Psychotherapeutic interventions for patients with prolonged recovery after mild traumatic brain injury

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Abstract

The objective of this thesis was to do a systematic review of the literature on psychotherapeutic interventions for patients suffering from prolonged recovery after mild traumatic brain injury (MTBI). Prolonged recovery was defined as symptoms persisting three months after injury.

We conducted an extensive literature search of the databases Embase, MedLine, PsycInfo, CINAHL and SPORTDiscus. The search yielded 1925 hits, whereof 3 were considered to fulfil our criteria. Despite several earlier literature reviews pointing out the lack of methodically strong studies exploring the effect of psychotherapy after MTBI, such studies are still sparse. 3 studies were chosen for a thorough review, employing different interventions and outcome measures. In addition, 3 studies examining possible risk factor for and prevention of persistent symptoms were considered.

Results from the main review suggested that computer-based interventions and mindfulness-based techniques, as well as cognitive-behavioural therapy in combination with cognitive remediation can all have positive effects on persistent symptoms after MTBI. The studies that looked at risk factors and prevention suggested that patients with a history of psychiatric illness is a subgroup of MTBI patients that seem to benefit from individualised treatment including psychotherapy. The construct of illness perceptions, how one interprets ones symptoms, might also help predict which patients might be in need of, and benefit from, psychotherapy.

Treatment studies for patients with prolonged recovery after MTBI yielded results not easily comparable, due to employing different modes of treatment. Overall, the empirical support for psychological treatments of persistent symptoms following MTBI is not unanimous. Some of the studies indicated that interventions should be aimed specifically at patients thought to be especially at risk for prolonged recovery. However, the field demonstrates a reluctance to adhere to recommendations made on the basis of previous research and systematic reviews.

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1. Introduction and theoretic background

1.1. Mild traumatic brain injuries

Traumatic brain injuries (TBI) are a worldwide public health problem. Those affected may experience permanent disability as well as psychological sequelae following their abruptly altered life situation. Mild traumatic brain injuries (MTBI) are the most common of traumatic brain injuries, with an incidence rate that may exceed 300/100.000 (Cassidy, Carroll, Peloso, et al., 2004). Although most patients recover quickly after an MTBI, some, often referred to as "the miserable minority" (Ruff, Camenzuli, & Mueller, 1996) go on to develop persisting symptoms. There is currently a lack of evidence-based treatment options for this group (Sayegh, Sandford, & Carson, 2010) . This thesis systematically reviews research on psychotherapeutic interventions for patients experiencing prolonged recovery from symptoms following MTBI, months and years after the initial diagnose.

The following sections provide definitions of central concepts needed to understand TBI severity, measurement and diagnosis as well as a brief discussion of the lack of agreement on central inclusion criteria and diagnostic variables between researchers studying MTBI. It will also present incidence rates for MTBI, the causes of MTBI and its mechanisms.

1.1.1. Defining traumatic brain injury.

To better understand MTBI, a brief description of TBI as a general concept is provided. On behalf of the Demographics and Clinical Assessment Working Group of the International and Interagency Initiative towards Common Data Elements for Research on Traumatic Brain Injury and Psychological Health, Menon, Schwab, Wright, and Maas (2010), provide a consensus definition of TBI: "TBI is defined as an alteration in brain function, or other evidence of brain pathology, caused by an external force" (Menon et al., 2010, p. 1637). Alteration in brain function is defined as any period of loss of or a decreased level of consciousness, any loss of memory for events immediately before (retrograde amnesia) or after the injury (post-traumatic amnesia, PTA), neurologic deficits (weakness, loss of balance, change in vision, dyspraxia paresis/plegia [paralysis], sensory loss, aphasia etc.), or any alteration in mental state at the time of the injury (confusion, disorientation, slowed thinking etc.). Further,

> "'Other evidence of brain pathology' may include visual, neuroradiologic, or laboratory confirmation of damage to the brain. 'Caused by an external force' may include the head being struck by an object, the head striking an object, the brain undergoing an acceleration/deceleration movement without direct external trauma to

the head, a foreign body penetrating the brain, forces generated from events such as a blast or explosion, or other force yet to be defined" (Menon et al., 2010, p. 1638).

TBIs are differentiated according to severity. The most common distinction is between severe, moderate and mild TBI. One way to differentiate is based on a patient's score on the Glasgow Coma Scale (GCS). A score lower than 8 indicates a severe injury, a score between 9 and 12 indicates a moderate injury, and a score of 13-15 indicates a mild injury. These thresholds are the subject of constant debate. Because imaging techniques are improving, it has become more common to discover lesions in for example MRIs of patients with a GCS of 13. This has led some researchers and clinicians to include a GCS of 13 in the moderate range (L. J. Carroll et al., 2004). This may reflect that the GCS was not intended as a measurement of brain injury severity, and that there are no true thresholds between severity categories, at least not within today's diagnostic paradigms.

1.1.2. Defining mild traumatic brain injury.

Defining MTBI has proven particularly difficult. According to Iverson and Lange (2011), there are three commonly used definitions of MTBI in the literature. These definitions are developed by (1) The Interdisciplinary Special Interest Group of the American Congress of Rehabilitation Medicine (ACRM MTBI Committee), (2) Centre for Disease Control Working Group (CDC Working group), and (3) World Health Organization (WHO) Collaborating Task Force on Mild Traumatic Brain Injury (L. J. Carroll et al., 2004).

The ACRM definition is presented in table 1. This definition is fairly broad, and does not exclude open head injuries (as opposed to closed injuries, see section 1.1.7.). The ACRM-definition does not have loss of consciousness (LOC) as an absolute criterion. According to Ruff (2005), this represents a significant advance in the diagnosis of MTBI. Prior to this definition, most neurologists diagnosed a concussion or MTBI *only* if an LOC was observed (Ruff, 2005). According to the ACRM definition, an LOC is sufficient, but not necessary, to

Table 1: ACRM (Mild Traumatic Brain Injury Committee 1993) definition of mild traumatic brain injury.

A traumatically induced physiological disruption of brain function, as manifested by *at least* one of the following:

1. Any loss of consciousness
2. Any loss of memory for events immediately before or after the accident.
3. Any alteration in mental state at the time of the accident (e.g., feeling dazed, disoriented, or confused) and
4. Focal neurological deficit(s) that may or may not be transient.

But where the severity of the injury does not exceed the following

- Loss of consciousness of approximately 30 minutes or less.
- After 30 minutes, an initial GCS-score of 13-15 and
- Posttraumatic amnesia not greater than 24 hours.

(Kay, Harrington, & Adams, 1993)

diagnose MTBI. This means that post-traumatic amnesia (PTA) or neurological symptoms alone are sufficient to render an MTBI-diagnosis.

The CDC Working group definition is presented in table 2. This definition is narrower than the ACRM definition in that it does not include penetrating injury to the definition. Otherwise worth noting, is that this definition does not specify any cut-off point on the GCS, and refers to "Dysfunctions of memory around the time of the injury" as an indication of memory failure, rather than PTA.

Table 2: National Center for Injury Prevention and Control (2003) conceptual definition of MTBI
The conceptual definition of MTBI is an injury to the head as a result of blunt trauma or acceleration or deceleration forces that result in one or more of the conditions listed below

Any period of observed or self-reported

- Transient confusion, disorientation, or impaired consciousness
- Dysfunction of memory around the time of injury
- Loss of consciousness lasting less than 30 minutes
- Observed signs of neurological or neuropsychological dysfunction, such as:
    - Seizures acutely following injury to the head
    - Among infants and very young children: irritability, lethargy, or vomiting following head injury
    - Symptoms among older children and adults such as headache, dizziness, irritability, fatigue or poor concentration, when identified soon after injury, can be used to support the diagnosis of mild TBI, but cannot be used to make the diagnosis in the absence of loss of consciousness or altered consciousness. Research may provide additional guidance in this area

More severe brain injuries were excluded from the definition of MTBI and include *one or more* of the following conditions attributable to the injury

- Loss of consciousness lasting longer than 30 minutes
- Posttraumatic amnesia lasting longer than 24 hours
- Penetration craniocerebral injury

The WHO-definition is presented in table 3. The WHO-definition, in addition to the ACRM definition, rely on scores on the GCS and PTA.

Table 3. WHO-Definition of MTBI

MTBI is an acute brain injury resulting from mechanical energy to the head from external physical forces. Operational criteria for clinical identification include: (i) 1 or more of the following: confusion or disorientation, loss of consciousness for 30 minutes or less, post-traumatic amnesia for less than 24 hours, and/or other transient neurological abnormalities such as focal signs, seizure, and intracranial lesion not requiring surgery; (ii) Glasgow Coma Scale score of 13–15 after 30 minutes post-injury or later upon presentation for healthcare. These manifestations of MTBI must not be due to drugs, alcohol, medications, caused by other injuries or treatment for other injuries (e.g. systemic injuries, facial injuries or intubation), caused by other problems (e.g. psychological trauma, language barrier or coexisting medical conditions) or caused by penetrating craniocerebral injury.

(Carroll, Cassidy, Holm, Kraus, & Coronado, 2004)

Systematic reviews conducted in the last decade (Borg et al., 2004; Comper, Bisschop, Carnide, & Tricco, 2005; Marshall, Bayley, McCullagh, Velikonja, & Berrigan, 2012; Nygren-de Boussard et al., 2014; Snell, Surgenor, Hay-Smith, & Siegert, 2008) show that despite consensus definitions of MTBI now being readily available, there is a reluctance among MTBI-researchers to employ them. Even though there seems to be an increase in studies using one of the three MTBI consensus definitions outlined here, results indicate that about 50% of intervention studies do not employ any of them (Snell et al., 2008).

The systematic reviews also point out that even though one can expect a favourable outcome for most patients suffering from MTBI, a subgroup of patients develop persisting difficulties in the wake of an MTBI. Lacking a consensus diagnosis or definition for this subgroup of patients, findings from intervention studies treating this patient group are difficult to generalize (Nygren-de Boussard et al., 2014).

It is common to differentiate between complicated and uncomplicated MTBI (Williams, Levin, & Eisenberg, 1990). If a patient has a GCS-score between 13 and 15, and there are also positive findings on computed tomography (CT) or magnetic resonance imaging (MRI), the MTBI is considered complicated. Positive findings include oedema, hematoma and contusions (Iverson & Lange, 2011). Also, skull fractures are characteristic of complicated MTBIs (Williams et al., 1990). Iverson and Lange (2011) note that patients suffering from complicated MTBI show a functional recovery pattern that is more similar to that of persons with moderate brain injuries. Conversely, when the patient scores 13-15 on the GCS, but no abnormalities related to the injury are detected on brain imaging scans, it is considered an uncomplicated MTBI. Borgaro et al. (2003) use a stricter definition, by specifying that the positive imaging findings should reveal space-occupying lesions. They found affective disturbances both among patients with complicated and uncomplicated injuries, whereas only the complicated group showed reduced cognitive functioning. This suggests that the severity of the injury may produce qualitatively different sequelae.

1.1.3. Defining prolonged recovery after mild traumatic brain injuries.

Post Concussive Syndrome (PCS), as described in the International Classification of Disease, 10th revision (ICD-10, F07), is a syndrome occurring after head injuries (World Health Organization, 1992). The head injuries are *usually* severe enough to cause a loss of consciousness, implying that LOC is not an absolute prerequisite for the diagnosis. Some of the symptoms include headaches, dizziness, irritability, disorders of memory, and a lowered threshold for stress, emotional strain and alcohol. It is worth noting that the diagnosis does not specifically include *brain* injuries, but *head* injuries. The PCS-description emphasizes that some of the secondary sequelae associated with PCS, such as anxiety, hypochondria and depression, may take on a chronic course.

The ICD-10-diagnosis preceded the first MTBI consensus definition. Work on the ICD-10 began in 1983, and was finalized in 1992, one year prior to the publication of the ACRM consensus definition of MTBI. At this time, many of the issues pertaining to MTBI had not yet been resolved, and could therefore not be among the diagnostic criteria.

Post Concussive Disorder (PCD) is the Diagnostics and Statistics Manual of Mental Disorders, 4th revision (DSM-IV) (American Psychiatric Association, 2000) equivalent to the ICD-10 PCS. The DSM-IV-criteria are discussed here, instead of the DSM-V-criteria, because they have frequently been a part of research and debate since their publication in 1994. However, the DSM-IV does not include PCD as a separate diagnostic category per se. It was discussed for full inclusion in DSM-IV, but ended up being marked as a set of criteria for further study. The DSM-IV criteria for PCD remained unchanged in the 2000 revision of DSM (DSM-IV-TR). Therefore, the DSM-IV-criteria also predate most of the consensus definitions of MTBI.

Like PCS, PCD includes a description of the acute brain injury symptoms leading to the residual symptoms. These include at least two of the following: a loss of consciousness, a period of post-traumatic amnesia of at least 12 hours, or an onset of seizures within the first six months after the closed head injury. In addition, cognitive deficits must be evident after the injury. Finally, three or more symptoms have to be present for at least three months after the injury. Among others, these symptoms include disordered sleep, headache, vertigo, anxiety, depression and apathy. See DSM-IV for a complete list.

The DSM-criteria are stricter than the ICD-criteria. This means that the prevalence of PCS is higher than the prevalence of PCD. According to McCauley et al. (2005), the PCS prevalence has been reported to be six times as high as the PCD prevalence.

There are substantial validity and reliability issues pertaining to both of these diagnoses (L. Carroll et al., 2004; Marshall et al., 2012; McCauley et al., 2005; Ruff, 2005). One consequence of these validity and reliability issues, is that these diagnoses have not been able to build sufficient consensus and explanatory momentum in the field. Another consequence of this lack of consensus, is that a myriad of idiosyncratic definitions, descriptions and interpretations of “prolonged symptoms” have spawned in the research literature, and the condition goes by many different names and abbreviations even today.

When discussing prolonged symptoms in this thesis, we simply referred to patients experiencing prolonged recovery or persistent symptoms, regardless of how they conformed to the various diagnostic categories in use today. When needed or warranted, we employed the ICD-10 diagnostic definition of PCS, as the ICD-10 is the official diagnostic framework in Norway. When the ICD-10-diagnosis is employed, either by the authors of the present study, or in the reviewed literature, we have used the abbreviation PCS. When discussing research employing DSM-IV-criteria, we used the abbreviation PCD. When it was unclear

what diagnosis was being employed in the reviewed research, any idiosyncratic definition being used has been described.

1.1.4. Concussions.

When head injuries occur in relation to sports, the term "concussion" is normally used, both in clinical and research settings (Iverson & Lange, 2011). Although concussion is used almost interchangeably with MTBI, it is implied that concussions are injuries in the milder end of the MTBI spectrum (Iverson & Lange, 2011). The authors argue that the concept of concussion is easier to explain to most patients, and that it is a word more readily associated with positive outcomes (Iverson & Lange, 2011). A range of symptoms are reported by athletes suffering concussion. Headaches, fatigue, drowsiness, a feeling of being slowed down, dizzy, mentally foggy and having problems concentrating are among those reported most frequently (Lovell et al., 2006). Concussion (commotio cerebri) can be found as a diagnostic category in ICD-10 (S06.0). As described above, lasting sequelae after concussion are defined as post-concussional syndrome (F07.2). Post-concussional syndrome specifically excludes the diagnosis of a current concussion, although ICD-10 does not specify at what point in time symptoms cease to be defined as a current concussion.

1.1.5. Level and loss of consciousness, Post-traumatic Amnesia and the Glasgow Coma Scale.

The consensus definitions of MTBI described above, all rely on several measures of injury severity. There is reasonable consensus on the definition(s) of MTBI, but these definitions can never be more valid or reliable than their individual measurement components. Measurements consistently used in brain injury severity assessment include LOC, measurements of PTA, and GCS-score. These will be presented briefly.

1.1.5.1. The Glasgow Coma Scale.

In 1974, Teasdale and Jennett introduced the Glasgow Coma Scale, for assessing depth and duration of loss of consciousness in patients (Teasdale & Jennett, 1974). The scale consists of three subscales: motor responsiveness, verbal performance and eye opening. Patients are rated on a scale of 1 - 4, 1 - 5 and 1 - 6 on the independent measures, which results in a final score of 3 - 15. The final scores are used to establish the severity of the injury. As described above, a GCS of 13-15 is considered a mild brain injury, while anything below is considered either moderate (9 - 12) or severe (< 8). Worth noting is that when the GCS was developed, scores in the range 13 - 15 were actually considered insignificant (Ruff, 2005). It is important to note that this scale was developed to study level of consciousness

and functioning in coma patients, not to categorize brain injuries, although today it is often used to classify cases into severe, moderate and mild cases for research and clinical purposes.

1.1.5.2. Loss of Consciousness.

While *level* of consciousness is measured using the GCS (see section 1.1.5.3 below), *loss* of consciousness (LOC) is also commonly used as an inclusion criterion when diagnosing MTBI, and as an indicator of injury severity. However, as discussed previously, the consensus definitions of MTBI do not employ it as an exclusive criterion. LOC is sufficient, but not necessary, to establish an MTBI-diagnosis. However, a loss of consciousness or an altered state of consciousness is difficult to assess properly in the acute phase: often patients or bystanders are asked to recall the presence and duration of the LOC instead of it being assessed by trained medical personnel.

1.1.5.3. Post-traumatic amnesia.

PTA is widely used as an indicator of TBI severity, as well as for a range of treatment-relevant and prognostic factors concerning TBI (King et al., 1997; Marshman, Jakabek, Hennessy, Quirk, & Guazzo, 2013; Stuss et al., 1999). However, there is no consistent definition of PTA (King et al., 1997; Marshman et al., 2013; Stuss et al., 1999). According to King et al. (1997), PTA is usually defined as the "time between receiving a head injury and the resumption of normal continuous memory" (King et al., 1997, p. 38), although they do not clearly state what is meant by the resumption of normal continuous memory. Marshman et al. describes PTA as an integrated component of a larger "post-TBI syndrome". Marshman et al. thoroughly describe issues with merely stating that normal memory is resumed, and shows how the same patient may at the same time be described as both being and not being in a state of PTA or post-traumatic confusion, depending on what measure is being used (2013). According both to Marshman et al. and Stuss et al., the term post-traumatic *amnesia* misplaces the focus on the amnestic features of PTA. They argue convincingly that amnesia is secondary to the primary impairment: a disruption of attention (Marshman et al., 2013; Stuss et al., 1999).

1.1.6. Incidence of mild traumatic brain injuries.

Cassidy, Carroll, Peloso, et al. (2004) reviewed the literature on MTBI incidence in the years spanning from 1980 to 2002. In summary, Cassidy estimates that the prevalence of hospital treated MTBI is in the range between 100 and 300/100.000 in the adult population, between 70 % and 90 % of all hospitalized cases of TBI. However, Cassidy et al. note significant limitations in the literature, which makes it difficult to make consistent conclusions. Some of the limitations have to do with the definition of MTBI. As noted above,

before 1993, there were no consensus definitions of MTBI. And even today, there is no universally agreed-upon definition of these injuries. As a consequence, different authors use different inclusion and exclusion criteria. In addition, Cassidy et al. note, there is considerable information bias and there are substantial information retrieval problems. Moreover, the commonly used diagnoses may not capture all cases of MTBI, leaving even hospitalized MTBI under-reported. Cassidy et al. estimate that the actual rate of MTBI, both hospitalized and non-hospitalized cases, is probably in excess of 600/100.000. At best, this means that at least 50 % of MTBI-cases are never registered. The same problems arise in Andelic et al.'s study investigating incidence of MTBI in Norway (2008). In this study, GCS-scores are the only inclusion criteria for considering mild injuries (13-15). As noted above, this may deflate the incidence, because PTA and consciousness level are not considered. Andelic et al. estimate the total incidence of hospitalised MTBI at 61.2/100.000 in the Oslo region.

1.1.7. Causes and mechanisms of mild traumatic brain injuries.

The leading causes of MTBI in both Norway and in other countries, are fall accidents and transport accidents, and the highest reported frequencies of TBI are in the youngest children and the oldest age groups (Cassidy, Carroll, Peloso, et al., 2004).

It is common to distinguish between open and closed head injuries, which is commonly understood as head injuries with and without skull fractures. Both can result in TBIs, while it is most common to exclude MTBI in cases of open head injuries. Saatman et al. (2008) lists four main pathoanatomical mechanisms underlying TBI: Contusions (i.e. micro-haemorrhages in the brain tissue), subarachnoid haemorrhage (i.e. haemorrhage in the subarachnoid space), haematomas (i.e. a concentration of blood outside the blood vessels, both epidural, subdural and intracerebral) and diffuse axonal injuries (i.e. shearing forces applied to the axons of the brains white matter, of sufficient force to damage them). In addition, they mention other pathophysiologic insults that may be included as underlying TBI, although they are usually considered secondary insults: ischemic injuries (i.e. lack of blood flow to sustain the metabolic demands of the brain) and cerebral oedema (i.e. excess fluid concentration in intracranial space, displacing brain tissue). According to Saatman et al. (2008), while there is general consensus on the definitions, there have been some debate as to the definition of diffuse axonal injuries. As imaging techniques get better, it is now possible to detect diffuse axonal injuries that earlier were only possible to detect post mortem, and the authors recommend careful definition of these injuries in studies investigating TBI. Important to repeat here, as described above, is that if an injury is severe enough to be identified in brain

imaging examination, it is considered a complicated MTBI, with outcomes more similar to the outcome after moderate TBI (Iverson & Lange, 2011).

It is not always possible to appraise the extent of the damage caused by an MTBI immediately, as neurochemical reactions initiated by the traumatic insult may continue and not present clinically until several days after the actual injury (Signoretti, Vagnozzi, Tavazzi, & Lazzarino, 2010). The stretching of the axolemma, the neural membrane of the axons, causes dysregulation in the influx and efflux of ions across the membrane. This leads to more neurotransmitter activity, which in turn maintains the imbalance of the ionic flux. As the brain struggles to restore balance, energy stores are depleted, and subsequent hypofunction may occur (Barkhoudarian, Hovda, & Giza, 2011). These neurochemical cascade reactions after an MTBI seem to be similar to those occurring after more severe injury. In TBI at the milder end of the spectrum, however, these changes are transient, while after more severe injuries, this does not seem to be the case (Signoretti et al., 2010).

While histological changes must be of a certain magnitude to be detected by conventional neuroradiological methods (Inglese et al., 2005), chemical compounds in the brain can serve as biomarkers of neuronal health (Signoretti et al., 2010). One such marker is NAA(N-acetylaspartate). A decrease in NAA levels indicates that the metabolism in the brain is compromised after an MTBI. Animal models have shown that two MTBIs within a limited time window can be as deteriorating as one severe injury. This is known as the "second impact syndrome", and increases the chances of lasting sequelae and even death. An important clinical implication of this is that measures must be taken to ensure that another traumatic insult does not occur until metabolism is normalised. Monitoring NAA levels through MR spectroscopy provides a possible means of accomplishing this, and making it possible to detect when brain metabolism is back to normal (Signoretti et al., 2010). Such knowledge would not only help health personnel give their patients the best care, but also enable the patients and those around them limit the extent of the injury.

1.2. Outcome, predictors of outcome and rehabilitation after MTBI

Symptoms frequently reported after MTBI include headaches, sensitivity to noise, dizziness, fatigue, reduced concentration, anxiety and depression (King, 1996). As several researchers have noted, these symptoms are not specific to MTBI (L. Carroll et al., 2004), and both in the acute phase and later on in the recovery, it is almost impossible to prove a direct connection between the symptoms and the injury. A lot of diffuse symptoms are common in the normal population, and after an injury, it is easy to attribute such symptoms to the injury, even when the two are not related. A study from 1999 found evidence of this "recall bias" in

athletes. Participants who had sustained an MTBI, underestimated the incidence of their pre-concussion symptoms by 97 % (Ferguson, Mittenberg, Barone, & Schneider, 1999). Paniak et al. (2002) explored which symptoms sufferers of MTBI endorsed within one month post-injury, compared to a group of healthy controls. Although there was an overlap, a lot of symptoms were reported significantly more often by the MTBI group. The MTBI group also reported more severe symptoms. By combining the symptoms that showed the largest discrepancy between the two groups, Paniak et al. (2002) were able to predict group identity with 81 % accuracy (92 % sensitivity, 70 % specificity). The symptoms endorsed most frequently by the MTBI group were fatigue, headaches and forgetfulness (Paniak et al., 2002).

For most patients, these kinds of symptoms will recede within three months. Is it possible to predict for whom the symptoms will not be resolved by three months? Several studies have explored possible predictors for prolonged recovery. Carroll et al.'s review found that there is a clear association between prolonged recovery and being involved in litigation or making claims for financial compensation. Although this association has been reported in several studies, there is a need for confirmatory studies and studies exploring possible causal connections (L. Carroll et al., 2004). It is of course possible that people involved in litigation might aggravate their symptoms, but it is also logical that those whose symptoms are more disabling are in greater need for monetary compensation, and hence more likely to pursue litigation. This especially holds true in countries without universal health care. Carroll et al. found that being involved in litigation and financial compensation predicted prolonged recovery. Apart from this, they did not find any consistency in predictive factors. This is, at least in part, due to the fact that there is great variation in the factors being studied. Thus, replications of findings and confirmatory studies could provide more predictive power by revealing other predictors. In 2012, Hou et al. conducted a prospective study where patients from emergency departments completed a baseline questionnaire within two weeks of injury. They then retested the patients at three and six months post-injury. Negative perceptions of the injury, along with an all-or-nothing-behaviour (defined as alternating intervals of over activity during symptom-free periods and then long periods of recovery when symptoms returned) proved to be the best predictors of PCS three and six months after the injury (Hou et al., 2012). Interestingly, this study did not find the "litigation effect" that previous studies have reported.

A study that looked at MMPI-2 profiles of claimants before and after injury, found that they had abnormal MMPI-2 profiles, characterized by somatoform symptoms (Greiffenstein & Baker, 2001). This indicates that personality is a contributing factor. There

were several limitations to this study. Firstly, the fact that premorbid MMPI-2 profiles were available in their medical records, makes this a biased sample. Secondly, all of the participants were involved in compensation claims. The personality profiles may therefore not be generalized to patients with prolonged recovery who are not involved in such claims. It appears from Carroll et al. (2004) that the role of personality in postconcussive symptoms has not been explored thoroughly, and this may be an interesting field for further research.

1.2.1. Cognitive functions outcome and predictors of cognitive functions in mild traumatic brain injury.

As previously mentioned, it may be useful to divide MTBIs into the subtypes complicated and uncomplicated, for several purposes (Williams et al., 1990). An MTBI is typically considered complicated when the patient has a GCS score that indicates a mild injury, but still shows some signs of brain abnormality on either a CT or an MRI scan. There is some evidence that patients with complicated injuries show poorer neuropsychological functioning compared with patients with uncomplicated injuries, at least on some tests, but the difference is more pronounced when it comes to functional outcome (Iverson & Lange, 2011). Some studies systematically exclude complicated cases, arguing that the presence of a lesion is incompatible with the diagnosis of MTBI (L. J. Carroll et al., 2004).

Iverson and Lange (2011) present evidence that both athletes and trauma patients show reduced performance on neuropsychological tests up to a month after injury. These reductions in performance seem to subside after 1 - 3 weeks and 1 - 3 months for athletes and trauma patients respectively. Neuropsychological outcome may also be influenced by duration of LOC and PTA. An association between length of PTA and neuropsychological outcome has been found in athletes, this held true both for immediate outcome and long-term recovery. In trauma patients, similar results have been found for short-term outcome (Iverson & Lange, 2011).

There seems to be an association between severity and length of recovery also within the boundaries of MTBI. As mentioned earlier, complicated injuries tend to show slower recovery, and this holds true also for the recovery of cognitive functions. Complicated MTBIs are associated with poorer cognitive functioning in the acute phase, and some have found their recovery pattern to be comparable to that of patients with moderate TBI (Williams et al., 1990). Other studies found that groups of patients with complicated and uncomplicated MTBIs could not be differentiated by neuropsychological tests, although they did differ significantly on some measures (Iverson, 2006).

For patients with severe traumatic brain injuries, variables typically used to predict illness and mortality, such as GCS and Marshal CT classifications, have proven to be poor predictors of cognitive outcome (Thais et al., 2012). Tellier et al. (2009) found similar results in the mild range when comparing MTBI patients with a GCS score of 15 to patients whose score was 13 or 14. In this study, the two subgroups did not differ significantly on post-concussive symptoms, neurobehavioural measures, neuropsychological performance or CT scan abnormalities. However, when PTA was used as the defining measure for the two groups, they differed on both intracranial abnormalities and aggressive and disinhibited behaviour six months post injury. Tellier et al. dichotomized the variable of PTA by creating a cut-off point at 30 minutes. Because most definitions of MTBI allow for PTA up to 24 hours post injury, it would be interesting to know whether the association between the length of PTA and aggressive behaviour are correlated in a dose-dependent manner, or whether it is simply the presence of PTA that is crucial. Since PTA was measured retrospectively by self-report, it might be that those reporting a PTA of less than 30 minutes did in fact not experience any PTA at all.

It has been demonstrated that recovery occurs at different rates for different cognitive domains (Brewer, Metzger, & Therrien, 2002). An important implication of this is that the effectiveness of interventions can be enhanced by timing them according to the differing recovery slopes of the different domains. More knowledge about this could be crucial, since animal studies indicate that unfortunate timing may not only waste chances of recovery, but also facilitate maladaptive rewiring of the central nervous system (Kleim & Jones, 2008). In their study of minor brain injury, Brewer et al. (2002) administered 15 different cognitive measures, and found that some showed improvement only between 24 and 48 hours after injury, whereas others continued to improve over the next thirty days. Additionally, they demonstrated differences in cognitive outcome between those who had experienced loss of consciousness and those who had not. Participants with LOC showed sustained impairment in directed attention, whereas those without LOC showed only a minor impairment that subsided within the first 48 hours (Brewer et al., 2002). Although this suggests a predictive value of LOC, Iverson and Lange (2011) conclude that PTA is a better predictor of short-term outcome than LOC, in cases of short LOC duration. Since cases where LOC exceeds 30 minutes are usually defined as moderate or severe, as opposed to mild traumatic brain injuries, the predictive value of LOC in cases of MTBI may be restricted by the limited variability. Several alternatives to these measures have been suggested for more precise

prediction of outcome after MTBIs (Ruff, 2005), but these do not frequently feature in the research literature.

1.2.2. Emotional outcome and predictors of emotional outcome in mild traumatic brain injury.

Depression is commonly observed after MTBI. Iverson and Lange (2011) report rates ranging from 12% to 44% within the first three months post injury. It is important to note that it is unclear whether depression is a direct result of the injury, of biological factors, a psychological reaction to the incident that caused the injury, a reaction to the consequences of the injury, or a combination (Iverson & Lange, 2011). With the biopsychosocial model in mind, one could argue that it is no more meaningful to look for a single cause for depression in these cases than it is when depression occurs in individuals who have not suffered an MTBI. This would of course depend on whether or not the aetiology of the depression is relevant to the choice of treatment. The question of aetiology is complicated further by the fact that it is virtually impossible to separate the symptoms of depression from the symptoms of PCD or PCS. In fact, a person diagnosed with depression will meet most of the diagnostic criteria for a post-concussive disorder, except for the concussion itself (Iverson & Lange, 2011). This is also the case for several other conditions often seen in patients with MTBI. Patients with post-traumatic stress disorder, chronic pain, chronic sleep problems and substance abuse disorders all have symptoms which are effectively the same as in PCD and PCS (Iverson & Lange, 2011). The WHO task force on MTBI is also critical of these diagnoses, mostly because of the problems of connecting the symptoms to the brain injury (L. Carroll et al., 2004). Thus, it seems appropriate to question whether PCD and PCS are expedient diagnoses that add any further explanatory value above and beyond that of for example a depression post-injury.

Borgaro and colleagues claim that the affective sequelae after MTBI are less understood and studied than cognitive and physical problems, although it is widely acknowledged that these problems exist (Borgaro et al., 2003). They mention irritability, anxiety and depression as common affective sequelae. In a pilot study, Borgaro et al. (2003) compared a group of 14 patients with uncomplicated MTBI and 14 patients with complicated MTBI, as defined by the presence of a space-occupying lesion, on a standardized test of neuropsychological functions. The two groups were matched by GCS scores. Additionally, both groups were compared to a group of healthy controls (Borgaro et al., 2003). The Barrow Neurological Institute Screen for Higher Cerebral Functions was administered to all subjects. The results indicated that although complicated injuries were associated with poorer

performance on cognitive subtests, both complicated and uncomplicated injuries showed similar impairments in the sub-tests of affective disturbances (Borgaro et al., 2003). Thus, it may seem that though research has mainly focused on cognitive sequelae, affective disturbances are in fact more common. All subjects were tested within 40 days of their injury, and exclusion criteria included prior TBI and significant psychiatric illness (Borgaro et al., 2003).

1.2.3. Holistic rehabilitation and psychotherapeutic interventions after MTBI

Marshall and colleagues (2012) present a set of clinical practice guidelines for diagnosing and treating MTBI. They rate each of their recommendations according to how much supporting evidence that exists. A-rated guidelines were backed by at least one RCT, meta-analysis or systematic review. For the B-rated guidelines, at least one cohort comparison, case study or other type of experimental study was required. Finally, the guidelines received a rating of C if they had no research evidence, but represented an expert opinion, or the experience of a consensus panel (Marshall et al., 2012). Of their 71 recommendations, 50 were classified as grade C, which means that only a minority of the guidelines were based on research evidence. Although some of them do not lend themselves easily to rigorous experimental investigation (e.g. the recommendation of referring the patients to a specialist if they show persisting symptoms), others, like the effectiveness of trauma-focused CBT on PTSD symptoms (8.8), should be fairly easy to establish.

One of the A-rated recommendations in Marshall et al.'s guidelines is early education and reassurance of patients. This should be provided within one week of injury. Snell et al. (2008) also discuss education early in the recovery, and conclude that it is the only intervention with sufficient evidence. It is worth noticing that most of the studies Snell et al. reviewed excluded individuals with psychiatric illnesses, substance abuse, other comorbid health conditions or previous TBI. This is an especially interesting point, since one of the studies they reviewed (Ghaffar, McCullagh, Ouchterlony, & Feinstein, 2006) found that although participants in general did not benefit from the multidisciplinary treatment they administered, a subgroup of participants did. These were people who had histories of psychiatric disorders. The participants in this study received rehabilitation tailored to their needs, so these results might be difficult to replicate. Nevertheless, patients with histories of psychiatric illness in the intervention group showed fewer signs of depression later on than their counterparts in the control group. Psychiatric illness is, along with chronic pain, a factor associated with longer and more problematic recovery (Mooney, Speed, & Sheppard, 2005). This leaves the possibility that intervention studies that exclude participants on these grounds,

or that fail to look at this group separately, discard interventions that might have an effect. If the need for internal validity leads to intervention studies systematically overlooking those groups that may gain the most from therapy, then there is good reason to look more specifically at who might benefit from which kinds of interventions. Snell et al. (2008) point out that there are few methodically strong studies examining the management of persisting symptoms.

While there are few high-quality studies looking at persistent symptoms in general, affective/emotional symptoms appear to be particularly neglected. The dearth of studies exploring the affective sequelae of MTBI so far makes it difficult to say anything certain about effective psychotherapeutic treatment, though there are some studies that make preliminary recommendations. Borgaro et al. (2003) conclude that early intervention (within 40 days in their case) strategies should include interventions aimed at appropriate expression of affect and interpretation of affective responses. This conclusion might be a bit premature, though this is definitely a subject that calls for further exploration. Given the short time that had elapsed since the injury when this study took place, there is always the chance that patients with these affective disturbances would have recovered spontaneously at a later stage. Thus, there is a need for longitudinal follow-up studies to clarify this issue.

The studies conducted so far, although few in numbers, have looked at a wide range of problems that may arise in the aftermath of an MTBI. After an MTBI, people differ in both the amount of problems they experience, and the subjective distress that these problems cause. This will depend on each person's sense of self, and what level of functioning their daily activities demand. For some individuals, a high level of cognitive functioning is important, whereas for others, problems with interpersonal relations and psychosocial functioning might be more distressing. Because of this, rehabilitation after brain injury often takes a holistic approach. This means that interventions are aimed both at cognitive, emotional, and social functions (Wilson, Gracey, Evans, & Bateman, 2009). Because these functions are interrelated and work closely together, it can be difficult and not always useful to address them separately in the clinical setting. Thus, both in research and in clinical settings, the definition of "rehabilitation" is rather wide and includes vocational therapy and physical therapy as well as psychosocial intervention and more conventional psychotherapy.

For this reason, it was necessary to choose a definition of psychotherapeutic interventions for the selection of studies in our thesis. We chose to employ the definition of psychotherapy used by the American Psychological Association (APA) in their recognition of psychotherapy effectiveness (American Psychological Association, 2012).

> Psychotherapy is the informed and intentional application of clinical methods and interpersonal stances derived from established psychological principles for the purpose of assisting people to modify their behaviors, cognitions, emotions, and/or other personal characteristics in directions that the participants deem desirable (Norcross, 1990).

This is a wide definition, which does not require that the patient suffers from an illness or symptoms that verify a diagnosis. Although using such a wide definition has its advantages, it also leaves room for interpretation, and so we had to make some choices concerning what we considered to be encompassed by such a definition. We chose to exclude interventions aimed only at cognitive functions, such as learning and memory. Although we included therapeutic interventions that included a wide range of treatments, it was a prerequisite that at least parts of the intervention was aimed at emotional or social functioning. Furthermore, the definition state that interventions should be "derived from established psychological principles". This means, in our opinion, that also treatments beyond the conventional schools of psychotherapy must be included, as long as they have their foundation in such principles.

1.3. State of MTBI treatment research today

Ruff (2005) provides insight in the brief history of MTBI-research: When the GCS was introduced in 1974, a score in the range 13-15 was considered insignificant. No follow-up was provided for patients in this group. In the 1980's, research was mainly focused on the more severe cases of TBI.

But come the 1990's, the field saw a substantial growth in research on MTBIs. In the 90's, research was mainly driven forward through litigation. American soldiers who had experienced MTBIs in the field, still experienced adverse symptoms long after the injury. As a result, the soldiers took legal action against the government. According to Ruff, this created a dualism in the field. On the one hand, the soldiers' attorneys provided evidence – mainly neuropsychological assessment results - that MTBI was a genuine condition, resulting from an actual brain injury. On the other hand, the defence provided evidence of the opposite – that the soldiers were malingerers, and that persisting MTBI-symptoms were a psychological artefact. This dualistic distinction has gained foothold in public opinion. It is either biological *or* psychological. According to Ruff, this distinction has slowed progress in the field. One could also be sceptical of a research field driven by patients' demands for injury compensation, and the government's reluctance to provide it.

Research on MTBI and its treatments has gained both momentum and respect over the past two decades. From the artificial dualism of American courtrooms, to a more sober acknowledgement that MTBI is a very complex biopsychosocial phenomenon. As the field is gathering around consensus definitions of MTBI, and we are entering an era with a new generation of diagnostic tools, one thing becomes evident: There is a mismatch between the research on diagnoses and definitions, and the research on treatment. Despite the recognition of persistent symptoms of MTBI as a complex condition, with clear psychological and psychosocial influences, there is a remarkable lack of research on psychological interventions and neuropsychotherapy. For instance, as discussed earlier, there is substantial evidence that MTBI is associated with depression, anxiety, PTSD and disturbances of sleep.

The research investigating non-surgical, non-pharmacological interventions on MTBI-patients from 1980 to the present day, is thoroughly discussed and highlighted in five systematic review articles (Borg et al., 2004; Comper et al., 2005; Marshall et al., 2012; Nygren-de Boussard et al., 2014; Snell et al., 2008).

Comper et al. (2005) systematically reviewed the literature on the effectiveness of interventions for adult MTBI-patients. The review covers research in the period from 1980 to 2003, and only the studies investigating early educational interventions used satisfactory rigorous methods. Additionally, the reviewed studies lacked severely in validity.

Borg et al. (2004) did a similar systematic review of the existing literature, and point out the same weaknesses in definition and scientific rigour as Comper et al. (2005) did. According to Borg et al., the lack of valid consensus definitions based on valid diagnostic procedures, makes it difficult to assess and compare the actual effect of intervention studies.

Snell et al. (2008) used Comper et al. (2005) and Borg et al. (2004) as a basis for conducting a similar study, using data from 2003 through 2006. In this time-period, 8 new studies were included for review. The only studies of satisfactory scientific rigour, were again studies investigating early educational interventions. Snell et al. (2008) also point out that a meta-analysis was impossible to conduct, due to the heterogeneity of case definitions throughout the literature.

Marshall et al. (2012) did a similar review to provide best practice guidelines for MTBI and patients suffering prolonged recovery. Most of their recommendations are based on clinical expertise and experience, while again, the only recommendation solidly founded in the literature is early educational interventions. And, as will be discussed later, this type of intervention might not have any effect for patients suffering a prolonged recovery.

The latest systematic review of the literature (Nygren-de Boussard et al., 2014), systematically reviewed the literature on non-surgical interventions for MTBI in the years between 2001 and 2012. They applied even stricter methodological criteria for inclusion, and hence they found even fewer satisfactory studies than the previous systematic reviews. 1 of the 2 studies they deemed scientifically acceptable found that early educational interventions could be effective, and the other found that the advice to stay in bed for a prolonged time-period subsequent to an MTBI, did not have any scientific foundation.

All in all, the systematic studies we have identified, paint a sombre picture of a field in need of high quality research adhering to consensus measures and definitions. Over all, studies investigating non-surgical or non-pharmacological interventions on MTBI-patients lack in both methodological stringency, agreed-upon inclusion criteria for the study, and a variety of different outcome measures. Perhaps most disappointing is the fact that since Borg et al. (2004) and Comper et al. (2005) highlighted systematic problems with the research, and how those problems could be addressed in future research, very little has been done to fill this gap in the literature.

1.4. Why it was important to conduct the present systematic review

While reviews appraising treatment after MTBI have been conducted earlier, we believe the present review can make a novel contribution to the field. Of the five systematic reviews mentioned in section 1.3, two (Borg et al., 2004; Nygren-de Boussard et al., 2014) had a wider focus, looking at non-surgical interventions in general. The review by Comper et al. (2005) also included a wider range of treatments, in addition it looked at treatment for all MTBI sufferers, not focusing on prolonged recovery. The review by Snell et al.(2008) looks more specifically at psychological treatments, but like the review by Comper et al., it includes all MTBI patients, regardless of symptom duration. Marshall et al.(2012) present clinical practice guidelines, which are partially based on a systematic literature search. However, they also include guidelines based on expert advice and consensus, and thus have a less evidence-based approach. In our work with this systematic review, we also came across a review by Al Sayegh et al., published in 2010. The review by Al Sayegh et al. looks specifically at patients with prolonged recovery, defined as “postconcussion syndrome, postconcussion symptoms or other psychiatric or psychological problems after mild acquired brain injury”(Al Sayegh, Sandford, & Carson, 2010, p. 1129). However, their inclusion criteria, when it comes to injury definition as well as definition of treatment interventions, are less specific than ours. It is also worth mentioning that their literature search ended in 2008, six years before ours did. This means that we can present a more updated review of the literature. By looking

exclusively at persisting symptoms after MTBI and psychotherapeutic interventions aimed at the relief of such symptoms, the present review represents a unique approach to a complex condition. In addition to this, we have included an extended discussion that addresses the methodological dilemmas of MTBI research.

1.4.1. Persisting symptoms

The present thesis reviewed only studies with participants suffering from symptoms of prolonged recovery after MTBI, defined as continued sequelae three months post-injury. There are two main reasons for this.

The first reason pertains to prevalence. Sufferers of MTBI present with a range of symptoms that vary both in kind and degree of severity. For most of them, complete remission occurs within days or weeks after injury. For a small, yet substantial group, this is not the case. This group, often referred to as the "miserable minority" (Ruff, 2005) might benefit from interventions that MTBI patients in general have no need for (Ghaffar et al., 2006). As the term "miserable minority" implies, only a few of those who suffer an MTBI experience these persisting symptoms. Nevertheless, the base rate of MTBI is still large enough for this minority to matter. The actual size of the minority varies from study to study, but 15% is a common estimate (Cassidy, Carroll, Peloso, et al., 2004; Wood, 2004). Even though this miserable minority only has a prevalence of about 15 % in the MTBI population, the base population of patients suffering from MTBI is so large (Cassidy, Carroll, Peloso, et al., 2004), that this group is still substantial. The numbers are comparable to the prevalence of Parkinson's disease (Wood, 2004). Also, as pointed out by Wood (2004), PCS has such a pervasive effect on lifestyle, relationships and employability that its impact goes beyond those directly affected.

The second reason is that risk factors for persisting symptoms are not properly identified. Although studies identifying the risk factors are emerging (Hou et al., 2012), there is a lack of studies implementing this knowledge in clinical investigations. Even so, a lot of the putative risk factors, such as psychiatric disorders and former TBI, are frequently used as exclusion criteria, and groups who are known to be in risk of persisting symptoms are frequently removed after screening (Snell et al., 2008). There are several advantages in doing this. The patient sample is more homogeneous, it more closely resembles the population it is thought to represent, and, as a consequence, it reduces the risk of random noise cancelling out important effects. This strengthens the internal validity, because possible confounding variables are being kept constant. In one sense this also gives strengthened ecological validity, because it makes it possible to generalize from the sample to the general, healthy population.

But doing this is not without issues. The clinical reality is complex, and people seldom present with just one diagnosis. Iverson and Lange (2011) mention comorbid conditions, such as chronic pain, depression and anxiety disorders, as well as pre-existing factors like personality characteristics and pre-existing problems with mental and physical health, as elements likely to affect long-term problems after MTBI. These factors may also influence the way individuals respond to treatment interventions. If individuals with pre-existing health problems are systematically kept out of the studies, the ecological validity may not be so strong after all. Furthermore, if these are the patients most likely to benefit from psychological interventions, research on treatment interventions may miss valuable information by asking questions that are not specific enough, and that do not separate the miserable minority from the favourable majority.

Therefore, this thesis aimed to look specifically at those with persisting symptoms three months after injury. We have chosen three months post injury as our cut-off point, because this is commonly used in the literature (Wood, 2004), and it is also the cut-off point endorsed by the DSM-IV in their definition of PCD. The WHO collaboration centre task force on mild traumatic brain injury also acknowledged that for the majority of MTBI patients, cognitive symptoms seem to have ceased at this point (L. Carroll et al., 2004). Hou et al. (2012) investigated rate of PCS in an MTBI sample 3 and 6 months post-injury, and found the prevalence to be 22% and 21% respectively. Thus, it seems that by three months post-injury, symptoms have already stabilized, and for the next three months, not much changes.

Furthermore, we wished to investigate whether any studies had acknowledged these groups and explored the mechanisms that make them especially vulnerable, and further looked at the effect of psychotherapeutic interventions. Is there new evidence supporting the effect of psychotherapy for these groups? Is there enough research conducted to enable us to make predictions as to which factors might be important, and thus make recommendations for further research?

1.4.2. Why psychotherapy?

We believe psyhotherapeutic interventions represent a promising approach to the treatment of persistent symptoms after MTBI. The factors related to poor outcome are, in several studies, found to be factors that can readily be addressed by psychotherapeutic approaches. Kay et al. (1992) describe how psychological factors may contribute to maintaining the problems caused by an MTBI. Mooney et al. (2005) found depression and pain to be among the predictive factors. Psychotherapeutic treatment for chronic pain has yielded good results (Morley, Eccleston, & Williams, 1999), and it has also shown moderate

effects on depression (Cuijpers et al., 2010). Earlier systematic reviews of MTBI treatment also report an effect of psychotherapy (Amal Al Sayegh, David Sandford, & Alan J. Carson, 2010; Snell et al., 2008), although it is obvious from these reviews that the matter needs further investigation for firm conclusions to be drawn. In pain management, a biopsychosocial perspective has allowed for the usage of psychotherapeutic interventions in a field that was previously thought to be strictly somatic. There are several similarities between chronic pain and persistent symptoms after MTBI; in both cases, symptoms persist long after the injuries causing them are believed to have healed. Studies highlighting the importance of illness perceptions (Robert Whittaker, Steven Kemp, & Allan House, 2007) in maintaining symptoms, give further support to considering psychotherapeutic treatment for persisting symptoms, since perceptions and beliefs are the main objects of cognitive therapy.
In sum, it seems likely that psychotherapy may offer effective relief of persistent symptoms, and this is definitely a subject that warrants further research.

2. Methods

2.1. Search Strategy

The search was conducted according to our terms and specifications by a research librarian at the Medicine and Health Library at St. Olav university hospital. For a detailed search strategy, see appendix 1.

2.2. Screening for eligibility and selection of studies

Ideally, studies included in the present systematic review should adhere to one of the three consensus-definitions of MTBI presented in section 1. But given the persistent heterogeneity of definitions and still unsolved issues in MTBI-diagnostics as discussed in section 1, we considered it premature to exclude studies because they employed non-consensus definitions of MTBI. The interventions included in the studies should be compatible with our chosen definition of psychotherapy, described in section 1.2.3. Because of the beforementioned difficulties with heterogeneous diagnostic criteria prior to 2004, as well as overlap with other systematic reviews, we decided to only review research done after 2004.

We set the following relevance criteria for inclusion in the present systematic review:

1. Was the study conducted after 2004?
2. Did the study include a psychotherapeutic intervention compatible with our chosen definition?
3. Were the participants aged 16 or older?
4. Was the study not a case study?

5. Did the study investigate MTBI exclusively? Or, if other injuries were included in the study, were the results of MTBI participants analysed separately?
6. Did the dependent variables include any measures of psychological symptoms or emotional or social functioning?
7. Was the intervention administered at least three months post-injury?

The databases Embase, Medline, PsycInfo, CINAHL, and SPORTDiscus were searched for relevant words and expression (Appendix 1). These databases were chosen because they are among those most frequently used in the field of MTBI research, and they were the databases of choice for the update of WHOs findings published in 2012 (Cancelliere et al., 2012). After removing duplicates, 1925 hits remained. Of these, 31 were published prior to 2004, leaving 1894. At the next step, we excluded papers that did not include an intervention. These were reviews, book chapter, validity tests of assessment batteries et cetera. 1717 studies were excluded for not being intervention studies, leaving 177. A further 88 studies whose interventions were not compatible with our definition of psychotherapy, e.g. pharmaceutical studies, were excluded next. Of the remaining 89, another 11 studies were excluded because the participants were under 16 years of age. Of the remaining 78 studies, 16 were case studies, and thus excluded. At this point 62 studies remained, and were looked up to determine whether or not they complied with our fifth criterion, which was that the participants had to be MTBI patients. In cases where TBI of several severities were included, MTBI cases had to be distinguishable in the analyses. Thirty-eight studies were excluded because they did not meet this criterion, and 4 studies (see appendix 3) were excluded because we, after extensive search, were not able to find the full text of the original paper. This left 20 studies, of which 10 did not examine the outcome variables we were interested in, e.g. they examined only memory or pain relief. Of the remaining 10, only three studies administered their intervention more than three months postinjury, and were included in our review (See table 4 for an illustration of the exclusion process). In addition, three of the remaining seven studies were also considered in this thesis, as an extension of the review. These were studies that did not look at the subgroup suffering prolonged recovery, but that in different ways explored the possibilities of preventing persisting symptoms in patients at risk. This marks, in our opinion, an interesting distinction in the literature. While those who are deemed at risk for prolonged recovery in the acute phase represents a different population than those who end up with prolonged recovery after three months, the investigation of risk factors and the possible preventive interventions aimed at these should be of great interest to those diagnosing and

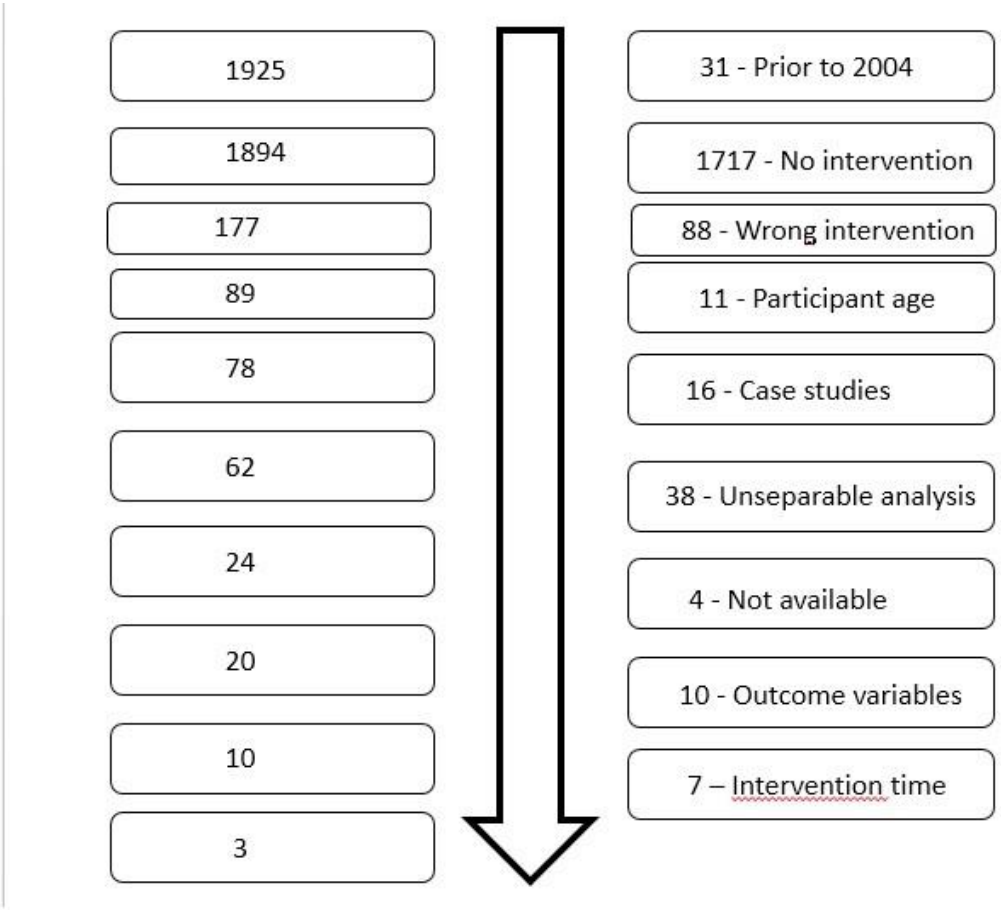

Table 4: Flowchart of selection of studies

treating persistent symptoms. Therefore, we will first present the three studies that fulfilled our criteria, and their findings. Then we will supplement these results with the knowledge derived from the three prevention studies.

2.3. Assessment of susceptibility to bias

Of the three studies included in our systematic review, only one (Tiersky et al., 2005) was a randomised controlled trial. The other two (Azulay, Smart, Mott, & Cicerone, 2013; King et al., 2013) did not include control groups. Of the three studies looking at prevention of persistent symptoms in at-risk patients, all were RCTs. The Cochrane Collaboration handbook presents a tool for assessing risk of bias in randomised controlled trials (Higgins, 2012). The four studies that could be considered RCTs were evaluated using this tool (appendix 2), and the results are summarized in table 5.

This tool allows investigators to examine the risk of different types of bias in the research they are reviewing. One study is presented per row, while the columns represent the different risks of bias for the individual studies. The green cells indicates a low risk of bias,

the red cells indicates a high risk of bias, whereas the yellow cells indicate that assessment of risk was not possible.

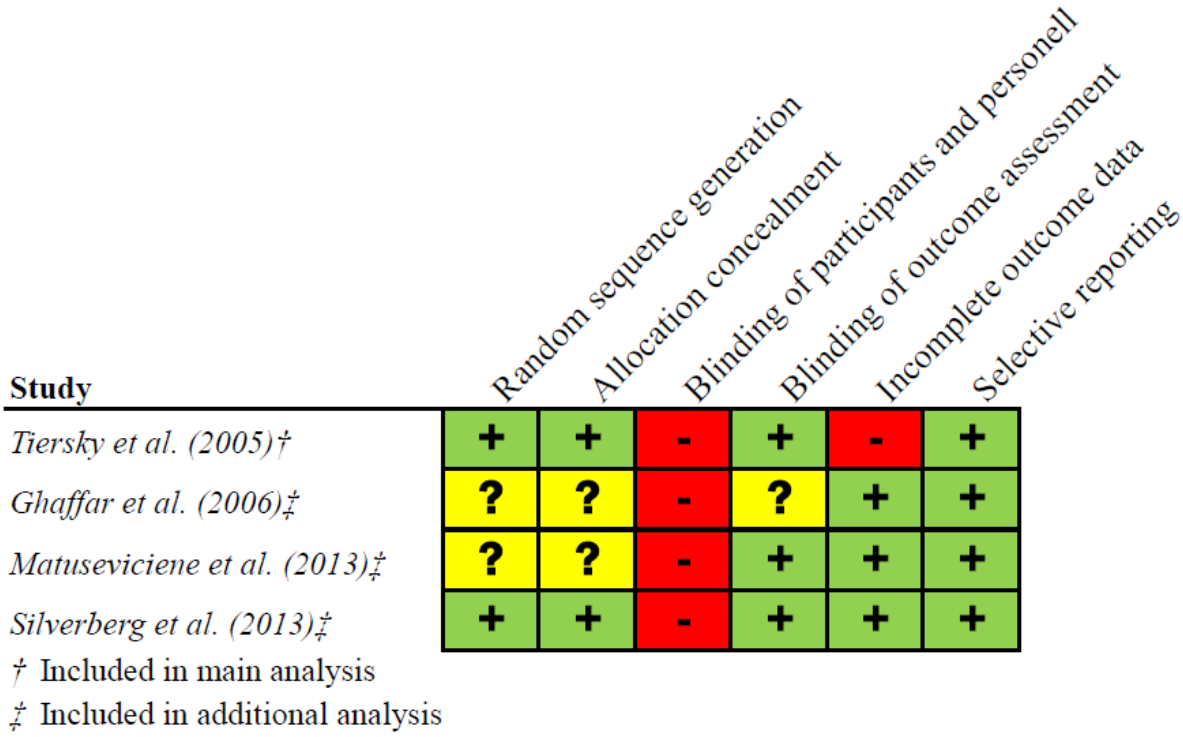

Table 5: Assessment of risk of bias

The sources of bias in the other, methodically less stringent studies, will be addressed in the results, and further evaluated in the discussion.

2.4. Data extraction and analysis

The studies we have reviewed differ both in methods and scope. Interventions range from mindfulness to cognitive-behavioural therapy and more holistic, individualized treatments. A range of outcome measures was employed. This makes comparison of intervention effects difficult. Therefore, statistical pooling of the results was not possible. Instead, we present each of the six studies, and summarize the findings in an evidence table (Table 6).

Overview of Reviewed Articles

Study	*Study Design*	*Participant characteristics*	*Intervention*	*Outcome Measures*	*Main Results*
Tiersky et al. (2005)†	Single-blind randomized, wait-listed controlled trial, with waitlist as control group. The study employed repeated measures and multiple baselines.	Twenty persons with persisting complaints after mild and moderate TBI (11 in treatment group, 9 controls). On average, the sample was middle-aged (range, 19–62y), well-educated, white, and female. (Male to female ratio: 6:5 in the intervention group and 3:6 in the control group). ACRM criteria.	The experimental group received both 50 minutes of individual cognitive-behavioral psychotherapy and 50 minutes of individual cognitive remediation, 3 times a week for 11 weeks. The control group was wait-listed and received treatment after conclusion of follow-up.	Paced Auditory Serial Addition Task (PASAT), the Rey Auditory Verbal Learning Test (RAVLT), ACFI, Attention Questionnaire, Coping Response Inventory (CRI), SCL-90R, Community Integration Questionnaire (CIQ).	There was a statistically significant treatment effect on GSI (SCL-90R) (p=0.046), and on the SCL-90R subscales of anxiety (p=0.031) and depression (p=0.029). There was also a significant effect on the PASAT (p=0.011), and on the RAVLT (p=0.010).
Ghaffar et al. (2006)‡	A randomized, controlled treatment trial.	191 MTBI patients were recruited from the emergency departments of two tertiary trauma centers in association with the University of Toronto. The male to female ratio was 64:33 in the treatment group and 60:34 in the control group. ACRM definition of MTBI.	Treatment group (n=97) were given an appointment in a multidisciplinary TBI clinic within 1 week of injury, and further treatments were tailored according to each individual patient's need. Control group (n=94) were not offered follow-up visits or treatment.	RPCQ, Rivermead Follow-up Questionnaire, the General Health Questionnaire, Stroop Color-Word Test, Symbol-Digit Modalities Test, PASAT, Simple Reaction Time, Choice Reaction Time, Hopkins Verbal Learning Test, the Vocabulary subtest of Wechsler Adult Intelligence Scale – Third Edition (WAIS-III), Letter-Number Sequencing subtest of WAIS-III, the Matrix-Reasoning subtest of WAIS-III.	The treatment group and the control group did not differ significantly on any of the measures 6 months post-injury. However, subjects with a psychiatric history showed significantly less depression on the GHQ subscale at the 6-month follow-up.

Study	*Study Design*	*Participant characteristics*	*Intervention*	*Outcome Measures*	*Main Results*
Azulay et al. (2013)†	Over a 2-year period, a convenience sample was recruited from clinical referrals. Participants completed outcome measures before and after treatment intervention.	22 individuals with MTBI, more than 7 months after injury. 11 male and 11 female participants aged 18–62 years. ACRM criteria.	A 10-week group (one 2-hour session per week) modeled after Kabat-Zinn's MBSR program. Modifications were made to meet cognitive challenges typical for this population. This tailored treatment was then manualized to ensure treatment consistency across groups and leaders.	The Perceived Quality of Life (PQOL) scale, the Perceived Self-Efficacy Scale, the Neurobehavioral Symptom Inventory (NSI), the Continuous Performance Test of Attention, the Paced Auditory Serial Addition Task (PASAT), the California Verbal Learning Test-II, the Social Problem-Solving Inventory –Revised Short Form and the Mindfulness Attention Awareness Scale.	Statistically significant changes were seen on Perceived Self-Efficacy Scale, PQOL, the Social Problem-Solving Inventory, the Continuous Performance Test of Attention and the PASAT. For one third of participants (n=7), a clinically significant change was seen (from a lower functioning category to a higher functioning category on one or both of the attention measures).
King et al. (2013)†	A pilot study involving 25 active duty, veteran and civilian participants. At baseline, each participant completed a self-run psychoeducational computer-based treatment. 1 month postintervention, participants were assessed via phone to evaluate the severity of postconcussive symptoms.	25 participants aged 18–55. Participants were recruited over a 12-month period from three health care facilities; a VA* Polytrauma Rehabilitation Center (91% male), a civilian hospital (50% male), and a naval medical center (100% male). PTA ¡24 hours and/or LOC ¡30 min.	A computer-based treatment based on a modified version of *Recovering from Head Injury: A Guide for Patients*. The entire protocol including the educational portion, questionnaires and quiz took approximately 20–30 min.	The Neurobehavioral Symptom Inventory, (NSI), the Patient Health Questionnaire-9 (PHQ-9), the Posttraumatic Stress Disorder Checklist Civilian Version (PCL-C).	Participants were divided into Acute (<3 months postinjury) and Chronic (>3 months postinjury) groups. Chronic participants reported significantly more symptoms overall, $F(1,23)=162.16$, $p<0.001$, but both groups significantly improved over time, $F(1,23)=18.40$, $p<.001$, $d=.99$. The lack of a group by time interaction $F(1,23)=.105$, $p=.748$ indicated comparable rates of improvement in both groups.

Study	*Study Design*	*Participant characteristics*	*Intervention*	*Outcome Measures*	*Main Results*
Matusevicius et al. (2013)‡	Randomized controlled trial.	173 patients, aged between 16 and 70, recruited from seven regional and county hospitals in five Swedish cities. Participants were seen in the emergency room (ER) within 24 hours after injury. The male to female ration was 40:36 in the non-randomized group, 23:26 in the control group and 15:33 in the treatment group. LOC≤30 min and/or PTA ≤ 1 hour, plus GCS 14–15.	All participants received written information about MTBI. High-risk (n=97) patients were randomized to either early visit to a doctor or to treatment as usual (TAU); all patients including the 76 low-risk patients were followed up at 3 months. Interventions for identified problems related to the MTBI or to comorbidities were provided as needed.	RPQ and the Hospital Anxiety and Depression Scale.	There was a statistically significant difference between the groups at baseline (higher symptom load in the intervention group), but the groups did not differ in amelioration rate.
Silverberg et al. (2013)‡	A pilot randomized controlled trial. Masked outcome assessment after 3 months.	28 patients aged 18–65 with uncomplicated mild traumatic brain injury. Patients were recruited within 6 weeks after injury, and determined to be at risk for chronic PCS. Male to female ratio: 6:9 in the treatment group, 5:8 in the control group. ACRM criteria.	Participants were randomized to either (1) treatment as usual (education, reassurance, and symptom management strategies) from an occupational therapist, or (2) treatment as usual plus CBT delivered by a psychologist. Intervention started within 6 weeks postinjury.	RPQ, Mayo-Portland Participation Index (M2PI), Illness Perception Questionnaire-Revised (IPQ-R), Hospital Anxiety and Depression Scale (HADS), Credibility/Expectancy Questionnaire, (items adapted to make reference to PCS). A structured psychodiagnostic interview was administered, and participants were asked about their compensation-seeking status.	In the TAU group, 10 of 11 participants met ICD-10 criteria for PCS at follow-up, whereas 7 of 13 participants in the TAU+CBT group. This proportional difference was significant ($\chi^2 = 3.962$, $p=0.47$).

† Studies included in the main analysis
‡ Studies included in the additional analysis

Table 6: Summary of findings

3. Results

3.1. Tiersky et al. (2005)

This study looked at both mild and moderate brain injuries, but was included because the treatment group consisted of only mild cases. The aim of the study was to see if neuropsychological rehabilitation could be of help to people who still experienced symptoms more than one year after traumatic brain injury. The participants were 20 patients with persistent symptoms after TBI, 1 - 20 years post-injury. The intervention consisted of two components: cognitive-behavioural therapy (CBT) and cognitive remediation, both based on a treatment manual. Participants received two 50 minutes sessions per day, three days a week for 11 consecutive weeks. Several measures of cognitive and emotional functioning were administered to establish a baseline. Post-intervention follow-up tests were administered at three points: Immediately after treatment/waitlist, one month later and three months later. Of the primary outcomes, ANOVA showed a statistically significant ($P \leq 0.05$) effect on General Symptoms Index (GSI) as a whole, and on the subscales depression and anxiety. A treatment effect was also seen on the Paced Auditory Serial Addition Task (PASAT). No effect was seen on problem solving (CRI) or attention (Attention Questionnaire). Tiersky et al. also conducted five planned post hoc analyses, of which only one (Rey Auditory Verbal Learning Test, RAVLT) showed statistically significant improvement. The authors concluded that the interventions "appear to diminish psychologic [*sic*] distress and improve cognitive functioning among community-living persons with mild and moderate TBI" (Tiersky et al., 2005, p. 1565).

3.2. Azulay et al. (2013)

Azulay et al. presented a pilot study examining the effect of a mindfulness-based stress reduction (MBSR) programme on postconcussive syndrome, also referred to by the authors as "chronic mild traumatic brain injury". Participants were medically stable adults who had suffered a TBI that met the ACRM criteria of MTBI. All were at least three months post injury. The intervention lasted for 10 weeks, with one 2-hour session each week. The stress reduction programme was based on the model of Kabat-Zinn, with certain modifications to make it suitable for PCS patients. The changes made were standardised, to ensure that all groups followed the same guidelines. Treatment effect was measured by comparing pre- and posttest results on five self-report measures and three neuropsychological tests (see table 6). Of the five self-report measures, statistically significant improvements were found on both the Perceived Self-Efficacy Scale and the Perceived Quality Of Life (PQOL) scale. Participants' scores on the Neurobehavioural Symptom Inventory (NSI) were reduced, but not to a

statistically significant degree. Self-reported social problem-solving skills did not improve significantly, neither did the patients' self-reported mindful attention awareness. Three neuropsychological tests were conducted. Significant improvements were seen on two measures of attention (Paced Auditory Serial Addition Test (PASAT) and Continuous Performance Test of Attention), but not on the California Verbal Learning Test-II, a measure of new learning. Seven of the 21 participants showed a clinically significant improvement on a least one of the measures of attention, moving from a lower to a higher category of functioning. The authors conclude that "Improved performance on measures associated with improved quality of life and self-efficacy may be related to treatment directed at improving awareness and acceptance, thereby minimizing the catastrophic assessment of symptoms associated with MTBI and chronic disability" (Azulay et al., 2013, p. 323). It should be noted that there was no control group in this study. Furthermore, the authors reported that the participants were receiving rehabilitation while taking part in the study. Therefore, caution should be taken in attributing the improvement to the MBSR programme.

3.3. King et al. (2013)

King et al. (2013) conducted a pilot study of a novel intervention for postconcussive symptoms for soldiers and civilians. The inclusion criteria included PTA less than one day, and LOC less than 30 minutes, English-speaking, between 18 and 55 years old. Exclusion criteria included history of moderate or severe TBI, history of major psychiatric disorders other than PTSD, currently involved in litigation, and failure on effort tests (i.e. indication of malingering). The study investigated the feasibility of an educational computer programme for reducing postconcussive symptoms, as well as investigating factors related to patient and treatment-site. The study also included feedback from participants on the intervention. The participants were recruited from different sites. For that reason, they received the intervention at different time-intervals after their injury, varying from within days post-injury, to months post-injury. This made it possible to compare between an acute group and a chronic group. The study did not employ a control group. The results of the intervention showed that those with chronic dysfunction had more symptoms than those who received the intervention in the acute phase $F(1,23) = 162$, $p < .001$. Both groups showed a significant reduction in symptoms. This suggests, according to the authors, that this type of intervention may remediate symptoms, not only for acute patients, but also for the "miserable minority".

3.4. Synthesis of evidence from the three studies

The three studies reviewed above represent three approaches to the treatment of persisting symptoms after MTBI which are quite different, but which still fall within our

definition of psychotherapeutic interventions. While Tiersky et al. looked at a combination of CBT and cognitive remediation, Azulay et al. explored a less conventional approach by employing mindfulness-based techniques to this population. King et al. relied on an educational method, by providing participants with a computer programme that encompassed both information and suggestions for symptom-relieving strategies. The participants in the study by Tiersky et al. showed improvement on GSI, indicating that at least one of the two interventions had an effect. The participants in Azulay et al.'s study also improved, but also in this study results are confounded by the fact that the participants were receiving concurrent rehabilitation. The computer-based intervention in King et al.'s study improved participants' symptoms. Thus, while the three studies employed different methods of intervention, they all appear to offer symptom relief to a certain degree.

3.5. Results derived from studies of preventive interventions

The following three studies did not look at treatment interventions three months post injury, but at the effect of early treatment interventions on later outcome, with a particular focus on possible risk factors. They are included here because they, although they do not directly address the topic of our thesis, represent an alternative approach to the subject of prolonged recovery after MTBI, which can supplement the treatment research. An exploratory analysis of these studies are relevant, also because they illustrate a trend in the literature to look at preventive measures in addition to treating the prolonged symptoms after they occur. A knowledge of what preventive measures prove valuable, may inform research on what interventions may be fruitful after the symptoms appear.

3.5.1. Ghaffar et al. (2006)

This study investigated whether long-lasting sequelae after MTBI could be prevented by multidisciplinary treatment in the acute phase. The authors also explored whether certain putative risk factors – previous head injury, a history of psychiatric illness and being involved in litigation – could predict worse outcome. 191 participants were recruited from two tertiary trauma centres, and were assessed within one week of injury. The treatment group (n=97) was evaluated by a multidisciplinary team of health personnel, and received individualized treatment including psychotherapy, pharmacotherapy, physiotherapy and occupational therapy. 6 months after injury, all participants were measured on a range of tests (see table 6). The two groups did not differ significantly on any of the measures. With respect to the putative risk factors, previous head injury did not seem to influence the outcome. Participants in the control group with a history of head injury did not differ from their counterparts in the treatment group. Psychiatric history, on the other hand, did show an interaction with

treatment. Participants in the treatment group with a history of psychiatric illness showed significantly lower depression scores six months post-injury than those in the control group. The third putative risk factor Ghaffar et al. looked at was involvement in litigation. Litigants did not differ from non-litigants on measures after treatment. Ghaffar et al. conclude that treatment aimed at all patients in the acute phase after an MTBI does not seem beneficial in the long run. Targeting those at risk of prolonged recovery (those with a history of psychiatric illness) may be more expedient and cost-effective.

3.5.2. Matuseviciene et al. (2013)

The study by Matuseviciene et al. compared the effect of an early diagnostic and intervening visit to a specialist in neuro-rehabilitation, to treatment as usual (TAU). Participants suffered from MTBI, and the goal was to prevent the development of persisting disability after the injury. The inclusion criteria were LOC less than 30 minutes and/or PTA less than 60 minutes, and GCS 14-15 on arrival to ER. Patients with intracranial injury, but not in need of surgery, were also included. Patients were considered at high-risk for developing persisting disability, if three or more symptoms were indicated on the Rivermead Post Concussion Symptoms Questionnaire (RPQ) 10 days post-injury. With this definition of high-risk patients, more than 50 % of the participants ended up being included in the high-risk group. This is considerably higher than the "miserable minority" in other studies (Ruff, 2005). Exclusion criteria included need for surgery or intensive care, other significant physical injury requiring surgery, or an ongoing somatic or psychiatric disease with a probable impact on activities of daily living. The participants, aged 15-70, were recruited from seven hospitals in five Swedish cities. 173 participants were recruited, 97 were classified as high risk. The high-risk patients were randomised in blocks of four, 48 to the intervention group, 49 to the TAU-group. The total dropout was at 17 %, evenly distributed between the groups. Patients in both groups received medication and treatment as needed, in addition to the treatment as usual and the intervention. The result indicated no statistical significant difference between the intervention group and the TAU-groups. In the low-risk group, symptom level did not change significantly from baseline to follow-up, indicating that the assumed high-risk criteria did indeed represent risk factors.

3.5.3. Silverberg et al. (2013)

The goal of Silverberg et al.’s study was to examine and estimate the effect of CBT delivered after MTBI, to patients at risk for developing postconcussion syndrome (Silverberg et al., 2013). The study is in part based on the findings of illness perceptions in patients with MTBI and PCS, and the interventions are based on themes uncovered in earlier research

(Robert Whittaker et al., 2007). Inclusion criteria included injury no more than six weeks before the intervention was delivered, so that one should be able to finish the intervention before three months post injury, as this is considered a "common upper threshold for the subacute recovery phase" (p. 315). The study also explicitly employs the ACRM consensus definition of MTBI. Further inclusion criteria included English as preferred language, patients considered to be in the PCS-risk group, and aged between 18 and 65. The risk factors were based on Whittaker et al (2007), and included acute symptom severity as well as an expectation that symptoms were persistent, and had devastating consequences. Exclusion criteria included intracranial abnormality (i.e. complicated MTBI), previous neurological disease, or MTBI in the previous six months. Prior to randomization, the participants were referred to other treatments as needed.

The intervention consisted of treatment as usual for all patients, and the intervention group subsequently received CBT. The investigators constructed a CBT-protocol specifically designed for MTBI-patients, and the intervention consisted of weekly 50-minutes sessions for six weeks. Outcome measures included RPQ, Mayo-Portland Participation Index (M2PI), Illness Questionnaire-Revised (IPQ-R), and Hospital Anxiety and Depression Scale (HADS). In addition, a structured psychodiagnostic interview was conducted to map the litigation and compensation-seeking status of the participants.

Pre-intervention, 27 of the 28 participants fulfilled the ICD-10-criteria for PCS. Post-intervention, 10 of 11 of the participants in the control group and seven of 13 of the participants in the intervention group still met the ICD-10 criteria for PCS. The authors conclude that a specialized CBT-protocol administered to patients identified as being at high risk for developing PCS based on illness perceptions, probably prevents the development of PCS to some degree. In addition, the authors note, the fact that the control group received treatment as usual, and 10 of the 11 participants still developed PCS, may be an indication that educational interventions may not be an efficient type of intervention for this patient group.

3.6. Characteristics of participants and settings

Of the six articles we included in in our study, three were conducted in the United States of America (Azulay et al., 2013; King et al., 2013; Tiersky et al., 2005), two in Canada (Ghaffar et al., 2006; Silverberg et al., 2013), and one in Sweden (Matuseviciene, Borg, Stalnacke, Ulfarsson, & de Boussard, 2013). Participants' age ranged from 15 to 70. One study (King et al., 2013) included active duty and veteran military personnel; the rest of the participants were recruited from civilian health care. Some were from outpatient clinics, some

from emergency rooms, and some from hospitals. This study also included patients earlier in their recovery than three months, but separated the groups in the analysis. Tiersky et al. (2005) specifically recruited participants describing persisting symptoms. For one study (Azulay et al., 2013) the symptom status of the participants was not stated, but since they were still receiving rehabilitation, it is assumed that they were still experiencing postconcussion symptoms. The study by Silverberg et al. (2013) and the study by Matuseviciene et al. (2013) used samples consisting of individuals presumed to be at risk of developing chronic symptoms. The study by Ghaffar et al. (2006) did not exclusively look at patients at risk, but separated at-risk patients from the rest in the analysis. The male to female ratio differed widely between the studies, with three studies (Matuseviciene et al., 2013; Silverberg et al., 2013; Tiersky et al., 2005), of which two were among those added for perspective, reporting more female than male participants.

3.7. Synthesis of existing evidence

3.7.1. Cognitive-behavioural therapy.

One of the studies in the main review (Tiersky et al., 2005), and one of the additional three (Silverberg et al., 2013), investigated the effect of cognitive-behavioural therapy (CBT). Tiersky et al. had a dual treatment programme consisting of both CBT and cognitive remediation, and their participants were individuals experiencing persisting symptoms. Silverberg et al. had a preventive approach, aimed at individuals deemed to be at risk of developing chronic symptoms. Both studies found that the treatment had statistically significant effect.

3.7.2. Individually tailored treatment.

Two of the additional studies implemented treatment specifically tailored to each participant (Ghaffar et al., 2006; Matuseviciene et al., 2013). This involved a range of health care services, including pharmacotherapy when deemed necessary. Ghaffar et al. found no statistically significant difference between the groups at the six months follow-up. However, they did find that participants in the treatment group with a history of psychiatric illness showed a reduction in depression symptoms compared to their counterparts in the control group. In the study by Matuseviciene et al., both the intervention group and the TAU control group consisted of at-risk patients. At baseline, the groups differed with respect to symptom load. Post treatment, the groups did not differ in the rate with which symptoms had subsided. In summary, none of the studies of individually tailored treatments demonstrated any effect, except for participants with a history of psychiatric illness.

3.7.3. Mindfulness-Based Stress Reduction.

One of the main studies in our systematic review (Azulay et al., 2013) examined the effect of a modified Mindfulness-Based Stress Reduction programme on chronic symptoms after MTBI. The participants showed statistically significant changes on measures of self-efficacy, perceived quality of life and social problem-solving, as well as PASAT and the CPT of attention.

3.7.4. Computer-based treatment of post-concussive symptoms.

One of the main studies in this systematic review (King et al., 2013) looked at the effectiveness of a computer-based intervention in relieving postconcussive symptoms. The intervention took about 20 - 30 minutes to complete in its entirety, and focused on education about symptoms and expected recovery, as well as strategies for managing symptoms. Participants were recruited from a civilian hospital, a VA (Veteran Affairs) polytrauma rehabilitation centre, and a naval medical centre. Patients at the civilian hospital had suffered their trauma only days prior to the intervention, whereas for the others, weeks and months had passed since the injury. Therefore, participants were divided into two groups for the analysis; one group of participants considered to be in the acute phase (<3 months post-injury), and one in the subacute phase (>3 months post-injury). The acute subgroup consisted mainly of civilian participants, while the sub-acute group was comprised of active duty and veteran participants. Analyses showed that there were no differences between participants from the three hospitals with respect to age and education, but they did differ significantly when it came to ethnicity: 100 % of the patients from the civilian hospital were Caucasian, while the numbers were 91% and 50% in the VA rehabilitation centre and the naval medical centre respectively. Participants recruited from the three sites did not differ on the number of postconcussive symptoms reported at baseline, or on history of earlier MTBI. When reassessed 1 month after the intervention, both the acute and the sub-acute group reported significantly fewer symptoms than at baseline.

4. Discussion

4.1. Discussion of main results

4.1.1. A small number of studies

Like all the past systematic reviews, we found that a very small number of studies met our criteria. This is perhaps the most important of our findings. Despite previous reviews' call for more methodologically sound studies, the three main studies included in our systematic review are methodologically weak, and only one is an RCT. It is curious that everyone within the field seem to agree that more high quality research is needed, yet mostly weak studies

with small sample sizes are conducted. One could speculate that this is caused, in part, by a number of small research communities with their own interests and agendas. Whatever the cause, it is obvious that the field suffers from this lack of unity.

4.1.2. A wide range of treatments

The three main studies we included in our review look at very different treatments. Tiersky et al. looked at CBT and cognitive remediation, Azulay et al. tested a mindfulness-based technique, and King et al. investigated the effect of a computer-based programme based on education about symptoms and expected recovery, and strategies for managing symptoms. This diversity of methods makes comparisons difficult. One possible solution to this problem is to use a more narrow definition of psychotherapy in future reviews, or, possibly, review only studies using one mode of psychotherapy, for example CBT. However, considering the small number of studies available, it is unlikely that one would find enough studies within one mode of psychotherapy for such a review to be possible, at least not without including methodically dubious studies. This heterogeneity could also be seen as a symptom of an absence of unity in this field of research.

4.1.3. Treatment studies vs. preventive studies

We found that some studies met all of our criteria except one: instead of looking at treatment for those already suffering from prolonged recovery, they tried to predict and prevent it. This is interesting because effective prevention may spare individuals of unnecessary distress. If prediction is successful, prevention can also be aimed at only those at risk, and thus also be cost-effective. In the aftermath of psychological trauma, it is now recommended to focus on those at risk of developing PTSD instead of administering interventions such as debriefing, to all of those who have experienced a possibly traumatic event (Rose, Bisson, Churchill, & Wessely, 2002). Applying this logic to MTBI as well might be sensible. However, the diversity of treatment methods was also apparent in the prevention studies. This approach as well might benefit from research becoming more unified and directed.

4.1.4. Existent, but small effects

As mentioned, the three main studies reviewed in this thesis all employ different treatment methods, and all appear effective to a certain degree. This situation makes it clear why treatment recommendations and guidelines are vague and heterogeneous (Marshall et al., 2012). Larger studies, and studies aiming to replicate small but promising findings, are needed to make clear which treatment approaches warrant further investigation, and which are unlikely to be effective.

The majority of the studies we reviewed had very small samples. Only two studies (Ghaffar et al., 2006; Matuseviciene et al., 2013), both from the additional analysis, had samples of appropriate size. This, in combination with a lot of outcome measures, heightens the risk of a type I error, i.e. incorrectly concluding that there are statistically significant effects. The practical importance of the results, hence the practical clinical significance, is in many cases not reported.

4.2. Clinical implications of results

The idea that interventions should target those in risk of prolonged recovery specifically, as opposed to providing an early intervention for all MTBI patients, gains further support from the three additional studies added to this review for perspective. Ghaffar et al. (2006) found that although multidisciplinary treatment did not improve the outcome of the participants in their study, additional analyses suggested that treatment was helpful for the subset of participants with a history of psychiatric difficulties.

Previous systematic reviews looking at MTBI treatment more in general, have suggested that the only treatment with enough evidence to warrant a recommendation is early educational intervention. This is not necessarily because this is the only intervention that is effective, but because studies investigating this have been the methodologically strongest of the intervention studies (Comper et al., 2005). While this is promising, it is unclear whether early education is sufficient for the patients at risk. In a review of psychological approaches to PCS, Al Sayegh et al. (2010) found mixed results concerning educational interventions, and imply that the usefulness of education and reassurance may be exaggerated. This is also supported in our review by the findings of Silverberg et al. (2013), which demonstrated that treatment-as-usual was not very effective in ameliorating postconcussive symptoms. It is possible that this kind of intervention is sufficient for most of the MTBI patients, but that further treatment is needed for some. Some argue that medical attention may be iatrogenic (Wood, 2004), and so reassurance and normalization should be stressed, as well as information about the likelihood of imminent recovery. Future studies should address this issue.

The effectiveness of CBT in cases of persistent symptoms after MTBI was also considered by Al Sayegh et al. (2010). While the study by Tiersky et al. (2005) was included in Al Sayegh et al.'s review, the study by Silverberg et al. was not. The results of the latter contribute to the evidence base that CBT might have an effect not only in treating postconcussion symptoms once patients have reached the chronic phase, but also in preventing their chronicity.

While it may seem counterintuitive that individually tailored treatment is not an effective approach to treating symptoms after MTBI, the results from the studies we reviewed suggest that this is the case. While the study by Ghaffar et al. (2006) indicated that this might be different if only patients at risk of prolonged recovery are targeted, the study by Matuseviciene et al. (2013) did not support this notion. The two studies employed different definitions of at-risk patients, so the results of the two are not easily comparable.

4.3. Generalizability of results

A large proportion of the MTBI studies conducted focus on military personnel or athletes. None of our studies looked at athletes specifically. As pointed out previously, athletes tend to recover more quickly than other MTBI patients (Iverson & Lange, 2011). This might be because their injuries are milder in general, or because they may play down their injuries so as not to miss game-time. In our sample of studies, only one (King et al., 2013) included military participants. It is not known how or if the population of military personnel differs from the general MTBI population.

Men outnumber women in the MTBI population (Tagliaferri, Compagnone, Korsic, Servadei, & Kraus, 2006), but often this is not reflected in the samples being studied. An interesting point here is that some studies have found gender to be predictive of outcome, with more women than men experiencing prolonged recovery (Bazarian et al., 1999). Hence, an overrepresentation of women in studies may overestimate the occurrence of persisting symptoms in the MTBI population. However, the prognostic value of gender has not been unanimous (Cassidy, Carroll, Côte, Holm, & Nygren, 2004; Thornhill et al., 2000). In our sample, one of the main studies (Tiersky et al., 2005) and two of the additional studies (Matuseviciene et al., 2013; Silverberg et al., 2013) reported more female than male participants.

The elusive nature of MTBI makes it particularly difficult to investigate. One challenge in this field of research, is the ratio between the hospitalized and treated cases of MTBI, and the non-hospitalized cases. As Cassidy et al. (2004) point out, for every patient who seeks treatment, as many as six patients never do. Therefore, we know little of the course of the consequences of the injury for the patients who do not seek treatment. While injury severity is likely to influence who will seek treatment and who will not, other factors may also play a role. Health behaviours, behaviours related to individually experienced symptoms, may be one such factor. We know that males in our culture, more so than females, pursue an image characterized by masculine ideals, also in their health behaviours (Oliver, Pearson, Coe, & Gunnell, 2005). Men have fewer visits to their General Practitioner, and when they

experience symptoms, they wait longer than women to have them checked. It may be fair to assume that, as with most other symptoms, the degree of adherence to culturally masculine behaviours would also affect MTBI-related health-behaviours. If that is the case, then patients seeking treatment for MTBIs, are not necessarily the severest of the MTBI cases. It could be that the ones most inclined to seek treatment for *any* reason are those most likely to seek treatment after an MTBI. Because all the studies included in this review recruited participants through health care facilities, the results cannot necessarily be generalized to the majority of MTBI sufferers who do not seek treatment.

It may also be that those who do not seek medical help after an MTBI are people who for some reason do not subjectively experience symptoms, or consider the symptoms to be insignificant. People with psychiatric disorders or drug addictions may be subject to a loss of function without being aware of it. If the loss of function is in a domain that is not important to the patients in their daily life, they may not experience any subjective sequelae, and thus no seek treatment. An implication of this is that participants recruited through hospitals may differ from MTBI sufferers in general in terms of mental health an education level. When drugs or alcohol are involved, the memory of the injury can be lost either to drug-induced amnesia or post-traumatic amnesia disguised as drug-induced amnesia, and the experienced symptoms may be attributed to the after-effects of the intoxication. Then, even if the patients *do* experience even the severest subjective MTBI-symptoms, they may never get the proper diagnose or treatment.

Another side of the issue is that a lot of the MTBI sufferers who do not initially seek medical treatment may do so later, if they experience problems with for instance memory or concentration. Because they do not realize the severity of the trauma, they may not see the connection between the head injury and the problems they experience later. If this is the case, a lot of diffuse and subtle cognitive impairments may actually be sequelae of MTBI. To the degree that post-injury depression and anxiety are secondary to the injury, caused by the slight cognitive impairments and the frustration of dealing with these, MTBIs might also contribute substantially to these commonly experienced mental health problems.

4.4. Issues of methodology and internal validity in the included studies

4.4.1. Issues of methodology and internal validity in the three main studies

In their article on prognosis after MTBI, Carroll et al. (2004) state that the evidence for prognosis in adults with MTBI is limited, in part because studies do not use appropriate control groups and lack sufficient consideration of confounding factors. This is also a concern with most of the studies we reviewed. In the study by Tiersky et al. (2005), the question of

appropriate control groups arises. The aim of the study was to test the effectiveness of neuropsychological rehabilitation on affective and cognitive sequelae in *mild-spectrum* traumatic brain injury; *mild-spectrum* being defined as mild and moderate cases. By grouping these two categories together, one ends up with a very wide range of severity. For example, the GCS scores might range from 9 to 15. Individual GCS scores were not reported in this study, but duration of LOC is reported as three categories: 0 minutes, 1 - 29 minutes or >29 minutes. There was only one participant in the latter category, but it is not stated for how much longer than 29 minutes this participant experienced LOC. According to the CDC definition of moderate traumatic brain injury, it could be as little as 30 minutes, or as much as 24 hours (Centers for Disease Control and Prevention, 2008). Only two of the 20 participants in the study had injuries of moderate severity, but both cases were allocated to the control group. Although the authors state that the groups did not differ by injury severity, this is based simply on testing if the percentage of moderate cases differed significantly between the groups, which it did not. This does not really say much, when the difference in severity between the moderate and the mild cases is not known. Stated differently, the within group variance in severity is not really tested or accounted for. This problem is further emphasized by the inflation of the treatment effect as measured by ANOVA, caused by a deterioration of symptoms in the control group. Another related concern is the variation in time post-injury. The time since the injury ranged from 1 to 20 years. Although the participants are all beyond the acute phase, and symptoms can be assumed to have stabilized somewhat, it is difficult to rule out the possibility that those participants whose injury occurred one year earlier might still be recovering. Tiersky et al. point out that further investigation is needed to identify the effective components of their intervention (Tiersky et al., 2005). By applying both psychotherapy and cognitive remediation, they obscure any causal connections between interventions and results. However, they theorize that both approaches could be necessary, as they address somewhat different issues.

The study by Azulay et al. (2013) did not use a control group. The objective of this study was to evaluate the effectiveness of an MBSR programme specifically tailored to be employed by MTBI patients. All of the participants were in rehabilitation while taking part in the study, so the symptom reduction they experienced cannot be attributed solely to the intervention. A replication of the study controlling for the possible effects of other intervention is needed to confirm the efficacy of the MBSR programme. It is also worth noticing that while the title of the article implies that the intervention addresses people with PCS, this diagnosis is not mentioned among the inclusion criteria. While it is reasonable to

assume that the majority of the participants suffered post concussive symptoms (15 of 22 participants listed their employment status as disabled, and all were receiving treatment), the inclusion criteria did not specify any kind or degree of symptoms. Further studies should address this issue, either by endorsing the ICD-10 definition of PCS, or by using a different definition and specify this in the inclusion criteria.

The pilot-study of E.G. King et al. (2013) did not have a control group. This makes it difficult to assess whether any improvements are due to the intervention, natural recovery, the effect of attention or other factors aside from the actual intervention. In addition, the study employed a convenience sample of participants. Convenience samples are common in the literature, but it is hard to estimate the impact of systematic and random error affecting the results. This is even harder with no control group. Even though the study does not include a control sample, it does compare acute patients to chronic patients. This could highlight if the intervention has a different effect on the acute group and the chronic group. However, the study does not include data on the previous treatment interventions the chronic sample has received. King et al. (2013) do not clearly specify which definition of MTBI is used. The inclusion criteria include PTA < 24h, and LOC < 30 minutes, but severity on GCS is not included, neither are any of the other criteria used in the consensus definitions of MTBI. In addition, it is unclear how the authors define postconcussive symptoms. They abbreviate them PCS, and state that "the physical, cognitive, and emotional symptom complains following a MTBI have become known as postconcussive symptoms (PCS)", without citing any source. As the WHO pointed out in 2004, one of the main issues in the research on MTBI and prolonged symptoms treatment is the lack of consistent nomenclature (L. J. Carroll et al., 2004). Ten years later, this is still an issue.

4.4.2. Issues of methodology and internal validity in the three additional studies.

Ghaffar et al. (2006) compared their intervention group to a no-treatment control group. However, their treatment was individualized so as to be of optimal benefit to each participant. They also employed a broad spectrum of treatments, including pharmacotherapy and physiotherapy. While there is evidence in favour of such multidiscipline and broad spectre treatments, this approach makes it difficult to single out any possible effective component of the intervention. The study did not find any statistically significant differences between the treatment group and the control group. The RPCQ was only administered at the six month follow-up, not at baseline, so the magnitude of change – if any – in the groups is not known.

The Matuseviciene study from 2013 also has several methodological issues. A convenience sample was employed to gather eligible patients for study. Defining criteria for MTBI were PTA < 1 hour and/or LOC < 30 minutes and a GCS of 14-15 upon presentation in the ER. For PTA, this is stricter than the consensus definitions (PTA < 24h). This makes it difficult for future researchers employing the consensus definitions to compare their findings to Matuseviciene's findings. The GCS-criterion is also stricter than the consensus-definitions, in that it does not include the score 13. It should be noted that this is not a critique of the choice to employ these MTBI-criteria per se, they may be valid clinical indicators of brain injury. Rather, it is a critique of the fact that they do not explain the rationale behind deviating from the guidelines and definitions recommended by the WHO to strengthen the research on MTBI.

Patients participating in the study completed a Swedish edition of the RPQ at 10 days after injury. Patients reporting three or more symptoms at 10 days post injury were defined as having elevated risk for developing PCS, and received the intervention. However, the authors give no reason for choosing three symptoms as a cut-off; neither do they explain why they use 10 days rather than five or 20. Of the 173 patients completing the RPQ, 97 (56%) were classified as high risk patients. This is considerably higher than any size estimate of the group of patients developing PCS. The intervention was delivered by a specialist in rehabilitation medicine, and consisted of information about the course of MTBI (in addition to the written information also given to the TAU-group), an interview about current symptoms and daily functioning and a standard examination of somatic status.

The authors found no difference in effect of the intervention between the intervention-group and the TAU-group. However, they found that both the TAU-group and the intervention-group reported considerably fewer symptoms at post-intervention than at pre-intervention. However, it is impossible to know if this was due to the shared intervention (TAU), time-variables or patient-variables. Using a cut-off that places more than half of the patients in the high-risk group, may place many "non-risk" patients in the intervention-group. If the high-risk patients indeed represent a qualitatively different patient population, in need of different interventions, a large component of low-risk patients in the high-risk group would contaminate the data, possibly averaging out any actual effects of the intervention.

Silverberg et al.'s 2013 pilot RCT study of cognitive-behavioural prevention of PCS after suffering MTBI, adheres to both the ACRM consensus definition of MTBI, as well as the ICD-10 criteria for PCS. Silverberg et al.'s study rests on Whittaker et al.'s theory that a patients' illness perception is a strong predictor of prolonged recovery (Whittaker, Kemp, &

House, 2007), which is also investigated by Snell (2010). Adherence to standardized definitions and diagnoses, as well as a clear definition of assumed mechanisms of PCS, make the findings more replicable for future researchers. However, the study is not without limitations. For instance, the authors could have employed an outcome measurement between the TAU and CBT for the intervention group. That way, one could determine with greater certainty whether the effects were actually explained by CBT alone, or if there was an interaction effect of the two interventions (TAU + CBT). However, it is hard to criticise the work of Silverberg et al., when it adheres to so many of the recommendations from the systematic literature reviews, as well as the recommendations of the WHO Collaborating Centre Task Force on MTBI of 2004. The proclaimed goal of the study was to determine sample size requirements for a future phase III clinical trial. This is also praiseworthy, especially given the methodological quality of the study, as it explicitly defines necessary steps to enhance our understanding of the development of PCS.

4.4.3. Issues of methodology and internal validity in general

The weak methodology of several of the studies may reflect that the main focus have been a clinical one, with treatment of patients as a first priority, and empirical evidence as a secondary goal. However, it should be noted that practically all the reviewed studies cite the WHO Collaborating Centre Task Force on MTBI and/or one or more of the systematic literature reviews, and yet they still display the very weaknesses they are being warned against. The definitions of MTBI employed by the studies were compatible, with four studies using the ACRM definition of MTBI, and the other three relying on measures of GCS and PTA, and in one case also LOC.

While some of the studies we reviewed excluded individuals with a prior history of psychiatric disorders (Matuseviciene et al., 2013), others studies have found that this group benefits from interventions (Ghaffar et al., 2006). Again, this is a matter of definitions. If one wants to rule out other possible factors contributing to symptoms, it makes sense to exclude this group. On the other hand, the correlation between psychiatric disorders and PCS might not be a causal one. In other words, simply because some of the factors predictive of prolonged recovery are not directly caused by the MTBI itself, this does not mean that the injury plays no role in the persistent symptoms. Rather, these premorbid factors contribute to the individual vulnerability, making the person especially susceptible to the detrimental effects of an MTBI. Pain may also play a role in this equation, perhaps as a mediator. For a more thorough discussion of this, see Wood (2004).

4.5. The composition of the “miserable minority”

Even though the phenomenon of enduring symptoms in the wake of MTBI is recognised by the field as a legitimate condition, there are no consensus definitions of this condition. This resembles the situation for MTBI in the early 1990’s. Just as the nomenclature surrounding MTBI was vague in the 1980’s and 1990’s, so is the nomenclature describing persisting symptoms consistently vague in the literature even today.

According to Ruff (2005) the failure to distinguish properly between the patients who will suffer from a prolonged recovery, and the patients who will make a swift recovery contaminates research in at least three ways. First, a failure to distinguish between these patient groups can lead to insufficient sample sizes. If, out of a sample of 30 MTBI-patients, 3 - 6 patients belong to the “miserable minority”, this is too small a sample size to yield any meaningful conclusions regarding whatever question is being investigated. (For a contrasting view, see Rohling, Larrabee, and Millis (2012)) . Second, averaging data may cancel out important findings, since the miserable minority may not be evenly distributed between samples. The conclusions reached by investigating these different samples, will be widely different, but both will be attributed to MTBI as a whole. As a consequence of these two points, the clinical relevance of the research suffers. Data from the “favourable majority” is not relevant for patients belonging to the miserable minority.

The studies included in our systematic review look specifically at patients who experience, or are at risk for experiencing, prolonged recovery. Thus, at first glance, the literature does not look contaminated in the ways Ruff et al. (2005) warn about. But, as became evident in section 4.3., one of the major flaws of the literature reviewed, is the lack of proper nomenclature, diagnosing and definitions. One consequence of this may be that these three types of data contamination may be hidden or disguised by the lack of proper operationalization, and influence the results. This way, the data will be skewed undetected and systematically within the individual studies. Given enough different cut-offs and differing definitions, the between-studies noise will have the capacity to average out the clinically important differences.

In our review, perhaps the clearest example of this is Matuseviciene et al. (2013), where it is likely that their definition of high-risk patients may have been too liberal, so that data from low-risk patients may have contaminated the data on high-risk patients. This means, as Ruff (2005) warns, that the clinical relevance suffers. Perhaps the Matuseviciene intervention in fact had clear clinical implications for the "actual" high-risk patients.

Usage of composite scores is another issue that may cancel out differences. Ruff (2005) proposes that some patients may have deficits in memory and learning, while others may have problems primarily with attention and concentration. Others, again, may show reduced performance in all of these domains. If the results of these measures are lumped together as a mean score of a patient's neuropsychological functioning, valuable information is lost.

In the introduction, we stated that we could not endorse either the ICD-10 or DSM-IV diagnoses, but that we recommended them used for the sake of continuity and consistency. One of the problems with these two diagnoses specifically, is that there is a mismatch between them and the consensus definitions of MTBI. Like the consensus definitions of MTBI, the PCD and PCS criteria also include a description of acute symptoms, but the acute criteria included deviate from the more recent and valid criteria of the consensus definitions, for instance the inclusion of LOC as an absolute criterion in the definition of PCD.

Unlike the consensus definitions, ICD-10 and DSM-IV do include a description of functioning in the time following the injury. For instance, the DSM-IV criteria require that at least three symptoms of reduced functioning last at least 3 months post injury. The ICD-10 criteria do not specify the duration of the symptoms, but the nature of the symptoms required to meet the diagnostic criteria indicate that at least some time has passed after the injury. Because they require that time passes, and because of their increasingly archaic description of acute symptomatology, both the DSM-IV and ICD-10 diagnoses are by definition incompatible with the consensus definitions of MTBI. This is in itself a paradox, considering that both the WHO consensus definition of MTBI and the ICD-10 diagnosis of PCS are authored by the WHO.

So, in diagnosing the unfortunate few that experience a prolonged recovery after their brain injury, researchers face a dilemma. They could use the stringent and modern definitions of MTBI to describe the patients' acute injury. However, when symptoms persist, they are no longer captured by the consensus definitions. If the researchers then choose to use either the ICD-10 or DSM-IV criteria to diagnose the persisting symptoms, the patients may not meet the acute criteria of these categories, because of the mismatch described above. This problem could, for instance, affect the Silverberg RCT, where the ICD-10 diagnosis of PCS is used. Methodologically, this compromises validity. The result is that researchers use idiosyncratic non-consensus definitions when describing this patient group, in order to capture the heterogeneity of symptoms and their duration.

Carroll et al. (2004) note that in their review of MTBI-research, they found no correlation between the severity of the brain injury, and the development of prolonged recovery. Carroll et al. maintain that this is at the core of the problems with the PCS/PCD-diagnoses – that they require certain acute symptoms of sufficient magnitude, which themselves are statistically unrelated to the outcome. These findings, that measures of injury severity and outcome may be unrelated, can have two possible explanations. First, it could be that the measures of severity currently used are not reliable. We will elaborate on this point in paragraph 4.6. Another possibility is that other factors than injury severity can better explain outcome. Whittaker et al., (2007), Snell et al. (2010) and Hou (2012) suggest that beliefs and perceptions of illness is one possible explanatory factor. This is also what one of the additional studies in our systematic review (Silverberg et al., 2013), base their prediction on. Attributional style and perceptions of one's surroundings and one's self lie close to the concept of personality. More research into the role of personality, both from a clinical point of view, like the Greiffenstein and Baker (2001) study mentioned earlier, and a more normal viewpoint, employing for example the NEO-PI-R, could perhaps shed further light on this issue.

4.6. Reliance on PTA and LOC for MTBI diagnosis

Most of the studies included in our review use criteria compatible with the consensus definitions of MTBI. Of the three main studies, both Tiersky et al. (2005) and Azulay (2013) employ the ACRM definition, while King (2013) use criteria compatible with it (PTA <24 h/LOC <30 min). Of the three additional studies, Silverberg et al. (2013) and Ghaffar et al. (2006) also use the ACRM definition. Matuseviciene et al. (2013) state that their criteria were either PTA <1 hour, or LOC <30 minutes, as well as an initial GCS of 14 or 15. While the last two criteria are compatible with consensus definitions, the 1-hour limit of PTA differs markedly from the normal 24 hour criterion. This, as well as their exclusion of patients with GCS of 13, could result in a sample that is less severely injured than, and thus not comparable to, the other studies. Excluding patients with a GCS of 13 is not uncommon, in many instances a GCS-score of 13 is considered a moderate TBI (L. J. Carroll et al., 2004). Even when a score of 13 is included, the range of 13—15 is very narrow. Moreover, GCS was never intended for measuring the severity of brain injuries in the first place, but as a coma-measurement (Teasdale & Jennett, 1974).

An LOC of less than 30 minutes is included in all three definitions of MTBI and in all of the studies we reviewed. While LOC may in itself be a good indicator of injury severity, there are many issues regarding the assessment of LOC duration. The LOC-measure is often

based on self-report or observer-reports. Ruff, Iverson, Barth, Bush, and Broshek (2009) highlight many issues with this practice. Firstly, the transition from LOC to PTA may not be easy to establish. While this may especially be a problem when self-report is employed, observer-reports of LOC are also vulnerable to human error, as reliably assessing a person's state of consciousness is a difficult task. Secondly, as Ruff et al. (2009) point out, it may not be the absolute duration of an absolute LOC that is indicative of injury severity, but *any* alteration in level of consciousness. If that is the case, untrained observers, in an often chaotic situation, cannot be expected to assess the patient's altered consciousness properly.

Similar issues plague the use of PTA as a determining factor of injury severity. Self-report measures of PTA can by their nature not be reliable. The patient has to rely on some external information regarding his or her own state, in order to make an assumption about the duration of the PTA. The fluid nature of memory-consolidation will also affect the accuracy of the actual memory of the event. Memory functions may seem to be back to normal for short periods, long before they are actually stable. When level of consciousness is reported, rather than loss of consciousness, it can be especially hard to separate an altered state of consciousness from post-traumatic amnesia or post-traumatic confusion (King et al., 1997). And, as previously mentioned, the amnestic features of the PTA may in fact be secondary to disruptions in attention (Marshman et al., 2013).

A possible solution to the shortcomings of these three measures is to find better markers of severity. In the last few years, much research has focused on identifying possible biomarkers for MTBI. In a study using diffusion tensor imaging (DTI), Kraus et al.(2007) noticed that the overlap between injury severity assigned and degree of pathology, though existent, was far from perfect. Some cases initially diagnosed as mild based on measures of GCS, PTA and LOC, appeared more similar to moderate cases based on later measures of pathology. While the consensus definitions represent an improvement in the diagnosis of MTBI, they still rely heavily on measures of PTA, GCS and LOC. No matter how good the definitions are, they cannot be better than the definitions of their individual components. Basing classification of severity on biomarkers instead of relying on PTA, LOC and GCS, may thus improve diagnosis and prognosis. If the three factors that make up the foundation of the three severity categories have outplayed their role, it might also be appropriate to question whether the categories themselves are in need of replacement. Including TBIs of all severities in one study and analysing severity as a continuous variable, like Kraus et al.(2007), bypasses the methodological limitations posed by the imprecise tripartite categorisation. In this way,

one can avoid some of the methodological problems that arise from making mutually exclusive categories out of what in reality might be more of a continuum.

4.7. Conclusions

This thesis has systematically reviewed the recent literature on psychotherapeutic interventions aimed at prolonged recovery after mild traumatic brain injury. The main finding was that, despite several previous reviews pointing out the need for more methodically rigorous studies, few such studies have been conducted. Furthermore, the results suggested that diverse forms of psychotherapy may be beneficial for those struggling with persistent symptoms more than three months after an MTBI. This includes CBT, mindfulness-based treatment and computer-based, symptom-focused interventions. Although it is promising that a wide range of treatments might be effective, this diversity also represents a weakness in the field, because of a reluctance among researchers to replicate and expand on previous findings. Interventions aimed at preventing prolonged recovery in patients at risk also show promising results, although prevention studies are also few in numbers.

It is clear that more research is needed to identify factors that put MTBI patients at risk for persistent symptoms, and to identify and develop treatment that are efficient for those whose symptoms persist. Replicating studies, using larger samples and appropriate control groups to confirm promising findings, is one part of the solution. All in all, future research should try to expand on existing findings, and seek to learn from the studies already conducted.

When the prevalence of MTBI is considered, it is clear that even the so-called miserable minority constitutes a substantial group of patients. Providing this large group with effective, evidence-based treatment options could save a lot of health care resources, and contribute to better quality of life for thousands of people every year.

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6. Appendices

6.1. Appendix 1 – Search strategies

6.1.1. PsycInfo

Search date: 20.10.2014

1. exp traumatic brain injury/
2. exp head injuries/
3. brain damage/ or brain damage*.mp.
4. head injur*.mp.
5. (mild or minor).mp.
6. 1 or 2 or 3 or 4
7. 5 and 6
8. mtbi.mp.
9. mild tbi.mp.
10. minor tbi.mp.
11. concussion*.mp.
12. post?concussion*.mp.
13. minor tbi.mp.
14. 7 or 8 or 9 or 11 or 12 or 13
15. exp psychosocial rehabilitation/
16. psychosocial readjustment/
17. psychosocial.mp.
18. exp psychotherapy/
19. psychother*.mp.
20. psychological intervent*.mp.
21. psychological treatment*.mp.
22. psychological therap*.mp.
23. neuropsychological.mp. or exp Neuropsychological Rehabilitation/
24. neurorehabilitation.mp. or exp Neurorehabilitation/
25. treatment effect*.mp.
26. neuropsychol*.mp.
27. exp intervention/
28. mindfulness.mp. or exp Mindfulness/
29. cognitive rehabilitation.mp. or exp Cognitive Rehabilitation/
30. exp Cognitive Behavior Therapy/

31. cognitive adj (behav?or therap*).mp.
32. cbt.mp.
33. exp Multimodal Treatment Approach/ or multimodal.mp.
34. exp treatment/
35. rehabilitation/
36. 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30

or 31 or 32 or 33 or 34 or 35

37. 14 and 36
38. limit 37 to yr="2004 -Current"

6.1.2. Embase

Search date: 20.10.2014

1. (minor or mild).mp.
2. Traumatic brain injury/ or head injury/ or brain damage/
3. 1 and 2
4. mtbi.mp.
5. mild tbi.mp.
6. minor tbi.mp.
7. mild traumatic brain injur*.mp.
8. traumatic brain injur*.mp.
9. exp concussion/
10. postconcussion syndrome/
11. 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10
18. psychosocial rehabilitation/
19. psychosocial care/
20. psychosocial.mp.
21. exp psychotherapy/
22. psychother*.mp.
23. psychological intervention*.mp.
24. psychological treatment*.mp.
25. psychological therap*.mp.
26. neuropsychological rehabilitation*.mp.
27. neurorehabilitation.mp.

28. mindfulness/
29. cognitive rehabilitation.mp.
30. (cognitive adj2 therap*).mp.
31. cbt.mp.
32. (multimodal adj3 treatment*).mp.
33. 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32
34. 11 and 33
35. limit 34 to yr="2004 -Current"

6.1.3. SPORTDiscus

Search date: 11.11.2014

1. DE " BRAIN-concussion" OR DE "POSTCONCUSSION-syndrome"
2. DE "Brain—Wounds&injuries"
3. DE "CEREBRAL hemorrhage"
4. DE "HEAD injuries"
5. 1 OR 2 OR 3 OR 4
6. TX mild OR minor
7. 5 AND 6
8. TX mtbi
9. TX mild tbi
10. TX minor tbi
11. TX mild traumatic brain
12. TX minor traumatic brain
13. TX concussion*
14. TX post N concussion*
15. TX mild head injur*
16. Postconcussive*
17. Post N concuss*
18. TX postconcussion*
19. 7 OR 8 OR 9 OR 10 OR 11 OR 12 OR 13 OR 14 OR 15 OR 16 OR 17 OR 18
20. DE "PSYCHOTHERPY" OR DE "ART therapy" OR DE "BIOFEEDBACK training" OR DE "COGNITIVE therapy"
21. DE "HEALTH counseling" OR DE "MENTORING" OR DE "MOTIVATIONAL interviewing"

22. DE "MENTAL training"
23. DE "MENTAL health" OR DE "STRESS management"
24. DE "PSYCHIATRY"
25. DE "NEUROPSYCHOLOGICAL rehabilitation"
26. TX psychosocial
27. TX psychother*
28. TX psychological intervention*
29. TX psychological treatment*
30. TX psychological therap*
31. TX psychological rehabilita*
32. Neuropsychological rehabilitation
33. TX neurorehabilit*
34. TX mindfulness
35. TX cognitive rehabilitation*
36. TX cognitive N3 therap*
37. TX cbt
38. TX multimodal N3 (treatment* OR therap*)
39. 20 OR 21 OR 22 OR 23 OR 24 OR 25 OR 26 OR 27 OR 28 OR 29 OR 30 OR 31 OR 32 OR 33 OR 34 OR 35 OR 36 OR 37 OR 38
40. 19 AND 40

6.1.4. CINAHL searched 11.11.2014

1. MH "Brain injuries+ "
2. MH "Head injuries +"
3. MH "Intracranial Hemorrhage+"
4. TX mild OR minor
5. 1 OR 2 OR 3
6. 4 AND 5
7. TX mtbi
8. TX mild tbi
9. TX minor tbi
10. TX mild traumatic
11. TX minor traumatic
12. MH "Brain Concussion+"
13. TX concussi*

14. TX post concussi*
15. TX postconcussi*
16. TX mild head injur*
17. 6 OR 7 OR 8 OR 9 OR 19 OR 11 OR 12 OR 13 OR 14 OR 15 OR 16
18. MH "Psychotherapy+"
19. MH "Mental Health Services+" OR MH "Mental Health Care(Saba CCC) " OR MH "Mental Health Treatment (SABA CCC) " OR MH "Community Mental Health Nursing"
20. TX psychosocial*
21. TX psychother*
22. TX psychological intervention*
23. TX psychological treatment*
24. TX psychological therap*
25. TX psychological rehabil*
26. TX neuropsychological rehabil*
27. TX neurorehabil*
28. TX mindfulness*
29. TX cognitive rehabilitation
30. TX cognitive N3 therap*
31. TX cbt
32. TX multimodal N3 therap*
33. 18 OR 19 OR 20 OR 21 OR 22 OR 23 OR 24 OR 25 OR 26 OR 27 OR 28 OR 29 OR 30 OR 31 OR 32
34. 17 AND 33
35. 34 Limiters- Published Date: 20040101 – 20151231

6.2. Appendix 2 – Assessment of risk of bias

Assessment of risk: Matuseviciene et al. (2013)

Entry	*Judgement*	*Support for judgement*
Random sequence generation (selection bias)	Unclear risk	"(...) 97 were classified as high-risk patients and thus randomized in blocks of four". The study also report results from the non-randomized low-risk group.
Allocation concealment (selection bias)	Unclear risk	
Blinding of participants and personnel (performance bias)	High Risk	It is not stated whether the patients and health personnel were aware of the aim of the study or not. Due to the design, they knew which treatment they were receiving, but it is unclear if they knew the significance of this.
Blinding of outcome assessment (detection bias) (patient-reported outcomes)	Low risk	The outcome measures were self-reported, and thus no interpretation on behalf of the researchers were needed.
Blinding of outcome assessment (detection bias) (Mortality)	Low risk	N/A
Incomplete outcome data addressed (attrition bias) (Short-term outcomes (2-6 weeks))	Low risk	"At the diagnostic and intervention visit 2 weeks post-injury, four patients were identified as having been treated for anxiety and depression disorders. These were included according to intention-to-treat(...)"
Incomplete outcome data addressed (attrition bias) (Longer-term outcomes (>6 weeks))	Low risk	N/A
Selective reporting (reporting bias)	Low risk	Both measurements introduced in the methods section are reported in the results section.

Assessment of risk: Ghaffar et al. (2006)

Entry	*Judgement*	*Support for judgement*
Random sequence generation (selection bias)	Unclear risk	"Subjects were assigned randomly to treatment or no treatment (control) groups" Comment: No mention of how this was done.
Allocation concealment (selection bias)	Unclear risk	Not stated.
Blinding of participants and personnel (performance bias)	High Risk	Due to the nature of the intervention, participants knew what kind of treatment they were receiving. It is not clear whether patients and health personnel knew about the hypotheses of the study.
Blinding of outcome assessment (detection bias) (patient-reported outcomes)	Unclear risk	Some of the measures were conducted by trained research assistant, the rest were self-report. It is not clear whether or not the research assistant was aware of the paticipants' group allocation.
Blinding of outcome assessment (detection bias) (Mortality)	Low risk	N/A
Incomplete outcome data addressed (attrition bias) (Short-term outcomes (2-6 weeks))	Low risk	N/A
Incomplete outcome data addressed (attrition bias) (Longer-term outcomes (>6 weeks))	Low risk	"At 6 months follow-up assessment, the number of subjects decreased to 86 in the treatment group (88,7%) and 84 in the control group (89,4 %). There was no group difference in this regard (p=1.0). Dropout rates did not differ based on psychiatric history (P=.66), priorTBI (P=.46) or the decision to pursue litigation (p=1.0). The outcome of subjects who dropped out is not known)."
Selective reporting (reporting bias)	Low risk	All the measures introduced were reported.

Assessment of risk: Silverberg et al.(2013)

Entry	*Judgement*	*Support for judgement*
Random sequence generation (selection bias)	Unclear risk	"The simple randomization sequence was created with a Web-based random number generator and maintained by personnel external to the study"
Allocation concealment (selection bias)	Low risk	"The next group allocation was concealed until after a participant's eligibility was confirmed and they had completed TAU".
Blinding of participants and personnel (performance bias)	High Risk	"We masked assessors to reduce bias, but expectation effects could have contributed to positive outcomes because participants knew whether they had been assigned to the control or experimental treatment group" Comment: due to the nature of the intervention, therapists were aware of the intervention they were giving.
Blinding of outcome assessment (detection bias) (patient-reported outcomes)	Low Risk	"We masked assessors to reduce bias"
Blinding of outcome assessment (detection bias) (Mortality)	Low risk	N/A
Incomplete outcome data addressed (attrition bias) (Short-term outcomes (2-6 weeks))	Low risk	N/A
Incomplete outcome data addressed (attrition bias) (Longer-term outcomes (>6 weeks))	Low risk	"Data from participants who were lost to follow-up (n=4) were not analysed" Comment: Diagram of participants flow through the study shows that the number of participants lost to follow-up was equal between the two groups. Reason for attrition was the same in both groups; the participants could not be reached, and were given up after three attempts.
Selective reporting (reporting bias)	Low risk	All the measurements listed in methods are reported in the result section.

Assessment of risk: Tiersky et al.(2005)

Entry	*Judgement*	*Support for judgement*
Random sequence generation (selection bias)	Low Risk	"Each participant was randomly assigned to the treatment or control group(...). A random numbers table was used to make the group assignments."
Allocation concealment (selection bias)	Low risk	"Each participant was randomly assigned to the treatment or control group by a clerical staff member who was not directly involved in the study. This staff member was blind to information collected during the evaluation process. (...) Randomization was completed after pretest to facilitate scheduling. (...) The examiners completing the testing were not aware of the participants' group membership".
Blinding of participants and personnel (performance bias)	High Risk	"However, subjects were not informed of their group status until all pretesting was completed." Comment: Due to the nature of the intervention, participants were aware of the treatment they received.
Blinding of outcome assessment (detection bias) (patient-reported outcomes)	Low Risk	"Pre- and posttesting was completed by two researchers (...) who were blinded to each individual's group membership"
Blinding of outcome assessment (detection bias) (Mortality)	Low risk	N/A
Incomplete outcome data addressed (attrition bias) (Short-term outcomes (2-6 weeks))	High risk	After baseline testing, 2 participants were lost from the treatment group, and 6 from the control group. Comment: reasons for drop-out were similar across group, but the drop-outs differed significantly from the non-drop out in education level.
Incomplete outcome data addressed (attrition bias) (Longer-term outcomes (>6 weeks))	Low risk	N/A
Selective reporting (reporting bias)	Low risk	One participant was lost from the treatment group.

6.3. Appendix 3 – Articles we were unable to retrieve

Gurr, B. (2011). The effectiveness of cognitive-behavioural therapy for post-traumatic headaches. *Cephalalgia, 31*, 154.

Leonard, K. N. (2004). Cognitive-behavioral intervention in persistent postconcussion syndrome: A controlled treatment outcome study. *Dissertation Abstracts International: Section B: The Sciences and Engineering, 64*(12-B), 6332.

Potter, S., Fleminger, S., & Brown, R. (2010). Cognitive behavioural therapy for persistent PCS: Preliminary results from a randomised control trial. *Brain Injury, 24 (3)*, 205-206.

Velikonja, D., Brum, C., & Scott, S. (2014). The impact of group cognitive behavioural therapy on individuals with an acquired/ traumatic brain injury. *Brain Injury, 28 (5-6)*, 743.