The impact of a single mild traumatic brain injury on neurocognitive performance

The studies described in this thesis were carried out at the Maastricht Brain & Behaviour Institute of the Maastricht University (department of Psychology) and the University Hospital Maastricht.

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Content

- **Chapter 1** -

The issue of Mild Traumatic Brain Injury

Introduction and justification

A significant number of studies have shown that mild traumatic brain injury (mild TBI) accounts for a substantial proportion of all brain trauma admissions to hospitals (Kraus, McArthur & Silberman, 1994). There is, however, still uncertainty about the basic characteristics of this condition despite continuous reports in the professional literature. Although every study uniformly agrees that the greatest proportion of brain injuries are 'mild', the published literature is critically lacking in methodological consistency. The appraisal of the existing literature on mild TBI is complicated by substantial differences in issues relating to diagnosis, characterizing features, classification definitions and outcome measures.

Ten to 15% of mild TBI patients report continuing neuropsychological symptoms that suggest chronic brain damage (Alexander, 1995). Much effort was put in studying this subgroup of patients suffering from the so called 'postconcussional syndrome', resulting in a variety of explanations, ranging from *psychogenic* to *organic*. In the meanwhile the majority of mild TBI patients that recover 'successfully' is ignored. In this thesis the impact of a single mild TBI on neurocognitive performance is studied in those patients that do *not* meet criteria for postconcussional syndrome. The common goals of the described experimental studies are (1) to achieve better understanding of the mechanism of subacute and longterm neurocognitive disturbances after mild TBI, and (2) limiting the number of alternative explanations for possible neurocognitive disorders.

Epidemiology of mild TBI

Traumatic brain injuries have been studied in great detail from a clinical perspective in patients who seek help in a medical environment. A much smaller body of epidemiological research, which attempts to provide an accurate assessment of the occurrence, characteristics, and consequences of brain injury in the population, is disparate in its approach. Definitions of mild TBI vary widely. Of particular concern is that the assessment of initial severity of the injury (and determination that the injury is 'mild') is often the product of negative rather than positive clinical findings. Additionally, many cases of mild TBI are either unwitnessed, unreported, or treated on an outpatient basis and are thus missed by conventional case-finding strategies (Segalowitz and Brown, 1991).

Much uncertainty remains about the true incidence and incidence rates of mild TBI. As has long been recognized, age and gender are an important determinant of brain injury incidence. TBIs occur roughly in a bimodal distribution with peaks in early adulthood and late life, and incidence rate is approximately twice as high for males as for females. In western industrialized countries the incidence rate of TBIs requiring hospitalisation varies between 88 and 313 cases per 100.000 persons each year (Meerhoff, De Kruijk, Rutten, Leffers & Twijnstra, 2000). Among persons admitted to a hospital alive after an injury to the head, studies generally agree that about 80% are mild cases. Along with both self-reported concussions and skull fractures, this estimate includes many different types of intracranial injuries, some without neurologic damage. Causes of these injuries are traffic related, involving a motor vehicle (42%), in most of the cases. Falls (23%), assault (14%), and sport or recreational activities each account for 6% of all injuries (Kraus et al., 1994).

Financial consequences limited to mild TBI are unknown. To calculate the consequences of mild TBI in economical terms, information is needed which reflects the direct costs of health care services and the indirect costs which are related to a loss of market earnings because of unemployment.

Neuropsychological consequences of mild traumatic brain injury: The problem and scientific questions

Mild traumatic brain injury (TBI) is considered a benign and trivial neurologic condition resulting in apparently uneventful recovery (Binder, Rohling, and Larrabee, 1997). However, a minority of the mild TBI patients (10-15%) experience continuing postconcussional complaints (i.e. subtle memory and concentration weakness, fatigue, dizziness, anxiety and depressive symptoms) suggesting chronic brain damage (Alexander, 1995). Clinicians in the field often encounter this significant group of patients also referred to as 'the miserable minority' (Ruff, Camenzuli, & Mueller, 1996). It is this population, suffering from a relatively minor neurological incident that is responsible for an ongoing debate among experts in the field. We still do not know what constitutes a protracted posttraumatic disorder. Prolonged postconcussional symptoms may be related to underdiagnosis of initial brain injury severity, other bodily injuries, chronic pain, psychosocial stressors (including malingering), or misattribution of everyday symptoms (Reitan & Wolfson, 1999).

From the early days, the neuropsychological discipline has always shown a special interest in the TBI problem. Neuropsychology, being a specialism in brain-behaviour relations and assessment of (subtle) cognitive deficits, has been responsible for major advances in this field of research. These advances have been due to the continual process of 'boot-strapping', whereby increases in the fund of knowledge and theoretical framework regarding brain-behaviour relationships have lead to increasingly sophisticated neuropsychological instruments in terms of sensitivity and specificity. The data derived from these tests has enabled investigators to advance their understanding of brain-behaviour relationships. Specific examples of this process abound in research on TBI, for example, in the role of axonal shearing in speed of information processing (Gronwall, 1977) and the role of frontal systems in attention, working memory, and executive functioning (Levin, Eisenberg & Benton, 1991).

In part, these conceptual advances in neuropsychology have come about because of the information provided by structural brain-imaging techniques and cognitive psychology. In terms of structural imaging, computerized tomography (CT) and magnetic

resonance imaging (MRI) have allowed more accurate and quantifiable measurement of brain-structures. This has allowed for much more accurate correlation of structural changes and behaviour in individuals with TBI (Bigler, 1991). The ability of neuropsychologists and neuroanatomists to examine conjointly unimpaired subjects has been of major importance, as it circumvents two significant problems. First, neurological insults very rarely occur only in those specific neuroanatomical regions of interest to researchers, and typically have generalized, as well as localized, effects, making the interpretation of function of specific neuroanatomical sites problematic. The second problem posed by neuroanatomical studies of humans with acquired lesions is a conceptual one. The functional neuroanatomy of the brain involves the organization of cortical and subcortical processing areas, into integrated systems (Mesulam, 1981). Because of this integration, localized lesions can disrupt the function of entire systems. So, one cannot infer that the functional deficits caused by a lesion to a specific area indicate that that area alone is responsible for that function.

If advances in other areas of TBI research have come about due to the influence of assessment/methodology and conceptualization, the relative lack of progress in research on persisting symptoms in mild TBI certainly has been due to the converse: a lack of clear conceptualization of the nature of the deficits, rigorous methodology, and specific and sensitive tests. In fact, assessment of mild TBI may represent the 'acid test' of neuropsychological assessment because of the variable and often subtle deficits and the earlier mentioned confounds of motivation, pain, and emotional issues that cloud the assessment and diagnosis process (Newcombe, Rabbitt, and Briggs, 1994).

The faces of mild TBI

Cognitive symptoms are almost by definition part of the symptom complex following a mild TBI but tend to resolve within days to weeks after injury. Studies of mild TBI have produced widely mixed findings. Binder, Rohling, and Larrabee (1997) suggested that the effect of mild TBI on overall cognitive functioning and specific cognitive domains is small. While overall group effects may be small, it is important to

recognize that mild TBI actually comprises a heterogeneous group. A significant minority of individuals with mild TBI have abnormal CT findings (Hsiang, Yeung, Yu & Poon, 1997). This subgroup may or may not overlap with the 10-15% of individuals with mild TBI who report persisting symptoms. Studies indicate that orthopedic injury, chronic pain, and other factors may alter cognitive functioning (Alfano & Satz, 2000). Furthermore, recent studies have shown an unexpectedly high rate of postconcussional complaints in normal groups (Wong, Regennitter & Barrios, 1994). Taken in conjunction, these findings suggest that mild TBI may neither be necessary, nor sufficient to cause persistent postconcussional symptoms, given that the cognitive deficits and subjective complaints seen in mild TBI also are reported in non-TBI populations, and that only a minority of the mild TBI population exhibit persisting cognitive difficulties. In short, the assumption that the findings following mild TBI are due to the direct neurological effects of the injury remains to be demonstrated (Alfano & Satz, 2000).

Definition and diagnosis of mild traumatic brain injury

Diagnosing a mild TBI is a frustrating endeavour. Compared to moderate and severe TBIs, characterized by evident episodes of loss of consciousness (LOC), posttraumatic or retrograde amnesia, and consensus on Glasgow Coma Scale (GCS) scores, mild TBI diagnosis is surrounded by uncertainty. There is still no consensus on the definition of a mild TBI. And although the American Congress of Rehabilitation Medicine (ACRM, 1993) has published guidelines for definition and a GCS score of '13' is considered in general an unlucky number, a variety of definitions are used in studies on mild TBI. There is however a tendency to restrict mild TBI to those injuries not exceeding LOC of 15 minutes, PTA of less than 1 hours and GCS scores of >13 (De Kruijk, 2001). This lack of consensus on definition of mild TBI is probably one of the major causes of the contradicting conclusions in research literature so far.

Clinical diagnosis is possibly even more hazardous. Single mild uncomplicated TBIs, object of interest in the majority of research literature on mild TBI, are rarely encountered in clinical practice. Precise diagnosis is often troubled by the influence of

alcohol intoxication or party drugs. Famous for its effect on level of consciousness and so enhancing the chance of overestimating the level of injury severity. We also know that retrospective estimates of the patient regarding duration of LOC or PTA are very unreliable. Alcohol and drug influences interfere with this judgment. Alcohol intoxication resulting in lowered level of consciousness can misplace a head injury for a mild TBI. Other bodily injuries, like orthopaedic or thoracic injuries, often accompany mild TBIs and are of primary interest in emergency departments. This may be the cause of the fact that diagnosis of mild TBI is overlooked, or classified as head- or whiplash injuries (Ruff & Jurica, 1999).

Neuropathological consequences following mild TBI

A variety of studies have found evidence for diffuse axonal injury after mild TBI. These studies, using different techniques for diagnosing brain damage, report different prevalence of pathology after a mild TBI. Neuroradiology has shown that the MRI scan is superior compared to the CT scan in visualizing neuropathology after a mild TBI (Hofman, 2000). These sensitive MRI scanning techniques show that the prevalence of neuropathology after mild TBI is in general underestimated. These neuroimaging studies were initiated by a famous, and often cited postmortem study by Oppenheimer (1968) who showed that the brains of mild TBI victims showed evidence of extensive diffuse axonal injury. The relation between neuropathology on imaging studies and the reporting of postconcussional symptoms is far from clear. The state of the art MR imaging techniques have proven to be very sensitive for demonstrating neuropathology, however, the specificity for predicting postconcussional symptoms is still not resolved (Hofman, Stapert, Van Kroonenburgh, Jolles, De Kruijk & Wilmink, 2001).

The search for neurochemical cerebro-spinal fluid and serum markers as indicators for brain injury severity has been advanced recently. Especially the protein S-100B, found in most parts of the central nervous system in glial cells, is a promising marker for extent of brain damage (De Kruijk, 2001). The relation between this protein S-100B and neurocognitive performance in mild TBI and a variety of neurological

conditions is the object of different studies at this moment. It is suggested that there is a relation between postconcussional cognitive state of the mild TBI patient and initial S-100B serum marker (Herrmann, Curio, Jost, Grubich, Ebert, Fork & Synowitz, 2001).

The relation between biological markers and postconcussional disorders is the object of neuropsychological studies, because advances in this domain will have a significant effect on the psychosocial and medicolegal aspects of these injuries.

Mild TBI and the cognitive aging process

Moderate to severe TBIs are associated with posttraumatic periods of cognitive dysfunction and atypical aging processes. Epidemiological studies, suggesting a relation between TBI and Alzheimer's disease (Lye & Shores, 2000), are responsible for a new accent in the studies on cognitive sequelae of a mild TBI. Though the majority of longitudinal studies on neuropsychological performance after mild TBI confirm the clinical picture of successful recovery, recent studies suggest that a mild TBI has a chronic effect on cognitive reserve capacity (Satz, 1993). Because these cognitive effects are not accompanied by subjective neuropsychological symptoms, they are of limited clinical significance. These subclinical effects are however of major epidemiological importance, because a significant reduction in cognitive reserve could interfere with the cognitive aging process. Klein, Houx, and Jolles (1996) were among the first to demonstrate that even in absence of subjective health complaints a remote mild to moderate TBI can have chronic effects on cognitive performance. It is even suggested that repeated subclinical concussions can result in chronic cognitive impairement (Matser et al., 1999).

The 'age questions' in relation to mild TBI and cognitive effects have so far not received the attention they deserve from the research community. If a mild TBI has a significant impact on cognitive reserve capacity than it is likely that the cognitive aging process is influenced by this mild TBI. In terms of experimental designs, a mild TBI can have a 'static' or a 'dynamic' influence on the aging process. 'Static' refers to a once and single reduced cognitive reserve that is unaffected by age at time of injury or time elapsed

since injury, i.e. age at neuropsychological assessment. 'Dynamic' refers to an accelerated cognitive aging route influenced by the age at injury and the age at assessment of the patient. Younger age could be protective against the immediate cognitive effects, but the aging process will be continuously influenced by this remote neurological incident, leading eventually to clinical cognitive symptoms at older age. A well-known example of a dynamic route is geriatric traumatic brain injury, resulting in immediate cognitive symptoms and acceleration of the cognitive aging process. Advanced age at injury has always been considered a risk for prolonged recovery processes and lingering symptoms. Few clinical studies have taken a closer look at this suggestion and evidence is weak (Rapoport & Feinstein, 2000).

Aims of experimental studies on the neurocognitive effects of mild TBI

The extensive literature on mild TBI describes various neurologic and behavioural outcomes following mild TBI. This literature is problematic.The knowledge of postconcussional symptom development and especially the neurocognitive effects after mild TBI is substantial, and various disciplines have shown interest in this subject. And although the clinical picture of recovery after a mild TBI has been established (Binder, 1997), the mild TBI literature can be characterized as a spurious collection of facts that are difficult to integrate. A variety of definitions for mild TBI were used, symptomatic and asymptomatic patients have been selected and studied, single or multiple mild TBIs in one individual were included, cross-sectional retrospective and prospective study designs were used, homogeneous versus heterogeneous samples of patients were studied, time since injury of measurements varied between acute, subacute and chronic stage after injury, and different dependent variables (endpoints) were choosen (Bernstein, 1999). The status of scientific neuropsychological literature on mild TBI can be summarized in a nutshell by two striking observations:

1) The symptomatic patients are outnumbered by (subjectively) successfully recovered mild TBI subjects.

2) Evidence for long-term or even chronic aftereffects of a mild TBI (in absence of subjective complaints) is accumulating.

Reviewing the neuropsychological literature on mild TBI, it was decided to conduct five new studies on the neurocognitive effects of mild TBI. Keeping the methodological limitations of earlier studies in mind, we included a homogeneous subject selection of TBI patients with a single uncomplicated very mild TBI (with exception of chapter five, which included also moderate TBI subjects). These subjects were free of subjective postconcussional complaints and in good general health. We decided for this approach to maximize isolation of the factor mild TBI from other factors with known impact on cognitive functioning. To measure the neurocognitive performance and to estimate the brain integrity of these mild TBI subjects we used a neuropsychological test battery with proven sensitivity for picking up mild cognitive impairments after a mild TBI and a variety of other subclinical neurological insults (Bosma, Van Boxtel, Ponds, Houx & Jolles, 2000; Klein, Houx & Jolles, 1996). The psychometric characteristics of these tests are well known, and stem from a prospective cross-sectional study into determinants of cognitive aging (Maastricht Aging Study; Van Boxtel, Buntinx, Houx, Metsemaekers, Knottnerus & Jolles, 1998).

Outline of this thesis

Chapter two identifies and clarifies some of the main methodological issues responsible for inconsistencies in the literature regarding neurocognitive outcome of mild TBI. Chapter three and four present studies on the relation between a single injury variable and neurocognitive performance. Chapter three covers a prospective study on the relation between evidence of posttraumatic lesions on subacute brain MRI scans and neurocognitive performance. Performance of mild TBI subjects with positive MRI findings were compared with performance of mild TBI patients with negative MRI findings in the first six months after injury. Chapter four is a cross-sectional study on the relation between serum S-100B concentrations after mild TBI and neurocognitive performance in the subacute stage after injury. Performance of mild TBI patients with

different concentrations of protein serum S-100B levels is compared with performance of healthy control subjects.

Chapter five and six take a closer look at the long-term and immediate effects on neurocognitive performance after mild TBI and the effect of age at assessment. Chapter five is a cross-sectional prospective study on the long-term effects of remote mild to moderate TBIs on cognitive performance. Brain reserve capacity in relation to age of the subjects is tested in a large population study on the determinants of cognitive aging. The subacute effects of a single mild TBI on neurocognitive performance is tested in chapter six. Interactions of age at injury and mild TBI are tested in a cross-sectional case-control design.

Chapter seven is a study on the recovery of neurocognitive performance after a single mild TBI. In this prospective case-control study the cognitive performance of single mild TBI patients is compared with healthy controls in the first six months after injury. A general discussion and recommendations for further research are provided in chapter eight.

This dissertation has one central purpose: to study the immediate and long-term effect of a very mild TBI on cognitive performance in a healthy population. With that purpose in mind, and the example set by Ferrari (1999), fasten your seat belts and adjust your head restraints. Here we go.

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- **Chapter 2 -**

Pitfalls in research on the neurocognitive effects of mild traumatic brain injury

Objective- *This chapter identifies and clarifies some of the methodological issues responsible for inconsistenties in the literature regarding outcome of mild traumatic brain injury (TBI). These issues include classification and diagnosis of TBI severity, neuropathology, selection of patients with mild TBI, and use of controls, research designs, pre-existing conditions, and emotional reactions to and circumstances surrounding the incident.*

The natural history of recovery from subjective complaints or postconcussional or posttraumatic symptoms (headaches, dizziness, fatigability, irritability, and complaints of memory and concentration) after mild TBI is uncertain. Although there is consistency among patients in early symptoms, there is considerable variation in the number and combination of symptoms reported on the long run. Not all patients with mild TBI complain of posttraumatic symptoms, and most of those who do complain improve after a period of time without further intervention. In a fraction of the cases, however, the postconcussive symptoms persist and may evolve into the so-called postconcussional syndrome. Owing to the high incidence of mild TBIs, this fraction of cases translates into a sizeable group of patients, who may be significantly disabled in resuming their preinjury lifestyle. There are no reliable estimates of late symptom rates and estimates of incidence rates for postconcussional syndromes do not appear to exist.

The mechanisms responsible for the late postconcussional symptoms or postconcussional syndrome have been a topic of great interest and debate over decades. Some have suggested that brain damage or dysfunction is responsible for persistent complaints, whereas others have claimed that psychological factors or malingering are of utmost importance in this regard.

This chapter aims at identifying and clarifying some of the methodological causes of the controversies with the hope that this will help to understand the different faces of mild TBI.

Definition of mild TBI

Defining a mild TBI is a frustrating exercise because uncertainty is inherent to the diagnosis. The uncertainty of whether the patient suffered chronic brain impairment from the trauma. This uncertainty makes the diagnosis of mild TBI unstable because once permanent brain impairment is confirmed the diagnosis should be upgraded to mild permanent brain injury. Conversely, once permanent brain impairment is ruled out the diagnosis should be downgraded to mild *head* trauma. And if the patient initially suffered neurologic symptoms but not permanent brain impairment, the diagnosis should be changed to temporary brain injury or brain dysfunction.

A mild TBI, then, is any trauma-induced combination of symptoms, signs, and results on laboratory tests that raises a reasonable suspicion of brain damage resulting from the trauma. The diagnosis of mild TBI should persist, only so long as the issue of temporary or permanent brain impairment remains unsettled.

In 1993, the American Congress of Rehabilitation Medicine (ACRM, 1993) established the symptom threshold of traumatic brain injury as: loss of consciousness; or loss of memory for events immediately before or after; or alteration in mental state (i.e. feeling dazed, disoriented, or confused); or transient focal neurologic deficit. This definition did not address the issue of permanency.

Brain damage as the cause of postconcussive symptoms

The symptoms comprising the post concussion syndrome following mild TBI fall into three broad categories: cognitive, emotional, and somatic. The cognitive symptoms include difficulty in concentrating, memory loss, decreased speed of information processing, inability to multitask, and difficulty in initiating and planning. The emotional symptoms include depression, irritability, anger, mood swings, and loss of libido. And the

somatic complaints include headaches, phonophobia, photophobia, insomnia, fatigue, blurred vision, and dizziness. Within a month following a mild TBI 88% of patients will complain of at least some symptoms in the postconcussional syndrome (Levin, Mattis, Ruff, Eisenberg, Marshall, Tabbador, High & Frankowski, 1987), by six months 15-29% (Bohnen, Twijnstra & Jolles, 1993), and by one year 10-15% of these subjects will continue to be symptomatic (Rutherford, Merrett &McDonald, 1979).

Many investigators attribute the postconcussional syndrome to permanent traumatic brain damage, but while the postconcussion syndrome is consistent with traumatic brain damage, in fact, similar symptoms can occur without head trauma or any cerebral insult at all. For example, patients with chronic fatigue syndrome suffer psychomotor slowing, impaired attention, slowed learning rate, delayed recall, impaired information processing speed, and disturbances of memory and concentration (Michiels et al., 1996). Chronic pain, including headaches, has been reported to cause postconcussive-type symptoms (Iverson & McCracken, 1997), as has toxic exposure (White, Feldman & Proctor, 1992), and fibromyalgia (Sletvold, Stiles & Landro, 1995). Complicating matters even more is the fact that postconcussive symptoms seem to be very common in the normal population (Wong, Regennitte & Barrios, 1994).

To prove that cognitive symptoms in any given patient are due to permanent brain impairment as a result of mild TBI, one must know: 1) the amount of force necessary to cause permanent brain damage; 2) that the patient was exposed to sufficient force in the accident; 3) that the patient has permanent brain damage traceable to the accident, and 4) that the brain damage occurred in the appropriate location and extent to account for the patient's postconcussional syndrome.

Possible nature of brain changes after mild TBI

From a biomechanical point of view there should be a threshold of force below which the brain is never injured, a threshold above which the brain is temporarily injured, and a threshold above which the brain is permanently injured. Force is loosely equated with g of acceleration (F= ma) because the mass of the brain is relatively constant. In early studies jet test pilots were subjected to up to 450 g without signs of concussion

(Snively & Chichester, 1961). Helmeted car racers have walked away without brain injury from accidents involving head decelerations of over 200 g (Snively & Chichester, 1961). Helmeted football players have been recorded to withstand 230 g to over 1000 g without suffering permanent brain damage (Moon, Beedle & Kovacic, 1971). In most studies, amateur boxers manifest no significant neuropsychological impairment compared to other athletes (Haglund & Eriksson, 1993). Though these studies may be outdated on some methodological aspects, they definitely place discussion on outcome after very mild TBIs in perspective.

Since the introduction of CT and MRI, there has been no documented traumatic brain damage from a blunt head trauma or whiplash injury in the absence of loss of consciousness and with a normal CT and MRI (Alexander, 1998).

On the other hand, there is considerable evidence to suggest that repeated mild TBIs can cause permanent brain damage. Professional boxers are at high risk of developing chronic brain damage, as reviewed by Ryan (Ryan, 1998). Soccer players who suffer repeated concussions perform worse on neuropsychological testing (Matser, Kessels, Lezak, Jordan & Troost, 1999), and soccer players known for 'heading' the ball have a higher incidence of neuropsychological impairment than 'nonheaders' (Matser, Kessels, Lezak, Jordan & Troost, 1998).

There is also evidence that a single mild TBI can cause, if not permanent brain damage, disturbances of brain function. For example, many mild TBI patients manifest abnormal neuropsychological test performance (Brown, Fann & Grant, 1994) and abnormal brain perfusion as assessed by SPECT studies (Kant, Smith-Seemiller, Isaac & Duffy, 1997). Using functional MRI, McAllister demonstrated that a month after mild TBI subjects have difficulty recruiting working memory (McAllister, Saykin, Flashman, Sparling, Johnson, Guerin, Mamourian, Weaver & Yanofsky, 1999).

Of interest is Kotapka's report (1991) of hippocampal neuronal loss in monkeys subjected to mild rotational acceleration. In other animal studies, mild percussion of the exposed cerebral cortex has been shown to cause axonal retraction balls (Lighthall, Goshgarian & Pinderski, 1990; Povlishock, Becker & Cheng, 1983), Purkinje cell loss (Fukuda, Aihara, Sagar, Sharp, Pitts, Honkaniemi & Noble, 1996), and hippocampal

neuronal loss (Hicks, Smith, Lowenstein, Saint Marie & McIntosh, 1993), but the clinical significance of these pathological injuries in human mild TBI is still unclear.

Diffuse axonal injury

The usual pathologic explanation for brain damage in mild TBI is diffuse axonal injury. Axon retraction balls have been seen throughout the white matter (Povlishock, 1993).

Most researchers and clinicians agree that diffuse axonal injury requires a sudden severe acceleration-deceleration which stretches delicate axons (Gennarelli, Thibault & Graham, 1998). Over the first 4-24 hours after the trauma the stretched axons undergo transection with death of the distal axonal segment and sealing off of the proximal axonal stump, accumulating eventually in disruption of axonal transport (Fitzpatrick, Maxwell & Graham, 1998; Maxwell, Povlishock & Graham, 1997). If the initial forces were not too great, the only injury to the axon is a temporary stagnation of axonal transport. The amount of force necessary to cause axonal stagnation is still unknown, as is the threshold force for axonal transection. Whether axonal stagnation causes clinical symptoms is also unknown. It is probable that not all axons share the same risk for these pathologies caused by biomechanical forces. The long axons in the ascending trajectories are likely to be the most vulnerable.

Translational injuries, in which the head remains fixed relative to the shoulders, are not thought to cause diffuse axonal damage. Maintaining the head in a rigid posture may help to explain why 'Indy' race car drivers have survived crashes of 50-80 g (Melvin, Baron, Little, Pierce & Trammell, 1996) and why woodpeckers can decelerate their brains up to 1200 g (May, Fuster, Haber & Hirschman 1979).

Diffuse axonal injury cannot be seen on MRI. Indirect evidence consists of small, low-attenuation lesions with their long axis parallel to the direction of the affected axon. Because of its sensitivity to blood products, MRI is particularly sensitive to subtle haemorrhages. Hofman and colleagues (2001) reported evidence of diffuse axonal injury in 12 of 21 cases of mild TBI. The clinical significance of these MRI findings is yet to be determined: the neurocognitive performance did not differ between the two patient

groups, and qualtity and extent of postconssusional symptoms was almost equal in the two groups (see chapter 3 for further evaluation).

The g of rotational acceleration necessary to produce diffuse axonal injury is still unknown. The absence of neurologic symptoms after staged car crashes (whiplash injury) is not surprising considering the fact that the head is subjected to almost 10 g of acceleration by simply plopping down into an easy chair (Allen, Weir-Jones, Motiuk, Flewin, Goring, Kobetitch & Broadhurst 1994). After evaluating primary experiments and clinical profiles of typical mild TBI patients, Alexander concluded that:

There is no credible mechanism for clinically meaningful DAI (diffuse axonal injury) in pure whiplash in awake humans who do not report loss of consciousness or amnesia beyond that psychologically appropriate for the acutely stressful time immediately around the accident and injury (Alexander, 1998).

Was the patient exposed to sufficient force to permanently injure the brain?

According to some investigators the most reliable indicators of the forces at the time of impact (apart from skull fractures and cortical contusions) are loss of consciousness, retrograde or anterograde amnesia (Forrester, Encel & Geffen, 1994; Wilson, Teasdale, Hadley, Wiedmann & Lang, 1994). It is frequently difficult to judge whether loss of consciousness and posttraumatic amnesia truly occurred because a patient's first reaction to an accident is simply to make sense of the sudden unexpected impact and to focus on any imminent threats. These initial moments may manifest themselves as an unawareness of surrounding events, and thus be misinterpreted as a state of unconsciousness or posttraumatic amnesia. As King cautioned against placing too much weight on posttraumatic amnesia alone is to be avoided. In fact, in his opinion, the usefulness of posttraumatic amnesia and the Glasgow Coma Scale score have yet to proved in this respect (King, 1997).

Is permanent brain damage traceable to the accident?

A long latency of months between the accident and the onset of cognitive dysfunction is generally inconsistent with traumatic brain damage. The most symptomatic day for a mild TBI injured patient should be the first day after the accident after which the symptoms improve (Hugenholtz, Stuss, Stethem & Richard 1988; Levin et al., 1987). Therefore, worsening of cognitive symptoms is also contrary to the natural history of traumatic brain injury (Alexander, 1996; Stuss, 1995). Intermittent cognitive loss separated by periods of normal cognition is also not due to structural brain damage, but rather some other factors – depression, pain, anxiety, fatigue, preoccupation, psychotropic medication, psychosocial stressors (including malingering) – affecting a structurally normal brain.

Neurologic signs should not develop months after a mild TBI, and should manifest some improvement over time. There may be some waxing and waning of the signs as they improve, but they should not be frankly intermittent. Purely transient neurological signs indicate transient neurological dysfunction, not permanent brain damage.

In order to attribute an abnormal laboratory or radiologic test to a specific traumatic insult, the abnormality should be absent on the same test performed prior to the injury, and after a subacute period should remain anatomically fixed and unchanged in size on repeat testing. True brain damage causes an anatomically fixed lesion. Abnormalities that move about are inconsistent with resolving brain trauma.

Neuropsychological testing

Neuropsychological testing can be very helpful in quantifying various aspects of cognitive function, especially improvement or worsening over a period of months or years. It cannot diagnose brain damage. It can only identify brain dysfunction, which may or may not be due to brain damage (AAN, 1996).

Neuropsychological testing, especially when the object is to test the limits of cognitive performance, depends for its validity on patient attentiveness and motivation

(Cohen, 1982; Keefe, 1995). Neuropsychological testing is also dependent for its validity on a proper control group against which the patient is compared. The control group should match the patient on all relevant variables except for the mild TBI. Since neuropsychological testing can be adversely affected by chronic pain, fatigue, anxiety, depression, and the medications used to treat those conditions, the control group should match the patient with regard to these variables (Margulies, 2000).

The repeated testing of subjects with a neurocognitive test battery to assess recovery of cognitive function presents many methodological problems. One major problem concerns learning effects resulting from repeated testing. These may seem to suggest recovery when, in fact, they reflect improvement due to implicit or explicit memory effects. Recovery involves an improvement in performance over time which cannot be attributed to retest effects. Recovery does not imply complete restoration of functions, as any degree of improvement may be viewed as a sign of recovery. Even when studies meet the requirements of both a longitudinal design and a control group, there are still other problems when general conclusions have to be drawn about recovery (Spikman, Timmerman, Van Zomeren & Deelman, 1999). A major problem is the differential sensitivity of neuropsychological tests to severity of deficits and to changes over time. The differential sensitivity of tests to impairment can be attributable to two categories of factors: task specific factors and subject specific factors. Task characteristics may affect the extent to which a task can be learned within or over trials and thus the extent to which retest effects may occur. Subject characteristics, like age or educational level, may affect the ability to learn, which may in turn be expressed both in initial performance and in improvement over time. It can be concluded that no simple, linear relationship can be expected between test performance and the time course or extent of recovery. Knowledge of the relevant factors should enhance the clinical value of tests with respect to prediction of recovery.

Axonal damage and aging

Considering the billions of axons coursing through the cerebral hemispheres and brainstem, can degenerating axons in the cerebral hemispheres account for the multitude of cognitive complaints and neuropsychological deficits found in the postconcussive symptom complex? According to Lashley's law of mass action, the magnitude of neurocognitive deficit is directly related to the size of the injury (Lashley, 1931). Or, as Povlishock (1995) pointed out:

Unfortunately, in all studies conducted to date, there has been no attempt to actually explain precisely how such axonal damage could translate into morbidity reflected in unconsciousness and enduring behavioural dysfunction. In this context, it is well recognized that the traumatically induced axonal damage detected by morphological endpoints involves only a relatively modest proportion of the total axons coursing in the anatomical field under investigation. Therefore, based upon this observation, it is difficult to explain how such limited axonal damage could translate into such widespread global neurological abnormalities.

Beginning around age 55 our brains begin a significant decline in weight (Coleman & Flood, 1987; Terry, DeTeresa & Hansen, 1987). Guttman attributes the majority of aging changes to decreasing white matter, specifically, loss of myelin (Guttman, Jolesz, Kikines, Killiany, Moss, Sandor & Albert, 1998). He also references reports of substantial age-related neuronal loss in selected subcortical regions involved in cognitive function. Thus, even if rare axonal degeneration does occur after mild TBIs, compared to normal ongoing neuronal and myelin deterioration over the age of 55, rare degenerating axons are inadequate to account for the cognitive loss complained of by mild TBI patients.

Even assuming that rare axonal degeneration could cause cognitive detectable deficits resulting from tiny neurologic lesions, these cognitive deficits should recover. It is suggested that the brain is quite capable of compensating for small areas of anatomic dysruption through various mechanisms of neuronal plasticity. In the great majority of cases any minute damage should recover clinically. In those cases that are not self-limiting, it is possible that the condition may have been misdiagnosed. A lesion may have

been missed, or nonanatomic/psychological factors may be involved (Elson & Ward, 1992).

Conclusions

Based on current information, few question the early effects of mild TBI. Much of the confusion and controversy relates to chronic or long-term effects in cases with complicated recoveries and those with the so-called postconcussional syndrome. These are the cases that are difficult to figure out and problematic for clinicians to treat. These are also the cases that eventually should receive more focused research, but only after we have answered some basic questions.

In studying psychological and functional consequences of disease or trauma, important questions involve whether the condition is associated with morbidities and whether the morbidities are caused by the condition. These questions appear to be straightforward, but the answers, particularly to the question of cause are complex. This is particularly the case in conditions where the subjective complaints are difficult to explain on the basis of subtle or difficult to identify impairments. Mild TBI and numerous other conditions resulting in complaints of pain or fatigue (back pain, post whiplash syndrome, chronic fatigue syndrome) are examples of such conditions.

Identification of probable cause involves careful differential diagnosis, as the cause is not necessarily brain injury. As reviewed here, although brain damage due to mild TBI may be the cause in certain cases, there are multiple other potential causes, including those predating the injury, injuries to systems other than the brain, circumstances surrounding the accident, and circumstances facing the individual afterward.

Controversy regarding the etiology of postconcussional symptoms has a long history, but advances in this area of research have been slow. One of the reasons for this is perhaps the narrow view of causality (organic or psychogenic). To understand the sources of difficulties of such patients, much broader conceptual frameworks and

theoretical models than the implied medical model need to be applied (King, 1997). Additional factors that have to be considered include the relevance of the impairment and its magnitude to the functioning (for example cognitive functioning) of the individual and the way the individual handles, copes with, and adjusts to illness and illness-related losses (Kay, Newman, Cavallo, Ezrachi & Resnick, 1992).

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- Chapter 3 -

Posttraumatic brain lesions and neurocognitive dysfunction after mild traumatic brain injury: A MRI based prospective study[1]

[1] S. Stapert, P. Hofman, P. Houx, J. de Kruijk, J. Wilmink, & J. Jolles, *submitted for publication*

Objective- To evaluate whether MRI measures of brain damage after mild traumatic brain injury (mild TBI) are related to neuropsychological measures of impaired performance and postconcussional syndrome.

Method- Twenty-one mild-TBI patients, aged 15-42 years, were subjected to MRI scanning and neuropsychological examination within 5 days after injury. Neuropsychological assessment was repeated at 2 and 6 months after injury. MRI examination was repeated at 6 months post injury. A case-control design was adopted in which a group of patients with MRI evidence of brain lesions was compared to patients without brain lesions. Cognitive speed and memory performance of both groups of mild-TBI patients were compared with performance of a healthy control group.

Results- Twelve out of 21 mild-TBI patients had posttraumatic lesions on MRI scanning. Neuropsychological performance of TBI patients was inferior on measures for cognitive speed and memory performance compared to a healthy control group. There were no significant differences among mild TBI patients with or without MRI abnormalities on measures for cognitive speed and memory.

Conclusions- This study shows that the prevalence of traumatic brain lesions after mild-TBI is generally underestimated. Subacute (< 5 days after injury) MRI evidence of posttraumatic lesions after mild-TBI does not predict recovery of cognitive speed and memory performance in mild TBI patients.

Mild traumatic brain injury (TBI) is one of the most common neurological disorders (Kraus, McArthur & Silberman, 1994). It is also noted that mild TBI is the most common and controversial category of traumatic brain injury (Paniak, MacDonald, Toller-Lobe, Durand & Nagy, 1998). Although the clinical picture of recovery after mild TBI has been established and is considered a relatively benign condition (Binder, 1997; King, 1997), controversy continues to exist about the long-term effects of mild TBI on cognitive and behavioural functioning (Newcombe, Rabbitt & Briggs, 1994). Clinicians have recognized that many patients with a mild TBI endorse disabling symptoms including headache, fatigue, insomnia, dizziness, concentration difficulties, memory loss, irritability, depressive symptoms, and anxiety (Alexander, 1995). This cluster of symptoms has gained nosological status as the post-concussive syndrome (PCS; Brown, Fann & Grant, 1994) and suggests significant brain impairment. It is this sample of patients suffering from chronic PCS that contributes to the differences in conclusions among experts in the field. What maintains a persistent postconcussive syndrome is unclear: the maintaining factors may relate to malingering (Jacobson, 1995), psychiatric problems elicited by either the head injury or surrounding circumstances (Fox, Lees-Haley, Earnest & Dolezal-Wood, 1995), a tendency to complain following an adverse event (Ferrari & Schrader, 2001), or subtle but underdiagnosed brain pathology (Reitan & Wolfson, 1999). Though a biological marker is still missing, a partially organic origin of the postconcussive syndrome is suggested (Bohnen & Jolles, 1992; Brown, Fann & Grant, 1994). Focussed research is needed to disentangle some of these relations, both in the acute and long-term stages of recovery.

The possible neuropathological basis of enduring cognitive and behavioural symptoms after mild TBI remains elusive. Some of these patients have structural lesions identified by computerized tomography (CT) (Iverson, Lovell, Smith & Franzen, 2000) or MRI (Hofman, Stapert, Van Kroonenburgh, Jolles, De Kruijk & Wilmink, 2001). Because of the limited sensitivity of CT, this technique is less suitable for studying mild TBI. Especially in the detection of non-haemorrhagic contusion and diffuse axonal injury, lesions commonly found in mild TBI, MRI technique has proven to be superior over CT (Mittl, Grossman, Hiehle, Hurst, Kauder, Gennarelli & Alburger, 1993). From a neuropathological perspective, axonal shearing is an important potential mechanism of structural damage (Bigler, 2001). It is likely that axonal damage in mild TBI is subtle, because of the absence of systematic, white matter abnormalities in the majority of published cases of CT and/or MRI abnormalities in mild TBI (Bigler & Snyder, 1995; Mittl et al., 1993). Compatible with this notion is our recent finding that patients who have persistent neurocognitive complaints one year after brain trauma are characterized by structural brain changes as assessed by MRI (Hofman, Verhey, Wilmink & Jolles, 2001).

Although there is growing evidence from these studies that organic pathology (which may or may not be visible on imaging or functional studies) can occur after mild TBI, what is less clear is what factors determine whose brains are most vulnerable to the functional effects of such insults. Besides injury-related organic factors, pre-existing factors must also be considered. Patients with and without persistent sequelae are not clearly different in terms of personality characteristics and socio-demographic factors (Binder, 1997).

Despite the persistence of neuropsychological sequelae in a significant number of mild TBI patients and evidence of MRI-detected lesions in sufferers of the postconcussional syndrome (Hofman, Verhey, Wilmink & Jolles, 2001), the prevalence of MRI abnormalities in mild TBI in the acute to subchronic phase (up till half a year after trauma) is still unclear. In addition, little is known about the relationship between brain damage and the outcome of patients after mild TBI. Levin and colleagues (1992) published a longitudinal study on patients who had sustained mild-to-moderate TBI, using neuroimaging and neurocognitive follow-up. They found heterogeneity in the relation between MRI findings and neurocognitive test results. Diminution of lesion volume on MR imaging did not necessarily accompany improvement of neuropsychological performance.

The present study evaluates whether mild TBI patients who are characterized by brain lesions as shown by MR imaging have inferior neurocognitive performance. Advanced MRI techniques were used, which have recently become available (Hofman et al., 2001), and which have shown that a larger proportion of patients suffering from mild TBI has evidence of lesions after mild TBI (Van der Naalt, Hew, Van Zomeren, Sluiter, Minderhoud, 1999). To this end, we performed a prospective study with a carefully selected group of mild TBI patients and examined the relation between MRI evidence of posttraumatic lesions, cognitive speed and memory performance in the subgroup of subjects with evidence of brain lesions versus the subgroup of patients without. We tested the hypothesis that a single injury variable, namely evidence of brain lesions on MRI (MRI +), would result in an inferior memory and cognitive speed performance compared

to performance of lesion free counterparts (MRI -). It was also evaluated whether MRI + patients would report more subjective postconcussional symptoms than MRI - subjects.

Method

Definition of mild traumatic brain injury

This study used a definition of mild TBI that fell within the limits proposed by the Head Injury Interdisciplinary Special Interest Group of The American Congress of Rehabilitation Medicine (1993). We used this more conservative definition to include a homogeneous sample of patients falling in the low end of the mild TBI spectrum. This definition stated that a person with uncomplicated mild TBI has had a physiological disruption of brain function as manifested by at least one of the following:

(1) Glasgow Coma Scale score of 14-15

(2) Loss of consciousness for less than 20 minutes

(3) Post-traumatic amnesia for less than 6 hours

Subject selection and characteristics

Consecutive patients aged under 45 presenting at the emergency department with uncomplicated mild TBI were included in the study. Patients requiring anaesthesia or suffering from significant extra-cranial injury were excluded. Previous head injuries,

alcohol or other substance abuse, major psychiatric, neurological or medical conditions were also used as criteria for exclusion. Control subjects (N= 29) were recruited by means of advertisements placed in local newspapers and were paid for their participation. The advertisement stressed that participants should be healthy. Using a semi-structured interview, the control subjects were screened for absence of chronic medical conditions and health related factors. The controls were matched individually to the patients with respect to age, sex and education (see table I).

Twenty-one subjects were included in the study (9 females). The mean age was 22.8 years (SD= 7.7, range 15-42 years). The mean educational level was 5 on a scale from 1 (only primary school) to 8 (university education), and the mean number of educational years was 13.5 (range 9-23). The mean GCS score at presentation was 14.5 (SD= 0.6, range 14-15) with a mean duration of unconsciousness of 4 minutes (SD= 4.4, range 0-15 minutes), and a post-traumatic amnesia period of 67 minutes (SD= 83.8, range 0-300 minutes). The accidents were traffic-related in 16 cases, sports-related in 4 patients, and one patient had fallen from the stairs. Twenty-one patients had the initial MRI. One subject only had a follow-up examination at six months, while three subjects were lost to follow-up.

Table I: Subject and injury characteristics per group

	MRI +	MRI -	controls	F-value	significance
N	12	9	29		
Age	23.3 (8.3)	24.0 (7.2)	23.3 (7.5)	.032	n.s.
Education level	5.1 (1.7)	5.0 (1.6)	4.9 (1.4)	.067	n.s.
Years of education	13.3 (2.4)	13.8 (4.3)	13.8 (2.5)	.114	n.s.
GCS score	14.4 (0.7)	14.6 (0.5)	-	.485	n.s.
PTA	57.5 (75.4)	80.0 (96.9)	-	.359	n.s.
LOC	3.7 (4.0)	4.4 (5.1)	-	.129	n.s.

Image acquisition and postprocessing

Structural MR images were acquired working on a system operating at 1.5 Tesla. The MR examination protocol consisted of three pulse sequences; axial dual T2-weighted fast spin-echo, axial T2-weighted fluid-attenuated inversion recovery (FLAIR), and axial T2*-weighted gradient echo.

The ventricle-to-brain ratio (VBR) was measured as a measure of brain atrophy. The VBR was calculated, and the ratio measured on the initial scan was divided by the ratio from the scan performed at 6 months (tVBR). In five patients, tVBR could not be determined; three patients were lost in follow-up, and in two patients the raw data of the axial T2-weighted images were unavailable. For detailed specifications see Hofman and colleagues (2001).

Neuropsychological tests

All patients were evaluated using a fixed battery approach. The choice of neurocognitive tests was based upon earlier studies in mild TBI patients by our research group.The following tests were used because of proven sensitivity for detecting neurocognitive impairment after mild TBI and subclinical incidents (Bohnen & Jolles, 1992; Klein, Houx & Jolles, 1996).

The Visual Verbal Learning Test (VVLT). This memory test is a visual version of the Rey Auditory Verbal Learning Test (Rey, 1964). In three consecutive trials, a list of 15 words has to be memorized and reproduced followed by a delayed recall procedure after 20 minutes (Brand & Jolles, 1985). Dependent variables are the 1st trial immediate recall score, total immediate recall score from 3 trials, and the delayed recall score.

The abbreviated version of the Stroop Colour Word Test (SCWT; Bohnen, Jolles & Twijnstra, 1992; Klein, Ponds, Houx & Jolles, 1997). This test has often been used to test selective attention, mental speed, and interference susceptibility (Lezak, 1995). The test uses three cards displaying fourty stimuli each; colour names (SCWT I), colour patches (SCWT II), and colour names printed in incongruously coloured ink (SCWT III). The dependent variables are the times (secs.) needed to read (SCWT I), to name the colour of the patches (SCWT II) or the printing ink (SCWT III).

Letter Digit Coding Test (LDCT). This test is a modification of the procedurally identical Symbol-Digit-Modalities Test (Lezak, 1995; Smith, 1968). The subjects are supplied with a code at the top of a page, which links a digit to a letter. Subjects have to fill in blanks which correspond to the correct codes. The coding test is used to measure

the speed of processing of general information. The dependent variable is the total number of digits written correctly in 60 seconds.

Subjective complaints were assessed with the neurovegetative questionnaire (Bohnen, Twijnstra & Jolles, 1992). This questionnaire correlates with persistent symptoms after mild traumatic brain injury. We used the postconcussion subscale to assess post-traumatic symptoms. This subscale consists of 11 items with a score range of 11 (minimum) to 44 (maximum). The postconcussion scale covers subjective complaints like headache, hypersensitivity to light and noise, mental slowness, fatigue, concentration disorders, dizziness and loss of initiative. Subjective postconcussional complaints were assessed at first and final follow up.

Procedure

The protocol specified completion of a cerebral MRI examination and neuropsychological assessment within two to five days after injury. All studies were performed on the same day, starting with the neuropsychological examination. Neuropsychological follow-up was conducted at 2 and 6 months after injury, and MRI was repeated after 6 months. The control subjects had no MRI study.

The study was approved by the Medical Ethics Committee of the University Hospital Maastricht, and all the patients gave their informed consent.

Statistical analysis

Differences in group performance were tested using a repeated measures MANOVA technique with group (MRI+, MRI- and controls) as between subjects factor and follow up measurement (< 5 days, 2 months and 6 months after injury) as within subjects factor. For in depth analyses one-way ANOVA and Tukey's HSD post-hoc procedure was used for each test moment. All tests were two-tailed.

In a secondary analysis we used dichotomous endpoints. Neurocognitive impaired performance was defined as a performance falling within the 10^{th} percentile of age and education corrected norms on at least two of the following subtasks: VVLT immediate recall, VVLT delayed recall, SCWT III and the substitution task. Reference values from the Maastricht Aging Study (MAAS; Jolles, Houx, Van Boxtel & Ponds, 1995) were used. In these analyses we compared the cognitive performance of the three groups using chi-square analyses.

Results

MRI lesions

Twelve patients appeared to have brain lesions as shown by MRI scanning (57%). The majority of lesions was found in the frontal lobe (42 lesions) and temporal lobe (16 lesions). One cerebellar lesion was found, but no brainstem lesions. The average number of lesions per patient in the MRI positive group was 5 (range 1-10). Two patients appeared to have an additional extra-cerebral haemorrhage.

Table II: group means of neurocognitive variables for each test moment

		Verbal learning Test: 1st trial	Verbal learning test: total score	Verbal learning test: delayed recall	SCWT I	SCWT II	SCWT III	Substitution	PCS
			M (SD)	M (SD)	M (SD)	M (SD)	M (SD)	M (SD)	M (SD)
baseline	MRI +	7.5 (1.5)	29.3 (4.3)	9.4 (2.4)	15.2 (1.4)	21.5 (4.9)	35.2 (11.7)	36.1 (9.6)	-
	MRI -	7.0 (1.5)	29.0 (5.4)	9.4 (3.5)	16.4 (3.5)[a]	21.9 (8.6)	36.6 (14.6)	38.8 (7.6)	-
	controls	8.2 (2.5)	32.8 (5.3)	11.6 (2.5)	14.2 (1.9)	20.7 (2.9)	34.1 (6.6)	41.2 (6.8)	-
1st follow up	MRI +	7.8 (2.0)[b]	32.6 (4.6)	11.9 (2.9)	15.5 (2.0)[b]	21.4 (4.6)	32.0 (6.8)	38.5 (7.0)	16.7 (4.4)
	MRI -	8.3 (1.1)	32.1 (4.2)	10.7 (3.9)	15.6 (1.0)[a]	20.6 (1.7)	31.4 (5.7)	40.4 (5.4)	22.0 (8.0)
	controls	10.2 (3.0)	36.6 (5.9)	13.2 (2.0)	13.8 (1.7)	19.4 (2.8)	29.7 (4.9)	42.7 (6.7)	17.2 (3.9)
2nd follow up	MRI +	8.5 (1.9)	34.6 (3.4)	12.3 (2.1)	14.4 (1.6)	19.7 (3.8)	30.1 (7.8)	43.4 (6.1)	16.3 (4.2)
	MRI -	9.4 (0.7)	34.6 (4.1)	10.9 (2.9)[a]	15.4 (2.2)	19.8 (2.9)	29.5 (5.3)	45.1 (8.1)	22.4 (8.4)[a c]
	controls	10.1 (3.1)	37.8 (5.2)	13.1 (1.9)	13.1 (1.7)	19.2 (3.0)	29.0 (5.6)	44.6 (7.1)	16.6 (3.6)

a: significant difference between MRI- and control subjects according to Tukey's HSD post-hoc procedure ($p < .05$)
b: significant difference between MRI+ and control subjects according to Tukey's HSD post-hoc procedure ($p < .05$)
c: significant difference between MRI- and MRI+ subjects according to Tukey's HSD post-hoc procedure ($p < .05$)

Patients with abnormal imaging study showed brain atrophy after six months, as expressed by a decreased tVBR. tVBR was significantly lower in patients with a positive MRI than in those with a negative MRI (negative: *M*= 1.04, *SD*= 0.03; positive: *M*= 0.94, *SD*= 0.08; *t*(16)= -0.222, *p*= *ns*). Patients and controls did not differ in age, educational level, and years of formal education (F (2, 47) < .114, $p = ns$) (see table I).

Neurocognitive performance

Between subjects effects of the repeated measures MANOVA did not reveal any differences in neurocognitive performance between the MRI+ and MRI- group. In depth analyses, post-hoc Tukey HSD and planned univariate comparisons, did not reveal any significant differences between both patient groups (see table II & III).

Table III : results of repeated measures MANOVA

	Main group effect; F (2, 43)=	significance	Within subjects effect; F (2, 86)=	significance
memory				
VVLT 1st trial score	2.251	n.s.	14.644	<.001
VVLT total score	3.530	<.05	25.842	<.001
VVLT delayed recall score	3.963	<.05	13.800	<.001
Cognitive speed				
SCWT I	6.386	<.01	6.918	<.01
SCWT II	1.130	n.s.	7.041	<.01
SCWT III	0.433	n.s.	21.930	<.001
substitution	1.686	n.s.	36.182	<.001

All groups, including controls, showed improvement on neurocognitive measures at follow up (within subjects effects). Inspection of cell means showed that control subjects' performance was superior compared to the MRI+ and MRI- group on all measures. A significant between groups effect was found on measures for immediate total recall, delayed recall and SCWT I (see table III). The effect, however, proved not to be very robust because of loss of significance after post-hoc procedures.

Planned univariate comparisons on baseline showed significant main effects for group on delayed recall of VVLT ($F(2, 47)= 3.906$, $p < .03$) and SCWT I ($F(2, 47)= 3.543$, $p < .04$). Post-hoc tests (Tukey HSD) revealed a significant difference between control group and MRI- group ($p < .04$) on the delayed recall test. Post-hoc procedure approached significance on the SCWT I ($p = .06$) between controls and the MRI + group.

First follow up measurements, two months after injury, showed significant main effects for group on the immediate 1st trial recall of VVLT ($F(2, 43)= 3.788$, $p < .04$), delayed recall ($F(2, 43)= 3.274$, $p < .05$) and SCWT I ($F(2, 43)= 6.068$, $p < .01$). Post-hoc tests showed significant differences on immediate 1st trial recall between the MRI+ group and control subjects ($p < .05$). Post-hoc procedures showed that control performance was superior compared to both MRI+ group ($p < .02$) and MRI- group ($p < .04$) on the SCWT I subtask. The difference in performance of the MRI- and control group on the delayed recall subtest was near significant ($p= .06$) according to post-hoc procedures.

We found significant main effects for group on the VVLT recall score ($F(2, 44)= 3.788$, $p < .05$) and the SCWT I performance ($F(2, 44)= 5.525$, $p < .01$) on the last follow

up measurements. Control subjects performed better than the MRI- group on delayed recall ($p < .04$) and SCWT I ($p < .01$).

Subjective postconcussional symptoms

At the first follow up the MRI- group reported more subjective postconcussional complaints than the MRI+- and the control group. This difference was significant at the $p = 0.05$ level ($F(2, 43) = 3.179$). This difference was more pronounced at the final follow up ($F(2, 43) = 4.865$, $p < .02$), with the MRI- group reporting significant more complaints than the MRI+ group ($p < .02$) and the control group ($p < .05$). At the first follow up we found a low, but significant correlation, between subjective postconcussional complaints and performance on the substitution task ($r = -0.373$, $p = .012$). This indicates that high levels of subjective complaints were related to low performance on the coding task at two months after injury. No significant correlations between postconcussional complaints and neurocognitive performance were found at the final follow up moment.

Prevalence of subjects with impaired performance

After cross-tabulations and chi-square analysis for each test moment separately, the proportion of subjects per group with an impaired neurocognitive performance according to our definition (method section) did not reveal significant differences within 5 days after injury ($\chi^2(df = 2) = 3.843$, $p = 0.15$), two months ($\chi^2(df = 2) = 3.292$, $p = 0.19$) and six months after injury ($\chi^2(df = 2) = 1.708$, $p = 0.43$) (see table IV).

Table IV: Percentage of subjects per group with performance below the 10th percentile

	Baseline			First follow up			Second follow up		
	MRI+	MRI-	contr	MRI+	MRI-	contr	MRI+	MRI-	contr
memory									
VVLT total score	0	11%	3%	0	0	0	0	0	0
VVLT delayed recall	42%	44%	17%	17%	33%	3%	17%	22%	7%
cognitive speed									
SCWT III	42%	33%	24%	25%	22%	10%	25%	22%	10%
substitution	33%	22%	7%	17%	11%	3%	17%	11%	3%
Impaired neurocognitive performance	42%	22%	14%	8%	22%	3%	0	11%	3%

For definition of impaired neurocognitive performance see methods section

Discussion

Two findings from the present study are salient. First, the prevalence of abnormal MRI findings in 12 patients (57%) was unexpectedly high. Especially considering the prevalence of lesions (44%) found in a recent study by Van der Naalt et al. (1999) in mild-to-moderate brain injured patients. On the basis of the location and the MR characteristics, lesions can be attributed to the trauma. Small extra-axial hematoma, nonhaemorrhagic contusions, and haemorrhagic contusions were found. We also identified lesion characteristics for diffuse axonal injury in accordance with another study (Hofman, Verhey, Wilmink & Jolles, 2001).

According to a recent meta-analysis the prevalence of haemorrhagic lesions in the mild TBI patient group was estimated to be approximately 8% (Hofman, Nelemans, Kemerink

& Wilmink, 2000). This prevalence shows the high sensitivity of MR for posttraumatic lesions. Evidence of brain atrophy as illustrated by the decrease in tVBR has not been previously reported in mild TBI patients, only in patients with moderate-to-severe TBIs (Blatter, Bigler, Gale, Johnson, Anderson, Burnett, Ryser, Macnamara & Bailey, 1997). These findings illustrate that mild TBI is accompanied by organic damage in over half of the mild TBI population and that this damage persists over a period of up to a half year.

The second salient finding was the rejection of our hypothesis that patients with evidence of posttraumatic lesions on MRI scans would have an inferior neurocognitive performance compared to their non-damaged counterparts. Although inspection of cell means showed superior performance of the control group compared to combined patient groups, even after six months, it is notable that the majority of patients with mild TBIs did not obtain unusually low scores on neuropsychological tests (see table IV). The population of TBI patients with absence of lesions on MRI study even tended to perform worse than the MRI+ group.

The heterogeneity of the brain-injured population, as well in demographic characteristics as in injury related variables, makes it difficult to demonstrate a relation between lesions and specific neurocognitive deficits. We chose to assess cognitive speed and memory performance with cognitive tests that have proven sensitivity for detecting mild neurocognitive deficits. Classically, the underlying mechanism of neurocognitive symptoms, is believed to be a disturbance in the speed of information processing due to diffuse injury. Memory complaints are believed to be secondary to disturbances in speed of information processing. We found that control subjects performed better on a task for simple cognitive speed (SCWT I), compared to the mild-TBI patients. Two months after

injury performance was still significantly below level of controls. After six months patients were still slower on the SCWT I task, though this difference was not significant. We found no differences in performance on complex and general speed of information processing tasks.

The immediate and delayed recall performance of the patients was worse compared to the controls. At two months after injury, the MRI+ group displayed the worse performance on immediate 1st trial recall of the VVLT. This neurocognitive task can be regarded as a measure for working memory. Some reduction in memory performance is in accordance with evidence of diffuse damage on MR imaging (McAllister, Saykin, Flashman, Sparling, Johnson, Guerin, Mamourian, Weaver & Yanofsky, 1999).

We also hypothesized that the patients with evidence of organic cerebral damage on MRI study would report more subjective postconcussional complaints than patients without evidence of cerebral damage and healthy control subjects. The MRI- group reported the most postconcussional symptoms, while the MRI+ and control subjects reported the same level of postconcussional complaints at first and final follow up. A more elaborate prospective study is needed to elucidate this issue. The need for such a study arises from the non-specific nature of most postconcussional symptoms. The relation between subtle neurological injury, PCS symptomatology and the presence of psychological conditions is of crucial clinical and forensic importance (Trahan, Ross & Trahan, 2001).

It is not sure whether patients were completely recovered after six months. Patients' as well as control subjects' neurocognitive performance improved over the two

follow-up measurements. This indicates that subjects benefited from practice effects due to follow up measurements. The design does not allow to explain the differences in performance in terms of practice effects, because the groups did not differ in age and years of formal education.

Although lesions were located predominantly in the frontal and temporal lobes, the size and location differed considerably among patients. This heterogeneity can possibly be explained by differences in trauma mechanisms. The neurocognitive data also showed a heterogeneous image; different cognitive domains were more or less severely affected. This heterogeneity of both organic lesions and neurocognitive deficits may explain why an association between these was not demonstrated. This also shows that though neuroimaging information is critical to the comprehensive evaluation of the neurologic patient, neuroimaging findings alone have only limited predictive ability with regard to neurobehavioural symptoms. Future research will have to focus on the specificity of brain-behaviour relations. Stuss and colleagues found that only frontal lesions produced significant impairment on the Stroop interference task (Stuss, Floden, Alexander, Levine & Katz, 2001) and trailmaking test part B (Stuss, Bisschop, Alexander, Levine, Katz & Izukawa, 2001) compared to lesions in nonfrontal regions. Our data do not allow such specific brain-behaviour analyses because of the diffuse lesion pattern in our patient sample.

Absence of detectable abnormalities on MRI study in the MRI- group should not be interpreted as meaning absence of pathology. In animal percussion models, mild injury, while not producing tissue tears, does produce neuronal cytoskeleton abnormalities that have the potential to leave the cell dysfunctional (Bigler, 2001). A

dysfunctional cell does not necessarily die and therefore, structure dependent MRI scan might appear grossly normal. Using fMRI techniques, McAllister et al. (1999) have shown different cerebral activation patterns during working memory tasks in mild TBI subjects when compared to controls. Mild TBI subjects required greater recruitment of cortical areas for performing the same task, suggesting a disruption in the efficiency of neural networks in the mid TBI brain, the type of deficit that would be predicted with white matter injury. There is convincing evidence that absence of abnormalities on MR scans of the TBI patients who has experienced a significant injury may simply be below the threshold of detection. This might explain the absence of a relation between neurocognitive performance and subacute imaging abnormalities in our study. Although there is some evidence for a psychological rather than a neurological disorder in persistent postconcussion syndrome (Mittenberg & Strauman, 2000), it is argued that as greater sophistication develops in neuroimaging and neuroimaging protocols to detect structure-function relationships, this type of position will no longer be tenable (Bigler, 2001). Although our data do not support the routine application of MR imaging in the management of mild TBI, the correlation between MR findings and neurocognitive performance does justify further study. New imaging techniques may increase the sensitivity of imaging for traumatic lesions and increase correlation to neurocognitive deficits, and eventually to long-term outcome.

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- Chapter 4 -

Serum S-100B concentration is not related to neurocognitive performance after mild traumatic brain injury[2]

[2] S. Stapert, J. de Kruijk, P. Houx, P. Menheere, A. Twijnstra, & J. Jolles, *submitted for publication*

Objective- The serum concentration of S-100B is reported to reflect the severity of brain damage. The purpose of this study was to determine whether elevated serum S-100B concentrations were related to neuropsychological test performance of patients in the subacute phase of recovery from mild traumatic brain injury (mild TBI).

Method- S-100B concentrations were measured in blood samples taken within 6 hours after TBI. Serum S-100B was estimated using an immunoluminometric assay. Cognitive speed and memory were assessed with neuropsychological tests at a median of 13 days (range 7-21 days) after injury. The two groups, formed on a median split of initial serum S-100B concentrations (> or < 0.22 μg/L) did not differ in age or education. The neuropsychological performance of the TBI patients was also compared with that of a healthy control group.

Results- Cognitive speed and memory performance of mild TBI patients were inferior compared to those of healthy subjects. There were no significant differences within the TBI group when serum S-100B concentration was taken into consideration.

Conclusions- Serum S-100B levels after mild TBI are not predictive of neuropsychological performance in the subacute stage of recovery.

Although mild traumatic brain injury (TBI) is considered a benign neurological condition and is associated with uneventful recovery, many patients experience mild impairment of neurocognitive functioning in the first days to weeks after injury. Most experience completion of neuropsychological recovery in 1 to 3 months, although there is some variability in results (Binder, 1997). However, a substantial number of patients (about 10-29%) complain about long-term neuropsychological deficits. It is assumed that these patients have persistent postconcussive syndromes (Alexander, 1995; Bohnen, Twijnstra & Jolles, 1993).

Reported risk factors for long-term neurobehavioural disorders include: underdiagnosis of initial injury severity (Alexander, 1998), duration of posttraumatic amnesia and unconsciousness (Iverson, Lovell & Smith, 2000), age, sex, multiple mild TBIs (Binder, 1997), chronic pain (Iverson & McCracken, 1997), comorbid depression (Busch & Alpern, 1998), psychosocial stressors, or misattribution of everyday symptoms (Bernstein, 1999). In order to predict and prevent neuropsychological sequelae after mild TBI and possible development of postconcussional syndrome, there is need for an early sensitive marker of brain damage in patients.

Serum levels of protein S-100B are reported to be increased after mild TBI (Herrmann, Curio, Jost, Grubich, Ebert, Fork & Synowitz , 2001; Waterloo, Ingebrigtsen & Romner, 1997). This protein is synthesized in astroglial cells in all parts of CNS, so that high serum levels indicate damage to glial cells and blood-brain barrier dysfunction. Ingebrigtsen and colleagues (Ingebrigtsen, Romner & Trumpy, 1997; Waterloo, Ingebrigtsen & Romner, 1997) showed that serum concentrations of S-100B measured early after head trauma provide information on diffuse brain damage and seem to be associated with neuropsychological outcome even in mild TBI. Little is known about the relation between serum S-100B and neuropsychological performance in the subacute stage of recovery. Comparison of the predictive value of neurological status and neuron-specific enolase and S-100B concentrations showed the initial protein S-100B concentration (median: 27 hours after trauma) to be the best predictor of long term neuropsychological disorders (Herrmann et al., 2001). Patients with mild-to-moderate TBI and neuropsychological deficits at 2 weeks postinjury had significantly higher serum levels of S-100B release than TBI patients without neuropsychological deficits.

The purpose of this study was to examine whether S-100B levels as a marker of injury severity are associated with neuropsychological test performance in a sample of patients with mild uncomplicated TBI. We hypothesized that subjects who had increased serum S-100B levels would have a poorer cognitive function than subjects who had a less pronounced increase in serum S-100B levels.

Method and patients

Method

Patients who arrived at the emergency department within 6 hours of a trauma and who met criteria for mild TBI were asked to give their informed consent for taking blood samples for S-100B measurement. S-100B levels were measured using an immunoluminometric assay as described by De Kruijk, Leffers, Menheere, Meerhoff and Twijnstra (2001). According to the study protocol, all patients were assessed neuropsychologically between 7-21 days injury. Control subjects (N= 56) were recruited by means of advertisements placed in local newspapers and were paid for their participation. The advertisement stressed that participants should be healthy. Control participants were screened for the same exclusion criteria as the mild TBI patients and underwent the same procedure of neuropsychological evaluation as the patient group.

Neuropsychological assessment

The choice of the fixed neuropsychological testbattery was based upon earlier neuropsychological studies of mild TBI patients by Bohnen, Twijnstra and Jolles (1992) and Klein, Houx and Jolles (1996). These tests have proven sensitivity for detecting subtle neurocognitive impairment after mild TBI and a variety of subclinical neurological incidents (Bosma, van Boxtel, Ponds, Houx & Jolles, 2000; Houx, Vreeling & Jolles, 1993; Klein, Houx & Jolles, 1996; Moller, Cluitmans, Rasmussen, Houx, Rasmussen, Canet, Rabbitt, Jolles, Larsen, Hanning, Langeron, Johnson, Lauven, Kristensen, Biedler, Van Beem, Fraidakis, Silverstein, Beneken & Gravenstein, 1998; Van Exel, Gussekloo,

De Craen, Bootsma van der Wiel, Houx, Knook & Westendorp, 2001). Cognitive speed was measured with two neuropsychological tests, the 40-item version of the Stroop test (Klein, Ponds, Houx & Jolles, 1997) (selective attention) and the Letter Digit Coding test (Lezak, 1995) (processing speed). For data analysis we used the third Stroop card showing colour words printed in ink of different colours. Memory was measured with the 15-word learning test, which tests immediate and delayed recall (Brand & Jolles, 1985).

Statistical analysis

Patients were divided into two groups based on a median split of their initial S-100B serum concentrations. We compared a group with low S-100B levels (< 0.23 μg/L; N = 22) with a group with high S-100B levels (> 0.22 μg/L; N = 28). The range of S-100B concentrations in serum was 0.02 - 0.90 μg/L.

Poor cognitive speed was defined as a score below the 10^{th} percentile on both the Stroop test and the Letter Digit Coding test. Poor memory was defined as a score below the 10^{th} percentile on both the immediate recall test and the delayed recall test. The neuropsychological scores were converted into percentile scores by using available norms from the Maastricht Aging Study [19]. Normative comparisons were corrected for age and education.

A one-way ANOVA was used to determine initial differences in injury characteristics and demographic variables between patient groups. To determine the effect of initial S-100B concentrations on cognitive performance, we used dichotomous endpoints, poor and good cognitive speed (Stroop and Letter Digit test) and poor and good memory (immediate and delayed recall on the Word Learning test). In these analyses we compared the cognitive function of mild TBI patients with high S-100B concentrations with that of patients with low S-100B concentrations. Odds ratios and 95% confidence intervals were obtained by logistic regression analysis.

Patients

Consecutive patients (N = 50) who visited the emergency department with an uncomplicated TBI were screened for inclusion in the study. Patients were included if they met clinical criteria for mild TBI: 1) a blunt blow to the head resulting in post-

traumatic amnesia not exceeding 1 hour; 2) feeling dazed or initial loss of consciousness of less than 15 minutes; 3) Glasgow Coma Scale score of 14-15 on presentation at the emergency department and 4) absence of focal neurological deficits. These criteria fell within the limits proposed by the American Congress of Rehabilitation Medicine (ACRM, 1993). We chose to use these more conservative criteria to select a homogenous sample of mild TBI patients who fall at the 'mildest' end of the TBI spectrum.

Patients with previous head injuries, surgical conditions, alcohol or substance abuse, and patients with major psychiatric, neurological, medical problems or severe extracranial injuries (fractures, burns) were excluded. Patients with evidence of secondary intracranial complications were also excluded.

To detect intracranial complications in the first 24 hours following the injury 'home observation instructions' were given to a responsible person accompanying the patient. If a participant sustained significant injury in the interval between S-100B measurement and neuropsychological assessment he or she was excluded from data-analysis. Estimates of the duration of posttraumatic amnesia and of loss of consciousness were based on the information provided by patient and witnesses.

On average, patients lost consciousness for 3.2 minutes (*SD*= 4.1; range 0-15 minutes) and posttraumatic amnesia lasted 18.9 minutes (*SD*= 19.0; range 1-60 minutes). At presentation the Glasgow coma scores were higher than 13. Only 4 patients had scores of 14. There were no significant differences between patient groups in the duration of unconsciousness, $F(1, 48) = 1.215$, $p < .28$, or posttraumatic amnesia, $F(1, 48) = .036$, $p < .90$. Twenty-three patients (N = 50) were female (46%).

The average age of the total sample (N = 106) was 35.2 years (*SD*= 15.9), and the average education was 12.9 years (*SD*= 3.4). No significant differences were found between groups in age, $F(2, 103) = 1.043$, $p < .40$, or years of education, $F(2, 103)$, 1.781, $p < .20$.

Results

No mild TBI patients were excluded from data analysis, because of secondary intracranial complications. At a median of 13 days after injury (range 7-24 days) neuropsychological

assessment was completed. Before neuropsychological screening every patient was neurologically examined. No abnormalities that could compromise neuropsychological testing were found.

We calculated the probability that poor cognitive function dependended on the serum S-100B concentration. Elevated serum S-100B level did not increase the risk of poor cognitive speed (OR 0.5, 95% CI 0.1-3.2) or poor memory performance (OR 1.7, 95% CI 0.3-10.1) (see Tables I and II). Nine percent of the patients with low S-100B levels and 14% of the patients with high S-100B levels had an impaired memory performance. Cognitive speed was impaired in 7% of the patients with high S-100B levels and in 14% of the patients with low S-100B levels. Parametric comparisons of extreme groups, based on S-100B concentrations, did not reveal differences in cognitive performance (data not shown).

We also calculated the probability that mild TBI resulted in poor cognitive function (yes/no). Memory performance was impaired in 12% of mild-TBI patients but in only 4% of the controls (OR 3.7; 95% CI 0.7-19.2)). Cognitive speed was impaired in 10% of mild TBI patients compared to 2% in the controls (OR 6.1; 95% CI 0.7-54.2).

Table I. Descriptive statistics for the three groups

Dependent variables	Serum s-100B < .23 N = 22		Serum s-100B >.22 N = 28		Control Subjects N = 56	
	M	SD	M	SD	M	SD
Immediate recall	26.5	5.4	28.6	7.1	31.5	5.7
Delayed recall	9.4	2.9	10.3	3.6	11.0	2.6
Stroop test	42.7	12.3	38.3	7.8	38.1	11.2
Letter digit coding	33.2	7.3	34.5	7.7	38.4	6.8

For explanation of dependent variables see method section

Table II. Percentage of subjects with poor cognitive speed or poor memory performance for each group

Dependent variables	Serum s-100B < .23 N = 22	Serum s-100B >.22 N = 28	Control Subjects N = 56
Poor cognitive speed	14%	7%	2%
Poor memory	9%	14%	4%

For definitions of poor cognitive speed and poor memory see method section

Discussion

There is still no biological marker to predict continuing neuropsychological symptoms after mild TBI. Detecting patients at risk of developing postconcussional symptoms is of potential interest, because neurobehavioural rehabilitation can reduce the risk of persistent symptoms (Mittenberg, Tremont, Zielinski, Fichera & Rayls, 1996). In this study we focused on subacute serum levels of protein S-100B as a marker for brain damage after mild TBI in relation to neurocognitive performance.

Cognitive speed and memory function were not different in patients with or without high serum levels of protein S-100B, but were worse than those of healthy subjects. These results suggest that an elevated serum S-100B level is not predictive of neuropsychological performance during recovery from mild TBI. Although neuropsychological decrements are common in this population, it is notable that the majority of mild TBI patients did not have unusually low scores on cognitive measures for speed and memory.

However, other studies with mild TBI patients have used different cut-off values for serum S-100B levels (0.2-0.5 μg/L) (Ingebrigtsen, Romner, Marup-Jensen, Dons, Lundqvist, Bellner, Alling & Borgesen, 2000; Waterloo, Ingebrigtsen & Romner, 1997) and thus it is possible that higher concentrations of serum S-100B than those found in this study are associated with poorer subacute neurocognitive performance.

Blood samples were drawn within 6 hours after injury. We are not sure whether this is the right time frame to accurately measure the concentration of S-100B levels. There is still no consensus in literature on dynamics of S-100B after TBI, although there is some indication that levels of S-100B tend to fall rapidly after release following severe traumatic brain injury (Jackson, Samra, Radcliffe, Clark & Price, 2000). A variety of studies using different outcome variables have choosen different intervals between injury (or surgery) and collection of serum S-100B (1 to 48 hours) (Biberthaler, Mussack, Wiedemann, Kanz, Koelsch, Gippner-Steppert, & Jochum, 2001; Herrmann et al., 2001; Rasmussen, Christiansen, Hansen & Moller, 1999; Samra, Radcliffe, Clark & Price, 2000) .

We chose 1-3 weeks after injury for neuropsychological assessment, because it is well known that pain, anxiety and stress have a significant influence on neuropsychological performance (Alexander, 1995; Binder, 1997) . These are common symptoms following a mild TBI but tend to resolve within days after injury. Possible influences of these symptoms on neurocognitive performance are minimized in this way.

This study suggests that blood levels of S-100B do not reflect cognitive dysfunction after mild TBI. However, it is possible that our results would have been different if the blood samples had been taken at a different time.

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- **Chapter 5 -**

Effect of remote traumatic brain injury on cognitive performance: A test of the brain reserve capacity hypothesis in the Maastricht Aging Study[3]

[3] S. Stapert, H. Bosma, P. Houx, R. Ponds, & J. Jolles

Objective – Traumatic brain injury (TBI) is associated with cognitive disorders and atypical cognitive aging. Epidemiological studies even suggest an association between TBI sustained early in life and Alzheimer's Disease (AD). The link between remote TBI and AD is explained by a brain reserve capacity that is lowered by a TBI. We tested the hypothesis that a self reported mild-to-moderate TBI results in lowered cognitive performance in a healthy population.

Method- The effect of a remote TBI on cognitive performance was evaluated, using data from a prospective cohort study of cognitive aging (Maastricht Aging Study). We used cross-sectional data for all subjects (n=1823). Follow-up measurement after 3 years (n= 830) for subjects older than 50 years was also available. The effect of remote TBI on memory performance, selective attention, coding speed, verbal fluency and changes therein were analyzed using regression analyses.

Results- We found no significant effect of a remote TBI on selected cognitive variables (cross sectional data). Follow-up measurement also failed to show evidence of differential longitudinal cognitive changes. No significant interactions between age and TBI were found.

Conclusion- A self reported mild-to-moderate TBI sustained earlier in life (about 26 years) does not compromise cognitive performance in a healthy population. These results suggest that a TBI sustained long ago is neither a necessary nor sufficient event for the development of lowered brain reserve capacity, resulting in accentuated cognitive decline.

Traumatic brain injuries (TBIs) and resulting cognitive impairments represent a significant problem in today's society. These TBIs occur quite easily and are mainly caused by motor vehicle accidents, falls, assaults, industrial accidents, and sports injuries. In the Netherlands the incidence of TBIs is estimated to be 837/100.000 each year (Meerhoff, De Kruijk, Rutten, Leffers & Twijnstra, 2000).

While most TBIs are not life threatening, there is substantial evidence that moderate-to-severe TBIs contribute to lasting cognitive impairments that can substantially impact work or academic abilities. Deficits in certain types of attention, including information processing speed, reaction time, divided attention (Ponsford & Kinsella, 1992; Stuss, Stethem, Hugenholtz, Picton, Pivik & Richard, 1989; Van Zomeren & Van den Burg, 1985), and working memory (Berg, 1993) have been commonly associated with TBIs and may be evident even after apparent recovery (Klein, Houx & Jolles, 1996, Matser, Kessels, Lezak, Jordan, & Troost, 1999). Similarly, long-term memory for verbal information, or declarative memory, has been shown to be impaired following TBIs of varying severity (Levin, High, Meyers, Laufen, Hayder & Eisenberg, 1985; Maring, Deelman & Brouwer, 1985).

The evidence that even mild TBIs can result in longterm neurobehavioural impairment is controversial (Bernstein, 1999). While it is now virtually uncontested that the majority of mild TBIs result in good recovery (Binder, 1997; Binder & Rohling, 1997; Satz, Zaucha, McClearly, Light, Asarnow & Becker, 1997), it is still unclear what deficits persist in which people and why. Additional work is needed to clarify the present picture regarding the length and extent of cognitive recovery following TBI.

Interestingly, TBIs have been linked to the cognitive aging process and Alzheimer's disease (AD; Guo et al., 2000). Not only do these conditions have many similar neuropathological characteristics, but the cognitive characteristics also show some parallels as well (Bigler, 2001). The plausibility of a proposed link between TBI and AD arose from evidence of epidemiological studies suggesting a major role for TBI as a pathogenic agent in the development of AD (Lye & Shores, 2000). The link between between TBI and AD has been evaluated in terms of a theoretical perspective advanced by Satz (1993). Satz' concept of a cerebral reserve implicitly raises the notion of a 'threshold effect' whereby an individual may remain functionally intact and

neurologically asymptomatic until a critical threshold of neuronal loss is surpassed. The theoretical framework proposed by Satz potentially provides a means of explaining how a brain reserve artificially lowered by TBI may predispose an individual to a neurodegenerative disorder such as AD.

A similar, though less dramatic, concept was introduced by Houx and colleagues (Houx, Jolles, & Vreeling, 1993; Houx, Vreeling, & Jolles, 1991; Klein, Houx, & Jolles, 1996), who found that certain biological life events could accentuate the effect of "usual" cognitive aging in subjects who considered themselves to be normal and healthy. They found that a single mild-to-moderate TBI sustained earlier in life (about 30 years) may cause permanent sequelae in specific domains of cognitive functioning, and that it might attenuate the age-related decline in cognitive functioning.

The main objective of this study was to test the hypothesis that neurocognitive performance is compromised in healthy individuals with mild-to-moderate TBI many years after the trauma. A second objective, inherent to our main objective, was to evaluate whether there was an interaction between age and TBI. On an exploratory basis, we evaluated the factor "interval between injury and assessment" to look for effects of recovery after TBI on cognitive performance.

Method

Subjects and procedure

We used data from the Maastricht Aging Study, which is a prospective cohort study of cognitive aging in the southern Netherlands (MAAS; Jolles, Houx, Van Boxtel, & Ponds, 1995). After the 1993-95 baseline examination of 1823 non-demented people aged 25-85 years, there was a 3-year follow-up examination (1996-1998) of 830 people who were older than 50 years. As a result of the MAAS study design, follow-up data for the fifty-minus group were not available

All subjects were thus normal and healthy according to regular gerontological criteria. The subjects who were enrolled in the study completed a postal questionnaire and participated in an extensive neuropsychological investigation. The standardized postal questionnaire covered a subjective report on medical history and demographic information.

Severity of TBI as a possible predictor of outcome was estimated by asking the subjects about coma duration, memory loss, and postconcussional complaints. Coma duration and memory loss were scored on a 4-point scale as less than 15 minutes, 15 minutes to 1 hour, 1 to 24 hours, or more than 24 hours. The duration of postconcussional complaints was also scored on a 4-point scale as being either less than 1 week, 1 to 4 weeks, 1 to 6 months, or 6 months and longer.

According to criteria proposed by Houx, Vreeling & Jolles (1993) a significant TBI had to meet the following injury characteristics: loss of consciousness and/or memory for more than 1 hour or duration of postconcussional complaints for more than 1 month.

Neurocognitive tests

The neuropsychological assessment comprised tests of memory, selective attention, coding speed, and retrieval from semantic memory. The Visual Verbal Learning Test (VVLT; Brand & Jolles, 1985) was used to evaluate retrieval from memory (total recall and delayed recall). As measures of speed of information processing the Stroop Colour Word Test (SCWT; Stroop, 1935) and the Letter Digit Coding Test (Lezak, 1995; Smith, 1968) were used. For purpose of data analysis we used the interference subtask of the Stroop Colour Word Test. Retrieval from semantic memory was measured using the verbal fluency task from the Groningen Intelligence Test (Luteijn & Van der Ploeg, 1983).

Statistical Analysis

We used a hierarchical regression analyses to estimate the effect of a remote TBI on neuropsychological performance. In the cross-sectional data analyses (n= 1823) we controlled for the effects of age (in years), sex and level of education (eight ordinal categories). In the longitudinal follow-up (n= 830) we also entered the baseline measurement and interval between baseline and follow-up measurement (days) in the equation.

The TBI group was also compared with a pair-matched control group (age, sex and level of education) on neuropsychological performance, using a paired sample t-test (cross-sectional data only). The effect of recovery was tested using a regression analysis for the TBI group only, entering the time since injury (in years) in the regression equation.

Results

Sixty-two subjects reported to have sustained a TBI that met our criteria. Mean age at injury was 24.1 years (SD= 16.3; range 3-73) and mean interval between injury and neuropsychological assessment was 26.3 years (SD= 15.6; range 1-74). Sixty-six percent (N= 41) of these subjects was male. Mean level of education was 3.6 (SD= 1.8; range 1-8) and age at cross-sectional neuropsychological assessment was 50.4 years (SD= 15.5; range 25-80). Twenty-six TBI subjects participated in follow-up assessment.

Neurocognitive performance. Except for coding speed we found no effect of a remote TBI on the selected cognitive measures in the baseline measurements (table 1). A TBI was associated with worse performance on the letter digit coding test ($p < .05$). This effect, however, was not found in the cross-sectional data for indivduals > 50 years (table 2). The TBI effect also was not consistently in the expected direction over all cognitive variables.

Table 1: Summary of regression analysis for variables predicting cognitive performance (n= 1832). Table shows unstandardized regression coefficients (B) from the cross-sectional data.

		age	sex	education	TBI
VVLT tot		-.259**	4.391**	1.198**	-0.668
VVLT recall		-.077**	1.254**	.275**	-0.495
SCWT III		.808**	-5.304**	-3.644**	-1.193
Coding		-.398**	1.002*	1.828**	-2.198*
Fluency		-.091**	.386	.987**	.157

*p < .05; ** p < .01; Age in years; Sex (1= male, 2= female); Education (1= primary school to 7= university education); TBI (0= no TBI, 2= TBI).

Follow-up examination did not reveal significant effects for a TBI, suggesting that individuals with a TBI did not show accelerated decline in cognitive performance compared to their non-injured counterparts (table 3). No interaction effect of age x TBI on cognitive variables was found (data not shown). Individual case-control matching also did not reveal any differences between TBI subjects and control subjects (table 4).

Regression analyses did not show any effect of interval between injury and cognitive assessment in the TBI group, suggesting that recent TBIs do not differ in their impact on

Table 2: Summary of regression analysis for variables predicting cognitive performance (n= 838, age > 50 yrs.). Table shows unstandardized regression coefficients (B) from the cross-sectional data for those individuals who also completed follow-up measurement.

		age	sex	education	TBI
VVLT tot		-.344**	4.331**	1.111**	0 .772
VVLT recall		-.097**	1.257**	.230**	-0.278
SCWT III		1.220**	-4.105*	-4.128**	-7.175
Coding		-.490**	-.333	2.204**	-0.435
Fluency		-.120**	-.024	.953**	-.240

** p < .05; ** p < .01; Age in years; Sex (1= male, 2= female); Education (1= primary school to 7= university education). TBI (0= no TBI, 2= TBI).*

cognitive function from TBIs that occurred a longer time ago. Unstardardized regression coefficients were 0.106 and 0.034 for respectively total and delayed recall on the VVLT (non significant). SCWT III, coding and verbal fluency also did not reveal any significant coefficients (-0.149, 0.034, and –0.059).

Table 3: Summary of regression analysis for variables predicting cognitive performance (n= 830, age > 50 yrs.). Table shows unstandardized regression coefficients (B) from the longitudinal follow-up data controlling for baseline measurement and interval between measurements.

		age	sex	education	TBI
VVLT tot		-.235**	.843	.570**	-0.410
VVLT recall		-.078**	.356*	.196**	-0.003
SCWT III		.752**	-3.766*	-.574	2.041
Coding		-.172**	.671	.551**	-0.720
Fluency		-.109**	.120	.239*	.335

* p < .05; ** p < .01; Age in years; Sex (1= male, 2= female); Education (1= primary school to 7= university education). TBI (0= no TBI, 2= TBI).

Table 4: Neuropsychological performance for the TBI group compared to age, sex and level of education matched controls (cross-sectional data) using paired sample t-test.

	TBI N= 62	Control subjects N= 62	t-test value df = 122
	M (SD)	M (SD)	
VVLT total	44.5 (9.0)	43.2 (10.0)	-.858, n.s.
VVLT recall	9.1 (2.9)	8.9 (3.1)	-.426, n.s.
SCWT III	37.4 (11.4)	38.1 (10.1)	.663, n.s.
Letter Digit Coding	46.6 (11.1)	48.8 (10.7)	1.469, n.s.
Verbal Fluency	24.3 (6.2)	23.1 (6.5)	-1.183, n.s.

For explanation of variables see method section

Discussion

It is suggested that a TBI sustained earlier in life may affect cognitive functioning many years after injury in absence of subjective health and cognitive complaints (Klein, Houx & Jolles, 1996; Lye & Shores, 2000). There is even a relation between TBI and AD proposed in terms of a brain reserve capacity model advanced by Satz (1993). TBI is believed to artificially lower the brain reserve capacity resulting in clinical symptoms after brain injury. To this end longitudinal neuropsychological studies are recommended to ascertain more precisely how much sooner progressive deterioration may be expected to become clinically evident in an individual with a history of TBI.

In this large prospective cohort study we found no consistent significant effect of a remote TBI on objective cognitive functioning. We selected a group of TBI subjects that met injury criteria used in earlier studies from our research group (Houx, Vreeling & Jolles, 1993; Klein, Houx & Jolles, 1996). In accordance with results from these studies we expected to find a long-term effect of a mild-to-moderate TBI on cognitive functioning.

Some possible explanations can be mentioned why we could not replicate this finding using data from the MAAS study. MAAS is a study into the determinants of cognitive aging using healthy subjects. To meet inclusion criteria all subjects had to be free of physical and cognitive impairment. This implies that there were no subjective complaints about postconcussional symptoms. Klein, Houx and Jolles (1996) found in a similar study that individuals with a remote TBI performed worse than pair-matched controls on several cognitive tasks, also in absence of postconcussional complaints. In this study we used the same criteria for a significant TBI and mean interval between injury and assessment was within the same range. However, in the Klein study subjects were included by means of advertisements in newspapers stressing that possible subjects had to be healthy and had experienced a significant TBI at some point in their lives. This procedure might reveal aspects of the purpose of the study, which could result in a selection of subjects. The individuals that were enrolled in MAAS were blind for the precise purpose of this particular project. This could also reflect the reliability of

reporting on the injury characteristics. It is likely that the severity of injury in the MAAS subjects differed from the reported injuries in the Klein et al. study.

Though not the core question of this study, we also explored the interplay between objective cognitive functioning and subjective complaints regarding these functions. In the longitudinal analyses, we found that the risk of developing complaints about subjective forgetfulness was almost 2.93 times higher among persons with TBI reported at baseline compared with TBI-free persons. The relation between subjective and objective cognitive disorders in clinical neuropsychology is notoriously complicated (Ponds & Jolles, 1996; Scogin, Storandt & Lott, 1985), and therefore requires additional and more detailed studies regarding remote TBI and the relation between subjective and cognitive complaints.

The results from this study are in accordance with findings from The Rotterdam Study (Mehta, Ott, Kalmijn, Slooter, Van Duijn, Hofman & Breteler, 1999), who found that mild TBI is not a major risk factor for dementia or AD in the elderly. It can be questioned whether a remote TBI is sufficient to produce longlasting cognitive effects or even a higher risk for development of AD at an old age. A TBI more than likely constitutes only one of many risk factors that combine in predisposed individuals to induce the complex cascade of events that lead to chronic mild neurocognitive disorders or a neurodegenerative syndrome. Although there is accumulating evidence that a remote mild-to-moderate TBI can influence the cognitive aging by lowering the brain reserve capacity, we found no indication for such an effect in this study. Our findings suggest that chronic neurocognitive impairment is a multifactorial disorder with at best a minor role for a self-reported TBI.

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- **Chapter 6 -**

Neurocognitive fitness in the subacute stage after mild TBI: The effect of age [4]

[4] S. Stapert, P. Houx, J. de Kruijk, R. Ponds, J. Rutten, & J. Jolles, *submitted for publication*

Objective- Age is assumed to be a negative prognostic factor in recovery from moderate to severe traumatic brain injury (TBI). Little is known on cognitive performance after mild TBI in relation to age in the subacute stage after injury.

Method- Ninety-nine mild TBI subjects (age 15-75) were compared with 91 healthy control subjects (age 14-74) in a case-control design. Patients were matched on age, sex, and level of education, with control subjects. Mean interval between injury and cognitive assessment was 13 days. Neurocognitive test battery contained tests of verbal memory, selective attention, general speed of information processing, and verbal fluency.

Results- We found an overall effect of a single mild TBI on neurocognitive performance in the subacute stage after injury. Age did not add significantly to the effect of mild TBI on cognitive functioning.

Conclusion- Patients suffering from mild TBI are characterized by subtle neurocognitive deficits in the weeks directly following the trauma. The notion that elderly subjects have a worse outcome in the subacute period after mild TBI needs to be reconsidered.

The incidence of traumatic brain injury (TBI) follows a bimodal distribution, with peaks in young adulthood and old age (Fields and Coffey, 1994). There is overwhelming evidence that age is a negative prognostic factor in TBI. Mortality following severe brain injury rises steadily with age, with death being a virtual certainty after age 75 (Jennett, 1982). Elderly patients with moderate brain injuries also have a higher mortality rate (Fogel & Duffy, 1994) and even mild TBI is associated with suggestions of worse outcome in the elderly. However, the discriminating effects of age are less certain in the latter case (Rapoport & Feinstein, 2001).

Elderly patients are more likely than young TBI patients to develop traumatic mass lesions, including subdural hematomas and intracerebral hemorrhage, from mild to moderate injury (Jennet, 1982; Miller & Pentland, 1989; Moulton, 1992). They are more likely to develop permanent disability as a result of their injuries, and tend to have longer hospital stays (Miller & Pentland, 1989). Age is also associated with a greater number of postconcussional symptoms at both 6 weeks and 1 year after injury (Rutherford et al., 1977; Rutherford et al., 1979). Elderly TBI patients also are believed to be at increased risk for developing the chronic postconcussional symptom complex after TBI (Alexander, 1982; Levin et al., 1982), including depression, apathy, irritability, and impulsive behaviour.

With respect to the neuropsychological consequences of mild TBI different views have been expressed. Binder (1997) and Binder, Rohling, and Larrabee (1997) reviewed this literature and confirmed the evidence of mild initial impairment followed by uneventful recovery. On the basis of this literature, it appears that mild TBI generally does not cause continuing clinical problems. Nevertheless, clinicians have recognized that some patients with a mild TBI have recurrent deficits that suggest significant brain impairment. Alexander (1995) estimated this sample to include 10-15% of the mild TBI population. Thus, even though many persons recover, it appears that some continue to have clinical difficulties, and it is this sample that contributes to the differences in conclusions among experts in the field.

The suggestion that elderly patients have a worse outcome following a TBI than younger patients can be explained in terms of Brain Reserve Capacity (BRC) advanced by Satz (1993), suggesting that there might be protective factors against cognitive

symptoms following a TBI (A younger age and higher levels of mental capabilities are important in that respect). Evidence for this hypothesis regarding moderate-to-severe TBI is compelling. At least, it is quite likely that preexisting (subclinical) brain injury from any cause will make a cognitive decline process clinically manifest at an earlier stage, because there will be less reserve capacity. The notion that TBI may set in motion a specific degenerative process is more speculative. In contrast with this knowledge on moderate-to-severe trauma, little is known about this cognitive reserve hypothesis in mild TBI, especially in the subacute stage after TBI.

Though researchers tend to focus on long-term outcome, the subacute stage after injury is underestimated in its clinical value. Both as a baseline state from which recovery sets in and prediction of possible symptom chronicity on the long run, this screening moment is of importance especially for evaluation of cognitive states. Influence of shock, stress, anxiety, pain and other minor bodily injuries (encountered in the acute stage) is negligible at this postinjury stage.

The aim of this case-control study is to explore the impact of age on neurocognitive functioning in the subacute period following mild TBI. Care was taken to include younger and older patients without other possible comorbid conditions which might influence cognitive funtioning, in view of evidence that age-related cognitive dysfunction might be caused by a cumulation of risk factors (Jolles et al., 1994). It is hypothesized that neurocognitive performance is more affected in the elderly compared to their younger counterparts.

METHOD

Subjects and procedure

Consecutive patients (March 1997 until July 1999) who were admitted to the emergency department of the University Hospital Maastricht with an uncomplicated mild TBI were included in the study. Criteria for mild TBI were: (1) GCS >13, (2) posttraumatic amnesia (PTA) of less than 1 hour, (3) and loss of consciousness (LOC) not exceeding 15 minutes. These criteria fell within the limits proposed by the American

Congress of Rehabilitation Medicine (1993; ACRM). TBI subjects had to be free from other medical conditions and health related factors that interfere with optimal cognitive functioning (Houx, Vreeling & Jolles, 1993). We choose to use these more conservative criteria in order to select a homogenous sample of patients that fell at the less severe end of the mild TBI spectrum. Mild TBI patients were matched on age, level of education, and sex with healthy control subjects. Control subjects were selected from the Maastricht Aging Study (Jolles, Houx, Van Boxtel & Ponds, 1995) in combination with recruitment by advertisements in local newspapers. Newspaper advertisement stressed that all patients had to be healthy, meaning that they had to meet inclusion criteria that were also used in the Maastricht Aging Study (i.e., free from medical conditions with known impact on optimal cognitive functioning).

All patients with a TBI were diagnosed before inclusion in the study by a neurologist or emergency physician at the emergency department. The protocol specified that after informed consent and inclusion in the study an appointment for a neuropsychological examination was scheduled preferably within 2 weeks and not earlier than 3 days after injury.

Neuropsychological Tests

All participants were evaluated using a fixed battery approach. The choice of neurocognitive tests was based upon earlier studies in mild TBI patients. These tests were used because of their sensitivity for detecting neurocognitive impairment after mild TBI and subclinical incidents (Bohnen & Jolles, 1992; Klein, Houx & Jolles, 1996).

The Visual Verbal Learning Test (VVLT). This memory test is a visual version of the Rey Auditory Verbal Learning Test (Rey, 1964). In three consecutive trials, a list of 15 words has to be memorized and reproduced followed by a delayed recall procedure after 20 minutes (Brand & Jolles, 1985). Dependent variables are the total immediate recall score from 3 trials (VVLTtot), and the delayed recall score (VVLTrecall).

The abbreviated version of the Stroop Colour Word Test (SCWT; Bohnen, Jolles & Twijnstra, 1992; Klein, Ponds, Houx & Jolles, 1997). This test has often been used to

test selective attention, mental speed, and interference susceptibility (Lezak, 1995). The test uses three cards displaying fourty stimuli each; colour names (SCWT I), colour patches (SCWT II), and colour names printed in incongruously coloured ink (SCWT III). The dependent variables are the times (secs.) needed to read (SCWT I), to name the colour of the patches (SCWT II) or the printing ink (SCWT III). The dependent variable for purpose of data analysis is the time needed to complete SCWT III.

Letter Digit Coding Test (LDCT). This test is a modification of the procedurally identical Symbol-Digit-Modalities Test (Lezak, 1995; Smith, 1968). The subjects are supplied with a code at the top of a page, which links a digit to a letter. Subjects have to fill in blanks which correspond to the correct codes. The coding test is used to measure the speed of processing of general information. The dependent variable is the total number of digits written correctly in 90 seconds.

Verbal Fluency (Lezak, 1995; Luteijn and Van der Ploeg, 1983). Fluency is defined as the ability to produce as many words as possible in a given category, within a fixed time span. It can be regarded as a measure for the adequate, strategy-driven retrieval of information from semantic memory. The subject is requested to name as many animals as possible within one minute.

Data analysis

Possible demographic between-group differences were tested using dependent sample t-tests. Multiple hierarchical regression analyses were used to estimate the effect of mild TBI on selected cognitive variables. We controlled for age (years), sex and level of education (8 ordinal categories) in these analyses. Interaction effect of age*TBI was also tested by entering the product of this factor into the equation.

RESULTS

We included 99 mild TBI patients and 91 control subjects (for demographic variables see table 1). There were no differences regarding age ($t(188)= 0.835$, *n.s.*), level

of education ($t(188)= 0.328$, *n.s.*) and distribution of sexes between the two groups ($\chi^2= 1.236$, *n.s.*). The interval between neuropsychological assessment and injury was 12.8 days (*SD*= 4.8).

Table 1: Demographic characteristics of patients and control subjects

	TBI (N= 99) *M* (*SD*; range)	Controls (N= 91) *M* (*SD*; range)
Age	34.7 (16.0; 15-75)	36.5 (14.3; 14-74)
Level of education	4.0 (2.0; 1-8)	4.2 (1.8; 1-8)
Sex (m/f)	58/41	46/45

Age in years; Level of education (1= primary education to 8= university education); sex (m= male; f= female)

Regression analyses showed a significant effect of mild TBI on all cognitive variables, except for immediate recall score on the visual verbal learning test (see table 2).

With one test, the coding test, we found a significant interaction between age and TBI on test performance (B= -1.867, $p < .05$). Younger patients were slower in 90 secs. than healthy age-mates, but elderly patients showed no such difference. Difference in performance only reached significance (univariate comparison) in the young TBI versus young control group (F (1, 56)= 7.605, $p < .01$).

Table 2: Summary of regression analyses for variables predicting cognitive performance
Table shows unstandardized regression coefficients (B)

		Age	sex	education	TBI
VVLT tot		-0.152**	0.858	1.164**	-1.149
VVLT recall		-0.049**	0.876*	0.373**	-1.500**
SCWT III		0.181**	-2.547	-1.708**	5.923**
Coding		-0.267**	1.891	1.821**	-3.293*
Fluency		-0.018	1.224**	0.325	-1.980*

p < .05; ** p < .01; Age in years; Sex (1= male, 2= female); Education (1= primary school to 8= university education); TBI (0= no TBI, 1= TBI).

DISCUSSION

In this study on the neurocognitive effects of a single mild TBI in the subacute stage after injury, we found an overall effect of mild TBI on cognitive performance. Absence of interactions with age suggests that advanced age has no influence on the extent of mild neurocognitive disorder in the subacute stage after injury. Performance on a coding task, reflecting general speed of information processing, was even less affected by a mild TBI in the elderly patients than in the younger patients.

These results are of interest because they have been obtained in a large group of mild TBI patients who were without cognitive sequelae immediately after the trauma. There are not many studies who have evaluated cognitive performance in the early weeks after trauma. The fact that performance is compromised in the whole group of patients is in accordance with earlier studies and accentuates the notion that indeed subtle decrements in cognitive performance can be monitored in patients who are without complaints and major neurological dysfunction. The finding that old subjects are not disproportionally compromised in their performance – as predicted by the Brain Reserve Capacity hypothesis – can be interpreted in two ways. A first possibility is that the Brain Reserve Capacity hypothesis proposed by Satz (1993) does not apply, thereby reducing the value of this theory and the general opinion that age is a negative prognostic factor in mild to moderate TBI. Up till now, the prognostic value of a single mild TBI is uncertain. According to the BRC theory, it was hypothesised that older patients would be more affected by a mild TBI than younger patients on their neuropsychological performance. Satz suggested that the consequences of a neurological incident affecting the brain would be less evident and limiting in those with younger age than older patients and also in patients with higher levels of intelligence.

A second possible interpretation is that the time post trauma is too short to contribute substantially to the development of chronic posttraumatic cognitive symptoms. In other words, the brain reserve in older subjects is protective at a similar level as in the younger subjects, and only after a prolonged period of maybe weeks to months gives rise to the additional deterioration in performance as expected according to the BRC hypothesis. The results of the present study suggest that a nuance should be incorporated

in the theory and that further research should be performed in order to evaluate the opposing possibilities in more detail.

The other major protecting factor against cognitive decline, according to the BRC theory, is level of mental capabilities or intelligence. Though we did not include a formal test of intelligence in our test battery, we tested interactions between TBI and educational level. No such interactions were found (results not shown).

Strict comparisons with earlier studies are problematic, given that neurocognitive performance was looked at within days to weeks after injury, and mild TBI was focused on. Nevertheless, some factors could account for the absence of difference in outcome between older and younger patients, and the better performance in the elderly patients on a task reflecting general speed of information processing.

TBI may influence the ageing process in a dynamic way, such that adverse effects only become discernable after sufficient time has elapsed. In support of this, there is now literature implicating TBI as a potential causative factor in Alzheimer's disease (Lye & Shores, 2000). Klein, Houx, and Jolles (1996) found long lasting effects of a remote TBI on neurocognitive performance in a study limited to mild-to-moderate TBIs. However, they found no interaction effect of TBI and age. Though their inclusion of moderate TBI makes generalization to a very mild TBI population problematic, we found a similar result in the subacute stage after mild TBI. These results suggest that a single mild TBI has only a static influence on the cognitive aging process instead of a dynamic influence.

Rapoport and Feinstein (2001), using a global measure of outcome (Glasgow Outcome Scale), also did not find evidence for the assumption that elderly subjects have a worse outcome in the acute recovery period following mild TBI.

The most salient difference between older and younger TBI patients is the much greater likelihood of pre-existing or coincident medical or neurological disease in the former (Miller & Pentland, 1989). Cognitive and behavioural consequences of TBI in older patients may be potentiated by preexisting age-related cognitive changes or cognitive dysfunction. Traumatic effects superimposed on pre-existing age-related changes might produce greater clinical deficits. Although this phenomenon may be regarded as one of comorbidity, the interaction hypothesized in this study is with normal age-associated changes, rather than age-associated disease.

No study to date has addressed the risk of subtle cognitive impairment in a large sample of previously intact subjects after a clearly documented mild TBI. The assumption that elderly subjects have a worse outcome following TBI needs to be reconsidered, at least within the subacute recovery period. A different constellation of age-related and neurological factors may well alter the picture.

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- Chapter 7 -

Persistent subtle neurocognitive impairment six months after mild traumatic brain injury: A follow-up study[5]

[5] S. Stapert, P. Houx, J. de Kruijk, R. Ponds, J. Rutten, & J. Jolles, *submitted for publication*

Objective - A single mild traumatic brain injury (mild TBI) is associated with uneventful recovery. We tested the hypothesis that this neurological incident can result in long-term cognitive deficits.

Method - Fifty-eight mild TBI patients were matched with 56 healthy control subjects for age, sex, and educational level. Neurocognitive performance (memory, and several speed tasks) of these subjects was assessed at 3 test occasions (2 weeks, 3 months, and 6 months) after injury. Healthy controls followed the same procedure.

Results - Mild TBI patients showed evidence of mild neurocognitive impairment on measures for memory, simple-, complex-, and processing speed up to six months after injury. By contrast we found no differences in quality and quantity of subjective post-concussional complaints after a single mild TBI compared to healthy controls.

Conclusion - A single mild TBI can result in long-lasting objective neurocognitive deficits. The general point of view that such an injury is benign and compatible with full cognitive recovery has to be readdressed.

Mild traumatic brain injury (TBI) accounts for between 55% and 90% of new cases of medically diagnosed traumatic brain injuries each year, making it one of the most common neurological disorders (Kraus, McArthur & Silberman, 1994; Kurtzke & Kurlan, 1997). Though 50% of individuals experiencing a mild TBI endorse symptoms including headache, fatigue, insomnia, dizziness, concentration difficulties, memory loss, irritability, and hypersensitivity to noise and light (Binder, 1986) in the subacute stage after injury, it is considered a relatively benign neurological condition resulting in uneventful recovery (Levin, Mattis, Ruff, Eisenberg, Marshall, Tabbador, High & Frankowski, 1987). This cluster of symptoms has gained nosological status as post-concussional syndrome (PCS). Although the pattern of clinical recovery after mild TBI has been established (Binder, 1997; King, 1997), controversy continues about the long-term effects of mild TBI on neurocognitive and behavioural functioning (Newcombe, Rabbitt, & Briggs, 1994). For example, a recent meta-analysis of studies of mild TBI by Binder, Rohling, and Larrabee (1997) found that the effect of mild TBI on overall cognitive functioning as well as specific cognitive domains was small and of little clinical significance. On the other hand, Matser and colleagues (1999) found neuropsychological differences between soccer players and controls, suggesting that repeated subclinical neurological incidents ("heading" the ball) may result in chronic neurocognitive impairment. In another study, Klein, Houx and Jolles (1997) compared two groups of individuals with self-reported mild-to-moderate TBI to age and sex matched controls 30 years after injury. Despite what would be termed 'good recovery', meaning no cognitive or emotional complaints and normal intellectual functioning, the TBI groups performed worse on all aspects of primary and secondary memory and on most attention tasks used. These two reports demonstrate that cognitive impairment may persist many years after mild TBI, suggesting that a mild TBI may not be such a mild form of injury after all.

Alexander (1995) described a subgroup of individuals with mild TBI who report symptoms long after the incident injury. He considers this PCS a highly prevalent neurological disorder with serious health consequences and discussed two general factors that play a significant role in PCS. First, he concluded that the initial injury in PCS probably involves a small neurological disruption (physiogenesis) sufficient to produce

the cognitive symptoms. However, he characterized the subsequent symptom picture as largely dominated by symptoms of depression, anxiety, and chronic pain (psychogenesis). In addition, other factors are believed to either lowering the threshold for expression of PCS or maintaining or exacerbating the symptom picture. Lowered threshold is associated with factors as advanced age or prior psychiatric and/or accident history. In terms of symptoms he noted that current litigation represent factors, that when aggregated with the initial injury, may exacerbate the symptom picture and prolong the recovery course.

Although there is much evidence in the literature to suggest that most mild TBI cases involving cognitive and/or behavioural deficits resolve within 6 months (Levin et al., 1987; MacFlynn, Montgomery, Fenton & Rutherford, 1984), there are mounting data that indicate long-term impairment (Klein, Houx & Jolles, 1997). There are also several investigators who have argued that the effects of mild TBI may be permanent (Bernstein, 1999; Matser, Kessels, Lezak, Jordan & Troost, 1999). This raises a problem with the mild TBI literature. Most studies have utilized a neuropsychological battery that covers various aspects of attention and memory processes. It is generally assumed that these measures are reliable and valid. However, there is a need for more specific and demanding measures that can detect subtle neurocognitive impairment (Bernstein, 1999). This is of interest because it can be questioned whether a return to normal performance on neuropsychological tests does imply a return to normal functioning (Gronwall, 1991; Mateer & Mapou, 1996).

Another methodological problem in the mild TBI literature pertains to the re-testing of participants on the same cognitive or behavioural tasks. Change as a function of trauma may be confounded by practice effects (Dikmen, Heaton, Grant & Temkin, 1999). Interpretation of results of repeated testing is a complicated endeavour (Spikman, Timmerman, Van Zomeren & Deelman, 1999). Participants with mild TBI often display a gradual improvement in their performance over the first weeks and months, while controls start at ceiling on many of these tasks, thus preventing a marked improvement in their scores over time. Usage of suitable control groups (patients with orthopedic injury or healthy controls) who undergo the same assessment procedure as the mild TBI patients is one solution to this problem. The development of a psychometrically sound

neurocognitive test battery with parallel versions is another solution to this problem. Either approach would eliminate practice effects.

A further obstacle in mild TBI research is to prove that the observed deficits are the result of injury (Binder, 1997). Because many of the deficits observed after mild TBI involve attention, perhaps a pre-existing lack of attention will leave the individual vulnerable to accidents resulting in mild TBI. Neuroimaging work has helped establish the view that mild TBI produces diffuse axonal injury (Hofman, Stapert, Van Kroonenburgh, Jolles, De Kruijk & Wilmink, 2001). However, the precise relationship between injury severity and neurobehavioural outcome remains obscure. Another issue concerns the number of mild TBIs sustained. It is possible that the evidence in favour of persistent neurocognitive deficits is the result, at least in part, of multiple mild TBIs. It is suggested that the effects of mild TBIs tend to be cumulative (Gronwall & Wrightson, 1975). As such, multiple mild TBIs might be associated with more persistent cognitive impairment. Most of the studies showing long-term neurobehavioural deficits failed to mention the prior incidence of mild TBI (Bernstein, 1999).

From both a clinical and academic perspective there is need for longitudinal assessment of mild TBI using demanding and sensitive neurocognitive tasks. Such a study might clarify the present picture of PCS, including the establishment of symptom development. To this end we followed a cohort of carefully selected individuals with a single mild TBI and a group of matched controls to identify specific neurocognitive symptoms for the mild TBI group during recovery in the first 6 months after injury. We used a neuropsychological test battery with proven sensitivity for mild cognitive impairment and consequences of subclinical neurological incidents (Klein, Houx & Jolles, 1997). We tested the hypothesis that a single mild TBI would result in an inferior neurocognitive performance compared to performance of a healthy control group. It was also evaluated whether mild TBI patients would report more subjective postconcussional symptoms than control subjects

Method

Subjects

The patient group consisted of 58 patients with mild TBI. The control group consisted of 56 healthy subjects matched for age, sex, and educational level. Consecutive patients presenting at the emergency department with a single uncomplicated mild TBI were included in the study. We used a definition of mild TBI that met criteria proposed by the Head Injury Interdisciplinary Special Interest Group of The American Congress of Rehabilitation Medicine (1993). In order to include a homogeneous sample of patients with the 'mildest' mild TBI we choose to use an even more conservative definition. This definition stated that a person with uncomplicated mild TBI has had a physiological disruption of brain function as manifested by at least one of the following: (1) Glasgow Coma Scale Score of 14-15, (2) Loss of consciousness (LOC) for less than 20 minutes, (3) Post-traumatic amnesia (PTA) for less than 6 hours. Patients requiring anaesthesia and those suffering from extra-cranial injuries were excluded. For both groups, the criteria for inclusion in the study were: No history of previous neurological or psychiatric disturbance, a primary school education, absence of alcohol or other substance abuse. Control subjects were recruited by means of advertisements placed in local newspapers and they were paid for their participation. The advertisements stressed that participants should be healthy. Using a semi-structured interview, the control subjects were screened for absence of chronic medical conditions and health related factors with known impact on cognitive functioning.

Duration of PTA and LOC was scored by a neurologist or traumatologist based on subjective reports of the patient and witness reports (if possible) at presentation at the emergency department. The mean subjective PTA duration was 19.5 minutes (*SD*= 18.6; range 1-60) and LOC duration was 3.1 minutes (*SD*= 4.6; range 0-20). Glasgow Coma Scale (GCS) were documented in 56 of 58 cases. Eight subjects had a Glasgow Coma Score of 14 the other patients scored a maximum of 15 on the Glasgow Coma Scale.

Sixty-seven percent of these patients (*N*= 39) were injured in a traffic related accident involving a motorized vehicle. Eight patients sustained a work-related (falls)

mild-TBI (14%). Four of the mild TBIs were sports related (7%) and an additional 7 mild TBIs were caused by violence (12%).

The mean interval between injury and the first neuropsychological assessment was 13.8 days (*SD*= 6.0; median= 13.0). The mean age of the patients was 34.3 years (*SD*= 16.9 years; range 15-75 years) and of the control subjects 34.5 years (*SD*= 17.5; range 14-72 years). Educational level was rated on an 8-point scale (De Bie, 1987) ranging from 1 (primary education) to 8 (higher vocational and university). The mean score for both the patients and the controls was 4.3 (*SD*= 1.8; range 1-8). The number of years of formal education was 13.4 (*SD* = 3.1; range 6-20) for both groups.

Fifty-three percent of the patient group and 46% of the control group were male. Statistical testing (one-way ANOVAs and chi-square tests) showed no difference between the groups with respect to age, sex, level of education and years of formal education.

Materials and procedures

After informed consent and inclusion in the study, a first appointment for neuropsychological assessment was scheduled, preferably within two weeks after injury. Follow-up assessment took place at 3 and 6 months after date of injury. The aim of the study was to investigate neurocognitive functions longitudinally. All participants were evaluated using a fixed battery approach, using parallel tests at each test occasion. Our research group based the choice of neurocognitive tests upon earlier studies in mild TBI patients. These tests were used because of their sensitivity for detecting neurocognitive impairment after mild TBI and subclinical incidents (Bohnen & Jolles, 1992; Klein, Houx & Jolles, 1996).

The Visual Verbal Learning Test (VVLT). This memory test is a visual version of the Rey Auditory Verbal Learning Test (Rey, 1964). In three consecutive trials, a list of 15 words has to be memorized and reproduced followed by a delayed recall procedure after 20 minutes (Brand & Jolles, 1985). Dependent variables are the 1st trial immediate recall score (VVLT1), total immediate recall score from 3 trials (VVLTtot), and the delayed recall score (VVLTrecall).

Concept Shifting Test (CST; Houx & Jolles, 1994). This test is derived from the Trail Making Test (Lezak, 1995), which is used to measure the ease of shifting between different concepts. There are four task conditions: the participant has to cross out, in the proper order, 16 circles containing only digits (1 to 16; part A), letters (A to P; part B), or both (1-A-2-B, etc; part C). In the latter subtest, participants have to shift between the concepts 'digits' and 'letters'. The last subtest demands crossing out 16 empty circles 'clockwise' to estimate basic motor speed of each participant (CST0). The dependent variables are the times needed to complete each subtest.

The abbreviated version of the Stroop Colour Word Test (SCWT; Bohnen, Jolles & Twijnstra, 1992; Klein, Ponds, Houx & Jolles, 1997). This test has often been used to test selective attention, mental speed, and interference susceptibility (Lezak, 1995). The test uses three cards displaying fourty stimuli each; colour names (SCWT I), colour patches (SCWT II), and colour names printed in incongruously coloured ink (SCWT III). The dependent variables are the times (secs.) needed to read (SCWT I), to name the colour of the patches (SCWT II) or the printing ink (SCWT III).

Letter Digit Coding Test (LDCT). This test is a modification of the procedurally identical Symbol-Digit-Modalities Test (Lezak, 1995; Smith, 1968). The subjects are supplied with a code at the top of a page, which links a digit to a letter. Subjects have to fill in blanks which correspond to the correct codes. The coding test is used to measure the speed of processing of general information. The dependent variable is the total number of digits written correctly in 60 seconds.

Subjective complaints were assessed with a questionnaire probing neurovegetative symptoms. This questionnaire correlates with persistent symptoms after mild traumatic brain injury (Bohnen, Twijnstra & Jolles, 1992). We used the postconcussion subscale to assess post-traumatic symptoms. This subscale consists of 11 items with a score range of 11 (minimum) to 44 (maximum). The postconcussion scale covers subjective complaints like headache, hypersensitivity to light and noise, mental slowness, fatigue, concentration disorders, dizziness and loss of initiative. Subjective postconcussional complaints were assessed at first and final follow up.

Statistical analyses

To provide an overview of the differences between the groups and the change over time of the dependent variables compound scores were computed using the following formulas: memory Z(VVLTI + VVLTtot + VVLTrecall)/3, simple speed – Z(CSTA + CTSB + CST0 + SCWTI + SCWTII)/5, complex speed –Z(SCWTIII + CSTC)/2 and processing speed Z(LDCT). Reference values from the Maastricht Aging Study (MAAS; Jolles, Houx, Van Boxtel & Ponds, 1995) were used.

Between groups effect of mild TBI patients versus control participants using ANOVA technique for repeated measures was tested. Because a recovery/retest effect was expected for the mild TBI group, multivariate interactions between group and time (3 test moments) were tested.

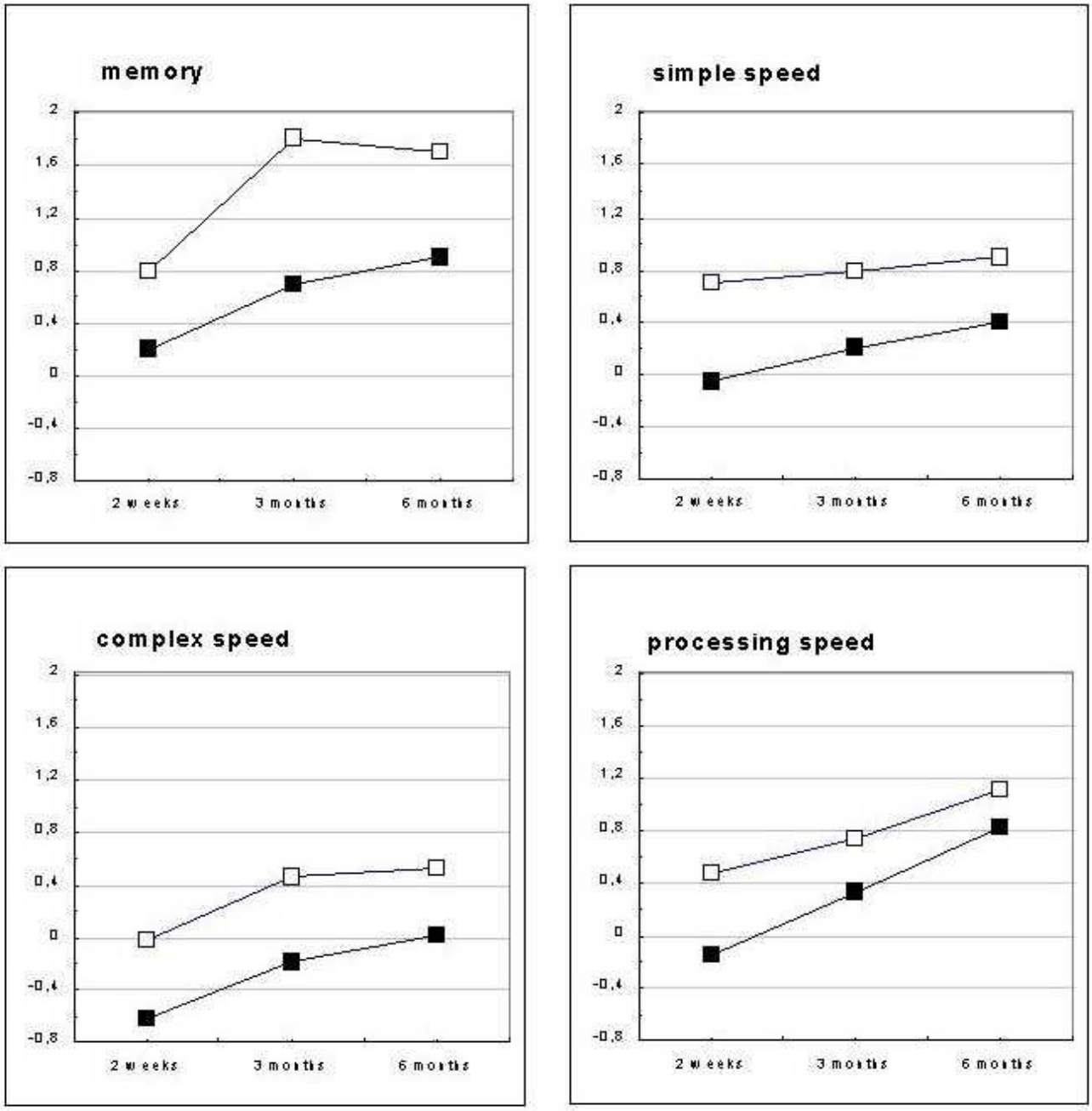
Results

Neurocognitive performance

In Table I the mean scores of the controls and the patient group on each test occasion are displayed. The curves of the mean test scores on each test occasion are shown separately for the mild TBI patients and control subjects in figure I, to provide an overview of the differences between the groups and the change over time of the dependent variables. It is clear that for each test the average for patients and controls differed at all test occasions. The mean slope of the patient group indicates that performance improves over time on all tests. However, for most tests this is also the case with respect to the control group, suggesting practice effects due to repeated measurement.

We found significant between group effects on all the neurocognitive compound scores: memory (F (1, 112) = 24.174, $p < .001$), simple speed (F (1, 112) = 23.503, $p < .001$), complex speed (F (1, 112) = 10.338, $p < .01$), and general speed (F (1, 110) = 5.157, $p < .05$).

Figure I. Compound scores for each group at test moments



Note: y-axes show age and education corrected standardized Z-scores. For explanation of compound scores see method section

□= control subjects; ■= mild TBI subjects

Multivariate interactions (group x time) did not reach significance ($F(2, 111) \leq 2.790$, n.s.) on any of the dependent variables.

Table I. Mean compound scores for control subjects and mild TBI patients at each test occasion

Compound score	Controls			Mild-TBI		
(occasions 1 to 3)	M	SD	N	M	SD	N
Memory						
1	0.85	1.00	56	0.25	1.06	58
2	1.75	1.07	56	0.75	0.88	58
3	1.74	1.09	56	0.92	0.97	58
Simple speed						
1	0.67	0.63	56	-0.06	1.22	58
2	0.81	0.61	56	0.19	0.83	58
3	0.89	0.55	56	0.37	0.68	58
Complex speed						
1	-0.02	0.82	56	-0.62	1.67	58
2	0.46	0.65	56	-0.19	1.39	58
3	0.53	0.61	56	0.02	1.00	58
General speed						
1	0.46	0.92	56	-0.15	1.22	56
2	0.73	0.96	56	0.33	1.12	56
3	1.11	1.04	56	0.83	1.23	56

For explanation of compound scores see method section

Subjective postconcussional complaints

Mean scores on the Post Concussional Scale of the neurovegetative questionnaire did not reveal any significant differences between the two groups at first (t (106)= .063, *ns*) and final follow up (t (109)= -.195, *ns*). Mean scores at first follow were 18.6 (*SD*= 5.9) for the TBI subjects and 18.7 (*SD*= 4.7) for the control subjects. At the last test occasion this was respectively 18.4 (*SD*= 6.5) and 18.2 (*SD*= 4.3).

We found low and non-significant correlations between the PCS score and the neurocognitive measures, except for the correlation between PCS score and the simple speed measure (r = -.20, $p < .05$). This low but significant correlation indicates that the

severity of postconcussional complaints is related to a somehow inferior performance on the simple speed measure.

Table II summarizes the proportion of subjects with complaints for each item of the PCS scale. The proportions are almost equally divided in the two groups for each of the test occasions indicating that the prevalence of complaints did not differ between the two groups.

Table II. Prevalence of post concussional complaints for each group on 1st and 2nd follow up

Subjective complaint	Controls		Mild-TBI	
	1st Follow Up	2nd Follow Up	1st Follow Up	2nd Follow Up
	N= 56	N= 56	N= 52	N= 55
Headache	14% (8)	13% (7)	15% (8)	16% (9)
Work	11% (6)	9% (5)	12% (6)	11% (6)
Light	32% (18)	38% (21)	27% (14)	44% (24)
Small effort	9% (5)	9% (5)	8% (4)	5% (3)
Concentration	32% (18)	21% (12)	29% (15)	35% (19)
Trouble	23% (13)	18% (10)	23% (12)	29% (16)
Tired	9% (5)	9% (5)	17% (9)	9% (5)
Noise	11% (6)	13% (7)	10% (5)	11% (6)
Simultaneous	18% (10)	16% (9)	27% (14)	15% (8)
Dizzy	4% (2)	5% (3)	15% (8)	9% (5)
Initiative	14% (8)	11% (6)	10% (5)	11% (6)

Concentration= trouble concentrating; Initiative= loss of initiative; Light= intolerance to light; Noise= intolerance to noise; Simultaneous= trouble doing things simultaneously; Small efforts= small effort requires much energy; Tired= tires easily; Trouble= has trouble being interrupted by others; Work= decreased work performance

Discussion

This follow-up study on the neurocognitive sequelae after a single mild TBI shows that at 6 months after injury, neurocognitive performance of mild TBI subjects is inferior compared to a group of age, sex and education matched healthy controls.

Although the mild TBI subjects did not obtain unusually low scores on the neurocognitive tests, these data suggest that neurocognitive functioning of these subjects is not fully recovered six months after injury. We found no differences in quality and extent of subjective PCS complaints between these two groups. Therefore, differences in neurocognitive performance cannot be explained by subjective factors.

We carefully selected a group of mild TBI patients with very mild injuries. A category of TBI patients that is believed to recover successfully. Some of the methodological limitations of earlier studies suggesting long lasting effects of mild TBI are controlled for in our study. We used an age, sex and education matched healthy control group that underwent the same procedure as our mild TBI subjects. The performance of the control group was used as reference value for effects of repeated neurocognitive measurements. Adding this to the use of parallel tests on different test occasions, does not allow to explain the between groups differences in terms of test-retest effects. The absence of significant interactions between group and time (test occasion) shows that both groups had the same benefit of the effect of repeated testing. We presume that mild TBI patients can benefit in the same amount from these practice effects as our control group.

It is believed that classical neuropsychological tests are not capable of identifying the specific neurocognitive problems experienced by mild TBI patients (Gronwall, 1991). The neurocognitive test battery we used in this study has proven to be sensitive for identifying subtle neurocognitive impairment after subclinical neurological incidents. It has been able to pick up chronic neurocognitive effects of health related factors in absence of subjective complaints (Houx, Vreeling & Jolles, 1991; Klein, Houx & Jolles, 1997).

In relation to the absence of difference in subjective complaints between the TBI patients and the control group it can be argued whether ‘good recovery’ implies the absence of subjective cognitive deficits. We believe that ‘good recovery’ implies return to premorbid objective cognitive functioning or cognitive functioning that can be expected based on age, sex and education corrected norm scores. A major methodological problem in mild TBI research is to prove that the observed cognitive deficits are the result of injury. We cannot rule out the possibility that these deficits exist prior to injury.

However, we found that our TBI subjects performed worse compared to their injury free counterparts. The clinical significance of this finding can be argued because very few subjects scored in the defined impaired range. Although our data suggest that mild TBI patients loose some of their neurocognitive capacity, we cannot be sure that the recovery process is still in process 6 months after injury. Our data support the hypothesis that diminution of cognitive reserve is chronic, because we did not find interactions between test occasion and group performance. This suggests that the performance of the TBI group did not improve proportionally more than the control groups performance.

This finding is in accordance with earlier results reported by our group. We found that a mild-to-moderate TBI results in long-term neurocognitive impairment in absence of subjective complaints (Klein, Houx & Jolles, 1997). The generalizabilty of this finding to the population of mild TBI patients was problematic, because of inclusion of moderate TBI subjects in the study. This study shows that at least up to 6 months after a single mild TBI subtle neurocognitive impairment can be detected, suggesting that neurocognitive capacity has been diminished. Though the clinical significance of this study and our earlier studies (Houx, Vreeling & Jolles, 1991; Klein, Houx & Jolles, 1997) is limited, it is of epidemiological significance. If cognitive reserve can be chronically diminished by a single mild TBI, then this incident might be of consequence for the usual cognitive aging process of such a person. In terms of brain reserve capacity (Satz, 1993), this means that threshold for cognitive problems at a clinical level might be earlier reached with advancing age than normally expected. This issue has to be resolved in future research.

The absence of significant subjective complaints and good subjective recovery of our patient group can be explained as a positive side effect of the study itself. Our patients underwent immediate neurological evaluation followed by neuropsychological assessment. It is likely that they exhibited better and faster recovery than people who did not receive similar medical attention. Our patients were better educated about symptoms and recovery process than patients who do not receive medical treatment. We did not specifically check for involvement in litigation after injury. We cannot completely rule out the possibility that performance of the mild TBI subjects is somehow influenced by involvement in litigation. However, the level of post concussional complaints does not allow explanation of results in such a direction. Future research on cognitive effects of

mild TBI has to include psychometrically well-validated tests for detection of motivationally impaired performance.

This study suggests that there is a need for more acceptance of the possibility that even a single mild TBI can lead to long-lasting, if not permanent, subtle neurocognitive deficits. The notion that mild TBIs are compatible with full cognitive recovery needs to be readdressed.

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- **Chapter 8 -**

Concluding remarks

As noted in the introduction, the central issue of this thesis is the hypothesis that a mild traumatic brain injury (TBI) results in minor cognitive impairments in absence of specific postconcussional complaints. In the experimental chapters of this thesis the relationship between mild traumatic brain injury (TBI) and neurocognitive performance was studied. All experimental studies are characterized by inclusion of mild TBI patients who experienced no significant subjective postconcussional symptoms following this mild injury. The neurocognitive performance (verbal memory, attention, and mental speed) of these patients was compared with healthy controls in order to assess possible subtle cognitive deficits resulting from this mild TBI. The neurocognitive performance of these mild TBI patients was studied in the subacute stage after injury, up to six months after injury, and longterm cognitive effects were studied using data from a population based cognitive aging study.

The relationship between biological markers (chapters 3 and 4) and cognitive performance was studied to assess the prognostic value of these markers on cognitive recovery. Cognitive reserve capacity in relation to cognitive aging processes after a remote TBI was assessed in a large population study into the effects of cognitive aging (chapter 5). We took a closer look at the interplay of age and mild TBI on neurocognitive performance to evaluate whether cognitive recovery after a mild TBI is significantly affected by age of the patient (chapter 6). In the final experimental chapter the objective cognitive after-effects of a single mild TBI were studied up to six months after injury in a population of patients who had sustained very mild TBIs.

Towards a synthesis

Biological markers and neurocognitive performance after mild TBI

There is much about recovery from brain injury that we still do not understand. The recovery process is active and dynamic and can be striking. The mechanisms of neural degeneration following TBI are poorly understood and prediction of recovery of function is uncertain in most cases. Also, no adequate treatment is currently available for the prevention of traumatic brain damage in humans. It was shown that a single mild TBI is associated with an unexpectedly high prevalence of posttraumatic lesions on MR imaging (chapter 3) and with the release of S-100B in serum (chapter 4). The object of these two studies was to relate these two separate biological markers to neurocognitive performance in mild TBI subjects. These studies suggest that the brain can be significantly damaged in a very mild TBI. However, the exact relation with cognitive performance in these subjects is still uncertain. This uncertainty is inherent to methods used in these studies.

In contrast with earlier studies we have shown that in the majority of mild cases of TBI detectable abnormalities are present using state of the art MR imaging techniques. In 9 out of twelve patients there was no evidence of lesions on MR imaging in combination with evidence of acute brain dysfunction (PTA and/or LOC). This should, however, not be interpreted as meaning absence of pathology (McAllister et al., 1999). Animal studies, using a fluid percussion model, have shown that mild injuries, while not producing tears, do produce neuronal cytoskeleton abnormalities that have the potential to render the cell dysfunctional. The cell may not 'die', and therefore the structure dependent MR scan appears grossly normal (Bigler, 2001). Many neuropathological consequences of TBI take time before the full pathological expression of the injury is observed. The best moment for evaluation of structural brain damage is still unknown. However, follow-up after 6 months did not reveal new lesions in our MRI study. It is very well possible that the 'obscure' lesions in our lesion-free group are responsible for the absence of a difference in cognitive perfomance between the two patient groups. So far, none of the attempts to quantify and classify structural damage to the brain has been very predictive

of neuropsychological outcome (Bigler, 2001). With a structure as complex as the human brain, it should come as no surprise that for most brain areas there is not a linear relationship between the size and location of a particular 'lesion' and neuropsychological deficit.

In chapter 4 we choose a different approach for quantifying the extent of brain damage. Recently, biochemical markers indicative of injury to the brain have gained a renewed interest as methodology to adequately measure these markers in serum have improved. Recent studies showed an association between clinical outcome and CSF or serum concentrations of protein S-100B in patients with severe TBI. Protein S-100B forms part of a large family of Ca^{2+} binding proteins and its cellular synthesis has been localized primarily in astrocytes. Although the release mechanism and the intracellular function of S-100B are not definitely identified, it has been shown that overexpression of S-100B induces cell death and apoptosis in astrocyte-neuron cultures. Increased S-100B concentration in peripheral blood flow is also considered as a marker for dysfunction of the blood-brain barrier and protein S-100B release in peripheral blood may indicate functional brain dysfunction without visible pathology in CT imaging (Herrmann et al., 2000). In our study we focused on a patient group who was able to perform a comprehensive neuropsychological test battery soon after TBI. The prevalence of mild cognitive disorder in patients with elevated S-100B serum concentrations (29 out of 50 mild TBI patients) was not different from the prevalence in patients with 'normal' S-100B serum concentrations. We choose to collect S-100B serum within six hours after injury. As the biodynamics of S-100B are not yet uniformly agreed upon, it could be that this time frame of S-100B collection is not ideal (Herrmann et al., 2000). In our study we concluded that S-100B has no predictive value for neurocognitive performance in the subacute stage after injury. Long-term predictive value could alter the picture yet again. It could be that S-100B is more important in monitoring secondary injury processes, than it is a suitable marker for estimating primary severity of injury. If future research on biodynamics of S-100B, especially half time values in serum, should decide that concentrations have to be assessed within one to two hours after injury, we believe that this marker is not a suitable clinical predictor for cognitive recovery. Everyday emergency room practice and triage of trauma victims learns that it is strictly academic to

collect serum samples within one to two hours after injury, should these patients decide to visit the emergency department at all. The influence of alcohol intoxication and party drugs on these S-100B concentrations have to be assessed in future research. As long as these issues remain unsolved, we believe that S-100B serum concentrations do not add significantly to the 'classic' injury severity markers (i.e. GCS score, PTA, and LOC).

With respect to the biological markers for TBI used in these two studies we can almost be certain that our included patients did sustain significant brain injury. These injuries resulted in mild cognitive dysfunction. The prognostic value of the biological markers on cognitive functioning was, however, absent.

Aging, brain atrophy, TBI, and dementia

Delayed neurobehavioral sequelae of TBI have been studied for some time (Gualtieri & Cox, 1991). Previously, Bigler and colleagues (2000), have shown that brain volume inexorably decreases with age, which probably accelerates in older age (>75 years). While still a somewhat controversial area, several studies have demonstrated a relationship between TBI and dementia (Lye & Shores, 2000). Recently, in the most comprehensive analysis to date, Guo et al. (2000) clearly demonstrated that brain injury is a risk factor for Alzheimer's Disease. Severity of injury appeared to be a significant issue. This seems to be a very intuitive relation since the brain atrophies with age, and if an injury further reduces brain volume, that brain volume loss is probably accelerated when it interacts with the aging process and the inexorable occurrence of atrophy. If there is cell loss associated with aging and the brain is injured, aging will continue to result in programmed cell loss secondary to aging. In the damaged brain, there will be fewer cells, and with fewer cells the proportional drop-off of cells will accelerate the cognitive decline. Patients with TBI will cross the threshold for cognitive symptom onset earlier in their life span due to the influence of aging and injury. Satz (1993) advanced this idea by hypothesizing a cognitive brain reserve capacity that is threatened by injury to the brain. From this point of view it is believed that TBI subjects would be at great risk for the earliest onset of dementia.

We did not find a relation between remote TBI and the usual cognitive aging process (chapter 5). In a large population based study, mild to moderate TBI did not affect or interfere with cognitive aging. The subjects that were enrolled in this study were selected for their subjectively experienced health. And although Houx (1991) found that selected health related factors (including TBI), interfere with cognitive aging at a subclinical level, we could not replicate this finding. However, this finding was replicated by Klein, Houx and Jolles (1996) in a study that included mild-to-moderate TBI subjects, but used a different methodology to include TBI subjects. At a subacute stage after mild TBI we found that cognitive reserve was affected in mild TBI subjects regardless of age, meaning that age has no dynamic interplay with cognitive reserve in the subacute stage after injury (chapter 6). Integrating the results from chapter five and six we suggest that mild TBI does influence the cognitive reserve, leading to initial mild cognitive impairment (see chapter 7). This cognitive impairment will eventually disappear in the effects of the cognitive aging process. In other words the mild TBI effect on cognitive reserve is caught up by the usual cognitive aging processes, and does not add significantly to these processes. We cannot be certain whether this speculation also applies to the effect of repeated mild TBIs on cognitive reserve. Matser and colleagues (1998, 1999) found a chronic effect of repeated subclinical mild TBIs on cognitive reserve.

Tracking recovery of function

Neuropsychology has a long tradition of tracking recovery of function. The clinical picture of recovery after mild TBI has been established (Binder, 1997). Mild TBI victims can experience postconcussion symptoms in the first days to weeks after injury, but these tend to resolve within weeks to months after injury. We demonstrated, however, that in a population suffering from a single very mild TBI cognitive function has not been restored six months after injury. This was also reported by Bohnen, Jolles, and Twijnstra (1993) using a patient sample with persistent subjective symptoms after mild TBI. Our study shows that subjective recovery does not imply recovery to premorbid levels of cognitive functioning. All these patients had recovered successfully and their level and

quality of subjective postconcussion symptoms did not differ from a healthy matched control group. TBI subjects benefited to the same extent from practice effects on the short cognitive battery. This implies that integrity of cognitive reserve has been violated by a single mild TBI. We do not know whether this is a chronic diminution of cognitive reserve or that cognitive functions are still in the process of restoration.

Implications for the clinical neuropsychologist

Because individual brains are unique compositions of genetic constellation and environmental interaction, brain-behaviour relationships are unique for each individual (with the exception of some dedicated motor and sensory pathways). Neuropathological and neuroimaging studies demonstrate diffuse damage as a consequence of mild TBI, regardless of whether focal damage exists or not. Even though lesion-localization relationships do occur in trauma, the neuropsychologist should not have expectations of finding a particular lateralized or focal brain-behaviour relationship, just because a lesion is detected in a scan. The absence of an imaging abnormality is not equivalent to absence of an abnormality. In cases where no neuroimaging findings are positive, the patients history is significant. If LOC and/or PTA are reported, trust that a brain injury, with all its microstructure abnormalities, has occurred. If *valid* neuropsychological evaluation and testing supports residual deficits, trust that those deficits are organically based and that the neuropsychological technique remains sensitive in the detection of neurobehavioural consequences of TBI, even if no neuropathology or neuroimaging abnormality is detected (Bigler, 2001). However, everyday neuropsychological practice learns that diagnosis of mild TBI patients with prolonged postconcussive symptoms is at the least complicated. Secondary symptom development (depression, anxiety, fatigue, chronic pain, malingering) may interfere significantly with cognitive performance (Alfano & Satz, 2000). Interpretation of neuropsychological test results should rule out possible alternative explanations for subtle neuropychological disturbances.

A major challenge to traditional neuropsychological assessment is rapidly emerging. What was once speculation is now becoming reality, and as

neuropsychologists we must address these assessment issues quickly. Using functional neuroimaging techniques, neurobehavioural probes are being developed wherein function and anatomy can be simultaneously assessed. The fMRI techniques are rapidly permitting 'noninvasive' visualization of fundamental processing modules in the human brain. These techniques hold great promise for further refining methods of integrating neurobehavioural assessment and imaging, particularly in the assessment of mild TBI (McAllister et al., 1999). Success in the areas of functional brain imaging will eventually change the face of neuropsychological assessment. Bigler (2001) foresees dramatic changes for the practicing clinical neuropsychologist. As technology drives further refinement in neuroimaging techniques interfaced with sophisticated neurobehavioural probes, simultaneous neurobehavioural assessment with imaging will occur. Successful implementation of these methods will eventually refine and improve many of the classical methods of neuropsychological assessment.

Future directions

As can be concluded from the previous chapters, research examining the neurocognitive outcome of mild TBI has resulted in inconsistent and contradictory findings. These findings have been attributed to a variety of methodological weaknesses, such as failure to consider the premorbid status of the patient, lack of control groups, and variability in outcome time points. The classification of mild TBI (ACRM, 1993) may permit heterogenity in TBI severity and may also contribute to the variability in neurobehavioural outcome. In the classification system for hurricanes, storms are ranked by level of severity. However, all homes involved in a class-3 hurricane do not suffer exactly the same amount of damage. Although a similar classification system can be devised for the severity of PTA, LOC and overall severity of TBI , this does not mean that all patients with a mild TBI will suffer exactly the same amount of damage, nor will their outcome be exactly the same. Just as one house may be better built than another, one individual may have a greater neuronal reserve or different psychological makeup than another, and these variables interact with the impact of the damage (Ruff & Jurica, 1999). From a clinical perspective, classifying TBI severity provides a scale against which

recovery may be predicted. To assume that this is the only predictor of the effect of an injury would be a disservice to the patient. Nonetheless patients with mild TBI are best served by non-ambiguous definitions that are applied uniformly among disciplines.

At this point it is recommended that subtypes are studied that fall within the broad ACRM diagnosis criteria (1993). Given the constructivistic perspective, one is open to a range of definitions. Entering additional variables into the definition could eventually lead to a construct of diagnostic criteria that can be validated retrospectively by the clinician and his or her colleagues. At this point neuroimaging variables seem to be more promising in the subacute stage after injury than biochemical marker variables, because the latter are subject to more uncertainty than the former in relation to TBI and its circumstances. Biochemical markers may play a more significant role in the long-term effects of mild TBI on cognitive reserve.

Two very important studies have demonstrated the role of APOE (apolipoprotein) in TBI (Friedman et al., 1999; Jordan, Relkin, & Ravdin, 1997). APOE is probably involved in some form of neuronal health and maintenance. It is shown that possessing the allele that confers increased risk for AD, the *e*4 allele, is associated with smaller hippocampal volumes in cognitively normal individuals and those with the earliest stage of Alzheimer's disease (Bigler et al., 2000; Plassman et al., 1997). Accordingly, there may well be a genetic predisposition factor that needs to be taken in to account with regard to outcome following injury and neuropsychological sequelae. TBI patients with the *e*4 allele may be destined for greater and prolonged deficits.

One interesting link between cognitive aging, dementia, and TBI is the deposition of β-amyloid protein following TBI and the role that β-amyloid protein plays in AD and its relationship to the 04 allele apoliprotein E (APOE). Naslund et al. (2000) correlated β-amyloid with cognitive decline. The role that β-amyloid plays in neurocognitive deficits following trauma is not known at this time.

There is suggestive evidence for long-term neurobehavioural impairment associated with mild TBI, but the evidence is not strong (Klein, Houx and Jolles, 1996). Also, it is unclear, what exactly is meant by the term 'good recovery'. Because 'good recovery' does not imply the absence of cognitive deficits, it is difficult to determine whether the recovery is physiological, psychological or psychosocial (e.g. compensation

and coping), or a combination of these factors. Additional work will help clarify the present picture regarding the length and extent of recovery following mild TBI. More research should be performed on unhospitalized cases of mild TBI. These are by far the majority of mild TBI cases, thus they deserve more attention.

There is need for more studies examining cognitive sequelae 1 year or more after mild TBI. Obviously, more longitudinal work is needed. In addition, there is need for more prospective studies which include pre-morbid cognitive status. Such work can help reduce the number of factors associated with long-lasting postconcussional complaints and neurobehavioural impairment. Much can be expected from sportsneuropsychology in this regard. Pre- and postseason cognitive testing of contactsports athletes (i.e. American footlball, soccer, boxing, ice hockey, skiing, car- and motor racing), with an ever present risk of sustaining concussions, can help clarify some of the major questions.

In an attempt to clarify the interplay between subjective cognitive complaints and objective neurobehavioural deficits, mild TBI subjects should be separated into subgroups based on the presence or absence of cognitive complaint (Satz et al., 1999). Controls should then be matched to mild TBI subjects in terms of age, sex, age, education and cognitive complaint. More demanding and sophisticated measures to detect subtle cognitive deficits in divided attention and in information processing speed and capacity should be developed, standardized and used (Bernstein, 1999).

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- **Chapter 9 -**

Summary

Of all brain injuries the mild traumatic brain injury (TBI) is the most common. Although it is frequently observed in clinical practice, the consequences, neuropathology and symptomatology are still poorly understood. The clinical picture of recovery has been described, but remains subject of debate among experts in this field of research. Mild TBI is in general considered as a benign injury resulting in uneventful recovery. However, a minority of patients (10-15%) complain about chronic postconcussive symptoms (fatigue, concentration and memory weakness, disturbances in mental flexibility, depressive symptoms and anxiety) that suggest that the structure or function of the brain is compromized. This postconcussional syndrome has been extensively studied, but causes of the syndrome and the evolution of symptomatology is still unresolved. It has up till now not received enough consideration in the scientific literature that the majority of mild TBI patients recovers successfully. It is this group of mild TBI patients that might provide some important pieces to the completion of the mild TBI puzzle. In this thesis studies are presented which evaluate the impact of a single mild TBI on neurocognitive performance in a population which is free from significant postconcussive symptomatology. Neurocognitive performance is used as a dependent variable throughout this thesis as performance on sensitive tests is believed to give a good approximation of the functioning or dysfunctioning of the brain in these patients. Effects of mild TBI on neurocognitive performance are studied in the acute, subacute and chronic stage after injury.

Chapter 1 describes the problem of mild TBI. Epidemiology, neuropathology and clinical injury characteristics are reviewed in relation to recovery and symptomatology after a mild TBI. The faces of mild TBI are presented at different stages in the recovery process after injury. The focus of interest is the neurocognitive performance of these patients. The neurocognitive consequences of mild TBI can be explained by a diminution of cognitive capacity. Apart from TBI, cognitive reserve can be threatened by other

factors. It is suggested that advanced age is also associated with reduced cognitive reserve capacity, as a consequence of exposure to factors which compromize cognitive reserve. A relation between mild TBI, immediate cognitive consequences and the cognitive aging process is suggested.

Methodological aspects of mild TBI research are discussed in chapter 2. Studies on consequences of mild TBI appear to be characterized by heterogeneity in the characteristics of the subjects who are included. It is suggested that this is a result of absence of consensus on the definition of mild TBI. Other pitfalls in mild TBI research are the uncertainties surrounding the clinical diagnosis of mild TBI and the lack of knowledge on permanence of brain damage after such an injury. Neuropsychological studies on the cognitive effects of a mild TBI have used a variety of test batteries, that complicate generalization of cognitive effects. Absence of - and selection of different control groups has complicated the interpretation of neurocognitive performance in mild TBI patients. The effects of repeated testing with the same neurocognitive tests, in order to monitor cognitive revovery, can easily be misinterpreted. Practice effects on neurocognitive tests interfere with recovery and are difficult to isolate from clinical recovery in absence of a control group. Longterm effects of a remote mild TBI on cognitive performance are subjected to the methodological drawbacks of retrospective study designs, i.e. selective subject inclusion, subjective injury reports, and opportunity for alternative explanations of observed impairments.

Chapter 3 describes an experimental study on the relation between a single injury variable, presence of cerebral lesions on MRI scans, and neurocognitive performance (verbal memory, attention and processing speed). In this longitudinal study we compared the neurocognitive performance of mild TBI patients with evidence of posttraumatic lesions on MRI scans with the performance of lesion free mild TBI subjects. In the subacute stage after injury all included mild TBI patients were subjected to a ‘state of the art’ MRI study of the brain. The neurocognitive performance of all subjects was measured within five days, and after two and six months after injury. The MR imaging was repeated at six months after injury. The prevalence of posttraumatic lesions appeared

to be unexpectedly high in over half of the mild TBI subjects. We found, however, no difference in neurocognitive performance between the two mild TBI groups. No new lesions were detected at final follow-up. Comparison of the neurocognitive performance of the mild TBI subjects with a matched healthy control group showed that cognitive performance of the mild TBI subjects was only modestly impaired and did not result in subjective experience of postconcussive symptoms. We concluded that evidence of lesions on MRI scans in the subacute stage after injury has no predictive value for neurocognitive performance up to six months after mild TBI.

Chapter 4 describes a study on the relation between serum protein S-100B and neurocognitive performance (verbal memory, attention and processing speed) in the subacute stage after injury in a mild TBI population. Protein S-100B is released in serum after damage to glial cells, and is considered to be a sensitive marker for brain damage after TBI. Serum samples were collected within six hours after injury and neurocognitive performance was assessed within two weeks after injury. We found no relation between protein S-100B concentrations in serum and neurocognitive performance in the subacute stage after injury. We concluded that S-100B serum concentrations within six hours after injury have no relation with neurocognitive performance. Uncertainty on biodynamics of protein S-100B after release in serum could account for this absence of relation.

The longterm effects of a mild to moderate TBI on neurocognitive performance (verbal memory, attention, coding speed and verbal fluency) are discussed in chapter 5. The effect of a remote TBI on cognitive reserve is studied in a prospective cross-sectional study design. To test the hypothesis that TBI has a permanent effect on neurocognitive performance we used data from the Maastrcht Aging Study. We found no effect of a remote TBI on neurocognitive performance in this data set. Interactions with age at neurocognitive assessment of the TBI subjects were also absent. Three year follow-up data were available for those subjects who were older than 50 years. Contrary to the hypothesis, we found no evidence for accelerated cognitive decline in these subjects. We concluded that a remote mild to moderate TBI has no effect on cognitive reserve capacity

reflected by neurocognitive performance. This suggests that a mild to moderate TBI does not interfere with the usual cognitive aging process, at least in the age-period tested.

Chapter 6 presents a study on the effect of age on neurocognitive performance (memory, attention, coding speed and verbal fluency) in the subacute stage after a single mid TBI. Advanced age is believed to be accompanied by a decline in cognitive reserve capacity. We tested the hypothesis that the effect on cognitive reserve capacity of a single mild TBI is dependent on age of the patient. We hypothesized that older mild TBI patients have a cognitive performance which is more clearly compromized than the performance of young mild TBI subjects in the subacute stage after injury. We used a case control design in which mild TBI subjects were matched with healthy controls. We did find a main effect for mild TBI on neurocognitive performance. Interactions between age and mild TBI on neurocognitive performance were absent, however, except for the coding speed performance. However, this interaction was in the other direction than predicted, in that the younger patients were compromized more than the older patients, when compared to their age-matched controls. We concluded that advanced age is no risk factor for more severe neurocognitive impairment after a single mild TBI in the subacute stage after injury.

Chapter 7 describes a follow-up study on the effect of a single mild TBI on neurocognitive performance up to six months after injury. Neurocognitive performance (memory, simple-, complex speed, and processing speed) was assessed at two weeks, three and six months after injury. Mild TBI subjects were individually matched with healthy control subjects. We hypothesized that mild TBI subjects would have an inferior neurocognitive performance compared to their non-damaged counterparts. We found that mild TBI subjects showed an inferior neurocognitive performance on all four cognitive domains at the three test occasions. This suggests that a mild TBI affects cognitive reserve capacity reflected by neurocognitive performance. This neurocognitive performance is not restored within 6 months after injury. Mild TBI subjects did not differ in severity of postconcussive complaints at 6 months after injury compared to the control group.

In chapter 8 the results of the experimental studies are discussed, integrated and recommendations for further research are provided. It is concluded that a single mild TBI has an effect on neurocognitive performance up to six months after injury in absence of subjective postconcussive complaints. Whether this subtle effect is permanent or these cognitive functions will restore after 6 months is uncertain. We found no permanent effect of mild to moderate TBI on cognitive reserve in a large population based study, which suggests that the cognitive reserve capacity is not permanently affected by a remote TBI. Brain reserve capacity reflected by neurocognitive performance is lowered as a function of age. This reserve capacity is however not affected by a TBI sustained at some point in life. The subacute effect of a single mild TBI on neurocognitive performance is not dependent on age of the mild TBI patient, which is commonly believed. This suggests that mild TBI does not interact with age or accentuates the cognitive aging process, at least in the age range up till young-old. It is possible that the subtle effects of a single mild TBI on cognitive performance will disappear in the cognitive changes that accompany the aging process, or that the subject is able to cope with these slight effects in the course of his or her life.

In order to predict which mild TBI patients are at risk for the development of protracted posttraumatic complaints, we studied the relation between two separate biological markers and neurocognitive performance. We found no relation between these single injury variables and neurocognitive performance after mild TBI. Evidence of posttraumatic lesions on MRI scans and serum protein S-100B concentrations did not proof to be of extra diagnostic value to the 'classical' injury variables, i.e. Glasgow Coma Scores, loss of consciousness and duration of posttraumatic amnesia.

In conclusion, the presented studies show that the effects of a single mild TBI on neurocognitive performance are subtle, not permanent, and do not result in significant subjective postconcussional complaints. This suggests that development of postconcussional syndromes is influenced by extra-injury variables, like psychosocial stressors, personality styles and preinjury morbidity. The interaction of mild TBI with other factors that threaten brain reserve capacity should be the object of study in future

research. The interplay of mild TBI with vulnerability factors like the APOE e4 allel and amyloid B deposition has to be studied in relation to cognitive aging processes.

- Hoofstuk 10 -

Samenvatting

Van alle hersenletsels komt het licht traumatisch hersenletsel (hersenschudding) het meest voor. Hoewel het licht traumatisch hersenletsel vaak wordt aangetroffen in de klinische praktijk, worden de gevolgen, neuropathologie en symptomatologie nog steeds slecht begrepen. Het klinisch herstel na een licht traumatisch hersenletsel is dan wel beschreven, maar blijft onderwerp van discussie onder de specialisten in dit vakgebied. Een licht traumatisch hersenletsel wordt in het algemeen gezien als een goedaardig letsel dat resulteert in succesvol herstel. Echter, een minderheid van deze patiënten (10-15%) klaagt over chronisch post-commotionele symptomen (vermoeidheid, concentratie- en geheugenzwakte, verstoorde mentale flexibiliteit, depressieve symptomen en angst) die suggereren dat de structuur of functie van het brein is aangetast. Het post-commotioneel syndroom is uitgebreid bestudeerd, maar de oorzaken van het syndroom en de ontwikkeling van de symptomatologie blijven vragen oproepen. Tot dusver is er in de wetenschappelijke literatuur weinig aandacht geweest voor het feit dat de meerderheid van de patiënten met licht traumatisch hersenletsel restloos lijkt te herstellen. Het is juist deze groep van patiënten met een licht traumatisch hersenletsel die een substantiële bijdrage zou kunnen leveren aan de oplossing van de puzzel die het licht traumatisch hersenletsel vormt. In de gepresenteerde onderzoeken in dit proefschrift wordt de impact van een eenmalig licht traumatisch hersenletsel op de neurocognitive prestatie (vooral metingen van geheugen, aandacht en snelheid) bestuurd in een populatie die vrij is van subjectieve postcommotionele symptomatologie. De neurocognitieve prestatie als afhankelijke variabele wordt beschouwd als een sensitieve test die een goede schatting geeft van de (dys)functie van de hersenen van deze patiënten.

Hoofdstuk 1 beschrijft het probleem van het licht traumatisch hersenletsel. Epidemiologie, neuropathologie en de klinische karakteristieken van het letsel worden besproken in relatie tot herstel en symptomatologie na een licht traumatisch hersenletsel. De verschijningsvormen van het licht traumatisch hersenletsel worden besproken in de verschillende stadia van herstel na letsel. De interesse gaat in het bijzonder uit naar de neurocognitieve prestatie van deze patiënten. De neurocognitieve gevolgen van een licht traumatisch hersenletsel kunnen worden verklaard in termen van een aantasting van de neurocognitieve capaciteit. Naast traumatisch hersenletsel wordt de neurocognitieve reserve bedreigd door andere factoren. In de literatuur wordt gesuggereerd dat de neurocognitieve reservecapaciteit kan worden bedreigd door leeftijd-gerelateerde achteruitgang, als gevolg van blootstelling aan gezondheidsgerelateerde factoren. Een relatie tussen licht traumatisch hersenletsel, directe cognitieve gevolgen en het cognitief verouderingsproces wordt verondersteld.

Methodologische aspecten van onderzoek naar de effecten van licht traumatisch hersenletsel worden besproken in hoofdstuk 2. Wetenschappelijke onderzoeken naar de gevolgen van licht traumatisch hersenletsel worden gekarakteriseerd door heterogeniteit in de eigenschappen van geïncludeerde patiënten. Er wordt gesuggereerd dat dit het gevolg is van afwezigheid van consensus over de definitie van licht traumatisch hersenletsel. Andere valkuilen in het wetenschappelijk onderzoek naar licht traumatisch hersenletsel zijn de onzekerheden die de klinische diagnose van licht traumatisch hersenletsel omringen en het gebrek aan kennis over de chroniciteit van hersenschade na een dergelijk letsel. Neuropsychologische onderzoeken naar de cognitieve effecten van een licht traumatisch hersenletsel hebben een verscheidenheid aan testbatterijen gebruikt die de generaliseerbaarheid van de cognitieve effecten compliceren. Afwezigheid en selectie van verschillende controlegroepen heeft de interpretatie van de neurocognitieve prestatie van patiënten met licht traumatisch hersenletsel tot dusver bemoeilijkt. De effecten van herhaald testen met dezelfde neurocognitieve testbatterij, met als doel het cognitief herstel te beschrijven, kunnen gemakkelijk verkeerd geïnterpreteerd worden. Oefeneffecten op neurocognitieve testen kunnen interfereren met 'herstel' en zijn moeilijk te isoleren van klinische herstel in afwezigheid van een controlegroep. Conclusies over de lange-termijn-effecten van een licht traumatisch hersenletsel op de cognitieve prestatie worden gekleurd door de tekortkomingen van retrospectieve onderzoeksdesigns, zoals selectieve inclusie van proefpersonen, subjectieve rapportage met betrekking tot de ernst van het letsel en de gelegenheid tot het geven van alternatieve verklaringen voor de geobserveerde stoornissen.

Hoofdstuk 3 beschrijft een experimenteel onderzoek naar de relatie tussen aanwezigheid van cerebrale laesies op hersenscans en neurocognitieve prestatie (verbaal geheugen, aandacht en informatieverwerkingssnelheid). In dit longitudinale onderzoek hebben we de neurocognitieve prestatie van patiënten met een licht traumatisch hersenletsel, waarbij schade aan de hersenen was te zien op een MRI-scan, vergeleken met de prestatie van patiënten zonder aanwijzingen voor deze hersenschade. In het subacute stadium na letsel ondergingen al de geïncludeerde patiënten een MRI-scan van de hersenen. De neurocognitieve prestatie van deze patiënten werd binnen 5 dagen na letsel gemeten, na 2 maanden en uiteindelijk na 6 maanden vond er follow-up onderzoek plaats. Het MRI-onderzoek werd 6 maanden na letsel herhaald. De aanwezigheid van posttraumatische laesies bij meer dan de helft van deze patiënten bleek onverwacht hoog te zijn. Er werd echter geen verschil gevonden in de neurocognitieve prestatie tussen deze twee groepen licht traumatisch hersenletsel patiënten. Er werden geen nieuwe laesies aangetroffen bij de laatste follow-up. Vergelijking van de neurocognitieve prestatie van de patiëntengroep met een gematchte gezonde controlegroep liet zien dat de cognitieve prestatie van de patiëntengroep slechts licht gestoord was en niet resulteerde in subjectief ervaren cognitieve symptomen. De bevinding laesies op een MRI-scan in het subacute stadium na licht traumatisch hersenletsel heeft geen voorspellende waarde voor de neurocognitieve prestatie tot 6 maanden na letsel.

Hoofdstuk 4 beschrijft de relatie tussen serum-proteïne S-100B en neurocognitieve prestatie (verbaal geheugen, aandacht en snelheid van informatieverwerking) in het subacute stadium na licht traumatisch hersenletsel. Het proteïne S-100B wordt in het bloed vrijgelaten na schade aan gliacellen. Bloedconcentraties van dit proteïne worden dan ook beschouwd als een sensitieve marker voor hersenschade na traumatisch hersenletsel. Binnen 6 uur na een licht traumatisch hersenletsel werd bloed afgenomen bij patiënten met een licht traumatisch hersenletsel en de neurocognitieve prestatie werd binnen 2 weken na letsel bepaald. Er werd geen relatie gevonden tussen proteïne S-100B-serum-concentraties en neurocognitieve prestatie in het subacute stadium na letsel. Serum-S-100B-concentraties binnen 6 uur na letsel hebben geen relatie met neurocognitieve prestatie. Onduidelijkheid over de verandering van de spiegel van proteïne S-100B na het vrijkomen in de bloedbaan kan de afwezigheid van deze relatie mogelijk verklaren.

De lange-termijn-effecten van een licht tot middelzwaar traumatisch hersenletsel op de neurocognitieve prestatie (verbaal geheugen, aandacht, codeersnelheid en verbale fluency) worden besproken in hoofdstuk 5. Het effect van een ‘oud’ (vele jaren eerder opgelopen) traumatisch hersenletsel op de cognitieve reserve werd bestudeerd in een prospectief cross-sectioneel onderzoeksdesign. Om de hypothese te toetsen dat een traumatisch hersenletsel een permanent effect heeft op de neurocognitieve prestatie werden gegevens gebruikt van de Maastricht Aging Study. Er werd geen effect gevonden van een ‘oud’ hersenletsel op de neurocognitieve prestatie in deze dataset. Interacties met leeftijd van de proefpersonen waren eveneens afwezig. Follow-up-gegevens 3 jaar na baseline-meting waren beschikbaar van proefpersonen met een leeftijd van 50 jaar en ouder. Tegen de verwachting in werd er geen aanwijzing gevonden voor een versnelde cognitieve achteruitgang bij deze groep proefpersonen. Er werd dan ook geconcludeerd dat een ‘oud’ licht tot middelzwaar hersenletsel geen effect heeft op de cognitieve reservecapaciteit.

Hoofdstuk 6 is een onderzoek naar het effect van leeftijd op de neurocognitieve prestatie (geheugen, aandacht, codeersnelheid en verbale fluency) in het subacute stadium na een eenmalig licht traumatisch hersenletsel. Leeftijd wordt in verband gebracht met een achteruitgang in cognitieve reservecapaciteit. De hypothese dat het effect op de cognitieve reservecapaciteit van een licht traumatisch hersenletsel afhankelijk is van de leeftijd van de patiënt werd getoetst. Er werd voorspeld dat ‘oudere’ hersenletsel-patiënten meer inleveren aan cognitieve reserve dan ‘jongere’ patiënten in het subacute stadium na letsel. Er werd gebruik gemaakt van een case-control design waarbij patiënten met een licht traumatisch hersenletsel werden gematched met gezonde controlepersonen. Er werd een hoofdeffect gevonden voor letsel op de neurocognitieve prestatie. Interacties tussen leeftijd en letsel waren afwezig, behalve in het geval van de prestatie op een codeertaak. Deze interactie was echter in tegengestelde richting dan voorspeld. De jongere patiënten hadden relatief meer ingeleverd aan cognitieve prestatie in vergelijking met de oudere patiënten, wanneer ze werden vergeleken met een gezonde gematchte controlegroep. Er

werd geconcludeerd dat gevorderde leeftijd geen risicofactor is voor proportioneel ernstigere neurocognitieve stoornissen na een eenmalig licht traumatisch hersenletsel in het subactute stadium na letsel.

Hoofdstuk 7 beschrijft een follow-up onderzoek naar het effect van een eenmalig licht traumatisch hersenletsel op de neurocognitieve prestatie tot 6 maanden na letsel. Neurocognitieve prestatie (geheugen, eenvoudige-, complexe informatieverwerkingssnelheid en codeersnelheid) werden gemeten op 2 weken, 3 en 6 maanden na letsel. De patiënten werden individueel gematched met gezonde controlepersonen. Er werd voorspeld dat de letselgroep een slechtere neurocognitieve prestatie zou laten zien dan de controlegroep. Deze voorspelling werd bevestigd voor alle 4 de cognitieve domeinen op elk testmoment. Dit suggereert dat een licht traumatisch hersenletsel de cognitieve reservecapaciteit beïnvloedt zoals gemeten door neurocognitieve prestatie. Deze neurocognitieve prestatie herstelt zich niet binnen 6 maanden na letsel. De patiëntengroep verschilde bovendien niet aangaande ervaren postcommotionele klachten vergeleken met de controlegroep.

In hoofdstuk 8 worden de resultaten van de experimentele onderzoeken bediscussieerd, geïntegreerd en worden aanbevelingen gedaan voor verder onderzoek. Er wordt geconcludeerd dat een eenmalig licht traumatisch hersenletsel een effect heeft op de neurocognitieve prestatie tot 6 maanden na letsel in afwezigheid van subjectieve postcommotionele klachten. Of dit subtiele effect permanent is of dat de cognitieve prestaties zullen herstellen na 6 maanden is onzeker. Er werden geen aanwijzingen gevonden voor een permanent effect van een licht tot middelzwaar hersenletsel op de cognitieve reserve in een groot bevolkingsonderzoek, hetgeen suggereert dat de cognitieve reservecapaciteit niet permanent wordt beïnvloed door een ‘oud’ traumatisch hersenletsel. Hersenreservecapaciteit, zoals gemeten met neurocognitief presteren, neemt af als functie van leeftijd. Deze reservecapaciteit wordt echter niet beïnvloed door een traumatisch hersenletsel op een bepaald moment in het leven opgelopen. Het subacute effect van een licht traumatisch hersenletsel op de neurocognitieve prestatie is niet afhankelijk van de leeftijd van de patiënt. Dit suggereert dat de gevolgen van een licht traumatisch hersenletsel niet beïnvloed worden door leeftijd of interfereren met het cognitief verouderingsproces, hetgeen in het algemeen wordt aangenomen. Het is mogelijk dat de subtiele effecten van een eenmalig licht traumatisch hersenletsel op de cognitieve prestatie ‘verdwijnen’ in de cognitieve veranderingen die gepaard gaan met het verouderingsproces, of dat de betreffende persoon in staat is om deze kleine cognitieve tekorten tijdens zijn of haar leven te compenseren.

Om te voorspellen welke patiënten een kwetsbaarheid hebben voor het ontwikkelen van langdurige postcommotionele klachten, werd de relatie bestudeerd tussen twee verschillende biologische markers en neurocognitieve prestatie. Er werd geen relatie gevonden tussen deze letsel-variabelen en neurocognitieve prestatie na een licht traumatisch hersenletsel. De bevinding van hersenschade op een MRI scan en serum proteïne S-100B concentraties blijken geen toegevoegde diagnostische waarde te hebben

boven de ‘klassieke’ letselvariabelen, zoals de Glasgow Coma Score, duur van bewusteloosheid of posttraumatische amnesie.

De gepresenteerde onderzoeken laten zien dat een eenmalig licht traumatisch hersenletsel een subtiel en waarschijnlijk tijdelijk effect heeft op de neurocognitieve prestatie en niet resulteert in significante postcommotionele klachten. Dit suggereert dat de ontwikkeling van het post-commotioneel syndroom wordt beïnvloed door variabelen als psychosociale stressoren, persoonlijkheid en premorbide factoren. De interactie van licht traumatisch hersenletsel met andere factoren die de hersenreservecapaciteit bedreigen zal het doel moeten worden van toekomstig onderzoek. Het samenspel van licht traumatisch hersenletsel met kwetsbaarheidsfactoren zoals het APOE-e4-allel en afzettingen van amyloide-B zijn veelbelovend in relatie tot het cognitief verouderingsproces.

Curriculum Vitae

Sven Stapert werd op 29 december 1971 geboren in Mwambani (Tanzania). Na het behalen van het gymnasium-β diploma (1990) aan het Jacobus College te Enschede, studeerde hij psychologie aan de Universiteit van Amsterdam. Hij liep klinische stages op de afdelingen medische psychologie van het Slotervaart Ziekenhuis en het Onze Lieve Vrouwe Gasthuis in Amsterdam. In januari 1997 studeerde hij af met specialisatie klinische psychobiologie & neuropsychologie. In april 1997 werd hij als AIO aangesteld bij de capgroep Biologische Psychologie van de Faculteit der Psychologie, Universiteit Maastricht . Momenteel is hij als GZ-psycholoog in opleiding verbonden aan de afdeling Psychiatrie van het Academisch Ziekenhuis Maastricht en als Universitair Docent aan de capgroep Neurocognitie van de Faculteit der Psychologie, Universiteit Maastricht.

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