Neurocognitive fitness in the sub-acute stage after mild TBI: The effect of age

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Abstract
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 sub-acute 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: An overall effect was found of a single mild TBI on neurocognitive performance in the sub-acute 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 sub-acute period after mild TBI is at least not in line with the results of this study.

Keywords: Mild TBI, age, brain reserve capacity, neurocognitive performance

Introduction
The incidence of traumatic brain injury (TBI) follows a bimodal distribution, with peaks in young adulthood and old age [1]. 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 [2]. Elderly patients with moderate brain injuries also have a higher mortality rate [3] 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 [4].

Elderly patients are more likely than young TBI patients to develop traumatic mass lesions, including subdural haematomas and intra-cerebral haemorrhage, from mild-to-moderate injury [2, 5, 6]. They are more likely to develop permanent disability as a result of their injuries and tend to have longer hospital stays [5, 7]. Age is also associated with a greater number of post-concussional symptoms at both 6 weeks and 1 year after injury [8, 9]. Elderly TBI patients also are believed to be at increased risk for developing the chronic post-concussional symptom complex after TBI [10, 11], including depression, apathy, irritability and impulsive behaviour.

With respect to the neuropsychological consequences of mild TBI, different views have been expressed. Binder [12], Binder et al. [13] and recently Frencham et al. [14] 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

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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 [15] 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 [16], 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 pre-existing (sub-clinical) 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 sub-acute stage after TBI.

Although researchers tend to focus on long-term outcome, the sub-acute 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 post-injury stage.

The aim of this case-control study is to explore the impact of age on neurocognitive functioning in the sub-acute period following mild TBI. Care was taken to include younger and older patients without other possible co-morbid conditions which might influence cognitive functioning, in view of evidence that age-related cognitive dysfunction might be caused by a cumulation of risk factors [17]. It is hypothesized that neurocognitive performance is more affected in the elderly compared to their younger counterparts.

Methods

Subjects and procedure

Consecutive patients (March 1997–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) Glasgow Coma Score (GCS) > 13, (2) post-traumatic amnesia (PTA) of less than 1 hour and (3) loss of consciousness (LOC) not exceeding 15 minutes. These criteria fell within the limits proposed by the American Congress of Rehabilitation Medicine [18]. Persons with brain injury had to be free from other medical conditions and health related factors that interfere with optimal cognitive functioning [19]. We chose 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 Ageing Study [17] 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 Ageing 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 sub-clinical incidents [20, 21].

- **The Visual Verbal Learning Test (VvLT).** This memory test is a visual version of the Rey Auditory Verbal Learning Test [22]. In three consecutive trials, a list of 15 words has to be memorized and reproduced followed by a delayed recall procedure after 20 minutes [23]. Dependent variables are the total immediate recall score from three trials (VvLTrot) and the delayed recall score (VvLTr).  

- **The abbreviated version of the Swoop Colour Word Test (SCWT [24, 25]).** This test has often been used to test selective attention, mental speed and interference susceptibility [26]. The test uses three cards displaying forty 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 (seconds) 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 [26, 27]. 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** [26, 28]. 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 1 minute.

### Data analysis

Possible demographic between-group differences were tested using dependent sample t-tests. One-way-ANOVA were used to estimate the effect of mild TBI on selected cognitive variables. Because an age effect was expected for the mild TBI group, an interaction (two-way ANOVA) between group and age was tested. Three age groups were created (14–19 years (n = 68); 30–49 years (n = 82); 50–75 years (n = 40)).

### Results

Ninety-nine mild TBI patients and 91 control subjects were included (for demographic variables see Table I). There were no differences regarding age (t(188) = 0.835, ns), level of education (t(188) = 0.328, ns) and distribution of sexes between the two groups (χ² = 1.236, ns). The interval between neuropsychological assessment and injury was 12.8 days (SD = 4.8).

One way ANOVAs showed significant main effects of mild TBI on all cognitive variables, except for immediate recall score on the visual verbal learning test. No significant interactions were found between age and mild TBI on the selected cognitive variables (see Table II).

### Discussion

In this study on the neuropsychological effects of a single mild TBI in the sub-acute stage after injury, an overall effect was found of mild TBI on cognitive performance. Absence of interactions with age suggests that advanced age has no influence on the extent of mild neuropsychological disorder in the sub-acute stage after injury.

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

### Table I. Demographic characteristics of patients and control subjects.

<table>
<thead>
<tr>
<th>Variables</th>
<th>TBI (n = 99), M (SD; range)</th>
<th>Controls (n = 91), M (SD; range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>34.7 (16.0; 15–75)</td>
<td>36.5 (14.3; 14–74)</td>
</tr>
<tr>
<td>Level of education</td>
<td>4.0 (2.0; 1–8)</td>
<td>4.2 (1.8; 1–8)</td>
</tr>
<tr>
<td>Sex (m/f)</td>
<td>58/41</td>
<td>46/45</td>
</tr>
</tbody>
</table>

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

### Table II. Neuropsychological performance of mild TBI patients and control subjects.

<table>
<thead>
<tr>
<th>Variables</th>
<th>Mild TBI, M (SD; range)</th>
<th>Control group, M (SD; range)</th>
<th>Main effect, F(1, 188)</th>
<th>Group × age, F(2, 184)</th>
</tr>
</thead>
<tbody>
<tr>
<td>VLT tot</td>
<td>27.5 (6.6; 10–43)</td>
<td>28.8 (6.6; 11–43)</td>
<td>1.73, ns</td>
<td>0.64, ns</td>
</tr>
<tr>
<td>VLT recall</td>
<td>9.4 (3.1; 2–15)</td>
<td>10.9 (2.8; 4–15)</td>
<td>13.32**</td>
<td>2.06, ns</td>
</tr>
<tr>
<td>SCWT III</td>
<td>41.2 (14.3; 21.2–108.8)</td>
<td>35.1 (8.1; 22.2–67.7)</td>
<td>12.92**</td>
<td>0.49, ns</td>
</tr>
<tr>
<td>Coding</td>
<td>50.0 (11.1; 26–79)</td>
<td>54.6 (10.3; 28–77)</td>
<td>5.01*</td>
<td>1.51, ns</td>
</tr>
<tr>
<td>Fluency</td>
<td>22.7 (6.6; 8–39)</td>
<td>25.0 (6.1; 12–39)</td>
<td>5.97*</td>
<td>1.00, ns</td>
</tr>
</tbody>
</table>

*Group differences were tested using one-way ANOVAs. Interaction effects (age × group) were tested using a two-way ANOVA; See method section for age group explanation; **p < 0.001; *p < 0.05.*
possibility is that the Brain Reserve Capacity hypothesis proposed by Satz [16] 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 until now, the prognostic value of a single mild TBI is uncertain. According to the BRC theory, it was hypothesized that older patients would be more affected by a mild TBI than younger patients on their neuropsychological performance. Satz [16] 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 post-traumatic 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. Although no formal test of intelligence was included in the test battery, interactions were tested 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 discernible after sufficient time has elapsed. In support of this, there is now literature implicating TBI as a potential causative factor in Alzheimer’s disease [29]. Klein et al. [21] 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. Although their inclusion of moderate TBI makes generalization to a very mild TBI population problematic, a similar result was found in the sub-acute stage after mild TBI. These results suggest that a single mild TBI has only a static influence on the cognitive ageing process instead of a dynamic influence.

Rapoport and Feinstein [4], 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 [5]. Cognitive and behavioural consequences of TBI in older patients may be potentiated by pre-existing 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 co-morbidity, 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 sub-acute recovery period. A different constellation of age-related and neurological factors may well alter the picture.

References


