Traumatic brain injury in children

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PART I

THE LITERATURE SECTION


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CHAPTER 2

POST-TRAUMATIC AMNESIA PREDICTS INTELLIGENCE IMPAIRMENT FOLLOWING TRAUMATIC BRAIN INJURY

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ABSTRACT

BACKGROUND

Worldwide, millions of patients with traumatic brain injury (TBI) suffer from persistent and disabling intelligence impairment. Post-traumatic amnesia (PTA) duration is a promising predictor of intelligence following TBI. This study aimed to determine: (1) the impact of TBI on intelligence throughout the lifespan; and (2) the predictive value of PTA duration for intelligence impairment, using meta-analytic methods.

METHODS

Electronic databases were searched for peer-reviewed articles, published until February 2012. Studies reporting intelligence following TBI and injury severity by PTA duration were included. Meta-analytic methods generated effect sizes for full-scale IQ (FSIQ), performance IQ (PIQ) and verbal IQ (VIQ), following mild TBI (PTA duration 1-24 hours) and severe TBI (PTA duration > 7 days), during the subacute phase of recovery (≤ 6 months post-injury) and the chronic phase (> 6 months post-injury). Meta-regression elucidated the predictive value of PTA duration for intelligence impairment.

RESULTS

Patients with severe TBI exhibited large depressions of FSIQ in the subacute phase of recovery ($p < .001$, $d = -1.07$), persisting into the chronic phase ($p < .001$, $d = -0.78$). PIQ was more severely affected than VIQ in the subacute phase ($Q(1) = 3.9$, $P < .05$), but not in the chronic phase ($Q(1) = 0.0$, $p = .87$). Most importantly, longer PTA duration strongly predicted greater depressions of FSIQ and PIQ in the subacute phase ($-.76 \leq \beta s \leq -.73$, $ps < .01$) and FSIQ, PIQ and VIQ in the chronic phase ($-.80 \leq \beta s \leq -.61$, $ps < .05$).

CONCLUSIONS

PTA duration is a valuable predictor of intelligence impairment following TBI. Results support the routine assessment of PTA duration in clinical settings.

INTRODUCTION

In the USA, 1.4 million individuals sustain traumatic brain injury (TBI) each year (Langlois, Rutland-Brown, & Thomas, 2004). The corresponding figure for Europe is 0.8 million cases (Tagliaferri, Compagnone, Korsic, Servadei, & Kraus, 2006). TBI frequently has adverse effects on functioning, including pronounced intelligence impairment (Babikian & Asarnow, 2009; Carroll et al., 2004).

While mild TBI has only a limited impact on IQ, severe TBI can cause medium to large-sized depressions in IQ (Babikian & Asarnow, 2009; Carroll et al., 2004). Although considerable recovery may take place, predominantly in the first six months following severe TBI (Bond, 1976; Mandleberg & Brooks, 1975), intelligence impairment frequently persists (Babikian & Asarnow, 2009; Bond, 1976; Mandleberg & Brooks, 1975). Regarding the impact of TBI on intelligence, it has been suggested that children are more vulnerable than adults (Anderson, Catroppa, Morse, Haritou, & Rosenfeld, 2000; Donders & Warschausky, 2007; Verger et al., 2000). Importantly, the presence of intelligence impairment interferes with academic performance, vocational performance, social relations and mental health (Anderson, Brown, Newitt, & Hoile, 2011; Bowman, 1996; Donders & Warschausky, 2007; Donders, 1994; Yasuda, Wehman, Targett, Cifu, & West, 2001). This highlights the clinical value of accurate predictors of intelligence impairment in patients with TBI.

Post-traumatic amnesia (PTA) duration has been suggested to be the best single predictor of functional outcome following TBI (Greenwood, 1997). In this respect, PTA duration is potentially superior to the widely used Glasgow Coma Scale (GCS; which measures the level of consciousness) and to the duration of loss of consciousness (LOC; Knights et al., 1991; McDonald et al., 1994; Tremont, Mittenberg, & Miller, 1999). Unfortunately, studies into the predictive value of PTA duration show a striking heterogeneity in the definition of PTA duration (Ahmed, Bierley, Sheikh, & Date, 2000), questioning its current usefulness as a prognostic standard in clinical settings.

The aim of this study was to improve the accurate prediction of intelligence impairment following TBI, facilitating early referral to rehabilitation care. We applied meta-analytic methods to the available body of evidence in order to (1) determine the impact of TBI on intelligence and (2) elucidate the predictive value of PTA duration in terms of intelligence impairment. We also investigated the role of recovery and age at injury, given the reported moderating effects of these factors on post-TBI intelligence impairment (Anderson et al., 2000; Babikian & Asarnow, 2009; Bond, 1976; Donders & Warschausky, 2007; Mandleberg & Brooks, 1975; Verger et al., 2000).

METHODS

STUDY SELECTION

This meta-analysis was performed according to guidelines provided by Stroup, et al (2000). We included studies that: (1) investigated patients with TBI; (2) reported mean or median post-injury IQ according to the most widely used measure of intelligence: the Wechsler Intelligence Scales (either full or short forms); (3) reported PTA duration in days; and (4) reported the time elapsed between injury and assessment of IQ, enabling us to track the recovery of IQ. No language restrictions were set.

The electronic databases PubMed, Web of Science, EMBASE and PsycINFO were searched using the standard key words *Wechsler*, *Amnesia* and *Injury* (by M.K.) for studies published prior to February 2012. This search retrieved 1,271 peer-reviewed articles. A total of 209 studies was selected based on assessment of titles and abstracts. The reference lists of all selected articles were manually searched for additional studies meeting inclusion criteria, retrieving 11 relevant studies. Where necessary, additional data were requested from the authors concerned. A detailed inspection of 220 studies revealed 23 studies that satisfied the inclusion criteria. Of these studies, one study was excluded because data on PTA duration was restricted to a subgroup of the patient sample (Bittner & Crowe, 2006), and another because the patient sample consisted of only litigants (Langeluddecke & Lucas, 2003).

STUDY DESCRIPTION

Table 1 gives details of the 21 included studies. Four of these used orthopedic control groups, another four used normal control groups, while thirteen studies only reported intelligence of TBI groups. Five studies were longitudinal investigations, while the other sixteen studies were cross-sectional in nature. Six studies investigated pediatric TBI (age range 5-17), while fifteen studies investigated adult TBI (age range 19-41). Two studies investigated the role of substance abuse in patients with TBI (Kaplan & Corrigan, 1992; Kelly, Johnson, Knoller, Drubach, & Winslow, 1997), of which only subsamples with negative toxicology screens were included. Another study focused predominantly on frontal TBI and aberrant executive functioning in two age groups, which were included in the analysis as separate samples (Barker, Andrade, Morton, Romanowski, & Bowles, 2010). Finally, one study investigated the effect of repetitive TBI on IQ, but only the TBI group without prior head injury was included (Ropacki & Elias, 2003).

All of the included studies reported their findings in English, except for one Spanish article (Ferri et al., 2004) which was translated by a native Spanish speaker.

MODERATOR AND DEPENDENT VARIABLES

INTELLIGENCE

Intelligence was defined according to Wechsler and was measured by age-corrected standardized scores on various versions of the Wechsler Adult Intelligence Scale (WAIS) and the Wechsler Intelligence Scale for Children (WISC), with a mean of 100 (SD=15; (Wechsler, 1949, 1955, 1974, 1981, 1991, 1997). Short forms were included since they show high agreement with full-administrations of the WAIS and the WISC ($r \geq .90$; Guilmette, Dabrowski, Kennedy, & Gnys, 1999; Silverstein, 1967). Mean full-scale IQ (FSIQ), performance IQ (PIQ) and verbal IQ (VIQ) and accompanying SDs were extracted from the articles for the TBI groups and control groups (if available).

Table 1. Studies included for meta-analysis reporting intelligence following TBI

	Study Methodology							Injury Severity			Demographics			
Ref	*n*	Injury	Design	Control	IQ Scale	PTA Scale	Quality	PTA (*d*)	GCS score	TPI (*m*)	Age (*y*)	Age Injury (*y*)	Education (*y*)	Males (%)
Total Sample														
	854	**-**	**-**	**-**	**-**	**M (SD):**		**28.0 (32.2)**	**10.6 (3.9)**	**22.7 (30.1)**	**26.6 (10.2)**	**25.0 (9.9)**	**12.3 (0.9)**	**71.6 (7.4)**
		-	**-**	**-**	**-**	**Range:**		**0.5-120**	**5-15**	**0-127**	**9-44**	**9-43**	**10-14**	**53-94**
Subacute phase of recovery														
[1]	19	HI	L	OC	WISC (6)[a]	Retro	7	0.5	n/a	0.6	9.6	9.6	n/a	75.9
[2]	63	TBI	L	OC	WAIS	Retro	6	0.5	14.8	1.0	26.5	26.5	12.9	67.0
[3]	24	TBI	CS	OC	WAIS-R (5)[a]	Retro	5	0.5	14.8	0.2	31.2	31.2	n/a	66.7
[4]	27	CHI	CS	-	WISC-III	Pro (TPP)	3	0.5	14.3	1.7	10.4	10.4	n/a	70.4
[5]	25	CHI	L	-	WISC-III	Pro (TPP)	3	0.5	14.2	3.0	10.5	10.5	n/a	76.0
[6]	30	CHI	CS	OC	WISC-III	COAT	6	4.0	n/a	0.2	10.9	10.9	12.7[b]	67.0
[7]	17	CHI	CS	-	WAIS-R	Retro	3	15.2	9.4	discharge	42.9	42.9	12.1	52.9
[8]	26	TBI	L	-	WISC-R	Pro (TPP)	1	29.0	5.5	discharge	10.8	10.8	n/a	66.7
[9]	23	CHI	CS	C	WAIS-R	Westmead	5	29.0	9.0	0.5	26.2	26.2	10.0	81.0
[10]	50	CHI	CS	-	WAIS-R	n/a	2	30.0	10.6	1.6	41.5	41.5	11.6	74.8
[11]	39	CHI	CS	-	WAIS-R	OGMS	2	66.8	n/a	PTA clearance	27.6	27.6	11.7	n/a
[12]	20	CHI	L	-	WISC	n/a	3	69.0	5	PTA clearance	12.2	12.2	n/a	65.0
Total: 363						**M (SD):**	**3.8 (1.9)**	**23.3 (12.2)**	**11.5 (3.7)**	**2.5 (2.4)**	**23.3 (12.2)**	**23.3 (12.2)**	**12.0 (0.9)**	**69.8 (6.5)**
						Range:	**1-7**	**1-69**	**15-5**	**0-6**	**10-43**	**9 - 43**	**10-13**	**53-81**
Chronic phase of recovery														
[1]	19	HI	L	OC	WISC (6)[a]	Retro	7	0.5	n/a	12.0	10.6	9.6	n/a	75.9
[2]	63	TBI	L	OC	WAIS	Retro	6	0.5	14.8	12.0	27.5	26.5	12.9	67.0
[13]	41	CHI	CS	-	WAIS-R	n/a	1	0.5	n/a	21.8	34.4	32.6	12.8	n/a
[5]	25	CHI	L	-	WISC-III	Pro (TPP)	3	0.5	14.2	24.0	10.5	10.5	n/a	76.0
[14]	118	CHI	CS	-	WAIS-III	n/a	3	17.3	8.4	34.8	35.5	32.6	n/a	71.2
[15]	81	CHI	CS	-	WAIS-R	n/a	1	21.0	n/a	33.6	32.0	29.2	12.0	61.7
[16]	16	TBI	CS	C	WAIS-III	n/a	2	22.1	5.4	n/a	24.7	18.6	n/a	93.8

Study Methodology								Injury Severity			Demographics			
Ref	*n*	Injury	Design	Control	IQ Scale	PTA Scale	Quality	PTA (*d*)	GCS score	TPI (*m*)	Age (*y*)	Age Injury (*y*)	Education (*y*)	Males (%)
Chronic phase of recovery (Continued)														
[17]	78	TBI	CS	-	WAIS-R	Retro	3	23.7	n/a	34.3	29.8	29.7	n/a	80.7
[8]	26	TBI	L	-	WISC-R	Pro (TPP)	1	29.0	5.5	9.0	11.6	10.8	n/a	66.7
[16]	16	TBI	CS	C	WAIS-III	n/a	2	62.5	4.7	n/a	44.4	40.6	n/a	87.5
[18]	55	CHI	CS	-	WAIS-R	n/a	1	67.5	n/a	88.9	29.3	21.9	n/a	79.0
[12]	20	CHI	L	-	WISC	n/a	3	69.0	5.0	116.4	22.3	12.2	n/a	65.0
[19]	22	CHI	CS	C	WAIS-R (4)[a]	Retro	4	74.8	n/a	126.6	35.6	25.3	14.0	83.3
[20]	44	CHI	CS	-	WAIS-III	GOAT	3	110.5	n/a	10.4	27.4	26.5	11.7	71.7
[21]	20	CHI	CS	C	WAIS-R (4)[a]	Retro	4	125.0	n/a	65.0	29.3	23.9	14.1	70.0
Total: 644						**M (SD):**	**2.9 (1.8)**	**34.0[c] (36.1)**	**9.4 (4.0)**	**39.2 (32.0)**	**29.2 (7.6)**	**26.3 (7.6)**	**12.6 (0.8)**	**72.9 (7.9)**
						Range:	**1-7**	**1-125**	**15-5**	**12-127**	**11-41**	**10-44**	**12-14**	**62-94**

Note. Means were weighted for sample size. C = control group; CS = Cross-sectional; CHI= closed head injury; COAT = Children Orientation and Amnesia Test; GCS = Glasgow Coma Scale; GOAT = Galveston Orientation and Amnesia Test; HI = head injury; L = Longitudinal; M (SD) = mean (standard deviation); *n* = number of subjects; OC = orthopedic control group; OGMS = Orientation Group Monitoring System; Pro (TPP) = prospectively administrated (orientation in time, person and place); PTA = post-traumatic amnesia; retro = retrospectively administrated by interviewing; Ref = reference (see List of articles included in meta-analysis); TBI = traumatic brain injury (not otherwise specified); TPI = time post injury; WAIS = Wechsler Adult Intelligence Scale; WAIS-R = Wechsler Adult Intelligence Scale Revised; WAIS-III = Wechsler Adult Intelligence scale, Third Edition; WISC = Wechsler Intelligence Scale for Children; WISC-R = Wechsler Intelligence Scale for Children Revised; WISC-III = Wechsler Intelligence Scale for Children, Third Edition.

[a]IQ prorated based on (*n*) subtests. [b]Parental years of education. [c]After the exclusion of two outliers in terms of TBI severity (Ferri et al., 2004; Schmitter-Edgecombe, Marks, Fahy, & Long, 1992), mean PTA duration in the chronic phase group was 25.0 days (SD = 24.7).

TIME POST-INJURY (TPI)

In order to investigate recovery from TBI, we distinguished between the subacute phase of recovery (≤ 6 months post-injury) and the chronic phase (> 6 months post-injury). This distinction in phases of recovery is in accordance with findings by Babikian and Asarnow (2009).

Four studies did not report mean TPI. Of these, two performed intelligence testing on clearing of PTA, while mean PTA durations were well within six months (Cattelani, Lombardi, Brianti, & Mazzucchi, 1998; Kaplan & Corrigan, 1992). The other two studies performed intelligence testing at the time of discharge from the hospital (Knights et al., 1991; Ropacki & Elias, 2003). It has been reported that the average duration of hospitalization for patients with severe TBI is well within six months (Fakhry, Trask, & Waller, 2004), hence the four studies that did not report PTA duration were assigned to the subacute TPI group. Their TPI was conservatively estimated at 6 months, thereby diminishing the chances of finding a difference in TPI between the subacute and chronic groups.

PTA DURATION

Injury severity was measured by PTA duration in days. The definition of PTA duration varied considerably across studies. This is reflected by the heterogeneity in the methodology applied to assess PTA duration (see Table 1): seven studies used retrospective self-reports or standardized interviews, while another seven studies used prospective methods, including measurement of time until recovery to orientation in time, place and person took place, and administration of the Children's Orientation and Amnesia Test, Westmead PTA scale, Orientation Group Monitoring System or Galveston Orientation and Amnesia Test. A further seven studies gave no details of the methodology used. The best general description of PTA duration across studies is the period between injury and the recovery of anterograde amnesia and/or orientation.

In the analyses aimed at quantifying the impact of TBI on intelligence, injury severity was categorized into mild (PTA duration 1-24 hours), moderate (PTA duration 1-7 days) and severe TBI (PTA duration > 7 days; Catroppa & Anderson, 2005). This method showed strong agreement (81%) with alternative classification according to the widely used GCS, indicating that PTA duration is a valid method to categorize injury severity of TBI. The moderate TBI group consisted of only one study (Tremont et al., 1999) and therefore this study was excluded from all analyses that focused on mild and severe TBI.

In the analyses aimed at determining the predictive value of PTA duration for the impact of TBI on intelligence, PTA duration was used as a continuous measure. Studies on mild TBI did not specify mean or median PTA duration and therefore, mean PTA duration was estimated at 0.5 days (see Table 1). One study reported median PTA duration (Watt, Shores, Baguley, Dorsch, & Fearnside, 2006) and techniques developed by Hozo, Djulbegovic and Hozo (2005) were used to calculate mean PTA duration for this study.

DEMOGRAPHIC VARIABLES

Mean age, age at injury, years of education and gender ratio were used as demographic variables to determine the comparability of the subacute and chronic phase groups as well as the mild and severe TBI groups (Table 1). In case studies in the chronic phase group did not report age at injury, this variable was calculated by subtracting TPI from age at time of IQ assessment.

STUDY QUALITY

The quality of included studies was independently assessed by two authors (M.K. and J.F. de K.) using the Newcastle-Ottowa Scale (Wells et al., 2012). This measure allows study quality to be quantified on the basis of the selection of subjects (4 points), comparability of experimental and control groups (2 points) and exposure of subjects to the condition assessed (3 points). Higher scores reflect better study quality (0-9 points). Inter-rater agreement was satisfactory (intraclass correlation = .81) and any rating discrepancies were resolved by consensus.

STATISTICAL ANALYSIS

Statistical analysis was performed using Comprehensive Meta-Analysis (Borenstein, 2005) and SPSS version 17.0 (SPSS Statistics for Windows, 2008). Firstly, we assessed group comparability in terms of demographic and injury related variables using independent t-tests comparing mean age, age at injury, years of education, gender ratio, PTA duration and TPI between the subacute and chronic groups as well as between the mild and severe TBI groups.

Secondly, we determined the impact of TBI on FSIQ, PIQ and VIQ for the mild and severe TBI groups in both the subacute and chronic phase groups. The effect size for each individual study was calculated using the mean IQ and associated SD of the TBI group and either: (1) the mean IQ and SD of the control group for controlled studies; or (2) the Wechsler normative mean and associated SD for uncontrolled studies (assuming a sample size equal to that of the TBI group). The comparability of the results obtained using these two

methods was assessed by calculating the effect sizes for controlled studies using both methods and comparing possible differences with *Q*-testing. There was no significant difference between the effect sizes for FSIQ, PIQ and VIQ derived using these methods, $Q(1) = 0.0$, $p = .91$; $Q(1) = 0.4$, $p = .53$ and $Q(1) = 0.1$, $p = .74$, respectively. This justifies our decision to use normative data for comparison with the TBI data for uncontrolled studies. The effect sizes for individual studies were weighted by inverse variance, thereby accounting for sample size and measurement error (Hedges & Olkin, 1985). Heterogeneity of the effect was assessed using *Q*-testing (Cochran, 1954). Homogeneous effects were analyzed using a fixed approach, whereas heterogeneous effects were analyzed using a random approach. Negative effect sizes indicate inferior performance of the TBI group as compared to that of the comparison group. Cohen's guidelines for the interpretation of effect sizes were used, translating $d = -0.20$ into small, $d = -0.50$ into medium and $d = -0.80$ into large effect sizes (Cohen, 1988).

Thirdly, we clarified the effects of TBI severity (as measured by PTA duration), recovery (as measured by TPI) and age at injury on IQ. To this end, we compared effect sizes for FSIQ, PIQ and VIQ, of the mild and severe TBI groups within and between the subacute and chronic phase groups, using *Q*-testing. Two studies were excluded from comparisons between TPI groups, as they were considered outliers in terms of TBI severity (PTA duration > M + 2SD; Ferri et al., 2004; Schmitter-Edgecombe, Marks, Fahy, & Long, 1992), which could potentially mask the effects of recovery. The role of age at injury was investigated by performing a meta-regression between age at injury and effect-sizes for FSIQ, PIQ and VIQ. Meta-regression analyses were performed using the *method of moments* (DerSimonian & Laird, 1986).

Fourthly, we determined the predictive power of PTA duration for intelligence impairment in patients with TBI using meta-regression in the total sample and separately in the subacute phase group and in the chronic phase group. The regression slopes were manually standardized by multiplying them by the ratio between the SD of the independent variable (PTA duration) and the SD of the dependent variable (Luskin, 1991). They were interpreted as correlation coefficients according to Cohen, translating $\beta = -.10$ into weak, $\beta = -.30$ into moderate and $\beta = -.50$ into strong relations, respectively (Cohen, 1988). In order to study differences in the strength of associations between PTA duration and FSIQ, PIQ and VIQ, we compared the standardized slopes for the three IQ measures using independent sample t-tests.

Finally, the possibility of publication bias was assessed for all meta-analytic effect sizes using four complementary methods: (1) Rosenthal's fail-safe N was calculated to determine the number of studies required to nullify the meta-analytic effect size

(Rosenthal, 1995); (2) we investigated the possible influence of the tendency that significant results in small samples are easier to publish than nonsignificant results, which would appear as a significant positive association between sample size and effect size in meta-regression (with smaller samples being associated with more negative effect sizes signifying worse performance in TBI); (3) we used the linear regression methods as proposed by Egger, Smith, Schneider and Minder to determine the degree of funnel plot asymmetry (Egger, Smith, Schneider, & Minder, 1997); and (4) the possibility that study quality might moderate effect sizes was investigated using meta-regression analysis. In all analyses, significance testing was two-sided and α was set at .05.

RESULTS

DEMOGRAPHIC AND INJURY RELATED VARIABLES

Demographic and injury related information on the samples of patients with TBI is given in Table 1. Apart from the anticipated findings that PTA duration was longer in the severe TBI group than in the mild TBI group ($t(11.9) = -4.9$, $p < 0.001$) and that the subacute phase group had a shorter TPI than the chronic phase group ($t(11.4) = -4.1$, $p < .01$) no differences in age, age at injury, years of education, gender ratio, TPI or PTA duration were found between the mild and severe TBI groups and the subacute and chronic groups ($-1.4 \leq t\text{s} \leq 1.7$, $p\text{s} \geq 0.10$). The mild TBI group tended to have a shorter TPI and lower age than the severe TBI group ($t(17) = -2.0$, $p = .06$ and $t(11) = -2.0$, $p = .07$, respectively).

INTELLIGENCE FOLLOWING MILD AND SEVERE TBI

The results of analyses aimed at quantifying the impact of TBI on FSIQ, PIQ and VIQ in the total sample are shown in Figure 1. Table 2 shows the meta-analytic effects of mild (PTA duration M = 0.5 days, SD = 0) and severe TBI (PTA duration M = 43, SD = 31.1) on IQ, in both the subacute phase and the chronic phase. The effect sizes for IQ in patients with mild TBI showed no significant heterogeneity, indicating that there were only minor differences in effect sizes between studies. In contrast, all effect sizes for IQ in patients with severe TBI, (except for VIQ in the chronic phase) were heterogeneously distributed, indicating considerable differences in effect sizes between studies that assessed patients with severe TBI.

Patients with mild TBI showed no significant depressions in FSIQ, PIQ and VIQ in the subacute and chronic phases of recovery. In contrast, patients with severe TBI exhibited a large depression in FSIQ in the subacute phase of recovery and a medium to large-sized depression in the chronic phase. This difference over time was not statistically significant ($Q(1) = 2.1$, $p = .15$). Furthermore, patients with severe TBI showed a large depression in PIQ in the subacute phase and medium-sized depression in PIQ in the chronic phase. The magnitude of the deficit in PIQ was significantly larger in the subacute phase than in the chronic phase ($Q(1) = 8.6$, $p < .05$). In contrast, patients with severe TBI had a medium to large-sized depression in VIQ, showing no significant differences between the subacute and chronic phase ($Q(1) = 0.0$, $p = .88$).

Figure 2 shows the effects of mild and severe TBI on the three IQ measures in both the subacute and chronic phase. As expected, comparisons between patients with mild and severe TBI revealed that severe TBI caused significantly larger depressions in FSIQ, PIQ and

VIQ in both the subacute phase and the chronic phase (Qs(1) ≥ 4.0, ps < .05). Comparison between IQ-indices revealed that patients with severe TBI exhibit a significantly larger depression in PIQ than in VIQ in the subacute phase (Q(1) = 3.9, p < .05), but not in the chronic phase (Q(1) = 0.03, p = .87).

Finally, age at injury was not significantly associated with effect sizes for FSIQ (β = -.27, p = .21), PIQ (β = -.14, p = .54) and VIQ (β = -.22, p = .34), suggesting that the effects of TBI on intelligence are not significantly affected by age at injury.

IQ-index	Ref	Severity	PTA duration[a]	TPI group	Effect Size Statistics				
					Cohen's *d*	SE	95% CI		*p*
	3	Mild	0.50	Subacute	-0.10	0.31	-0.71	0.50	.74
	4	Mild	0.50	Subacute	0.13	0.27	-0.40	0.66	.63
	5	Mild	0.50	Subacute	0.17	0.28	-0.39	0.72	.55
	13	Mild	0.50	Chronic	-0.28	0.24	-0.76	0.19	.24
	5	Mild	0.50	Chronic	0.22	0.28	-0.33	0.78	.43
	6	Moderate	4.00	Subacute	-0.81	0.27	-1.33	-0.28	.00
	7	Severe	15.24	Subacute	-0.85	0.36	-1.55	-0.14	.02
	14	Severe	17.31	Chronic	-0.83	0.14	-1.10	-0.56	.00
	16	Severe	22.10	Chronic	-0.13	0.35	-0.83	0.56	.71
	17	Severe	23.70	Chronic	-0.81	0.17	-1.13	-0.48	.00
	8	Severe	29.00	Subacute	-1.53	0.32	-2.14	-0.91	.00
	8	Severe	29.00	Chronic	-0.40	0.28	-0.95	0.15	.16
	6	Severe	29.03	Subacute	-0.26	0.30	-0.84	0.32	.37
	10	Severe	30.00	Subacute	-1.11	0.21	-1.53	-0.69	.00
	16	Severe	62.50	Chronic	-0.26	0.36	-0.95	0.44	.47
	11	Severe	66.80	Subacute	-1.53	0.26	-2.04	-1.03	.00
	18	Severe	67.52	Chronic	-1.20	0.21	-1.61	-0.79	.00
	19	Severe	74.83	Chronic	-0.53	0.30	-1.12	0.06	.08
	20	Severe	110.50	Chronic	-1.66	0.25	-2.14	-1.17	.00
	21	Severe	125.00	Chronic	-0.77	0.34	-1.43	-0.11	.02
FSIQ	*Q (19) = 87.1, p < .001*				**-0.64**	**0.12**	**-0.88**	**-0.40**	**.00**
	2	Mild	0.50	Subacute	0.20	0.16	-0.11	0.51	.22
	3	Mild	0.50	Subacute	-0.13	0.31	-0.73	0.48	.68
	5	Mild	0.50	Subacute	-0.23	0.31	-0.83	0.36	.44
	4	Mild	0.50	Subacute	0.38	0.27	-0.16	0.92	.17
	2	Mild	0.50	Chronic	0.17	0.18	-0.18	0.52	.33
	1	Mild	0.50	Chronic	-0.42	0.30	-1.01	0.17	.16
	13	Mild	0.50	Chronic	-0.22	0.24	-0.69	0.25	.36
	6	Moderate	4.00	Subacute	-0.79	0.27	-1.31	-0.26	.00
	7	Severe	15.24	Subacute	-1.07	0.37	-1.79	-0.35	.00
	14	Severe	17.31	Chronic	-0.81	0.14	-1.07	-0.54	.00
	15	Severe	21.00	Chronic	-0.59	0.16	-0.90	-0.27	.00
	16	Severe	22.10	Chronic	-0.47	0.36	-1.18	0.23	.19
	8	Severe	29.00	Subacute	-1.69	0.32	-2.33	-1.06	.00
	8	Severe	29.00	Chronic	-0.13	0.28	-0.67	0.42	.65
	9	Severe	29.03	Subacute	-0.59	0.30	-1.18	0.00	.05
	10	Severe	30.00	Subacute	-1.26	0.22	-1.69	-0.83	.00
	16	Severe	62.50	Chronic	-0.33	0.36	-1.03	0.37	.36
	11	Severe	66.80	Subacute	-1.83	0.27	-2.36	-1.30	.00
	12	Severe	69.00	Subacute	-0.94	0.33	-1.59	-0.29	.00
	12	Severe	69.00	Chronic	-0.86	0.33	-1.51	-0.21	.01
	20	Severe	110.50	Chronic	-1.64	0.25	-2.12	-1.16	.00
PIQ	*Q (20) = 131.4, p < .001*				**-0.62**	**0.14**	**-0.89**	**-0.35**	**.00**
	3	Mild	0.50	Subacute	-0.36	0.31	-0.96	0.24	.23
	1	Mild	0.50	Subacute	-0.34	0.31	-0.94	0.26	.27
	4	Mild	0.50	Subacute	-0.11	0.27	-0.65	0.42	.68
	1	Mild	0.50	Chronic	-0.40	0.30	-0.99	0.19	.18
	13	Mild	0.50	Chronic	-0.33	0.24	-0.80	0.14	.17
	6	Moderate	4.00	Subacute	-0.66	0.27	-1.18	-0.14	.01
	7	Severe	15.24	Subacute	-0.66	0.35	-1.35	0.03	.06
	14	Severe	17.31	Chronic	-0.81	0.14	-1.08	-0.55	.00
	15	Severe	21.00	Chronic	-0.84	0.16	-1.16	-0.52	.00
	16	Severe	22.10	Chronic	-0.18	0.35	-0.87	0.52	.62
	8	Severe	29.00	Subacute	-1.19	0.30	-1.78	-0.60	.00
	8	Severe	29.00	Chronic	-0.52	0.28	-1.07	0.04	.07
	9	Severe	29.03	Subacute	0.05	0.29	-0.53	0.62	.88
	10	Severe	30.00	Subacute	-0.83	0.21	-1.24	-0.42	.00
	16	Severe	62.50	Chronic	-0.54	0.36	-1.25	0.16	.13
	11	Severe	66.80	Subacute	-1.05	0.24	-1.52	-0.57	.00
	12	Severe	69.00	Subacute	-0.66	0.32	-1.30	-0.03	.04
	12	Severe	69.00	Chronic	-0.47	0.32	-1.10	0.16	.14
	20	Severe	110.50	Chronic	-1.38	0.23	-1.84	-0.92	.00
VIQ	*Q (18) = 35.1, p < .01*				**-0.63**	**0.08**	**-0.79**	**-0.47**	**.00**

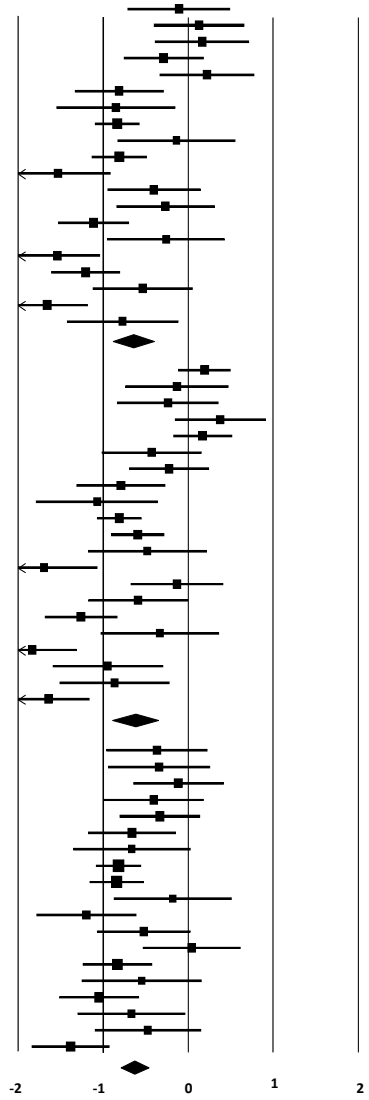

Figure 1. Effect sizes for each study, ordered by PTA duration

Note. CI = confidence interval; FSIQ = full-scale intelligence quotient; PIQ = performance intelligence quotient; PTA = post-traumatic amnesia; SE = standard error; TPI = time post-injury; Ref = Reference; VIQ = verbal intelligence quotient.

[a]PTA duration displayed in days

Table 2. Effect sizes reflecting the impact of mild and severe TBI on IQ, in the subacute and chronic phase of recovery

	FSIQ					PIQ					VIQ				
Group	*k*	ES	*95% CI*	*p*	*Q*	*k*	ES	*95% CI*	*p*	*Q*	*k*	ES	*95% CI*	*p*	*Q*
Mild TBI															
Subacute Phase	3	0.08	-0.25 to 0.40	.65	0.5	4	0.12	-0.11 to 0.35	.30	3.1	3	-0.26	-0.59 to 0.07	.13	0.5
Chronic Phase	2	-0.07	-0.43 to 0.29	.70	1.9	3	-0.05	-0.30 to 0.20	.70	3.6	2	-0.36	-0.73 to 0.01	.06	0.0
Severe TBI															
Subacute Phase	5	-1.07	-1.52 to -0.62	**<.001**	13.1*	6	-1.24	-1.62 to -0.87	**<.001**	12.4*	6	-0.74	-1.08 to -0.40	**<.001**	11.2*
Chronic Phase	9	-0.78	-1.06 to -0.51	**<.001**	24.3**	7	-0.71	-1.05 to -0.38	**<.001**	21.3**	7	-0.79	-0.95 to -0.63	**<.001**	11.8

Note. CI = confidence interval; ES = effect size (Cohen's *d*); FSIQ = full-scale intelligence quotient; *k* = number of studies; PIQ = performance intelligence quotient; VIQ = verbal intelligence quotient.
*$p < .05$. **$p < .01$. ***$p < .001$.

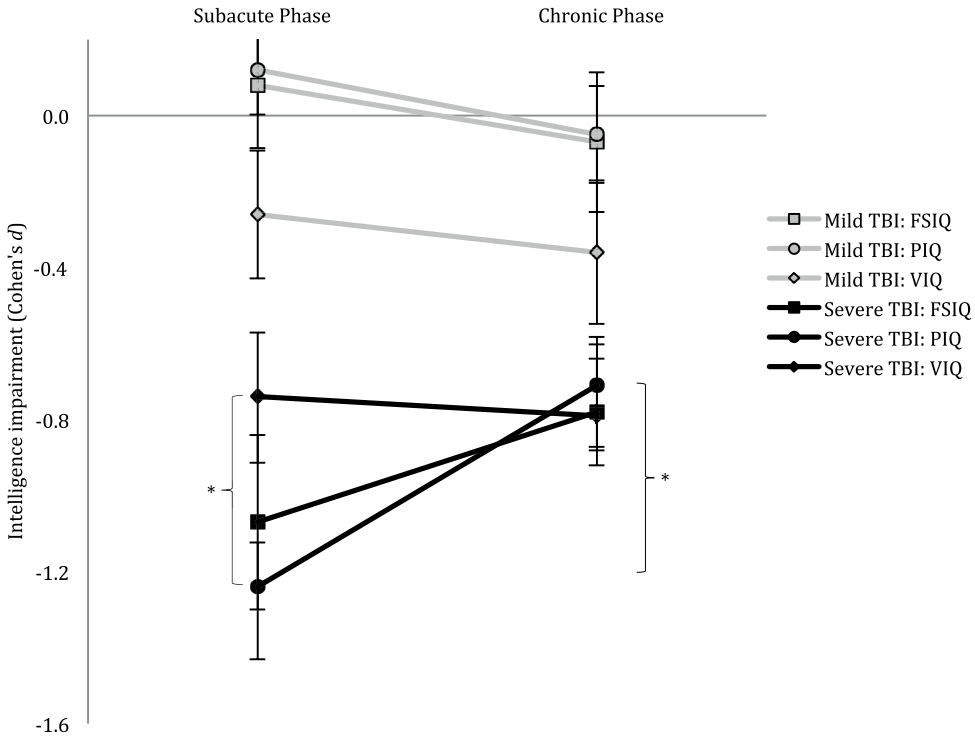

Figure 2. Intelligence impairment in patients with mild and severe TBI

Note. Error bars represent standard error. Asterisks in the chart area indicate that patients with severe TBI exhibited significantly greater depressions of PIQ in the subacute phase of recovery than in the chronic phase (left), and that patients with severe TBI exhibited significantly greater depressions of PIQ than of VIQ, in the subacute phase (right). FSIQ = full-scale intelligence quotient; PIQ = performance intelligence quotient; TBI = traumatic brain injury; VIQ = verbal intelligence quotient.

PREDICTIVE VALUE OF PTA DURATION FOR IMPAIRMENTS IN INTELLIGENCE

Table 3 shows the results of the meta-regression analysis between PTA duration and intelligence impairment. Longer PTA duration was strongly predictive of greater depressions in FSIQ, PIQ and VIQ in the total sample, the subacute phase as well as the chronic phase. While longer PTA duration was strongly predictive of greater VIQ depressions in the subacute phase, this relationship did not reach conventional levels of significance. There were no significant differences in the predictive value of PTA duration for FSIQ, PIQ and VIQ in the subacute or chronic phases (*t*s ≤ 0.6, *p*s ≥ .55).

Table 3. Results of the meta-regression assessing the predictive value of PTA duration

	FSIQ			PIQ			VIQ		
Group	*k*	β[a]	*p*	*k*	β[a]	*p*	*k*	β[a]	*p*
Total Sample	20	-.58	**.002**	21	-.68	**< .001**	19	-.56	**.003**
Subacute Phase	9	-.76	**.001**	11	-.73	**.001**	10	-.52	.08
Chronic Phase	11	-.63	**.01**	10	-.80	**.001**	9	-.61	**.03**

Note. FSIQ = full-scale intelligence quotient; *k* = number of studies; PIQ = performance intelligence quotient; VIQ = verbal intelligence quotient.

[a]Standardized regression slopes.

PUBLICATION BIAS

It was not possible to perform publication bias analyses for reports on FSIQ and VIQ in patients with mild TBI in the chronic phase group, as there were too few studies available to conduct these analyses. For the remaining reports on mild TBI, there was some evidence for publication bias: fail-safe N values did not exceed 0, the Egger funnel plot asymmetry approached significance (*p*s ≥ .07) and some strong positive associations between sample size and effect size were found for FSIQ, PIQ and VIQ (-.20 ≤ βs ≤ .99, *p*s ≥ .06).

In contrast, reports on severe TBI showed no evidence of publication bias in either the subacute phase or the chronic phase groups. The fail-safe N values were greater than 61, the Egger funnel plot asymmetry did not reach significance (*p*s ≥ .30) nor did the associations between effect sizes and sample size did not reach significance (-.44 ≤ βs ≤ -.21, *p*s ≥ .31).

There were no significant negative associations between study quality and effect sizes for FSIQ, PIQ and VIQ in either the subacute phase or the chronic phase in patients with either mild or severe TBI (βs ≥ -.66, *p*s ≥ .08). This indicates that lower study quality was not associated with larger effect sizes, also arguing against the possibility of publication bias.

DISCUSSION

This meta-analysis demonstrates that longer PTA duration strongly predicts intelligence impairment, as defined by the widely used Wechsler intelligence scales, in a large sample of 854 patients with TBI derived from 21 peer-reviewed articles. Despite the marked variability in the methodology used to assess PTA duration, which introduced heterogeneity to this measurement, PTA duration strongly predicted depressions in FSIQ, PIQ and VIQ in both the subacute phase of recovery (correlations ranging between -0.76 and -0.52) and the chronic phase (correlations ranging between -0.80 and -0.61). Our findings indicate that PTA duration is a valuable predictor of intelligence impairment following TBI.

The outcomes of previous investigations (Knights et al., 1991; McDonald et al., 1994; Tremont et al., 1999) are in line with the current findings, reporting moderate to strong relations between PTA duration and Wechsler Scale FSIQ, PIQ and VIQ in children with TBI (correlations ranging between -.61 and -.35). These studies investigated the predictive value of PTA duration for intelligence, while we investigated its predictive value for *declines in intelligence.* Our approach partly corrects for premorbid functioning when using appropriate control groups, which may account for the somewhat higher predictive values of PTA duration derived in the current study, than those reported elsewhere in the literature.

It is important to note that there is evidence supporting the idea that the predictive value of PTA duration for intelligence is superior to those obtained with the widely used GCS score (correlations ranging between .16 and .42) and LOC duration (correlations ranging between -.52 and -.24; Knights et al., 1991; McDonald et al., 1994; Tremont et al., 1999). One explanation for this discrepancy is that the GCS score and LOC duration are measures of consciousness, which is a low-order neurocognitive function underlying higher neurocognitive functions. In contrast, the resolution of PTA requires the recovery of attention and memory (Tittle & Burgess, 2011), which are higher-order neurocognitive functions allowing higher levels of functioning than would be obtained after regaining consciousness only. Consequently, the resolution of PTA reflects the initial recovery of neurocognitive functions that are more directly related to intelligence (high-order neurocognitive function). This would explain that PTA duration is superior to the GCS score and LOC duration in predicting intelligence following TBI. However, more research is needed to test the predictive value of PTA duration in comparison with those of the GCS and LOC duration.

Analyses aimed at elucidating the impact of TBI on IQ are in line with a World Health Organization report which stated that mild TBI does not affect IQ (Carroll et al., 2004). In contrast, patients with severe TBI showed medium to large-sized depressions in IQ in the subacute phase of recovery (Cohen's *d* ranging between -1.24 and -0.74), persisting into the chronic phase (Cohen's *d* ranging between -0.79 and -0.71). These chronic deficits in patients with severe TBI translate into an FSIQ score that is on average 12 points lower than expected, emphasizing the fact that severe TBI has major consequences for intelligence. Although patients with severe TBI exhibited medium to large-sized depressions in both PIQ and VIQ up to the chronic phase of recovery, PIQ was more severely affected than VIQ in the subacute phase, but not in the chronic phase. This observation has previously been described, and was explained by the greater vulnerability of fluid aspects of intelligence (such as attention, psychomotor speed and visuospatial function) to TBI, as compared to crystallized aspects (such as verbal comprehension; Babikian & Asarnow, 2009). However, our results also indicate recovery of PIQ following severe TBI, while VIQ remained unchanged. This could possibly interfere with the development of verbal skills in children, which are strongly related to academic achievement following TBI (Donders, 1994).

Age at injury was not related to the magnitude of intelligence impairment in this meta-analysis. Our finding contrasts with previous studies, reporting an inverse relationship between age at injury and the magnitude of intelligence impairment (Anderson et al., 2000; Donders, 1994; Verger et al., 2000). This contrast may be explained by a lack of power, caused by the relatively small number of studies on pediatric TBI (six out of twenty one). Furthermore, three out of six studies on pediatric TBI concerned mild injuries. As our results indicate that mild TBI does not affect intelligence, this further reduced the chances of identifying the previously described negative association between age and injury and magnitude of intelligence impairment.

This meta-analysis has, to some extent, been compromised by a limited number of studies linking TBI severity to PTA duration. Although there was some evidence for publication bias regarding the reports on mild TBI, the relevant effect sizes were not significant. In contrast, there was found no evidence of publication bias for reports on severe TBI. Furthermore, the effect sizes on IQ suffered from a degree of heterogeneity, which possibly reflected differences in terms of injury severity within the mild and severe TBI groups, as was shown by the strong moderating role of PTA duration on intelligence impairment. Finally, we pooled uncontrolled and controlled studies and applied a cross-sectional approach to track the recovery of intelligence following TBI. We confirmed the validity of these strategies by showing that controlled and uncontrolled studies did not

yield significantly different results, and that the subacute and chronic groups did not differ in terms of the relevant demographic and injury-related variables.

In conclusion, current findings indicate that PTA duration is a clinically valuable predictor of intelligence impairment, up to the chronic phase of recovery from TBI. Therefore, our results support the routine assessment of PTA duration in clinical settings. Future studies need to address the important question of whether PTA duration is indeed a more valuable predictor of intelligence impairment than classic indices of TBI severity.

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