Improvement and prediction of memory and executive functions in patients admitted to a neurosurgery service with complicated and uncomplicated mild traumatic brain injury

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ACKNOWLEDGEMENTS

The authors thank all the participants who took part in the study. The authors declare that there is no conflict of interests or sources of financial support regarding the publication.

Abstract

Objectives: To compare neuropsychological performances between patients with and without intracranial abnormalities after mild traumatic brain injury (mTBI) and assess the relationship between demographics, injury severity, and self-reported symptom characteristics with improvements in memory and executive functions (8 weeks to 1-year post-injury). **Setting:** Inpatient/outpatient followed up at the Department of Physical Medicine and Rehabilitation, Oslo, Norway. **Participants:** Patients were divided into groups of complicated (n=73) or uncomplicated mTBI (n=77) based on intracranial findings on CT or MRI brain scans. **Design:** Prospective, longitudinal cohort study. **Main Measures:** Neuropsychological assessments of memory and executive functions, self-reports of post-concussion, depression, post-traumatic stress symptoms and general functioning at 8 weeks and 1-year post-injury. **Results:** Longitudinal data showed that patients with complicated and uncomplicated mTBI had similar cognitive performance and improvements. Hierarchical Linear Modeling (HLM) revealed that individuals with early PTSD and/or depressive symptoms performed worse on measures of Memory, and those with younger age (<40 years) and lower education (<12 years) performed worse on measures of Executive Functions. **Conclusion:** Findings are suggestive of a good cognitive outcome following complicated and uncomplicated mTBI. Early assessments of PTSD and depression seem useful in identifying those most vulnerable having poorer cognitive outcomes, providing further interventions that may affect emotional and cognitive recovery.

Key words: Post-concussion, recovery, post-traumatic stress, depression, neuropsychology.

INTRODUCTION

The existence of injury-severity differences in cognitive outcomes after a mild traumatic brain injury (mTBI) can provide valuable information in the clinical presentation and rehabilitation management. A substantial number of individuals sustain mTBI and the population-based incidence of mTBI is estimated to be above 600 per 100,000[1], whereas the annual incidence of hospital-treated mTBI is approximately 100-300 per 100,000.[1]

Based on the consciousness assessment with the most commonly used injury severity scale, Glasgow Coma scale (GCS), mTBI comprises 70 – 90% of traumatic brain injuries (TBI).[1,2] Most mTBI patients do not show trauma-related abnormalities on computed tomography (CT) scans and are termed as "uncomplicated" mTBI. "Complicated" mTBI can be used to refer to those with presence of intracranial injuries such as subarachnoid hemorrhage, intracranial contusions, or small extra-axial hematomas.[3,4] Studies of mTBI have shown intracranial pathology to range from 7 to 27% on CT scans.[5-7] However, 25 to 30% of mTBI patients with a normal CT scan are shown to have intracranial injuries on an MRI scan.[7,8] Some have argued that the distinction between "complicated" and "uncomplicated" might not be the best way to classify mTBI.[5,8-10] Studies have questioned the prognostic and clinical relevance of this distinction in determining post-traumatic complaints[8,10] and cognitive outcomes of mTBI,[5,10,11] although it might be an important indicator of neurological trauma and preexisting lesions.[12]

Neuropsychological research indicates that initial cognitive dysfunctions seen in patients with mTBI, compared to healthy controls, may resolve between 3 and 6 months following injury.[13-16] However, cognitive impairments in some cases with complicated mTBI can resemble impairments seen in patients with moderate TBI, even after 6 months.[4] Some neuropsychological studies (see Supplemental Digital Content) indicate greater cognitive deficits within <40 days post-injury in complicated mTBIs compared to uncomplicated mTBIs,[8,17,18] whereas others show no group differences in this early phase.[5,9,10] Longitudinal neuropsychological research has also yielded mixed results.[11,19,20] One study found no differences between complicated and uncomplicated mTBI groups in terms of memory functions in the acute phase and 1 year follow-up,[11] while others found memory deficits to be more pronounced in the complicated group at 1-year.[20] Surprisingly, one study showed a trend of poorer cognitive function and more symptoms over time within the uncomplicated mTBI group.[10] Meta-analyses of prospective samples of mTBI have found a moderate effect on neuropsychological test performance 1 to 7 days after injury and a negligible effect >90 days post-injury.[21,22] A review of cognitive prognosis after mTBI found various cognitive deficits (e.g., distractibility, attention, memory, processing speed) during the first two weeks after injury, but limited evidence that these deficits last longer than 3 months, with most cognitive deficits resolved in the longer term (>1 year post-injury).[23]A recent review indicates that some patients may remain chronically impaired into the post-acute phase after mTBI, but the size of this subgroup is debatable.[24] Previous studies have shown personal characteristics (e.g., socioeconomic status, cognitive reserve, age, education),[25-28] injury severity (e.g., post-traumatic amnesia),[29,30] and self-reported emotional and psychiatric symptoms (e.g., depression, anxiety, post-traumatic stress)[19,31-33] to be important to cognitive outcomes following mTBI.

In sum, neuropsychological outcome studies have mostly focused on a single follow-up in the early phase when comparing cognitive functions in complicated and uncomplicated mTBI.[5,8-10] Findings of previous studies addressing cognitive functions in both early and chronic phases (see Supplemental Digital Content) demonstrated contradictory findings, using small sample sizes with complicated mTBI (for example, 15[20], 27[11] and 31 patients[18]). Moreover, these studies have not used the components of age, education, and emotional distress (e.g., anxiety, depression, post-traumatic stress-, and post-concussion symptoms) in the modeling of cognitive outcome prediction. Therefore, the impetus for this longitudinal study was to conduct an evaluation of the impact of mTBI on a broad range of neuropsychological tests and self-reported measures during the first year in a large sample of patients admitted to a neurosurgery service following mTBI. Such data will allow an assessment of the relationship between demographics, injury severity, intracranial abnormalities (CT and MRI scans), self-reported symptom characteristics, and cognitive functioning, and will enable the comparison between patients with complicated and uncomplicated mTBI on cognitive improvements over time (8 weeks to 1-year post-injury). Based on the literature above, it was hypothesized that those with complicated mTBI would demonstrate poorer neuropsychological performance in the early phase at 8 weeks and show improvements over time, expecting no differences between complicated and uncomplicated mTBIs on neuropsychological measures at 1-year follow-up. The secondary aim was to determine which demographic, injury severity and self-reported symptom characteristics were associated with improvements in Memory and Executive Functions (8 weeks to 1-year post-injury).

METHOD

Study sample

The study was conducted at the Oslo University Hospital (OUH), Norway, including patients over a two-year period (September 2011 - September 2013). At the OUH there are two emergency departments. The city-center emergency department receives and treats patients with minor/mild injuries where clinical evaluations and CT-scans are performed, but has neither the facilities for extensive clinical observation nor the neurosurgical expertise. As a consequence, there is a low threshold for transferring patients to the Neurosurgery

Department for a neurosurgical evaluation and clinical observation (6-24 hours). Individuals consecutively admitted to the Neurosurgery Department with the International Classification of Diseases, Tenth Revision (ICD-10) diagnosis S06.0 – S06.9 (intracranial injuries) were recruited and followed up at the Department of Physical Medicine and Rehabilitation.[34] Mild TBI was defined as a Glasgow Coma Scale (GCS) score of 13 to 15 at hospitalization, less than 30 minutes loss of consciousness and posttraumatic amnesia (PTA) lasting less than 24 hours.[35] This study is a part of a larger mTBI project where the functional outcomes and MRI data have been published in previous studies.[34,36-38] The inclusion criteria were: (1) age 16 to 65 years, (2) injury occurring within 24 hours, and (3) adequate Norwegian language abilities to partake in neuropsychological testing. Exclusion criteria were previous brain injury or progressive neurological disease, contraindications for MRI (including pregnancy and claustrophobia), previous ICD-10 diagnosis of alcohol and/or narcotics dependence, and severe psychiatric disorder (e.g., psychotic or bipolar disorder diagnosed by a psychiatrist or psychologist).[36]

Procedure

Medical and clinical characteristics were based on data from hospital admission medical records during the acute hospital stay. At 1 to 2 weeks post-injury, patients who met the inclusion criteria received a telephone call with information regarding the study and were invited to participate in follow-ups at 8 weeks and 1-year post-injury. Both follow-ups included a medical examination, interviews, self-reports of symptoms and neuropsychological assessments. This study was approved by the Regional Committee for Medical Research Ethics in Southeast Norway (approval id 2010/1899) and completed in accordance with the Helsinki Declaration. Written consent was obtained from all participants.

Participants

A total of 223 patients admitted to the Neurosurgery Department agreed to participate. Figure 1 shows the inclusion procedure. Forty-two patients failed to show for the consultation at 8 weeks, 5 patients had no MRI scans and 26 patients were withdrawn. Thus, a total of 150 patients with mTBI were followed up at both time points (77 uncomplicated and 73 complicated). The group assigned as non-participants (n=73) did not significantly differ from the group of participants (n=150) regarding age (t (179)=-.220, p=.826), gender ($\chi^2(1)$=2.672, p=.102), employment status at time of injury ($\chi^2(1)$=.586, p=.444), PTA (t(178)=.236, p=.814), GCS (t(179)=-.903, p=.368), or the acute hospital length of stay (t(179)=-.186, p=.853). The group of non-participants did have significantly lower education compared with the participants ($\chi^2(1)$=6.070, p=.014).

[INSERT FIGURE 1 HERE]

Measures

Medical records were reviewed to collect demographical (age, gender, education, and employment) and medical data (GCS, PTA). The length of stay (LOS) corresponds to the number of days the patient remained hospitalized in the acute phase, from admission to discharge. Patients underwent a CT-scan of the head on admittance to the hospital.

MRI brain imaging was performed using a 3T whole-body MRI system (Signa HDxt, GE Medical Systems, Milwaukee, WI, USA). MRI data was obtained routinely at 4 weeks post injury, as part of a research protocol. This protocol included a 3D Fast Spoiled Gradient Echo (FSPGR) T1-weighted sequence that is used for morphometric assessments. Acquisition parameters were optimized to increase the gray/white matter contrast. In addition, a T2-weighted sequence and a T2 susceptibility-weighted angiography (SWAN) sequence were performed to depict hemorrhagic or other abnormalities. There was no major scanner upgrade in the study period. All patients' MRI data were evaluated with regard to extra-axial hemorrhage and parenchymal injury (contusion, intraparenchymal hematoma and diffuse axonal injury) by a board-certified neuroradiologist. Participants were divided into groups based on positive (complicated mTBI, n=73) or negative (uncomplicated mTBI, n=77) intracranial findings on CT or MRI brain scans.

Memory: The California Verbal Learning Test-II (CVLT-II; List A trials 1-5)[39] was used to assess learning and memory. This test measures explicit recall of 16 words presented over 5 trials (List A) and a delayed recall of the word list after 20 minutes. In this study, the sum of correctly recalled words (List A trials 1-5) and delayed recall were of interest. The Rey-Osterrieth Complex Figure Test (ROCF)[40] measures visual-spatial constructional ability and visual memory. The participant copies a complex figure and after a short (ca. 3 minutes) and longer delay (20-30 minutes) draws the same figure from memory. The ROCF was administered in a standardized way but only the delayed task was used in the present study. Neuropsychological raw scores were transformed to standardized scores according to age-corrected original normative data. Both the CVLT-II (List A)[39] and ROCF[40] are given by a *T*-score (*M*=50, *SD*=10). However, the CVLT-II delayed recall use *z*-scores (*M*=0, *SD*=1) but was transformed into a *T*-score before computing a Memory composite score.

Executive Functions: The Letter Fluency Task from the Delis-Kaplan Executive Function System (D-KEFS)[41] requires the participant to say as many words as possible in 60 seconds beginning with a specified letter, and was used as a measure of phonemic word fluency. The Color-Word Interference Test (CWIT, condition 3) from the D-KEFS requires the participant to name the color of the ink in which color words are written, and in the subsequent condition (CWIT, condition 4) the participant needs to switch between naming the color of the ink and reading color names. These conditions are considered to assess the executive functions of inhibition and mental flexibility (switching), respectively. The Letter-Number Sequencing from the Wechsler Adult Intelligence Scale Third Edition (WAIS-III)[42] requires the participant to repeat combinations of numbers and letters and arrange them with numbers in ascending order and letters in alphabetic order. This test assesses verbal working memory and divided attention. The subtasks scores of the D-KEFS[41] and WAIS-III[42] utilize scaled scores (M=10, SD=3).

Lack of motivation: The Rey Fifteen-Item Test (FIT) is a test used to assess symptom validity. The participant is shown 15 items for 10 seconds and is then requested to draw what they recall. In this study, a lack of motivation was defined as a score of ≤ 9. Four patients were excluded due to low scores on the FIT.

Self-reported measures at 8 weeks and 1-year: The Hospital Anxiety and Depression Scale (HADS) is a valid instrument for detecting symptoms of anxiety (HADS-A) or depression (HADS-D).[43] Each of the two subscales is made up of 7 items, with a maximum subscale score of 21. A subscale score above 7 indicates possible anxiety or depression. Participants were specifically asked about pre-existing anxiety and/or depression, which was rated as "yes" or "no", established at the assessment at 8 weeks post-injury.

The Posttraumatic Stress Symptoms-10 (PTSS-10) is a validated 10-item screening scale measuring the presence of post-traumatic stress symptoms, graded from 1 (never) to 7 (always), with a maximum score of 70.[44] The questionnaire has shown high internal consistency with a score above 35 suggestive for the diagnosis of posttraumatic stress syndrome.[44]

The Rivermead Post Concussion Symptoms Questionnaire (RPQ) is a 16-item self-report checklist designed to evaluate post-concussion symptoms (cognitive, emotional and somatic).[45] Each symptom is reported by its severity over the last 24 hours on a scale of 0 (not experienced at all) to 4 (a severe problem), with a maximum score of 64, excluding ratings of 1 (resolved symptoms).[45]

The Glasgow Outcome Scale-Extended (GOSE) is a structured interview to assess areas of independence, work, leisure activities, and participation in social life.[46] The GOSE scores represent the following: 1 = dead, 2 = vegetative state, 3 - 4 = lower/upper severe disability, 5 - 6 = lower/upper moderate disability, 7 - 8 = lower/upper good recovery.

Statistical analysis

A *t*-test and a chi-square test (χ^2) were used to examine differences in demographics and injury characteristics between the complicated and uncomplicated mTBI groups. An independent *t*-test was used to compare mTBI groups on neuropsychological measures at 8 weeks follow-up. In addition, equivalence testing was applied to assess that the two groups differ, using the *t*-test approach adopted from Stegner et al.[47] with Cohens d=0.2. The hypothesis for the first *t*-test (t_1) is that the uncomplicated group mean is 20% greater compared to the complicated group, and the hypothesis for the second *t*-test (t_2) is that the uncomplicated group mean is 20% lower. The hypothesis is rejected if the *t*-value (t_1, t_2) is greater than the critical value *t*-score at $t_{.05}$.

Memory (*T*-scores) and Executive Functions (scaled scores) composite scores were calculated as the mean of the age-corrected standardized scores within each domain. Composite scores were constructed to provide a broad view of domain functioning and to use the scores as dependent variables in Hierarchical Linear Modeling (HLM) analysis. Eight participants had missing scores on 3 neuropsychological measures at 8 weeks follow-up (ranging from 1 missing on Letter Fluency Task to 5 missing on ROCF) and 11 participants had missing scores on 5 neuropsychological measures at 1-year (ranging from 3 missing on ROCF to 5 missing on CWIT 4). These cases were assigned the sample's mean value for each measure.

HLM analysis was used to examine predictors for two separate models of Memory and Executive Functions. There were two time points (8 weeks and 1-year follow-ups). Covariates included in the models were as follows: gender, age, education, employment status at injury, acute GCS score, length of PTA, length of stay at emergency department, as well as self-reports (at 8 weeks) of post-traumatic stress (PTSS-10), depression (HADS), and general functioning (GOSE). The correlation between PTSS-10 and HADS scores was assessed with Pearson's correlation (PTSS-10 and HADS-total score r=0.84, p<.001; PTSS-10 and HADS-A r=0.80, p<.001; and PTSS-10 and HADS-D r=0.70, p<.001). Because of the high correlation between HADS-A and PTSS-10 (r >.70 cutoff for multicolinearity among predictors) and previous research suggesting that post-traumatic stress disorder (PTSD) is an important contributor to neuropsychological performance,[32] we chose to exclude HADS-A and include PTSS-10 as a covariate in the HLM analyses.

Covariate data were entered simultaneously as fixed effects. Continuous predictor variables were centralized with the total sample mean values and category predictor variables were given a reference point of 0 before being entered into the HLM. Because type of injury was classified into four categories it was not included in the HLM analyses. Statistically significant fixed effects on the Memory and the Executive Functions composite scores were then graphed across each of the time points. Main effects would indicate that the composite scores over time vary as a function of the predictor variable. The statistical significance was set at p<.05. Statistical analyses were performed using IBM SPSS, version 23 (SPSS Inc., Chicago, IL, United States).

RESULTS

Demographics, injury-related variables and self-reports of participants with mTBI are presented in Table 1. Participants were predominantly males with a high school education and a median age of 40 years (range 16 - 65). The two mTBI groups did not differ significantly regarding age, gender, education, or employment status (pre-injury and one year post-injury). Participants with complicated mTBI (n=73) were hospitalized significantly longer ($t(147)=-2.675$, $p<.008$). In the complicated mTBI group, location of focal lesions seen on MRI at 8 weeks (n=50) were in the frontal (n=33), temporal (n=28), parietal (n=14) and occipital (n=10) areas. Regional overlap of lesions was seen in 30 patients. Group differences existed for external type of injury (χ^2 (3, N=150)=9.98, $p<.05$). To determine if there was an association between type of injury and cognitive outcome, post hoc subgroup comparison using Tukey test showed that the assault group performed significantly worse on composite scores of Executive Functions at both 8 weeks and 1-year post-injury, compared to the road traffic accident group (ps<.05).

No significant group differences were seen on self-reported measures (RPQ, HADS, PTSS-10) or GOSE at 8 weeks or 1-year post-injury. The results showed that 9.3% of the participants experienced having anxiety and/or depression pre-injury, with non-significant difference between the mTBI groups (p=.648). Data on the RPQ were analyzed to see how many participants reported three or more remaining post-concussion symptoms, i.e. at least one cognitive, one emotional and one somatic symptom (scores >1).[48] At 8 weeks after injury, 55 (36.7%) participants reported three or more post-concussion symptoms. At 1-year follow-up, 60 (40%) participants reported three or more post-concussion symptoms.

[INSERT TABLE 1 HERE]

The means and standard deviations for neuropsychological test scores are presented in Table 2. The data for the 7 neuropsychological measures and the 2 composite scores assessed at 8 weeks were analyzed with *t*-tests and none of the comparisons between the complicated and uncomplicated mTBI groups proved to be significant (see Table 2). A total of 9 equivalency tests assessed neuropsychological functioning comparing individuals with complicated mTBI to those with uncomplicated mTBI. As shown in Table 2, the complicated group was equivalent to the uncomplicated on all neuropsychological measures.

[INSERT TABLE 2 HERE]

Demographic, injury severity and self-reported symptom covariates as predictors are presented in the models of the Memory (T-scores) and the Executive Functions (scaled scores) composite scores in Tables 3 and 4, respectively. Significant effects of time suggested that the Memory composite score increased from 50.0 (9.4) at 8 weeks to 53.4 (9.4) at 1-year, and the Executive Functions composite score increased from 10.2 (2.2) to 10.7 (2.2), *p*s < 0.001. Self-reported symptoms of depression and post-traumatic stress as well as education yielded statistically significant effects over time on the Memory composite scores. Participants who reported lower levels of depression (HADS-D; $p = 0.010$; Figure 2A) and of post-traumatic stress (PTSS-10; $p = 0.016$; Figure 2B) had better overall scores on Memory. Because of this result and assuming that a number of individuals with mTBI may suffer from anxiety without PTSD, we ran an additional HLM in the Memory model (not shown), including HADS-A and excluding PTSS-10, with the same covariates as above (see statistical analysis). The HADS-A was not statistically significant in this model (*B* (SE) = -0.22 (0.28); $p = 0.437$).

Age at injury was positively associated with the Executive Functions. Older individuals (p = 0.002; Figure 3A) and those with higher education (p = 0.002; Figure 3B) had better scores across the two time points. A mean-split procedure was used to generate separate lines in the figures.

[INSERT TABLES 3 AND 4 HERE]

[INSERT FIGURES 2 AND 3 HERE]

DISCUSSION

In this prospective study with follow-up of 150 patients admitted to a neurosurgery department with mTBI, it was hypothesized that those with complicated mTBI would demonstrate poorer neuropsychological performance (i.e., memory and executive functions) at 8 weeks after injury compared to uncomplicated mTBI. The present findings did not support this hypothesis and revealed that patients with complicated and uncomplicated mTBI did not differ in their neuropsychological performance in the short-term (8 weeks post injury) or long-term (1-year post injury) perspectives. Findings further demonstrated that neuropsychological performance improved significantly from 8 weeks to 1-year follow-up, but was within the “normal” or “average” range at both evaluations on all tests. The best predictors of Memory improvements were early subjective symptoms of post-traumatic stress and depression followed by education, while the best predictors of Executive Functions improvements were age and education. However, none of the injury severity variables (e.g., GCS, PTA, length of stay in emergency department) predicted cognitive improvements.

Current findings are consistent with previous research which found no differences on neuropsychological measures between complicated and uncomplicated mTBI during the first two months after injury in different samples of patients recruited from the Emergency Department and outpatient clinics,[5,9,10,20] showing very small to medium effect sizes.[9] Furthermore, other longitudinal neuropsychological studies found no differences between the complicated and uncomplicated mTBI groups in longer term follow-ups (>6 months).[11,20]

In contrast to our findings, other research suggests that the neurocognitive impact (small-to-moderate effect size)[3] is most significant in the early period (<40 days) following complicated mTBI,[3,4,8,17] specially on measures of processing speed and recognition memory,[4] attention,[8] and verbal fluency and mental flexibility.[3,17] One study showed that patients with complicated mTBI, compared to matched controls, had a slower speed of processing at 1 week post-injury which had resolved by 3 months, with no further improvements on measures at 6 and 12 months.[49] There is also evidence suggesting that patients with complicated mTBI have poorer cognitive performance at 6 months post-injury.[50] Discrepancies of findings with regard to the mTBI severity (complicated versus uncomplicated) and cognitive outcomes may partly be due to differences in the timing and selection of neuropsychological measures, definition of mTBI, variations in sample sizes, and selection of brain scans (CT/MRI) for the detection of complicated mTBI. This study included only patients in need of neurosurgery services and our sample may therefore represent a 'severe' selection of mTBI patients. It is unlikely that pre-injury functioning influenced present findings as estimates of premorbid levels (education, employment) suggest no group differences. Other studies found no differences on pre-injury IQ functioning[9] or education[5,10,18,20] between complicated and uncomplicated mTBIs, though this is not supported by all studies.[8]

The distinction of complicated vs. uncomplicated mTBI remains controversial. Our findings contradict its clinical relevance in establishing treatment plans because of group equivalence.

This study supports the importance of deciding treatment goals and plans based on the individual's specific TBI-related cognitive and emotional challenges, regardless of intracranial injuries. Importantly, results indicate more problems over time (RPQ, PTSS-10, HADS) and raises the question of whether many of the individuals were in need of tailored treatment. Assessment of anxiety disorders into routine healthcare could be used to identify the presence of PTSD in individuals who might benefit from trauma treatment and intensive follow-up. Type of injury, for example assault, may also dictate treatment as this subgroup might have executive difficulties (e.g., response inhibition) and benefit from early guidance to identify problems in daily life. This is in line with other researchers that have argued that complicated and uncomplicated mTBI groups represent a broad spectrum of injury and cognitive and functional outcomes.[9,10,18] Panenka and colleagues[9] suggest that it may also be more useful to identify subgroups with different types of intracranial pathology (e.g., diffuse axonal injury, contusions) to understand the complexity of mTBI severity.

Our findings indicate that early traumatic reactions (i.e., sleep problems, nightmares, intense fear, and muscular tension) and depression symptoms predicted memory outcomes. The association of anxiety symptoms with memory was only found with an analysis including the PTSS-10 and not the HADS-A. This indicated that memory difficulties were not common for all anxiety participants but seen only for those with trauma-related reactions. This finding may suggest that memory problems in PTSD might be associated with pathological brain alteration. We should note, however, that this result may not be solely specific to PTSD, but to other anxiety disorders and more research is needed. There is good evidence that PTSD impacts areas of learning and recalling new information,[32,51] consistent with current results. A recent study on military populations provides some insight into the longitudinal relationship of post-traumatic stress symptoms, mTBI and neurocognitive deficits, showing that increase in post-traumatic stress symptoms may sustain verbal and visual memory deficits over long time (>7 years).[52] Similarly, post-traumatic stress and depression symptomatology following mTBI in deployed soldiers was associated with neuropsychological deficits (e.g., simple reaction time, learning/recalling digit-symbol pairs) as well as somatic health-related functional impairment.[32]

The results from this study illustrate that older patients (41-65 years) and those with higher level of education (>12 years) seem to exhibit better executive functions, consistent with recent studies showing positive effects of education, intelligence and cognitive reserve on cognition after TBI.[25,26] Our finding may be explained by older age interacting with higher educational level and probably with higher work demands. Studies have shown that there is not a consistent relationship between age and cognitive outcome after mTBI.[28,53] One study found that older adults (>65 years) with mTBI performed worse on measures of memory and attention compared with healthy matched controls at 3 months post-injury,[28] while another study suggest that cognitive outcomes after uncomplicated mTBI are similar in adults over 55 years and healthy older adults.[53]

In present study, scores on measures of Memory and Executive functions were in the normal range, based on healthy standardization samples. By examining Figures 2 and 3, this also applied for the subgroups with higher scores on PTSS-10 and HADS-D, younger age and lower education. These data suggest these factors influence outcome but may not manifest with cognitive dysfunction below normal range. One caveat of this study is that healthy matched controls were not included for comparisons, making it impossible to know whether change in neuropsychological function is attributable to genuine improvement or simply reflects practice effects. Studies have demonstrated that healthy controls can exhibit higher IQ[20] and better neuropsychological functioning[11] when compared to patients with complicated mTBI, although others did not found that trauma controls differed from those with mTBIs in regards to cognition.[16,31]

The strength of this study is the large sample size in this area of brain research and neuropsychological assessment. This study adhered strictly to the American Congress of Rehabilitation Medicine[35] criteria of mTBI and solely included patients with documented injury from the Neurosurgery Department. This may restrict the generalizability to the admitted patients and not to the general mTBI population in the emergency department. We excluded patients with previous brain injury, progressive neurological disease, severe substance abuse and psychiatric disorders and limited the inclusion to patients aged 16 to 65 years. However, it is possible that some of the individuals had pre-existing PTSD, but this information was not collected. We only asked about pre-existing anxiety and/or depression and excluded patients with severe psychiatric disorders such as psychotic or bipolar disorder diagnosed by a psychiatrist or psychologist.[34]

In conclusion, patients with complicated and uncomplicated mTBI had similar cognitive performance and improvements (8 weeks to 1-year post-injury). However, identifying symptomatic individuals early after injury seems important and data show that there is potential for cognitive improvement for those individuals in the long-term. Middle age individuals and those with higher education might have cognitive reserve capacity that can help them to better compensate for the consequences of mTBI. Conditions of PTSD and depression may complicate the health care management in individual cases. Future studies should document early tailored interventions (either medication or psychotherapy) and include assessments of coping techniques and resilience to see how these may affect cognitive outcomes in the long-term perspective.

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Table 1. Differences in demographics, injury-related and self-reported variables by MTBI group.

	Total MTBI (*n*=150) M (SD, range)	Complicated MTBI (*n*=73) M (SD, range)	Uncomplicated MTBI (*n*=77) M (SD, range)	*p*
Age	39.8 (14.2, 16-65)	39.9 (14.8, 16-65)	39.7 (13.7, 16-65)	.935
Males	93 (62.0 %)	49 (67.1 %)	44 (57.1 %)	.208
Education > 12 yrs	80 (53.3 %)	35 (47.9 %)	45 (58.4 %)	.198
Employment preinjury	122 (81.3 %)	61 (83.6 %)	61 (79.2 %)	.495
Employment 1-year	118 (78.7 %)	56 (76.7 %)	62 (80.5 %)	.569
TBI severity				
GCS on admission	14.7 (0.5, 13-15)	14.7 (0.5, 13-15)	14.7 (0.5, 13-15)	.849
PTA (hours)	3.7 (5.9, 0-29)	4.6 (6.3, 0-29)[a]	2.8 (5.4, 0-24)	.064
LOS (days)	2.4 (2.4, 1-16)	2.9 (2.7, 1-16)[b]	1.9 (2.0, 1-12)	.008
Brain scans				
CT intracranial findings	53 (35.3 %)	53	0	
CT isolated skull fractures	8 (5.3 %)	8	0	
MRI intracranial findings	50 (33.3 %)	50	0	
External type of injury				
Road traffic accident	59 (39.3 %)	21 (28.8 %)	38 (49.3 %)	.019
Fall	59 (39.3 %)	37 (50.7 %)	22 (28.6 %)	
Assault	18 (12 %)	10 (13.7 %)	8 (10.4 %)	
Other	14 (9.4)	5 (6.8 %)	9 (11.7 %)	

Self-reports				
RPQ at 8 weeks	11.8 (12.4)	11.1 (11.5)	12.3 (13.3)	.564
RPQ at 1-year	12.8 (13.6)	12.8 (14.1)	12.7 (13.2)	.952
PTSS-10 at 8 weeks	20.8 (11.5)	20.8 (11.9)	20.9 (11.3)	.957
PTSS-10 at 1-year	25.9 (17.8)	26.7 (19.0)	25.0 (16.7)	.564
HADS Anxiety at 8 weeks	4.7 (3.9)	4.8 (4.2)	4.7 (3.6)	.869
HADS Anxiety at 1-year	5.2 (4.0)	5.0 (4.2)	5.5 (3.7)	.391
HADS Depression at 8 weeks	2.7 (3.1)	2.7 (3.0)	2.8 (3.2)	.734
HADS Depression at 1-year	2.9 (3.2)	2.7 (3.0)	3.1 (3.4)	.422
GOSE at 8 weeks	6.7 (0.9)	6.8 (0.9)	6.7 (0.9)	.743
GOSE at 1-year	7.2 (0.8)	7.2 (0.9)	7.2 (0.8)	.925

Note. Complicated = presence of intracranial abnormalities on CT/MRI scans; Uncomplicated = absence of intracranial abnormalities on CT/MRI scans; GCS = Glasgow Coma Scale; PTA = Post-traumatic amnesia; ICD-10 = International Classification of Diseases; RPQ = The Rivermead Post Concussion Symptoms Questionnaire; PTSS-10 = The Posttraumatic stress symptoms-10; HADS = The Hospital Anxiety and Depression Scale; GOSE = The Glasgow Outcome Scale-Extended.

M = mean; *SD* = standard deviation.

[a] One case excluded with PTA of 72 hours.

[b] One case excluded with length of stay 31 days.

Table 2. Differences in mean neuropsychological scores (age-corrected) by MTBI group admitted to a neurosurgery service.

	Complicated MTBI (n = 73)		Uncomplicated MTBI (n = 77)		*t*-test 8 weeks	Equivalency testing values between groups at 8 weeks #		
	8 weeks	1-year	8 weeks	1-year		Critical value		
Neuropsychological tests	*M (SD)*	*M (SD)*	*M (SD)*	*M (SD)*	p	$t_{.05}$	t_1	t_2
Memory Composite Score	**49.4 (8.9)**	**52.5 (8.6)**	**50.5 (9.9)**	**54.4 (10.0)**	**.444**	1.65	5.84	-7.27
CVLT-II trials 1-5 *T*-score	52.3 (10.1)	54.0 (10.9)	54.1 (10.9)	55.7 (10.6)	.294	1.65	5.38	-7.77
CVLT-II Delayed Recall *T*-score	51.3 (10.2)	53.2 (9.0)	52.1 (10.4)	55.1 (10.0)	.616	1.65	6.04	-7.08
ROCF Delayed Recall *T*-score	44.6 (14.2)	50.6 (14.1)	45.5 (14.3)	52.9 (14.2)	.698	1.65	5.97	-7.14
Executive Functions Composite Score	**10.1 (2.2)**	**10.7 (2.1)**	**10.2 (2.2)**	**10.7 (2.3)**	**.649**	1.65	5.40	-5.96
Letter Fluency Test scaled score	10.9 (3.7)	11.9 (3.8)	11.2 (3.8)	11.9 (3.8)	.605	1.65	4.85	-6.52
Letter-Number Sequencing scaled score	9.6 (2.8)	9.9 (2.6)	9.6 (2.9)	9.6 (2.7)	.995	1.65	5.68	-5.68
CWIT 3 scaled score	10.1 (3.2)	10.9 (2.5)	10.2 (2.7)	10.8 (2.6)	.714	1.65	5.40	-5.96
CWIT 4 scaled score	9.8 (2.8)	10.2 (3.0)	10.0 (2.7)	10.5 (2.7)	.715	1.65	5.13	-6.24

Note. Complicated = presence of intracranial abnormalities on CT/MRI scans; Uncomplicated = absence of intracranial abnormalities on CT/MRI scans; CVLT-II = California Verbal Learning Test-II; ROCF = Rey-Osterrieth Complex Figure Test; CWIT = Color-Word Interference Test.

Equivalence can be concluded if absolute values of both t_1 and t_2 are greater than the $t_{.05}$ critical value.

Table 3. Predictors of Memory trajectories at 8 weeks and 1 year after MTBI

Fixed effect	*B* (SE)	*t*	*p*	*95 % Confidence Interval*	
				Upper	Lower
Intercept	48.73 (1.24)	39.42	***0.001	46.41	51.23
Time	3.33 (0.50)	6.82	***0.001	2.41	4.38
Gender (male)#	-0.59 (1.47)	-0.40	0.690	-3.79	1.95
Age at Injury	0.06 (0.05)	1.19	0.238	-0.03	0.15
Education (<12 years)#	3.26 (1.41)	2.31	*0.022	0.70	6.25
Employment at Injury (no)#	0.54 (1.83)	0.30	0.768	-4.17	3.01
Glasgow Coma Scale	2.23 (1.36)	1.64	0.102	-0.34	4.99
Posttraumatic Amnesia	0.16 (0.13)	1.31	0.191	-0.08	0.40
Length of Stay Emergency dep.	0.04 (0.28)	0.14	0.889	-0.55	0.54
Rivermead PCQ	-0.10 (0.11)	-0.90	0.370	-0.30	0.14
Posttraumatic Stress Symptoms-10	-0.30 (0.12)	-2.45	*0.016	-0.55	-0.09
HADS Depression subscale	0.86 (0.33)	2.60	**0.010	0.23	1.54
Glasgow Outcome Scale Extended	0.71 (0.87)	0.82	0.415	-1.16	2.34

Note: # Reference group.

Table 4. Predictors of Executive Functions trajectories at 8 weeks and 1 year after MTBI

Fixed effect	*B* (SE)	*t*	*p*	*95 % Confidence Interval*	
				Upper	Lower
Intercept	9.48 (0.30)	32.00	***0.001	8.91	10.09
Time	0.57 (0.10)	5.71	***0.001	0.38	0.77
Gender (male)#	0.52 (0.35)	1.46	0.148	-0.28	1.12
Age at Injury	0.04 (0.01)	3.21	**0.002	0.01	0.06
Education (<12 years)#	1.05 (0.34)	3.10	**0.002	0.43	1.78
Employment at Injury (no)#	0.39 (0.44)	0.87	0.384	-1.28	0.47
Glasgow Coma Scale	-0.02 (0.33)	-0.06	0.954	-0.66	0.64
Posttraumatic Amnesia	0.02 (0.03)	0.69	0.490	-0.04	0.08
Length of Stay Emergency dep.	0.04 (0.07)	0.68	0.501	-0.10	0.17
Rivermead PCQ	-0.02 (0.03)	-0.75	0.455	-0.06	0.05
Posttraumatic Stress Symptoms-10	-0.02 (0.03)	-0.82	0.412	-0.09	0.02
HADS Depression subscale	0.05 (0.08)	0.62	0.535	-0.11	0.21
Glasgow Outcome Scale Extended	0.22 (0.21)	1.03	0.304	-0.17	0.68

Note: # Reference group.

Figure titles.

Figure 1.
Flow diagram of the inclusion procedure and participants withdrawing.

Figure 2.
Memory improvement trajectories for participants with scores under and over the mean on HADS-D (A) and PTSS-10 (B). Dots and lines are means and error bars are standard errors.

Figure 3.
Executive Functions improvement trajectories for age (A) and education (B). Dots and lines are means and error bars are standard errors.

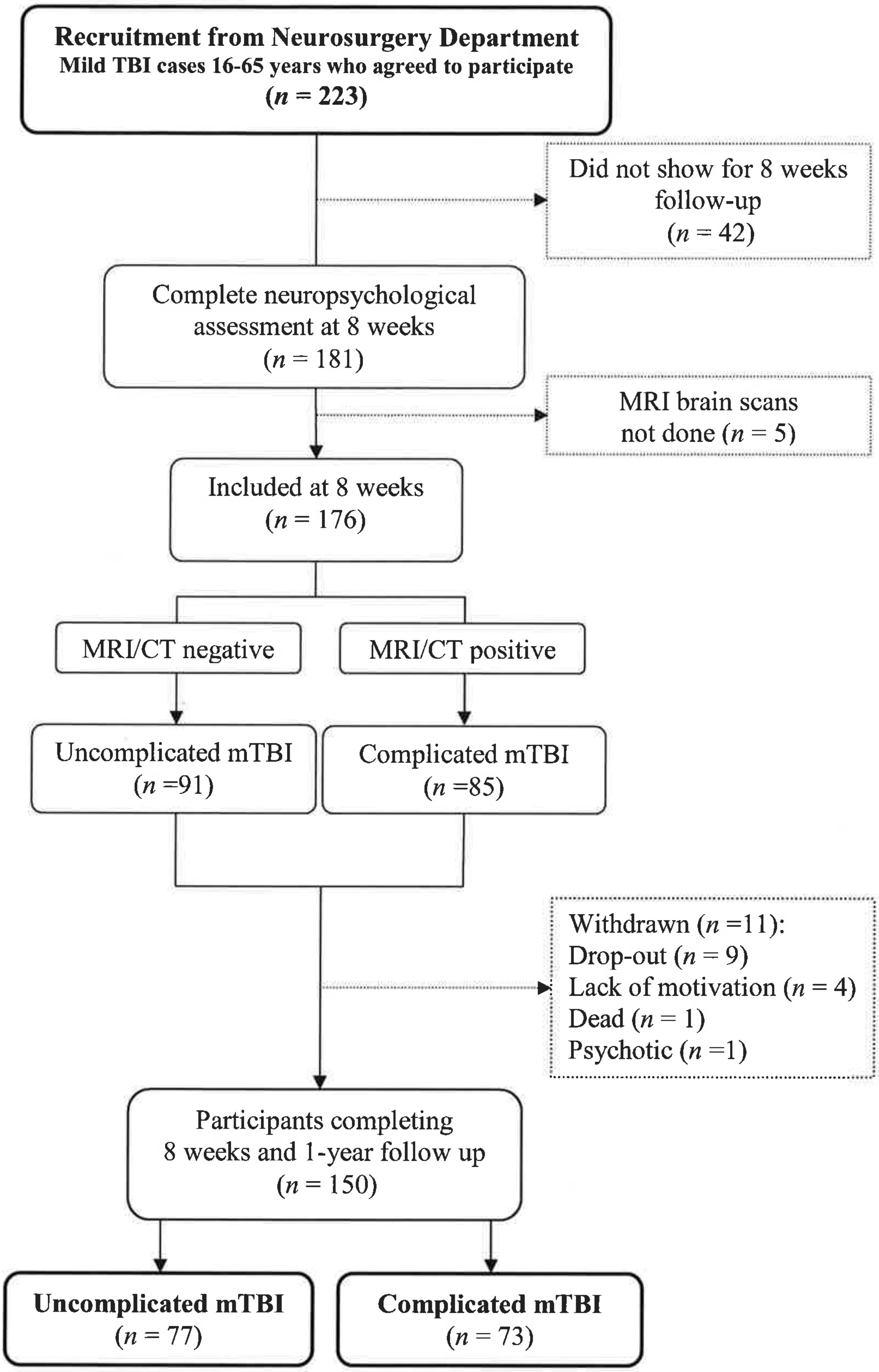
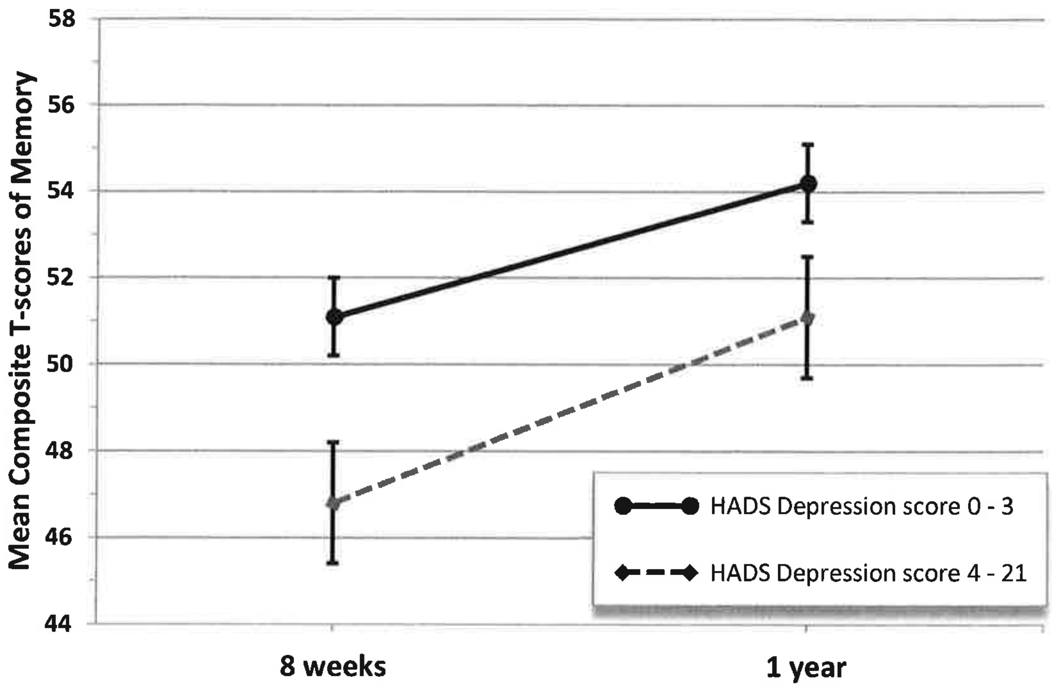


Figure 1. Flow diagram of the inclusion procedure and participants withdrawing.

Figure 2. Memory improvement trajectories for participants with scores under and over the mean on HADS (A) and PTSS (B). Dots and lines are means and error bars are standard errors.

A.



B.

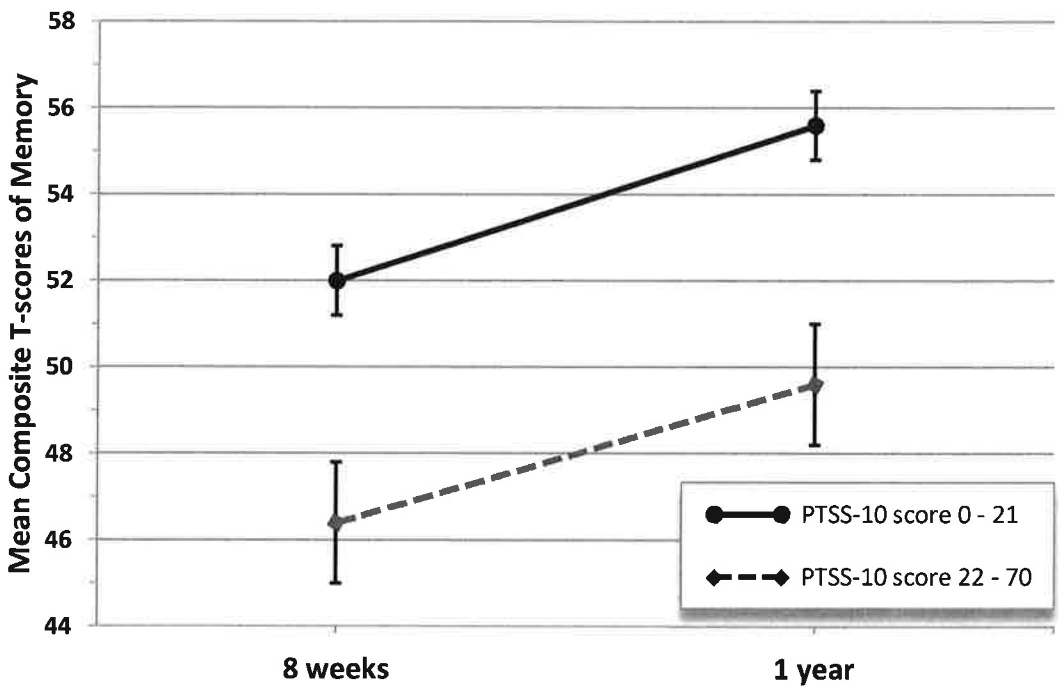
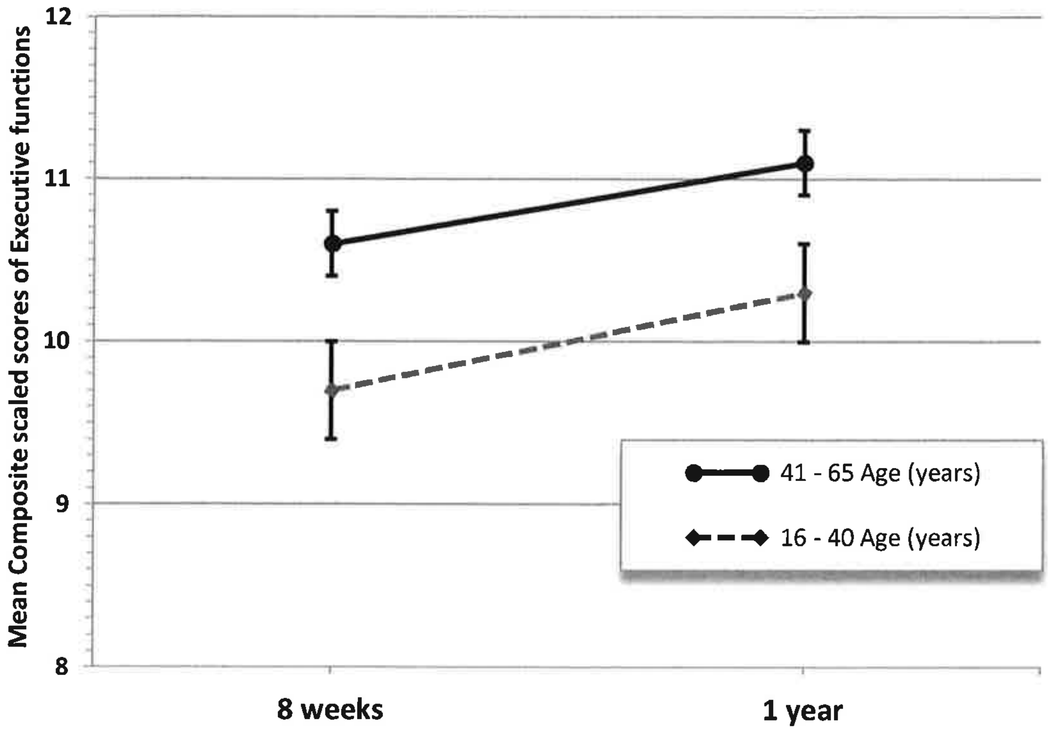
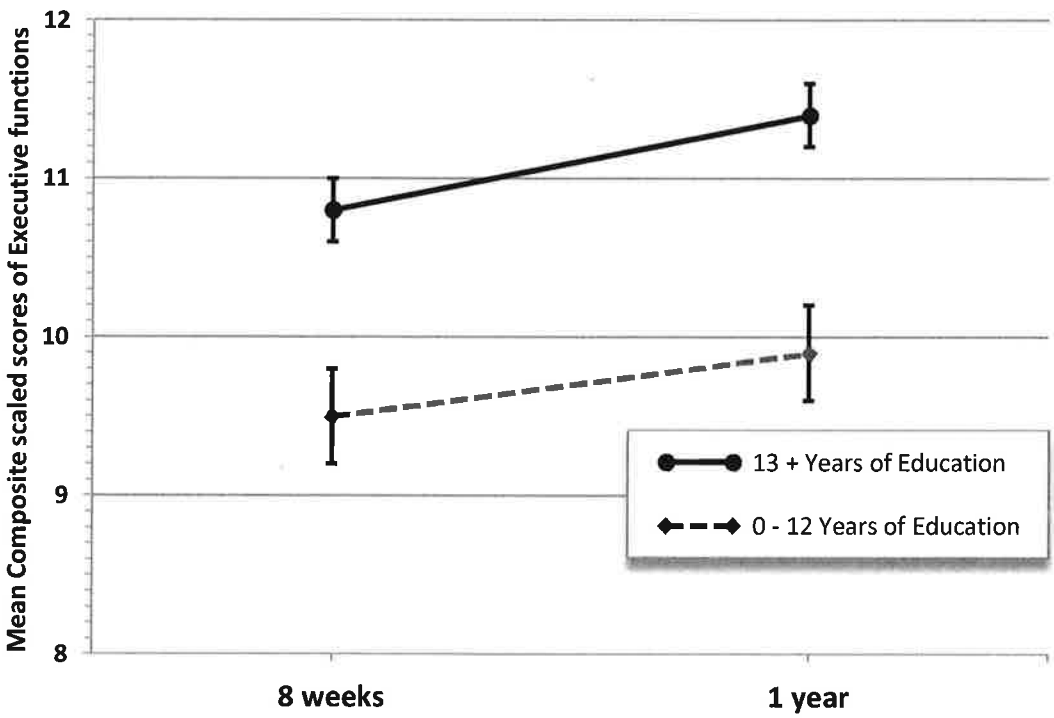


Figure 3. Executive Functions improvement trajectories for age (A) and education (B). Dots and lines are means and error bars are standard errors.

A.



B.



Supplemental Digital Content.

Neuropsychological (NP) outcome studies of complicated and uncomplicated mild traumatic brain injury (mTBI) in adults

First author	Year	Aim	Inclusion criteria	Total mTBI N	Timing of neuropsychological tests	Imaging method: % intracranial abnormalities	Main results on neuropsychological (NP) tests
de Guise [5]	2010	Compare the acute clinical profile (neurological examination, post-concussive symptoms and cognitive assessment) of uncomplicated and complicated mTBI	Patients with mTBI followed in an ambulatory outpatient TBI clinic	176	2 weeks post-injury	CT after arrival to emergency room: 26%	No significant differences on NP tests between patients with uncomplicated and complicated mTBI
Hughes [8]	2004	Describe MRI abnormalities and whether MRI provides predictive information about impairment	Patients aged 18-60 years at emergency department with mTBI	80	Within 72 h	MRI between 24-72 h after injury: 33%	Significant difference for attention comparing patients with normal and abnormal MRI scans
Iverson [3]	2006	Examine the effects of day-of-injury intra-cranial abnormalities on short-term NP outcome using matched mTBI groups	Patients aged 18-64 derived from an archival database, GCS 13-15	100	Within 14 days (average 3-5 days post-injury)	CT on admission: 50%	20-30% of complicated patients significantly worse on some tests (attention, memory, executive function), but mTBI groups showed more similar than dissimilar NP performance.
Iverson [10]	2012	Compare acute outcome following complicated versus uncomplicated mTBI using NP and self-reported measures	Patients aged 16-46 years presented to emergency department with mTBI	47	3-4 weeks after injury	CT within 24 h or MRI 3 weeks after injury: 28%	No significant differences between groups on NP or self-reported measures. Trends toward better NP performance and fewer symptoms in the complicated mTBI group

Lange [17]	2009	Compare the acute NP functioning of patients following complicated and uncomplicated mTBI	Patients selected and matched from database of 465 patients with GCS 13-15 from trauma service clinical pathway	66	< 7 days post-injury	CT on the day of injury: 30% (20 selected patients)	Significant differences on 3 of 13 NP measures during acute recovery (complicated mTBI worse)
Lee [11]	2008	Compare acute focal lesions on CT and MR scans with NP outcomes	Patients identified by Emergency Department staff. GCS 13-15	36	2 weeks, 1 month and 1 year after injury	CT at admission: 50% MRI: 75%	Intracranial findings did not predict NP functions at any stage. mTBI groups performed significantly poorer than healthy controls (n=18) on tasks of memory
Panenka [9]	2015	Examine whether intracranial abnormalities after mTBI are associated with worse subacute outcomes as measured by NP testing, symptom ratings, and diffusion tensor imaging	Patients aged 19-55 years admitted to emergency department (selected from 170 patients enrolled in a larger study)	62	6-8 weeks post injury	CT day-of-injury and MRI 6-8 weeks post-injury: 50%	No statistically significant differences between mTBI groups on NP tests
Tayim [20]	2016	Evaluate episodic memory in patients with mTBI	Patients aged 18-60 years admitted to emergency department with mTBI	92	1 month and 12 months post TBI	CT or MRI at the time of injury: 19%	Uncomplicated mTBI improved over time in encoding of verbal information while the complicated mTBI worsened over time
Veeramuthu [18]	2017	Evaluate the extent of persistent NP impairment in patients with complicated versus uncomplicated mTBI	Patients aged 18-60 years admitted to emergency department with mTBI	61	On admission after full GCS recovery and at 6 months follow up	CT after admission to emergency department: 66%	A trend of poorer NP performance among complicated mTBI during admission

Williams [4]	1990	Compare NP outcome in three groups with TBI	Patients aged 16-40 years with GCS 9-15 admitted to neurosurgery service	215	After resolution of PTA	CT on initial hospitalization: complicated mTBI 36% (n=77) and moderate TBI 28% (n=60)	Complicated mTBI and moderate TBI more NP impaired compared to uncomplicated on tests of verbal fluency, information processing, and recognition memory

Note. GCS = Glasgow Coma Scale; PTA = Post-traumatic amnesia; NP = Neuropsychological.