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## **Prospective memory 7 years after severe childhood traumatic brain injury – the TGE 2 prospective longitudinal study.**

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## Abstract

Objective: to investigate long term outcome in prospective memory (PM), seven years after childhood severe traumatic brain injury (TBI), in a prospective longitudinal cohort.

Participants: 76 young individuals (aged 7-22 years): 39 patients with a severe accidental TBI included prospectively seven years earlier, aged 0-15 years at injury, and 37 controls individually matched on age, gender and parental education. Main outcome measures: three novel short PM tasks varying in the delay, motivation and context (ecological versus paper and pencil task). Results: individuals with severe TBI showed significantly poorer PM than matched controls in the two low-motivation PM tasks: (1) the ecological long-delay task consisting of sending a letter on a rainy day ( $p=0.047$ , odds ratio = 2.6); (2) the non-ecological short-delay task consisting of taking off post-its while identifying facial emotions ( $p=0.004$ ,  $r=0.34$ ). Differences in PM on the high motivation were not significant. PM is impaired several years post severe TBI

## Introduction

Prospective memory (PM) is the ability to remember to perform intended activities<sup>1</sup>. Children with PM impairment can fail to deliver important messages to parents, forget appointments, or fail to bring necessary items for planned activities. Successful PM requires (a) that you remember what has to be done (this includes remembering the action to be performed and the proper target event) and (b) that you remember to perform the action at the appropriate time or in response to the appropriate target event<sup>2</sup>. PM tasks require retrospective memory to remember the task, but depend on executive functions (EF)<sup>3</sup> for successful goal maintenance, retrieval and execution at the right moment. At least three attributes are accepted as characterizing a PM task<sup>4</sup>: (1) a delay between formation of the intention and the opportunity to carry it out; (2) absence of an explicit reminder to carry out the task at an appropriate moment; (3) the need to interrupt one's ongoing activity in order to carry out the intention.

Although PM problems are reported as a major concern by the parents of children with traumatic brain injury (TBI)<sup>5</sup>, there are surprisingly few studies that have evaluated PM in children with TBI (as opposed to adults with TBI<sup>3,6,7</sup>). Ward et al.<sup>8</sup> found that children with TBI had poorer PM than their uninjured peers, and that this may be attributable to worse executive functioning, especially if the PM task is cognitively demanding. Recently, a real cooking task (Children's Cooking Task<sup>9,10</sup>) has been used to explore PM in children with acquired brain injury<sup>11</sup>: it showed a striking impairment in PM, with older (14-20 years) children with brain injuries performing close to young (8-10 years) healthy controls.

McCauley et al.<sup>12,13,14</sup> used a monetary incentive to increase children's performance on an event-based PM task consisting of asking the examiner for points (exchangeable for dollars or for pennies) before each new neuropsychological test. Children with severe TBI were impaired on PM. Motivation (dollars versus pennies) influenced PM performance of controls and of children with chronic severe TBI<sup>12</sup>, while it had no effect on children with subacute severe TBI<sup>13,14</sup>. However even the chronic severe TBI group performance remained significantly below the low-motivation condition performance of controls.

Limitations of these studies were that they used either a biased sample of children with TBI (recruited from patients referred for rehabilitation) or, for the one prospective study<sup>14</sup>, children examined early after their TBI. Therefore, the frequency and degree of PM impairment after severe TBI in the long term is unknown. This is particularly needed

information because PM can impair functional memory and daily life even more than episodic memory<sup>5</sup>, but most patients in clinical practice (and even in research or legal expertise) are assessed only on the latter.

The aim of this study was to investigate long term PM outcome following childhood severe TBI, using short novel ecological PM tasks in a prospective longitudinal cohort. Our hypothesis were that (1) individuals with a TBI would perform more poorly on all PM tasks; (2) in high motivation task, individuals with TBI would differ less from controls than on low motivation tasks; (3) that PM would be better in older individuals.

## **Methods**

Participants: Participants were a cohort of children with severe accidental TBI [defined as Glasgow Coma Scale (GCS) score of 8 or lower at admission and/or an Injury severity score<sup>15</sup> > 16], aged 0-15 years at the time of inclusion and recruited between 2005 and 2008 at the pediatric neurosurgical intensive care unit of Paris 5 University “Necker Enfants Malades” Hospital. The main aim of the follow up of this cohort was to assess cognitive functioning, participation and quality of life and after severe TBI (manuscripts in preparation). Exclusion criteria at the time of cohort recruitment were: children with no vital signs upon admission, children with non-accidental head injury, previous history of diagnosed neurological, psychiatric or learning disorders. Patients were assessed at seven years post inclusion for PM. By the seven year testing, the sample therefore contained both children (<18 years) and young adults (≥18 years). A population-based group of healthy controls was recruited at the seven year follow up point. Controls were matched individually in terms of age (±3 months of age), gender and parental education (± 2 years of education) with each individual from the TBI group. For controls, the exclusion criteria were the same as for the TBI sample plus the absence of any TBI history. Socio-demographic data collected included language spoken at home, type of schooling and TBI characteristics for the TBI group. This study is part of a larger study, which was approved by the CPP IDF VI ethic committee.

PM tasks: Three ecological tasks of PM were developed for the study. The tasks were embedded in an assessment of outcome and quality of life following TBI that is not reported here. Because PM performance is influenced by motivation<sup>12</sup>, by the ecological features of the task (meaningful task versus exercise type task, home versus laboratory context)<sup>16</sup> and

by delay<sup>17</sup> between formation of an intention (PM instructions in this case) and the opportunity to carry out the intention, the tasks were designed to vary on these three factors.

**Low-motivation, ecological context, ecological task, long delay: the letter task:** participants received an envelope with the address of the hospital and were asked to send to the examiner a short note the next time it rained in the place they live. The letter had to contain four pieces of information: name of the participant, date, place and a mention of rain. The participant was also told that even if s/he forgot to send the letter the first time it rained, s/he could still do it later on, the most important thing being to send the letter at some point. Instructions were given twice to the participant during the testing and the examiner checked if the individual had understood and encoded the instructions by asking him/her to repeat them. The task was not explained to parents, but they were warned the participant had a task to do when s/he was at home. They were told that this was the reason why s/he had an envelope for the hospital. They were asked not to help the participant. Data from the letter task was treated as categorical (success or failure) in relation to two components: (1) sending the letter with all adequate information (which comprised a retrospective memory component - the letter content - as with most PM tasks of daily life) and (2) sending the letter irrespective of content (which assessed the prospective component of PM, as the child only had to remember the intention to send a letter).

**High-motivation, ecological task, non-ecological context, medium delay task: the amusement park prize-draw competition:** at the beginning of the testing, individuals were told they could enter a prize-draw competition to thank them for participating in the study. The examiner showed them a colored entry sheet that mentioned the draw. They were told that they could enter their name for the draw after the end of testing. The prize was two entries for an amusement park of their choice. At the end of the testing (6-7 hours after the instructions for the participants with TBI and 2.5-3 hours after the instructions for the controls who had less tests to complete), the examiner said "ok, we have finished all the tests, well done". If the participant did not ask spontaneously to enter the draw, the examiner made discreetly visible the colored competition entry-sheet so that it came into the participant visual space but without giving it to him/her. If the participant did not react to this visual cue, the examiner used a verbal non-specific cue: "did you want to do to

something else before leaving?”. If this was not enough, the participant was reminded explicitly s/he could enter his/her name for the draw competition. Data from the draw competition PM task was treated as ordinal: 3 points were awarded for individuals succeeding without cues (individuals asking spontaneously to enter the competition at the end of testing); 2 points for individuals needing the visual cue only; 1 point for individuals needing the verbal cue and zero points for individuals needing an explicit reminder to enter their name for the draw. On the competition entry-sheet the participant was instructed to add his/her name and telephone number. In addition, there was an instruction to read and to tell the examiner which amusement park s/he would like to go to if s/he won, and to fold the completed sheet in two for the draw box. These tasks did not constitute PM tasks as they could be carried out immediately, but tested the child’s ability to follow through a series of task instructions.

**Low-motivation, exercise-type, non-ecological context, short delay (retrieve-execute):**

**post-it/faces task:** in the last task, the delay was short. For this task, we used two existing tests as the on-going task: the NEPSY-2 affect recognition subtest (< 18 years) and the Bordeaux Faces Test<sup>18</sup> (≥ 18 years). In the adult version and most items of the child version, the individual had to name an emotion by looking at a face. Colored post-its were placed on some pages of these tests. The individuals were told to remove all the post-its apart from the pink ones throughout the task, but only after they had stated the emotion, not before. There were 9 post-its to remove (and 4 pink post-its to leave), placed in pre-determined positions on nine of the 39 (children version) or 40 (adult version) pages of the test. The instruction to take off only post-its of certain colors was meant to increase task difficulty and prevent the individuals from automatizing post-it removal without effortful processing. Face recognition was used as the ongoing task, because we considered this close to everyday life: usually face recognition happens conjunctively with complex reasoning (“what have I said? Is he angry or sad?”), prospective memory or multitasking (thinking of the bus arriving in 5 minutes while searching for keys and trying to figure out if our companion is cross following the previous conversation).

Statistical analysis: All analyses were performed with IBM SPSS 21. Individuals with severe TBI participating in the study were compared to individuals lost to follow-up, by Mann-Whitney tests on Glasgow Coma Scale score, coma length, age at injury, and one-year post

injury intellectual quotients and executive functioning. Further, Chi squared test was used to compare participants for language spoken at home, gender and parental education (defined as high if above high school or low if high school and below). The same tests were used to compare the participating severe TBI group to the control group on age at testing, parental education, gender and language spoken at home. Controls and individuals with TBI were compared for categorical PM data using Chi squared test. Effect size was calculated by odds ratios. The draw competition PM data was ordinal and therefore analyzed also using Mann-Whitney test. The Post-it task yielded a score of number of post-its taken out which was analyzed between groups using Mann-Whitney tests because score distribution was not normal, and effect size was calculated using  $r = \frac{z}{\sqrt{N}}$  and interpreted according to Cohen's guidelines<sup>19</sup>. Additionally, among each group (TBI and controls), adults' performance was compared to childrens' performance using Mann-Whitney test or Fisher's exact test.

## **Results and Discussion**

Participants: Eighty-one children were included at the acute stage of TBI between January 2005 and December 2008. Causes of accidental TBI were falls, car accidents. Sixteen children died during acute care, leaving 65 children entering the follow-up. Most children (83%) received a multidisciplinary rehabilitation after acute care, similar to that described by Chevignard et al<sup>20</sup>. By seven years post-injury, 26 were lost to follow-up, leaving 39 patients, aged 7-22 at PM assessment. Three of them could not be tested for PM (one was too fatigued, one had a severe depression, one agreed to participate initially and then refused to finish the testing). Individuals remaining at 7 years follow-up did not differ significantly from those lost to follow-up on GCS score, coma length, parental education, language used at home, age at injury, nor on their one year post-injury intellectual quotients and executive functioning (all  $ps > 0.05$ ). Detailed description and results of IQ and EF used at one year follow-up can be found elsewhere<sup>21</sup>. Most individuals (26) were still children at the time of the study but 13 had become young adults. Thirty-seven controls were recruited (two controls could not be recruited within the time frame of the study). There was no significant difference between the TBI and the control groups on gender, age at testing, parental education, and language spoken at home (see table 1).

PM tasks: Results are summarized in Table 2.



**Letter task** – Overall, 56 % of participants sent a letter. Individuals with TBI failed significantly more on both the prospective and the retrospective component of the task. One letter from a control contained weather and date information but no name and therefore it was not included in the analysis. If an individual had sustained a TBI he was 2.6 times more likely to forget to send the letter and 3.7 times less likely to send a letter with all required information.

**Amusement park prize-draw task** - Although unequal delay between instructions and opportunity to carry out the intention may have disadvantaged the individuals with TBI on this task, there was no significant difference between individuals with TBI (Mean Rank = 36.8) and controls (Mean Rank =37.16) in the prize-draw competition ( $U=660$ ,  $z=-0.07$ ,  $p=0.94$ ).

Capacity to follow the 5 instructions to enter the draw: When entering the amusement park draw competition, individuals with TBI managed to follow less instructions (fill in name, read instructions, fill in table with phone number, state the amusement park they would like to go to, fold the participation sheet for the draw) than controls (mean in TBI group = 3.7, mean in controls = 4.2; Mann-Whitney  $U=452.5$ ,  $z=-2.20$ ,  $p=0.028$ ,  $r=0.26$ ).

**Post-it Task-** Individuals with TBI remembered to take out significantly less post-its (Mean = 5.06, SD = 4.07) than their matched controls [Mean = 7.35, SD = 3.07, ( $U=420.5$ ,  $z=-2.87$ ,  $p=0.004$ ,  $r=0.34$ )]. Apart from one control who took out all four pink post its, individuals respected the rule of leaving the pink post its equally well in the TBI and the control group ( $p=0.16$ ). Performance on the on-going tasks (emotion recognition) was not significantly different between controls and individuals with TBI ( $p=0.11$  for children and  $p=0.12$  for adults).

Demographic and injury effects: None of the PM tasks was influenced by parental education, initial GCS or coma length. In the whole sample, individuals whose parents had higher education (Mann-Whitney  $U=789$ ,  $z=2.28$ ,  $p=0.023$ ,  $r=0.27$ ) and who spoke exclusively French at home (Mann-Whitney  $U=377$ ,  $z=-2.34$ ,  $p=0.019$ ,  $r=0.28$ ) followed more instructions.

Age at testing effects: Children performed poorer than young adults on the Post-it Task, irrespective of injury status (in the TBI group: Mann-Whitney  $U=210$ ,  $z=2.61$ ,  $p=0.009$ ,  $r=0.38$ ; in the typically developing controls: Mann-Whitney  $U=237$ ,  $z=2.69$ ,  $p=0.007$ ,  $r=0.44$ ). On the prospective component of the letter task (sending a letter irrespective of content), there was a trend for adults to perform better than children in both groups (Fisher's exact test = 0.068 in the TBI group and 0.084 in the typically developing controls group). There was no difference between younger and older participants for the prize-draw competition and the overall letter task.

Regarding the study hypothesis, individuals with severe TBI showed significantly poorer PM than matched controls in the two low-motivation PM tasks. Differences in PM on the high motivation were not significant. Developmental effects varied across tasks: children performed poorer than young adults on the Post-it Task, irrespective of injury status; there was no difference between younger and older participants for the other tasks.

This is to our knowledge the largest cohort of severe childhood TBI. Most cohorts usually include heterogeneous samples of children with a range of TBI severity, where severe TBI are usually relatively few. It is also to our knowledge the first cohort study that assessed PM at long-term post injury. The prospective longitudinal nature of this study was expected to capture more positive outcomes compared to retrospective studies based on the inclusion of patients in rehabilitation; nonetheless PM impairment appeared significant. This should raise awareness about frequent PM deficits, that are not explored by usual memory tests used in children and adults, and that should be given more attention, given the consequences of PM deficits on everyday life.

Our results are consistent with previous publications on both developmental<sup>22</sup> and clinical samples<sup>12</sup> that showed that deficits in PM performance may be reduced under high motivation conditions. The lack of age effects in the high motivation condition may have been due to an unequal degree of motivation, as the experimenter noted qualitatively that younger children seemed more enthusiastic about the prize-draw, while some young adults and adolescents appeared less interested (one did not even want to enter the draw). An unequal motivation effect was probably also present for the letter task, which was designed to be a low motivation condition: children aged 7-10 seemed very proud to have a letter to write and post and many parents reported the enthusiasm of their child for the task. Also,

we cannot exclude that parents helped their children with the letter task, because young children are not expected to send a letter on their own and it may have seemed natural for their parents to help them despite the examiner's explanations. Finally, task familiarity may have influenced results as younger children are not familiar with sending letters. Finally, task familiarity may have influenced results as younger children are not familiar with sending letters. The more ideas are associated with an event, the less efficacious that event will be for retrieval of those ideas in PM<sup>2</sup>. Therefore, uncommon and unfamiliar target events, are expected to provide little interference with the PM task and make the PM task easier. Even if the target event -rainy day – had the same familiarity for all individuals, sending a letter was a more unusual activity for children and may have made the PM easier. This was probably counterbalanced by the relative greater difficulty to send the letter for younger participants.

Whether PM improves with age is still a matter of debate. Small children as young as two can succeed in PM if motivation is high (remind their Mum to buy them sweets)<sup>22</sup>. Age effects that have been documented in the literature may be entirely attributable to factors such as: (1) unequal difficulty of the on-going task, allowing less attentional resources to PM tasks in younger children; (2) retrospective memory component; (3) motivation. When taking these into account (adapting ongoing task difficulty to the child's age, verifying if PM failure is not due to retrospective memory component that is known to be weaker in younger children, creating tasks that are highly motivating for children), age effects of PM are typically small<sup>23</sup>. This is in line with our findings, as the prize-draw competition showed no difference between age groups.

Limitations: The way the tasks were designed did not allow to systematically evaluate the three variables of delay, motivation and context, because comparable conditions were not constructed for each of the two conditions of the three variables. The differences observed between the high and low motivation tasks may be due to unequal task difficulty and not the motivation factor per se. Therefore, it is difficult to draw firm conclusions, on how motivation and the other factors influenced PM. Most tasks generated categorical or ordinal data that did not allow assessment of PM impairment severity. The advantage of using these three different 1-item PM tasks that tried in different ways to be close to real life (ecological context of the letter task, ecological real-life activity of entering an amusement park draw,

use of joint facial recognition and PM task similar to real life conditions) was counterbalanced by the question of reliability and validity of those tasks. However, this study was not aiming at precisely characterizing and quantify PM impairment but rather provide pilot data on PM without relying on usual paper-and-pencil tests that underestimate PM<sup>11</sup> or don't even screen for PM impairment. It would have been interesting to assess PM using questionnaires of PM in daily life completed by parents, which was not possible because families had already many questionnaires and interviews to complete for other parts of the study. Also, because all individuals were assessed 7 years post injury, those injured youngest had also the youngest age at testing; therefore, age at injury effects could not be explored (would have been confounded with developmental effects). Finally, it would be interesting to explore if poorer executive functions contributed to poorer EF performance as the role of EF in PM in children is a matter of debate<sup>23</sup> and to explore if poorer retrospective memory or attentional resources could not account for the differences in PM observed in our tasks.

The post-it task could be argued to reflect rather a dual task (dependent more on working memory ability than prospective memory), as the target (non-pink post-its) were relatively frequent (9 targets out of 40 pages), while other experimental laboratory PM tasks tend to use less frequent targets (e.g.: 2 out of 13<sup>24</sup>, 1 out of 20<sup>25</sup>) but not always (e.g.: 3 out of 10<sup>1</sup>). Probably, the higher the number of target stimuli, the more the task relies on working memory, because the frequent target acts as a constant reminder of the intention and is therefore kept in the attentional focus of working memory<sup>26</sup>. On the other hand, if the target is infrequent, as the on-going task proceeds, the intention drops progressively to lower attentional levels. Further, dual task performance is more about switching between two activities while PM more about delaying an intention until a favorable moment to execute it is encountered. Our post-it task may have better assessed PM if the target stimuli were less frequent. Further, because children had to switch between facial recognition, post-it removal and pink post-it inhibition of removal, the task evaluated probably both working memory and PM. The post-it/faces task used non focal PM cues (post-its of 3 different colours to remove). It would have been interesting to compare it to a focal cue condition

(one colour of post-it only) and see if it influences the ongoing task (faces recognition) as reported in other experiments in adults<sup>27</sup>.

Implications: There is now more evidence that PM is a common sequelae of childhood severe TBI<sup>5,11,12</sup>, that can persist over time. When assessing sequelae post TBI, the evaluation should include an assessment of PM in addition to classical episodic memory assessment, especially in legal expertise in order not to underestimate memory impairment in daily life. When PM is found impaired, interventions should aim at using high motivation tasks/incentives for most essential PM tasks of daily life as motivation may be an enhancer of PM performance<sup>12</sup>. However other methods should also be considered (e.g. pager, alarms), given the frequent overall PM impairment.

Conclusions: Across the large age span of 7-22, individuals with severe TBI systematically recruited for a longitudinal prospective follow-up showed significantly poorer PM seven years' post-injury than matched controls in two PM tasks. The ecological task consisting of sending a letter on a rainy day, showed significant differences both in its PM component (sending the letter irrespective of adequate content), and the overall task (sending the letter containing all adequate information). Individuals with TBI had more difficulty performing a simple PM task while identifying facial emotions. Performance on a high motivation PM task did not differ from controls. High motivation conditions may enhance PM. More ecological tests of PM should be designed and administered to assess PM after childhood severe TBI.

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**Table 1.** Demographic variables of the TBI and the control groups and injury variables of the TBI group.

	Individuals with severe		<i>p</i>
	TBI	Controls	
<i>N</i>	39	37	–
Age mean in years (SD)	15.1 (4.4)	15.1 (4.8)	.97
Gender ( <i>N</i> female/ <i>N</i> male)	13/26	13/24	.53
Parental education (high school and below; <i>N</i> , %)*	19 (49%)	13 (35%)	.17
Language spoken at home (French exclusively, <i>N</i> , %)	22 (56%)	26 (72%)	.20
Schooling: Ordinary schooling/ Specialized schooling/Finished education (%)**	61.5/23.5/15	100/0/0	<0.001
Age at injury in years (SD)	8.9 years (4.5)	–	
GCS score (SD)	6.5 (1.4)	–	
Initial coma length in days (SD)	6.4 (5)	–	

GCS: Glasgow Coma Scale.

\*Each control was matched individually to one patient in terms of age, gender and parental education. However, due to recruitment difficulties of individuals from parental very low education background, the last four controls had to be matched more loosely on parental education.

\*\*Controls could not be matched for type of schooling as the exclusion criteria excluded controls with neurological and learning disorders and therefore children needing special schooling were excluded.

**Table 2.** Results of prospective memory tasks in the TBI group and the control group.

	Individuals with severe TBI	Controls	Test statistic
<b>Letter Task</b>			
% individuals who succeeded in sending the letter with all information required	20%	49%	$\chi^2(1) = 6.68, p = 0.01^*$ odds ratio = 3.7
% individuals who succeeded in sending a letter, irrespective of adequate content	44%	68%	$\chi^2(1) = 3.96, p = 0.047^*$ odds ratio = 2.6
<b>Prize-Draw Competition</b>			
% individuals who spontaneously entered their name for the draw	28%	27%	U = 660, z = -0.07, p = 0.94
% individuals who needed <i>visual</i> cues to enter their name for the draw	19%	14%	$\chi^2(3) = 2.30, p = 0.51$
% individuals who needed <i>verbal</i> cues to enter their name for the draw	31%	46%	
% individuals who needed an explicit reminder to enter their name for the draw	22%	13%	
<b>Post-it Task</b>			
% individuals who totally forgot to take out the post-its	36%	13%	U = 420.5, z = -2.87, p = 0.004*, r = 0.34
% individuals who remembered to take off all required (non-pink) post-its	28%	60%	$\chi^2(2) = 8.43, p = 0.015^*$
% individuals who partially remembered to take off required (non-pink) post-its	36%	27%	