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ORIGINAL ARTICLE

Long-term cognitive and emotional consequences of mild traumatic brain injury

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Background. The objective of this study was to investigate long-term cognitive and emotional sequelae of mild traumatic brain injury (mTBI), as previous research has remained inconclusive with respect to their prevalence and extent.

Method. Thirty-three individuals who had sustained mTBI on average 6 years prior to the study and 33 healthy control subjects were matched according to age, gender and education. Structural brain damage at time of testing was excluded by magnetic resonance imaging (MRI). A comprehensive neuropsychological test battery was conducted to assess learning, recall, working memory, attention and executive function. Psychiatric symptoms were assessed by the Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-I) and the Beck Depression Inventory (BDI). Possible negative response bias was ruled out by implementing the Word Memory Test (WMT).

Results. The mTBI individuals had significant impairments in all cognitive domains compared to the healthy control subjects. Effect sizes of cognitive deficits were medium to large, and could not be accounted for by self-perceived deficits, depression, compensation claims or negative response bias. BDI scores were significantly higher in the patient group, and three patients fulfilled DSM-IV criteria for a mild episode of major depression.

Conclusions. Primarily, well-recovered individuals who had sustained a minor trauma more than half a decade ago continue to have long-term cognitive and emotional sequelae relevant for everyday social and professional life. mTBI may lead to a lasting disruption of neurofunctional circuits not detectable by standard structural MRI and needs to be taken seriously in clinical and forensic evaluations.

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Introduction

Mild traumatic brain injury (mTBI) is a frequent medical condition with an incidence of about 100 to 300 per 100 000. mTBI is often used interchangeably with related terms such as concussion, cerebral concussion or mild head injury (Anderson *et al*. 2006). Various definitions of mTBI or concussion exist, mainly including an induction by biomechanical forces, a rapid onset of neurological functional impairments, and grossly normal neuroimaging studies (mTBI Committee, 1993; Aubry *et al*. 2002; Carroll *et al*. 2004; Cantu *et al*. 2006; Ruff, 2009). mTBI may be caused by relatively minor traumata, such as sport injuries, household accidents, whiplash injuries or falls (Rickels *et al*. 2006). Possible acute symptoms of mTBI comprise short-time unconsciousness, headache, dizziness, irritability, anxiety and impaired neuropsychological functions such as reduced attention, concentration or memory problems (Evans, 1992; Hall *et al*. 2005). Remission frequently occurs within hours up to a 1 or 2 months (Jacobson, 1995; Binder *et al*. 1997; Schretlen & Shapiro, 2003; Frencham *et al*. 2005), but may take up to 1 year (Dikmen *et al*. 1986, 1995; Alexander, 1995). However, some patients suffer from physical, cognitive or psychological impairments

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even years after the trauma, which may hamper their reintegration into social, familial and professional life (Barth *et al*. 1996; Gasquoine, 1997; McAllister & Arciniegas, 2002; Ponsford & Schönberger, 2010).

Long-lasting symptoms are often referred to as 'post-concussion syndrome' and include somatic symptoms such as chronic headaches, chronic pain syndromes, dizziness and visual disturbances. Frequently encountered cognitive symptoms include attentional deficits, slowed information processing, reduced verbal and working memory, and impaired executive functions. Psychiatric symptoms such as depressed mood, anxiety, irritability, agitation, poor motivation, social withdrawal and interpersonal difficulties are also reported frequently (Binder, 1986; Ashman *et al*. 2004). The reported prevalence rates for long-lasting post-concussion symptoms that occur after mTBI vary from 7–8% (Binder, 1986) to 10–20% (Alexander, 1995), up to 33% (Rimel *et al*. 1981). Patients with post-concussion symptoms repeatedly consult health-care services, constituting a therapeutic challenge for neurologists, psychiatrists and psychologists. As these patients often present with symptoms several years after mTBI, in the absence of visible brain damage according to standard clinical neuroimaging methods, they often arouse the suspicion of malingering and stir up a debate about the necessity of treatment and the fair forensic evaluation of patients who sustained mTBI earlier in life (Green *et al*. 1999; Paniak *et al*. 2002; Flaro *et al*. 2007; Ruff *et al*. 2009).

Despite their social and scientific relevance, convincing studies on long-term sequelae of mTBI are rare, and as a recent review pointed out, there is insufficient evidence to determine whether mTBI is associated with cognitive deficits 6 months or longer post-injury (Dikmen *et al*. 2009). The few studies covering a time period of several years differ with respect to methods and reveal heterogeneous and sometimes conflicting results (Table 1). Segalowitz *et al*. (2001) investigated students who, on average, suffered from mTBI 6.4 years ago and did not report any subjective impairment at the time of investigation. Nevertheless, a comprehensive neuropsychological assessment revealed attention and information processing deficits. Similarly, Vanderploeg *et al*. (2005, 2007) found impairments in partial aspects of complex attention and working memory, on average 8 years post-injury. By contrast, several studies did not find evidence of cognitive or psychological deficits several years after the trauma. For example, Ettenhofer & Abeles (2009) reported that mTBI does not result in cognitive impairment or psychiatric dysfunction; however, follow-up testing was performed 2.9 years after injury.

Diverging methodological approaches, such as differences in study design or in the assessment of confounding variables, constitute a crucial issue (Gasquoine, 1997; Mathias & Coats, 1999). The lack of a consistent definition of mTBI is one of several methodological problems. Many authors refer exclusively to the initial Glasgow Coma Scale (Teasdale & Jennett, 1974) to assess the degree of trauma, whereas others base their diagnosis on additional criteria, such as those suggested by the Mild Traumatic Brain Injury Committee of the American Congress of Rehabilitation Medicine (ACRM) (mTBI Committee, 1993; Carroll *et al*. 2004; Lezak *et al*. 2004). Most investigations rely on retrospective self-reports, that is diagnosis and classification are based on patients' reports years after the trauma. The selection of the study sample constitutes another difficulty in mTBI research. Many studies were unable to exclude false-positive findings influenced by secondary reinforcers such as compensation claims (Paniak *et al*. 2002; Flaro *et al*. 2007), an issue of paramount importance in evaluating mTBI (Arciniegas *et al*. 2005; Merten *et al*. 2005). Furthermore, there is the possibility that investigators overestimate the consequences and subjective meaning of mTBI in the life of the patients by selecting their study sample from a clinical population still receiving medical care at the time of assessment. This issue was confirmed by the meta-analysis of Belanger *et al*. (2005), who reported that cognitive impairments after mTBI in clinical populations yielded effect sizes of $d = 0.74$, compared to unselected prospective samples with effect sizes of $d = 0.04$. This underlines the importance of the recruitment procedure for this kind of study. It is essential to include subjects based on objective criteria (e.g. time of injury) rather than selecting them according to subjective criteria such as the presence of self-reported complaints.

Given that the long-term consequences of mTBI remain inconclusive, we conducted an investigation of patients who had sustained mTBI on average 6 years ago, but with a methodological improvement. Patients who fulfilled the criteria of the Mild Traumatic Brain Injury Committee of the ACRM were selected from the initial clinical charts and included irrespective of current symptoms. State-of-the-art magnetic resonance imaging (MRI) was conducted to exclude any structural brain damage at time of testing. We investigated a broad range of cognitive domains, while controlling for psychiatric conditions and malingering, using established psychometric methods. We hypothesized that mTBI leads to cognitive impairments that are still detectable 6 years after trauma and relevant for daily living. We further hypothesized that emotional disturbances are also more frequent after having sustained mTBI.

Table 1. *Studies investigating long-term cognitive and emotional consequences after a minimum of 6 years after mild traumatic brain injury (mTBI)*

Study First-named author (year)	Mean interval after TBI (years)	Sample size (*n*)	Severity of TBI	Main results
Bernstein (2002)	8	13 mTBI, 10 controls	Mild[a]	Reduced P300 amplitude in a set of attention tasks, poorer performance in demanding cognitive tasks
Segalowitz (2001)	6.4	10 TBI, 12 controls	Mild[a]	Normal functioning on standard neuropsychological measures, but drop in attentional performance in a demanding context (oddball task), paralleled by electrophysiological changes
Sterr (2006)	6.8	38 TBI, 38 controls	Mild[b]	Higher error rate in patients with unaffected reaction times indicate that cognitive loads exceed a certain threshold in TBI patients earlier than in controls. Subjectively experienced symptoms and difficulties are related to objectively measurable parameters in neurocognitive function
Vanderploeg (2005)	8	254 TBI, 539 motor vehicle accident controls 3214 healthy controls	Mild[a]	No group differences in a standard neuropsychological test battery, but in subtle aspects of complex attention and working memory
Vanderploeg (2007)	8	254 TBI, 539 motor vehicle accident controls 3214 healthy controls	Mild[a]	Increased likelihood of depression and post-concussion syndrome, visual imperceptions and tandem gait. Poorer psychosocial outcomes, for example self-reported disability, underemployment, low income and marital problems
Draper (2007)	10.56	53 TBI	Mild to very severe[b]	Psychosocial functioning lowest in occupational activity domain, highest in the living skills domains; poor performance on some cognitive tests associated with functional outcome; anxiety and depression were strongest predictors for outcome
Hetherington (1996)	5 *v.* 10	10 TBI 5 years after TBI, 10 TBI 10 years after TBI, 10 controls	Mild to severe[b]	No significant group differences in mean reaction time; in TBI group, response latency was related to age and to task demands; no correlations between any dependent measure and severity of injury
Himanen (2006)	31	61 TBI, 31 controls	Mild to very severe[b]	Mild cognitive decline during follow-up, associated with male gender and age at injury; by contrast, semantic memory showed improvement
Klein (1996)		25 TBI, mean age = 26.4 years, 25 TBI, mean age = 35.7 years, 50 controls	Mild to moderate[a]	Inferior performance of TBI patients to controls in memory parameters, both consolidation and retrieval; generalized reduced rate of information processing; evidence for accelerated cognitive aging
Ponsford (2008)	10.58	60 TBI, 43 controls	Mild to severe[b]	Overall good functional outcome after TBI; post-traumatic amnesia and lower pre-injury education strongest predictors of outcome; patients with poorer outcome performed worse on information processing speed, attention, memory and executive function; anxiety strongly correlated with outcome
Draper (2009)	10.61	54 TBI, 54 close others	Mild to severe[b]	Reports of TBI patients and close others showed high agreement. There was no strong correlation of subjective reports with test performance. Relationship of test performance with Hospital Anxiety and Depression Scale (HADS) anxiety and depression scores was much high

[a] Self-reported TBI.

[b] TBI defined by diagnostic criteria.

The first five studies included patients with mild TBI only. The inclusion was based on self-report in four cases or defined diagnostic criteria in one case, but not on magnetic resonance imaging (MRI)-based exclusion of brain lesions at the time of testing. The next six studies included patients with mild to moderate or very severe TBI; thus their results may be influenced by the higher degree of severity.

Method

Ethical guidelines

All procedures were approved by the Institutional Ethical Review Board. The ethical standards of the Declaration of Helsinki were met and all participants provided written informed consent.

Subjects

Patients with the clinical diagnosis of mTBI treated at the University of Muenster in the years 2001 to 2003 were identified by systematic screening of patients' charts. Inclusion criteria were documentation of the clinical diagnosis, age at time of testing between 18 and 65 years, and conformance to the research diagnostic criteria of the ACRM (mTBI Committee, 1993). These criteria include any period of loss of consciousness for a maximum of 30 min and/or post-traumatic amnesia for a maximum of 24 h and/or any alteration in mental state at the time of the accident and/or focal neurological deficit(s) that may or may not be transient. Furthermore, an initial Glasgow Coma Scale score (if available) of 13–15 measured 30 min post-injury was required. As language-based neuropsychological tests were used, only native German-speaking patients were included. An initial telephone screening was performed to exclude individuals with head injuries additional to the index mTBI, psychopharmacological medication, neurological diseases, or MRI contra-indications. According to the charts, 233 patients suffered from mTBI. Of these, 136 could not be contacted because of missing or inaccurate contact information. Of the remaining 97 patients who could be contacted, 53 did not give written informed consent. In the remaining 44, two patients suffered from claustrophobia and terminated the MRI scan prematurely and three others did not attend for neuropsychological testing. Three more patients completed the neuropsychological testing but denied participation in the MRI. In two out of 36 patients (5.6%) and one out of 36 controls (2.8%), the MRI scan showed structural lesions. These patients and the associated control subjects were excluded from further analysis, thus 33 matched pairs entered the final analysis.

Healthy volunteers were recruited by advertisement and matched individually to the patients according to gender (same gender), age ($\pm$2 years) and education level (defined as highest graduation level). As in patients, an initial telephone screening was performed to exclude prior head injury, any medical or neurological diseases, or MRI contra-indications.

Inclusion into final analysis using additional neuroimaging criteria

Thirty-six patients and 36 matched healthy controls met the inclusion criteria. As a unique step for quality assurance distinguishing this study from other neuropsychological investigations and as part of a larger investigation, a structural MRI was performed at the time of testing to screen for previously undetected brain lesions. MRI data were acquired on a 3-T whole-body scanner (Gyroscan Intera T30, Philips Medical Systems, The Netherlands). The imaging protocol comprised the following sequences:

(1) Axial T2-weighted turbo-spin-echo [echo time (TE)/repetition time (TR) 80/3000 ms; flip angle 90°; 36 contiguous slices; slice thickness 3.6 mm; field of view (FOV) 240 mm; matrix 400 × 512; scan duration 5:15 min].
(2) Axial T2*-weighted fast-field-echo sequence (TE/TR 16 ms/shortest; flip angle 18°; 36 contiguous slices; slice thickness 3.6 mm; FOV 230 mm; matrix 256 × 512; scan duration 4:09 min).
(3) Sagittally acquired 3D T1-weighted turbo-field-echo (TE/TR 3.4/7.4 ms; flip angle 9°; 320 slices; FOV 256 mm × 205 mm × 160 mm; matrix 512 × 410 × 320 resulting in isotropic voxels with an edge length of 0.5 mm; scan duration 11:09 min).

All scans were evaluated by a radiologist experienced in neurosurgery (H.S.) who was blinded to subjects status (patient or control). For two out of 36 patients (5.6%) and one out of 36 controls (2.8%), the MRI scan showed structural lesions. These patients and the associated control subjects were excluded from further analysis, thus 33 matched pairs entered the final analysis.

Characteristics

The group demographic characteristics of the remaining 66 participants are displayed in Table 2. None of the characteristics differed significantly between groups. In the final cohort, 18 patients had sustained mTBI due to a traffic accident, six due to a sports injury, and nine due to a fall or a collision. The mean time elapsed between injury and testing was 6.02 years (range 4.75–7.25 years).

Materials and procedures

A neuropsychological and psychiatric test battery containing the following standardized instruments was performed:

(1) Auditory Verbal Learning Test (AVLT), German version: Verbaler Lern- und Merkfähigkeitstest

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Table 2. *Characteristics of the study population*

	mTBI patients	Controls	Statistics
Number of subjects	33	33	
Gender (frequencies)			$\chi^2(1) = 0.0$, $p = 1.0$
Female	16	16	
Male	17	17	
Age at time of testing (years), mean ± S.D.	36.7 ± 12.4	37.0 ± 12.0	$T(64) = 0.10$, $p = 0.92$
School education level (frequencies)[a]			$\chi^2(2) = 1.44$, $p = 0.49$
Hauptschul-degree	5	2	
Realschul-degree	10	11	
Abitur	18	20	
Further training after school education (frequencies)			$\chi^2(3) = 1.03$, $p = 0.79$
In training	6	6	
Apprenticeship completed	17	18	
University studies completed	9	9	
No further training	1	0	
Employment			$\chi^2(1) = 0.16$, $p = 0.69$
Unemployed	4	3	
Employed	29	30	

mTBI, Mild traumatic brain injury; S.D., standard deviation.

[a] German terms for school education are not translated into English, as the education systems are fundamentally different. The 'Hauptschul-degree' requires 9 years of education at a basic school, the 'Realschul-degree' requires 10 years at a higher level of education, and the 'Abitur' 12–13 years at the highest level of school education.

(Rey, 1964; Helmstaedter *et al*. 1996). Subjects learn, reproduce and recognize a list of 15 common nouns presented over five trials.

(2) Tests for Attentional Performance (TAP), German version: Testbatterie zur Aufmerksamkeitsprüfung, versions 1.02c and 1.7, computer-based (Zimmermann & Fimm, 1992). Attentional performance was tested using the working-memory, divided attention and go/nogo subtests of the TAP. In the working-memory test, subjects perform a two-back task based on digits, in the divided attention test subjects have to attend to and react to visual and auditory stimuli presented simultaneously, and in the go/nogo subtest subjects differentiate between critical and non-critical visual stimuli and prevent inadequate reactions.

(3) Trail Making Test Parts A and B (TMT-A and TMT-B; Reitan, 1958; Spreen & Strauss, 1998). Subjects connect numbered only circles, or both numbered and lettered circles.

(4) Word fluency tasks (Regensburger Wortflüssigkeits-Test, RWT). Subjects name as many words as possible for the categories 'initial letter S', 'animals' and 'alteration sports/fruit' (Aschenbrenner *et al*. 2000).

(5) Digit span of the Wechsler Memory Scale, Revised, German adaptation (WMS-R). Subjects repeat progressively longer strings of digits in the same or in reverse order respectively (Härting *et al*. 2000).

(6) Beck Depression Inventory (BDI, German adaptation) to assess subjective symptoms of depressed mood (Beck *et al*. 1961; Hautzinger *et al*. 1995).

(7) To measure patients' impairment in daily life, we constructed a 25-item questionnaire (Q-25), comparable with the Rivermead Post Concussion Symptoms Questionnaire (RPQ). Subjects rated subjectively perceived performance changes that occurred since their injury, taking into account different domains of daily living and cognitive functioning (King *et al*. 1995).

(8) A standardized Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-I) was conducted with all participants (Wittchen *et al*. 1997).

(9) A German adaptation of the Word Memory Test (WMT) was performed. This computer-based verbal learning test provides information on possible negative response bias during test taking, and measures immediate recognition (IR), delayed recognition (DR) and consistency (CNS) below 82.5% (Green, 2005).

The complete testing and clinical interview session was conducted individually for each participant and lasted

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Table 3. *List of (neuropsychological) test scores categorized into five cognitive domains, one mood domain and one suboptimal effort domain*

Test scores	Description
1. Episodic memory: acquisition and consolidation	
AVLT-Sum Trial 1 to 5	Cumulative learning
WMT-Multiple-Choice	Delayed cued recognition after 30 min
WMT-Paired-Associations	Delayed cued reproduction after 30 min
2. Episodic memory: retention and recognition	
AVLT-Trial 6	Recall after interference
AVLT-Trial 7	Delayed recall, 20 min
WMT-Free Recall	Delayed free recall after 30 min
WMT-Long Delay Free Recall	Long delayed free recall, 50 min
AVLT-Trial 5 minus 6	Loss after interference
AVLT-Trial 5 minus 7	Loss after delay
AVLT-Trial 8	Corrected recognition: hits minus false-positives
3. Working memory	
AVLT-Trial 1	Supraspan for verbal material
TAP-Working Memory	Working memory performance, reaction time
Digit Span Forwards	Supraspan for numerical material
Digit Span Backwards	Working memory for numerical material
4. Attention	
TAP-Divided Attention	Divided attention, reaction time
TAP-Go/Nogo	Reaction inhibition, reaction time
TMT-A	Information processing
TMT-B	Cognitive flexibility
5. Executive functions (word fluency)	
Word Fluency-S	Lexical word fluency
Word Fluency-Animals	Semantic word fluency
Word Fluency-Sports/Fruits	Semantic category-alteration
6. Impairment in daily life and depression	
BDI	Self-rating of depressive symptoms
Q-25	Self-rating of impairment in daily life
SCID-I	Rating of psychiatric disorders
7. Negative response bias	
WMT-IR	Suboptimal effort: score $<82.5\%$
WMT-DR	Suboptimal effort: score $<82.5\%$
WMT-CNS	Suboptimal effort: score $<82.5\%$

AVLT, Auditory Verbal Learning Test; WMT, Word Memory Test; TAP, Tests for Attentional Performance; TMT, Trail Making Test; BDI, Beck Depression Inventory; Q-25, 25-item questionnaire; SCID-I, Structured Clinical Interview for DSM-IV Axis I Disorders; IR, immediate recognition; DR, delayed recognition; CNS, consistency of immediate and delayed recognition responses.

about 2–3 h. Test scores were categorized into five cognitive domains: (1) episodic memory: acquisition and consolidation, (2) episodic memory: retention and recognition, (3) working memory, (4) attention, and (5) executive functions. To control for mood effects, we also assessed impairment in daily life and depression (see Table 3) .

For descriptive analysis, means and standard deviations (S.D.) were calculated. For statistical analysis, for each domain the effect of group (patient or control) on test scores was assessed using multivariate analysis of variance (MANOVA). Calculations were performed using SPSS version 15.0. The results of the SCID were analyzed descriptively.

Results

Group comparisons of neuropsychological and behavioral data

All seven MANOVAs revealed significant differences in cognitive performance between mTBI patients and control subjects. Table 4 shows means, standard deviations and univariate effects for the 21 neuropsychological, two mood and three suboptimal effort

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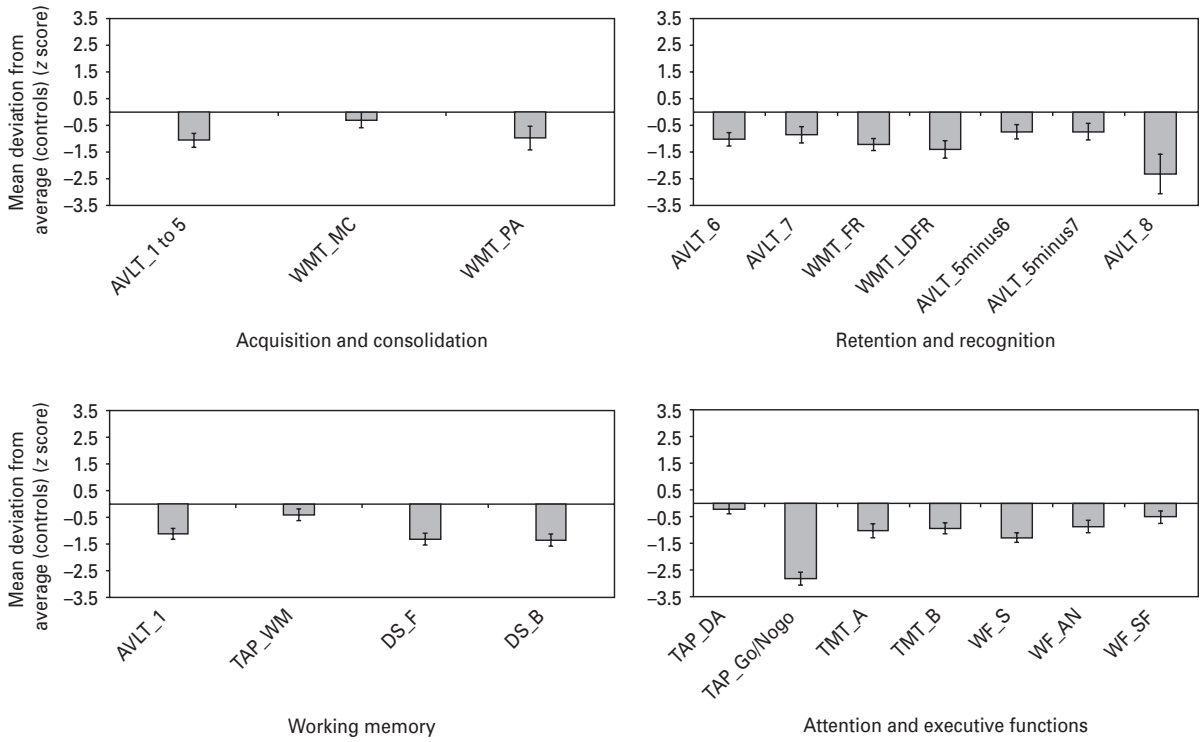

Fig. 1. Mean deviation from average of the controls (z scores). AVLT, Auditory Verbal Learning Test; WMT, Word Memory Test; MC, Multiple Choice; PA, Paired Associations; FR, Free Recall; LDFR, Long Delay Free Recall; TAP, Tests for Attentional Performance; WM, Working Memory; DS_F, Digit Span Forwards; DS_B, Digit Span Backwards; DA, Divided Attention; TMT, Trail Making Test, WF_S, Word Fluency – S; AN, Animals; S, Sports/Fruits.

measures across both groups. Fig. 1 displays deviations in cognitive performance of mTBI patients.

(1) *Episodic memory: acquisition and consolidation*. Group differences were highly significant [Wilks' $\lambda = 0.742$, $F(3.62) = 7.18$, $p < 0.001$, partial $\varepsilon^2 = 0.26$]. Between-group effects were significant for the parameters WMT-Paired-Associations and AVLT-Sum Trial 1 to 5. (2) *Episodic memory: retention and recognition*. The overall effect was highly significant [Wilks' $\lambda = 0.753$, $F(6.59) = 3.23$, $p < 0.01$, partial $\varepsilon^2 = 0.25$]. Between-group effects were significant for all measures except for AVLT-Trial 5 minus 7. (3) *Working memory*. Group differences were highly significant in multivariate analysis [Wilks' $\lambda = 0.654$, $F(4.61) = 8.07$, $p < 0.001$, partial $\varepsilon^2 = 0.35$]. Univariate statistics were significant for three out of four outcomes. (4) *Attention*. The main effect was highly significant for this analysis [Wilks' $\lambda = 0.785$, $F(4.61) = 4.17$, $p < 0.01$, partial $\varepsilon^2 = 0.22$]. Group differences were significant in the Trail Making Subtests. (5) *Executive functions* (*word fluency*). For this cognitive function, multivariate analysis was highly significant [Wilks' $\lambda = 0.700$, $F(3.61) = 8.73$, $p < 0.001$, partial $\varepsilon^2 = 0.30$]. Group differences were significant for semantic and lexical fluency. (6) *Impairment in daily life and Depression*. This analysis showed a highly significant overall analysis [Wilks' $\lambda = 0.718$, $F(2.63) = 12.39$, $p < 0.001$, partial $\varepsilon^2 = 0.29$]. Both the BDI and the Q-25 resulted in significant group differences. Three patients, but no controls, had a BDI sum score $\geqslant 18$. (7) *Response bias*. No subject fulfilled criteria for underachievement, defined as a score in the effort measures of the WMT $< 82.5\%$. There were no significant group differences in the effort measures of the WMT [Wilks' $\lambda = 0.931$, $F(3.62) = 1.532$, $p = 0.215$, partial $\varepsilon^2 = 0.07$]. None of the patients were involved in compensation claims due to cognitive and emotional consequences of mTBI.

To determine whether the above-reported group differences between mTBI patients and control subjects were modulated by self-reported impairment in daily life or by actual depressive symptoms, we performed an additional MANCOVA for each of the five cognitive domains; including BDI and Q-25 as covariates affected the reported results only minimally, and all main group differences remained significant.

Estimation of the prevalence of manifest neuropsychological impairment in mTBI patients was based on deteriorated performance with at least 1.5 S.D. below the mean of the controls in two or more cognitive domains. This resulted in 42.4% of the patients

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Table 4. *Results*

Variables	mTBI ($n=33$) Mean (S.D.)	Controls ($n=33$) Mean (S.D.)	MANOVAs df	F	p	Partial ε^2	d
1. Episodic memory: Acquisition and consolidation [Wilks' $\lambda=0.742$, $F(3.62)=7.18$, $p<0.001$, partial $\varepsilon^2=0.26$]							
AVLT-Sum Trial 1 to 5	58.67 (8.70)	64.58 (5.70)	1	10.65	<0.01**	0.14	0.8
WMT-Multiple-Choice	93.03 (11.72)	95.00 (6.85)	1	0.70	0.408	0.01	0.2
WMT-Paired-Associations	91.82 (13.28)	96.85 (5.21)	1	4.11	<0.05*	0.06	0.5
2. Episodic memory: Retention and recognition [Wilks' $\lambda=0.753$, $F(6.59)=3.23$, $p<0.01$, partial $\varepsilon^2=0.25$]							
AVLT-Trial 6	12.21 (2.62)	13.85 (1.60)	1	9.37	<0.01**	0.13	0.8
AVLT-Trial 7	12.55 (2.73)	13.85 (1.52)	1	5.74	<0.05*	0.08	0.6
WMT-Free Recall	64.64 (15.67)	78.67 (11.40)	1	17.26	<0.001***	0.21	1.0
WMT-Long Delay Free Recall	68.06 (16.43)	80.79 (8.94)	1	15.28	<0.001***	0.19	1.0
AVLT-Trial 5 minus 6	1.58 (1.72)	0.73 (1.13)	1	5.65	<0.05*	0.08	0.6
AVLT-Trial 5 minus 7	1.24 (2.02)	0.73 (1.02)	1	1.68	0.199	0.03	0.3
AVLT-Trial 8	13.52 (2.28)	14.73 (0.52)	1	8.88	<0.01**	0.12	0.7
3. Working memory [Wilks' $\lambda=0.654$, $F(4.61)=8.07$, $p<0.001$, partial $\varepsilon^2=0.35$]							
LMT-Trial 1	7.88 (1.80)	9.67 (1.60)	1	18.26	<0.001***	0.22	1.1
TAP-Working Memory	546.78 (152.39)	497.47 (118.89)	1	2.15	0.148	0.03	0.4
Digit Span Forwards	8.33 (1.93)	10.33 (1.51)	1	21.92	<0.001***	0.26	1.2
Digit Span Backwards	6.85 (2.24)	9.21 (1.73)	1	23.07	<0.001***	0.27	1.2
4. Attention [Wilks' $\lambda=0.785$, $F(4.61)=4.17$, $p<0.01$, partial $\varepsilon^2=0.22$]							
TAP-Divided Attention	635.95 (62.03)	624.71 (59.36)	1	0.57	0.455	0.01	0.2
TAP-Go/Nogo	495.73 (86.31)	467.12 (61.17)	1	2.42	0.125	0.04	0.4
TMT-A	24.73 (7.77)	19.48 (5.26)	1	10.30	<0.01**	0.12	0.8
TMT-B	59.97 (17.26)	46.48 (14.75)	1	11.64	<0.001***	0.15	0.8
5. Executive functions (word fluency) [Wilks' $\lambda=0.700$, $F(3.61)=8.73$, $p<0.001$, partial $\varepsilon^2=0.30$]							
Word Fluency-S	25.28 (7.98)	35.33 (7.93)	1	25.96	<0.001***	0.29	1.3
Word Fluency-Animals	42.03 (11.48)	49.58 (8.80)	1	8.87	<0.01**	0.12	0.7
Word Fluency-Sports/Fruit	25.19 (4.77	27.09 (3.99)	1	3.06	0.085	0.05	0.4
6. Impairment in daily life and depression [Wilks' $\lambda=0.718$, $F(2.63)=12.39$, $p<0.001$, partial $\varepsilon^2=0.29$]							
BDI	6.52 (6.05)	3.85 (4.00)	1	4.46	<0.05*	0.07	0.5
Q-25	49.27 (15.73)	34.48 (7.49)	1	23.79	<0.001***	0.27	1.2
7. Negative response bias [Wilks' $\lambda=0.931$, $F(3.62)=1.532$, $p=0.215$, partial $\varepsilon^2=0.07$]							
WMT-IR	97.33 (4.30)	98.94 (2.36)	1	3.54	0.064	0.05	0.5
WMT-DR	97.97 (4.85)	99.45 (1.54)	1	2.81	0.099	0.04	0.4
WMT-CNS	96.12 (6.17)	98.67 (2.79)	1	4.66	0.055	0.07	0.5

mTBI, Mild traumatic brain injury; AVLT, Auditory Verbal Learning Test; WMT, Word Memory Test; TAP, Tests for Attentional Performance; TMT, Trail Making Test; BDI, Beck Depression Inventory; Q-25, 25-item questionnaire; IR, immediate recognition; DR, delayed recognition; CNS, consistency of immediate and delayed recognition responses; df, degrees of freedom; S.D., standard deviation.

Significant group difference at: * $p<0.05$, ** $p<0.01$, *** $p<0.001$.

(14 out of 33) presenting with manifest neuropsychological impairment.

Results of the SCID diagnostic assessment

Healthy controls did not reveal any Axis I psychiatric disorders as assessed by SCID. Three patients had a mild episode of major depression at time of testing, two of these as a symptom of recurrent depression. One of these had already experienced two depressive episodes before mTBI. Another patient reported one mild episode of major depression in the time between mTBI and testing, but was remitted at the time of current assessment.

Discussion

In this study we investigated a broad range of cognitive domains in patients who sustained mTBI on average 6 years prior to the study, while controlling for psychiatric conditions and malingering. We could confirm our initial hypothesis that considerable cognitive deficits are present in a broad range of cognitive domains even 6 years after mTBI. Differences between

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mTBI patients and controls amounted to medium to large effect sizes in learning and long-term memory, working memory, attention, and executive functions.

Previous research on long-lasting consequences of mTBI yielded ambiguous results. Some investigators reported no or only subtle differences between control groups and patients several years after mTBI (Dikmen *et al*. 1986, 1995; Frencham *et al*. 2005; Vanderploeg *et al*. 2005). In a comparison of mild to moderate TBI within 2 months of trauma, Goldstein *et al*. (2001) identified no cognitive deficits in the mTBI group. By contrast, other researchers found significant cognitive impairments even many years after mTBI (Leininger *et al*. 1990; Bernstein, 2002; Sterr *et al*. 2006). Thus, the debate about long-term deficits of mTBI remains unresolved. A recent review concluded that, to date, there is insufficient evidence to determine whether mTBI is associated with cognitive deficits 6 months or longer post-injury (Dikmen *et al*. 2009).

It is possible that factors such as depression or negative response bias influence test performance; we therefore assessed these variables in the current study (Bessell *et al*. 2008). Furthermore, methodological differences between studies are large and complicate comparisons. Some of these investigations suffer from low sample size, diagnosis relying on self-reports instead of standardized diagnostic assessment at time of injury, inclusion of various degrees of severity, variable duration between injury and testing, and finally a large variety of neuropsychological assessment methods. In addition, the results of previous investigations may be influenced by the presence of undetected brain lesions. For our investigation, patients were selected from the initial clinical charts, the presence of established diagnostic criteria for mTBI in the initial clinical charts was assured, and patients were contacted irrespective of current treatment status. Absence of structural brain damage at the time of investigation was secured by performing a structural MRI scan specifically sensitive to TBI. In two out of the initial 36 patients and in one of the initial 36 controls, structural damage was detected and led to exclusion. This finding is in line with other investigations; for example, Bruns & Jagoda (2009) reported that about 15% of patients with clinically diagnosed mTBI present with acute intracranial lesions detected by cerebral computed tomography. Using 3-T MRI, as we did in this investigation, the rate of parenchymal lesions was reported to be even higher (Lee *et al*. 2008). The highest incidence rate was reported by a group who found structural lesions in 11 out of 20 mTBI patients (Datta *et al*. 2009). Our finding underlines the significance of initial brain imaging in TBI patients (Stein *et al*. 2006).

In our investigation, we identified significant deficits in working memory and attention about 6 years after mTBI. Short-term memory and attention are known to be affected by mTBI shortly after injury (Malojcic *et al*. 2008), but long-term consequences are less evident. Vanderploeg *et al*. (2005) investigated patients with mTBI about 8 years after trauma. Using non-traditional analysis methods, focusing on the continuation rate of the Paced Auditory Serial Addition Test and pro-active interference in the California Verbal Learning Test, they found subtle deficits in working memory and attention. Investigating 38 patients 6.8 years after mTBI, Sterr *et al*. (2006) also found deficits of working memory and attention. As mainly error rates, but not reaction times, were affected, they concluded that the threshold for inefficient simultaneous management of response accuracy and speed may be lowered even years after mTBI. In contrast to our investigation, the digit span forward and backward tests did not indicate working memory deficits in the sample of mTBI subjects; however, the validity of this observation is limited by the small sample size of 10 subjects (Segalowitz *et al*. 2001). Nevertheless, the authors corroborated deficits of attention by electrophysiological correlates in the P300 component of an oddball task (Segalowitz *et al*. 2001). Our findings on working memory are in line with a recent electroencephalographic (EEG) study in mTBI. mTBI patients showed impaired verbal and visuospatial attention span, and EEG coherence measures indicated impaired functional connectivity 2.13 months after mTBI (Kumar *et al*. 2009*b*). Thus, previous work on working memory and attention supports our observations of deficits even 6 years after mTBI.

In our investigation episodic memory as assessed by the AVLT and the memory measures of the WMT was significantly worse in patients compared to controls. This finding is of interest because there is still considerable debate about whether mTBI might cause lasting deficits in long-term memory, for example in encoding or retrieval. Most previous reports of memory deficits in mTBI are contaminated by the inclusion of more severe forms of TBI. Klein *et al*. (1996) identified impaired memory performance both for consolidating material into memory and for passive retrieval in 45 patients 3 years after mild or moderate TBI, even though subjects had no subjective complaints. Draper *et al*. (2007) and Ponsford *et al*. (2008) reported that memory performance correlated with functional outcome about 10 years after mild to severe TBI. Compromised memory functions were also found in one quarter of TBI patients with relatively preserved intellectual capacities (Levin *et al*. 1988). Gupta & Ghai (1991) reported poorer immediate and delayed free recall after TBI, whereas Hall & Bornstein (1991) concluded that poorer recall is a lasting feature of memory function after brain injury. By contrast, Himanen *et al*.

(2006) reported good recovery of semantic memory during a 30-year follow-up in patients with mild to severe TBI. For isolated mTBI, evidence is sparse. A recent investigation in high-school athletes showed that memory deficits persisted for about 7 days, but resolved by day 10 (Sim *et al*. 2008). However, Nolin (2006) reported poor performance in free recall as assessed by the California Verbal Memory Test in patients after mTBI, whereas cued recall remained unimpaired, pointing towards a selective dysfunction of registration and retrieval processes rather than a general storage problem. Divergent results may be explained by other influencing factors, such as attentional load. Recall performances of individuals with mTBI was similar to controls when words were encoded under full attention, whereas they performed worse when encoding in a divided attention condition (Blanchet *et al*. 2009). Our findings indicate that memory encoding and recall deficits are not confined to higher degrees of TBI severity, but may be detected several years after mTBI if a set of sophisticated neuropsychological tests is used.

In the domain of executive functions, word fluency tasks tap complex cognitive processes, involving the perception of a target word, online-maintenance in working memory, retrieval of its meaning, activation of related concepts and instruction-dependent active search for concepts with equivalent meaning (Konrad *et al*. 2008). Word fluency tasks have proven to be very sensitive for the characterization of patients after head trauma, and impaired performance in word fluency was observed in patients after TBI (Aschenbrenner *et al*. 2000). Word fluency tasks also have proven sensitivity in long-term follow-up of patients after TBI (Mathias & Coats 1999; Belanger *et al*. 2005; McHugh *et al*. 2006). We also found that word fluency was impaired in patients after mTBI. This is in line with the impairments of working and semantic memory reported above, and with the findings of Draper *et al*. (2007) and Ponsford *et al*. (2008), who reported that performance in the Controlled Oral Word Association Test (COWAT) correlated with functional outcome after mild to severe TBI.

Impairments in daily life were also assessed in our investigation and differed significantly between groups. Thus, subtle cognitive impairments indeed have consequences for daily living. Our finding is in line with Draper *et al*. (2007), who found impairments in self-assessed psychosocial outcome after mild to severe TBI, that is occupational activity, interpersonal relationships and independent living skills. By contrast, Ettenhofer & Abeles (2009) reported that single-incident mTBI is of little clinical significance to long-term cognitive and symptom outcome. Temkin *et al*. (2009) reported a dose–response relationship between severity of injury and social outcomes, but insufficient evidence for mTBI. Comparisons between studies are complicated by divergent definitions and assessment methods of impairments in daily life functioning. Furthermore, the interval between injury and testing differs between studies. Notably, self-assessed psychosocial impairments do not explain the cognitive impairments measured in this study, as the effect sizes remained stable after correction for Q-25.

The assessment of emotional consequences 6 years after mTBI represents another major point of our study. In daily clinical practice, complaints of depressive mood after mTBI are a frequent clinical and forensic problem. In studies investigating the occurrence of major depression in mTBI, in general about 10–20% of the patients meet diagnostic criteria for major depression (Deb *et al*. 1999; Rapoport *et al*. 2003, 2006). Long-term assessments are often hampered because patients with different degrees of TBI severity are included. For example, Draper *et al*. (2007) reported that 46% of patients with mild or moderate TBI met criteria for clinical depression, whereas Koponen *et al*. (2002) found that 26.7% experienced major depression in the time interval between mild to very severe TBI and the assessment but only 10% showed depression at the time of the interview about 30 years after TBI. Depression rates decreased from 31% after 1 month to 17% after 3–5 years in a sample including patients with mild to severe TBI (Dikmen *et al*. 2004). A decreasing depression rate with time after injury was also supported by Ashman *et al*. (2004). However, Whelan-Goodinson *et al*. (2009), who retrospectively established pre- and post-traumatic frequencies of psychiatric disorders (DSM-IV, Axis I), reported a dramatic increase of major depressive disorder from 17% before to 45% after head trauma, and anxiety from 13% before to 38% after head trauma. So far, investigations do not directly support a link between severity of TBI and occurrence of depression; that is, more severe trauma is not related to more frequent or severe depression (Hibbard *et al*. 1998). This is supported by our observation indicating an increased rate of depression even after mTBI.

In our investigation, three out of 33 (9%) patients fulfilled diagnostic criteria (SCID) of a mild episode of major depression about 6 years after mTBI. [Even if the patient who had recurrent episodes before the trauma is excluded, two out of 33 (6%) still meet diagnostic criteria.] At first sight, this rate seems low. However, bearing in mind that we rigorously excluded patients after moderate or severe TBI and that the interval between injury and assessment was 6 years on average, our observation is in line with the rates reported in the literature. Depressive symptoms were further assessed using BDI self-rating, as depressive symptoms

are often remarked by the patients themselves even when third-party raters evaluate normal depression ratings (Schöning *et al*. 2009). In line with the SCID diagnosis, patients scored significantly worse than healthy patients [mean = 6.52 (S.D. = 6.05) compared to mean = 3.85 (S.D. = 4.00), $p < 0.05$]. BDI scores did not interact with cognitive performance measures, as demonstrated in a MANCOVA model, thus neuropsychological impairments cannot be explained by depression.

Malingering is another frequent concern in the assessment of neurocognitive function in patients after TBI (Bordini *et al*. 2002). The rate of negative response bias in adults after mTBI is much higher than in second-grade or disabled children (Green *et al*. 2009). This is particularly evident when monetary compensation claims come into play, but may also be triggered by other conscious or unconscious motives (Boone & Lu, 2003). Although in our investigation no patients were involved in compensation claims, we tested putative symptoms fabrication using the WMT, a state-of-the-art measure for non-credible cognitive performance (Iverson *et al*. 1999; Green, 2005). We were thus able to rule out any negative response bias in our mTBI group and could ascertain the validity of our findings.

In summary, our investigation demonstrates significant cognitive and emotional impairments on average 6 years after mTBI. In this study we do not examine the causes of these impairments, thus we can only raise some hypotheses. Most frequently, deficits after TBI are explained by disruption of neuronal connections by the shearing and stretching forces of the incident (Graham *et al*. 2000; Smith *et al*. 2003). TBI might cause disruption of neurofunctional circuits, decreasing cerebral processing speed and interacting with cerebral functions. External forces seem to be transmitted mainly to certain predeliction sites that are more affected than other regions, such as the corpus callosum. Using diffusion tensor imaging (DTI), reduced fractional anisotropy (FA) as a marker of reduced fiber integrity has been observed in the corpus callosum of patients with moderate TBI, and this finding was associated with poor neuropsychological outcome (Kumar *et al*. 2009*a*). mTBI patients also showed reduced FA in some brain regions (Kraus *et al*. 2007), although findings in the corpus callosum seem to depend on the time after trauma. Patients with mild TBI investigated <3 months post-trauma had reduced FA in the genu, whereas patients with mild TBI investigated ⩾3 months post-trauma showed no significant differences (Rutgers *et al*. 2008). Altered EEG coherence demonstrates that these pathophysiological processes might indeed occur after mTBI (Kumar *et al*. 2009*b*). The emotional disturbances observed after mTBI may represent an indirect psychological reaction to the trauma, itself representing a major life event that is frequently associated with changes in psychosocial conditions. Emotional changes may also be a direct consequence of damage to the emotion regulation system (Draper *et al*. 2007); for example, left dorsofrontal brain lesions may increase the probability of developing depression after TBI (Fedoroff *et al*. 1992). A possible explanation for our observations on impaired cognitive and emotional function in mTBI may thus be explained by disruption of important neurofunctional circuits. Although not assessed by the T1-, T2- and T2*-weighted imaging sequences used routinely in the clinical context and applied in this study, such disruptions might still be present in the investigated population. DTI might be a useful imaging modality for assessing more subtle disruptions of structural brain connectivity.

Some limitations of our study need to be acknowledged. Although subjects were matched carefully for gender, age and education, we cannot fully exclude systematic differences between groups in other aspects. For example, it is possible that a subset of patients were more interested in participating than others, although the systematic screening of patients' charts and the systematic contact of all available patients independent from actual symptoms was performed to reduce selection bias. The broad age range (19–64 years) and the balanced gender distribution (16 females, 17 males) in each group do not favor this hypothesis; however, the high proportion of individuals with higher school education in both groups might indicate a stronger interest in scientific research. As education levels were matched across groups, this should not influence our results. Furthermore, our study cannot answer the question of cause and consequence. It is theoretically possible that subjects in the mTBI group sustained TBI because their pre-morbid cognitive or emotional function was already impaired before mTBI. However, this explanation seems rather far-fetched, and the fact that no differences existed between groups concerning age, gender, school and further education level makes it unlikely that systematic differences existed before the brain injury occurred. As a strength of this study, pre-injury and lifetime psychiatric diagnosis were excluded by the SCID. Using healthy subjects as the control sample, the effects we describe may not be specific to mTBI, but may instead reflect general changes due to traumatic events. As specificity was not the aim of our study, further research differentiating various traumatic events is needed.

In conclusion, our investigation contradicts claims that mTBI does not result in long-term cognitive or emotional impairments. By contrast, our investigation

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demonstrates that patients, even 6 years after mTBI, still show major impairments in a broad range of cognitive domains that can be revealed by thorough neuropsychological testing. In contrast to many other studies, we can exclude a significant influence of major confounding factors, such as depression, malingering or undetected structural brain damage. Effect sizes of cognitive deficits were medium to large in a variety of cognitive domains (partial $\varepsilon^2 = 0.22–0.35$, $d = 0.2–1.3$). According to our findings, the notion of complete recovery after mTBI is not supported. We suggest that long-term cognitive and emotional deficits in mTBI need to be taken seriously when evaluating or treating patients after mTBI.

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Declaration of Interest

None.

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