälkeen, ja arvioimme hidasaaltotoiminnan yhteyttä pitkittyneen jälkioireiston kehittymiseen. Lisäksi halusimme selvittää, eroaako rytmisen toiminnan muuntuminen muisti- ja tarkkaavaisuustehtävien aikana potilailla ja kontrollihenkilöillä, sekä löytää keinoja todentaa osalla potilaista esiintyviä tiedonkäsittelyn ongelmia.

Hidasaaltotoiminnan esiintyminen terveillä vähentäisi löydöksen diagnostista merkitystä vamman jälkeen. Sen vuoksi ensimmäisessä osatyössä loimme terveiden koehenkilöiden normaaliaineiston ja havaitsimme, että heistä vain 1.4%:lla esiintyy poikkeavaa hidasaaltotoimintaa. Toisessa osatyössä totesimme poikkeavaa theta-jaksoista (4-7 Hz) hidasaaltotoimintaa esiintyvän 7/26:lla lievän aivovamman sairastaneista potilaista. Kolmella heistä ei havaittu poikkeavia muutoksia aivojen rakenteellisessa magneettikuvauksessa. Seurantamittaus tehtiin 12 potilaalle, joista viidellä oli thetatoimintaa ensimmäisessä mittauksessa, mutta seurantamittauksessa vain kahdella. Aikainen mittausajankohta vamman jälkeen vaikuttaa siten parantavan tutkimuksen herkkyyttä. Alkuvaiheen hidasaaltotoiminta ei kuitenkaan ennustanut jälkioireiston kehittymistä potilaille.

Kolmannessa osatyössä tarkastelimme muisti- ja tarkkaavaisuustehtävien (Paced Auditory Serial Addition Test, PASAT ja toinen tarkkaavaisuustehtävä) vaikutusta aivojen rytmiseen toimintaan. Havaitsimme PASAT-tehtävän aikana potilaiden rytmisen toiminnan vaimentuvan lepotilanteeseen verrattuna voimakkaammin ja useammilla alueilla ns. alfa-taajuuskaistalla (8-14 Hz) kuin kontrollihenkilöillä ($p<0.05$). Alueellisten alfa-taajuuskaistan piikkitaajuuksien ja -amplitudien keskiarvojen tarkastelussa havaitsimme potilailla negatiivisen korrelaation piikkiamplitudien ja neuropsykologisen testisuoriutumisen välillä ($p<0.01$, ei korjattu). Myös alueelliset piikkitaajuudet käyttäytyivät eri tavalla kontrollihenkilöillä ja potilailla. Kontrolleilla tehtävän aikana takaraivolohkon alfa-taajuus nousi muiden alueiden pysyessä vakaana verrattuna lepotilaan,

kun potilailla sen sijaan takaraivolohkon alfa-taajuus säilyi ennallaan, mutta muiden alueiden laski verrattuna lepotilaan ($p=0.012$).

Tutkimuksemme perusteella theta-jaksoinen toiminta pian lievän aivovamman jälkeen voi osoittaa objektiivisesti aivotoiminnan häiriön. Potilailla aivojen rytminen toiminta vaativan kognitiivisen tehtävän (PASAT) aikana erosi kontrolleista. Havaintojemme perusteella sekä theta-jaksoisen rytmisen toiminnan esiintyminen, että rytmisen toiminnan muuntuminen kognitiivisten tehtävien aikana voivat jatkossa tarjota kliinisesti merkityksellisiä välineitä arvioitaessa tiedonkäsittelyn tehottomuutta lievän aivovamman jälkeen.

# CONTENTS

# LIST OF ORIGINAL PUBLICATIONS

This doctoral dissertation comprises the following studies, together with an overall summary of the field they examine:

I Kaltiainen HL, Helle L, Renvall H, Forss N. Slow wave oscillations in healthy subjects – methodological and physiological considerations. Journal of Clinical Neurophysiology 2016; Aug 33(4):367-72

II Kaltiainen HL, Helle L, Liljeström M, Renvall H, Forss N. Theta-band oscillations as an indicator mild traumatic brain injury. Brain Topography 2018; Nov;31(6):1037-1046. doi: 10.1007/s10548-018-0667-2. Epub 2018 Aug 10.

III Kaltiainen HL, Liljeström M, Helle L, Salo A, Hietanen M, Forss N, Renvall H. Mild traumatic brain injury affects cognitive processing and modifies oscillatory brain activity during attentional tasks. *In Press* in Journal of Neurotrauma

The publications are referred to in the text by their roman numerals.

# AUTHOR'S CONTRIBUTION

I have together with our team contributed to study design and been the principal author in all these publications.

Study I: Hanna Renvall had collected magnetoencephalography data for a previous work. I analyzed the data with help from Liisa Helle and was responsible for writing of the manuscript.

Study II: I was responsible for recruiting the patients, conducting the MEG measurements, analyzing the data with help from Liisa Helle and Mia Liljeström, and writing the manuscript.

Study III: I was responsible for recruiting the patients, conducting the MEG measurements and analyzing the data with help from Mia Liljeström and Liisa Helle. Anne Salo collected the behavioral data. I was responsible for behavioral data analysis and writing of the manuscript.

# ABBREVIATIONS

| | |
|---|---|
| ACRM | American Congress on Rehabilitation Medicine |
| AP | action potential |
| APF | alpha peak frequency |
| CT | computed tomography |
| DICS | dynamic imaging of coherent sources |
| DLPFC | dorso-lateral prefrontal cortex |
| DMPFC | dorso-medial prefrontal cortex |
| dSPM | dynamic statistical parameter mapping |
| DTI | diffusion tensor imaging |
| EC | eyes closed |
| ECG | electro-cardiogram |
| EEG | electroencephalography |
| EFNS | European Federation of Neurological Societies |
| e.g. | exempli gratia |
| EO | eyes open |
| EOG | electro-oculogram |
| ER | emergency room |
| etc. | et cetera |
| FA | fractional anisotropy |
| FFT | fast Fourier transform |
| fMRI | functional magnetic resonance imaging |
| GABA | gamma-amino butyric acid |
| GFAP | glial fibrillary acidic protein |
| GCS | Glasgow coma scale |
| ICA | independent component analysis |
| i.e. | id est |
| IPL | inferior parietal lobule |
| LFA | low frequency activity |
| LOC | loss of consciousness |
| MEG | magnetoencephalography |
| MNE | minimum norm estimate |
| MRI | magnetic resonance imaging |
| mTBI | mild traumatic brain injury |
| NSE | neuron specific enolase |
| PASAT | paced auditory serial addition test |
| PCS | post-concussion syndrome |
| PET | positron emission tomography |
| PSP | post-synaptic potential |
| PTA | post-traumatic amnesia |
| RPQ | Rivermead Post-Concussion Symptom Questionnaire |
| SPECT | single positron emission tomography |

| | |
|---|---|
| SQUID | Superconducting Quantum Interference Device |
| SSP | signal space projection |
| TBI | traumatic brain injury |
| TMT | trail-making test |
| tSSS | temporal signal space separation |
| UCH-L1 | ubiquitin C-terminal hydrolase isoenzyme L1 |
| WHO | World Health Organization |
| VT | vigilance test |

# 1 INTRODUCTION

Brain trauma has been recognized as a reason for morbidity and mortality since paleolithic era, and treatments, such as skull trepanation, have been attempted already several thousand years ago (Khsettry et al, 2007). Nowadays, traumatic brain injury (TBI) is among leading causes of long-time disability and lives lost in young adults up to forty years of age. The great majority of TBIs are mild, the estimates varying from 70% (Koskinen 2011, Peeters 2015) to 90% (Tagliaferri et al., 2006).

Most patients with mild TBI (mTBI) recuperate well within days or weeks after the injury, whereas in 5-20% the symptoms that are unspecific linger for over three months (Iverson et al., 2012; Losoi et al., 2016). In mTBI patients, structural imaging is often within normal ranges, and the correlation of possible lesions with outcome remains uncertain (B. Jacobs et al., 2010; Lee et al., 2008; Yuh et al., 2013). Despite strenuous research, specific biomarkers for mTBI are scarce, and mTBI still offers a diagnostic challenge. The diagnosis is currently clinical, based on assessing the level of consciousness after trauma, the length of loss of consciousness, and post-traumatic amnesia (Levin and Diaz-Arrastia, 2015).

This lack of objective indicators of altered neural processing after mTBI is detrimental to patients, who may be left alone without adequate counselling and support (D. Gronwall and Wrightson, 1974). In an unfavorable situation, often accompanied by other stress factors in life, the patient may evolve to present with so-called *post-concussion syndrome*, a constellation of unspecific symptoms without generally accepted measurable correlates (Ponsford et al., 2012).

In the following sections I will summarize the clinical and imaging assessment of TBI focusing on mild TBI (mTBI) in civilians, mainly excluding sports which is a special entity within mTBI. The text is largely based on Kobeissy FH et al., (2015) in clinical issues, and on Hämäläinen M et al., (1993), Hansen PC et al. (2010) and Hari and Puce (2017), when it comes to MEG methodology.

# 2 BACKGROUND

## 2.1 MILD TRAUMATIC BRAIN INJURY (MTBI)

### 2.1.1 EPIDEMIOLOGY AND RISK FACTORS FOR MTBI

#### *2.1.1.1 Incidence of mTBI*

TBI is among leading causes of long-time disability and lives lost in young adults up to forty years. Especially mTBIs are common: estimated 100 - 300/100 000 patients worldwide seek medical advice annually and many others recuperate well without any contact to healthcare services, yielding to estimated total incidence of 42 million people per year (Cassidy et al., 2004; Gardner and Yaffe, 2015). In European population, the severity rates of TBI have been estimated to be 22:1.5:1 for mild, moderate, and severe cases (Tagliaferri et al., 2006). In Finland, the incidence of TBI, estimated from healthcare registers, is approximately 100-220/100000 (Koskinen and Alaranta, 2008; Numminen, 2011) of which, with EFNS criteria (Table 1), 71% are considered to be mild (Numminen, 2011). The incidence of TBI in Finland, is thus approximately 12000 every year. As EFNS criteria for mTBI are tighter than “Käypä Hoito” criteria clinically used in Finland, the true annual incidence of mTBI in Finland is probably around 10000.

#### *2.1.1.2 Trauma-mechanisms, gender and age-distribution of mTBI*

The most common trauma mechanisms for mTBI comprise falls and traffic accidents, followed by sports and assaults (Cassidy et al., 2004; Isokuortti et al., 2016). Males are approximately at a twofold risk for mTBI compared with females, who on average are injured at older age than males (Cassidy et al., 2004; Feigin et al., 2013; Peeters et al., 2015). The incidence of mTBI, based on hospital derived samples, is largest in teenagers and young adults up to age 25, where a substantial proportion of traumas results from traffic accidents. Another peak in mTBI incidence occurs at older age (after 65), where the majority of them result from falls (Cassidy et al., 2004; Peeters et al., 2015). In a population health survey, the annual prevalence of mTBI was 110/100000, with peak-incidence in 14-35 age group with male predominance, sports-related injury being the most frequent cause (Gordon et al., 2006). It is thus probable that hospital-derived samples overestimate the incidence of traffic-related accidents, which more often result in visits to emergency room for evaluation, over sports-related accidents, which more often are from the mildest end of TBI spectrum. mTBI is associated especially with contact sports

and more frequently occurs during competitions compared with practice, the majority resulting from player to player contact (Laker, 2011). When similar sports are compared, mTBI seems to be more frequent in females than males (Laker, 2011).

### 2.1.2 PATHOPHYSIOLOGY OF MTBI

Knowledge on pathophysiology of mTBI relies mostly on animal models and few post-mortem studies. External mechanical force causes the immediate primary injury, which then launches a cascade of metabolic, molecular, and cellular events causing secondary trauma over longer period of time (Bolouri and Zetterberg, 2015). Indeed, traumatic brain injuries are currently increasingly viewed within wider perspective, taking into account the possible late manifestations of prior traumatic events on overall health and well-being (Masel and DeWitt, 2010; L. Wilson et al., 2017).

In mTBI, disruption of axonal integrity or function *i.e.* diffuse axonal injury (DAI) is believed to be the main cause of the following diverse symptoms (Buki and Povlishock, 2006; Blennow et al., 2012; Giza and Hovda, 2014). An external force may result in mechanical poration of lipid membranes in neurons and subsequent efflux of potassium together with influx of sodium and calcium, causing depolarization together with excess release of excitatory neurotransmitters, such as glutamate (Blennow et al., 2012; Buki and Povlishock, 2006; Giza and Hovda, 2014). If homeostasis is not regained acutely, excess of $Ca^{2+}$ then activates a cascade of neurometabolic changes causing damage to membrane cytoskeleton and mitochondria, and resulting in further release of cytochrome-c activating enzymes accelerating the vicious cycle and degrading the axonal cytoskeleton (Blennow et al., 2012; Buki and Povlishock, 2006; Giza and Hovda, 2014).

Mitochondrial damage and increased energy consumption due to attempts to retain the cellular homeostasis compromise cellular energy metabolism, and lead to accumulation of lactate and other metabolites such as free radicals, resulting in acidosis and edema (Blennow et al., 2012; Giza and Hovda, 2014). Besides neurons and glia cells, trauma also affects small microcapillaries resulting in blood-brain-barrier damage and focal ischemia further compromising cellular homeostasis and energy metabolism, as well as clearance of toxic metabolites (Blennow et al., 2012; Giza and Hovda, 2014). After initial hypermetabolic state, a period of glucose hypometabolism appears, lasting up to 7-10 days, during which a repeated trauma may cause further deterioration of clinical symptoms. The metabolic depression has also been related to the so-called “vulnerable period” reported to take place after the initial TBI (Giza and Hovda, 2014).

The disruption of axonal cytoskeleton and mechanical displacement of microtubules after trauma lead to altered axonal transport, accumulation of organelles, axonal swelling and - if repair mechanisms fail - eventually to axonal disconnection (Blennow et al., 2012; Buki and Povlishock, 2006). Axonal swellings and bulbs are most commonly seen in the interface of white and gray matter in the bottom of cortical sulci (Browne et al., 2011; Chen et

al., 2004). Axotomy results in gradual degeneration of the downstream axons (Wallerian degeneration) and fiber loss over weeks and months.
Besides degradation, brain trauma is accompanied by neuroplasticity and repair. Activation and migration of microglia and astrocytes to the lesion site might, on one hand, be generating undesirable inflammatory response, but, on the other hand, protect the surrounding cells from injury by suppressing inflammation via apoptosis of T-cells and exosome signaling (Blennow et al., 2012; Keyvani and Schallert, 2002; Werner and Stevens, 2015). Accumulation of amyloid precursor protein does not only result in Aβ-formation but also stabilizes $Ca^{2+}$ homeostasis, modifies synaptic plasticity, and promotes axonal regeneration (Blennow et al., 2012; Keyvani and Schallert, 2002). Traumatic axonal injury seems to initiate altered protein translation in neurons, followed with reparative changes lasting at least over one week. Furthermore, axonal deafferentation opens the possibility for axonal sprouting and formation of new synapses for restoring previous functions, more so after mild-to-moderate trauma (Buki and Povlishock, 2006).

### 2.1.3 CLASSIFICATION OF MTBI

TBI is defined as an acute alteration of brain function or other evidence of brain pathology caused by an external force (Menon et al., 2010). The external force consists of direct impact force, indirect rotational or acceleration-deceleration movement, blast or explosion, or some other form not defined. The alteration of brain function after trauma can present as a I) loss of consciousness, II) post-traumatic amnesia, III) alteration in mental status, such as disorientation, confusion or slow thinking, or IV) focal neurological sign, such as paresis, paresthesia, imbalance, problems with vision or dysphasia etc., together with, or without a demonstrable lesion in structural neuroimaging (Menon et al., 2010). The minimum criteria for mTBI is thus the appearance of at least one of those four symptoms acutely after trauma, or an imaging lesion compatible with TBI.

Different classifications of brain traumas have been in use since Hippocrates (Khsettry et al, 2007), with some variation in criteria. Table 1 summarizes the current mTBI classification criteria suggested by European Federation of Neurological Societies (EFNS), World Health Organization (WHO), American Congress on Rehabilitation Medicine (ACRM), and Finnish “Käypä Hoito” (2017). All of them use Glasgow Coma Scale (GCS), loss of consciousness (LOC) and post-traumatic amnesia (PTA) as measures of trauma severity, with varying emphasis on the structural imaging and clinical signs.

*Table 1. Mild traumatic brain injury classifications*

| | ACRM | EFNS | WHO | Finnish "KH" |
|---|---|---|---|---|
| GCS | 13-15 | 13-15 | 13-15 | 13-15 |
| PTA | ≤24h | ≤1h | ≤24h | ≤24h |
| LOC | ≤30min | ≤30min | ≤30min | ≤30min |
| Confusion | yes | na | yes | yes |
| Neurol. deficit | transient/permanent | no | transient | yes/no |
| CT/MRI lesion | yes/no | no | yes/no | minor*/no |
| Neurosurgery | no | no | no | no |

*etc. minor subdural hematoma, small amount of blood in subarachnoid space
GCS=Clasgow Coma Scale, PTA= post-traumatic amnesia, LOC=loss of consciousness, CT=computer tomography, MRI=magnetic resonance imaging, ACRM=American Congress on Rehabilitation Medicine, EFNS=European Federation of Neurological Societies, WHO=World Health Organization Task Force on mild traumatic brain injuries, KH=Käypä Hoito, na=not assessed

#### *2.1.3.1 Glasgow coma scale (GCS) and loss of consciousness (LOC)*

GCS is a widely used behavioral scale in TBI assessment. It comprises evaluation of eye opening (1-4 points), verbal response (1-5 points), and the best movement response (1-6 points), resulting in scores between 3-15. Scores 13-15 denote mild, 9-12 moderate, and ≤8 severe TBI, when measured 30 minutes after trauma or later (Teasdale and Jennett, 1974). GCS seems to correlate with the mortality and outcome at six months after TBI (Teasdale et al., 2014). In the case of mTBI (GCS 13-15), however, the association is between GCS and outcome not that clear (Carroll et al., 2014).

LOC, defined as GCS score of eight or less, denotes the time of unresponsiveness immediately after trauma and is a widely accepted sign of mTBI (Teasdale and Jennett, 1974). In mTBI its duration is defined as ≤30 min, while it seldom exceeds a few minutes (Carroll et al., 2004). The etiology of LOC in mTBI is supposedly related to changes in the function of the reticular formation in brainstem, either by trauma-induced impairment of ionic homeostasis, neurotransmitter release causing increased cholinergic activation, or axonal dysfunction due to shearing forces (Blyth and Bazarian, 2010). In a mTBI animal model, rotational acceleration force in axial plane elicited LOC, whereas after similar force in coronal plane LOC was not witnessed (Browne et al., 2011; Ohhashi et al., 2002). Signs of traumatic axonal injury (TAI, see Pathophysiology 1.3) were evident in neuropathological assessment at seven days after trauma in both cases, but with more pronounced changes, especially in brainstem, after trauma in axial plane (Browne et al., 2011). In mTBI patients assessed with diffusion tensor imaging (DTI), diffusional changes in uncinate fasciculus and inferior frontal occipital fasciculus were detected in patients with LOC when measured at 24h after injury, but not at 3 months (Wilde et al., 2016).

#### *2.1.3.2 Post-traumatic amnesia (PTA)*

PTA refers to loss of episodic memory of successive events immediately prior and/or after trauma, but also encompasses other symptoms, such as confusion, impaired comprehension and verbal fluency, delayed reaction time and agitation or quiet behavior (Friedland and Swash, 2016; B. A. Wilson et al., 1992). The pathophysiology of PTA remains poorly understood, but it has been associated with altered hippocampal or medial temporal lobe functioning after trauma (Ahmed et al., 2000), reduced perfusion in frontal gray matter and nucleus caudatus (Metting et al., 2010), and with abnormal functional connectivity between parahippocampal gyrus and posterior cingulate cortex (De Simoni et al., 2016).

In mTBI, the duration of PTA is restricted to be ≤ 24 h (Carroll et al., 2004), and it is best established prospectively or soon after trauma using standardized evaluation methods (King et al., 1997; Friedland and Swash, 2016). Several questionnaires have been developed for assessing PTA, but their implementation is complicated, since many of the patients may be intoxicated or in need of analgesics after the trauma, hampering the reliability of prompt clinical assessment (Marshman et al., 2013). Retrograde amnesia seems less affected by opioid analgesics (McLellan et al., 2017; Marshman et al., 2018), but firm association of retrograde amnesia with the outcome of mTBI is lacking (Luoto et al., 2015). Late after trauma the evaluation of PTA by both healthcare professionals and patients is inaccurate (King et al., 1997; Sherer et al., 2015).

#### *2.1.3.3 Alteration of mental status and focal clinical signs*

In ACRM criteria (ACRM 1993), alteration of mental status has been described as being “dazed, disoriented or confused” directly after trauma, whereas WHO criteria excludes dazedness (Carroll et al., 2004). This somewhat overlaps with the previous wider definition of PTA (Friedland and Swash, 2016; Wilson et al., 1992). Critically, one needs to assess whether the confusion or even amnesia of the patient was elicited by the biomechanical forces during head injury or associated with mental stress after psychologically traumatic event (Ruff et al., 2009).

Focal clinical signs after trauma that “may or may not be transient” (ACRM 1993) are also criteria for TBI. Most common focal signs after TBI include diplopia, hyposmia, or other cranial nerve deficits, problems with balance or gait, seizures, aphasia, and intracranial lesions in structural imaging, but in mTBI those are not always present (Ruff et al., 2009).

### 2.1.4 CLINICAL DIAGNOSIS OF MTBI

The diagnosis of mild TBI is challenging, especially in case the acute evaluation has been suboptimal due to e.g. need for analgesics and sedatives to treat concomitant injuries, or patient failed to contact the healthcare at the acute phase (Menon et al., 2010). Additionally, sub-optimal composition of

patient records during acute evaluation sometimes complicate the later assessment of TBI. The most common acute symptoms of mTBI include headache, nausea, balance problems, problems with vision, sensitivity to light and noise, confusion, slow reactions, problems concentrating, forgetfulness of recent events, irritability, sleep disturbances etc. (Management of Concussion/mTBI Working Group, 2009). Post-concussion symptoms are not specific to TBI etiology, and a physical trauma is often associated with traumatizing event that can cause pain or psychological distress, or be acquired while intoxicated by alcohol or drugs (Menon et al., 2010; Ruff et al., 2009). Assessment of the elements needed to classify TBI, *i.e.* GCS, LOC and PTA, is still the core component of the evaluation, with help of neuroimaging, and at later stage neuropsychological evaluations, when needed.

#### *2.1.4.1 Clinical evaluation*

Clinical assessment of mTBI patients relies on a detailed interview of the patient, as well as witnesses of the trauma, if possible. Information about LOC is virtually impossible to obtain solely by interviewing the patient alone, who is likely to experience a memory gap as LOC. In addition, the possibility of other factors than trauma causing LOC, such as syncope or seizure, must be evaluated (Ruff et al., 2009). With specific questions of memories before and after accident it is possible to assess if PTA existed, keeping in mind, that the patient might tell what they have heard, or deduced about the accident (Ruff et al., 2009). Neurological status is typically within normal ranges, with possible problems in balance, olfactory function and vision. Clear focal signs in mTBI patients are rare even in the ER settings (Ruff et al., 2009).

#### *2.1.4.2 Neuroimaging*

Neuroimaging (CT and MRI) are often used to exclude brain hemorrhage or contusion in patients with more severe symptoms. In mild symptoms, however, imaging is not always performed at early stages. Conventional clinical imaging methods such as CT and MRI readily detect hemorrhage, skull fractures and severe edema, whereas microscopic multifocal DAI-lesions often resulting from mTBI remain largely unnoticed.

When structural pathology in brain tissue is detected, the most common lesion types include fronto-basal contusions, intraparenchymal contusions resulting from rupture of microvasculature within brain parenchyma, and traumatic axonal injury. The axonal injury may visualize as petechial hemorrhage and edema, is caused by the tensile stretch to axons, and it is most often found in cortical gray-white-matter junction, corpus callosum and dorsolateral midbrain, followed by fornices of capsula interna and externa, periventricular white matter, and superior cerebellar peduncles (Gean and Fischbein, 2010).

**Computed tomography** (CT) is still the most frequently used imaging method for acute clinical neuroimaging of mTBI patients, due to its' good availability and good sensitivity for traumatic changes requiring acute interventions (Yuh et al., 2014). Many guidelines assess the need for acute CT after mTBI, most of them suggesting acute imaging in case of LOC for over 30 seconds to 1 minute, retro- or anterograde memory deficits, severe headache or vomiting, focal neurologic deficit or seizure, worsening symptoms, or age over 65 years (Morton and Korley, 2012; Unden et al., 2013; Yuh et al., 2014).

An acute CT scan presents trauma-related findings in 5-30% of mTBI patients (Borg et al., 2004; Unden et al., 2015; Yuh et al., 2013; Yuh et al., 2014), 5% in mTBI with GCS of 15 and 30% with GCS 13 (Borg et al., 2004). mTBI is sometimes classified as "complicated" when trauma-related CT abnormalities exist and "uncomplicated" when CT is normal (Yuh et al., 2014). Possible CT findings in mTBI include skull fracture, subarachnoid or intraventricular hemorrhage, subdural or epidural hematoma, intraparenchymal contusion or petechial hemorrhage as a sign of traumatic axonal injury (< three foci) or diffuse axonal injury (≥4 foci), and edema (Bigler and Maxwell, 2011; Yuh et al., 2014).

Positive CT after mTBI seems to predict outcome in the subacute phase up to at least two weeks to three months after injury (Carroll et al., 2014; Yuh et al., 2013), but not at one year after injury (McMahon et al., 2014a).

**Magnetic Resonance Imaging** (MRI) offers more sensitive detection of trauma-related parenchymal changes, such as hemorrhagic axonal injury, small contusions, and small extra-axial fluid collections in mTBI patients (Yuh et al., 2014; Bigler, 2015). It is, however, not usually accessible acutely, and is often obtained sub-acutely or even at a chronic state in case of persistent symptoms (Yuh et al., 2014). The most sensitive sequences for hemorrhage include T2* and susceptibility weighted imaging (SWI), which probably is superior to T2* in detecting mTBI abnormalities (Yuh et al., 2014; Liu et al., 2015). Higher magnetic fields are more sensitive to hemorrhagic changes due to bigger signal loss by blood breakdown products (Niogi and Mukherjee, 2010). Scheid and colleagues (2007) examined 14 TBI patients at median 61 months after injury and noticed a twofold amount of traumatic microbleeds in 3T compared with 1.5T MRI. At 7T field strength additional 40% of microbleeds were visualized, when imaging was acquired at one week after injury (Moenninghoff et al., 2015). The trauma-related lesions in MRI are most readily detected in the acute stage (Brandstack et al., 2006), and even 1.5T MRI presents trauma-related findings in approximately 30% of patients without lesions in CT (Yuh et al., 2013; Mittl et al., 1994).

The relationship of trauma-related MRI findings and clinical outcome has been under debate, as many studies have failed finding clear correlations with positive MRI and mTBI prognosis (Iverson et al., 2012; Jacobs et al., 2010; Lee et al., 2008; Carroll et al., 2014). A lesion in subacute MRI at approximately two weeks after injury, however, seems to correlate with the outcome measured with Glasgow Outcome Scale Extended at three months after injury (Yuh et al., 2013). In the future, special MRI techniques may enhance the value of MRI in evaluating mTBI prognosis.

#### *2.1.4.3 Changes in neuropsychological assessment*

At acute stage up to one week after injury mTBI patients have performed worse in information processing speed, reaction time, delayed recall and fluency (McMillan and Glucksman, 1987; Gronwall and Wrightson, 1974; Ponsford et al., 2000; McCauley et al., 2014; MacFlynn et al., 1984).

Ponsford et al. (Ponsford et al., 2000) assessed 84 mTBI patients at one week and three months after injury, finding that the symptoms at one week, e.g. headaches, dizziness, fatigue, visual disturbance, and memory difficulties, had mainly resolved by three months, with residual headaches and problems with concentration. In neuropsychological testing at one week, the patients exhibited slowing of information processing which had resolved by three months. However, at three months, 24% of patients continuously suffered from many symptoms and exhibited more psychopathology. In a questionnaire assessment, more than 50% of those with continuous symptoms reached the cutoff-value indicating psychopathology post-injury, even if their pre-injury scores estimated at 1-week post-injury, or performance in neuropsychological testing at three months did not significantly differ from those with good outcomes. Factors associated with residual symptoms included previous head injury, neurological or psychiatric problems, female gender, and motor vehicle accident as the trauma mechanism.

In longitudinal studies assessing neuropsychological sequelae, while the majority suggests the symptom severity to decline towards controls within three months (Ponsford et al., 2000; MacFlynn et al., 1984; Levin et al., 1987), the symptoms may continue to resolve even longer (Gronwall and Wrightson, 1974; Hugenholtz et al., 1988; Dikmen et al., 2017).

### 2.1.5 PROLONGED SYMPTOMS AFTER MTBI

#### *2.1.5.1 Prognosis of mTBI*

Of mTBI patients presenting in emergency room settings, 1.5-4% experience deterioration of symptoms, majority of those due to progressive intracranial hemorrhage. The risk of deterioration after the first 24 h is reported to be 0.8% (Choudhry et al., 2013; Borg et al., 2004), and only 1% of mTBI patients need neurosurgical intervention (Borg et al., 2004). Increased mortality after mTBI has not been reported with confidence, and when reported, it has remained under 0.9% (Cassidy et al., 2004; Carroll et al., 2014; Borg et al., 2004; Choudhry et al., 2013).

In general, prognosis after a mTBI is favorable: up to 96% of all mTBI patients have returned to work at one year after injury (Losoi et al., 2016). Trauma-derived changes in computed tomography (CT) and the length of LOC are probably related to early cognitive deficits, but the evidence is limited (Carroll et al., 2014). Subacute MRI lesions seem associated with symptoms at three months after injury, but even prospective studies are contradictory (Lee et al., 2008; Yuh et al., 2013). Cnossen and co-workers recently

developed a model for predicting persistent post-concussive symptoms (Cnossen et al., 2018). According to the study, female sex, neck pain at acute stage, two-week post-concussion symptoms and two-week post-traumatic symptoms were significant predictors of symptoms at six months. Motor vehicle accident (MVA) as a trauma-mechanism is associated with higher risk for persistent post-concussion symptoms compared with sports (Ponsford et al., 2000).

*Table 2. Factors affecting the outcome after mTBI*

| personality traits | injury characteristics | biological factors | psychosocial factors |
|---|---|---|---|
| perfectionism | severe symptoms in ER | age | education level |
| grandiosity | severe symptoms at 1 m | female gender | marital status |
| anxiety | mTBI severity | prior mTBI | substance abuse |
| borderline traits | extra-cranial injuries | poor health | chronic life stress |
| maladaptive coping | MVA > sports | genetics | occupational skills |
| low resilience | | mental health | involvement in litigation |

Ref: Prince et al., 2017, Van der Naalt et al., 2017, Ponsford et al., 2000, Iverson et al., 2012, Wäljas et al., 2014, Losoi et al., 2016

Despite good prognosis, some patients continue to have cognitive problems six months or even one year after trauma (Carroll et al., 2014; Dikmen et al., 2017; Wäljas et al., 2015). There is an abundance of possible confounding factors affecting the outcome after mTBI, also related with prior health and psychosocial situation of the patients, some of which are presented in Table 2 (van der Naalt et al., 2017).

#### *2.1.5.2 Post-concussion syndrome (PCS)*

According to the 2010 diagnostic criteria of ICD-10, post-concussional syndrome (F07.2) is defined as “A syndrome that occurs following head trauma (usually sufficiently severe to result in loss of consciousness) and includes a number of disparate symptoms such as headache, dizziness, fatigue, irritability, difficulty in concentration and performing mental tasks, impairment of memory, insomnia, and reduced tolerance to stress, emotional excitement, or alcohol.” The diagnosis requires that the symptoms are not due to acute brain injury.

The variety of possible symptoms is extensive (Table 2) and none of the symptoms are specific to mTBI. The incidence of PCS after mTBI, or prolonged symptoms lasting over three months, varies between 5-20% (Iverson et al., 2012; Losoi et al., 2016), some authors presenting figures as high as 77% (McMahon et al., 2014). Wäljas et al. compared the long- term symptoms of mTBI patients and orthopedic trauma patients without mTBI, and noticed that while 38% of mTBI patients were symptomatic at one year, even 31% of orthopedic controls exhibited post-concussion symptoms such as

headache, irritability, frustration and sleep disturbances at one-year follow-up, illustrating the unspecific nature and high frequency of mild symptoms in overall population (Wäljas et al., 2015).

*Table 3. Common post-concussion symptoms*

| somatic | cognitive | affective |
|---|---|---|
| headache | attention | irritability |
| dizziness | memory | emotional labillity |
| sleep problems | slow processing speed | anxiety |
| nausea | difficulties multitasking | depression |
| visual problems | increased distractibility | |
| photophobia | losing train of thought | |
| phonophobia | feeling foggy | |

Ref: Prince et al., 2017, Van der Naalt et al., 2017, Ponsford et al., 2000, Iverson et al., 2012

### 2.1.6 POTENTIAL EVALUATION METHODS FOR MTBI PATIENTS IN THE FUTURE

#### *2.1.6.1 Neuroimaging*

Potential future evaluation methods for mTBI patients are under research, or currently in use at few sites with special knowledge and/or instrumentation available. One such technique is *Diffusion Tensor Imaging* (DTI); a special entity of MRI, assessing the degree and direction of diffusion of water molecules within a tissue (Pierpaoli et al., 1996; Niogi and Mukherjee, 2010). In brain, where white matter tracts restrict the diffusion, the degree of constrained diffusion can be measured and given a value of fractional anisotropy (FA) between 0 and 1, 0 meaning unlimited diffusion and 1 meaning strictly directional diffusion. With DTI it is possible to compare FA maps between patients and controls, and estimate pathways of white matter tracts by tractography (Bigler, 2015; Yuh et al., 2014; Panenka et al., 2015; Aoki et al., 2012).

DTI is a promising method for assessing white matter integrity in brain. DTI has demonstrated time-dependent changes after a mTBI, most of the studies reporting an increase in FA at acute stage, probably due to axonal swelling, and reduction in FA in chronic patients due to axonal degeneration (Niogi and Mukherjee, 2010; Shenton et al., 2012). Chronic reductions in FA have also correlated with neuropsychological deficits (Niogi et al., 2008; Eierud et al., 2013), whereas in a prospective study of 126 mTBI patients DTI lesions did not correlate with clinical outcome (Wäljas et al., 2015). DTI method is not specific to TBI, and, e.g. in patients with depression reductions in FA are common in the same areas than after mTBI, such as corpus callosum,

uncinate fasciculus and superior longitudinal fasciculus (Tae et al., 2018). Furthermore, patients with fibromyalgia and even pre-diabetes have presented changes in DTI compared with healthy controls (Lutz et al., 2008; Liang et al., 2018). Even if DTI analysis can at group level present changes in mTBI patients, a generally accepted approach for assessing single patients in clinical settings is not yet available (Yuh et al., 2014).

*Single Positron Emission CT* (SPECT) is another promising neuroimaging method for assessing mTBI patients. It measures, three-dimensionally with rotating gamma-cameras, gamma radiation emitted from an isotope, such as $^{99m}$Tc-hexamethylpropylene amine oxime, that has been injected into circulation (Yuh et al., 2014; Shin et al., 2017).

mTBI patients usually exhibit reduction in cerebral blood flow in frontotemporal and parietal areas, and the reduction has been associated with post-concussive symptoms at one year after injury, also without concomitant structural abnormality (Jacobs et al., 1996; Shin et al., 2017; Yuh et al., 2014). Normal SPECT within one month after mild- to moderate TBI was associated with full recovery at three months in 97% of the patients, whereas 59% with abnormal SPECT at one month had post-concussive complaints at three months (Jacobs et al., 1996). SPECT thus seems a good candidate for imaging of mTBI patients, even if it is not specific to TBI.

Many other imaging methods, such as positron emission tomography (PET), magnetic resonance spectroscopy and functional MRI (fMRI) can present changes in intracerebral metabolism and connectivity after mTBI (Koerte et al., 2016; Yuh et al., 2014; Shin et al., 2017). The results are interesting, but the methods are not specific to TBI, and not yet valid for clinical use in assessing single patients.

In the case of mTBI, with acknowledged problems in visualizing the trauma, it is probable that the best sensitivity would be obtained by combining the most suitable imaging methods depending on the patient characteristics and the diagnostic problem addressed. SPECT and PET are promising, but invasive methods with limited availability and thus not well suitable for screening large patient populations. Therefore, non-invasive, easily accessible neuroimaging methods for assessing mTBI patients in subacute stage are needed.

#### *2.1.6.2 Serum biomarkers*

Finding a sensitive and specific serum biomarker for the diagnosis and prognosis of mTBI would be of great benefit for the patient care. It would enable selecting mTBI patients for further diagnostic testing and follow-up, as well as diminish unnecessary predisposition for radiation, when not necessary. It would also help in differential diagnostics of acute cognitive impairment after trauma, especially in intoxicated, elderly and traumatized persons, who might have similar symptoms as TBI patients but for different reasons.

Serum biomarkers can be divided to astrocyte biomarkers (*e.g.* S-100β, glial fibrillary acidic protein (GFAP)), neuronal biomarkers (*e.g.* neuron specific enolase (NSE), ubiquitin C-terminal hydrolase isoenzyme L1 *(UCH-L1))* and

axonal biomarkers (*e.g.* Alpha-II spectrin, tau-proteins and neuronal filaments) (Papa et al., 2015).

Of these biomarkers, S100β is in clinical use in some Nordic countries for assessing the need for CT scan in mTBI patients within six hours after injury (Undén et al., 2015). Its' low specificity to brain trauma hampers its' diagnostic use, however. A combination of GFAP and UCH-L1 has 97% specificity and 99% negative predictive value in detecting patients with trauma-related CT abnormalities (Bazarian et al., 2018). These biomarkers are not specific in differentiating mTBI patients with GCS 14-15 from orthopedic controls, and their value in mTBI diagnostics is therefore questionable (Posti et al., 2017).

Finding a molecule, with high sensitivity and specificity to TBI and stable kinetics enabling formation of clear cut-off values, would greatly improve the diagnosis and follow-up of mTBI patients, as well as guide the development of medication and other therapy methods for their rehabilitation.

### 2.1.7 EEG IN TBI

German neurologist Hans Berger was the first to publish measurements of occipital alpha-rhythm with EEG in 1929 and started using the new tool in evaluating clinical patients (Stone and Hughes, 2013). EEG directly measures the electrical activity arising from synchronous activity of pyramidal neurons. It is most sensitive to perpendicular neuronal sources located on top of the gyri but detects also tangential and deeper sources. EEG is a frequently used non-invasive method for assessing derangements in brain electrical activity such as epilepsy, as well as studying the brain function of healthy subjects. Besides spontaneous rhythmic brain activity, EEG can be used to assess evoked potentials that are time-locked to external stimuli. Additional advantages of EEG are its wide availability and affordability. It has been studied for use in the assessment of mTBI, but its' diagnostic value is currently ambiguous and further studies are needed (Haneef et al., 2013).

Most animal studies assessing EEG during TBI suggest an initial rapid attenuation of EEG amplitude, followed with irregular high-amplitude low-frequency oscillations, which gradually diminish as consciousness is regained (Williams and Denny-Brown, 1941; Dow et al., 1944; Ommaya et al., 1964). In humans, case reports (Moeller et al., 2011) have suggested qualitatively similar transient findings. Also epileptic discharges at the very first stage have been described, although such findings have later been considered as motion artifacts (Dow et al., 1945; Schmitt and Dichter, 2015).

It seems that mTBI patients may exhibit low-frequency activity (LFA) at 0.5 – 7 Hz and slowing of posterior 10-Hz activity during the first hours and days after the trauma (Koufen and Dichgans, 1978; Geets and Louette, 1985; Tebano et al., 1988; Bierbrauer et al., 1992). The prevalence of LFA varies between studies; while Geets et al. (1985) demonstrated increased LFA in only 2-17% of young adult mTBI patients within 48h after trauma, noticed Bierbrauer et al. (1992) slowing in 82% of acute predominantly mTBI patients in the acute phase. In follow-up measurements, in 50% of the patients the

oscillatory activity had normalized within 8 weeks. Generally, in many studies the slowing has been subtle and only detectable when compared with patient's own measurement after some recuperation period (Koufen and Dichgans, 1978; Geets and Louette, 1985). Slowing of 10-Hz rhythm occurred in 43% of patients when measured within 3 days after trauma, but in only 4% measured at 6 months after injury. Focal aberrant LFA was present in 32% within 3 days and in 13% at 6 months (Koufen and Dichgans, 1978). While epileptiform changes might be present in mTBI patients, the risk for post-traumatic epilepsy is only 1.5-fold compared with healthy subjects (Lewine et al., 2007a; Schmitt and Dichter, 2015).

In chronic phase, several months after injury, LFA has been shown to persist in up to 20% of mTBI patients (Lewine et al., 1999b). At group level an increase in < 4 Hz and decrease in ~10 Hz power has been discovered in post-concussion syndrome (PCS) –patients measured with EEG two weeks to 7 years after the trauma, compared with healthy controls (Korn et al., 2005). Thatcher and colleagues attempted to establish discriminant criteria for mTBI based on quantitative EEG (qEEG), but despite the good sensitivity for mTBI the specificity of the measurements has been low, with even up to 52% of false positives (Thatcher et al., 1989; Thatcher et al., 2001; Schmitt and Dichter, 2015).

In summary, changes in EEG after mTBI include presence of mixed-frequency LFA, and attenuation of posterior ~10-Hz frequency and power. The changes are usually transient and may disappear even in minutes after trauma. In up to 20% of patients with continuous symptoms the slowing may persist, whereas slowing may also be present in healthy subjects without TBI background, or any disease affecting the central nervous system.

As already mentioned, EEG directly measures the electrical activity of pyramidal neurons and is most sensitive to perpendicular sources located on top of the gyri. A closely related technique, magnetoencephalography (MEG), invented in late 1960s (Cohen, 1968), measures the minute magnetic fields that the synchronous activity of the same pyramidal neurons creates. It is most sensitive to superficial tangential sources in the walls of the sulci, not detecting the purely perpendicular currents in the top of the gyri: however, only very thin strips of gyri are such (Hillebrand and Barnes 2002). In mTBI, the axonal injury often affects the interface of grey and white matter in the bottom of the cortical sulci (see section 1.2). Thus, MEG might offer increased sensitivity to detect the changes compared with EEG, which is why we decided to use it in our study. EEG is easily carried out in clinical practice, whereas MEG, due to heavy instrumentation, is rarely available, and therefore mainly used in research purposes. MEG, however, offers capability for more precise source localization and recognition of phenomena that can easily be transferred to clinical use with EEG. In the following section I will briefly present the essential principles of MEG and its' current applications to mTBI research.

## 2.2 MAGNETOENCEPHALOGRAPHY

The following introduction to MEG is based on review article Magnetoencephalography – theory, instrumentation, and applications to

noninvasive studies of the working human brain (1993) by Hämäläinen M et al., and textbooks MEG - an introduction to methods (2010) by Hansen PC et al., and MEG – EEG primer by Hari and Puce (2017).

### 2.2.1 MEG PRINCIPLES

Cohen conducted the first MEG measurements in 1968, reporting magnetic fields derived from ~10-Hz oscillatory brain activity. The magnetic fields measurable extracranially are generated by synchronous electrical activity of tens of thousands of neurons. The post-synaptic currents in the long, aligned apical dendrites of the pyramidal cells give rise to the magnetic fields detected. As already mentioned, MEG detects readily those currents that originate in the sulci of the folded brain but may leave perpendicular currents in the cortical gyri almost undetected. In majority of the cortical mantle the net current is not strictly radial, and for MEG-recordings the depth of the source is often the most important restriction (Hillebrand and Barnes, 2002). The magnetic field – unlike EEG – is not affected by different conduction capacities of layers between skull and scalp, enabling collection of the signal with minimal distortion, and better spatial (within 3-5 mm) resolution than EEG. The temporal resolution of both EEG and MEG is high, within milliseconds, enabling reliable analysis of evolution of neuronal activity in time.

### 2.2.2 ELECTRIC SIGNALLING IN NEURONS

Neurons have a stable membrane potential, with about 60mV negative intracellular, compared with extracellular space. Action potentials (AP), that convey the signal to next neurons are distortions in this stable resting potential and elicited by synaptic activation. Synaptic neurotransmitters that evoke the postsynaptic potentials (PSP) may be either excitatory (e.g. glutamate) or inhibitory (e.g. gamma-amino butyric acid GABA). They bind to post-synaptic receptors and cause a change in membrane permeability and flux of ions through the membrane. This ion flux can cause either depolarization (and excitatory PSP) or hyperpolarization (and inhibitory PSP), which will spread passively towards soma, and the net-effect of total excitation decides whether new AP is elicited. Excitatory synapses are mainly located in the apical dendrites of the neurons, whereas inhibitory synapses exist near soma or basal dendrites. When the excitation in the axon hillock exceeds a certain threshold (between -55 and -40 mV), an AP starts propagating along the axon to the synaptic clefts. Pyramidal cells and their apical dendrites are arranged parallel to each other in the cerebral cortex, and therefore the net current of PSPs is strong enough to be measured outside the skull giving rise to MEG signal (Hari and Puce, 2017).

### 2.2.3 SPONTANEOUS OSCILLATORY BRAIN ACTIVITY

Since Hans Berger's EEG measurements in 1920's, brain oscillatory activity has been studied in both clinical and research purposes. Brain oscillations are typically divided to different frequency bands, with some difference in their division and nomenclature, depending on the brain area and functional system studied. Fig. 1 depicts a typical occipital amplitude spectrum of a healthy subject. Delta-activity refers to frequencies below 4 Hz, theta to 4–8 Hz activity, alpha to 8–14 Hz, beta to 14–30 Hz, and gamma those above 30 Hz (Schmitt and Dichter, 2015; Hari and Puce, 2017). In a healthy adult awake EEG alpha- and beta-activities typically dominate the recordings (Gomez et al., 2013; Hari and Puce, 2017).

*Posterior alpha activity* is the most prominent of brain oscillations. It originates in the parieto-occipital and calcarine sulci, and is modulated by, *e.g.* eye-closure, pain, drowsiness, and attention-demanding tasks (Hari and Puce, 2017). The dominating posterior rhythm changes across the lifespan, with slow oscillatory activity at around 4 Hz dominating in 3-4 months-old babies, 6 Hz at one year and 8 Hz at three years, reaching 10 Hz at around 12 years, with a large individual variation. In the elderly healthy people, the peak frequency of occipital alpha activity tends to slightly decrease (Hari and Puce, 2017).

Other prominent rhythms around the same frequency range include *tau -rhythm*, which arises from the supratemporal auditory cortices and typically varies between 8-10 Hz, and *mu -rhythm*, which arises from the sensorimotor cortex. Mu -rhythm has two frequency components, the 10 Hz component arising lateral and posterior to, and 20 Hz component arising more anterior to central sulcus, and thus being more associated with sensory-, and motor functions, respectively.

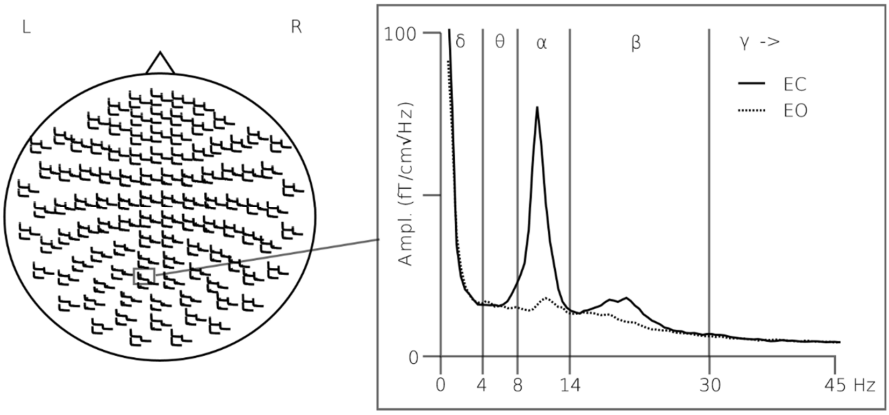



Figure 1. An example of MEG whole-head spectra (left), nose up, right on right, and an occipital channel (2043; right), demonstrating the effect of eyes-open (EO) and eyes-closed (EC) conditions on occipital alpha oscillatory activity, and different frequency bands; delta (0-4 Hz), theta (4-8 Hz), alpha (8-14 Hz), beta (14-30 Hz) and gamma (over 30 Hz). L=left, R=right

*Alpha peak frequency* (APF) is considered a stable and heritable marker within individuals (Mierau et al., 2017). High APF seems associated with increased resting-state brain metabolism in healthy individuals (Alper et al., 2006; Jann et al., 2010), and low APF with decreased cerebral blood flow in patients with e.g. carotid artery occlusion and healthy subjects during hypoxia (Mosmans et al., 1983; Van et al., 1991). Higher APF has also been associated in healthy subjects to higher FA values measured with DTI within fascicles that mediate long-distance connections between different brain regions (Valdés-Hernández et al., 2010; Jann et al., 2012). APF seems affected by different brain states, e.g. acute pain and cognitive work load increase APF (Nir et al., 2010; Haegens et al., 2014), and meditation decrease it (Saggar et al., 2012).

*Beta rhythm* often peaks around 20 Hz but has a wider frequency range of 14 Hz – 30 Hz. It arises predominantly within sensorimotor system, e.g. primary sensorimotor cortex, supplementary motor area, basal ganglia, and cerebellum. It is associated with wakeful and attentive behavior, and control of voluntary movements.

*Gamma rhythm* can be divided to low-gamma, usually at 30 – 60 Hz, high-gamma at 60 – 200 Hz, and ultra-fast gamma at 200 – 600 Hz. Gamma -activity has been associated with attention-demanding tasks, memory functions and coordinating behavioral activities.

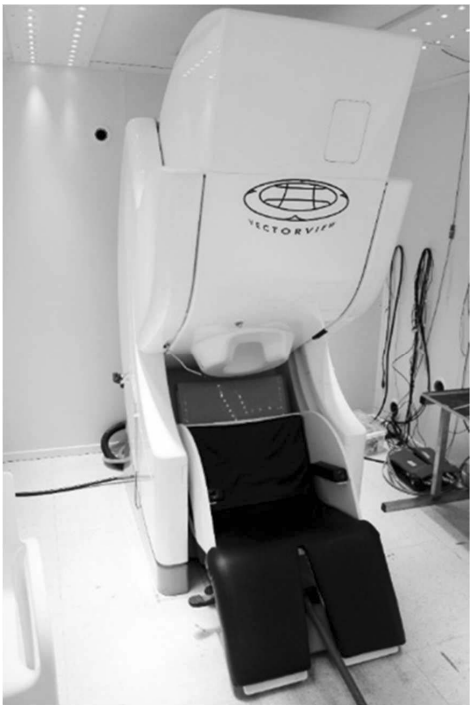
*Theta rhythm* at 4 – 7 Hz has been related to drowsiness or different brain pathologies, but it also appears to play a role in cognitive functions, such as episodic, and working memory, and communicating between distant cortical areas.

Slow brain rhythms at *delta-band* e.g. below 4 Hz, are present in healthy adults only during sleep. In awake adults, delta-activity is associated with brain pathologies. Ultra-slow fluctuations below 1 Hz are associated with sleep, but also present during somatosensory detection tasks, require special recording technologies and are easily prone to artifacts.

In the first two studies of this thesis, we concentrate on low-frequency activity (LFA), at 0.5 – 7 Hz. LFA is encountered in many pathological stages including brain tumors, stroke and epilepsy (Bosma et al., 2008; Ishibashi et al., 2002; Vieth, 1990a). The origins of delta-activity (<4 Hz) are suspected to be related to cortical layer V pyramidal neurons depleted with cholinergic stimulation due to underlying axonal injury (Gloor et al., 1977; Ball et al., 1977; Buzsaki et al., 1988; Steriade et al., 1990; Huang et al., 2009). Axonal injury may be structural, but in mild cases also functional derangement may occur due to compromised cellular metabolism after trauma (Oppenheimer, 1968; Gloor et al., 1977; Povlishock and Christman, 1995). The presence of LFA in pathological states seems thus associated with compromised blood-flow, metabolism, or derangement of the cytoarchitecture within the tissue (Kamada et al., 1997; Kamada et al., 2001; Ishibashi et al., 2002). If the axonal damage is situated in the vicinity of soma, it can induce changes in protein translation and compromised neuronal function, which might not necessarily lead to necrosis, but neuron regeneration over time (Buki and Povlishock, 2006).

### 2.2.4 MEG INSTRUMENTATION

The MEG instrumentation has evolved from single-channel instruments to whole-head systems first introduced in Finland in 1993 (Knuutila et al., 1993), and nowadays with up to 306 sensors arranged in a helmet-shaped sensor array. The MEG-system at Aalto University that served to conduct the measurements in this thesis is Elekta Neuromag® system (Elekta Oy, Helsinki; Finland), which comprises 306 channels arranged into 102 sensor elements. Each sensor consists of a triplet of two orthogonal planar gradiometer and a magnetometer pick-up coils, coupled with an input coil that is attached to Superconducting Quantum Interference Device (SQUID), sensitive enough to collect the signal when cooled down to -269°C with liquid. Planar gradiometers are most sensitive to sources right beneath them, whereas magnetometers detect the maximum signal next to the source.



The magnetic fields created by brain are tiny, typically of 100-500 fT/cm magnitude when collected outside the skull. Therefore, shielding to exclude external magnetic fields in the environment, such as Earths' magnetic field, power-lines, electrical devices and traffic, is of great importance. MEG measurements take place in a magnetically shielded room with typically two to three layers of mu-metal and which often lies on its own foundations to eliminate mechanical vibrations of the environment.

Figure 2 MEG-device at Aalto-University, Espoo

### 2.2.5 MEG ARTIFACT-REMOVAL

During the measurement, the signal quality should be carefully monitored for artifacts that can arise from outside the measurement room, within the measurement room (*e.g.* the stimulation and recording equipment), and from the subjects themselves (*e.g.* eye movements, heartbeat, muscle activity, respiration, or the subject's clothing). Many artifacts can be diminished by giving good instructions to the subject who is being measured, and by monitoring the physiological signals by electro-oculograms (EOG), electro-

cardiograms (ECG) or electromyograms (EMG) in order to identify and extract the possible artifacts from the data.

After the measurement, MEG signal can be further processed to improve signal-to-noise ratio, e.g. by filtering the signal to a frequency-band of interest and/or by rejecting data segments containing artifacts. If this is not possible, artifact-removal by other methods can be attempted.

*Independent component analysis (ICA*; Hyvärinen and Oja, 2000*)* separates a mixed signal into its components, which are assumed independent from each other either in time (temporal ICA) or space (spatial ICA). The temporal version is usually applied into MEG data, preferably after rejection of epochs with large artifacts arising from for example movements of the subject (Hyvärinen and Oja, 2000; Hari and Puce, 2017).

*Signal space projection (SSP*; Uusitalo and Ilmoniemi, 1997*)* method can utilize empty-room measurement data to estimate signal vector constituting noise subspace , which can then be projected out of the data obtained during real MEG measurement session (Hari and Puce, 2017). This method may also serve for e.g. cardiac artifact rejection in individual measurements.

*Signal space separation (SSS),* based on sensor geometry and Maxwell's equations, and its' temporal extension (tSSS) operate by dividing the measured signal sources into two volumes, one inside the measurement helmet and the other outside the helmet, and reconstructing the signal based on the sources originating inside the helmet (Taulu et al., 2004). Spatial SSS can separate artifact signals approximately 0.5 m away and tSSS is efficient for nearby artifacts (Taulu and Simola, 2006). The artifacts arising within the helmet, such as scalp muscle artifacts and eye-movement artifacts may not, however, be reliably removed with tSSS (Hari and Puce, 2017).

*Eye-related artifacts* arise because the eyeball is a dipole, where anterior cornea is positively charged compared with posterior retina. During blinks and eye movements this dipole moves creating a change in the magnetic field especially within lateral frontal channels and can be mixed with low-frequency cortical activity.

*Cardiac artifacts* arise when striated muscle of the heart contracts in synchrony. In addition, cardiac rejection of blood induces ballisto-cardiogram artifacts, which peak around 200 ms after the QRS-complex in ECG. Cardiac artifacts are most prominent in the left temporal and occipital MEG channels, and due to their usual frequency of 1-2/s can be mixed with low-frequency cortical activity.

*Respiration* can also cause low-frequency artifacts, usually due to metallic material moving on body with respiratory movements. Additional direct respiratory artifacts are assumed to exist, but the mechanism is not well understood.

### 2.2.6 MEG ANALYSIS

MEG allows analysis of spontaneous oscillatory brain activity in different frequency bands, as well as the analysis of time-locked evoked responses elicited by sensory stimuli from one of the sensory systems (*e.g.,* auditory, visual, tactile) or provoked by an activation related to behavioral events *e.g.,*

uttering a word or performing a movement. These responses can give information on simultaneous and successive processing of the activation in different brain areas at millisecond time-scale. Connectivity analysis can offer additional information of the interplay of multiple cortical areas (Salmelin and Kujala, 2006).

Selection of the most appropriate analysis methods is dependent on the assumptions regarding the possible sources of brain activity and the current research question. *Sensor-level analysis* offers an overview of the data, *e.g.,* of the oscillatory activity at each frequency band, together with an opportunity to visually objectively compare different experimental conditions. Spectral estimations are typically obtained using, *e.g.,* fast Fourier transform (FFT) algorithms, where the data is divided into epochs of equal length and averaged, or wavelet spectrograms, where a set of wavelets of different frequency bands are slid over the course of measured data.

In MEG, *source space analysis* requires solving the so called "inverse problem", *i.e.*, constructing the actual source currents in brain based on the measured magnetic fields. Physiological constraints, *e.g.,* structural MRI of the subject are used to refine the analysis. The analysis method selected thus explains the data according to its' restrictions, and a priori assumptions of the sources (*e.g.* point-like or widespread) affect the selection, as well as the results. *Equivalent Current Dipole models,* based on nonlinear least-squares, estimate the sources of the measured signals as localized current dipoles. They serve best when point-like sources are assumed to create the measured brain activity. *The minimum-norm estimates (MNE)* attempt to reproduce the data by the smallest possible norm (*i.e.*, overall power), resulting in superficial, distributed current estimates. Its' spatiotemporal variations can be estimated with dynamic statistical parametric mapping (dSPM) (Dale et al., 2000). *Beamformers* construct spatial filters for scanning the source space for best available solution. These methods allow the signal to spread even in case of local sources but require few a priori assumptions of the sources – as often is the case in real life. The beamformer method used in the present study is Dynamic Imaging of Coherent Sources (DICS)(Gross et al., 2001; Liljestrom et al., 2005; Kujala et al., 2008). It is a linearly constrained minimum variance beamformer that given a Current Source Density (CSD) matrix and a forward model of the neural currents, is designed to pass the activity in specific location, while suppressing activity from other locations using a weighted sum of the sensor signals (Van Veen et al., 1997).

### 2.2.7 MEG IN TBI

#### *2.2.7.1 MEG power analysis*

Probably due to limited availability in clinical environment, earlier MEG studies of mTBI have concentrated on patients in chronic stages and, compatible with EEG, found excess low-frequency activity. Lewine and colleagues (1999) were among the first to study mTBI patients with MEG. They compared twenty

healthy controls with ten asymptomatic and twenty symptomatic mTBI patients in a multimodal study with EEG, MEG, and MRI. MRI showed trauma-related changes in 20% of patients, EEG demonstrated abnormal slowing in 20% and spectral abnormalities in 30%, while MEG detected abnormal slow-wave activity with dipole modelling in 45%, and spectral abnormalities in 65% of 20 symptomatic patients 2-38 months after initial trauma (Lewine et al., 1999).

Later, Lewine and colleagues assessed 30 mTBI patients, with PCS symptoms lasting over one year, with MEG, SPECT, and MRI (Lewine et al., 2007). Abnormal slow-wave activity was detected with MEG in 63% of patients, SPECT abnormalities is 40% of patients and structural MRI lesions in 13%. 86% of patients with cognitive complaints harbored slow-wave activity, temporal slow-waves correlated with memory problems, parietal with attention and frontal with executive problems (Lewine et al., 2007).

Huang et al (2009) observed abnormal 1-4 Hz activity in 10/10 patients, part of them military veterans, with continuous symptoms at one to 46 months after mTBI. They correlated MEG findings with white matter tract lesions in DTI and suggested that the observed pathological 1-4 Hz activity arises from cortical neurons suffering de-afferentation after trauma. MEG was more sensitive in detecting lesions compared with DTI (Huang et al., 2009). With an automated analysis-method up to 85% of 84 mTBI patients presented low-frequency activity: 83% (40/48) of non-blast, and 86% (31/36) of blast-related mTBI patients (Huang et al., 2014). Using n-back task, Huang and colleagues reported increased activity within wide frequency range in frontal pole, ventromedial prefrontal, orbitofrontal, and anterior dorsolateral prefrontal cortices, but decreased activity in anterior cingulate cortex in 25 subacute and chronic blast mTBI patients compared with active duty members without mTBI (Huang et al., 2018).

Robb Swan and colleagues measured mTBI patients with ongoing symptoms at three months post-injury and noticed that MEG slow-wave amplitudes in different cortical areas were associated with neuropsychological test results in mTBI patients at group level, including some contradictory correlations (Robb Swan et al., 2015). In their study mTBI patients performed worse than healthy controls in cognitive flexibility, inhibition, initiation, working memory and processing speed, but their performance remained within the range of normal limits (Robb Swan et al., 2015). A recent study demonstrated a significant decrease in slow-wave activity together with symptoms after transcranial electrical stimulation (tES) in six patients with persistent post-concussive symptoms (Huang et al., 2017a).

#### *2.2.7.2 MEG connectivity analysis*

Connectivity analysis in TBI patients has gained increasing interest during the last years. It is a promising future method, but nowadays the lack of validated, automatic analysis protocols hampers its' use in clinical settings, particularly as the results are thus far interpreted at group-level.

Castellanos et al. observed increased low-frequency connectivity in 14 TBI patients with severe neuropsychological symptoms compared with controls in

pre-rehabilitation phase. In the post-rehabilitation phase the low-frequency connectivity had significantly reduced, and alpha and beta connectivity increased; these changes correlated with improvement in cognitive functioning (Castellanos et al., 2010). Tarapore and colleagues detected decreased alpha-band connectivity in 21 patients at chronic stage after TBI, some of them mild; Follow-up measurements exhibited improvement of disrupted connectivity in 2/5 patients (Tarapore et al., 2013).

Connectivity analysis of acute MEG recordings in 31 mTBI patients measured within 24 h after trauma have showed decreased amount of short-distance connections and increased proportion of long-distance connections compared with healthy controls (Dimitriadis et al., 2015). Antonakakis and colleagues applied cross-frequency coupling analysis to the same data and were able to create a classifier, that at specific frequency pairs correctly recognized over 90% of 30 mTBI patients measured with MEG 24h after trauma (Antonakakis et al., 2016). They also, studying the same dataset, suggest a different functional organization of short-distance connections and fewer strong long-distance connections in mTBI patients and classify mTBI patients and controls with high accuracy (98.6%) (Antonakakis et al., 2017).

Alterations in resting-state connectivity seem associated with mTBI. Alhourani et al observed a reduction in resting-state connectivity with an emphasis on alpha and delta frequencies in a study of 9 mTBI patients 3-96 months after injury (Alhourani et al., 2016). In contrary, Dunkley with colleagues detected increases in resting-state connectivity in alpha, beta and gamma frequencies in a study of 26 patients < 3 months after injury (Dunkley et al., 2018). Blast-related mTBI patients exhibited increased global functional connectivity in delta-, theta-, beta-, and gamma-bands, as well as decreased connectivity in frontal pole area (Huang et al., 2017b).

Post-traumatic stress disorder (PTSD) is often hard to differentiate from mTBI, due to overlapping symptoms. Dunkley posits that while mTBI seems associated with increased low-frequency (<10 Hz) connectivity, PTSD patients exhibit increased high-frequency (80-150 Hz) connectivity (left hippocampus and frontal regions, and were able to correlate the results with PTSD symptoms (Dunkley et al., 2014; Dunkley, 2015). Pang et al. compared 16 mTBI patients, measured with MEG within 2 months after trauma with healthy controls during a cognitive task with two difficulty levels. They noticed that patients – in contrary to controls – were unable to boost their occipital alpha connectivity with other brain regions during the more difficult task, accompanied with poorer task performance (Pang et al., 2015).

Changes in connectivity measures are present in several neuropsychiatric states, such as PTSD, depression and schizophrenia (Alamian et al., 2017a; Alamian et al., 2017b; Dunkley et al., 2014). The studies are currently conducted with variable methodology and the correlation of changes in connectivity with clinical measures are hard to reproduce.

Overall, the literature of MEG studies on mTBI patients using variable methodology indicate that MEG often detects low-frequency activity in patients with mTBI and post concussive symptoms, and methods based on MEG connectivity in the acute state may be able to classify patients with high accuracy (Antonakakis et al., 2016). The natural development of low-frequency activity after mTBI is, however, not well established, and the

prospective value of detected low-frequency activity at acute stage not well known. Inefficiency in cognitive processing is one of the main complaints after mTBI, however, it's neuronal correlates are still ambiguous.

# 3 AIMS OF THE STUDY

The aim of this thesis was to prospectively examine the occurrence and natural evolution of low frequency activity after mild traumatic brain injury, and to assess its association with prolonged symptoms after trauma. In addition, we wanted to examine the effect of mTBI to brain oscillatory activity during cognitive processing, which is often ineffective after trauma. Specific aims of the studies were:

- to assess the prevalence of slow-wave activity in healthy subjects, and create a normal database for future use in assessing patient populations (Study I)
- to examine the occurrence and natural evolution of slow-wave activity in mTBI patients, and the possible association of slow-wave activity with subjective symptoms of the patients (Study II)
- to evaluate the modulation of brain oscillatory activity during cognitive tasks in mTBI patients, and to correlate the effects with neuropsychological test results (Study III)

# 4 MATERIALS AND METHODS

## 4.1 SUBJECTS

### 4.1.1 MTBI PATIENTS

Thirty patients with first-ever mTBI gave their informed consent to participate in this study, which was approved by Ethics Committee of the Helsinki and Uusimaa Hospital District. The patients were 20–59 years old (average ± standard error mean (SEM) 41 ± 2; females 44 ± 3, males 41 ± 3). They were recruited from Brain Injury Clinic at Helsinki University Hospital, and their demographics are collected in Table 4. During the follow-up, two patients were excluded due to metallic artifacts preventing reliable analysis, and two due to pre-morbidities revealed after primary evaluation. One patient (P7) felt the MEG -recording seating uncomfortable, refused to continue after resting-state measurements, and was included only in Study II.

Patients participating in Studies II-III fulfilled GCS and LOC criteria for mild TBI according to ACRM (ACRM 1993) and WHO (Cancelliere et al., 2012): GCS ≥13 at 30 min after trauma, or at initial evaluation in the emergency room, and LOC < 30 min. The assessment of PTA was not prospective, and its' retrospective evaluation is unreliable. Some of the patients also required sedatives and analgesics for treatment of concomitant injuries. Therefore, we cannot exclude the possibility that some patients had PTA exceeding 24 hours. Trauma-mechanisms included ten bicycle accidents, six motor-vehicle accidents, five falls, four sports related accidents (two winter-sports and two equine sports), and one hit to head (Table 4).

Exclusion criteria for both patients and healthy control subjects comprised history of neuropsychiatric or developmental disorders, current use of central nervous system -affecting medications, or substance abuse.

### 4.1.2 HEALTHY CONTROLS

For Study I, we collected data of a large pool of 156 healthy subjects (110 females, 46 males) previously recruited for another study (Renvall et al., 2012). Subjects were 18–60 (average ± SEM 31±1) years old. They also served as healthy control subjects for Study II.

For Study I, the healthy subjects, who already for the previous study had been evaluated to exclude any neuropsychiatric or developmental disorders, answered a questionnaire addressing specifically the history of TBI, and engagement in hobbies with a high risk for head traumas.

Subjects with a history of any head trauma causing loss of consciousness or memory, transient neurological deficit, or any alteration of mental state at the time of the head trauma were excluded (15 subjects). In addition, one subject had been diagnosed with pituitary macro-adenoma and was excluded.

**Table 4. Demographics of the patients: age at the time of injury, gender, GCS at 30 min after injury, LOC, timing of MEG-measurements and MRI (after injury), trauma lesions in MRI and CT, results of Rivermead Post-Concussion Symptoms Questionnaires**

| Patient | Age | Gender | type of trauma | GCS | LOC | MEG1 | MEG2 | MRI | MRI lesion | CT lesion | RMPCQ1 | RMPCQ2 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | 43 | m | bike accident | 15 | +/- | 4 mo | | 16 m | - | - | 3 | |
| 2 | 50 | m | motorvehicle accident | 15 | + | 2 mo | | 12 m | +/s | + | 3 | |
| 3 | 42 | f | sports accident | 14 | + | 5 mo | | 15 m | +/d | + | 24 | |
| 4 | 46 | f | motorvehicle accident | 14 | +/- | 4.5 mo | | 4 m | +/d | + | 29 | |
| 5 | 37 | f | bike accident | 14 | +/- | 3.5 mo | | 8 m | +/d | + | 13 | |
| 6 | 32 | m | fall | 15 | - | 4 mo | | 11 m | +/d | + | 18 | |
| 7 | 50 | m | fall | 15 | +/- | 2 mo | | 9.5 m | +/d | - | 24 | |
| 8 | 59 | f | bike accident | 15 | - | 3 w | | 2 m | +/s | - | 3 | |
| 9 | 54 | f | fall | 15 | +/- | 2 mo | | 3 m | - | - | 8 | |
| 10 | 39 | m | motorvehicle accident | 15 | +/- | 2 mo | | 2.5 m | - | - | 31 | |
| 11 | 20 | m | sports accident | 14 | + | 1 mo | | 3.5 m | +/d | - | 2 | |
| 12 | 44 | m | motorvehicle accident | 14 | - | 1.5 mo | | 3 m | +/s | + | 27 | |
| 13 | 43 | m | bike accident | 14 | - | 6 mo | | 6 m | - | - | 28 | |
| 14 | 36 | f | motorvehicle accident | 14 | + | 1.5 mo | | 3 m | +/d | - | 25 | |
| 15 | 39 | m | hit to head | 15 | - | 3 w | 7 m | 2 m | - | - | 9 | 7 |
| 16 | 29 | m | sports accident | 14 | + | 1 mo | 6 m | 1.5 m | - | - | 3 | 2 |
| 17 | 37 | m | motorvehicle accident | 14 | + | 1 mo | 6 m | 1.5 m | +/d | + | 25 | 14 |
| 18 | 50 | m | fall | 14 | +/- | 2 mo | 6 m | 2 m | +/s | + | 6 | 3 |
| 19 | 28 | f | bike accident | 15 | + | 1 w | 6 m | 3.5 w | - | - | 16 | 14 |
| 20 | 29 | f | bike accident | 14 | + | 3 w | 6 m | 1 m | +/d | + | 3 | 2 |
| 21 | 59 | m | bike accident | 14 | + | 1 w | 6 m | 1 m | +/s | - | 36 | 18 |
| 22 | 53 | f | sports accident | 14 | + | 3 w | 6.5 m | 2.5 m | +/d | - | 34 | 6 |
| 23 | 51 | m | bike accident | 15 | +/- | 1 w | 6 m | 3 w | - | - | 14 | 6 |
| 24 | 23 | m | bike accident | 15 | +/- | 1 w | 6 m | 1 m | - | - | 25 | 0 |
| 25 | 40 | f | bike accident | 14 | + | 1 mo | 7 m | 2 m | +/s | - | 14 | 3 |
| 26 | 56 | f | fall | 15 | + | 3 w | 6 m | 2 m | - | - | 32 | 16 |

GCS = Glascow Coma Scale, LOC= loss of consciousness, RMPCQ = Rivermead Post-Concussion Symptoms Questionnaire, mo = months, w = weeks, d=deep, s=superficial, m=male, f=female.

Analyses included 140 subjects (102 female and 38 male). One subject was excluded in the analysis-phase due to head position deviating > 25 mm from the average head position of all control subjects, leading to differing distribution of noise and possible inconsistencies in channel-level analysis (Medvedovsky et al., 2007). Final analysis thus included 139 healthy subjects (102 female aged 30 ± 1 and 37 male aged 32 ± 2).

For Study III we recruited 20 healthy control subjects (8 females, 12 males) aged 39 ± 2 years (females 44 ± 3, males 36 ± 3) with similar exclusion criteria as in Study I. All control subjects for Studies I-III gave their written informed consent to participate in the studies.

## 4.2 CLINICAL EVALUATION AND NEUROPSYCHOLOGICAL ASSESSMENT

All patients were symptomatic at the time of the first MEG measurement session (1 week to six months after trauma). To assess the remaining symptoms at each MEG measurement session the patients filled in the Rivermead Post-Concussion Symptom Questionnaire (RPQ) questionnaire (Eyres et al., 2005; King et al., 1995). The RPQ assesses the occurrence of 16 symptoms, that can be further divided into cognitive, emotional and somatic domains. As the symptoms are not specific to mTBI, the patients are asked to evaluate their presence within the following 24h in a five-step scale, compared with the time before the trauma. The symptoms can be further divided into cognitive, emotional and somatic domains.

The patients also underwent careful neuropsychological testing at the subacute stage, 3.2 ± 0.43 (average ± SEM) months after trauma. Neuropsychological testing was implemented by two experienced neuropsychologists; Table 5 summarizes the tests included. Conversation, reading, writing and counting skills were also evaluated. Digit span, Trail Making Test A and B, Digit Symbol and Stroop tests have earlier correlated with PASAT results in TBI patients (Sherman et al., 1997; Madigan et al., 2000), and were here evaluated for correlation with MEG data. TMA and TMB tests measure focused attention (Sherman et al., 1997; Tombaugh, 2006), and they, as well as the difference in time accomplishing those tests were compared with healthy control values.

In addition, the patients and their significant others filled in The Dysexecutive (DEX) Questionnaire (Wilson et al., 1996) to rate difficulties in every-day-life executive functioning, and the patients the Beck Depression Scale (BDI, (Beck et al., 1974) to evaluate concomitant mood changes.

Of the 12 patients with repeated MEG recordings, 9 participated in a follow-up neuropsychological examination at 12.6 ± 0.25 months after trauma, focusing on executive functions, attention, processing speed, working memory, learning and mood (utilizing Trail Making Test, Stroop, Fluency, Digit span, List learning, Digit cancellation, BDI and the DEX questionnaire).

*Table 5. Neuropsychological tests administered*

| Neuropsychological test | Cognitive domain assessed |
|---|---|
| **Wechsler Adult Intelligence Scale Third edition (WAIS-III)[1]** | |
| Digit Span, Letter Number | attention, working memory |
| Similarities | conceptualization |
| Information | verbal knowledge |
| Block Design | visuospatial and constructive abilities |
| Picture Completion | visual detection |
| Symbol Search, Digit-Symbol | processing speed |
| **Wechsler Memory Scale (WMS-III)[2]** | |
| Logical memory, List Learning | memory functions |
| Visual reproduction | memory functions |
| Verbal Fluency (k/animals) | verbal fluency |
| **Trail Making Test[3]: A, B, difference** | attention, processing speed |
| **Stroop Colour Naming Test[4]** | attention, processing speed |
| **Brixton Spatial Anticipation Test[5]** | executive functioning |
| **Benton Visual Retention Test[6]** | visual perception and memory |
| **Boston Naming Test[7]** | naming, verbal functions |

References: 1) Wechsler, 1997a 2) Wechsler, 1997b 3) Reitan, 1958 4) MacLeod, 1991 5) Burgess and Shallice, 1997 6) Benton, A. L., 1974 7) Kaplan, et al., 1983

## 4.3 MAGNETIC RESONANCE IMAGE ACQUISITION

Structural magnetic resonance image (MRI) (GE Signa HDX 1.5T, Milwaukee, Wisconsin) were obtained from all patients at three weeks to 16 months after the injury (Table 4). One healthy control subject of Studies I-II, and all healthy control subjects of Study III underwent MRI with the same imaging protocol. The imaging included sagittal T2 Cube, fluid attenuated inversion recovery, axial fast spin echo, axial #D susceptibility weighted imaging and axial 3D fast SPGR T1 sequences.

## 4.4 MAGNETOENCEPHALOGRAPHY RECORDINGS

We conducted MEG measurements at Aalto Neuroimaging, MEG Core, Aalto University School of Science, Espoo, Finland in a magnetically shielded room with 306-channel whole-head device (Elekta Neuromag™, Elekta Oy, Helsinki, Finland). The device comprises 102 triplet sensors with two planar gradiometers and one magnetometer coupled with a Superconducting Quantum Interference Device sensor. Prior to the measurement we digitized

(Polhemus 3D Space® Fastrak™, Colchester, VT, US) nasion and two periauricular points to determine the head coordinate system.

For Study I, the MEG signals were collected with a sampling rate of 600 Hz and band-pass filtered to 0.03–200 Hz. Four head position indicator (HPI) coils, attached to scalp, determined the exact head position with respect to the MEG sensors, when a weak current was led into the HPI coils briefly before the measurement session. Horizontal and vertical electro-oculograms (EOG) monitored for eye blinks and eye movements.

For Studies II-III, collection of MEG signals occurred with a sampling rate of 1000 Hz and a band-pass filter of 0.03 – 330 Hz. During the measurement five HPI coils continuously monitored the exact head position inside the helmet throughout the measurement session. Horizontal and vertical EOG, and electrocardiogram (ECG) provided data for artefact management.

For Study I, three minutes of eyes-open (EO) and eyes-closed (EC) recordings were collected. For studies II-III, we collected EC and EO recordings 10 min each, together with recordings during experimental stimuli (see below). Patients were asked to sit relaxed, avoid any movements and fixate at a fixation cross during the EO recordings. We introduced a short pause at five minutes during the EO recordings and two short pauses during the EC recordings to assure that the subjects were awake and alert. Empty room –measurements, collected during measurement sessions provided data for artifact management.

## 4.5 EXPERIMENTAL STIMULI DURING MEG RECORDINGS

In Study III the patients and 20 control subjects completed two tasks during the MEG measurements: *Paced Auditory Serial Addition Test* (PASAT) and a "sustained counting" –type vigilance test (VT).

Paced Auditory Serial Addition Test was created in 1970s by Gronwall and Sampson, who examined processing speed in mTBI patients in the sub-acute phase (Gronwall and Sampson, 1974). They noticed a rapid normalization of PASAT scores, typically within 35 days after injury (Gronwall and Wrightson, 1974). Later on, the test has been used in assessing moderate and severe TBI patients, MS-patients and other neurological patient groups (Gronwall and Wrightson, 1981; Rao et al., 1991). The test simultaneously examines multiple areas of cognitive functioning, such as attention, working memory, processing speed, concentration, and executive function (Gronwall and Wrightson, 1981; Madigan et al., 2000; Christodoulou et al., 2001; Tombaugh, 2006). During the test subjects add two consecutive one-digit numbers presented serially at a fixed interval, which is shortened after each 50-number session. PASAT comes in several versions, using different inter-digit intervals (IDI) ranging from 3.0 s to 0.8 s , and different presentation modalities such as visual and even virtual-reality ones (Parsons et al., 2012; Woods et al., 2018; Tombaugh, 2006). PASAT as a test has shortcomings, one of which is its' stressful nature at faster IDIs, which sometimes leads to relinquishing during the test. Primary

deficits in mathematic skills and educational level can also affect PASAT results (Tombaugh, 2006).

Neuroimaging of healthy controls with fMRI and PET have revealed wide cortical activation during PASAT including mainly fronto-temporo-parietal areas as well as cerebellum and basal ganglia (Audoin et al., 2005; Cardinal et al., 2008; Forn et al., 2011; Lockwood et al., 2004; Lazeron et al., 2003). The activation pattern in healthy controls seems consistent between measurements at six-month interval, after learning effect is considered (Cardinal et al., 2008).

In Study III we applied the four conditions in identical order over subjects: the EO- and EC-conditions were followed by a short break including rehearsal for PASAT with 2.4 s inter-digit interval, after which the subjects performed PASAT and VT tasks. We used 2.4, 2.0 and 1.6 s inter-digit intervals with controls and well-performing patients. For those 11 patients, who expressed distress at rehearsal with 2.4 s IDI, we repeated the slower rate to exclude relinquishing during the recording session. The subjects performed the test quiet without reporting the results aloud to avoid movement artefacts. The PASAT recording lasted for approximately 6.5 minutes, depending on the IDIs used.

Vigilance*, i.e.,* the ability to maintain focused attention in an environment with a dearth of external stimuli, is often disturbed after mTBI, also at a chronic state (Burg et al., 1995; Chan, 2005; Pontifex et al., 2009). Vigilance can be explored with "sustained counting task", in which the rate of pre-defined stimuli is slow, and the task so easy, that maintaining attention requires special cognitive control (Shallice et al., 2008). In lesion studies and neuroimaging studies increased activation in right lateral frontal areas has been involved in this type of tasks (Pardo et al., 1991), whereas some other studies have failed to notice any special activation related (Ortuno et al., 2002).

In Study III the subjects underwent a variant of auditory "sustained counting" – task as a vigilance test (VT). The subjects listened to a story for 10 minutes and tried to count randomly scattered 13 words that were not part of the story and reported the amount of them after the measurement. VT also served as a low-demanding control task, for contrasting changes seen during the more arduous PASAT task.

## 4.6 DATA-ANALYSIS

### 4.6.1 PRE-PROCESSING

Study I consisted of measurements recorded previously, with a sampling rate of 600 Hz. To enable later comparison of this data in Study II to patient measurements recorded with a sampling rate of 1000 Hz, we down-sampled the data to 200 Hz. TSSS -method (MaxFilter™ Elekta Oy) (see 2.2.5. MEG artifact removal) served for artifact control, and when residual cardiac artifacts were present, Signal Space Projection (SSP)-method with 1-5 vectors (see 2.2.5) was utilized. The sensor-level data was transformed to average head position, calculated over all control subjects, using SSS-based head

transformation algorithm (Taulu et al., 2004). One subject had a head position differing more than 25 mm from the average head position and was excluded from the analysis due to a significant change in distribution of noise caused by the transformation (Medvedovsky et al., 2007).

The patient recordings obtained with a sampling rate 1000 Hz, were down-sampled to 200 Hz to enable comparison with the normal database created in Study I. For Study II, tSSS preprocessing with movement compensation (see 2.2.5) served for artifact control. When needed, we applied SSP-method for residual cardiac artifact removal, as explained above. The recordings were transformed to the average head position, as described above.

For study III, the pre-processing consisted of tSSS filtering with movement-compensation, and Independent Component Analysis (ICA) -based artifact removal with 1-2 vectors used for residual cardiac, and one vector for eye-movement artifacts, when needed. Head position correction to average head position was utilized when analyzing sensor-level data. For source-space analysis the measurements were morphed to an average atlas brain.

### 4.6.2 SENSOR-LEVEL ANALYSIS

Conducting the MEG analysis at channel-level, together with subsequent source localization analysis, offers swift and straightforward interpretation of the data and facilitates the later transition towards clinical applications with EEG.

For Studies I-II, sensor-level amplitude spectra were estimated with a 1024-point fast Fourier transform (FFT) with 50% overlap and Hann windowing (smoothing at the beginning and end of each segment), using Welch method. The low-frequency ranges (0.5–7 Hz) of each patient's spectra were then compared with the average spectra estimated over the control subjects. We first analyzed the data from the EC condition and continued with the EO condition, if we observed oscillatory activity exceeding the +2 SD limit of the healthy control group.

In Study III, the sensor level analysis was conducted estimating channel-level individual power spectra from the first five minutes of MEG data in each condition (EO, PASAT, VT) analyzed for this study, using Welch's method with 2048-point Fast Fourier Transform (FFT), 50% overlap and Hann windowing resulting in a frequency resolution of ~0.5 Hz. We calculated areal averages for left and right frontal, parietal, temporal, and occipital areas for obtaining areal peak amplitudes and frequencies at the analyzed (8-14Hz) frequency band.

### 4.6.3 SOURCE-SPACE ANALYSIS

In Study I, when slow oscillatory activity appeared, it was further analyzed with equivalent current dipoles (ECD) –method (see 2.2.6; Hämäläinen et al., 1993). For the source localization, the data around the observed low frequency peak was filtered at ±1 Hz. Sequential dipoles were fitted at every 10 ms to

define the centers of mass of the locations of 15 best-explaining ECDs at this frequency bands. For the subjects with occipital LFA, also the data around the alpha peak (~10 Hz) of the same subject was filtered at ±1 Hz, thereafter the average distance between the slow-wave and the alpha-band dipole clusters were calculated and compared.

In Study II, when slow oscillatory activity existed, we applied MNE-Python package (Gramfort et al., 2014) with Welch's method (8196-point FFT with 50 % overlap and Hann windowing, data sampling rate 1000 Hz) for estimating source-level power spectral densities. Cortically constrained L2 MNE (Gramfort et al., 2013; Hämäläinen and Ilmoniemi, 1994) served for source localization. The cortical mantle and cranial volume were segmented from anatomical T1 MR images using FreeSurfer software (Fischl et al., 2002), and noise-normalized MNEs (dSPMs) were calculated over the cortex for estimating the signal-to-noise ratios in potential source locations (Dale et al., 2000). Empty-room measurements in the same or near-by recording sessions provided data for noise covariance matrix estimations.

In Study III, source-level cortical activity was estimated using a spatial filter in the frequency domain (DICS; see 2.2.6) (Gross et al., 2001; Liljeström et al., 2005). DICS is a linearly constrained minimum variance beamformer that passes the activity in a specific location, while suppressing activity from other locations using a weighted sum of the sensor signals (Van Veen et al., 1997). The preprocessed continuous planar gradiometer data was divided into 2.048 second epochs, using the first 5 minutes of each condition to enable comparison between them. Time-frequency representations using Morlet wavelets with seven cycles (Tallon-Baudry et al., 1997) of the epochs were calculated, to yield cross-spectral densities (CSDs) between all channel combinations and averaged over the entire time interval. The obtained CSD matrices were averaged over the chosen 8-14 Hz frequency band.

To obtain cortex-wide estimates of neural activity, a surface-based cortical grid with 5124 nodes was established for each subject. T1 sequences of MR images, segmented using FreeSurfer (Fischl et al., 2002), determined the individual cortical mantles. Spatial filters were applied for each grid point and source orientation, with the regularization parameter set to 0.05. At each grid point the orientation that maximized the power was selected (VanVliet et al., 2018). To enable spatial comparison of MEG power-maps across subjects, the resulting power maps were morphed to an average atlas brain for group-level statistical analysis.

## 4.7 STATISTICAL ANALYSIS

For Studies I-II we created an average ± 2 standard deviations (SD) distribution of the healthy control channel-level amplitude spectra and compared the individual spectra of each subject (Study I) and patient (Study II) with those. For calculating between-group differences in Study II we used chi-square test, and for assessing RPQ scores relation with MEG and MRI findings we applied Mann-Whitney U two-independent-samples test.

For statistical analysis of channel-level measurement data in Study III, we applied IBM SPSS Statistics (version 24) nonparametric tests, due to small sample size and skewed distribution of data. For between-groups comparison, we utilized logarithmic transformation of the data to control for uneven variance of the data. For source-space results between conditions and groups, we applied cluster-based permutation tests in MNE Python with a cluster-forming threshold of p=0.05 (maximal geodesic distance between neighboring vertices of 0.010, 10000 permutations).

# 5 EXPERIMENTS

## 5.1 STUDY I: THE PREVALENCE OF LOW-FREQUENCY ACTIVITY (LFA) IN HEALTHY ADULT AWAKE MEG RECORDINGS.

### 5.1.1 BACKGROUND

Low-frequency activity (LFA) is a frequent finding in developing brain, dominating the awake oscillatory brain activity in neonates and diminishing gradually during childhood (Haddad et al., 2006; Lauronen et al., 2012; Hari and Puce, 2017). In adolescents and young adults traces of posterior polyrhythmic slow-wave activity at theta (4 – 7 Hz) -band may prevail up to the third decade of life, whereas any delta (<4 Hz) -activity in awake adult EEG is considered a sign of brain pathology (Pearl et al., 2017; Krishnan et al., 2017). It is known, however, that EEG is not as sensitive as MEG in capturing some features of resting-state oscillatory activity in healthy adults, such as the mu-rhythm of sensorimotor cortices (Hari and Puce, 2017). The prevalence of LFA in MEG recordings of healthy adults is not well documented, even though a gender difference, with males presenting more LFA in the fronto-central and females in the posterior regions, has been observed (Wienbruch, 2007).

### 5.1.2 EXPERIMENTAL PARADIGM

We analyzed three minutes of EO and EC spontaneous resting state MEG data of 156 healthy adults. After careful artifact management, we estimated the average channel-level amplitude spectra with ± 2 SD limits, and compared each subject's individual spectra at 0.5 – 7 Hz to those.

### 5.1.3 RESULTS AND DISCUSSION

Of all healthy subjects, 17 were excluded due to a background with mTBI or other neurological or psychiatric problems revealed in a detailed interview, or data-related issues (see 3.1.2 Control subjects and Fig. 3).

LFA was present in 12/139 (8.6%) of the subjects. In 7 subjects, LFA was widespread, and in 6/7 it was modulated by opening of the eyes. Due to its bilateral, symmetrical location in posterior parts of the brain and reactivity to eye-opening, it was identified as benign physiological posterior LFA (Westmoreland and Klass, 1990). One subject presented with parietal widespread LFA that was not reactive to eye-opening and it was thus classified as aberrant LFA.

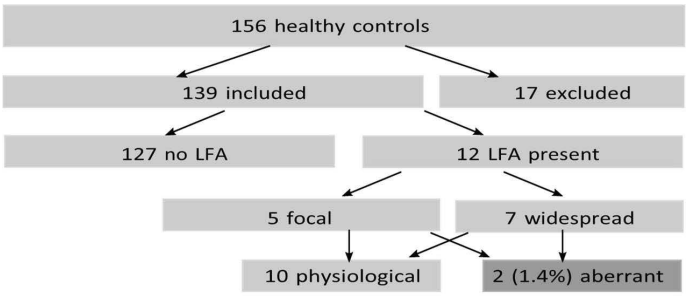



Figure 3. Prevalence of low-frequency activity (LFA) in healthy control subjects.

Focal LFA occurred in 5 subjects. In 4/5 of the subjects, focal LFA was located posteriorly near the maximum of alpha peak activity with a frequency that was ½ of their individual alpha peak frequency. LFA reacted to eye-opening in a similar way than alpha-activity, and was thus regarded as physiological slow-alpha variant activity (Beauchemin and Savard, 2012; Westmoreland and Klass, 1990). One subject presented with focal rolandic LFA, with maximal amplitude of 2.7 Hz, that was regarded as aberrant.

Altogether, aberrant LFA was observed only in 2/139 subjects suggesting ~1.4%. prevalence of LFA in healthy subjects. If LFA is observed in EC recordings, it is important to assess the data together with EO recordings, to exclude benign variants of LFA, such as slow alpha variant activity and widespread posterior activity sometimes encountered in healthy young adults. In addition, proper management of low-frequency artefacts arising from e.g. eye -movements and heartbeat is important for correct interpretation of the results. With this dataset we created a normal database for future use in assessing spectral estimates of different patient groups.

## 5.2 STUDY II: LOW-FREQUENCY ACTIVITY IN MTBI PATIENTS

### 5.2.1 BACKGROUND

Appearance of LFA is reported in many neurological and psychiatric patient groups including stroke, brain tumors, epilepsy and schizophrenia (Laaksonen et al., 2013; Kamada et al., 1997; Bosma et al., 2008; Ishibashi et al., 2002; Moran and Hong, 2011). In mTBI patients, LFA is often observed in the EEG at acute phase, with a gradual disappearance in repeated measurements (Bierbrauer et al., 1992; Geets and Louette, 1985).

MEG studies assessing mTBI patients have observed increased LFA even at a chronic state after trauma (Lewine et al., 1999; Lewine et al., 2007; Huang et al., 2009; Huang et al., 2012). In multimodal studies with structural MRI, EEG, SPECT and MEG, MEG was the most sensitive in capturing LFA

(Lewine et al., 2007). When comparing MEG and DTI results of the same mTBI patients, MEG appeared more sensitive (Huang et al., 2009).

The natural evolution of LFA after mTBI is, however, not well established, nor is its' ability to predict the patients who will get persistent symptoms after mTBI. Here, we wanted to prospectively study the appearance of LFA and its' persistence in follow-up with the symptoms of the mTBI patients. Instead of laborious and complicated connectivity analysis, we selected a simple screening method easily transferrable to clinical use with EEG.

### 5.2.2 EXPERIMENTAL PARADIGM

We compared spectral estimates of oscillatory brain activity at low-frequency (0.5 – 7 Hz) band in individual patients to those of the normal database created in Study I. The measurements occurred 6 days to 6 months after mTBI, in 13 patients within one month after injury. Of all patients, 12 underwent a follow-up measurement at six months after injury. When LFA was detected, we localized it with MNE -Python software (Gramfort et al., 2013) using cortically constrained L2 norm. The L2 minimum-norm estimate gives a current distribution with the smallest overall power that can create the measured activity on the cortex (Hämäläinen and Ilmoniemi, 1994). We correlated the LFA results with the symptoms reported in RPQ before each measurement. The effect of lesion-depth on the appearance of LFA was also assessed.

### 5.2.3 RESULTS AND DISCUSSION

At a single-subject level, LFA was present in 7/26 patients (chi-square statistic 27.6, p=0.00001, Fig. 4); three of those were without structural lesions in MRI. Of the patients with follow-up measurements, LFA was detectable in the first measurement in 5/12, and disappeared in 3 during follow-up. The difference between patients and controls remained significant even in the follow-up (chi-square statistic 16.3, p=0.0005). LFA was detected more frequently in patients with superficial lesions in MRI (chi-square statistic 7.2, p=0.01), compared with patients with deep white-matter lesions (chi-square statistic 2.4, p=0.12). LFA did not, however, correlate with symptoms reported in RPQ collected at the measurement sessions.

LFA incidence is higher in MEG recordings of mTBI patients at subacute phase, with a tendency to decline in the follow-up, in accordance with prior EEG and MEG studies (Tebano et al., 1988; Lewine et al., 1999). Detection of LFA, with EEG or MEG may be attempted as an objective indicator of mTBI in the acute phase, if structural imaging methods remain with minor changes or without any trauma-related lesions.

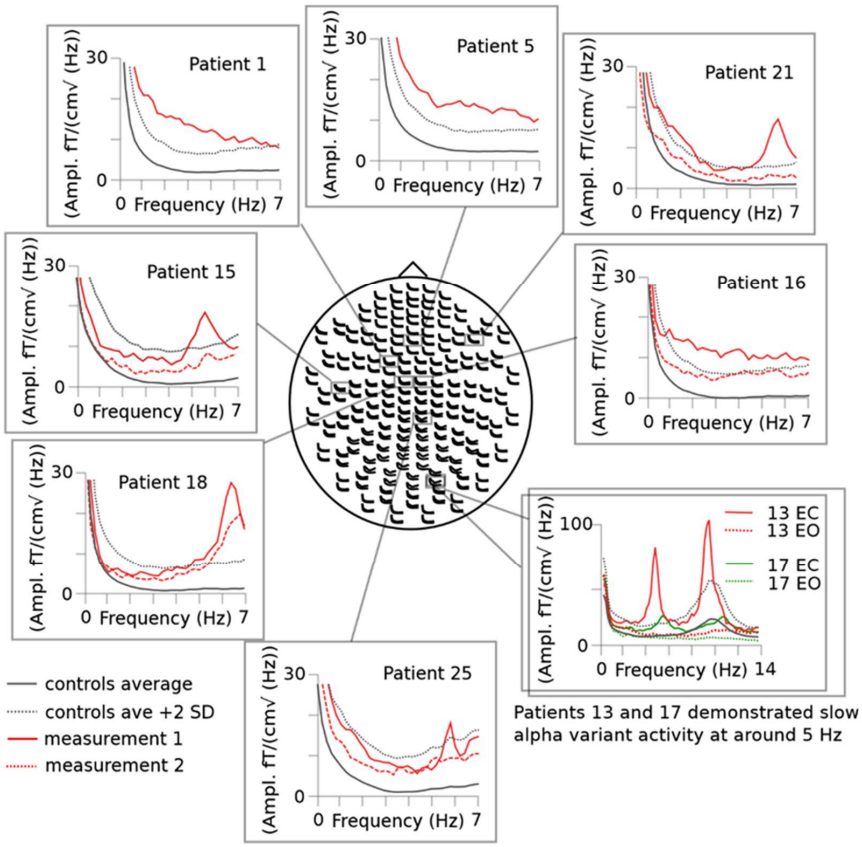



Figure 4. Slow oscillatory activity was detected in nine patients, compared here with the channel-level amplitude spectra averaged over all controls with + 2 SD curves. Rectangles indicate the channels that showed aberrant slow oscillatory activity in each individual patient. Patients 13 and 17 demonstrated benign slow variant of alpha-activity, only visible in eyes closed (EC) condition (right down corner). EO=eyes open

## 5.3 STUDY III: MEG RECORDINGS OF MTBI PATIENTS DURING COGNITIVE TASKS

### 5.3.1 BACKGROUND

Problems with attention, processing speed, executive functions and working memory are among the most common cognitive symptoms after mTBI (Binder et al., 1997; Frencham et al., 2005; Barker-Collo et al., 2015; Prince and Bruhns, 2017). Most mTBI patients seem to achieve full recovery by three months, whereas there seems to be a subgroup with subtle residual symptoms, noticeable in neuropsychological testing with challenging tasks (Cicerone and Azulay, 2002; Karr et al., 2014). We aimed at finding

neuroimaging tools for functional assessment of cognitive processing in patients with mTBI.

### 5.3.2 EXPERIMENTAL PARADIGM

We compared the spectral power of oscillatory brain activity at 8 – 14 Hz band during rest and two cognitive tasks, an easy vigilance test (VT) and an arduous Paced Auditory Serial Addition Test (PASAT), in 20 healthy controls and 25 mTBI patients. Power modulation was analyzed in the source space using spatial filter DICS in the frequency domain, and the modulation of areal alpha (8 – 14 Hz) peak frequencies from the channel-level average power spectra. We correlated the channel-level alpha peak powers with the results of neuropsychological tests that have previously been related with PASAT results (Tombaugh et al., 2006).

### 5.3.3 RESULTS AND DISCUSSION

The source space analysis presented wide temporo-parietal attenuation of 8-14 Hz oscillatory activity during PASAT compared with rest in both control and patient groups ($p<0.05$). In patients, attenuation of 8-14 Hz activity was also visible in frontal areas. Between-groups comparison during PASAT revealed that the attenuation of oscillatory power was stronger and visible at multiple regions in patients ($p<0.05$), consistently with previous results (Lazeron et al., 2003; Lockwood et al., 2004; Audoin et al., 2003). Patients exhibited statistically significant attenuation in left dorsolateral prefrontal cortex and right dorsomedial prefrontal areas not visible in controls (see Fig. 5c).

During VT, the oscillatory brain activity did not modulate significantly in control or patient groups compared with rest.

In repeated measurements of 12 mTBI patients the oscillatory brain activity at 8-14 Hz did not significantly differ from the first measurements.

Right temporal (correlation coefficient -0.715, $p=0.003$, uncorrected) and left parietal (correlation coefficient -0.639, $p=0.010$, uncorrected) alpha peak powers were negatively correlated with the difference in time spent to complete TMA vs. TMB, in percentiles of healthy individuals' performance (correlation coefficient -0.473, $p<0.017$, uncorrected). Lower alpha peak power was correlated with better TMT performance in patients, in accordance with prior studies relating alpha-band attenuation to better performance in working-memory tasks (Hanslmayr and Staudigl, 2014).

The channel-level analysis of the areal alpha peak frequencies indicated a difference in parieto-occipital alpha frequency modulation in patients and controls: while the occipital alpha frequency was significantly higher compared with parietal, temporal and frontal alpha frequencies during the challenging PASAT task in controls, in patients the occipital alpha frequency remained stable, but the parietal alpha together with frontal and temporal areas decreased during PASAT (interaction $p=0.012$; Fig. 6).

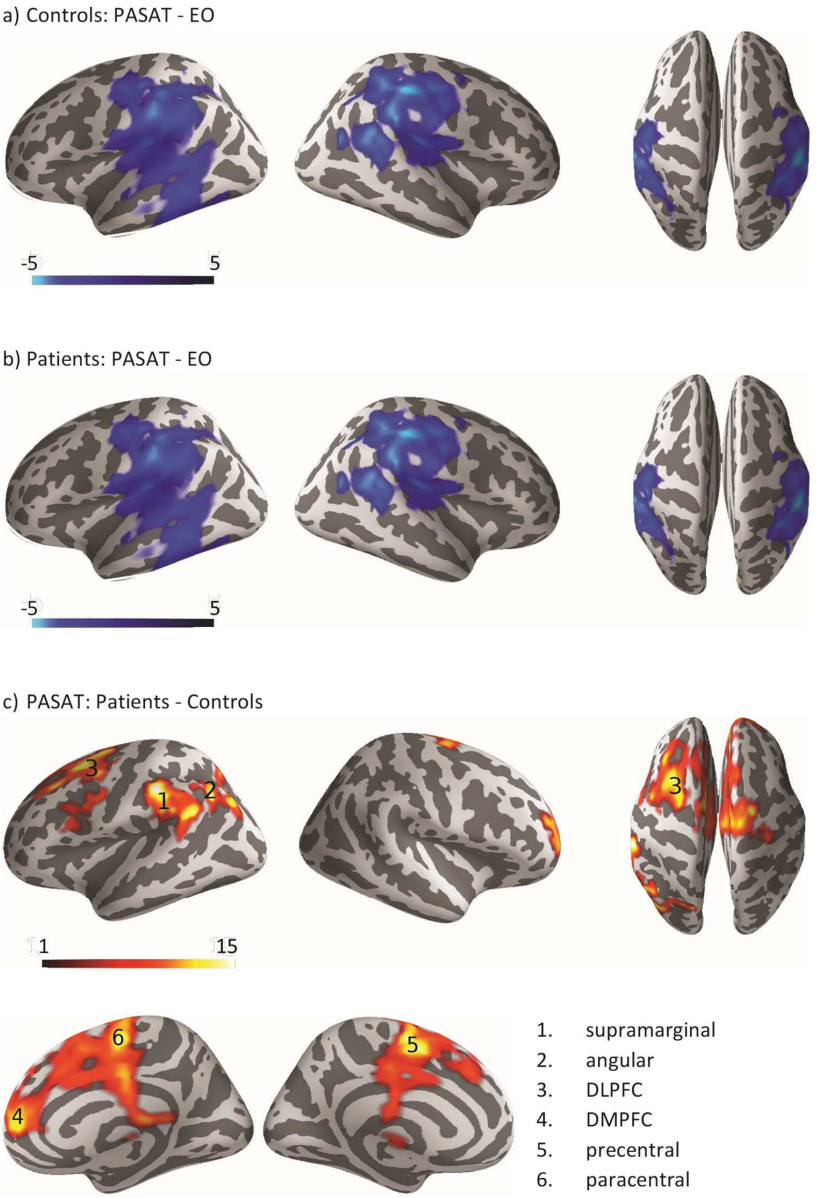



Figure 5. Activation patterns during PASAT. Controls exhibit attenuation of 8-14 Hz activity ($p<0.05$, corrected) in bilateral fronto-parieto-temporal areas during PASAT compared with EO. Patients (b) show multiple attenuation areas in frontal cortices. Between-groups -comparison during PASAT reveals stronger attenuation in patients in left supramarginal and angular gyri, left dorsolateral prefrontal cortex (DLPFC), right dorsomedial prefrontal cortex (DMPFC) and right and left medial precentral and right paracentral areas. PASAT=Paced Auditory Serial Addition Test, EO=eyes open.

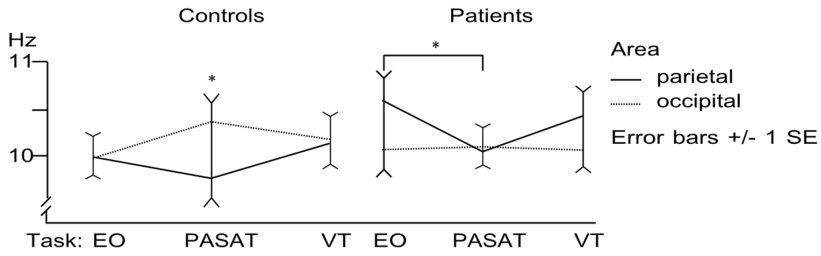



Figure 6. Areal alpha peak frequency modulation in parietal and occipital areas in controls and patients. Asterisks denote significant differences between areas in controls and tasks in patients.

The results suggest significant differences in oscillatory brain activity between controls and mTBI patients during a laborious cognitive task, relatable also to behavioral test results. Increased attenuation of 8-14 Hz activity during PASAT in the frontal cortical areas in patients may suggest inefficient cognitive functioning, with enhanced need for executive control from frontal areas during the laborious task. The altered areal alpha frequency modulation in patients during PASAT might illustrate the impaired interplay between different cortical areas during a task that requires simultaneous function of many cognitive domains.

# 6 GENERAL DISCUSSION

This thesis investigated the oscillatory brain activity after mTBI in a resting-state situation, as well as during cognitive tasks. Our aims were 1) to assess the prevalence of low-frequency activity in healthy control patients for creating a normal database of oscillatory brain activity at low-frequency range, 2) to assess the prevalence and natural evolution of low-frequency activity (LFA) in mTBI patients, and 3) to investigate the changes a mTBI causes to oscillatory brain activity during cognitive tasks and attempt to correlate the changes with neuropsychological test performance.

## 6.1 THE PREVALENCE OF LFA IN HEALTHY SUBJECTS

LFA at delta -frequency range (<4 Hz) in EEG or MEG recordings of awake adult subjects is considered an indicator of encephalopathy, a pathological process within the brain (Krishnan et al., 2017). Even healthy subjects, however, may present LFA that stems from physiological phenomena and artefacts, which hampers its' use as a diagnostic tool. At low-frequency range *e.g.* eye-movement and heart-beat related artefacts are often present and sometimes difficult to differentiate from electromagnetic activity arising from the brain (Hari and Puce, 2017). Adequate artefact-control with tSSS may enhance signal-to-noise ratio (SNR) with 100% and applying decomposition-based artefact rejection method (*e.g.* SSP or ICA) may improve SNR with over 30% (Gonzales-Moreno et al., 2014). ICA seems superior to SSP, which also reduces the original signal significantly (Haumann et al., 2016).

In our study, after state-of-the-art artefact management 12 of the healthy subjects exhibited LFA, but 10 of those were regarded as physiological variation in background activity. Therefore, after careful interpretation of the observed LFA, only 2/139 (1.4%) of healthy subjects presented aberrant LFA in their recordings. The physiological variates of oscillatory activity at low-frequency range could be differentiated by comparing eyes-closed (EC) and eyes-open (EO) recordings. If the activity is located over the posterior cortices and suppresses during EO, it probably represents slow variants of alpha-activity. Of those with physiological LFA, 6 subjects exhibited posterior slow activity sometimes present in EC recordings of young adults. In 4 subjects the LFA was considered low alpha harmonics, visible in EC recordings only (Beauchemin and Savard, 2012; Pearl et al., 2017; Krishnan et al., 2017; Westmoreland and Klass, 1990).

Our results suggest, that LFA is more often visible in EC recordings, and that especially at posterior areas LFA is mostly of benign nature and reversible with opening of the eyes, present in 10/139 (7%) of healthy subjects in our study. In the future LFA activity could thus be assessed from EO recordings, with adequate artifact control for, *e.g.,* eye-movements and cardiac artefacts.

## 6.2 THE PREVALENCE AND NATURAL EVOLUTION OF LFA IN MTBI PATIENTS

The prevalence of LFA in mTBI patients recruited to this study was significantly higher than in healthy control patients: 7/26 vs. 2/139. It was, however, significantly lower than in many other studies assessing mTBI patients that have reached prevalence rates of 46-85% (Lewine et al., 1999; Huang et al., 2014). This difference is probably due to the fact, that while attempting prospective evaluation in a subgroup of 12 patients with repeated MEG recordings, in some of our patients the symptoms had nearly resolved at the time of the first MEG measurement (Table 1). The difference in prevalence may also be related to differences in analysis methods, our method being robust and designed to enable easy assessment of clinical patients. In all MEG studies on mTBI patients thus far the sample size has been quite small, leaving some room for chance.

In the subgroup of patients with repeated measurements, the prevalence of LFA was higher in the first measurement where 5/12 (42%) of the patients exhibited LFA than in the second measurement (2/12, 17%). The prevalence of LFA thus appears higher when measured early, within the first weeks after the trauma, in line with earlier EEG findings (Bierbrauer et al., 1992; Geets and Louette, 1985; Tebano et al., 1988).

The prevalence of LFA in the MEG recordings was not correlated with the RPQ-score of our patients. Studies finding LFA in significantly larger proportion of mTBI patients have also produced ambiguous results on the association of LFA with the neuropsychological outcomes of the patients (Robb Swan et al., 2015). Since post-concussion syndrome (PCS) is a constellation of unspecific symptoms of probably mixed origins, the evaluation of the symptoms solely attempting correlations between RPQ and oscillatory brain activity is possibly too simplistic an approach for this patient group.

According to Study II, LFA is most readily detected early after trauma, speaking for the importance of prompt measurements in clinical patients. Recent results assessing mTBI prognosis confirm this view; post-concussion symptoms lingering at two weeks to one month after injury predict the prevalence of symptoms also at six months to one year after injury (Cnossen et al., 2018; Wäljas et al., 2015).

## 6.3 THE EFFECT OF LESION DEPTH ON DETECTION OF LFA

The depth of possible lesion in MRI, found in 16/26 patients also appeared to affect the detection probability of LFA in our patients. Superficial lesion (in 6 patients) located near the cortical mantle was more frequently associated with LFA in MEG recordings than a deep lesion (in 10 patients) within deep white matter or near the base of the skull. MEG is overall more sensitive to superficial sources, located in the sulci of the cortical mantle (Hillebrand and Barnes, 2002), and probably detects well cortical edema and minute lesions

in the junction of gray and white matter often observed in mTBI (Browne et al., 2011; Gean and Fischbein, 2010), but may be less sensitive for deep lesions within corpus callosum or the base of the skull also frequently encountered after mTBI (Yuh et al., 2014; Gean and Fischbein, 2010). LFA was visible in three patients without detectable MRI lesions, suggesting that MEG-recordings, conducted at a subacute stage after trauma might indeed offer additional information in the diagnostic work-up of mTBI patients, especially for those with superficial lesions.

In theory EEG may be more sensitive to deep sources than MEG. However, in a small patient group EEG offered no enhanced efficacy detecting changes after mTBI (Lewine et al., 1999). As EEG can be easily recorded during MEG -measurements, these methods should be assessed together for addressing their dual sensitivity in a larger patient group.

## 6.4 THE PATHOPHYSIOLOGICAL ORIGINS OF LFA

As previously mentioned, LFA in awake, adult resting-state MEG/EEG-recordings is encountered in many brain pathologies. Post-traumatic axonal sprouting and regeneration, however, may also induce LFA, which could thus be associated with neural repair mechanism (Carmichael and Chesselet, 2002). In stroke patients LFA, detected in the vicinity of cortical lesions, has been associated with plastic reorganization of the cortex (Vieth, 1990; Butz et al., 2004). LFA seems to be detectable even months or years after stroke, but its' specific relationship with functional recovery remains uncertain (Butz et al., 2004; Laaksonen et al., 2013).

The possible relationship of LFA with neural repair is of great interest. Heikman et al (2001) assessed the relationship of electroconvulsive therapy (ECT) with the presence of LFA and clinical symptoms in depression patients and found that 3-7 Hz activity increased during the therapy, and the increase of this theta -activity in left frontal region was associated with the therapeutic effect. The association of LFA with recuperation of the symptoms and the response to treatment has been assessed in mTBI patients as well; according to Ulam et al. (2015), mTBI patients harboring LFA soon after trauma recuperated better after transcranial direct current stimulation (tDCS) intervention than those with LFA and without intervention. The presence of theta -activity soon after trauma could thus help in selecting patients with disturbing cognitive complaints to rehabilitation interventions. It is known that patients expressing poor recovery within two weeks after injury are more prone to presenting long-lasting complaints after mTBI (Carroll et al., 2014; Iverson et al., 2017), and thus early EEG/MEG measurements and timely interventions directed to these patients could facilitate the recovery. In our patients the persistence of LFA at six months did not predict poorer recovery, but the sample size was too small to draw solid conclusions.

If early LFA after trauma is associated with neural repair, and late LFA with post-concussion symptoms, when is the time-point after which the LFA detected is not relatable with symptom resolution, but should be considered a sign of dysfunction? Further studies with larger sample sizes, prospective

design, multiple measurement sessions and more extensive data collection are needed to elucidate this important question.

## 6.5 THE EFFECT OF MTBI ON OSCILLATORY BRAIN ACTIVITY POWER DURING COGNITIVE TASKS

During a demanding cognitive task (PASAT), controls and patients expressed attenuation *i.e.* amplitude decrease of the oscillatory brain activity at 8-14 Hz in wide areas over fronto-temporo-parietal cortices when compared with rest. This finding is compatible with overall literature of PASAT task previously assessed with different neuroimaging methods, mainly fMRI and PET (Audoin et al., 2005; Lazeron et al., 2003; Lockwood et al., 2004; Forn et al., 2011; Cardinal et al., 2008). Contiguously with previous studies using PASAT in patient groups with mTBI and multiple sclerosis (MS), the mTBI patients expressed attenuation of oscillatory activity in multiple cortical areas compared with healthy controls (see fig. 5) (Audoin et al., 2003; Christodoulou et al., 2001). The areas with different activation patterns between controls and patients included right dorsomedial prefrontal cortex (DMPFC), which is associated with arithmetic functions (Barbey et al., 2012), as well as in maintenance of attention and motivation (Owen et al., 2005; Szczepanski and Knight, 2014), dorsolateral prefrontal cortices (DLPFC), which are involved in executive component of working memory processing (Owen et al., 2005; Szczepanski and Knight, 2014; McAllister et al., 2006), and left supramarginal gyrus and angular gyrus, which together form the inferior parietal lobule (IPL), connected with addition abilities (Delazer and Benke, 1997; van Harskamp and Cipolotti, 2001; Göbell et al., 2006; Dehaene et al., 2004; Salillas et al., 2012).

During successful memory processing, as well as sensory processing, decreases in alpha oscillatory power typically occur in relevant cortical areas (Hanslmayr and Staudigl, 2014; Hanslmayr et al., 2012; Long et al., 2014). This seemed to be the case in our study as well. In patients, the power decrease was stronger than in controls during PASAT, implying enhanced load for memory processing. In the less demanding vigilance task (VT), the activation pattern did not differ from that seen during rest. Even in the absence of oscillatory changes, there was a significant difference in test performance: Patients presented more incorrect responses during this easy task. As the task probed sustained attention, *i.e.* the capability to retain focus during scarcity of external stimuli, it was probably too easy to induce detectable changes in the oscillatory brain activity with the analysis methods used. It served, however, to confirm that the changes observed in oscillatory brain activity during the more challenging PASAT task were not a result of auditory stimulation alone, nor general differences in the attentional level.

In Study III, the patients exhibited increased attenuation of oscillatory power compared with healthy controls in right DMPFC, bilateral DLPFC and left IPL during PASAT task. Arakaki and colleagues used n-back task and EEG

to compare mTBI patients with orthopedic controls at one week, two weeks and one month after trauma, and noticed increased desynchronization of induced alpha-activity at frontal regions (Arakaki et al., 2018). Furthermore, EEG event-related potentials recorded during PASAT show differences in the right anterior cingulate cortex and left ventrolateral prefrontal cortex between mTBI patients and healthy controls (Rogers et al., 2015). These compatible EEG findings, together with our findings suggest inefficient cognitive processing in mTBI patients and need to compensate for the inefficiency with enhanced frontal control of the task execution.

## 6.6 THE EFFECT OF MTBI ON ALPHA PEAK FREQUENCY MODULATION DURING COGNITIVE TASKS

Of great interest was the finding of deviant areal alpha peak frequency (APF) modulation during PASAT in Study III. In controls, the occipital APF was higher than parietal during the challenging cognitive task, while in patients the APF was similar between the areas (Fig. 6). In less demanding VT, these areal differences were not present. Previously n-back and Sternberg tasks have induced increase in occipital APF in healthy controls during high work load compared with rest (Haegens et al., 2014; Maurer et al., 2015). In our study this tendency was visible in healthy subjects, but not significant. In patients, however, the alpha peak frequency significantly declined in parietal areas during the challenging cognitive task PASAT. This finding could stem from derangements in brain metabolism and energy consumption noticed in healthy subjects to cause decline in APF (Mosmans et al., 1983; Van et al., 1991), probably here as a result of axonal injury, and serve as an indicator of inefficient cognitive processing after mTBI.

Occipital alpha frequency decline during rest has previously been observed in mTBI patients (Bierbrauer et al., 1992; Tebano et al., 1988), even if in our patients this was not visible, possibly due to later timing of the measurements. Slowing of occipital alpha frequency seems to associate with problems in white-matter integrity (Valdes-Hernandez et al., 2010). Pang and colleagues, using n-back task to compare connectivity measures in mTBI patients and healthy controls, noticed that mTBI patients failed to enhance occipital connectivity with other brain areas during increased task difficulty, as the healthy controls did (Pang, 2015). In our study the healthy controls exhibited a tendency towards increase of occipital alpha frequency during a challenging cognitive task while in mTBI patients the occipital alpha frequency remained stable. These findings together suggest that subtle problems in the integrity of brain structure in mTBI patients, may lead to impaired capacity of efficient interplay between different cortical areas and thus reduced performance level in tasks demanding integrated function of multiple cognitive domains.

Overall, we detected differences in cortical oscillatory patterns between mTBI patients and healthy controls in relevant cortical areas during a

challenging task evaluating multiple domains of cognitive functioning. The stronger attenuation of power in 8-14 Hz band during PASAT in patients might express increased cognitive work load in the patients; the stronger attenuation was correlated with better performance in Trail Making Test. Patients also exhibited stronger attenuation of oscillatory activity in multiple frontal areas compared with controls during PASAT, suggesting the need for enhanced frontal control during task-execution in patients. The changes in areal alpha frequency modulation might be an indicator of decreased efficiency of cortical network during a demanding cognitive task. The oscillatory activity of the patients did not significantly change between the measurement sessions, separated by six months, indicating that these differences in oscillatory activity might be visible also later in time. This is a clinically important feature, as the mTBI patients suffering from prolonged symptoms typically seek advice after subacute stage, at three to six months after injury (de Koning et al., 2017).

## 6.7 LIMITATIONS OF THE STUDY

The major limitations of the study are the heterogeneity of the patient group and the small sample size. Part of the patients were already assessed by neuropsychologist at the time of the first MEG-measurement and therefore had clear symptoms. Other patients were recruited early, and in some of them the symptoms had mainly resolved at the time of the first measurement. Lesions in MRI or CT were present in some patients, indicating more severe injury. The timing of the assessments with MEG, MRI, and neuropsychology was variable between patients, due to a scattered network of first-aid centers in Helsinki region, which created also problems in recruiting suitable candidates. On the other hand, this is also the typical situation in “real life”: Patients do not always seek medical advice immediately after trauma, and sometimes in the case of serious multi-trauma the possibility of concomitant TBI is assessed for the first time only in the rehabilitation phase. The design during cognitive tasks was targeted to be easily transferred to clinical assessments with EEG, to find new tools for clinical assessment of patients. Collecting reliable behavioral data in cognitive tasks such as PASAT during MEG recordings is not straight forward due to probable measurement artifacts but should be addressed in future studies.

# 7 CONCLUSIONS

The diagnosis of mTBI is not easy, especially when it is considered retrospectively after trauma. The prognosis after mTBI is favorable, but a substantial number of patients suffer from unspecific symptoms even one year after trauma. Reliable prognostic factors are scarce, and possible confounding factors many. Different serum biomarkers are under research, but clear cutoff-values discriminating patients and controls irrespective of time after injury are missing. Neuroimaging methods for diagnostics of mTBI are developing, with multiple new approaches available, but not yet in clinical use for assessing single patients.

Optimal clinical work-up of a mTBI patient would be a mixture of acute brain imaging and serum biomarker assessments directing a minority of patients to follow-up of recuperation and further assessments with different neuroimaging methods. Resting-state EEG/MEG at subacute phase after trauma could serve as a complementary evaluation method in patients with delayed recovery and cognitive complaints. LFA is a well-known indicator of mTBI at acute phase, and its' relationship with plastic remodeling and prospects of rehabilitation interventions, as well as long-lasting complaints, should be assessed with prospective study designs and larger patient groups.

In our study MEG revealed deviant modulation of alpha frequency during cognitive tasks in mTBI patients compared with healthy controls. Evaluation of areal modulation of alpha, which is the major oscillatory brain rhythm and easily detected with scalp EEG, during cognitive assessment could serve as an objective correlate of inefficient cognitive processing after mTBI. The changes in alpha frequency and power did not significantly change during follow-up, suggesting that they might serve objective measures of altered brain dynamics after mTBI also later after trauma. These findings should be replicated with larger control and patient groups and a research paradigm directed to the assessment of individual patients. Our results open interesting possibilities for assessing even other patient-groups, such as MS, in which inefficient cognitive processing is a major complaint.

Right-timed and adequate patient information and psychological support for patients with risk factors for delayed recovery are needed and should be easily accessed early after trauma, to support resilient attitude towards remaining symptoms, and avoid vicious cycle of symptom accumulation and building up of a long-lasting syndrome.

*"No head injury is too trivial to ignore"*

*-Hippocrates, 460-377 BC*

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