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Research Article

Prolonged duration of post-traumatic amnesia: A sensitive classification for predicting cognitive outcomes in children recovering from traumatic brain injury

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Abstract

Objective: A paucity of data exists regarding the duration of post-traumatic amnesia (PTA) as a predictor of cognitive functioning among children after traumatic brain injury (TBI). The study aimed to assess the relationship between PTA duration and areas of neurocognitive function among the pediatric population in the sub-acute phase of recovery and rehabilitation. **Methods:** Data were collected from medical files on 103 children aged 5.5–16.5 hospitalized at a pediatric rehabilitation department with a diagnosis of moderate–severe TBI (msTBI) between the years 2004–2019. The Children Orientation and Amnesia Test was used to evaluate PTA duration. Measures of high-order cognitive abilities of attention and executive function were collected using the Test of Everyday Attention–Child version (TEA-Ch). **Results:** Three PTA duration groups were assembled out of a cluster analysis: "Long PTA" (M = 21 days), "Very Long PTA" (M = 47 days), and "Extremely Long PTA" (M = 94 days). Analyses revealed that the "Long PTA" group preformed significantly better than the "Very Long PTA" and "Extremely Long PTA" groups on all TEA-Ch measures, that is, Selective Attention, Attentional Control Switching, and Sustained Attention. **Conclusions:** This study is the first to demonstrate that PTA duration is a useful predictor of high-order cognitive functions among children with msTBI in the sub-acute phase of recovery and rehabilitation. The findings emphasize the importance of using a more sensitive classification of prolonged PTA durations to improve outcome prediction and allocation of resources to those who can benefit most after severe brain injuries.

Keywords: acquired brain injury; pediatrics; cognitive assessment; post-traumatic amnesia (PTA); executive function; attention

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Introduction

Severity classification of traumatic brain injury (TBI) is essential for acute medical care and for the prediction of long-term outcome. Several variables related to injury severity serve as predictors of long-term outcomes after pediatric TBI. Among them are the Glasgow Coma Scale (GCS), the Length of Coma (LoC) measure, and duration of post-traumatic amnesia (PTA) (Hessen et al., 2007). The first two measures, GCS and LoC, can be biased, as they tend to be affected by early roadside interventions, sedation, system failure that is associated with multiple traumas, and pediatric intensive care unit (PICU) interventions. GCS can also be influenced by variations in post-injury assessment times, which are frequently not recorded (Malec et al., 2007). Furthermore, GCS and LoC have been reported to be inadequate and lacking the sensitivity necessary to establish cognitive and functional prognoses, especially in the pediatric population (Briggs et al., 2015; Sigurdardottir et al., 2015).

PTA is another well-documented marker of injury severity following TBI and is considered a sensitive measure for predicting outcome (Hessen et al., 2007; Nakase-Richardson et al., 2009). PTA reflects a transient period of confusion, amnesia, and behavioral agitation (Tate et al., 2000). Duration of PTA is commonly defined as the interval from the time of injury to the return of orientation or continuous memory, and is characterized by an inability to learn and recall new information (Levin et al., 1979). It occurs immediately following TBI and may last a few minutes, hours, days, or even months (Russell & Smith, 1961, Levin et al., 1979; Tate et al., 2000). Russell's scheme (1961) classified PTA duration into four groups associated with injury severity: (1) mild = up to 1 hr; (2) moderate = between 1 and 24 hr; (3) severe = between 1 and 7 days; and (4) very severe = above 7 days, with longer durations associated with poorer outcomes. This proposed scheme has been commonly used since the middle of the 20th century.

Several studies have shown that the duration of PTA is negatively associated with outcomes after TBI (Ellenberg et al., 1996;

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Zafonte et al., 1997; Ahmed et al., 2000; Brown et al., 2005). Among adult patients, the duration of PTA has been identified as the single most sensitive factor predicting disability 1 year after injury (Brown et al., 2005). Additionally, Nakase-Richardson et al., (2009) proposed a schema aimed at associating PTA duration with functional prognosis 1 year following injury among adults. According to these authors, 1 year post-injury, 68% of individuals with PTA duration shorter than 14 days were assessed as productive, whereas only 18% of individuals with PTA duration of more than 28 days were perceived as such. PTA duration has also been reported as an important factor in the day-to-day clinical management of TBI patients, influencing decisions such as the time of home discharge and the start of rehabilitation therapies (Tate et al., 2000).

Russell's and Smith's (1961) universal classification of PTA duration has been reported to help distinguish between mild and moderate–severe TBI (msTBI) patients (Lezak et al., 2012) and estimate long-term prognosis. However, according to Russell's and Smith's (1961) classification, very severe TBI (i.e., PTA duration > 7days) is nowadays commonly observed among patients in neuro-rehabilitation settings, due most probably to improved PICU and neurosurgical early interventions (e.g., decompressive craniectomy). Thus, while very severe TBI encompasses a broad range of potential outcomes (Brown et al., 2005; Nakase-Richardson et al., 2009), little is known about the implications of interindividual differences in PTA duration above 7 days.

Additionally, paucity of data exists regarding the ability of PTA duration to predict functional and cognitive outcomes among children and youth during the sub-acute phase of recovery and rehabilitation from msTBI (time post-injury < 6 month). The literature suggests that as many as one-third of childhood TBI survivors will sustain residual cognitive impairments and require ongoing intervention and support into adolescence and adult life (Kraus, 1995), and that the severity of the residual cognitive impairments is age related (Anderson & Catroppa, 2006). It has also been reported that pediatric TBI may impede the emerging of new skills and the development of skills that were in process of being acquired at the time of injury, in addition to the impairment of skills that had already been established at the time of injury (Spencer-Smith & Anderson, 2011). Therefore, various levels of cognitive deficits are commonly detected in the chronic phase of recovery as a function of age at injury, injury severity, location of brain insult (Dennis et al., 2007; Babikian & Asarnow, 2009; Spencer-Smith & Anderson, 2011), and premorbid cognitive reserve (e.g., parental education) (Donders & Kim, 2019). As injury severity is one of the major factors explaining the neuropsychological and functional outcome following pediatric brain injuries, there is a great need for research addressing the relationship between reliable measures of injury severity (e.g., PTA duration) and various outcome measures.

Previous studies have indicated that following pediatric TBI, the most affected cognitive abilities are attention, memory, speed of processing, and executive functions (EFs) (Anderson & Catroppa, 2006; Petranovich et al., 2020). Recent meta-analyses regarding the consequences of pediatric TBI indicate significant long-term impairments in IQ, EF, and attention, as well as in verbal memory (immediate and delayed), and in achievement of academic tasks (reading, writing, and math) and functioning (Babikian & Asarnow, 2009; Babikian et al., 2015; Briggs et al., 2015). Likewise, a recent study demonstrated poorer EF performance among children with acquired brain injury relative to controls, as measured by the Test of Everyday Attention–Children version (TEA-Ch) subtests. The study emphasized distinct patterns of specific EF deficits among each brain disorder (TBI, stroke, and tumors) (Araujo et al., 2017).

A recent systematic review (Briggs et al., 2015) showed that the duration of PTA is a more sensitive predictor of functional outcomes in children than GCS and LoC. In a comprehensive meta-analysis assessing 854 adult and pediatric TBI patients, longer PTA durations strongly predicted decrease in full scale IQ, performance IQ ,and verbal IQ, in both sub-acute and chronic phases of recovery (Königs et al., 2012). The results indicated that PTA was a valuable predictor of intelligence impairments following TBI (Königs et al., 2012). However, to the best of our knowledge, no study to date has assessed the relationship between PTA duration and specific areas of attention and executive functioning among the pediatric population in the sub-acute phase of recovery. This lack of knowledge may have some key consequences, as adequate rehabilitation interventions in this stage may reduce long-term neurocognitive impairments (Lee et al., 2019). For example, a recent meta-analysis suggested that early onset of neuro-rehabilitation care may promote functional recovery of patients with msTBI, when compared with usual care. Nevertheless, the optimal timing and intensity of neuro-rehabilitation remains still unknown (Königs et al., 2018).

As indicated above, there is paucity of data regarding the relationship between PTA duration and cognitive performance at the initial stages of recovery and rehabilitation from pediatric TBI. Therefore, the aims of this study were to: (1) explore if injury severity levels (measured by long PTA durations), can be profiled into unique homogeneous subgroups according to PTA similarities; and (2) examine if such exclusive PTA subgroups show significant differences in attention and executive functioning at the sub-acute phase of recovery from pediatric TBI.

Methods

Participants

The study followed a retrospective design in which data was collected from medical files on 154 children and adolescents following msTBI. All children were admitted to a pediatric rehabilitation department in central Israel between January 2004 and December 2019. Recruitment was from consecutive admissions. Inclusion criteria were: (1) documented evidence of closed head msTBI; (2) medical records sufficiently detailed to determine severity of injury which was based on diagnosis done by the pediatric rehabilitation physicians at triage; (3) age 5.5–16.5 (adhering to the TEA-Ch protocol); and (4) child's ability to complete the cognitive evaluation. All children were assessed during the sub-acute phase of recovery and rehabilitation of their inpatient rehabilitation using an extensive occupational therapy cognitive battery that evaluated performance on attention and EF tasks. Similar to Konigs et al., (2012) meta-analysis, the sub-acute phase was defined as the first 6 months post-injury.

Sample size was calculated using G × power analysis software. In order to achieve power of 0.80, at a significance level of $\alpha = 0.05$, with a medium effect size of $d = 0.25$, a multivariate analysis of variance (MANOVA) model including the three PTA-clusters as predictors and the three TEA-Ch scales as outcomes, was designed. This analysis revealed that a minimum of 98 participants are required to achieve sufficient power.

In the current study, out of the 154 children with msTBI admitted to the pediatric rehabilitation department, 27 patients were excluded due to age range (below 5.5 and above 16.5 years), and

Table 1. Sample characteristics

	Total		Long PTA*		Very Long PTA**		Extremely Long PTA***		F/ χ^2	df	P value	η^2/ϕ
	($n = 103$)		($n = 53$)		($n = 36$)		($n = 14$)					
Age (M, SD)	11.31 (3.42)		11.51 (3.40)		10.67 (3.4)		12.22 (3.49)		1.21	2, 100	0.30	.02
Boys (*n*, %)	69	67%	31	58.5%	26	72.2%	12	85.7%	4.39	2	0.11	.21
ADHD/ADD (*n*, %)	10	11.1%	6	14%	3	8.8%	1	7.7%	.686	2	0.71	.09

Note: PTA- post traumatic amnesia.
*Long PTA- Mean = 21.3 days.
**Very Long PTA- Mean = 46.9 days.
***Extremely Long PTA- Mean = 93.8 days.

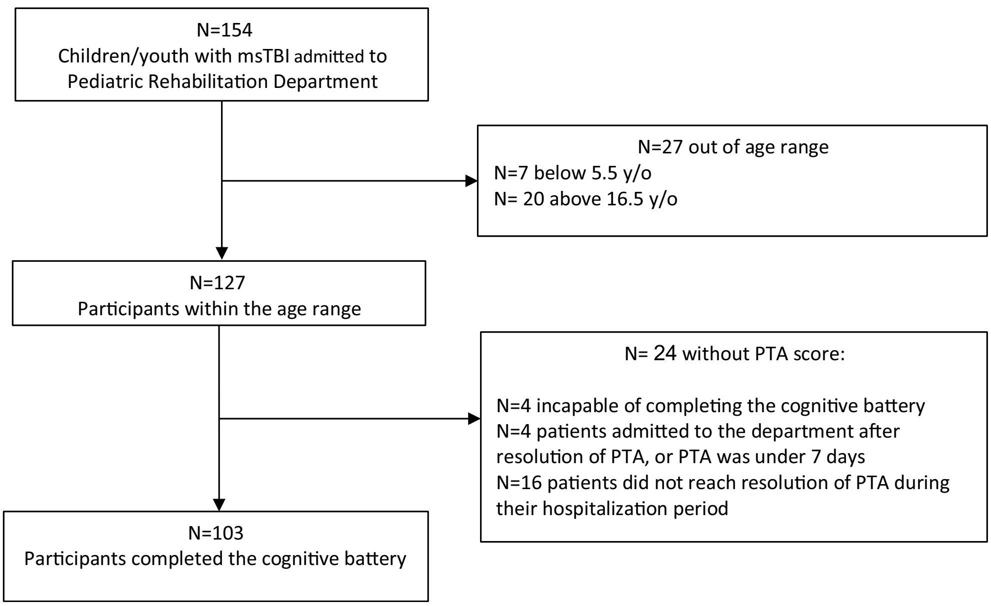

Figure 1. Participant flow chart.

additional 24 patients did not have a PTA over 7 days (4 were incapable to complete the PTA evaluation, 4 patients had PTA score below 7, and 16 did not reach resolution of PTA during their hospitalization period) (participant flow chart is shown in Figure 1). Thus, a total of 103 remaining children (mean age = 11.31, SD = 3.42) were included in subsequent analyses (see Table 1 for sample characteristics). All children included in the study have experienced closed-head brain injuries with 35 injured as pedestrians, 25 injured as bicycle riders, 23 as passengers in motor-vehicle accidents, 17 as a result of falls, and additional 3 were classified as "other," with injury cause not specified in medical charts.

Procedures and measures

Demographic information

Child's age, gender, date of injury, and days of hospitalization were all collected from medical files.

PTA duration

The Children's Orientation and Amnesia Test (COAT; Ewing-Cobbs et al., 1990; Iverson et al., 2002) was used to evaluate duration of PTA. The test was developed to serially assess cognition during the early stage of recovery from TBI in children and adolescents (Briggs et al., 2015) and serves as an adequate measure of the duration of PTA. The COAT consists of 16 items assessing three main areas: general orientation, temporal orientation, and memory. In children under 8, years of age temporal orientation items are not administered because these items were found to be developmentally inappropriate (Ewing-Cobbs et al., 1990; Briggs et al., 2015). A child is deemed to be out of PTA on the first of the two consecutive days on which a COAT score falls within the average range for that child's age (Briggs et al., 2015). PTA duration scores were calculated for each participant according to the time elapsed between injury and successful completion of the COAT (Annett & Dencoff, 2010).

Attention and EF measures

Within the first 2 weeks after PTA resolution, cognitive outcome measures were administered to all children using the TEA-Ch (Manly et al., 1999). The TEA-Ch has established reliability and validity in assessing aspects of attention and EF among attention-deficit/hyperactivity disorder (ADHD) samples and has been used as a measure in neuropsychological assessments among pediatric TBI patients (Anderson et al., 1998; Manly et al., 2001). The TEA-Ch consists of nine subtests, each measuring one factor of attention: Selective Attention (e.g., Sky Search and Map Mission scores), attentional control/switching (e.g., Creature Counting and Opposite Worlds subtests), and Sustained Attention (e.g., Score!, Code Transmission, Walk Don't Walk, Score dual task (DT), and Sky Search DT). Factor scores were based on the

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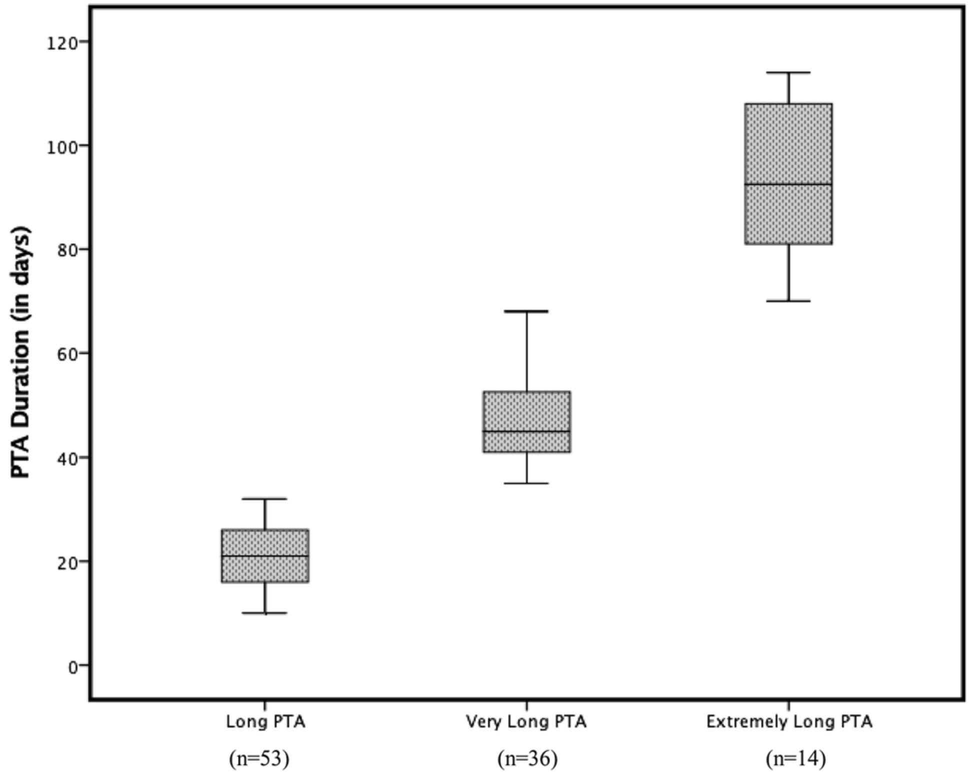

Figure 2. Two-step cluster analysis scattering.

mean Z-scores of the specific subtests included in each factor (Manly et al., 1999). The values of three diagnostics of the model (Comparative Fit Index, the Normed Fit Index, and the Non-Normed Fit Index) had a fit index of above 0.9 each (Manly et al., 1999). Recently, Araujo et al., 2017 reported that relative to controls, children with brain disorders showed poor performance on various subscales of the TEA-Ch.

All procedures were approved by the hospital's institutional review board and were in accordance with ethical standards (0296-13-SMC). The research was completed in accordance with Helsinki Declaration.

Data analysis

Data were analyzed using the SPSS software, version 25.0. Descriptive statistics were used to characterize the sample of children and adolescents following msTBI. In order to enable comparisons between the different tests, the TEA-Ch scaled scores were recoded into equivalent Z-scores according to population norms.

Two-step cluster analysis was conducted to establish injury severity sub-groups according to PTA duration. Cluster analysis is typically performed during the exploratory phase of research, mostly to discover structures in data without providing an explanation or interpretation. The two-step cluster analysis uses a distance measure to separate groups and then a probabilistic approach (similar to latent class analysis) to choose the optimal subgroup model (Jain, 2010). In the first step (pre-clustering), a sequential approach is used to pre-cluster the cases based on the definition of dense regions in the analyzed attribute space. In the second step (clustering), the pre-clusters are statistically merged in a stepwise way until all clusters are in one cluster. The two-step cluster analysis has been accepted as a reliable method in terms of the number of subgroups detected, classification probability of individuals to subgroups, and reproducibility of findings on clinical and other types of data (Gelbard et al., 2007). Following a parsimony criterion, the best cluster solution is considered the one with the strongest change and the lower number of clusters. This allows evaluating the most parsimonious cluster solution presenting the best fit.

Analysis of variance (ANOVA) and chi-square were produced to assess differences between severity groups. Next, a one-way MANOVA, with PTA group membership (Long PTA, Very Long PTA, Extremely Long PTA) as a fixed factor and the three TEA-Ch composites (Selective Attention, Sustained Attention, and Attentional Control) as dependent variables.

Finally, since the current study followed a retrospective design based on medical files in which some evaluations were missing due to differences in scoring protocols throughout the years, a multiple imputation technique (one-time stochastic regression) was used to complete missing data, which was lower than 10% for all measurements collected (Enders, 2010). This procedure allows the use of the full sample and gives unbiased parameter estimates, as long as the imputations were made completely at random (Missing Completely at Random [MCAR]). Little's test for MCAR showed that $X2(35) = 36.26$, $p = .410$ (Little, 1988), indicating that data were MCAR.

Results

The two-step cluster analysis produced three groups "Long PTA"; "Very long PTA"; and "Extremely Long PTA", with 53, 36, 14 members each. The "silhouette measure of cohesion and separation", a measure for clusters' goodness of fit was 0.7, suggesting a reasonable-strong structure (see Table 2 and Figure 2). Following this, the ANOVA verified significant differences in PTA duration for each severity group ($F(2, 100) = 434.92$, $p <$

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Table 2. Cluster analysis by PTA

Cluster	*n*	Days mean (SD)	Range	%
Long PTA	53	21.28 (6.16)	10–32	51.45
Very Long PTA	36	46.86 (8.22)	35–68	34.95
Extremely Long PTA	14	93.79 (14.27)	70–114	13.59

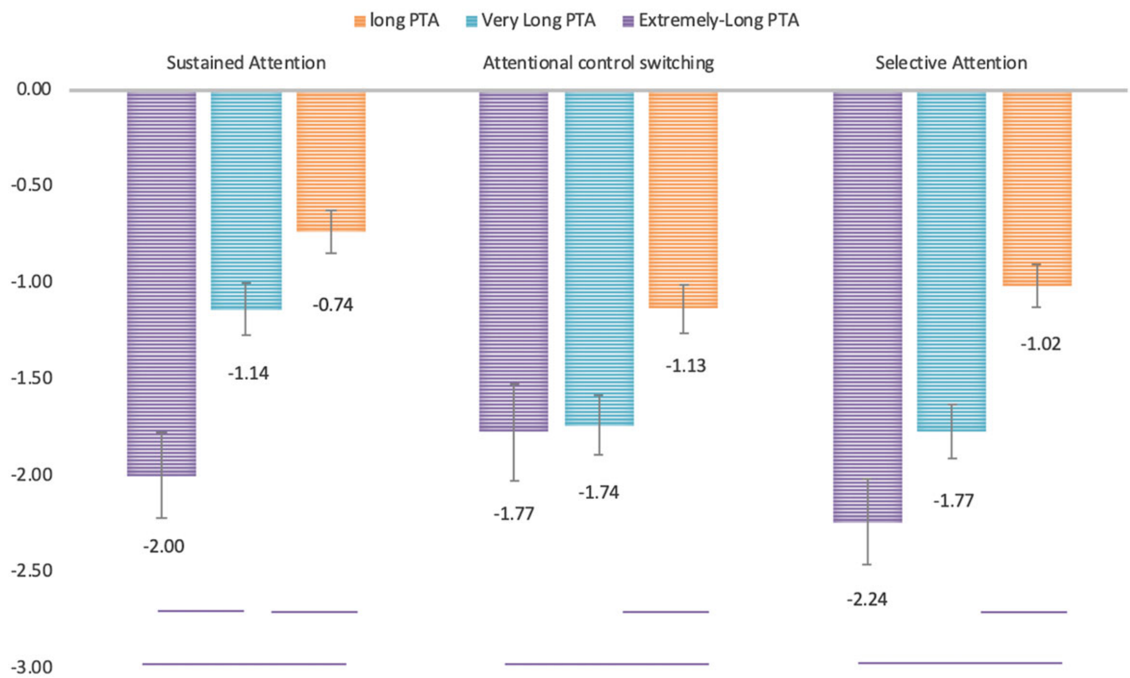

Figure 3. Performance on the TEA-Ch scales according to the PTA duration groups. *Note: Y axis represents mean TEA-Ch z-scores, with lower vales representing higher deviation from norms (z = 0).

.000, $\eta^2 = .897$). All the dependent variables were similar for both genders (Selective Attention ($t(101) = -0.99$, $p = .33$, $\eta^2 = .01$), Attentional Control Switching ($t(101) = -1.64$, $p = .10$, $\eta^2 = .03$), or Sustained Attention ($t(101) = -.53$, $p = .60$, $\eta^2 = .00$)). Moreover, no significant associations were found between PTA and gender ($t(101) = 1.65$, $p = .10$, $\eta^2 = .03$). Likewise, no significant correlation was found between age and PTA (r = .07, $p = .48$). Furthermore, no between-group differences were found regarding age, gender, or premorbid attention deficit disorders (see Table 1).

To examine the hypothesis that the three PTA duration groups impact cognitive performance differently, a one-way MANOVA was conducted with the three PTA duration groups as the independent variable and the three TEA-Ch attention/EF factors as the dependent variables. Tests of between-subject effects indicated significant PTA group differences (Wilkes' lambda = 0.66, $F(2,100) = 7.37$, $p < .001$, $\eta^2 = .18$). Post-hoc analysis for each TEA-Ch factor revealed significant group differences for Selective Attention ($F(2,100) = 16.01$, $p < .001$, $\eta^2 = .243$), Attentional Control ($F(2,100) = 5.50$, $p = .005$, $\eta^2 = .10$), and Sustained Attention ($F(2,100) = 12.97$, $p < .001$, $\eta^2 = .21$). MANOVA simple effects analysis indicated that the Long PTA group performed significantly better on the three factors, compared to both the Very Long PTA and the Extremely Long PTA groups. A significant difference between the Very Long and the Extremely Long PTA groups was found only for the Sustained Attention factor. No other significant differences were found (Figure 3). In addition, while performance on the different cognitive tests of the Long PTA group was within the average range ($1 \leq z \leq -1$), the Very Long and Extremely Long PTA duration groups performed mostly within the below average to exceptionally low range (i.e., $z < -1$).

Discussion

The present study is a first attempt to further elucidate the significance of PTA duration as a sensitive predictor of high-order cognitive functions among children with msTBI during the sub-acute phase of recovery and rehabilitation. Although PTA is a well-established indicator of brain damage severity and one of the best means for monitoring and predicting recovery (Wilson et al., 1999), the significance of prolonged PTA durations compared to the traditional classification of "above 7-days, very severe injury" has not been addressed in children and youth. Our results indicate that among children with a PTA duration of above 7 days, the length of the PTA was related to deficits in attention and EF. Moreover, the "Long PTA" group performed significantly better than the "Very Long PTA" and "Extremely Long PTA" groups, and this was evident for all TEA-Ch factors (i.e., Selective Attention, Attentional Control Switching, and Sustained Attention). The "Extremely Long PTA" group performed significantly poorer than the two other groups on the Sustained Attention factor. Our findings emphasize the wide cognitive diversity associated with prolonged PTA durations, especially regarding Sustained Attention during the sub-acute phase of recovery from pediatric TBI.

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PTA duration within commonly agreed time frames has shown to be a sensitive predictor of functional outcomes in children and associated with cognitive deficits (Kraus, 1995; Briggs et al., 2015). In the current study, three PTA duration groups were assembled out of a cluster analysis distinguishing between different attention and EF capabilities at the initial stages of recovery rehabilitation. The additional three PTA duration groups suggested here are complementary to Russell's scheme classification (Russell & Smith, 1961) becoming increasingly significant, as the number of patients who survive msTBI is increasing (Stein et al., (2010), especially among the younger patients (Luostarinen et al., 2022). Further research can use the PTA duration groups to evaluate the association of these markers with long-term cognitive outcomes (i.e., 1 year following pediatric TBI) and predict patterns of recovery.

Our findings of different injury severity profiles according to PTA duration, with different levels of attentional and executive deficits, may indicate a variety of different cognitive outcomes, thus explaining to some extent the heterogeneity of pediatric TBI outcomes (Babikian & Asarnow, 2009). In particular, our findings emphasize that better attention and EF performances are associated with shorter PTA durations on all TEA-Ch factors, with Sustained Attention most sensitive to prolonged PTA durations. Our results are consistent with previous findings, suggesting that attentional skills may be differently impaired after msTBI in children (Anderson et al., 1998). Babikian et al., (2015) suggested that distinctive aspects of attention and EF may show different patterns of development, which are affected differently by TBI in childhood. Cognitive skills that typically emerge later in life, such as the ability to shift attention, may continue to develop until adolescence, and thus may be more vulnerable to the adverse effects of pediatric TBI. While Sustained Attention was found to be relatively stable among adult TBI patients, variations in performance were found among the pediatric population, suggesting that this aspect of attention may not be fully developed and thus be more vulnerable to disruption in children following TBI (Anderson et al., 1998; Babikian et al., 2015).

Our findings also shed light on the lack of sex differences in PTA duration in the pediatric population. This finding is consisted with literature regarding adult patients, where no significant sex differences in the frequency, duration, presentation, or extent of post-traumatic agitation was found after TBI (Kadyan et al., 2004; Spiteri et al., 2021). To the best of our knowledge, no studies have addressed this issue in the pediatric population. Likewise, knowledge regarding the effect of age on PTA duration is also lacking. However, the absence of gender and age effects on PTA duration serves to encourage the utilization of the extended PTA subgroups suggested in this study, as a pure, less biased, injury severity measure.

This study has some limitations. First, the archival data did not include systematic reports regarding GCS and LoC, and therefore a comparison between PTA duration, GCS, and LoC could not be conducted. Likewise systematic information regarding SES variables was absent from further analysis, such as parental education and other information possibly associated with outcomes following pediatric TBI (Moran et al., 2016). Third, some of the most severely injured patients could not complete the evaluation and thus were excluded from this study, possibly affecting the range of PTA duration in our sample. Fourth, the attention and EF deficits described might not be specific but may be related to other general cognitive deficits (e.g., IQ or G, processing speed, etc.), which were not examined in the current study (Slomine et al., 2002; Wood & Liossi, 2007; Galbiati et al., 2009). In addition, we did not estimate the influence of premorbid cognitive reserve on cognitive deficits following pediatric TBI (Kesler et al., 2003; Steward et al., 2018; Donders & Kim, 2019). However, it should be noted that prevalence of ADHD/ADD was similar among the different PTA severity groups, possibly implying that premorbid conditions are less associated with attention and EF outcomes at the sub-acute phase of recovery and rehabilitation (see Table 1).

Taken together, the results underscore wide differences in neurocognitive deficits among children diagnosed with msTBI, despite belonging to the same severity subgroup according to Russel's and Smith's classification (i.e., very severe, PTA more than 7 days). Further research is needed to establish the correlation of cognitive outcomes to all severity subgroups and extended classification of long PTA durations. However, the relationship between PTA duration groups and cognitive performance at the initial stages of recovery and rehabilitation may suggest a useful way for evaluating cognitive and functional prognoses. As significant changes are commonly reported in cognitive functioning during the first year following msTBI (Anderson & Moore, 1995; Blackwell et al., 2020), the associations between cognitive functioning and the suggested extension of PTA groups should be evaluated also at the chronic phase (e.g., at least 1 year post-injury) as well as in the adult population.

The current findings have also clinical implications, resonating previous recommendations supporting routine assessment of PTA in children after TBI (Briggs et al., 2015). Furthermore, a deeper insight to the relationship between extremely long PTA duration and attentional capacities, may help develop more suitable rehabilitation protocols to better suit various levels of pediatric brain injuries, according to attentional capacities, working memory load, and processing speed. Therefore, similar to the need for increasingly detailed subdivision of preterm births to subcategories (low, very low, and extremely low) as a result of improved survival rates during the last decades, we suggest expanding the traditional classification of PTA duration (Russell & Smith, 1961) to longer duration groups to provide a finer indicator of cognitive functioning at the recovery phase from TBI. It is possible that the different PTA classification groups found in the current study will be more sensitive to predict rehabilitation gains in children following brain insults, similar to preliminary results by on GCS (Kramer et al., 2013; Blackwell et al., 2020). However, more research is needed in order to examine whether these detailed PTA duration groups would assist in planning more efficient and individualized rehabilitation programs.

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Conflicts of interest. None.

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