Assessment of memory functioning over two years following severe childhood traumatic brain injury: results of the TGE cohort.

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Running head: Memory following severe childhood brain injury

Abstract

The aims of this study were (1) to prospectively measure memory functioning following severe childhood Traumatic Brain Injury (TBI), and its evolution over 2 years; (2) to assess demographic and medical factors associated with memory function and recovery; (3) to explore relations between memory and other TBI outcomes.

Methods: Children (aged 0-15 years; *n*=65) consecutively admitted in a single trauma centre over a 3-year period, who survived severe non-inflicted TBI, were included in a prospective longitudinal study. Memory was assessed in 38 children aged 5-15 years at injury, using the Children's Memory Scale at 3, 12, and 24-months post-injury.

Results: Mean general memory score was low at 3 months (M=90.2, SD=20.3) but within the normal range at 12 and 24 months (M=100.6, SD=23.1 and M=108.6, SD=24.1, respectively), with high variability. Improvement was stronger for immediate visual memory than for other memory indices. Lower general memory score was associated with higher injury severity, lower intellectual ability and functional status, higher overall disability, and ongoing education.

Conclusion: Memory functioning is highly variable following severe childhood TBI, related to injury severity and functional, cognitive and educational outcomes; improvement is significant during the first-year post-injury, but varies according to the type of memory.

Keywords: severe traumatic brain injury, memory, outcome, longitudinal cohort study, child, adolescent, educational outcome.

Introduction

Traumatic Brain Injury (TBI) is the main cause of mortality and long-standing disability in children (1–3). According to a recent review (4), annual incidence of childhood TBI treated in emergency departments is around 691 per 100 000 in developed countries, with 3-7% of severe injuries (5).

TBI occurs in a context of brain immaturity and ongoing development of brain functions. Besides obvious deficits or loss of previously acquired abilities observed shortly post-injury, new deficits can emerge over time, as the child does not make age-expected acquisitions. Those deficits can remain unnoticed as long as the theoretical age of acquisition of a particular function or skill is not reached (6).

Severe paediatric TBI, defined by a Paediatric Glasgow Coma Scale (Ped-GCS) Score ≤ 8 (7), causes severe and long-standing impairments. Overall, severe TBI often results in impairments in children’s sensory-motor functioning, most often hemiparesis and cerebellar dysfunction, at least in the initial phase (8), and in a number of cognitive, behavioural, emotional and social functioning deficits, including deficits in language, visual-spatial skills, processing speed, memory, attention, working memory, and executive functioning (9–14). According to a meta-analysis, TBI severity is a major factor influencing outcomes in all cognitive domains (9). Those deficits in turn impact educational achievement (15–17) and autonomy and participation (17–19).

Research in the domain of outcomes following childhood brain injury tends to support evidence for some degree of plasticity, but also for early brain vulnerability, especially in the cognitive and behavioural domains, with more severe deficits following early compared to later injury. This is even more pronounced in children who sustained severe injuries, supporting the concept of the “double hazard model” which postulates an interaction (potentiation) of age at injury and injury severity (6,11,16,20–22). In most studies to date, outcomes have been reported in samples of children with TBI of various degrees of severity (mild to severe), with relatively small numbers of children with severe injuries, as severe TBI has a relatively low incidence compared to mild /moderate TBI (5).

It remains necessary to better understand the deficits caused by early brain lesions, and their evolution over time, in order to better anticipate patients' long-term needs and improve the care and interventions implemented for this population. A state of Chronic Brain Injury (CBI) as a lifelong condition after TBI, has been defined in the Gavelston Brain Injury Conference in 2012 (23). The frequency of an "invisible handicap" after TBI seems even higher in the paediatric than in the adult population (16,17).

Memory, defined as the persistence of the information learned over time, allowing its appropriate subsequent reuse, is a complex and dynamic process, divided into four stages: encoding, storage, consolidation and recall. Each stage can be involved in visual and verbal, immediate and delayed modalities, and those processes interact with other cognitive functions, such as executive functions, attention, and intellectual ability (24). Memory develops throughout childhood and adolescence and is essential for any learning, with obvious implication, among other domains of everyday life, in the child's education and school functioning. Tulving describes a sequential process for the development of memory, from procedural memory to episodic memory (25–27). Procedural memory abilities tend to mature earlier in the lifespan, while episodic recall ability matures at a later stage in life (25–27).

Numerous studies report that memory skills are impaired following childhood TBI of all severity, with a major repercussion on verbal and visual-spatial memory (14), working memory (28–30), and autobiographical memory (31,32). Recent studies suggest that TBI alters neuronal structures, including those supporting memory functioning and memory strategies, such as hippocampus, temporal lobe and prefrontal cortex (11,33–36). However, it remains difficult to know which type, or phase of memory is the most impacted by early TBI (36). Memory deficits after childhood TBI can also be confounded by multiple factors, such as behavioural or language impairments and should be screened systematically.

Memory difficulties are frequent after childhood TBI. In adults, memory complaints after severe TBI are the most frequent complaint in self-reports, and memory is the third most impaired skill in formal assessments (37).

Overall, memory impairment is reported to be more severe following severe (compared to mild or moderate) TBI, when compared with healthy matched controls (22), or with controls who sustained an orthopaedic injury (38). Severe TBI has been found to be responsible for lower performance in immediate and delayed verbal memory (9,39), visual memory (9), working memory (13,28), episodic autobiographical memory (31), and prospective memory (40–43). Visual memory seems to be more resistant to severe TBI than verbal memory, especially several years post-injury, but this could depend on the neural subtracts affected (9,11).

In addition to injury severity, many other factors may negatively influence memory functioning following childhood TBI, such as younger age at injury, (but not in all studies, see (11) for a review), older age at assessment (44), lower pre-injury level of education and presence of pre-injury learning difficulties (14), lower pre-injury level of child’s social abilities and lower socio-economic family background (45,46). Other authors found an effect of longer time since injury, lack of exposure to learning opportunities, or lack of medical treatments/procedures (including rehabilitation) (9,45).

Regarding studies who focused exclusively on children with severe TBI, age at injury was not related to autobiographical memory impairment, but it has been suggested that the deficit in recall of episodic details and in visual-spatial memory worsened in time for children and adolescents (31,47). Memory impairment has also been found to be related to lower intellectual ability (31).

Therefore, the primary aim of the present study was to prospectively assess memory functioning and its evolution over 2 years following severe childhood TBI. Secondary aims were to assess demographic and medical / severity factors associated with memory function, as well as associations between memory performance and other TBI outcomes, including overall level of disability, intellectual ability, functional and educational outcomes.

Methods

The present work is part of a larger prospective longitudinal study [TGE cohort: Traumatisme Grave de l'Enfant, i.e. Severe Childhood Trauma (48)] initiated at the Paris 5 University Hospital Necker Enfants Malades and conducted in the Rehabilitation Department for Children with Acquired Neurological Injury in the Saint Maurice Hospitals, aiming at determining overall and specific outcomes following severe childhood TBI.

Patients

Participants were children aged 0-15 years consecutively admitted to the paediatric neurosurgical intensive care unit (ICU) of the Necker Enfants Malades Hospital over a three-year period, within the first 6 hours following severe accidental TBI. Eighty-one children were included at the acute stage of TBI, defined as Glasgow Coma Scale (GCS) score ≤8 (7) at admission and/or an Injury Severity Score (ISS) > 16 (49). Causes of TBI were motor vehicle accidents and falls. Exclusion criteria were absence of vital signs upon admission, non-accidental head injury and a previous history of diagnosed neurological, psychiatric or learning disorders. Of the 81 children initially enrolled, 16 died during acute care, leaving 65 children available for follow-up. All children received treatment according to international guidelines for the management of severe TBI in the paediatric neurosurgical ICU of a regional paediatric trauma centre (50), and most children (83%) required and received multidisciplinary rehabilitation after acute care. Follow-up comprised serial comprehensive medical and neuropsychological assessments at 3, 12 and 24-months post-injury. The study was approved by the local ethics committee and all parents gave their informed written consent for this observational study.

Among the 65 survivors, 24 (37%) were younger than 5 years at 3-months post-injury, and/or were in a minimally responsive state, incompatible with neuropsychological assessment. In addition, three (5%) children had missing data on at least one of the memory assessments. Thus, the analysis sample was composed of 38 participants, as indicated in **Figure 1**.

< Insert figure 1 here >

Measures

Demographic, environmental and pre-injury history

Information on the child's pre-injury history and functioning was collected, such as family environment, parental education level (classified into two categories: medium/high: at least one parent graduated from high school; low: none of the parents reached high school graduation) and modalities of previous education: we recorded if the child had stayed back one year or had difficulty and/or extra help at school, according to parental reports.

Injury characteristics

We recorded the following markers of initial TBI severity:

TBI severity was defined using the Glasgow Coma Scale (GCS) score (7) which is based on motor, verbal and ocular responses. GCS scores range from 3 to 15: a score ≤8 defines presence of a coma (severe TBI) (51).

The Paediatric Trauma Score (PTS) (52) sums up the ratings (2, 1, or -1) attributed to 6 assessment categories (3 physiological and 3 anatomical conditions, including weight/body mass index, condition of access to airways, fracture, level of consciousness, systolic blood pressure and condition of wounds). Lower scores indicate more severe injuries. Previous studies have reported good intra-observer reproducibility, developmentally appropriateness of use in children, and significant correlations with outcome measures following traumatic injuries (53).

The Injury Severity Score (ISS) provides an established anatomical scoring system aimed at assessing trauma severity (54,55). Its appropriateness for use in patients with multiple injuries has been demonstrated based on its correlations with indicators of mortality, disability, and hospitalisation (56). The ISS is derived from the Abbreviated Injury Scale (AIS), which grades injury severity from 1 (minor injury) to 6 (un-survivable injury) across six body regions. The ISS is computed by summing the squared top three AIS severity scores attributed to the three most severely injured body regions (49). The ISS yields values from 0 to 75, with higher scores indicating greater injury severity.

The following medical data was also collected during the acute phase in the intensive care unit: age at injury, cause of injury, presence of a penetrating skull fracture; mean arterial blood pressure; hypotension (drop >10% from normal value of mean arterial pressure for age), intracranial pressure, minimal brain perfusion pressure, occurrence of severe hypoxic episodes (Sa02 <92% with additional oxygen), evidence of intracranial hypo-perfusion upon CT-scan examination and multimodal monitoring, length of coma (in days), occurrence of immediate and/or early seizures.

Outcome measures collected during clinical follow-up at 3, 12, and 24-months post-injury:

Motor deficits: Neurological and functional assessment allowed collecting information relative to the presence or absence of (1) hemiplegia or hemiparesis; (2) signs of cerebellar dysfunction (ataxia and / or coordination disorders).

Post-injury type of education (at 12 and 24-months post-injury): Ongoing type of education was classified into two categories: General education without help, adaptation, or grade retention *vs*. Specialized or General education with help and/or adaptation and/or grade retention.

Overall level of disability: Glasgow Outcome Scale modified for children (GOS-Peds) (57), a recognized gold standard for measuring TBI outcome, yielding 5 categories: (I) good outcome; (II) moderate disability, including hemiparesis and/or cognitive impairments and/or child referral for outpatient rehabilitation therapy; (III) severe disability, including severe motor deficit and/or cognitive assessment in the deficient range and/or referral for inpatient rehabilitation; (IV) minimally responsive or vegetative state, and (V) death.

Functional outcome: Paediatric Injury Functional Outcome Scale (PIFOS) (58). The PIFOS is a brief injury-specific multidimensional rating scale completed by parents/caregivers for children aged 3 to 15 years, based on a structured interview assessing a broad range of cognitive, physical, and psychological health areas commonly impacted by paediatric injury in children. This assessment was performed by a trained health care provider during structured interviews, with the same parent for all time points.

Neuropsychological assessment

Comprehensive neuropsychological assessment was performed by trained professionals, during one or several sessions, according to the patient's fatigue, in the Rehabilitation Department of the Saint-Maurice Hospitals. These assessments comprised standardised tests and questionnaires aimed at evaluating intellectual functioning, executive functioning [*e.g*. Behavior Rating Inventory of Executive Function (59)], behaviour, and memory. Results of detailed assessment of executive functioning have been published elsewhere [(*e.g*. (48)].

Memory: Memory assessment was conducted in children aged between 5 years and 15 years 11 months, using the French versions of the Children's Memory Scale (CMS) (60,61), and of the Wechsler Memory Scale (MEM-III) (62) for those aged 16 years and above.

The CMS provides eight index scores [Mean (M)=100, Standard Deviation (SD)=15]: Verbal Immediate and Delayed Memory, Visual Immediate and Delayed Memory, Attention/Concentration, Learning, Delayed Recognition and a General Memory Score based on the four verbal and visual immediate and delayed partial scores. Scores are drawn from six main subtests:

- "Stories": the child has to listen and remember a short story, and to recall it with as many details as possible, immediately and at 25-35 minutes, and then answer questions about it;
- "Word pairs": the child has to remember a list of matched words, with a learning phase where s/he is asked to recall the whole list of words on immediate and delayed recall; s/he also has to recognize the words previously learned among other words;
- "Dot location": the child has to remember the position of blue chips, and after a learning phase, to replace them in immediate and delayed recall inside a predawn grid;
- "Faces": the child has to remember series of faces and to recognize them, presented among distractors, in immediate and delayed recognition;
- "Numbers": forward and backwards digit span;
- "Sequences": the child has to recite different types of sequences, such as alphabet, numbers count, days of the week, among others.

The CMS has robust psychometric properties, such as good internal consistency (Cronbach alpha=.88 to .93), good interrater reliability (.98 or above) and good discriminant validity. However, retest allows gains of up to 1 SD when assessment is repeated.

No data from the MEM III was used in the analyses, as only one 16-year-old patient performed this battery at the 2-year follow-up, but he was excluded as he had missing data on one of the previous time points.

Intellectual functioning: Performance-based assessments evaluated intellectual ability through age-appropriate French versions of the Wechsler Intelligence Scale for Children-III (WISC-III) (63,64) and the Wechsler Preschool and Primary Scale of Intelligence-III (WPPSI-III) (65). The Full-Scale Intellectual Quotient (FSIQ), Verbal and Performance IQ (M=100; SD=15) estimated the patients' intellectual level at each time point.

Statistical analyses

Data analyses were conducted using the SAS ® software version 9 (66) and R software version 3.5.1. (67). Descriptive statistics were used to describe the sociodemographic characteristics, severity indices and, at each time-point (3, 12 and 24-months post-injury), the main outcomes (including memory scores).

Mean and standard deviations of the general memory score and the partial memory indices at all time-points were described, as well as the Pearson's correlation coefficients **of memory scores** between those periods. Univariate statistical analyses focused on the evolution of the main outcomes across the time-periods. In addition, we performed correlation analyses or *t*-tests to examine the association between general memory and the main TBI outcomes, namely motor deficits, FSIQ, PIFOS, GOS and ongoing education, at each time-point.

Linear mixed models were used to examine associations of general memory score with sociodemographic and injury-related characteristics. For the seven partial memory indices, a linear mixed effects model was estimated, explaining the indices scores from the memory score subtype, the time (three categories, **M3, M12, M24**) and the interaction between memory score subtype and time. The model included a random intercept for the subject but no random slope as the evolution was not assumed to be linear. A nested contrast was used for the time variable, in order to compare M12 to M3 and M24 to M12. A sum contrast matrix was used for the memory score subtype variable so that each memory score subtype was compared to the average of all memory score subtypes (including the one to be compared). Consequently, no reference category was chosen. The interaction between time and memory subtypes allowed testing differential evolution of memory subtypes compared to the general average evolution of all memory subtypes. Holm's multiple testing adjustment for *p*-values was performed on all effects of the linear mixed effects model (68).

Results

Description of the study sample

Demographic and severity characteristics of the 38 participants (31 boys) who underwent memory assessments over the 2-year follow-up are summarized in **Table 1**. Mean age at injury was 10.7 years; for 17 patients (45%), at least one parent had graduated from high school, and 11 (28%) had a history of pre-injury difficulties at school.

Children underwent severe injuries, with an initial median GCS score of 7 [range (3-8)], median ISS of 29 [range (4-50)], mean PTS of 4 [range (-1 - +9)], and a median length of coma of 5.5 days [range (1-22)].

< Insert Table 1 here >

Outcomes

All outcomes assessed at each time point are summarized in **Table 2**. Overall, motor impairments were relatively frequent at 3 months, but tended to resolve by 12 and 24 months for the majority of participants. Overall disability, measured using the GOS-Peds, indicated "severe disability" at 3-months post-injury for 34% of the patients, with only 5% of "good recovery". Most children remained with moderate to severe disability, with only 24% rated "good recovery" at 24 months. Mean overall intellectual ability (FSIQ) fell one standard deviation below expected value at 3-months, with significant improvement over time, mostly during the first year. Functional impairment was severe at 3-months post-injury, with improvement (decrease) of PIFOS scores mainly from 3 to 12-months post-injury. Children attending general education without help nor adaptation nor grade retention represented 41% of the sample at 12 and 24-months post-injury.

< Insert Table 2 here >

<u>Memory assessment</u>

The mean scores of all the memory indices at each time point are summarized in **Table 3**. Mean initial General Memory Score 3-months post-TBI (M=90.2) was below the expected value (M=100), but with high variability (SD=20.3, higher than expected: SD=15), with some patients performing in the deficit range while others displayed high performance. **Figure 2** illustrates the distribution and high variability of the general memory scores at 3, 12 and 24 months.

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< Insert Figure 2 here >

Univariate analysis (paired *t*-tests) showed that the general memory score improved significantly between 3 and 12 months (p<.001), and marginally between 12 and 24 months (p<.05) (Table 3). All partial memory indices, with the exception of visual delayed memory and attention/concentration, improved significantly between 3 and 12 months. Between 12 and 24 months, improvements were significant only for the partial memory indices of visual immediate memory and learning. The correlations of all memory scores between 3 and 12-months post-injury, and between 12 and 24 months, were significant, except for Visual

Immediate Memory between 12 and 24 months, and for Visual Delayed Memory between 3 and 12-months post-TBI.

The linear mixed effects model after Holm's correction for multiple testing showed that **(i)** initial (3 months) visual delayed memory was higher than the other memory indices ($p<.01$); **(ii)** a general tendency for improvement in memory scores between 3 and 12 months ($p<.001$), which was independent of the memory subtype; **(iii)** a general tendency for improvement in memory scores between 12 and 24 months ($p<.01$); which was significantly higher ($p=.03$) for the immediate visual memory compared to the other memory indices. **Figure 3** depicts these effects. Correlations between General Memory Scores (GMS) at 3 and 12 months was .82 ($p<.001$), and .68 ($p<.001$) between 12 and 24 months.

< Insert Figure 3 here >

<u>Factors associated with general memory scores</u>

The results of the linear mixed effects model indicated that lower general memory scores were significantly associated with lower PTS (increased severity) [(F(1,36)=7.4, $p=.01$], longer length of coma [F(1,36) =5.9, $p=.02$], and marginally associated with lower parental education level [F(1,36)=3.3, $p=.07$] and higher ISS (increased severity) [F(1,36)=3.7, $p=.06$]. The interactions of the above factors with period were not significant. When parental education level, PTS, length of coma and ISS were introduced simultaneously in the model, only PTS remained marginally significantly associated with the general memory score [F(1,33)=3.9, $p=.06$]. Age at injury, gender, pre-injury school difficulties, lowest GCS Score and other medical / severity variables were not associated with the general memory scores.

<u>Associations between general memory scores and other TBI outcomes</u>

Table 4 describes the associations between the General Memory Score and the other outcome measures at each time point. Higher (better) FSIQ and GOS-Peds scores, and lower (better)

PIFOS scores at 3, 12 and 24 months, and absence of motor deficits were significantly associated with higher (better) General Memory Scores at 3 months. Type of ongoing education at 12-months, and marginally at 24 months, was associated with the General Memory Score measured at the same time point.

< Insert Table 4 here>

Discussion

This study aimed to assess memory performance after severe childhood TBI and its evolution over two-years post-injury, and to determine demographic, medical and severity factors associated with memory performance and recovery. We report detailed memory outcomes in a large sample of children who sustained severe TBI and who underwent comprehensive medical and neuropsychological follow-up over two years, with very little attrition. Overall, results indicate relatively severe outcomes (although high variability was noted), with decreased intellectual ability, high proportions of children with persistent moderate to severe disability levels and functional impairments, and high proportions of children requiring school adaptations, extra help, or special education. Memory was significantly impaired at 3-months post-injury, with a high variability in test scores however, some patients displaying severe deficits, while others were functioning at superior levels. Significant improvement of memory performance was found over time, mostly during the first year. Visual memory was relatively preserved when compared to the other indices. Among factors influencing outcome, memory function was mostly correlated to markers of injury severity, and marginally associated to parental education level. Memory function was also associated with other post-injury outcomes such as intellectual ability, level of disability and functional outcome. Finally, memory performance was significantly associated with educational outcomes.

At 3-months post-injury, mean general memory score and most memory indices were below expected values. Improvement occurred over time, with mean group performance at 24 months in the normal range, despite the persistent and substantial variability observed in the high performances range. Improvement of general memory score at 24-months post-injury was mostly due to the better recovery of visual immediate memory and learning indices, with much less progress on verbal and attention/concentration scores. This could be partly related to the retest effect, possibly more prominent on the visual skills in our results. The CMS manual indicates that retest can account for differences of up to 1 SD (i.e. 15 points), which could have largely contributed to the improvement observed in this study (60). One could suspect possible differences in task difficulty according to the memory sub-tests, or an authentic better preservation/recovery of visual memory skills following childhood TBI, when compared to verbal memory, as suggested by a large meta-analysis (9). Indeed, in our study, impairment and recovery differed, with better overall outcome on visual memory skills. Those results are concordant with those reported by Catroppa & Anderson (22), i.e. less memory improvement one-year post-injury following severe TBI (when compared to mild and moderate TBI), and a larger effect of injury on verbal memory compared to visual memory. Moreover, the impairment of attention/concentration, strongly related to executive functions and working memory, confirms findings describing the impact of paediatric TBI on working memory skills (28,69).

Memory recovery was more pronounced in the first than in the second-year post-injury, consistent with the results of Babikian & Asarnow's meta-analysis and review (9,11). Indeed, time since injury has been reported as a significant predictor of memory performance, with recovery occurring mostly in the acute phase (30). One study found slightly different results, although it focused on children recruited in a rehabilitation department where they had been admitted following severe TBI, which probably biased recruitment towards more severe cases. In this study, little improvement in memory function (collected retrospectively) was observed during the first-year post-injury and at discharge from rehabilitation. At the follow-up assessment performed at least 3 years following discharge, children’s memory performance had not improved any further (70).

Regarding factors related to memory outcomes at various time points, memory was mostly influenced by initial TBI severity, but not by age at injury or presence of pre-injury difficulties at school. Parental education (used in this study as a marker of socio-economic status) was marginally associated with the memory outcomes. The effect of parental education level on cognitive (including memory) outcomes has been repeatedly reported in the literature (14,46,71). It relates to the environment the child lives in, with a positive impact of rich environment on cognitive skills development, including memory (36), due to permanent and various stimuli supporting child’s neurodevelopment. However, this socio-economic status effect has not been found to influence prospective memory or autobiographical memory (32,40), including one study performed in in the 7-year follow-up of the TGE cohort (40).

We found no correlation of memory function with age at injury. Other studies in the literature have suggested an effect of age at injury on memory outcomes (9) whereas others did not (47). A recent review also reported no effect of age at injury on memory recovery over time (11). According to the latter review, the previously reported effect of age at injury could have been masked by a preponderant effect of time since injury and TBI severity. Also, the development of memory is not linear (24,72) and maybe the use of larger age-at-injury groups could allow better understanding of the effect of age on outcome following brain insult (48,73).

In our study, memory function was significantly associated with initial TBI severity at each time point, i.e. PTS, length of coma (similar to findings by (13,30,47), with a marginal effect of ISS. This severity effect was present despite the inclusion of children who all sustained severe TBI. This effect has repeatedly been reported in the literature, in various samples, composed of children with mild-to-severe TBI (46) but also in samples of children with severe TBI (40,47).

The remaining initial medical / severity data, such as presence of a penetrating skull fracture; hypotension; maximal intracranial pressure and minimal brain perfusion pressure were not significantly associated with memory performance at any time-point. To our knowledge, these severity indices have not previously been studied in relation to memory function.

In the present work, memory function was correlated with other TBI outcomes. First, the General Memory Score was strongly correlated to overall intellectual ability at each time point, which confirms that memory and other more general cognitive skills are closely interdependent, as already described in a sample of children with TBI of various severity levels (31).

A relatively new finding was significant correlations of memory function at the different time-points with other more general and less obviously related outcomes, such as presence of motor deficits, overall level of disability, or functional outcome, which, to our knowledge, has not been reported previously. Although a recent study determined the relation between functional outcome (defined by the PIFOS) and overall intellectual ability after childhood TBI (58), the link with memory skills has not been explored yet. Similar findings have been reported in childhood stroke, where motor function was found to predict educational outcomes (74,75). These findings can probably be explained by the deleterious effect of TBI severity on a number of outcomes, reflecting the extent of brain lesions.

Finally, in this study, educational outcomes are worrying, with less than half of the sample following mainstream education without help and/or delay at 12 and 24-months post-injury. The general memory score influenced subsequent education modalities, with a significant effect at 12-months post-injury, that failed to reach significance at 24 months, confirming deleterious effects of severe TBI on subsequent learning skills and academic achievement. These findings reinforce those of previous studies, reporting high proportions of poor academic outcome following severe TBI (15–17). It has already been shown that academic achievement and more general educational outcomes are strongly influenced by cognitive functioning (especially memory, executive functioning and working memory, and intellectual ability) (76). Indeed, cognitive impairments, such as slow processing speed, or attention or working memory deficits, can alter the intake of meaningful information in the classroom (28). Further, memory impairment certainly reduces the amount of new learning a child can take in, consolidate, and efficiently reuse, especially if executive functions deficits are also present (77). Over time, if the deficits persist, the amount of information and skills that should be acquired (but is not) can increase and in turn lead to increasing difficulty in new skills understanding and mastering (31). Our results also show that the attention/concentration index was the most impaired, with few improvements over time. This finding suggests a deleterious impact of attention/concentration impairments on subsequent educational outcomes (28).

This study has a number of limitations: the main limitation is the lack of inclusion of a matched control group, which would have allowed controlling for the retest effect. The large progression in memory scores observed in this study, and the high scores obtained at 24 months, especially for visual immediate and delayed visual memory could be due to actual progress, and/or less vulnerability of this particular skill, but also to some degree of retest effect. Indeed, for some very high functioning individuals, the psychologist who administered the tests qualitatively noted that they mentioned remembering some of the tests, such as the stories, word pairs or visual memory stimuli. Without a control group and a systematic quantification of the patient's subtests recognition, this cannot be confirmed. Subsequent follow-up of this cohort with the use of a control group could help clarify this point. Secondly, brain imaging was performed, but was not systematically analysed and integrated in the database, which did not allow the analysis of the relations between memory performance, and brain lesions characteristics. Such analyses would have been very useful to support current researches about neural circuits of memory (33–36) and contribute to explain the large variability in the memory outcomes observed in the present study. Finally, we only used parental education as a measure of socio-economic status, which is not sufficient and should be completed by more precise indicators, such as occupation, family functioning, coping and parenting style, among others.

Conclusion and perspectives

Overall, we report significant, albeit highly variable memory impairment following severe childhood TBI. Improvement seems to occur over 2 years, especially during the first-year post-injury, with different patterns across memory functions, although part of the improvement could be due to the retest effect and this should be confirmed in studies including a control group. Few factors were strongly associated with memory performance, mainly TBI severity markers. Finally, memory outcome was related to other post-injury outcomes, such as motor, functional and intellectual outcomes, and overall level of disability, suggesting deleterious effects of TBI severity across domains. As reported previously and as expected, memory function was also related with the type of ongoing education post-TBI. Those results suggest that all patients with severe TBI should receive at least a comprehensive neuropsychological assessment, including memory assessment, shortly post-injury, in order to assess strengths and weaknesses and to plan adequate and timely rehabilitation interventions and school adaptations. Subsequent assessments should occur according to progress over time, persisting complaints and difficulties at home and at school. Long-term follow-up should be pursued until transition to adult services.

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Declaration of interest

The authors declare that they have no competing interest.

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Table 1. Demographic, pre-injury medical history and TBI severity of the 38 children included in the study.

	Mean (SD) [range]
Demographic characteristics	
Gender: Males; *n (%)*	25 (66)
Parental education (at least one parent graduated from high school); *n (%)*	17 (45)
Previous difficulties at school (extra help or stayed back one year); *n (%)*	11 (28)
Age at injury (years)	10.7 (2.7) [5.2 - 14.9]
Injury Severity - Initial scores	
Minimal GCS score, mean (SD) [range]	6.3 (1.7) [3 - 8]
Paediatric Trauma Score, mean (SD) [range]	4.5 (2.4) [-1 - +9]
Injury Severity Score, mean (SD) [range]	27.1 (8.9) [4 - 50]
Length of coma (days), mean (SD) [range]	6.1 (4.2) [1 - 22]
Injury characteristics	
Penetrating skull fracture; *n (%)*	5 (13)
Intracranial pressure (mmHg), mean (SD) [range]	21.0 (8.1) [6 - 38]
Brain perfusion pressure (mmHg), mean (SD) [range]	46.5 (8.7) [32 - 68]
Brain hypo-perfusion; *n (%)*	27 (75)
Intra-Cranial Hypertension; *n (%)*	11 (31)
Hypotension; *n (%)*	4 (11)
Initial seizures; *n (%)*	2 (5)
Subsequent Post-Traumatic Epilepsy; *n (%)*	0 (0)

SD: Standard Deviation.

Table 2. Main outcomes at 3, 12 and 24-months post-injury (*n*=38)

	3 months	12 months	24 months
Motor deficits: presence n (%)	14 (37)	8 (21)	3 (8)
Overall disability (GOS), n (%)			
Good Outcome	2 (5)	8 (21)	9 (24)
Moderate Disability	23 (61)	20 (53)	25 (66)
Severe Disability	13 (34)	10 (26)	4 (11)
Cognitive function, mean (SD) [range]			
FSIQ	86.2 (18.4) [53 – 130]	91.8 (19.1) [54 - 145]	93.1 (20.0) [58 – 141]
VIQ	92.2 (17.7) [61 -136]	96.3 (17.7) [63 – 142]	95.3 (18.2) [67 – 132]
PIQ	82.3 (16.8) [55 – 123]	88.9 (17.1) [55 – 133]	92.1 (19.4) [53 – 136]
Functional outcome, mean (SD) [range]			
PIFOS total score	29.8 (16.6) [2 - 68]	23.3 (14.9) [0 - 64]	21.7 (14.8) [0 - 51]

SD: Standard Deviation; FSIQ: Full Scale Intellectual Quotient; VIQ: Verbal IQ; PIQ: Performance IQ; GOS: Glasgow Outcome Scale; PIFOS: Paediatric Injury Functional Outcome Scale.

All differences between 3 and 12 months were significant: motor deficits (McNemar's test, $p<.001$), GOS (paired *t*-test, $p=.01$), FSIQ (paired *t*-test, $p<.001$), VIQ ($p=.01$), PIQ ($p<.001$) and PIFOS (paired *t*-test, $p<.001$). Differences between 12 and 24 months were significant for motor deficits ($p<.001$) and PIQ ($p<.05$).

Table 3. Memory indices and general memory scores 3, 12 and 24-months post-injury (*n*=38)

	M (SD) 3 months	M (SD) 12 months	M (SD) 24 months	Difference 12 - 3 months	Difference 24 - 12 months	*r* 12 - 3 months	*r* 24 - 12 months
Visual Immediate Memory	91.4 (13.7)	101.1 (14.2)	114.3 (16.2)	9.7 (14.8)***	13.2 (17.9)***	0.44**	0.31
Visual Delayed Memory	97.8 (15.7)	102.1 (15.3)	106.7 (18.6)	4.3 (19.4)	4.6 (16.3)	0.22	0.55***
Verbal Immediate Memory	91.1 (21.6)	98.9 (25.8)	101.5 (25.4)	7.8 (13.5)***	2.5 (15.1)	0.85***	0.83***
Verbal Delayed Memory	91.9 (20.3)	99.7 (25.3)	100.4 (23.5)	7.8 (14.1)**	0.7 (14.8)	0.83***	0.82***
Delayed Recognition	86.8 (20.1)	94.6 (17.7)	97.0 (15.0)	7.7 (14.3)**	2.4 (14.9)	0.72***	0.59***
Learning	89.6 (16.2)	94.9 (17.0)	101.5 (18.7)	5.3 (12.7)**	6.6 (14.2)**	0.71***	0.69***
Attention / Concentration	89.7 (20.3)	93.0 (15.6)	95.1 (16.9)	3.3 (13.3)	2.1 (12.4)	0.75***	0.71***
General Memory Score	90.2 (20.3)	100.6 (23.1)	108.6 (24.1)	10.3 (13.4)***	8.1 (18.9)*	0.82***	0.68***

r: Pearson correlation coefficient; * $p<0.05$; ** $p<0.01$; ***$p<0.001$.

Table 4. Associations between general memory scores and other outcomes at 3, 12, and 24-months post-injury

	General memory								
	3 months			12 months			24 months		
	N	**Mean (SD)**	***p***	**N**	**Mean (SD)**	***p***	**N**	**Mean (SD)**	***p***
Motor deficits, n mean (SD) †									
Absence	24	97.7 (18.5)		30	102.8 (23.8)		35	109.8 (24.7)	
Presence	14	77.4 (16.9)	**	8	92.1 (19.7)		3	95 (3)	
Ongoing Education, n mean (SD) †									
General education without help nor adaptation nor grade retention		-		15	118.1 (22.3)		19	118.9 (19.5)	
Special education with help and/or adaptation and/or grade retention		-		22	89.6 (15.5)	***	23	102.5 (25.3)	*
Overall disability (GOS-Peds), n mean (SD) †									
Good Outcome	2	103.5 (4.9)		8	126.5 (17.6)		9	132.4 (13.9)	
Moderate Disability	23	97.9 (18)		20	97.4 (19.3)		25	100 (20.9)	
Severe Disability	13	74.6 (16.3)	**	10	86.1 (17.9)	***	4	109 (28.1)	***
Cognitive function ††									
FSIQ	37	*r* = .73	***	38	*r* =.58	***	38	*r* =.59	***
Functional outcome ††									
PIFOS total score	37	*r* = -.65	***	38	*r* = -.65	***	38	*r* = -.38	*

* p<0.05; ** p<0.01; ***p<0.001; † Two-tailed Wilcoxon signed-rank test (*Z*); †† Pearson correlation coefficient (*r*); FSIQ: Full Scale Intellectual Quotient; GOS: Glasgow Outcome Scale; PIFOS: Pediatric Injury Functional Outcome Scale;

At each time point, the general memory score was associated with ongoing education, GOS, FSIQ and PIFOS. Motor deficits were associated with general memory at 3 months.

Figure Caption:

Figure 1. Flow-chart. Evolution of the sample of children included in the study.

Figure 2. Distribution of the general memory score over time (percentage of patients in each category of memory performance)

Figure 3. Linear mixed model of the partial memory indices according to type and subtype of memory.

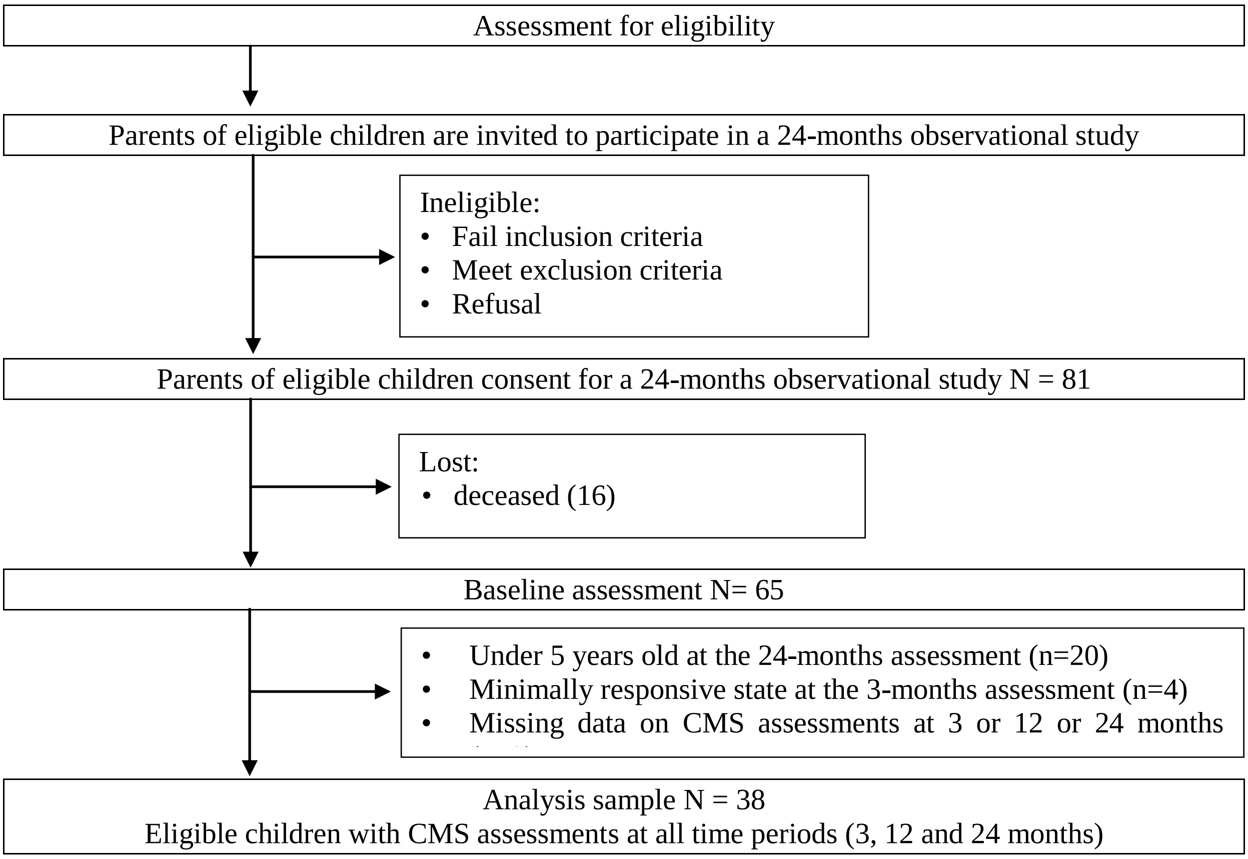
Assessment for eligibility
Parents of eligible children are invited to participate in a 24-months observational study
Ineligible:
• Fail inclusion criteria
• Meet exclusion criteria
• Refusal
Parents of eligible children consent for a 24-months observational study N = 81
Lost:
• deceased (16)
Baseline assessment N= 65
• Under 5 years old at the 24-months assessment (n=20)
• Minimally responsive state at the 3-months assessment (n=4)
• Missing data on CMS assessments at 3 or 12 or 24 months
Analysis sample N = 38
Eligible children with CMS assessments at all time periods (3, 12 and 24 months)

Figure 1.

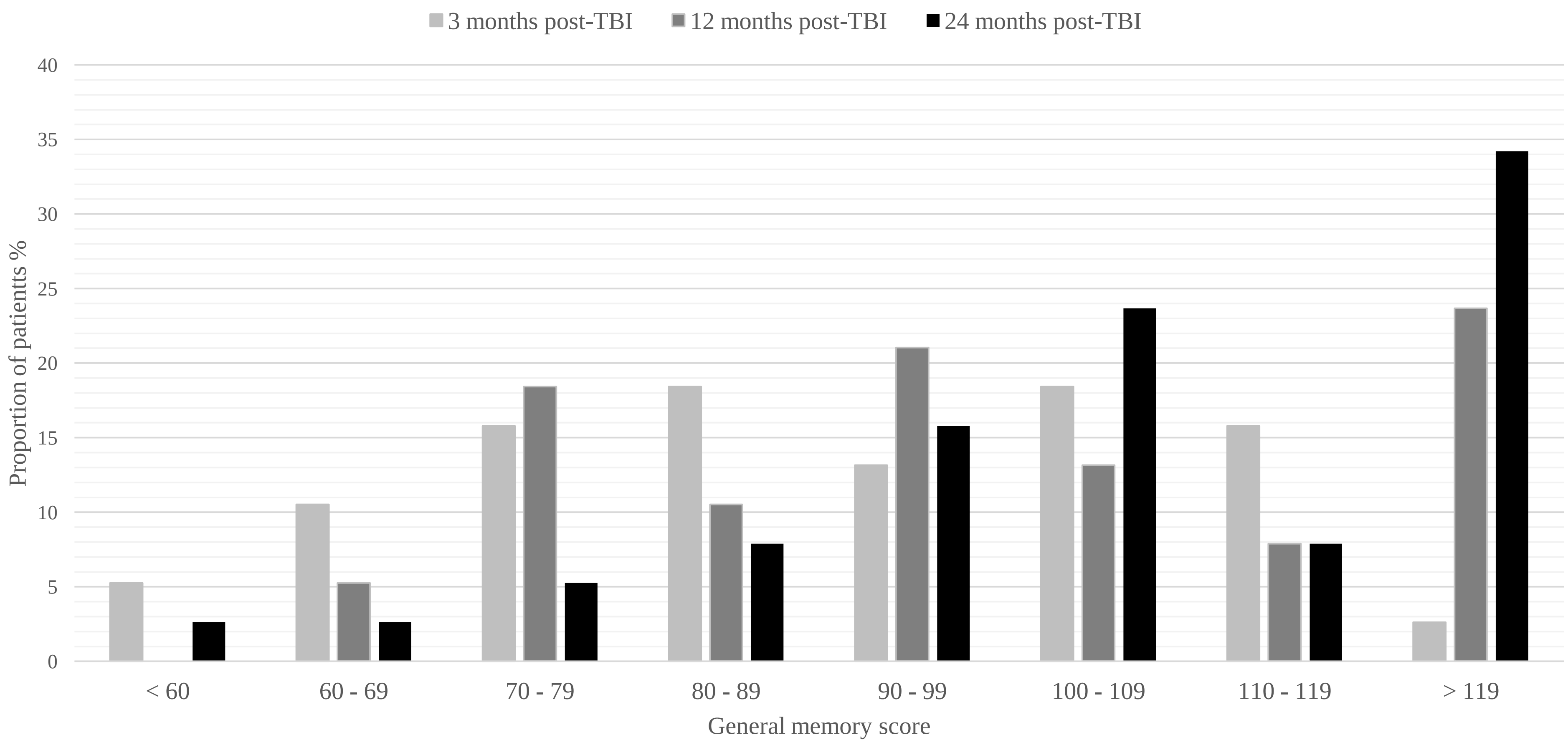
3 months post-TBI
12 months post-TBI
24 months post-TBI
40
35
30
25
20
15
10
5
0
Proportion of patientts %
< 60
60 - 69
70 - 79
80 - 89
90 - 99
100 - 109
110 - 119
> 119
General memory score

Figure 2.

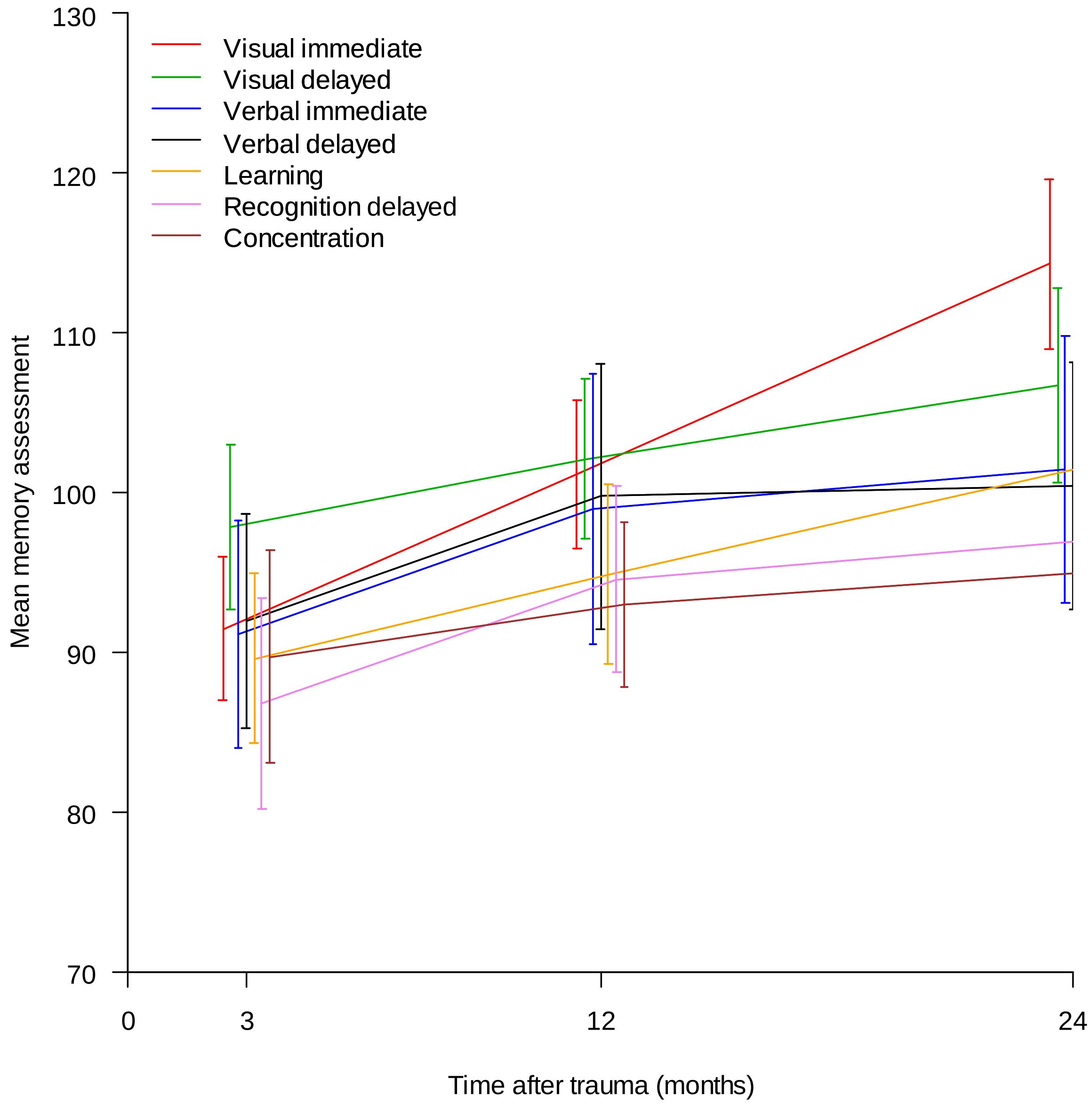
130
120
110
100
90
80
70
Visual immediate
Visual delayed
Verbal immediate
Verbal delayed
Learning
Recognition delayed
Concentration
Mean memory assessment
0
3
12
24
Time after trauma (months)

Figure 3.