

ACKNOWLEDGEMENTS

This thesis would not have been possible without the help of others. First and foremost I would like to thank patients and healthy controls that participated in the main project the data in this thesis is collected from. I would also like to thank employees at St. Olavs and NTNU, fellow students as well as radiographers who participated in the data collection for the project and this thesis.

The following people deserve special thanks:

My supervisor dr. Toril Skandsen, for letting me participate in this project, both as a research assistant and for letting me write this thesis. Thank you for sharing your insight and expertise in everything from neuroscience and medicine to scientific writing. I am grateful for all the help and all the hours you have put into supervising. You are a superhuman and you are awesome.

Co-supervisor Rune Karlsen, thank you for training me in neuropsychological testing and for comments regarding neuropsychology.

Thank you Line Folvik, my fellow master student and SPSS-expert. We would not have been done in time without our perfect collaboration.

Alexander Olsen, thank you for excellent advice and letting me borrow your doctoral thesis which have provided a much stronger literature list in this thesis, and tips on how to write this specific section (sorry for the rip-off of the layout).

Vegard Foldal, for all specific and general help, regarding everything.

I would like to thank the science-experts in my family, my big-sister Ingvild Saksvik-Lehouillier and father Per Øystein Saksvik for tips on scientific writing and for proof reading my thesis. Off course, thank you to the rest of my family especially my mother Siri Beate Berg and my sister Gunnhild Berg Saksvik for your support. And thank you Edona Zilkiqi (aka Eddy Gordo).

Trondheim, 27.05.15

ABSTRACT

This thesis examined the consequences mild Traumatic Brain Injury (TBI) has on neuropsychological measures of attention two weeks after injury, using the Cambridge Neuropsychological Test Automated Battery (CANTAB). Most studies report attention to be impaired after mild TBI. Moreover, attention might be more impaired in patients with findings on neuroimaging, characterized as having a complicated mild TBI, because networks controlling attention are widespread in the brain and axonal injuries like traumatic axonal injury are suggested pathophysiology after mild TBI. Mild TBI patients do also often report psychological complaints. Psychological and other mild TBI comorbid factors make it difficult to determine the effect neuropathology has on neuropsychological performance. The CANTAB is potentially better suited to assess neuropsychological functioning after mild TBI, since traditional neuropsychological measures have been criticized. It was hypothesized that I) Mild TBI patients would perform worse on neuropsychological measures of attention and report more distress on selected self-reported measures than healthy matched controls 2 weeks after injury. II) That complicated mild TBI patients would perform worse on neuropsychological measures of attention than uncomplicated mild TBI patients and healthy matched controls 2 weeks after injury. A final sample of 62 patients with mild TBI and 49 healthy matched controls were compared on performance in the CANTAB analyzed with multivariate and univariate analysis. The participants answered questionnaires assessing self-reported symptoms, these were analyzed with univariate measures. All patients were examined with MRI at 3 Tesla within 72 hours after injury. There was no statistical significant difference between patients with mild TBI and matched healthy controls on measures of attention. CT and MRI results identified 7 patients with complicated mild TBI, a group too small to analyze statistically. The patients reported significantly more complaints on concentration, memory and pain compared to controls. It was concluded that the sample in this thesis was representative for the mild TBI population and that although some patients reported complaints on some self-reported measures, most patients with mild TBI show good neuropsychological outcome of attention two weeks after injury.

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List of abbreviations

ACC	Anterior cingulate cortex
ADHD	Attention deficits hyperactivity disorder
AST	The attention swithching task
BC-PSI	The British Colombia post-concussion symptom inventory
CANTAB	Cambridge neuropsychological test automated battery
CT	Computerized tomography
DLPFC	Dorsolateral prefrontal cortex
DTI	Diffusion tensor imaging
DWI	Diffusion weigthed imaging
FLAIR	Fluid-attenuated inversion-recovery
GCS	Glasgow coma scale
LOC	Altered or complete loss of consciousness
MRI	Magnetic resonance imaging
NE	Norepinephrine
PTA	Post traumatic amnesia
RVP	Rapid visual information processing
SSP	Spatial span
SWI	Susceptibility-weighted imaging
SWM	Spatial working memory
TBI	Traumatic brain injury

INTRODUCTION

Traumatic brain injury (TBI) can be defined as a brain injury caused by an external mechanical force that can be evidenced by alterations in brain function or other evidence of brain pathology (Menon et al., 2010). In Norway the incidence rate of hospitalized TBI has been reported to be 83.3/100 000 and 86% of hospitalized TBIs are categorized as mild. Falls and motor vehicle accidents are the most common causes of TBI (Andelic et al., 2008). Although there is evidence for neuropsychological impairments following TBI (Dikmen et al., 2009, Mathias and Wheaton, 2007, Skandsen et al., 2010a), the consequences of mild TBI have been debated (Dikmen et al., 2009, Ruff, 2011). The debate involves whether the cognitive problems following mild TBI are mainly caused by brain injury or caused by other psychological and physical factors. Attention deficits are often reported as one of the neuropsychological impairments following mild TBI, especially in the acute stage (Carroll et al., 2014, Ruff, 2011), the period up until two weeks after injury (Eierud et al., 2014). Some patients diagnosed with mild TBI also report persisting symptoms beyond the acute stage (Ponsford et al., 2000). In the heterogeneous patient group with mild TBI, there is a small subgroup of patients with abnormalities on Computerized Tomography (CT) or Magnetic Resonance Imaging (MRI). It is logical to assume that the patients with abnormalities on neuroimaging perform worse on measures of attention than the larger group of patients without abnormalities; however the results are mixed (Iverson et al., 2012, Panenka et al., 2015).

Diagnosing mild TBI

TBI is frequently classified by severity based on the Glasgow coma scale (GCS) which assesses eye, verbal and motor responses (Teasdale and Jennett, 1974). GCS scores vary between 3 (deep coma) and 15 (oriented and alert) and it is common to use the GCS score to classify TBI into mild, moderate and severe (Teasdale et al., 2014). Other characteristics applied in the classification of TBI is the period of altered or complete loss of consciousness (LOC) or signs of altered brain function like post traumatic amnesia (PTA) (Marshman et al., 2013). A widely accepted definition of mild TBI is a LOC (if present) <30 minutes, PTA (if present) < 24 hours and a GCS score between 13 and 15 (Mild Traumatic Brain Injury Committee). However, some diagnostic criteria like confusion/disorientation and transient neurologic deficits may be difficult to capture. Verification of LOC and PTA can be difficult in situations where patients are intoxicated or in situations when there are no

witnesses to the accident. Therefore a careful clinical interview is often necessary for diagnosis of TBI (Menon et al., 2010). Neuroimaging is not useful as a diagnostic tool for mild TBI. Rather it is used to check for hematomas and to rule out complications from more severe injuries. CT is the standard imaging modality in the emergency department, but there is a growing interest in using MRI in mild TBI-research (Eierud et al., 2014). In the literature patients with findings on CT or MRI are often characterized as complicated mild TBI, while those who do not have findings, are characterized as uncomplicated mild TBI (Iverson et al., 2012)

Neuropathology of mild TBI

The frontal and anterior cortices are assumed to be vulnerable to cortical contusion. Likewise, axonal bundles are vulnerable to rotational and linear forces which may lead to traumatic axonal injury (Eierud et al., 2014). Axonal damage resulting from rotational, acceleration or deceleration forces is termed traumatic axonal injury or diffuse axonal injury and has long been found in patients with TBI (Skandsen et al., 2010b). Neuronal damage in mild TBI is usually not linked to macroscopic damage. Conversely, the pathophysiological process in mild TBI has been linked to microstructural damage, which refers to physical changes not visible in CT or MRI. The pathophysiological process following mild TBI has been described as a neurometabolic cascade of events. These mechanisms can cause an imbalance in ionic flux leading to excessive glutamate release (Giza and Hovda, 2014). Excessive glutamate can induce neurotoxicity where multiple intra- and extracellular events leads to an energy crisis in neurons which eventually may cause cell death (Giza and Hovda, 2014, Wang and Qin, 2010). Cell death, however, is not an inevitable consequence in mild TBI. On the contrary, axonal damage has been found to lead to shrinkage and atrophy of the damaged neuron (Singleton et al., 2002). Still, such severely damaged neurons are assumed to not be capable of normal functioning (Giza and Hovda, 2014). Neuroinflammation is inflammatory responses within the brain and includes activation of cells such as microglia and increased production of inflammatory mediators such as cytokines. Inflammatory responses both within the brain and outside the brain might contribute to abnormal functioning following mild TBI, responses that are independent of cell death (Rathbone et al., 2015).

Axonal injury implies damage to neural networks and this type of damage has been linked to reduced neuropsychological performance in patients with moderate and severe TBI (Giza and Hovda, 2014, Skandsen et al., 2010a). Pathways in neuronal networks are

dependent on axon integrity for normal functioning (Bigler, 2013). In recent years there have been interests in identifying traumatic axonal injury in patients with mild TBI. Though less frequent than in more severe cases, traumatic axonal injury has also been identified in patients with mild TBI (Yuh et al., 2013).

In addition to axonal injury, altered synapses and neurotransmission are common pathophysiology after mild TBI. Axonal injury and impaired neurotransmission following mild TBI have been suggested to be linked to acute neuropsychological impairments like slowed processing and slowed reaction time, in addition to a general reduction in neuropsychological performance (Giza and Hovda, 2014). Inflammatory responses within the brain and outside the brain that follows a mild TBI have in recent years been linked to reduced neuropsychological performance after injury. The association between inflammation and reduced neuropsychological performance has not been closely examined in humans, but are supported by evidence in animal models. Inflammatory responses after a mild TBI are not visible on neuroimaging (Rathbone et al., 2015). Traumatic axonal injury and other lesion types are, however, better detectable with newer imaging techniques and in recent years there has been a growing interest in linking neuropsychological performance to neuroimaging results (Eierud et al., 2014).

Neuroimaging

Microstructural damage associated with mild TBI is not detectable with CT (Giza and Hovda, 2014). Hence, it is not common for patients with mild TBI to have findings on CT imaging (Carroll et al., 2004), and most mild TBI patients fall in the uncomplicated mild TBI category (Iverson et al., 2012). Still, there are studies reporting a minority of patients with mild TBI with lesions visible on CT (Iverson et al., 1999, Sadowski-Cron et al., 2006, Stulemeijer et al., 2008, de Guise et al., 2010, Dagher et al., 2013, Kumar et al., 2014). Traumatic axonal injury, but also other lesion types, are better depicted by MRI than CT (Ashikaga et al., 1997, Mittl et al., 1994). In a recent study 28% of 98 patients diagnosed with mild TBI and normal CT had abnormalities in MRI (Yuh et al., 2013).

MRI sequences such as those based on Fluid-attenuated inversion-recovery (FLAIR) is more sensitive than CT and standard MRI T2 weighted spin echo sequences in detecting smaller lesions, such as traumatic axonal injury (Ashikaga et al., 1997). Adding Susceptibility-weighted imaging (SWI) and Diffusion weighted imaging (DWI) to the MRI sequence increased the sensitivity even more (Edlow and Wu, 2012, Spitz et al., 2013a).

Especially the sensitivity of SWI can be improved by increasing the magnetic field strength from 1.5T to 3T (Spitz et al., 2013a). Sequences with FLAIR, SWI and DWI are now standard in many hospitals (Edlow and Wu, 2012). Other diffusion MRI sequences like diffusion tensor imaging (DTI) are also much used in TBI research to investigate white-matter microstructure (Eierud et al., 2014), such sequences will, however, not be analyzed in this thesis.

Even though MRI has been suggested as a diagnostic tool for mild TBI (Uchino et al., 2001, Voller et al., 2001), it has been disregarded because MRI is not readily available, takes longer time, and is more expensive than CT (Wallesch et al., 2001). However, MRI findings can still give a better picture of the underlying neuropathology and consequences of mild TBI than CT, especially when related to neuropsychological findings, and are therefore often used along with standard CT in TBI research (Eierud et al., 2014).

Complicated mild TBI

By increasing the sensitivity for detecting lesions in newer imaging techniques patients previously categorized as uncomplicated now can be categorized as complicated (Iverson et al., 2012). The WHO Collaborative Task Force has reported an association between disability and complicated mild TBI (Carroll et al., 2004, Carroll et al., 2014). Furthermore, patients with complicated mild TBI have been found to perform worse than patients with uncomplicated mild TBI on neuropsychological measures (Borgaro et al., 2003, Iverson, 2006a, Kurca et al., 2006, Lange et al., 2009). Conversely, in two more recent studies there was no significant difference in neuropsychological performance between complicated and uncomplicated groups, identified with both CT and MRI (Iverson et al., 2012, Panenka et al., 2015). Still patients with complicated mild TBI have been compared and found to have similar neuropsychological outcome as patients with moderate TBI one year after injury (Kashluba et al., 2008). Overall the literature appears to support a negative relationship between a complicated mild TBI and neuropsychological performance, though the effect seems small (Panenka et al., 2015).

With newer and more sensitive techniques more complicated mild TBI patients can be identified (Iverson et al., 2012), enabling comparison between large enough samples of patients with uncomplicated and complicated mild TBI on neuropsychological measures. In the mild TBI literature one of the neuropsychological domains often reported as being affected by injury is attention (Carroll et al., 2014). Assessment of attention is a good

candidate for mild TBI studies because attention-networks are widespread between several brain areas (Petersen and Posner, 2012) and axonal dysfunctions are among the most common pathophysiologies after a mild TBI (Giza and Hovda, 2014). Moreover, frontal areas might be more vulnerable to damage after a mild TBI (Eierud et al., 2014), areas that are associated with neuropsychological attention-performance (Cohen, 2014).

Attention

In the acute stage of mild TBI neuropsychological performance scores on attention are lower for patient groups with mild TBI compared to control groups (Ruff, 2011). In 1890 William James defined attention in the “Principles of Psychology”: *“It (attention) is the taking possession of the mind, in clear and vivid form, of one out of what seem several simultaneously possible objects or trains of thought (...). It implies withdrawal from some things in order to deal effectively with others”* (James, 1890, pp. 403-404). This definition is still being used by authors today (Cohen, 2014). TBI patients with attention deficits usually experience impairments in efficient and flexible processing of the environment. In order to describe how attention is affected after TBI, attention is often quite arbitrary divided into sub-elements or component processes in the literature (Williamson et al., 1996).

In “The Neuropsychology of attention” Ronald A. Cohen reviews years of research to implement an integrated theory of attention. Cohen describes attention as consisting of four elements; I) sensory selective attention, II) Focused attention – capacity, III) Executive attention and IV) sustained attention. These attention-processes are interrelated and can often occur in a temporal sequence. This is evident by the fact that most tasks require all forms of attention, where in certain situations some elements are more important than others (Cohen, 2014).

At an early stage in information processing certain stimuli are prioritized over others and are the subject for further processing. This process is called sensory selective attention and is a covert and relatively automatic process (Cohen, 2014). Sensory selective attention involves both a selection of modality and location (in the environment) (Petersen and Posner, 2012). Shiffrin and Schneider divided attention into automatic and controlled attention (Shiffrin and Schneider, 1984). Similarly, Donald Stuss and his colleagues made a distinction between top-down attention processing and bottom-up attention processing (Stuss et al., 1995, Stuss, 2006). In this sense, sensory selective attention is an automatic process that is the subject to bottom-up processing (Cohen, 2014). The automaticity of sensory selective

attention is evident from the “cocktail phenomenon”, where a person’s attention can be automatically redirected if the person’s name is mentioned in an unattended conversation across the room (Wood and Cowan, 1995). A person can also voluntarily select what to attend to, this volitional selection, however, involves a shift into more controlled processing, which introduces more demand for focused attention (Cohen, 2014).

Focused attention requires more controlled top-down processing than sensory selective attention. The focus of attention varies in intensity and as the task demands increase, more controlled processing is required and the focus becomes more intense (Cohen, 2014). Focused attention is closely linked to the capacity of attention, which refers to the maximal amount of information processing possible at a given time (Kahneman, 1973). Consequently, the attention-capacity and the degree of focus of attention is limited (Cohen, 2014). This limitation is due to the nature of controlled attention, which is processed serially as opposed to automatic attention which can be processed in parallel (Sternberg and Mio, 2009). Working memory (Baddeley, 1986) is therefore important for controlled focused attention (Cohen, 2014, Willmott et al., 2009), because working memory is an active controlled process involving rehearsal and manipulation of temporary stored information, it is affected by load and requires high levels of focused attention (Cohen, 2014). The focused attention is also restrained when attention is allocated to more than one task at a time, which is called divided attention (Cohen, 2014, Williamson et al., 1996).

In addition to requiring more focused attention, controlled processing also increases the demand for executive-attention (Cohen, 2014). Conscious attention is believed to be under the control of a central executive originally introduced by (Shallice, 1982). As mentioned earlier, volitional selection involves a shift to more controlled processing. When the selection of attention enters the awareness it is the subject to conscious processing that is controlled by the executive-attention (Cohen, 2014). The executive-attention is in this way similar to the concept of cognitive control. Cognitive control involves goal directed behavior that is controlled by top down processes (Miller and Cohen, 2001). Similarly, the broader term executive functions involve goal-directed complex processing consisting of several sub-processes (Elliott, 2003). The terms executive functioning, cognitive control and attention are often used to describe similar processes, and the line between them is not sharply drawn (Williamson et al., 1996). Executive functions like abstraction, planning and organization are not directly related to attention, though they certainly require a substantial amount of focused

attention. While functions like selection, initiation, sequencing, maintenance, intention and switching often are categorized as functions of executive-attention (Cohen, 2014).

When demands for sensory selective attention, focused attention and executive attention acts over time, the need for sustained attention increases (Cohen, 2014). Sustained attention is the ability to maintain attention over a period of time (Williamson et al., 1996), is therefore temporal in nature and is in this way separated from the other elements of attention (Cohen, 2014). A great deal of arousal is necessary to maintain alertness and optimal vigilance in tasks requiring sustained attention (Petersen and Posner, 2012, Cohen, 2014). The demand for sustained attention varies according to which process of attention that is required for the task. Controlled processes like focused attention and executive attention, pose more strain on sustained attention than automatic processes like sensory selective attention. Most tasks require all forms of attention, where some processes are more important than others in certain situations (Cohen, 2014).

Neural correlate of attention

The elements of attention can work both in sequence and in parallel and these processes are distributed between several brain regions and have both distinct and shared functional neural correlates. Arousal and alertness is important for maintenance of attention, hence, sustained attention (Cohen, 2014). Specifically projections originating in the locus coeruleus in the brainstem that contain the neuromodulator norepinephrine (NE) has an important role in this type of maintenance (Richardson et al., 2013). NE neurons have major projections to frontal and parietal areas and are important for sustaining vigilance (Petersen and Posner, 2012) and switching of attention to different tasks (Petersen and Posner, 2012, Richardson et al., 2013). Alertness provided by the NE network is important for optimal performance in complex tasks (Fan et al., 2009). The neuromodulator Acetylcholine, with projections originating in the basal forebrain, are important for orienting attention towards sensory stimuli. The orienting of attention (sensory selective attention) is controlled by a dorsal network involving the superior parietal lobe and the frontal eye fields, as well as a ventral network consisting of the ventral frontal cortex and the temporoparietal junction (Petersen and Posner, 2012). These networks are involved in bottom up automatic attention that occur in the early stage of attention processing (Cohen, 2014). Improved sensory attention might be caused by synchronization of the activity in the dorsal and the ventral

orienting networks. In this way the networks can increase the sensitivity of sensory modalities and allow for faster responses (Petersen and Posner, 2012).

When processing demands increase in complex tasks involving focused attention and executive attention, functional neuroimaging studies show increased activation in the anterior cingulate cortex (ACC) and the dorsolateral prefrontal cortex (DLPFC) (Cohen, 2014). Cognitive control theories argue for a single control system, where the prefrontal cortex provide the top down control signals (Miller and Cohen, 2001). There appears, however, to be evidence for two such controlling networks that are involved in the control of attention. The ACC and the DLPFC might be involved in two different, but related networks that pose top down control over tasks involving focused and executive attention; the cingulo-opercular network and the frontoparietal network. The cingulo-opercular network provides top down maintenance of controlled attention. In contrast, the frontoparietal network is thought to control swithing, initiation and adjustments of tasks involving controlled attention (Petersen and Posner, 2012).

Neuropsychological assessment of attention

Compared to healthy persons, patients with brain injury usually make more mistakes and have longer reaction times on neuropsychological tests of attention. Moreover, they tend to perform worse as the complexity of the task increases (Cohen, 2014). A wide range of different neuropsychological tests have been used to assess deficits in attention in patients sustaining a mild TBI (Eierud et al., 2014). Conflict tasks are often being used to assess focused attention and executive attention (Cohen, 2014). In conflict tasks, such as those assessing the classical Stroop effect, reaction times are reduced on incongruent trials compared to congruent trials (Petersen and Posner, 2012). In incongruent trials in the Stroop test for example, participants must name the ink color of a word that indicates another color (e.g. the word RED written in blue ink color) (Sternberg and Mio, 2009). Hence, conflicting information on incongruent trials prolongs the decision making process. Performance on conflict tasks have been used to assess individual differences in the efficiency of attention networks (Petersen and Posner, 2012).

Tasks that require working memory have been one of the main methods of assessing focused attention (Cohen, 2014). Traditionally, working memory has been assessed with tests like the letter span, word span, digit span (Mathias and Wheaton, 2007) and N-back

(McAllister et al., 2001). Most of these tasks measure the amount of items participants can successfully recall, e.g. in the digit span participants are presented an increased number of digits, the number of digits the participants can recall quantifies the working memory capacity and hence the capacity of focused attention (Mathias and Wheaton, 2007). Functional neuroimaging has related working-memory tasks to the DLPFC (Eierud et al., 2014) and parietal regions (McAllister et al., 2001) implicating such task in the frontoparietal attention network.

Neuropsychological tasks that require sensory selective attention, focused attention and executive attention over time depended on sustained attention. Hence, sustained attention is often assessed with neuropsychological tests that continue over time (Cohen, 2014). Visual search tasks have been used to assess sustained attention in TBI-research. In visual search participants are asked to search for a target hidden among distractors (Mathias and Wheaton, 2007). Performance in neuropsychological tasks assessing sustained attention requires participants to maintain a high level of arousal and alertness (Cohen, 2014). Hence, sustained attention-tasks require normal functioning of the NE-network, in addition to requiring normal functioning of the other attention networks, as sustained attention implement all the other elements of attention over time (Petersen and Posner, 2012).

Without a unified theory of attention, many studies rely on different definitions of attention with its different sub-elements (Cohen, 2014). Moreover most of the mentioned traditional pen and paper neuropsychological tests have been criticized as being insensitive, non-specific and lacking ecological validity. Improved approaches have been proposed. In recent years there has been an increasing interest in using computerized neuropsychological tests in both research and clinical practice (Eierud et al., 2014). One increasingly popular computerized neuropsychological test-battery is the Cambridge Neuropsychological Test Automated Battery (CANTAB). This test battery consists of a series of nonverbal tests of cognition including attention (Smith et al., 2013). The CANTAB has been shown to be sensitive in detecting neuropsychological changes in both normal and neurological populations (De Luca et al., 2003, Mehta et al., 2000). Most studies rely on different neuropsychological test-batteries, and at this point, there does not seem to be any consistency in test-batteries used for neuropsychological testing in TBI-research. More sensitive, standardized assessments that are specially adapted to mild TBI are needed to further reduce the limitations of studies focusing on traditional neuropsychological measures (Eierud et al., 2014).

Deficits in attention following mild TBI

The controlled processes of attention, executive control and focused attention, are more affected following mild TBI than automatic processes like sensory selective attention (Cohen, 2014). A patient with neglect syndrome, for example, does not recognize an area in the visual field, despite intact sensory systems, this syndrome involves sensory selective attention and is not common following mild TBI (Williamson et al., 1996). Conversely, TBI-related attention deficits involve controlled attention processes (Cohen, 2014), involving the cingulo-opercular network and the frontoparietal network. The arosal pathways and orienting pathways (sensory selective pathways) does, however, provide an important fundament for efficient processing of attention (Petersen and Posner, 2012). Distruption of any of the networks of attention, e.g. due to traumatic axonal injury, might therefore contribute to impairment in neuropsychological performance following mild TBI.

There is some evidence indicating that neuropsychological deficits can occur also in the absence of structural brain changes visible on CT, conventional MRI (Carroll et al., 2014) and even more sensitive MRI sequences including DTI (Bigler, 2013). These findings suggest that attention deficits, might be caused by structural changes too small to be visualized on neuroimaging, neurinflammatory responses, or psychological factors (Rathbone et al., 2015). These mechanisms, however, also applies to patients with complicated mild TBI, and one could hypothesise that patients with injury related brain changes visible on neuroimaging, especially changes related to networks of attention, would show *more* deficits in attention compared to other patients with mild TBI without findings on neuroimaging.

Most studies observe specific attention deficits in the acute stage following a mild TBI (Haltermann et al., 2006, Kwok et al., 2008, Landre et al., 2006, Malojcic et al., 2008, Mathias et al., 2004, Pare et al., 2009, McAllister et al., 2001). These studies vary however in the types of elements of attention that are reported to be affected after a mild TBI. One study reported mild TBI patients to have reductions in sustained attention and executive attention, but not in focused attention assessed with divided attention tasks (Mathias et al., 2004). Another study reported reductions in sustained attention and focused attention, assessed with working memory tasks, but not in executive attention assessed with duration of decision making (Malojcic et al., 2008). Conversely, one study did not find any difference between healthy control participants and patients with mild TBI on measures sustained attention and focused attention assessed with both divided attention task and working memory tasks (Heitger et al.,

2006). In studies on sports injured athletes with mild TBI there are evidence for impairments in attention in the first hours and days after injury, and attention impairments in sports related mild TBIs usually improve within the first days after injury (Ruff, 2011). Sports related mild TBI are often seen as less severe than mild TBI caused by e.g. falls and motor vehicle accidents (Ruff, 2011, Bigler, 2008).

These findings add further complexity and diversity to the mild TBI. Methodological differences and theoretical differences between studies using neuropsychological tests in TBI research makes it difficult to compare them (Carroll et al., 2014, Mathias and Wheaton, 2007). A recent systematic review investigated neuropsychological outcome in the acute stage in mild TBI patients. Although most studies found reduced neuropsychological performance in mild TBI patients, the type of deficits and magnitude of these varies across studies (Carroll et al., 2014). Moreover, the majority of patients with mild TBI appear to recover from neuropsychological impairment during the acute period (Bigler, 2008).

Post-concussion symptoms

There is a debate whether the impairment in attention that have been observed following mild TBI is caused by structural brain damage caused by the head trauma or other physical and psychological factors (Ruff, 2011). Self-reported problems with attention are along with self-reported somatic, emotional and other self-reported neuropsychological deficits, referred to as post-concussion symptoms. Common post-concussion symptoms are listed in table 1.

Post-concussion symptoms (table adapted from Al Sayegh et al. 2010)(Al Sayegh et al., 2010)

Physical	Cognitive	Emotional
Headache	Memory deficits	Irritability
Dizziness	Attention/concentration deficits	Depression
Fatigue	Executive function deficits	Anxiety
Visual disturbances		
Noise sensitivity		
Light sensitivity		
Insomnia		

Objectively measured neuropsychological impairment following mild TBI cannot be solely explained by neuropathological damage (Pare et al., 2009). It is possible that neuropsychological impairments are caused by physical and emotional post-concussive

factors (Carroll, 2004). However other factors like pain, acute stress-disorder, prior health and compensation/litigation issues might also affect both reported symptoms and objectively measured neuropsychological impairment (Al Sayegh et al., 2010, Ponsford et al., 2011). Post-concussion symptoms have also been reported following other acute traumas without head injury (Meares et al., 2011), indicating that post-concussive symptoms are not exclusive to mild TBI, and that it is the injury itself that causes post-concussive symptoms (Carroll et al., 2014). Especially factors like pain, anxiety, depression, post-traumatic stress and litigation are factors that are associated with subjective symptoms following most acute traumas (Cassidy et al., 2014).

Conversely, one study comparing patients with mild TBI with patients sustaining other acute traumas found the patients with mild TBI to have significantly more impairment in attention, but not to report more post-concussive symptoms than the trauma controls (Landre et al., 2006). This study potentially controls for the contributions of acute post-concussion factors on attention outcome. However, it is difficult to determine whether the injury severity in the two groups was similar (Carroll et al., 2014). Post-concussion symptoms have been linked to mechanical injuries to the brain like traumatic axonal injury (Maruta et al., 2010). Therefore it is possible that patients with complicated mild TBI might be more vulnerable to post-concussion symptoms than patients with injuries to other parts of the body, as well as patients with uncomplicated mild TBI. However studies examining the correlation between traumatic axonal injury and post-concussion symptoms are mixed (Panenka et al., 2015), and one study did not find patients with complicated mild TBI to report more post-concussive symptoms than uncomplicated mild TBI patients (McCauley et al., 2001). Most cases of mild TBI are not associated with findings on neuroimaging (Carroll et al., 2014). Therefore it is possible that most post-concussive symptoms are either caused by factors too small to be detected on neuroimaging or by other factors, such as inflammatory responses or psychological factors (Rathbone et al., 2015). Either way, to identify the role mild TBI related brain injuries plays on attention it is therefore important consider post-concussive symptoms, prior health, pain and other mild TBI comorbid factors (Ruff, 2011).

Aims

The purpose of this thesis is to assess attention and self-reported outcomes two weeks after a mild TBI, to investigate whether 2 weeks outcome of mild TBI can be related to brain injury visible on neuroimaging and to assess the usefulness of the CANTAB in assessing

attention functions after mild TBI. It was hypothesized that I) Mild TBI patients will perform worse on neuropsychological measures of attention and report more distress on self-reported measures of memory, concentration, depression, anxiety, somatization, sleep, pain and fatigue than healthy matched controls 2 weeks after injury. II) That complicated mild TBI patients will perform worse on neuropsychological measures of attention than uncomplicated mild TBI patients and healthy matched controls 2 weeks after injury

METHODS

Participants

Out of all patients eligible for inclusion in this thesis 32% consented to participate in the project with MRI and neuropsychological testing (See Appendix), leaving 76 patients with mild TBI that were admitted to St. Olavs Hospital department of neurosurgery or admitted to Trondheim municipal clinic. Mild TBI patients were included if they I) were between 16 and 60 years old II) were speaking Norwegian and living in Norway, IV) had not sustained a moderate or severe TBI, V) had not sustained a prior complicated mild TBI, VI) did not have any contradictions for MRI and VII) did not have any severe psychiatric, neurological or medical disease. Primary endpoints, demographic variables and injury related information were registered. The severity of the TBI was measured by the Glasgow Coma Scale (GCS), Post traumatic amnesia (PTA) and level of consciousness (LOC). For the TBI to be classified as mild the patients had a GCS score between 13 and 15, PTA for not more than 24 hours and a LOC no longer than 30 minutes. Injury characteristics of patients are presented in table 1.

A total of 52 participants were recruited for the control group. Participants for the control group were recruited from friends and family of the patients, employees working at St. Olavs Hospital, students at St. Olavs Hospital and friends and family of employees and students at St. Olavs Hospital. The participants were matched with the patient group in terms of age, gender and length of education. Years of education was categorized into low (10-13 years), medium (14-16 years) and high (17-18 years). A comparison of demographic variables between the patient group and control group are listed in table 2.

Persons were included in the control group if they I) were between 16 and 60 years old, II) were fluent in Norwegian and living in Norway, III) did not have any contradictions for MRI and IV) did not have any severe psychiatric, neurological or medical disease. The recruitment of participants for the control group was done in a two-stage process. Participants in the control group in the present thesis comprise the participants recruited in the first stage. More participants will be recruited in the next stage as a part of a bigger project at NTNU and St. Olavs hospital.

Table 1: Patient characteristics, n=76

Variable	Number of patients	Percent
GCS score		
13	2	2%
14	16	21%
15	53	70%
Unknown	5	7%
PTA duration		
No PTA	1	1%
< 1 hour	45	59%
1 hour - 24 hours	25	32%
PTA, but unknown duration	3	4%
Unknown	2	3%
LOC duration		
No LOC	10	13%
< 5 min	30	39%
5-15 min	8	11%
15-30 min	-	-
> 30 min	-	-
Unknown	28	37%
Injury mechanism		
Fall	29	38%
Motor Vehicle accident	8	10%
Bike accident	16	21%
Violence	6	8%
Other	16	21%
Missing	1	1%

Table 2: List of demographic variables: Patient group and control group

Variable	Number of patients with mild TBI (%)	Number of healthy controls Controls (%)
Gender		
Men	46 (61%)	26 (50%)
Women	30 (39%)	26(50%)
Education		
Low education	38 (50%)	16 (31%)
Medium education	24 (31%)	24 (46%)
High education	14 (19%)	12 (23%)
Age		
Mean (SD)	32.08 (13,22)	28.33 (9,51)
15-19 years	11 (14%)	6 (11%)
20-29 years	27 (35%)	32 (62%)
30-39 years	16 (21%)	6 (12%)
40-49 years	9 (12%)	5 (9%)
50+ years	13 (17%)	3 (6%)
Prior uncomplicated mild TBI		
0	41 (54%)	37 (71%)
1	27 (35%)	13 (25%)
2	5 (6%)	2 (4%)
3	3 (4%)	0

Education: low =10-13 years, medium =14-16 years, high=17-18 years

Procedure

Data collection took place between April 2014 and January 2014. The patients either received information about the study personally, at the hospital or received a telephone call as soon as possible after being discharged from the hospital. The patients provided their written consent either after the information about the study was given or at the first assessment. Exclusion for the study was performed on basis of information in the first meeting at the hospital or during a phone call. Some patients were excluded from the study following the first meeting after being screened with a short check list. This was to avoid unnecessary MRI and testing for patients that had to be excluded.

In the patient group MRI was performed within 72 hours after injury. Two weeks after their injury the patients were tested with neuropsychological tests. The control group was tested with neuropsychological tests first and MRI at the same day. Every participant received

a gift certificate (500 NOK/59.6 EUR) for each attendance that included neuropsychological testing. Prior to arrival, the participants had filled out questionnaires handed out during the recruitment. Participants who did not fill out questionnaires prior to arrival were asked to answer the questionnaires after neuropsychological testing. Blood samples of all participants (both patient group and control group) were collected upon arrival. These will be analyzed to identify protein biomarkers relevant for another project. Following blood samples the participants conducted neuropsychological tests. Some participants underwent neuropsychological testing before the blood samples were collected.

Assessments

Neuropsychological tests

The computerized neuropsychological test battery CANTAB was used to assess neuropsychological performance. The testing were conducted by a psychologist and 5 students trained by the psychologist, including the author of this thesis. Subtests in CANTAB are categorized according to function. Functions relevant for the present thesis is attention and executive function which involves the subtests: “Rapid Visual Information Processing”, “Spatial Span”, “Spatial Working Memory” and “Attention Switching Task”

Rapid Visual Information Processing

Rapid Visual Information Processing is a measure of sustained attention. In a box in the middle of the screen numbers from 2-9 rapidly switches in a rate of 100 numbers per minute. The participants must look for a sequence of three numbers, 3, 5, and 7. Whenever the number 7 is shown after 3 and 5 the participants are asked to press a button. Two additional number sequences are added, 2-4-6 and 4-6-8. The participants are asked to press the button when the last number in one of the three number sequences is shown. The test last for 4 minutes and the participants are asked to respond as quickly as possible and at the same time try not to make any mistakes. The outcome measures “RVPA” is a measure of the participants signal detection sensitivity; it quantifies how good the participants are at detecting the target sequences.

Spatial Span

This subtest assesses working memory capacity and is a measure of focused attention. The participants are asked to look at white boxes at the screen. The boxes will sequentially

change color and the participants must try to remember in what sequence the boxes changed color. After every box in each trial has changed color, the participants will hear a sound to indicate that they can start to press the boxes in the same order they changed color. In the first trial 2 boxes change color, the number of boxes will increase gradually up to 9 boxes or until the participants fail to push the correct boxes a given number of times. In this subtest the outcome measure “Span length” is a measure of the longest sequence of boxes the participants can successfully recall.

Spatial Working Memory

The test requires manipulation of visuospatial information and retention and assesses executive attention and focused attention. Colored boxes appear on the screen. The participants must look for blue symbols that are hid inside the boxes. Only one symbol will be hid at a time. When the participants find a blue symbol they must move them over to a black column on the right side of the screen. When a blue symbol is found the same box will never hide another blue symbol, so the participants must remember in which boxes they have found symbols. The number of boxes will increase gradually from 4 to 6 to 8. The outcome measure “Total error” is a measure of how many times the participants revisited a box where a blue symbol already had been found.

Attention Switching Task

This test measures the participants’ ability to switch attention and assesses executive attention and focused attention. Since the test lasts for an amount of time it also gives a measure of sustained attention. Arrows appear on the screen that will point either to the left or right. Before each problem there will be a heading on the top of the screen saying “Which direction?” or “Which Side?”. If the problem is “which direction?” the participants must push the button on the side the arrow is pointing towards, the left button if the arrow is pointing left or the right button if the arrow is pointing right. If the heading on the screen is saying “which side?” the participants must push the button on the side of the screen the arrow appears. If the arrow is on the left side they push the left button, if the arrow is on the right side they push the right button. The participants learns each rule separately first, before they are tested with both rules, switching at random. The attention switching task provide the outcome measure “Congruency cost”. “Congruency cost” measures the difference in response time on congruent and incongruent trials. If the arrow is located at the same side as it point to, the trial

is congruent. If the arrow is located on the opposite side as it points to, the trial is incongruent.

The participants did also go through other subtests in CANTAB and other pen and paper neuropsychological test, including the Trailmaking Test A and B, auditory verbal learning test and verbal fluency in addition to selected items from Wechsler Abbreviated Scale of Intelligence and the Wechsler Adult Intelligence Scale as a part of a bigger project at St.Olavs Hospital. These tests are not relevant for this thesis, and will not be described here. The duration of the neuropsychological assessment was approximately 2 hours.

Questionnaires

The patients were asked to fill out questionnaires about their functioning before their injury. These questionnaires included symptoms check for ADHD, questions about headache, questions about alcohol use, questions about personal characteristics, a life orientation test, questions about life events, problems the last 12 months and a resilience scale for adults. In addition the participants were asked to fill out questionnaires about their functioning two weeks after their injury. These questionnaires included selected items from the Rivermead Post Concussion Symptom Questionnaire, Epworth Sleepiness Scale, Brief Symptom Inventory 18 and the Fatigue Severity Scale. Questionnaires about functioning two weeks after injury are relevant for analysis in this thesis. Of the premorbid questionnaires only the ADHD questionnaire was relevant, and was used for descriptive purposes.

Symptom check-list ADHD

This check-list consists of 18 questions divided into two parts, A and B. The first six questions make up part A and are the questions that predict ADHD best. Only part A will be used in this thesis. Items are rated on a five-point scale. Participants get a score based on how they rate themselves on these questions that either indicates ADHD or not (Kessler et al., 2005).

The Epworth Sleepiness Scale

The Epworth sleepiness scale consists of 8 items measuring self-reported sleepiness. The 8 items represents real life situations where the participants must rate their chance of dozing off using a four point scale, 0-3. Total score indicates the extent of self-reported sleep propensity. Total score values above 11 is an indicator of increased sleepiness (Johns,

1991). The Norwegian version of the Epworth sleepiness scale has high reliability (Beiske et al., 2009) and high validity (Pallesen et al., 2007).

The Brief Symptom Inventory 18 (BSI 18)

BSI-18 measure self-reported psychological distress with 18 items, each of which rated at a five point scale, 0-4. Total score measures self-reported general psychological distress. The items can be subdivided into the domains anxiety, depression and somatization, consisting of 6 items each (Andreu et al., 2008), as well as measuring general psychological distress (Derogatis, 2000). BSI-18 has been found to be valid and reliable in assessing psychiatric changes in patients (Andreu et al., 2008). Clinical significant psychological distress is defined as a T-score above 63 in one of the subdomains (Derogatis, 2000).

The Fatigue Severity Scale

The fatigue severity scale measures self-reported feelings of fatigue with 9 items rated at a 7 point scale, 1-7. Higher scores indicate subjective feelings of fatigue. Total score gives the participants subjective fatigue score and scores over 36 is defined as clinical significant fatigue (Krupp et al., 1989). The fatigue severity scale has been found to be sensitive to detecting fatigue following TBI (Ziino and Ponsford, 2005)

Rivermead Post Concussion Symptom Questionnaire (RPCSQ)

RPCSQ measures self-reported symptoms of concussion including headache, dizziness, memory, nausea and attention. It includes 16 items rated at a five-point scale, 0-4. The RPCSQ has been reported to have; high internal consistency, high split half reliability and high validity (Sullivan and Garden, 2011). Two items concerning memory and concentration were selected for comparison between patients and controls.

The British Columbia Post Concussion Symptom Inventory (BC-PSI)

In the BC-PSI participants rates post-concussive symptoms in frequency and intensity the past two weeks. Both frequency and intensity are rated at a six-point scale, 0-5. Higher scores indicate higher frequency and higher intensity (Iverson, 2006b). BC-PSI has been reported as having; high internal consistency, high split half-reliability and high validity (Sullivan and Garden, 2011).

Controls were asked to fill out the same questionnaires as the patients, except that the controls did not receive the RPCSQ. In the main study, where the data used in this thesis were

gathered from, self-reported post-concussion symptoms are assessed with the BC-PSI at 3 month follow up. At 3 month follow up both the patient group and the control group are asked to fill out the BC-PSI. Since the control group did not receive the RPCSQ at the 2 week assessment, self-reported memory and concentration for the control group were selected from two items from the BC-PSI the controls filled out at the 3 month follow up. Hence, two different questionnaires had to be used to compare the patient group and control group on self-reported measures of concentration and memory. The BC-PSI and the RPCSQ have been compared and has been found to have a significant moderate positive correlation (0.78) (Sullivan and Garden, 2011). To analyze the questions the scales were recalculated to enable comparison. The RPCSQ used the question “Compared with before the accident, do you now (i.e., over the last 24 hours) suffer from: “Poor concentration”/”Poor memory”. RPCSQ defines each number in the scale as: 0: Not experienced at all, 1: No more of a problem, 2: A mild problem, 3: A moderate problem and 4: A severe problem. The BC-PSI asks the participants to “Grade your symptom on how much you suffer from, the last two weeks included today: “Poor concentration”/”Poor memory”. The intensity scale in the BC-PSI is the most comparable to the RPCSQ and the number in the scale are defined as: 0: No complaints, 1: Barely noticeable, 2: A mild problem, 3: A moderate problem, 4: A serious problem and 5: A severe problem. Alternative 4 and 5 was combined to enable comparison with the RPCQ.

Patients were interviewed during the first meeting at the hospital. Questions relevant for this thesis were questions about work, prior TBI and injury mechanism. At the first assessment patients were asked about sick leave, medications, sleep the night prior to testing, pain at the test day and food intake prior to neuropsychological testing. The question about pain provided a measure that was analyzed along with the other self-reported measures. Participants were asked to rate their pain on a scale of 0-100. Controls received similar questions at the day of the neuropsychological testing.

MR Imaging

Patients and controls were examined with MRI using a 3 Tesla system (Siemens Skyra) and a protocol consisting of clinical sequences: T1, T2, fluid-attenuated inversion recovery (FLAIR), susceptibility weighted imaging (SWI) and diffusion-weighted imaging (DWI), as well as Diffusion Tensor Imaging (DTI) and Diffusional Kurtosis Imaging (DKI). The DTI and DKI images were not relevant for this thesis. The examination lasted for about

45 minutes. Patients were examined within 72 hours after injury. A neuroradiologist inspected the images and in case of intracranial traumatic findings, the patients were categorized as having a complicated mild TBI.

Ethics

With extensive testing some patients might perceive their symptoms as more severe than they normally would. However it is likely that patients will find it comforting to be taken care of at the hospital. MRI scans were reviewed by a neuroradiologist and in the case of incidental findings a specialist in brain injury rehabilitation made a decision of further action. None of the methods used in the thesis pose any harm for the participants. Participants got sufficient information to give a written consent. The project is approved by the regional committee for medical research ethics (REK).

Statistics

IBM SPSS 20.0 was used for analysis. Chi-square tests were used to investigate the similarity between the patient and control group on the matched variables gender and length of education. An independent sample T-test was used to investigate possible differences in mean age between the patient group and control group. Pearson product-moment correlation was applied to investigate the relationship between age and CANTAB results and between length of education and CANTAB results.

A 3x4 one way between-groups multivariate analysis of variance (MANOVA) was performed to investigate group differences in neuropsychological measures of attention. The selected outcome measures: “RVP: RVPA”, “SSP: Span length”, “SWM: Total error” and “AST: Congruency cost” was used as dependent variables. The groups complicated mild TBI, uncomplicated mild TBI and healthy controls were used as fixed factors. Preliminary assumption testing for linearity, normality, univariate and multivariate outliers, multicollinearity and homogeneity of variance –covariance matrices was conducted. Z-scores for both the control group and the patient group were calculated to identify possible univariate outliers. Univariate results for the differences in mean between CANTAB outcome measures for patients and control was also reported. These results were however treated with caution as the familywise error, risk of type I error, increases with repeated univariate measures (Field, 2013).

Independent sample t-tests were used to analyze the mean difference between patients and controls in self-reported depression, anxiety, somatization, fatigue, memory, attention and sleepiness. Preliminary assumption testing for linearity and normality was conducted. Normality was assessed by using the Kolmogorov-Smirnov test, calculating Z-scores for both the control group and the patient group and by looking at normal QQ-plots. In case of non-normality a Mann Whitney U test was used to analyze the median difference in the self-reported measures. A Bonferroni correction according to number of tests was performed to reduce the family wise error.

T-scores for the depression, anxiety and somatization scores were calculated to identify participants over clinical cut off. The fatigue, sleepiness, depression, anxiety and somatization scores were categorized into over and under clinical cut off. 2x2 Chi-square tests were used to investigate if there were any difference in distribution of patients over clinical cut-off between the patient group and control group. For scores that were small with expected values under 5 in any cell, exact z pooled tests was conducted.

Adjustments

The patient group and the control group were, as a part of a bigger cohort study at St. Olavs Hospital, matched in terms of gender, length of education and age. The inclusion of control participants for the control group was not completed by the time the present thesis was written. Patients and controls are therefore not perfectly matched. There were 13 patients over 50 years, and 3 controls over 50 years. Additionally 2 out of 5 extreme outliers in the CANTAB results (Z-score over 3.29) were scored by patients over 50 years. A Pearson product-moment correlation was applied to investigate the relationship between age and CANTAB results. There were small to moderate correlations between three out of four CANTAB results and age (Table 4).

Since there was a different distribution of persons over 50 years of age in the control group and the patient group, some of these persons tended to score in the lower end of the distribution in several of the CANTAB tests and three CANTAB dependent variables were correlated with age, participants over 50 years of age were excluded from the thesis.

Table 3: Group characteristics: Patient and control group, participants <50 years old excluded, (N=111, n patients= 62, n controls = 49).

Variable	Mild TBI N (%)	Controls N (%)	P=
Gender			
Men	39 (63%)	25 (51%)	P=0.20
Women	23(37%)	24(49%)	
Education			
Low education	32 (52%)	16 (33%)	P= 0.09
Medium education	18 (29%)	23 (47%)	
High education	12 (19%)	10(20%)	
Age			
Mean (SD)	27.7 (9.8)	26.7 (7.1)	P= 0.641
15-19 years	11 (18%)	6 (12%)	
20-29 years	26 (42%)	32 (65%)	
30-39 years	16 (26%)	6 (12%)	
40-49 years	9 (14%)	5 (10%)	
Prior uncomplicated TBI			
0	32 (52%)	34 (69%)	
1	22 (35%)	13 (27%)	
2	5 (8%)	2 (4%)	
3	3 (5%)	0	
Over cut off for ADHD			
Yes	7 (11%)	6 (12%)	
No	49 (79%)	35 (71%)	
Missing	6 (10%)	8 (16%)	
Work			
Yes	32 (52%)	28 (57%)	
No	3 (4%)	3 (6%)	
Student	27 (44%)	18 (37%)	
Admitted/Not admitted			
Inpatient	18	29%	
Outpatient	44	71%	

Education: low =10-13 years, medium =14-16 years, high=17-18 years

RESULTS

Overview of the patient and control group without participants over 50 years old is listed in table 3. After removing persons over 50 years old, the mean age was more similar between the groups. An independent samples t-test showed no significant difference in mean age between the mild TBI group (M= 27.48, SD=9.72) and healthy controls (M=26.73, SD=7.13: $t(108.4) = 0.47, p=0.641$, two tailed). There were no statistical difference between the distribution of gender between the patient and control group, ($\chi^2_1, N= 111=1.134 p=0.29$ phi=0.21) and no significant difference in the distribution of length of education between the patient and the control group ($\chi^2_1, N= 111=4.67 p=0.097$ Cramer's V= 0.205). A Pearson product-moment correlation coefficient revealed no significant correlations between length of education and CANTAB dependent variables (table 5). It was therefore not performed any further adjustments.

Table 4: Pearson correlation between age and CANTAB dependent variables

Variable	AST: Congruency Cost	RVP: RVPA	SSP: Span Length	SWM: Total errors
Age	$r=0.23^{**}$	$r=-0.11$	$r=-0.48^{**}$	$r=0.36^{**}$

* Correlation significant at 0.05 level, ** Correlation significant at the 0.01 level

Table 5: Pearson correlation between length of education and CANTAB dependent variables

Variable	AST: Congruency Cost	RVP: RVPA	SSP: Span Length	SWM: Total errors
Length of education	$r=0.08$	$r=-0.19$	$r=-0.08$	$r=0.03$

Imaging results

A total of 7 out of 62 patients (11%) with mild TBI had intracranial lesions visible on MRI or CT. One of these patients had a visible intracranial lesion on CT, but did not complete the MRI. 6 patients had therefore intracranial lesions on both MRI and CT. None of the patients that were older than 50 years had intracranial lesions on CT or MRI. Hence, 7 out of 62 patients were qualified for the complicated mild TBI group. A sample size of 7 was considered too low to make up a group for analysis. Z-scores for the CANTAB scores for both the patient group and the control group were calculated as a part of preliminary analysis. The CANTAB Z-scores for the patients with complicated mild TBI, obtained from the mild

TBI patients CANTAB Z-scores, were decided to be reported to look for trends in the neuropsychological measures of attention. CANTAB z-scores for patients with complicated mild TBI are listed in table 6.

Table 6: CANTAB Z-scores complicated mild TBI patients (n=7)

Patient	Z-score AST: Congruency cost	Z-score RVP: RVPA	Z-score SSP: Span Length	Z-score SWM: Total errors	GCS	PTA	LOC
1	-0.200	1.167	0.122	-0.355	15	1 hour - 24 hours	<5 min
2	-0.971	1.122	0.122	-0.769	15	<1 hour	<5 min
3	-0.763	-1,877	0.123	0.676	13	1 hour - 24 hours	5-15 min
4	-0.113	-0.392	-1.197	-0.493	15	1 hour - 24 hours	Unknown
5	1.629	0.137	0.122	-0.906	15	1 hour - 24 hours	Unknown
6	0.588	0.472	0.783	0.126	15	< 1 hour	5-15 min
7	-1.046	-1.357	-0.537	-0.356	14	1 hour - 24 hours	5-15 min

Most of the mild TBI patients with findings on CT or MRI had Z-scores that indicated that they did not differ from other mild TBI patients. One patient had a low z-score on “RVP: RVPA” (-1,877), indicating poorer signal detection sensitivity. Another patient had a high score on AST: Congruency cost (1.629) indicating slower responses on incongruent trials (faster responses on congruent trials). These scores did not, however, indicate a significant difference (+/- Z-score of 1.96). 5 out of 7 patients with complicated mild TBI had PTA duration between 1 hour and 24 hours and 3 out of 7 patients with complicated mild TBI had LOC duration between 5 and 15 minutes.

Because the complicated mild TBI group was so small the analysis of the CANTAB results was performed between the patient and the control group using a 2x4 multivariate analysis (MANOVA).

CANTAB Results

No serious preliminary assumptions for the MANOVA were violated. Scatter-plot matrices between each pair of the dependent variables indicated linear relationships. The dependent variables were skewed and kurtotic. AST: Congruency Cost and SSP: Span length skewness and kurtosis did not differ significantly from normality (skewness and kurtosis z-scores between -1.96 and 1.96) and had normal QQ-plots. The dependent variables RVP:

RVPA and SWM: total errors had skewness and kurtosis scores that differed significantly from normality (skewness and kurtosis z-scores outside -1.96 and 1.96). These violations of normality were considered as minor, as MANOVA is robust to violations of normality (Pallant, 2010). Preliminary assumption testing for univariate outliers identified three scores characterized as extreme outliers (z-score > 3.20). Extreme outliers were winsorized into the highest score that was not an outlier. One multivariate outlier was identified using Mahalanobis distance, belonging to a patient, this participant was removed from the multivariate analysis.

Pearson product moment correlation coefficient showed appropriate statistical significant correlations between the dependent variables (Table 7). The Box's Test of Equality of Covariance Matrices was significant and hence, the assumption of homogeneity of variance-covariance was not violated. Because of different distribution of participants in the patient group (n= 62) and the control group (n=49) Pillai's trace was the preferred statistic as it is robust to unequal n-values (Pallant, 2010).

Table 7: Pearson correlation between the dependent variables

Variable	AST: Congruency Cost	RVP: RVPA	SSP: Span Length	SWM: Total errors
AST: Congruency Cost	r=1	r=-0.34**	r=-0.38**	r=0.21*
RVP: RVPA		r=1	r=0.28**	r=-0.18*
SSP: Span Length			r=1	r=-0.35**
SWM: Total errors				r=1

* Correlation significant at 0.05 level, ** Correlation significant at the 0.01 level

Table 8: Multivariate and univariate analysis of CANTAB variables

Variable	MANOVA	Group	n	Mean (SD)	95% CI of means	P	Effect size: η^2
F (0,607,)= , P= 0,658, η^2 = 0,22							
AST:		MildTBI	62	94.33 (72.52)	74.57-114.09	0.176	0.017
Congruency cost		Control	49	73.89 (85.51)	51.66-96.12		
RVP:RVPA		MildTBI	62	0.91 (0.05)	0.903-0,929	0.975	0.000
		Control	49	0.91 (0.04)	0.902-0,930		
SSP: Span Length		MildTBI	62	6.97 (1.42)	6.61-7.33	0.522	0.004
		Control	49	7.14 (1.43)	6.74-7.55		
SWM: Total errors		MildTBI	62	9.63 (10.17)	6.96-12.30	0.793	0.001
		Control	49	10.16 (11.13)	7.16-13.16		

AST: the Attention Switching Task. RVP, Rapid Visual Information Processing, SSP, Spatial Span, SWM, Spatial working memory

η^2 : Partial eta squared, variance explained by the four dependent variables

There were no statistical significant differences between the mild TBI group and the control group regarding the combined dependent variables, ($F(5,105) = 0.537$; Pillai's Trace = 0.748; Partial eta squared = 0.02). None of the dependent variables reached statistical significance when looked at separately (univariate results). The CANTAB results were highly similar for the patient and control group, there was however a small tendency for the control group ($M=94.33$, $SD=72.52$) to respond faster on incongruent trials than the patient group ($M=73.89$ $SD= 85.51$) on the Attention Switching Task, but this difference was not significant.

Self-report results

Preliminary analysis showed that Fatigue Severity Index scale scores had kurtosis and skewness z-scores that did not differ significantly from normality for the mild TBI group and the control group (z-scores within z-scores of -1.96 and 1.96). In addition the Kolmogorov-Smirnov test was not significant for both the mild TBI group ($p=0.068$) and the control group ($p=0.198$) at a 0.05 significance level. Histograms and normal QQ-plots looked approximately normal. Therefore was the assumption of normality met for the fatigue scores. The scores for somatization, anxiety, and depression measured with the Brief Symptom Inventory 18 had skewness and kurtosis z-scores that differed significantly from normality, except the control group's kurtosis z-value on the anxiety score. All of these scores had significant Kolmogorov-Smirnov tests for both the mild TBI group and control group. Histograms and normal QQ-plots did not look normally distributed. The Epworth sleepiness scale scores had according to the skewness and kurtosis z-scores, the Komologorov-Smirnov test, histograms and normal QQ-plots normally distributed data for the control group, but not the patient group. Memory and Concentration scores obtained from the Rivermead Post Concussion Symptom Inventory and the British Columbia Post Concussion Symptom Inventory as well as the pain measures was not normally distributed.

Differences between the mild TBI group and control group regarding self-reported fatigue was analyzed using an Independent samples T-test. Differences between the mild TBI group on self-reported anxiety, depression, somatization, memory, attention, sleepiness and pain were analyzed using Mann Whitney U tests. Due to multiple comparisons a Bonferroni correction according to number of measures was performed, the new significance level was set at 0,006. Differences between the patients and controls in distribution over and under clinical cut-off were investigated using 2x2-Chi-square tests for the self-reported variables fatigue, sleepiness and somatization, and with exact z pooled tests for the depression and anxiety cut of scores, as these scores had cells with expected value less than five.

Table 9: Analysis of self-reported measures.

Variable	Group	N	Mean(SD)/ Median (IR)	P	Effect size η^2/r	Participants over cut- off (%)	Chi-square over cut off/ under cut off
Fatigue	Mild TBI	56	M: 30.23 (12.59)	0.16	$\eta^2=0.01$	16	p= 0.43
	Control	41	M:26.88 (10.15)			8	
Sleepiness	Mild TBI	57	Md: 5.00 (15)	0.95	$r=-0.007$	15	p=0.16
	Control	34	Md: 5.50 (10)			4	
Somatization	Mild TBI	56	Md: 0.0 (5)	0.01	$r=-0.26$	12	p=0.094
	Control	34	Md: 0.0 (2)			1	
Depression	Mild TBI	56	Md: 0.0 (2)	0.45	$r=-0.078$	5	p= 0.344
	Control	34	Md: 0.0 (4)			4	
Anxiety	Mild TBI	56	Md: 0.0 (3)	0.13	$r=-0.160$	9	p=0.051
	Control	34	Md: 0.0 (2)			1	
Memory	Mild TBI	55	Md: 0.0 (2)	0.002*	$r=-0.32$		
	Control	38	Md: 0.0 (0)				
Concentration	Mild TBI	54	Md: 1,00 (2)	0.000*	$r=-0.39$		
	Control	38	Md: 0.00 (0)				
Pain	Mild TBI	61	Md: 5.0 (30)	0.000*	$r=-0.42$		
	Control	49	Md: 0.0 (0)				

* Significant at the 0.006 level.

SD= Standard Deviation, IR=Interquartile Range, η^2 = partial eta squared, $r= 0.1$ small effect, 0.3 medium effect, 0.5 large effect

There was a statistical significant difference between mild TBI patients and healthy controls in self-reported measures of memory, concentration and pain and all the significant results had medium effect sizes. There was no statistical significant difference in fatigue scores for mild TBI patients and healthy controls conducted with an independent samples t-test. There were no statistical significant difference between mild TBI patients and healthy controls on self-reported measures of sleepiness, depression, somatization and anxiety conducted with Mann Whitney U tests.

The distribution of participants over and under the clinical cut-off value was not significant for any of the self-reported measures. There was, however, a non-significant tendency for patients to report more scores over cut-off for somatization and anxiety compared to controls.

DISCUSSION

The aim of this thesis was to investigate the effects of mild TBI on neuropsychological measures of attention 2 weeks after injury, and to investigate if possible impaired performance on measures of attention could be related to brain injuries visible on neuroimaging, and to assess the usefulness of the CANTAB in detecting impairments in attention after mild TBI. Specifically to assess whether patients with mild TBI would perform worse than healthy controls on neuropsychological measures of attention, and to assess whether patients with abnormalities on neuroimaging, i.e. complicated mild TBI, would perform worse than patients without such findings. In addition were self-reported measures on depression, anxiety, somatization, sleep, pain and fatigue compared between the patients with mild TBI and healthy controls to assess whether patients reported more complaints on self-reported measures.

Based on the results obtained in this thesis the hypotheses were not supported. There was no significant difference in neuropsychological performance on attention between mild TBI patients and control persons neither in multivariate nor univariate analysis. The group of patients with complicated mild TBI (7 out of 76 patients) was not large enough to statistically analyze whether complicated mild TBI patients perform worse than uncomplicated mild TBI patients and healthy controls on neuropsychological measures of attention. Though mild TBI patients did not score significantly worse on neuropsychological measures of attention; the mild TBI patients reported significantly more problems with concentration, memory and pain than controls on self-report measures. There was no significant difference between patients and controls on self-reported fatigue, sleepiness, depression, somatization and anxiety, though the patient group had a tendency to report more problems with somatization than the control group.

Neuropsychological performance on measures of attention

There was no statistical difference in performance on measures of attention between control persons and mild TBI patients two weeks after injury. This was surprising, and not consistent with recent reviews reporting that most mild TBI studies find impairments in neuropsychological measures of attention in the acute stage (Carroll et al., 2014, Ruff, 2011). Specific impairments of attention have been found in focused attention (Haltermann et al., 2006, Kwok et al., 2008, Malojcic et al., 2008, Mathias et al., 2004, Pare et al., 2009, Landre et al., 2006), executive attention (Haltermann et al., 2006, Landre et al., 2006, Mathias et al.,

2004) and sustained attention (Kwok et al., 2008, Malojcic et al., 2008, Landre et al., 2006). However, some of these studies also found non-significant results on other specific elements of attention, and it varied across studies which type of attention-element that was affected. Some of these studies are less comparable with this thesis, Kwok et al. (2008) included only patients with findings on CT, Malojcic et al. (2008) performed neuropsychological assessment from 6 to 155 days after injury and Halterman et al. (2006) included few patients, with injuries mostly caused by sports injuries.

Most patients included in this thesis had GCS scores of 15 (68%), 16 patients had GCS scores of 14 (21%) and only 2 patients had GCS scores of 13 (2.6%). Most patients also scored in the lowest category of PTA and LOC duration. This distribution of injury severity is typical for patients with mild TBI (Meares et al., 2008). Moreover, the sample of patients with mild TBI in this thesis is consistent with previous studies along demographic variables like age, gender and education; most patients are young, have low education and there are more men than women in the sample, which are common characteristics representing patients with mild TBI (Heitger et al., 2006). We believe that the sample in this thesis is fairly representative for the population of patients with mild TBI. Some of the patients recruited were difficult to get a hold of and some patients did not want to participate, therefore there were some patients with mild TBI that did not participate in this thesis (see Appendix).

Five previous studies investigated differences between patients with mild TBI and controls on neuropsychological measures of attention, and recruited patient groups with comparable injury severity as the patients used in this thesis (Landre et al., 2006, Pare et al., 2009, Heitger et al., 2006, Meares et al., 2008, Mathias et al., 2004). However, these studies obtained different results from one another. Two studies found patients with mild TBI to have impairments in attention at approximately 1 week after injury (Pare et al., 2009, Landre et al., 2006). Pare et al. (2009) found patients with mild TBI to perform significantly worse than healthy controls on measures of focused attention assessed with divided attention tasks, patients had, however, significantly shorter education than controls, which is a possible confounder to the results in this study. Landre et al. (2006) found patients with mild TBI to perform significantly worse than patients with other traumatic injuries on measures of sustained attention, focused attention assessed with vigilance tasks and executive attention assessed with distractibility tasks. Mathias et al. (2004) compared mild TBI patients to matched healthy controls 4 weeks after injury and found mild TBI patients to perform significantly poorer on measures of sustained attention and executive attention assessed with

switching tasks while focused attention assessed with divided attention tasks was intact (Mathias et al., 2004).

The findings in this thesis are in line, however, with the results obtained by Heitger et al. (2006) and Meares et al. (2008). Similar to Landre et al. (2006), Meares et al. (2008) compared patients with mild TBI to patients with other traumatic injuries. As opposed to the results obtained by Landre et al. (2006), Meares et al. (2008) found no significance difference between patients with mild TBI and patients with other traumatic injuries on measures of focused attention assessed with working memory tasks. The study by Meares et al. (2008) is also superior to the other previous studies in terms of sample size (N=175). Heitger et al. (2006) compared patients with mild TBI to healthy matched controls and found, similar to this thesis, no difference between patients with mild TBI and controls on measures of sustained attention and focused attention assessed with both divided attention tasks and working memory tasks 1 week after injury.

The patients in this thesis were tested two weeks after injury. It is possible that patients in this thesis recovered from potential neuropsychological impairments by this time. Most synaptic reorganization following injury occurs during the acute stage (Povlishock and Katz, 2005), and the majority of mild TBI patients recover from acute symptoms after minutes, hours and days post-injury (Bigler, 2008). Schretlen and Shapiro (2003) studied the neuropsychological effects of TBI in a meta-analysis. The authors found a moderate effect size (d-pooled -0.41) of patients with mild TBI tested during the first six days after injury compared to matched controls. This effect size was trivial beyond 1 month after injury (d-pooled -0.08) indicating that most patients with mild TBI recover from neuropsychological impairments by this point (Schretlen and Shapiro, 2003).

Landre et al. (2006) suggested a relationship between injury mechanism and recovery pattern after mild TBI. For example, sports related mild TBI appear to be less severe than mild TBI caused by other mechanisms like falls or motor vehicle accidents (Bigler, 2008). In this thesis most mild TBIs were caused by falls (37%), bike accidents (20%) and other causes (20%). Bigler (2008) argued for some evolutionary aspects of mild TBI. Genes that have promoted positive recovery after mild TBI have likely been passed down. These mechanisms would, however, only be applicable to causes of mild TBI that also occurred prior to the modern area like falls, combat, fist-fights etc. and not to accidents in newer times, occurring in high speeds, such as motor vehicle accidents (Bigler, 2008). Based on this, one could

speculate that “newer” forms of injury like motor vehicle accidents might cause worse outcome for patients with mild TBI. This is supported by a recent systematic review that linked motor vehicle accidents to worse outcome after a mild TBI (Cassidy et al., 2014). Mild TBI caused by motor vehicle accidents accounted for 10% of the total injury mechanisms in this thesis. Moreover, several of the patients with mild TBI that had “Other” causes of mild TBI, experienced sports related mild TBIs.

It is a possibility that there was a larger proportion of patients with injury mechanisms that are not as severe included in this thesis compared to previous studies. Mathias et al. (2004) included patients with mild TBI caused by motor vehicle accident, falls, assaults and other causes. The authors did not, however, report how many participants that were included in each category of injury mechanism. Landre et al. (2006) found non-sports injured patients with mild TBI to perform significantly worse on measures of attention than patients with other trauma injuries. It is, however, noteworthy that only 37 patients with mild TBI were recruited over a two year period in the study by Landre et al. (2006), which makes a selection bias likely. Additionally, it is difficult to determine whether the injury severity was similar in the two patient groups. Meares et al. (2008) had similar samples of both patients with mild TBI and patients with other traumas as Landre et al. (2006). Meares et al. (2008) had however a much larger sample of patients in both patient groups than Landre et al (2006) and did not find any significance difference in measures of attention. The majority of injuries in the study by Meares et al. (2008) were caused by motor vehicle accidents (81% mild TBI, 74% in other traumas). Therefore one would expect patients with mild TBI to perform worse than other trauma patients, if motor vehicle accidents causing mild TBIs are more severe. Conversely, the authors did not find any difference between the two patient groups.

Self-reported measures

In this thesis the patients with mild TBI reported significantly more complaints on the self-reported measures on memory, concentration and pain compared to healthy controls. The patients did not differ from control persons on self-reported measures of depression, anxiety, somatization, fatigue and sleepiness. Moreover, there was no significant difference between patients and controls in distribution of values above clinical cut-off values in any of these measures. There was, however, a tendency for patients to report more values above clinical cut-off on measures of anxiety and somatization compared to controls. It is noteworthy that mild TBI patients reported more complaints with concentration and memory given that mild

TBI patients did not perform significantly worse than controls on neuropsychological measures of attention in this thesis. Potential slowed processing and reduced neuropsychological functioning after a TBI might be compensated by greater effort (Cohen, 2014). Therefore it is possible that the patients with mild TBI included in this thesis had some neuropsychological impairment, but were able to compensate with greater effort and enhance their performance. These findings might indicate that the CANTAB subtests assessing attention, used in this thesis, are not complex enough, as neuropsychological tasks, must be sufficiently complex for the effort not to matter (Cohen, 2014). However, most CANTAB subtests used in this thesis appear to be sensitive enough in detecting impairments in attention (see discussion below). Additionally, there are some limitations to the self-reported measures on concentration and memory as these measures are assessed with two different questionnaires for the patient group and control group (Strength and limitation section below).

Factors like pain have been suggested to contribute to self-reported post-concussive symptoms like concentration and memory, as well as observed neuropsychological impairments (Ponsford et al., 2011). In this thesis the patients with mild TBI reported significantly more complaints with pain, as well as a tendency towards more complaints with somatization compared to controls. These symptoms might therefore contribute to the increased self-reported complaints on concentration and memory, experienced by the patients with mild TBI. Pain after mild TBI has been linked to prolonged post-concussion symptoms (Bigler, 2008). Additionally, possible compensation mechanisms like increased effort might be contributors to the fatigue and poorer emotional long term outcome seen in some patients after mild TBI (Cohen, 2014). Therefore it is important to follow up the group of patients in this thesis to assess whether the pain persist beyond the acute phase and to assess further emotional changes. This will be done as a part of the main project, where patients will be re-assessed both at 3 months and 1 year after injury.

Although there was no statistical significant difference between patients with mild TBI and healthy controls on self-reported measures on sleepiness, fatigue, anxiety, depression and somatization, some patients reported over normal cut-off values on these self-reported measures. Scores above these cut-off values indicates clinical significance. 12 patients reported over normal cut off for somatization, 9 patients reported over normal cut off for anxiety, 16 patients reported over normal cut off for fatigue, 15 patients reported over normal cut off for sleepiness and 5 patients over normal cut off for depression. Therefore it might be a subpopulation of patients included in this thesis that have symptoms indicating post-

concussion symptoms. Bigler (2008) argued that total group effects can wash out clinical important symptoms, and a better solution is to compare symptomatic vs. non-symptomatic patients with mild TBI on neuropsychological tests. Studies that use this solution usually find symptomatic patients to perform worse on neuropsychological tests compared to non-symptomatic patients (Bigler, 2008). However, in this thesis there does not seem to be a relationship between the self-reported measures, e.g. those who score above cut-off for fatigue does not score above the cut-off for anxiety. 1 patient scored above cut-off on 4 measures, 4 patients scored above cut off on 3 measures, 11 patients scored above cut-off on 2 measures and 18 patients scored above cut off only on one measure. Additionally, some of the healthy controls also scored above clinical cut off in some of the self-reported measures and there was no significant difference between patients and controls on the distribution of scores above cut-off for any of the self-reported measures. Based on the low number of patients above clinical cut-off on the different self-reported measures and that some healthy controls also scored above clinical cut-off in some measures, it is difficult to relate these findings solely to the head impact. Still it is possible that the post-concussion symptoms experienced by some patients with mild TBI in this thesis might be related to the injury itself, as factors such as anxiety, pain, somatization and sleepiness are common after other acute traumas (Cassidy et al., 2014).

The studies by Landre et al. (2006) and Meares et al. (2008) both found patients with mild TBI not to report more post-concussive symptoms than patients with other traumas. The use of patients with other traumas can potentially specify the effects a mild TBI have on outcome after injury and the sensitivity of neuropsychological testing does not appear to be reduced when using trauma controls (Schretlen and Shapiro, 2003). The studies by Landre et al. (2006) and Meares et al. (2008) are however, as discussed above, different in findings of attention outcome after injury. Although injury related factors certainly can affect neuropsychological performance after injury (Meares et al., 2008), the performance might also be related to factors specific to mild TBI (Landre et al., 2006).

Complicated mild TBI

Despite the superior sensitivity of MRI over CT, only 6 out of 76 patients had abnormal MRI findings in this thesis and in all of these cases, there were also intracranial findings in the CT scan. One patient had visible intracranial lesions on CT, but did not complete the MRI. Leaving 7 patients characterized with a complicated mild TBI. MRI

including the sequences Fluid-attenuated inversion-recovery (FLAIR) Susceptibility-weighted imaging (SWI) and Diffusion weighted imaging (DWI) has been reported to be most sensitive in detecting brain changes following a mild TBI (Edlow and Wu, 2012, Spitz et al., 2013a). And axonal injuries often associated with mild TBI are better depicted by MRI than CT (Ashikaga et al., 1997, Mittl et al., 1994). Patients previously characterized as uncomplicated might be identified with visible lesions on MRI, that were not visible with CT (Iverson et al., 2012), evident by a study by Yuh et al. (2013) where 28% of mild TBI patients with normal CT had visible lesions on MRI. Iverson et al. (2012) identified 12 out of 47 (25%) mild TBI patients with abnormal MRI 3 weeks after injury. Based on these previous findings it was expected that in this thesis, earlier MRI conducted 72 hours after injury, would generate a larger subgroup of mild TBI patients with abnormal MRI findings. However, as seen in other studies the amount of mild TBI patients with abnormal findings on neuroimaging varies between large subgroups of complicated patients (Iverson et al., 1999, Lange et al., 2005, Dagher et al., 2013) and smaller subgroups (Borgaro et al., 2003, Iverson et al., 2012, Lange et al., 2009, Sadowski-Cron et al., 2006). The proportion of complicated patients is often found to be around 10-30% of the mild TBI patients (Iverson et al., 1999, Lange et al., 2005, Iverson et al., 2012, Sadowski-Cron et al., 2006, Stulemeijer et al., 2008, de Guise et al., 2010), (see Panenka et al. (2015) for a full table of studies comparing complicated and uncomplicated mild TBI patients).

The variation in proportion of patients with complicated mild TBI identified in previous studies might be due to different sampling procedures, leading some studies to include patients with more severe injuries. In this thesis patients were recruited from St. Olavs Hospital department of neurosurgery (29%) and patients admitted to Trondheim municipal clinic (71%). Patients with mild TBI that are hospitalized in acute care settings and patients with mild TBI that are recruited from outpatient clinics are significantly different from one another in terms of injury severity. Inpatients with mild TBI have a higher probability of having a complicated mild TBI, as well as lower GCS scores, longer LOC and PTA duration (Dagher et al., 2013). In this thesis five out of seven patients with complicated mild TBI had PTA duration between 1 hour and 24 hours. Most patients with mild TBI in this thesis had PTA duration less than an hour (58%). Additionally 3 out of seven complicated patients had LOC duration of 5-15 minutes, whereas the most common LOC duration in this thesis was < 5 minutes (38%). This might indicate that patients with complicated mild TBI in this thesis had more severe injuries than the other patients with mild TBI. In the study by Yuh et al.

(2013) there were a high proportion of motor vehicle accidents. This might explain the difference in number of patients with complicated mild TBI identified in this thesis compared to other studies.

Previous findings on neuropsychological outcome after complicated mild TBI are mixed (Borgaro et al., 2003, Iverson, 2006a, Iverson et al., 2012, Kurca et al., 2006, Panenka et al., 2015). Some of the studies report complicated mild TBI patients to perform worse than uncomplicated mild TBI patients (Borgaro et al., 2003, Iverson, 2006a, Kurca et al., 2006). The sample size in some of these studies were, however, quite low (Borgaro et al., 2003, Kurca et al., 2006). Especially the numbers of participants included in the complicated groups were low. Only Iverson (2006a) had a sample size considered large enough (50 patients in each group). Two recent studies found no difference between complicated mild TBI patients and uncomplicated mild TBI patients on neuropsychological measures (Iverson et al., 2012, Panenka et al., 2015). As pointed out by Panenka et al. (2015) the different findings might be due to different sampling of patients. The patients in the study by Panenka et al. (2015) were, similarly to most patients in this thesis, sampled from a hospital's emergency department. The criteria for mild TBI were, however, more rigorous in the study by Panenka et al. (2015) than in this thesis, e.g. LOC had to be witnessed. None of the complicated mild TBI patients in this thesis have CANTAB subtest Z-scores that indicate deviation from the rest of the mild TBI sample (None over a z-score of +/- 1.96). Though the sample of complicated mild TBI patients in this thesis is too small to generalize and to statistically analyze; the trend among the complicated mild TBI patients in this sample are similar to the findings of Panenka et al. (2015) and Iverson et al. (2012)

Panenka et al. (2015) provided several arguments for the lack of significant difference between the complicated and uncomplicated mild TBI patients. Including spontaneous biological recovery, that complicated mild TBI patients receive more reassurance by medical staff than uncomplicated mild TBI patients and that the categorization of complicated mild TBI might be too broad. In this thesis mild TBI patients did not differ significantly from healthy controls on neuropsychological measures of attention. Based on this, it can be argued that a potential draw back with the studies of Panenka et al. (2015) and Iverson et al. (2012) is that they did not include a control group in addition to the two mild TBI patient groups used. As already argued, there might be several factors causing mild TBI patients to perform similarly to healthy controls on neuropsychological measures. To ensure that the mild TBI patients in the studies by Iverson et al. (2012) and Panenka et al. (2015) had

neuropsychological deficits, the patients could have been compared to healthy controls or trauma controls.

Specific tracing of damages that are specific to neuropsychological performance might be a better strategy to categorize brain based etiology following mild TBI. Diffusion MRI sequences like diffusion tensor imaging (DTI) is an imaging technique that are increasingly popular in the TBI-literature in investigating white matter microstructure (Eierud et al., 2014, Shenton et al., 2012). Studies using DTI has linked white matter tracts to neuropsychological functioning (Little et al., 2010, Lo et al., 2009, Mayer et al., 2010, Niogi et al., 2008, Spitz et al., 2013b). Even in less severe cases of mild TBI, like sports related mild TBI, DTI have been shown to detect significant neuropathological injuries (Bigler, 2013). And specific tracing of white matter tracts might be important, because traumatic axonal injuries can also be present without known neuropsychological impairments (Bigler, 2008). However, the locations investigated and the nature of the damage in DTI-studies after mild TBI varies. Additionally there is a lack of longitudinal studies assessing how those who recover from mild TBI deviate from those who do not recover (Shenton et al., 2012).

Neuropsychological tests: The CANTAB

This thesis is the first attempt at using the CANTAB to assess impairments of attention in the acute stage following mild TBI. Subtests in the CANTAB have been found to be only moderately correlated with different traditional pen and paper neuropsychological tests, and appears to be better suited to measure general neuropsychological ability than neuropsychological subtypes like attention and executive functioning (Smith et al., 2013). Traditional pen and paper neuropsychological tests have, however, been criticized as being non-specific (Eierud et al., 2014) and without any standardized tests for neuropsychological assessment, it is difficult to conclude that the CANTAB is not specific for neuropsychological sub-modalities like attention. Moreover, the CANTAB have been widely used to assess neuropsychological performance on a variety of psychiatric, neurodevelopmental, metabolic and neurodegenerative diseases, and has been found to be sensitive in detecting impairments in neuropsychological domains, including attention (Wild and Musser, 2014).

The attention elements assessed by the CANTAB subtests assess different, but related aspects of attention (Cohen, 2014). One possible explanation for the lack of difference between mild TBI patients and controls in this thesis could be that the selected CANTAB subtests might not be sensitive enough in detecting differences. Tasks assessing attention

must be sufficiently effortful and complex to identify TBI-related impairments of attention (Cohen, 2014, Bigler, 2008). In this thesis four CANTAB subtests assessing attention were used, from these tests four outcome measures were selected, one for each test.

The CANTAB subtest Spatial Span is a test of working memory capacity and focused attention. The outcome measure “Spatial Span: Span length” was selected from this subtest. The maximal possible sequence possible to recall in this subtest is 9 sequences. A total of 12 of the participants in the control group and 10 patients reached this level, indicating a ceiling effect. It might have been possible to see larger differences between mild TBI patients and controls if the number of sequences possible to reach were greater. However the scores on this measure were approximately normally distributed for both the control group and the patient group. Furthermore the “SSP: Span Length” have been found sensitive in detecting attention deficits in patients with Attention deficits hyperactivity disorder (ADHD) (Gau and Huang, 2014). Therefore the test might be sufficiently sensitive in detecting working memory capacity and focused attention.

The rapid visual information processing task lasts for 4 minutes and requires high effort to hit sequences at the correct time. “Rapid Visual Information Processing: RVPA” is an outcome measure that assesses the participants signal detection sensitivity, and is a measure of sustained attention. The measure ranges from 0-1, where 1 indicates perfect signal detection; hits on each target sequence, and no hits on non-target sequences. One patient scored a perfect score on this measure. The “RVP: RVPA” outcome measure has been proven sensitive to pharmacological manipulation (Wild and Musser, 2014) and detecting attention deficits in ADHD (Gau and Huang, 2014).

The outcome measure “Spatial Working Memory: total errors” is a measure of the number of times the participants revisited a box were a blue symbol already had been found. The test assesses executive function and focused attention by requiring retention and manipulation of visuospatial information. All together 21 participants, 10 mild TBI patients and 11 controls, made zero mistakes on the SWM task; such a high number of participants might indicate a ceiling effect. “Spatial Working Memory: total errors” have been found to be sensitive in detecting impairments in people with ADHD compared to people without ADHD (Wild and Musser, 2014). The high number of participants in this thesis with zero mistakes might therefore be due to other causes than the complexity of the task.

The Attention switching task (AST) is a conflict task that requires executive attention and focused attention. “AST: Congruency Cost” is the outcome measure that might be the most sensitive measure at detecting impairments in attention used in this thesis. It measures the response latency difference in congruent and incongruent trials. Hence, the attention switching task is similar to other conflict tasks previously used to assess executive attention and focused attention (Cohen, 2014). Most participants scored a positive score on this measure, indicating faster responses on congruent trials than incongruent trials. In the AST there was a small tendency for the patient group to respond slower on incongruent trials ($M=73.89$) than the control group ($M=94.33$), measured by the “AST: Congruency Cost” outcome measure, this difference was, however, not significant. It is a possibility that a type II error was made in this test. The effect size of $\eta^2=0.017$ indicates, however, that only 1.7% of the variation in the dependent variable “AST: Congruency Cost” can be explained by the independent variable mild TBI or control. Therefore it is not likely that a type II error was made.

The CANTAB provide several outcome measures for each subtest. The selected measures are however the measures that seemed most appropriate after careful review of each measure. Though unlikely, there is a possibility that other measures and other subtests might be more sensitive. However, based on previous studies using the CANTAB (Wild and Musser, 2014, Gau and Huang, 2014) and the similarity between the CANTAB tests and well-known neuropsychological tests (e.g. AST and traditional conflict tasks), the CANTAB subtest appear to be sufficiently sensitive.

Strengths and Limitations

There are some limitations to this thesis. Due to unsuccessful matching of the control group to the patients group, participants that were older than 50 years were excluded from this thesis. There was a larger amount of patients older than 50 years in the patients group than in the control group. Additionally, there was a significant moderate negative correlation between age and CANTAB results. Older participants with frontal lobe damage have previously been found to have a slower rehabilitation period compared to younger patients (Cohen, 2014). Moreover, older age has been shown as a predictor for worse outcome following mild TBI (Lingsma et al., 2015). However, age is also negatively correlated to performance on the CANTAB (Wild and Musser, 2014). Therefore it is difficult to conclude whether the tendency

for worse neuropsychological outcome due to age can be related to mild TBI, or that older participants are more unfamiliar with computers.

Motivation might affect results on neuropsychological testing. Patients with mild TBI might perform better when exposed to external motivation (Keller et al., 2000). It is possible that the mild TBI patients got more encouragement from examiners than the controls. Furthermore, mild TBI patients might have a higher motivation to perform on the neuropsychological assessments to overcome possible neuropsychological deficits and hence, put more effort into the tasks than the controls. The potential confounder of external motivation could have been solved with blinding the test-session for the examiners. This solution would, however, not been practical and difficult to carry out. Moreover, neuropsychological tests were conducted by six different persons. It is possible that the participants perform differently depending on the person in charge of testing (e.g. due to different motivational skills).

Three of the dependent variables used in this thesis were not normally distributed. MAOVA is robust to violations of normality, this robustness, however, is dependent on the sample size. The minimum amount of cases in each cell required in a MANOVA is 3 (Pallant, 2010), in this thesis there are eight cells (The independent variables, patients with mild TBI and healthy controls, have four cells each), hence the sample size of 111 (controls and patients after participants over 50 are removed), is above this required number. It has been argued that a sample size of 20 in each cell should ensure robustness (Pallant, 2010), the sample size distributed between the MANOVA cells in this thesis is 13, and falls short of this goal. One might therefore argue that the sample size in this thesis might not be large enough for the MANOVA to be robust to violations of normality.

In spite of this, the sample size in this thesis is also a potential strength. Especially the number of patients recruited in this thesis is larger compared to previous similar studies. The number of patients with mild TBI recruited in previous studies assessing post injury disturbance of attention ranges from 20 (Haltermann et al., 2006) to 40 (Mathias et al., 2004), and only Meares et al. (2008) included more patients with mild TBI (n=90) than patients recruited in this thesis. Mild TBI patients groups consist of a highly heterogeneous group of people in regards of neuropsychological outcome (Bigler, 2008), it is therefore important to include a large enough sample of patients in mild TBI research.

In this thesis, there were a high proportion of patients enrolled from the outpatient clinic (71%), which represents the real clinical pathway for the majority of patients with mild TBI (Luoto et al., 2013). Moreover, around 30% of all consecutive patients with mild TBI, consented to participate in this thesis, which is a higher participation than what is common in the mild TBI literature (Luoto et al., 2013). Hence we believe that this sample is reasonably representative for the age group that was studied.

Another limitation to this thesis is the lack of questionnaires handed in. Especially there was a lack of questionnaires from the controls, making the amount of self-reported data from the controls small compared to the patient group. There should have been a better follow up, to ensure that every participant delivered their questionnaires either before the test session or after. Proper precautions have been made, so that participants hands-in their questionnaires for the rest of the main study the data for this thesis is collected from.

Moreover, some of the self-reported data analyzed in this thesis might be less valid in comparing patients with mild TBI to control persons than those used in other studies. The patients and controls filled out two different questionnaires assessing self-reported concentration and memory, the Rivermead Post Concussion Symptom Questionnaire (RPCSQ) and the British Columbia Post Concussion Symptom Inventory (BC-PSI). The scale in the BC-PSI was recalculated to match the scale in the RPCSQ. Although the questions used by these two questionnaires were similar, the RPCSQ asked about complaints in the last 24 hours, while the BC-PSI asked about complaints in the last two weeks including the last 24 hours. It is possible that these two questions assess similar, but different aspects. Moreover the two questionnaires are only moderately positively correlated (Sullivan and Garden, 2011). The sub items assessing concentration and memory might, however, be more related to each other than the full questionnaires were.

Additionally, the measure of pain used in this thesis might be less sensitive than more standardized measures of pain used in previous studies. Still, this measure was able to differentiate between patients and controls on self-reported pain two weeks after injury. Furthermore, there are some issues regarding self-reported symptoms assessed with questionnaires. Patients have been found to overreport symptoms when answering questionnaires. This overendorsement might be due to such factors as misattribution of symptoms, expectation of symptoms as well as the nocebo effect (Iverson et al., 2010). Some previous studies also find compensation and litigation issues to be potential confounders to

both self-reported symptoms and neuropsychological impairments after mild TBI (Al Sayegh et al., 2010). Patients included in this thesis do not rely solely on insurance and compensation as the health care in Norway is free. Hence, the self-reported measures in this thesis might be more reliable than self-reported measures in studies conducted in other countries, e.g. the United States. Other factors related to overendorsement of symptoms can, however, not be ruled-out in this thesis.

Conclusion

This thesis examined neuropsychological functioning of attention in the acute stage after mild TBI. Based on previous research it was expected that patients with mild TBI would perform worse on neuropsychological measures of attention and report more complaints on self-reported measures compared to healthy controls. Additionally, it was expected that a subpopulation of patients would have abnormal findings on CT or MRI. There was no evidence for impairments in neuropsychological measures of attention two weeks after mild TBI when comparing patients to matched controls. Only 7 patients had abnormal findings on neuroimaging visible on CT or MRI, z-scores among these patients did not differ from the other patients with mild TBI. The patient group and control group did not differ on self-reported measures of depression, anxiety, somatization, fatigue and sleepiness, although seemingly more patients reported complaints over clinical cut-off values. Patients with mild TBI reported significantly more complaints with concentration, memory and pain compared to controls. The sample of patients in this thesis appeared to be reasonably representative for the mild TBI population and the CANTAB appeared to be sufficiently sensitive in detecting possible impairments of attention.

The results in this thesis, therefore, indicates that most patients have a good clinical outcome two weeks after a mild TBI, and that the neuropsychological attention-performance of patients in this thesis represents the performance of most patients with mild TBI. Patients reporting complaints on measures of pain as well as those reporting over clinical cut-off values on emotional and somatic measures need further follow up. Moreover, patients reporting complaints on memory and concentration can benefit from information about the lack of demonstrable neuropsychological impairment obtained in this thesis. More longitudinal studies including more sensitive imaging techniques and large samples of patients with mild TBI is needed to identify patients at risk of persistent disabilities.

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Appendix

In the main project, a list of consecutive head CTs performed is screened daily.

For 6 of the 9 months this master project lasted, this log is complete:



