Traumatic brain injury in children

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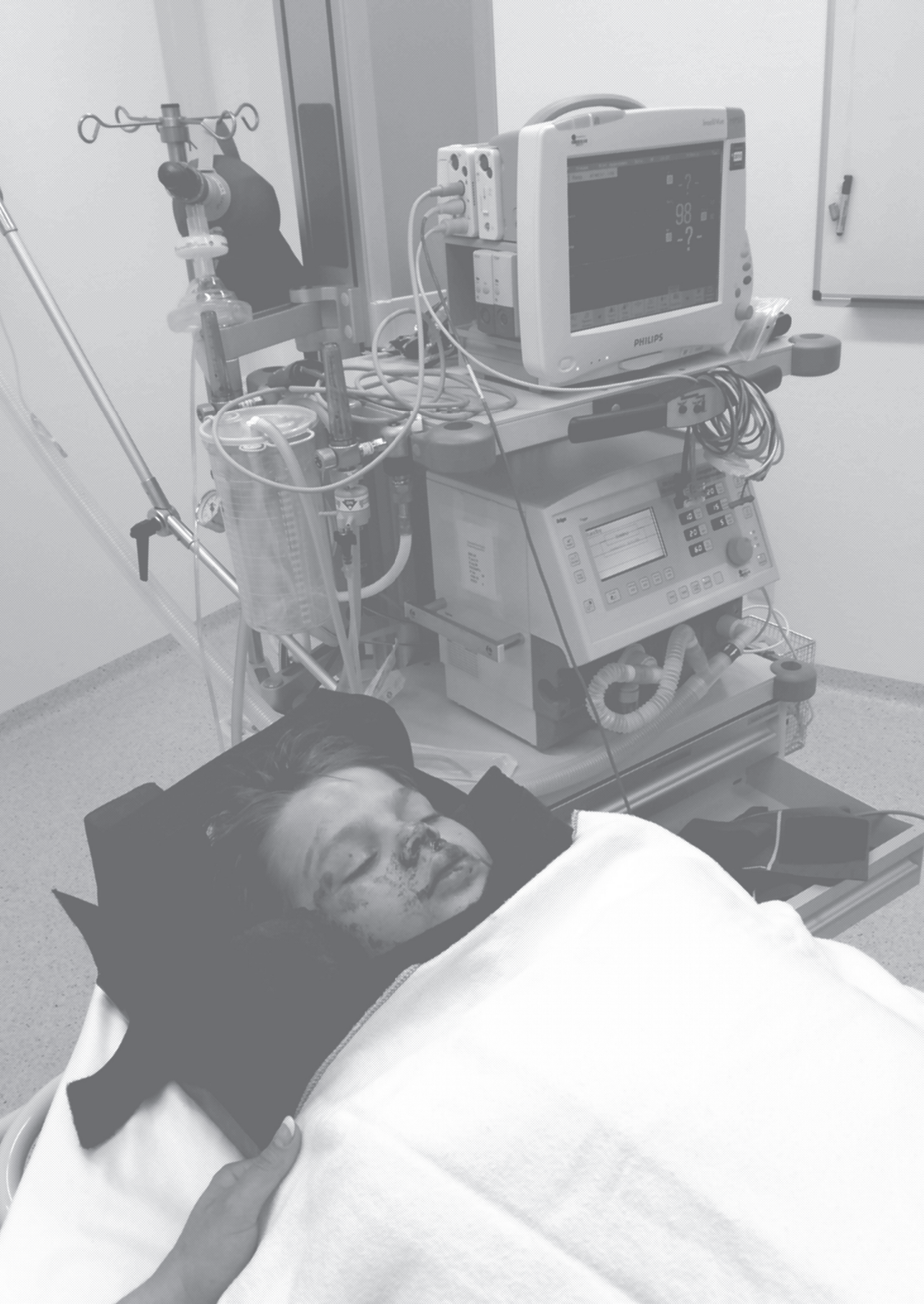
PHILIPS

CHAPTER 3

INTELLIGENCE AFTER TRAUMATIC BRAIN INJURY: META-ANALYSIS OF OUTCOMES AND PROGNOSIS

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ABSTRACT

BACKGROUND

Worldwide, 54-60 million individuals sustain traumatic brain injury (TBI) each year. This meta-analysis aimed to quantify intelligence impairments after TBI, and to determine the value of age and injury severity in the prognosis of TBI.

METHODS

Electronic database search identified 81 relevant peer-reviewed articles encompassing 3,890 patients. Full scale IQ (FSIQ), performance IQ (PIQ) and verbal IQ (VIQ) impairments were quantified (Cohen's *d*) for patients with mild, moderate and severe TBI in the subacute phase of recovery and the chronic phase. Meta-regressions explored prognostic values of age and injury severity measures for intelligence impairments.

RESULTS

In the subacute phase, FSIQ impairments were absent for patients with mild TBI, medium-sized for patients with moderate TBI ($p < .001$, $d = -0.61$) and large for patients with severe TBI ($p < .001$, $d = -1.09$). In the chronic phase, FSIQ impairments were small for patients with mild or moderate TBI ($ps \leq .008$, $ds = -0.37$ and -0.19) and large for patients with severe TBI ($p < .001$, $d = -0.80$). Adults with mild TBI had larger PIQ and VIQ impairments in the chronic phase than children ($Qs \geq 5.21$, $ps \leq .02$), while children with severe TBI had larger FSIQ and VIQ impairments than adults ($Qs \geq 4.40$, $ps \leq .04$). GCS score, LOC duration and PTA duration moderately to strongly predicted FSIQ, PIQ and VIQ impairments ($.41 \leq rs \leq .82$, $ps \leq .02$), but no differences in predictive value were observed.

CONCLUSIONS

TBI causes persisting intelligence impairments, where children may have better recovery from mild TBI and poorer recovery from severe TBI than adults. Injury severity measures predict intelligence impairments and do not outperform one another.

INTRODUCTION

Yearly, 54-60 million individuals sustain traumatic brain injury (TBI) worldwide (Feigin et al., 2013). Survivors of TBI often have impaired neurocognitive functions, prominently manifested in intelligence. In children, the impact of TBI is thought to slow down post-injury development of intelligence, which may translate into increasing intellectual delays (Crowe, Catroppa, Babl, Rosenfeld, & Anderson, 2012). Intelligence impairments in children with TBI have in turn been associated with psychiatric symptoms and poor academic attainment (Donders & Warschausky, 2007; Donders, 1994; Thaler et al., 2010). In adults with TBI, intelligence impairments relate to psychopathology, poor vocational placement and lower quality of life (Bowman, 1996; Yasuda, Wehman, Targett, Cifu, & West, 2001). These findings highlight intelligence as a crucial factor in the prognosis of TBI.

Clinicians use the Glasgow Coma Scale (GCS), duration of loss of consciousness (LOC) and/or post-traumatic amnesia (PTA) duration as predictive tools in the prognosis of TBI (Mandleberg, 1976; Winogron, Knights, & Bawden, 1984), while their concurrent prognostic utility remains unclear. Although the clinical application of PTA duration has been held back by marked variability in its definition and measurement methodology (Ahmed, Bierley, Sheikh, & Date, 2000), literature suggests that PTA duration may be superior to the GCS score and LOC duration in predicting a range of outcomes following TBI, including intelligence and functional independence (Greenwood, 1997; Perrin et al., 2014; Sherer, Struchen, Yablon, Wang, & Nick, 2008). These findings warrant the comparison of major prognostic factors for intelligence outcome of TBI. This study is the first to comprehensively quantify the impact of mild, moderate and severe TBI on intelligence in children and adults, and to determine the prognostic value of age at injury and injury severity using meta-analytic methods.

METHODS

STUDY SELECTION

This study was performed according to the PRISMA guidelines (Liberati et al., 2009). Included were studies that: (1) investigated patients with TBI; (2) reported on post-injury intelligence using any version of the most-widely used measure of intelligence: the Wechsler Intelligence Scales; (3) reported statistics allowing the calculation of effect sizes; and (4) reported on injury severity according to the mean or median GSC score, LOC duration and/or PTA duration. Excluded were studies that: (1) investigated patients with substance intoxication or prior head injury; (2) reported on injury severity based on < 75% of the patient sample; or (3) reported case studies.

The databases PubMed, Embase, PsycINFO and Web of Knowledge were searched for articles potentially meeting inclusion criteria using combinations of the following standard and thesaurus search terms: 'Wechsler', 'Head', 'Brain', 'Injury' and 'Trauma'. A total of 2,373 records were identified corresponding to 1,125 unique articles published before April 2014 (Figure 1). Titles and abstracts were assessed to further select articles meeting inclusion criteria. Two authors (M.K. and P.E.) independently assessed the full-text articles for eligibility. A total of 117 articles met all inclusion criteria, of which 36 were excluded for possibly overlapping samples based on the period and area of recruitment. Reference lists of included articles were searched for additional articles satisfying the inclusion criteria. Finally, eighty-one articles were included in the current analysis representing 3,890 patients with TBI (see Supporting Information).

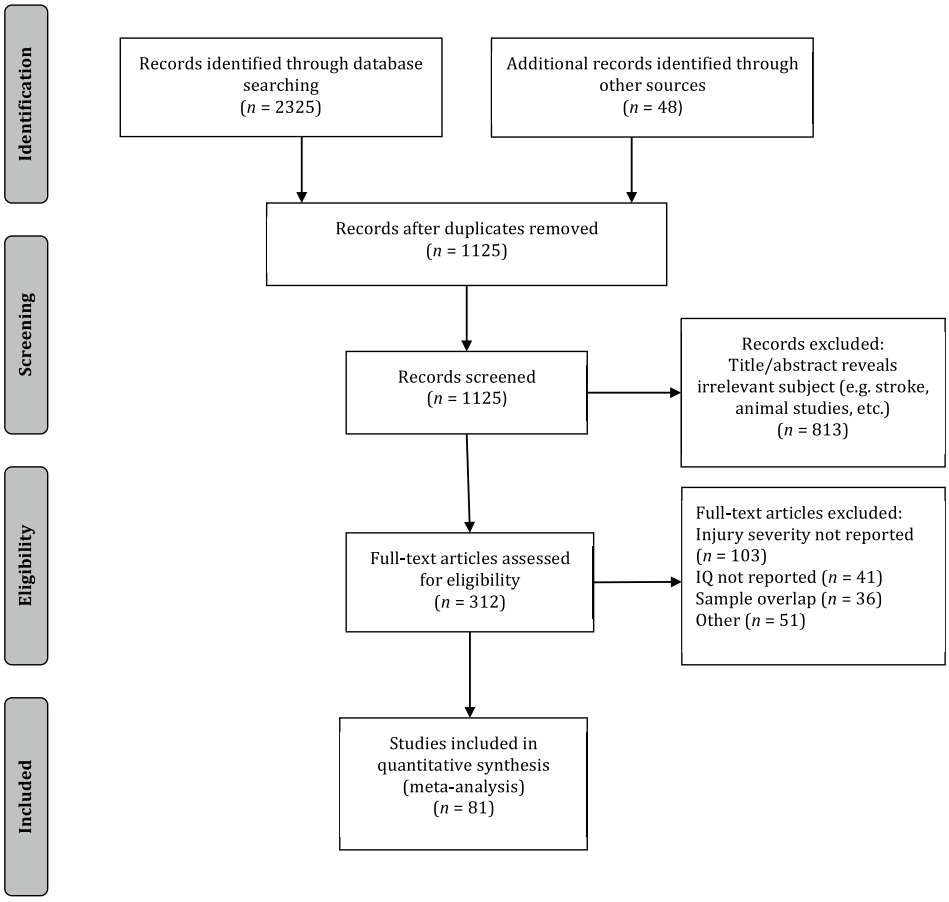

Figure 1. Flow diagram of the meta-analytic search and study selection
Note. IQ = intelligence quotient.

MODERATOR AND DEPENDENT VARIABLES

Samples of patients with TBI and controls were identified in the included articles. For these samples, information on injury severity, time post-injury (TPI), demographics and study quality was extracted.

INTELLIGENCE

Intelligence was defined and measured according age-corrected standard scores (M = 100, SD = 15) on the Wechsler Preschool and Primary Scale of Intelligence (Wechsler, 1967, 1989), Wechsler Intelligence Scales for Children (Wechsler, 1955, 1974, 1991, 2003) or the Wechsler Adult Intelligence Scales (Wechsler, 1955, 1981, 1997, 2008). Both full and short forms were included, as short forms are known to correlate strongly (.76< *r*s ≥.91) with full administrations of the Wechsler scales (Guilmette, Dabrowski, Kennedy, & Gnys, 1999; Sattler, 2001). The included articles allowed extraction of mean full-scale IQ (FSIQ), performance IQ (PIQ) and/or verbal IQ (VIQ) and the corresponding SD for samples of patients with TBI and control participants, if available. Only two studies used the WISC-IV. Therefore meta-analysis of WISC-IV factor scores dissecting FSIQ into verbal comprehension, perceptual reasoning, working memory and processing speed capabilities was not feasible.

INJURY SEVERITY

One or more of the following measures defined mild, moderate or severe TBI: GCS score (15-13; 12-9; and 8-3), LOC duration (< 30 minutes; 30 minutes - 24 hours; and > 24 hours) and PTA duration (<1 day; 1 - 7 days; and > 7 days, respectively; Tsao, 2010). The definition and measurement methodology of injury severity varied considerably among studies and are described in detail in the Supporting Information.

TIME POST-INJURY

To allow comparison of short- and long-term predictive values of injury severity measures, we distinguished between reports in the subacute phase of recovery (TPI < 6 months) and the chronic phase (TPI ≥ 6 months), in line with existing literature (Babikian & Asarnow, 2009; Königs, de Kieviet, & Oosterlaan, 2012).

DEMOGRAPHIC VARIABLES

Group means of the demographic variables age, age at injury, years of education and gender were extracted from the articles. Based on age at injury, we discriminated between childhood TBI (≤ 18 years) and adult TBI (> 18 years).

STUDY QUALITY

The quality of the included studies was independently assessed by two authors (M.K. and P.E.) using the Newcastle Ottawa Scale (NOS, (Wells et al., 2012). The NOS measures study quality concerning subject selection, group comparability and exposure to testing procedures. Higher scores reflect higher study quality (0 - 9 points). Discrepancies between author ratings were resolved by consensus, while inter-rater agreement was adequate (intraclass correlation = .69).

STATISTICAL ANALYSIS

Statistical analyses were performed using SPSS version 20.0 (SPSS inc., 2013) and Comprehensive Meta-Analysis software (Borenstein, 2005). First, we assessed comparability of the mild, moderate and severe TBI groups within the TPI groups (subacute and chronic phase) and between TPI groups using independent t-tests comparing age, age at injury, gender, years of education, TPI, GCS score (because this measure of injury severity was available for most of the TBI samples) and NOS study quality score.

Second, we determined the intelligence impairment for each sample of TBI patients derived from the included articles. We calculated the effect size (Cohen's *d*) using the mean IQ score and the corresponding SD of the TBI group and the mean IQ score and the corresponding SD of either: (1) the control group for controlled studies; or (2) the Wechsler normative mean and SD for uncontrolled studies. We investigated the validity of using the normative mean for uncontrolled studies by calculating the individual effect sizes for controlled studies using both methods and subsequently comparing the two acquired meta-analytic effect sizes using Q-testing. Effect sizes calculated using the normative mean were somewhat smaller than those calculated using the original control groups for FSIQ ($\Delta\ d = 0.17$), PIQ ($\Delta\ d = 0.10$) and VIQ ($\Delta\ d = .15$), although the differences were not significant ($ps \geq .12$). This indicates that using the normative mean for effect size calculation may provide conservative estimates of IQ impairments following TBI.

Meta-analytic effect sizes were calculated for IQ indices in the TBI severity groups, discriminating between the subacute phase of recovery and the chronic phase. The derived effect sizes were weighted by their inverse variance, thereby accounting for sample size and error of measurement (Borenstein, Hedges, Higgins, & Rothstein, 2009). All meta-analytic effect sizes were calculated using the random model, since heterogeneity may have been introduced by using data from different versions of the Wechsler scales. Heterogeneity of effect sizes was assessed using the I^2 statistic, where values of 25, 50 and 75% were indicative of low, moderate and high heterogeneity, respectively (Higgins, Thompson, Deeks, & Altman, 2003). To track the recovery of intelligence following TBI,

the meta-analytic effect sizes were compared between the TPI groups using *Q*-testing. All meta-analytic effect sizes were interpreted according to Cohen, translating d = -0.20 into small, d = -0.50 as medium and d = -0.80 as large effects (Cohen, 1988).

Subsequently, we investigated the predictive value of age at injury and the selected injury severity measures by performing meta-regressions between the study samples' individual effect sizes for FSIQ, PIQ and VIQ and the study samples' mean age at injury, mean GCS score, mean LOC duration and/or mean PTA duration for the two TPI groups separately. The average values of injury severity measures were rarely reported for patients with mild TBI. To allow inclusion of samples of patients with mild TBI in the meta-regression, we replaced missing values with the median of the mild TBI range for the GCS score, LOC duration and PTA duration (14, 0 days and 0.5 days, respectively; Carroll, Cassidy, Holm, Kraus, & Coronado, 2004). Meta-regression analysis was performed using the random model (method of moments; Borenstein et al., 2009). The predictive values of the GCS score, LOC duration and PTA duration for FSIQ, PIQ and VIQ impairments in the subacute phase of recovery and the chronic phase, were compared using t-tests while adjusting P-values for multiple comparisons according to Bonferroni (reported p = obtained p * m, where m denotes the number of comparisons). In all analyses, standardized correlations were interpreted according to Cohen, translating r = .10, r = .30 and r = .50 into weak, moderate and strong relations (Cohen, 1988).

The robustness of effect sizes was assessed by calculating Rosenthal's fail-safe n to determine the number of studies with a null effect that would be necessary to cancel out significant effect sizes (Rosenthal, 1995). Fail-safe n values > $5k + 10$ were considered robust, where k refers to the number of samples on which the relevant effect size was calculated (Rosenthal, 1995). Publication bias was assessed by Egger Funnel plot asymmetry (Egger, Smith, Schneider, & Minder, 1997). The possibility of a disproportionate influence of small-sized samples or poor quality studies with large effect sizes was investigated, which would become evident by positive associations between effect size and sample size or study quality, respectively. All tests of significance were two-sided with $\alpha = .05$.

RESULTS

GROUP COMPARABILITY

A description of analyses investigating comparability of the TBI severity groups and TPI groups in terms of age, age at injury, gender ratio, years of education, TPI, GCS score and NOS study quality score is provided in the Supporting Information (see Table 1 in Supporting Information for patient sample characteristics). No significant differences between groups were observed that would meaningfully confound the interpretation of effect sizes. Nevertheless, a large but non-significant difference in PTA duration was identified between the severe TBI groups in the subacute phase (M = 34.7, SD = 28.9) and chronic phase (M = 52.8, SD = 33.4). We matched these groups on injury severity during analyses comparing TPI groups, by excluding four studies from the chronic phase group (references 24, 64, 69-70 in Supporting Information), in order to prevent effects of injury severity to confound the analysis of recovery.

THE EFFECT OF TBI ON INTELLIGENCE

MILD TBI

Effect sizes for FSIQ, PIQ and VIQ in the subacute phase of recovery and the chronic phase showed moderate to high heterogeneity (Table 2), indicating that there was considerable variability in the magnitude of intelligence impairments. Patients with mild TBI had no significant intelligence impairments in the subacute phase of recovery, but there were found significant small-sized FSIQ and VIQ impairments in the chronic phase. There were no significant differences between the subacute phase of recovery and the chronic phase in the effects of mild TBI on any of the IQ indices ($Qs(1) \leq 0.5$, $ps \geq .49$), and the VIQ impairment in the chronic phase did not differ from the PIQ impairment ($Q(1) = 0.7$, $p = .41$).

MODERATE TBI

Effect sizes reflecting the effect of moderate TBI on intelligence showed low heterogeneity. Patients with moderate TBI had significant medium-sized FSIQ and PIQ impairments and a small VIQ impairment in the subacute phase of recovery. In the chronic phase, there were found significant small-sized FSIQ and VIQ impairments, but no impairment in PIQ was observed. The FSIQ and PIQ impairments were smaller in the chronic phase as compared to the subacute phase ($Q(1) = 7.6$, $p = .006$ and $Q(1) = 10.4$, $p = .001$, respectively), indicating ameliorating effects of recovery. There was no difference in the magnitude of VIQ impairments between the subacute and chronic phase ($Q(1) = 0.9$, $p = .33$). No significant difference was observed between the magnitude of PIQ and VIQ impairments in the subacute phase of recovery ($Q(1) = 1.9$, $p = .17$) or the chronic phase ($Q(1) = 1.4$, $p = 0.23$).

SEVERE TBI

There was found moderate to high heterogeneity in meta-analytic effect sizes reflecting the impact of severe TBI on intelligence. Patients with severe TBI exhibited significant large-sized FSIQ, PIQ and VIQ impairments in the subacute phase of recovery. In the chronic phase, severe TBI patients showed large-sized FSIQ and PIQ impairments, and a medium-sized VIQ impairment. There were found recovery effects for FSIQ and PIQ impairments (Qs ≥ 3.9, ps ≤ .05), but not for VIQ impairments ($Q(1) = 1.9$, $p = .17$). Severe TBI patients had significantly larger PIQ impairments as compared to VIQ impairments in the subacute phase of recovery ($Q(1) = 6.7$, $p = .01$), but such a difference did not reach conventional threshold of significance in the chronic phase ($Q(1) = 3.1$, $p = .08$).

Table 2. Meta-analytic effect sizes for intelligence impairments of patients with mild, moderate and severe TBI

	FSIQ									PIQ								
Group	*k*	ES	*95% CI*	*p*	I^2	*fsn*	*p(EF)*	*p(n)*	*p(NOS)*	*k*	ES	*95% CI*	*p*	I^2	*fsn*	*p(EF)*	*p(n)*	*p(NOS)*
Mild TBI																		
Subacute Phase	10	-0.29	-0.64 to 0.06	.11	78%	0	.56	.95	.28	10	-0.10	-0.36 to 0.17	.47	70%	0	.69	.79	.41
Chronic Phase	16	-0.37	-0.58 to -0.15	**<.001**	63%	119	.65	.67	.12	15	-0.16	-0.44 to 0.13	.29	83%	0	.79	.89	.18
Moderate TBI																		
Subacute Phase	5	-0.61	-0.89 to -0.34	**<.001**	0%	20	.55	.17	.11	6	-0.72	-1.02 to -0.42	**<.001**	15%	28	.30	.44	.68
Chronic Phase	11	-0.19	-0.32 to -0.05	**.008**	0%	0	.09	.18	.75	9	-0.10	-0.31 to 0.12	.12	32%	0	.12	.23	.74
Severe TBI																		
Subacute Phase	21	-1.09	-1.34 to -0.83	**<.001**	75%	4767	.78	.66	.09	21	-1.21	-1.45 to -0.97	**<.001**	69%	1602	.27	.84	.48
Chronic Phase	40	-0.80	-0.97 to -0.63	**<.001**	76%	3647	.50	.33	.44	29	-0.89	-1.07 to -0.70	**<.001**	72%	2188	.46	.97	.14

	VIQ								
Group	*k*	ES	*95% CI*	*p*	I^2	*fsn*	*p(EF)*	*p(n)*	*p(NOS)*
Mild TBI									
Subacute Phase	9	-0.19	-0.43 to 0.05	.13	55%	0	.18	.23	.41
Chronic Phase	15	-0.30	-0.50 to -0.10	**.003**	58%	67	.47	.69	.26
Moderate TBI									
Subacute Phase	6	-0.45	-0.71 to -0.19	**<.001**	0%	7	.40	.98	.22
Chronic Phase	9	-0.30	-0.46 to -0.13	**<.001**	0%	9	**.05**	.08	.40
Severe TBI									
Subacute Phase	21	-0.80	-0.98 to -0.63	**<.001**	44%	813	.56	.88	.53
Chronic Phase	31	-0.66	-0.83 to -0.48	**<.001**	71%	1475	.72	.46	.06

Note. Significant effect sizes are displayed in bold. CI = confidence interval; ES = effect size (Cohen's *d*); FSIQ = full-scale intelligence quotient; *fsn* = fail-safe *n; k* = number of samples; PIQ = performance intelligence quotient; *p*(EF) = *p* value of Egger funnel plot asymmetry; *p*(*n*) = *p* value of the relation between sample size and effect size; *p*(*NOS*) = *p* value of the relation between Newcastle Ottawa Scale quality score and effect size; TBI= traumatic brain injury; VIQ = verbal intelligence quotient.

THE ROLE OF AGE AT INJURY

Meta-regressions between age at injury and FSIQ, PIQ or VIQ impairments did not reach significance in the subacute or in the chronic phase of recovery (*p*s ≥ .14). To rule out effects of age at injury, we also explored group differences between child and adult TBI groups (Figure 2).

Children and adults with mild TBI showed no differences in FSIQ, PIQ and VIQ impairments in the subacute phase (*Q*s ≤ .33, *p*s ≥ .56). In the chronic phase, no difference was observed in FSIQ (*Q*(1) = 3.7, *p* = .06), but adults with mild TBI had larger PIQ and VIQ impairments than children (*Q*s ≥ 5.2, *p*s ≤ .02). No differences were found between children and adults with moderate TBI (*Q*s ≤ 2.8, *p*s ≥ .09) and between children and adults with severe TBI in the subacute phase (*Q*s ≤ 1.3, *p*s ≥ .25). In contrast, children with severe TBI in the chronic phase had larger FSIQ and VIQ impairments than adults (*Q*s ≥ 4.4, *p*s ≤ .04), while no difference was observed in PIQ (*Q*(1) = 0.5, *p* = .50).

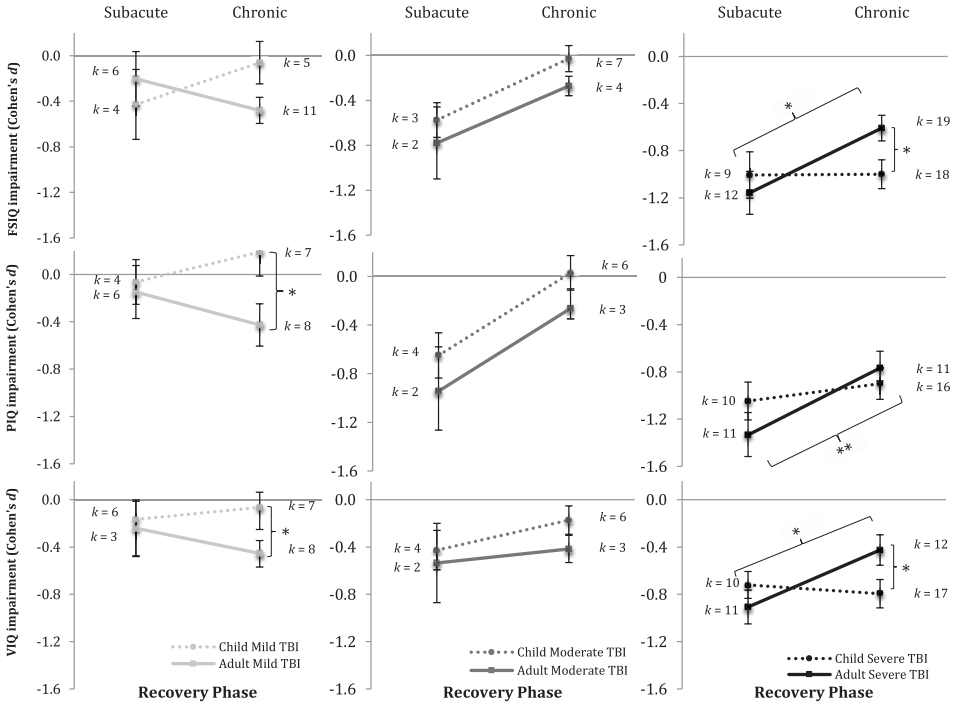

Figure 2. Group comparisons between children and adults with mild, moderate and severe TBI
Note. FSIQ = full-scale intelligence quotient; *k* = number of samples; TBI = traumatic brain injury; PIQ = performance intelligence quotient; VIQ = verbal intelligence quotient.

The observed differences between children and adults with mild TBI could not be explained by differential recovery tracks, as we found no recovery of IQ after mild TBI in children as well as adults (Qs ≤ 3.3, ps ≥ .07). In contrast, adults with severe TBI showed significant recovery of FSIQ, PIQ and VIQ impairments (Qs ≥ 6.7, ps ≤ .01), while no recovery was observed in children with severe TBI (Qs ≤ 0.4, ps ≥ .54). The observed differences between children and adults, and between the subacute and chronic phase of recovery, were not confounded by differences in GCS score, LOC duration or PTA duration (ts ≤ 1.4, ps ≥ .21).

PREDICTING INTELLIGENCE IMPAIRMENTS USING GCS, LOC AND PTA

GCS SCORE

Meta-regression analysis revealed that lower GCS scores strongly predicted larger FSIQ, PIQ and VIQ impairments among patients with mild to severe TBI in the subacute phase of recovery (see Table 3). In the chronic phase, GCS scores were not predictive of FSIQ impairments, but lower GCS scores were moderately predictive of larger PIQ and VIQ impairments.

LOC DURATION

Visual inspection of the meta-regression plots revealed two multivariate outliers that were removed from the analyses (references 30 and 66 in Supporting Information). Longer LOC duration strongly predicted larger FSIQ, PIQ and VIQ impairments in the subacute phase of recovery. In the chronic phase, longer LOC duration strongly predicted larger FSIQ and PIQ impairments and moderately predicted larger VIQ impairments.

Table 3. Predictive values of GCS scores, LOC duration and PTA duration for intelligence

	GSC score				LOC duration				PTA duration			
	k	*r*	SE	*p*	*k*	*r*	SE	*p*	*k*	*r*	SE	*p*
Subacute phase												
FSIQ	23	.63	0.14	**.001**	22	-.73	0.11	**< .001**	20	-.69	0.13	**< .001**
PIQ	28	.69	0.11	**< .001**	18	-.82	0.08	**< .001**	24	-.76	0.09	**< .001**
VIQ	27	.54	0.14	**.004**	18	-.76	0.11	**< .001**	24	-.58	0.15	**.003**
Chronic phase												
FSIQ	43	.22	0.15	.15	39	-.64	0.10	**< .001**	28	-.36	0.17	.06
PIQ	29	.43	0.16	**.02**	35	-.58	0.12	**< .001**	21	-.64	0.14	**.002**
VIQ	31	.41	0.16	**.004**	36	-.44	0.14	**.008**	22	-.52	0.17	**.01**

Note. Significant effect sizes are displayed in bold. FSIQ = full-scale intelligence quotient; GCS = Glasgow Coma Scale; *k* = number of samples; LOC = loss of consciousness; PIQ = performance intelligence quotient; PTA = post-traumatic amnesia; VIQ = verbal intelligence quotient; SE = standard error.

PTA DURATION

Longer PTA duration strongly predicted larger FSIQ, PIQ and VIQ impairments in the subacute phase of recovery. In the chronic phase, longer PTA duration was moderately predictive of larger FSIQ impairments, although this effect just escaped conventional levels of significance ($p = .06$), whereas longer PTA duration strongly predicted larger PIQ and VIQ impairments. Importantly, there were no significant differences between the predictive values of the GCS score, LOC duration and PTA duration for FSIQ, PIQ and VIQ impairments in the subacute phase of recovery ($ts \leq 1.1$, adjusted $ps \geq .99$) and the chronic phase ($ts \leq 2.3$, adjusted $ps \geq .36$).

PUBLICATION BIAS

An elaborate description of publication bias analysis (Table 2) is provided in the Supporting Information, indicating that it is unlikely that publication bias meaningfully influenced the reported effect sizes for the mild, moderate and severe TBI groups, with the single exception of VIQ impairments in the chronic phase after moderate TBI.

DISCUSSION

To our best knowledge, current meta-analysis of 81 peer-reviewed articles encompassing 3,890 patients with TBI is the most comprehensive study quantifying the impact of TBI on intelligence, and the first to use meta-analytic methods to elucidate the role of age at injury and compare the predictive powers of major prognostic factors for the magnitude of intelligence deficits after TBI. The results show that both moderate and severe TBI cause persisting intelligence impairments. Children seem to have better long-term outcome of mild TBI and poorer long-term outcome of severe TBI than adults. The GCS score, LOC duration and PTA duration moderately to strongly predict intelligence impairments of patients with TBI, but these prognostic factors do not outperform one another in predicting these impairments.

Patients with mild TBI showed no meaningful intelligence impairments in the subacute phase of recovery, but there were found small impairments in FSIQ and VIQ in the chronic phase. Patients with moderate TBI exhibited medium-sized FSIQ and PIQ impairments and small VIQ impairments in the subacute phase of recovery. The medium-sized FSIQ impairment as observed in the subacute phase reduced to a small effect in the chronic phase, whereas the medium-sized effect on PIQ as observed in the subacute phase disappeared in the chronic phase. No change was observed for the VIQ impairment in patients with moderate TBI. Patients with severe TBI exhibited large-sized FSIQ, PIQ and VIQ impairments in the subacute phase of recovery that persisted into the chronic phase, although the VIQ impairment did no longer pass the threshold for a large effect and was medium-sized in the chronic phase.

Patients with severe TBI showed stronger depressions of PIQ as compared to VIQ in the subacute phase, indicating that fluid aspects of intelligence (speed of information processing, attention and visuomotor functioning) are more vulnerable to the impact of TBI than crystallized aspects of intelligence (verbal knowledge). Recent studies using the latest Wechsler Intelligence Scale indicate that PIQ impairments after TBI are mainly accounted for by impairments in speed of processing (Donders & Strong, 2014). The discrepancy between PIQ and VIQ impairments in patients with severe TBI was not found in the chronic phase, likely reflecting relative recovery of processing speed over time.

Analyses differentiating between childhood and adult TBI suggest that the long-term outcome of mild TBI may be more favorable for children than adults. In contrast, children with severe TBI in the chronic phase had larger FSIQ and VIQ impairments than adults, traced back to an absence of recovery in children relative to distinct recovery of FSIQ, PIQ and VIQ impairments in adults. In line with the 'growing into deficit' theory, PIQ impairments in children with severe TBI may slow post-injury development of VIQ, in turn causing progressive delays in verbal skills.

The included studies applied highly variable definitions of injury severity and measurement

methodology. It was found that there is no consensus on the most suitable type of GCS score to be reported, the definition of LOC resolution, the definition of PTA duration and PTA measurement. Given the wide range of definitions and measures used to assess injury severity, it is striking that many studies do not report the definitions and measures applied. The results of the current meta-analysis show that lower GCS scores, longer LOC duration and longer PTA duration strongly predicted greater FSIQ, PIQ and VIQ impairments in the subacute phase. In the chronic phase, longer LOC duration moderately to strongly predicted FSIQ, PIQ and VIQ impairments, while lower GCS scores and longer PTA duration moderately to strongly predicted larger PIQ and VIQ impairments. Longer PTA duration showed moderate predictive power for larger FSIQ impairments in the chronic phase, but this effect just escaped the conventional level of significance. There was no evidence for differences between the GCS score, LOC duration and PTA duration regarding their predictive power for intelligence outcome of patients with mild to severe TBI, contradicting literature suggesting that PTA duration is superior in predicting intelligence after TBI.

This study has some limitations. First, we included uncontrolled studies and used the normative mean to calculate effect sizes for these studies. However, we also showed that this strategy to maximize study inclusion did not meaningfully influence effect sizes and would otherwise have provided slightly conservative estimates. Second, we applied a cross-sectional approach to track recovery effects of time, instead of including only (the scarcely available) longitudinal studies. However, for all comparisons we showed that the subacute and chronic groups involved were comparable in terms of demographic information and injury parameters. Third, some comparisons between childhood and adult TBI involved limited numbers of studies and should therefore be interpreted with caution. Fourth, included studies provided insufficient information to investigate the effect of injury mechanism (e.g. open vs. closed TBI). Last, it is likely that heterogeneity in the definition and measurement of injury severity contributed to measurement error in meta-regression analyses.

In conclusion, the current meta-analysis on a very large sample of patients with TBI indicates that intelligence impairments persist after moderate to severe TBI, while children may have better long-term outcome of mild TBI and poorer long-term outcome from severe TBI than adults. Although injury severity measures were shown to powerfully predict the future of patients with TBI, this study did not yield evidence for superiority of one or more of the measures in predicting intelligence outcome. We advise clinicians to recognize the importance of age at injury and the use of standardized measures of injury severity in the prognosis of intelligence after TBI.

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SUPPORTING INFORMATION

Table 1. Overview of studies included for meta-analysis

	Study Methodology													Injury Characteristics				Demographics			
Ref	Severity	*n*	IQ Index	Design	Control	Subsample	Injury	Wechsler Scale	GCS measure	LOC measure	PTA measure	NOS		GCS	LOC	PTA	TPI	Age	Age Injury	Males	Education
												(1-9)		(15-3)	(*d*)	(*d*)	(*y*)	(*y*)	(*y*)	(%)	(*y*)
										Subacute phase of recovery											
[1]	Mild	19	F P V	L	C	-	TBI	WISC-III/WPPSI-R	Admission	-	-	7		14.1	-	-	0.5	5.2	4.7	62	-
[2]	Mild	29	P V	L	OC	-	HI	WISC	-	-	Retro	7		14.0	0.0	0.5	0.1	9.6	9.6	76	-
[3]	Mild	44	P V	CS	C	-	CHI	WISC-R	-	-	-	5		14.6	-	-	0.3	10.1	9.8	52	-
[4]	Mild	32	F P V	L	-	-	TBI	WISC-R	Admission	Days to GCS = 15	Pro (TPP)	2		14.0	0.0	0.5	0.5	10.8	10.8	67	-
[5]	Mild	31	P V	CS	-	-	TBI	WISC-R	Admission	Obey commands	TPP	5		14.6	0.0	0.4	0.3	11.7	11.4	74	-
[6]	Mild	13	F	CS	C	-	TBI	WASI	-	-	-	5		14.0	0.0	0.5	0.1	13.3	13.3	62	-
[7]	Mild	19	F P V	CS	C	-	CHI	WAIS-R/WISC-R	Admission	-	-	6		14.0	0.0	0.5	0.1	15.3	15.2	53	9.6
	Mild									***Child Sample***	**Mean**	**5.3**		**14.2**	**0.0**	**0.5**	**0.3**	**10.9**	**10.7**	**63.7**	**9.6**
											SD	**1.7**		**0.3**	**0.0**	**0.0**	**0.2**	**3.2**	**3.3**	**9.4**	**.**
[8]	Mild	15	F	L	C	Women	HI	WAIS-R	-	-	-	4		14.0	0.0	0.5	0	24.2	24.2	0	7.9
[8]	Mild	15	F	L	C	Men	HI	WAIS-R	-	-	-	4		14.0	0.0	0.5	0	24.7	24.7	100	8.6
[9]	Mild	70	F P V	CS	-	-	CHI	WAIS/WISC-R	Admission	Retro (report)	-	4		-	0.0	-	0.3	22.6	25.3		11.5
[10]	Mild	157	P	L	OC	GCS	TBI	WAIS	Admission	-	Retro	7		14.4	-	-	0.1	28.5	28.4	71	12.5
[11]	Mild	22	F P V	CS	OC	-	TBI	WAIS-R	-	-	Retro	2		14.0	0.0	0.5	0	31.2	31.2	67	-
[12]	Mild	46	F	L	-	-	TBI	WAIS-R	-	-	-	4		-	0.0	-	0.1	33.2	33.1	78	12.1
[13]	Mild	28	F P V	CS	-	-	HI	WISC-R	-	-	-	2		14.0	0.0	0.5	0.3	35.5	35.2	78	-
	Mild									***Adult Sample***	**Mean**	**3.9**		**14.1**	**0.0**	**0.5**	**0.1**	**28.6**	**28.9**	**65.7**	**10.5**
											SD	**1.7**		**0.2**	**0.0**	**0.0**	**0.1**	**4.9**	**4.4**	**34.1**	**2.1**
	Total	**540**									**Mean**	**4.6**		**14.1**	**0.0**	**0.5**	**0.2**	**19.7**	**19.8**	**64.6**	**10.4**
											SD	**1.8**		**0.2**	**0.0**	**0.0**	**0.2**	**10.0**	**10.1**	**23.0**	**1.9**

			Study Methodology											Injury Characteristics				Demographics			
Ref	Severity	*n*	IQ Index	Design	Control	Subsample	Injury	Wechsler Scale	GCS measure	LOC measure	PTA measure	NOS	GCS	LOC	PTA	TPI	Age	Age Injury	Males	Education
												(1-9)	(15-3)	(*d*)	(*d*)	(*y*)	(*y*)	(*y*)	(%)	(*y*)
[1]	Mod	46	F P V	L	C	-	TBI	WISC-III/WPPSI-R	Admission	-	-	7	10.3	-	-	0.2	4.7	4.5	62	-
[4]	Mod	18	F P V	L	-	-	TBI	WISC-R	Admission	Days to GCS = 15	Pro (TPP)	2	11.2	-	-	0.5	10.8	10.8	67	-
[5]	Mod	7	P V	CS	-	-	TBI	WISC-R	Admission	Obey commands	Pro (TPP)	5	10.3	-	2.6	0.2	11.1	10.9	57	-
[14]	Mod	30	F P V	CS	OC	-	CHI	WISC-III	-	-	COAT	4	-	-	4	0	10.9	10.9	67	-
	Mod									***Child sample***	**Mean**	**4.5**	**10.6**	**-**	**3.3**	**0.2**	**9.4**	**9.3**	**63.3**	
											SD	**2.1**	**0.5**	**-**	**1.0**	**0.2**	**3.1**	**3.2**	**4.9**	
[15]	Mod	17	F P V	CS	-	-	CHI	WAIS-R	-	-	Retro	3	9.4	-	15.2	0.5	42.9	42.5	53	12.1
[16]	Mod	4	F P V	CS	-	MMI	BI	WAIS-R	Admission	-	GOAT	5	11.0	-	5	0	47.0	47.0	75	-
	Mod									***Adult Sample***	**Mean**	**4.3**	**10.2**	**-**	**6.7**	**0.2**	**21.2**	**21.1**	**63.5**	**12.1**
											SD	**1.8**	**1.1**	**-**	**5.8**	**0.2**	**18.6**	**18.5**	**7.9**	**0.2**
	Total	**122**									**Mean**	**4.6**	**10.4**	**5.4**	**6.7**	**0.2**	**22.6**	**20.2**	**66.0**	**12.0**
											SD	**1.8**	**0.7**	**1.5**	**5.8**	**0.2**	**17.9**	**16.1**	**8.1**	**0.2**
[1]	Severe	31	F P V	L	C	-	TBI	WISC-III/WPPSI-R	Admission	-	-	7	5.1	-	-	0.3	4.9	4.7	62	-
[17]	Severe	16	F P V	L	-	Early	HI	WISC-R/WPPSI-R	Lowest 24h	Days to GCS = 8	Orientation	4	5.3	9.2	14.6	0.4	6	5.7	59	-
[18]	Severe	42	F P V	CS	-	-	TBI	WISC-R	Admission	-	-	4	-	4.5	-	0.3	8.4	8.2	74	-
[3]	Severe	68	P V	CS	C	-	CHI	WISC-R	-	-	-	5	5.8	-	-	0.4	9.9	9.5	59	-
[17]	Severe	20	F P V	L	-	Late	HI	WISC-R/WPPSI-R	Lowest 24h	Days to GCS = 8	Orientation	4	5.2	7.8	18	0.4	11.2	10.8	59	-
[4]	Severe	26	F P V	L	-	-	TBI	WISC-R	Admission	Days to GCS = 15	Pro (TPP)	2	5.5	25.2	54.2	0.5	10.8	10.8	67	-
[19]	Severe	50	F	CS	OC	-	TBI	WASI	Lowest	-	-	7	-	6.4	-	0.2	11.3	11.1	74	-
[5]	Severe	13	P V	CS	-	-	TBI	WISC-R	Admission	Obey commands	TPP	5	5.0	3.3	20.8	0.3	11.6	11.4	69	-
[20]	Severe	17	F P V	L	-	-	TBI	WISC	-	-	-	4	-	17.6	-	0.2	12.0	11.8	39	-
[21]	Severe	30	F	CS	-	-	CHI	WISC-R	-	-	-	3	-	11.7	-	0.2	11.9	11.8	53	-
[22]	Severe	77	F P V	CS	-	-	TBI	WISC-III	-	-	-	5	6.0	24.1	-	0.4	12.3	11.8	74	-

							Study Methodology							Injury Characteristics				Demographics			
Ref	Severity	*n*	IQ Index	Design	Control	Subsample	Injury	Wechsler Scale	GCS measure	LOC measure	PTA measure	NOS	GCS	LOC	PTA	TPI	Age	Age Injury	Males	Education
												(1-9)	(15-3)	(*d*)	(*d*)	(*y*)	(*y*)	(*y*)	(%)	(*y*)
[23]	Severe	20	P V	L	-	-	TBI	WISC	Admission	-	-	4	5.0	16	69	0.5	12.2	12.2	65	-
	Severe									***Child Sample***	**Mean**	**4.5**	**5.4**	**12.6**	**35.3**	**0.3**	**10.2**	**10.0**	**62.8**	**-**
											SD	**1.4**	**0.4**	**7.8**	**24.7**	**0.1**	**2.5**	**2.5**	**10.2**	**-**
[24]	Severe	16	P V	L	-	Not RE	TBI	WAIS-R	Admission	-	-	4	-	-	107.8	0.5	23.3	22.8	62	11.8
[25]	Severe	52	F	L	-	-	TBI	WAIS-R	-	-	-	4	-	4.3	-	0.2	42.2	24.1	73	11.8
[26]	Severe	30	F	CS	-	-	HI	WAIS	-	-	-	5	-	54.8	-	0.5	24.7	24.2	70	13.1
[24]	Severe	19	P V	L	-	RE	TBI	WAIS-R	Admission	-	-	4	-	-	28	0.3	24.3	24.5	79	13.1
[12]	Severe	27	F	L	-	-	TBI	WAIS-R	-	-	-	4	-	20.1	-	0.2	24.8	24.6	67	11.9
[27]	Severe	8	F P V	CS	-	-	TBI	WAIS-III	Admission	-	-	3	7.5	-	-	0.2	26.0	25.8	88	-
[28]	Severe	23	F P V	CS	C	-	CHI	WAIS-R	Lowest	-	Westmead	6	9.0	-	28.5	0	26.2	26.1	81	10.0
[29]	Severe	39	F P V	CS	-	-	CHI	WAIS-R	-	-	OGMS	3	-	-	66.8	<0.5	27.6	27.6	-	11.7
[30]	Severe	10	F P V	CS	C	-	HI	WAIS	-	-	Aware 24h	6	-	-	22	0.5	29.0	28.5	92	-
[31]	Severe	15	F P V	CS	-	-	TBI	WAIS-R	Lowest 24h	Obey commands	-	4	-	3.3	-	0.4	33.4	33.0	64	12.0
[16]	Severe	6	F P V	CS	-	SMI	BI	WAIS-R	Admission	-	GOAT	5	9.0	-	10	0	35.1	35	83	-
[16]	Severe	20	F P V	CS	-	SMI	BI	WAIS-R	Admission	-	GOAT	5	9.0	-	12	0	38.1	38.0	70	-
[16]	Severe	7	F P V	CS	-	MMI	BI	WAIS-R	Admission	-	GOAT	5	8.0	-	9	0	41.1	41.0	71	-
[32]	Severe	50	F P V	CS	-	-	CHI	WAIS-R	-	-	NA	3	10.6	-	29.7	0.1	41.5	41.5	74	11.6
	Severe									***Adult Sample***	**Mean**	**4.4**	**8.9**	**20.6**	**34.9**	**0.2**	**31.2**	**29.8**	**74.9**	**11.9**
											SD	**1.0**	**1.1**	**24.0**	**32.5**	**0.2**	**7.1**	**6.6**	**9.1**	**0.9**
	Total	**732**									**Mean**	**4.4**	**7.1**	**14.9**	**34.7**	**0.3**	**22.3**	**21.4**	**69.3**	**11.9**
											SD	**1.2**	**1.9**	**1.8**	**28.9**	**0.2**	**12.0**	**11.3**	**11.3**	**0.9**
	Total TBI severity groups	**1394**									**Mean**	**4.5**	**10.3**	**8.3**	**19.3**	**0.3**	**20.9**	**20.4**	**67.0**	**11.3**
											SD	**1.5**	**3.6**	**11.8**	**12.1**	**15.2**	**1.4**	**1.5**	**15.2**	**1.5**

			Study Methodology											Injury Characteristics				Demographics			
Ref	Severity	*n*	IQ Index	Design	Control	Subsample	Injury	Wechsler Scale	GCS measure	LOC measure	PTA measure	NOS	GCS	LOC	PTA	TPI	Age	Age Injury	Males	Education
												(1-9)	(15-3)	(*d*)	(*d*)	(*y*)	(*y*)	(*y*)	(%)	(*y*)
									Chronic phase of recovery												
[1]	Mild	19	F P V	L	C	-	TBI	WISC-III/WPPSI-R	Admission	-	-	7	14.1	-	-	1.5	6.2	4.7	62	-
[33]	Mild	15	F	CS	C	-	TBI	WISC-III	Admission	-	-	7	15.0	0.0	0.0	1	8.3	7.3	33	-
[34]	Mild	67	P V	CS	-	-	HI	WISC-R	Stable GCS	-	-	4	14.7	-	-	2.4	10.0	7.6	-	-
[2]	Mild	29	P V	L	OC	-	HI	WISC	-	-	Retro	7	14.0	0.0	0.5	1	10.6	9.6	76	-
[35]	Mild	24	F P V	CS	OC	-	TBI	WISC-R	Lowest	Obey commands	-	5	14.5	0.0	-	2.4	11.2	8.8	75	-
[4]	Mild	32	F P V	L	-	-	TBI	WISC-R	Admission	Days to GCS = 15	Pro (TPP)	2	14.0	0.0	0.5	0.8	11.6	10.8	67	-
[36]	Mild	31	F P V	CS	C	-	TBI	WISC-III	-	-	-	6	14.0	0.0	0.5	2	11.7	8.9	60	-
[37]	Mild	7	V & P	CS	-	Adolescents	CHI	WISC/WAIS	Admission	-	-	3	-	0.03	-	1.3	17.8	16.5	-	-
	Mild									***Child Sample***	**Mean**	**5.1**	**14.3**	**0.0**	**0.4**	**1.6**	**10.9**	**9.3**	**62.2**	**-**
											SD	**2.0**	**0.4**	**0.0**	**0.3**	**0.6**	**3.4**	**3.4**	**15.7**	**-**
[8]	Mild	15	F	L	C	Women	HI	WAIS-R	-	-	-	4	14.0	0.0	0.5	0.5	24.2	24.2	0	7.9
[8]	Mild	15	F	L	C	Men	HI	WAIS-R	-	-	-	4	14.0	0.0	0.5	0.5	24.7	24.7	100	8.6
[10]	Mild	157	P	L	OC	GCS	TBI	WAIS	Admission	-	Retro	7	14.4	-	-	1	29.4	28.4	71	12.5
[25]	Mild	46	F	L	-	-	TBI	WAIS-R	-	-	-	4	-	0.0	-	1.03	34.1	33.1	78	12.1
[38]	Mild	22	F P V	CS	C	-	CHI	WAIS-R	-	-	-	5	14.0	0.0	0.5	1.1	34.3	33.3	64	14.6
[39]	Mild	41	F P V	CS	-	-	CHI	WAIS-R	-	-	-	2	14.0	0.0	0.5	1.8	34.5	32.6		12.8
[40]	Mild	42	V	CS	-		TBI	WAIS-III	-	-	-	3	14.0	0.0	0.5	8.8	35.6	26.8	45	12.9
[41]	Mild	23	F P V	CS	C	-	TBI	WAIS-III	-	-	-	5	-	0.0	0.0	1.18	35.7	34.6	52	12.9
[42]	Mild	26	F P V	CS	-	-	TBI	WAIS-III	-	-	-	3	14.0	0.0	0.5	1.12	38.6	37.5	73	12.0
[12]	Mild	22	F	CS	-	-	TBI	WAIS-III	Admission	-	-	4	14.6	-	-	-	43.2	-	59	13.1
[43]	Mild	34	F, P, V	CS	-	-	HI	WAIS-R/-III	-	-	-	4	-	0.0	-	≥1	45.4	-	73	12.0
[44]	Mild	29	F P V	CS	-	Women	TBI	K-WAIS	-	-	-	4	14.0	0.0	0.5	1.9	45.7	43.8	0	9.7
[44]	Mild	95	F P V	CS	-	Men	TBI	K-WAIS	-	-	-	4	14.0	0.0	0.5	1.9	45.7	43.8	100	9.7
	Mild									***Adult Sample***	**Mean**	**4.1**	**14.1**	**0.0**	**0.4**	**1.9**	**37.5**	**33.0**	**61.5**	**11.7**
											SD	**1.1**	**0.2**	**0.0**	**0.2**	**2.3**	**7.6**	**6.8**	**30.1**	**1.8**

													Study Methodology						Injury Characteristics		Demographics	
Ref	Severity	*n*	IQ Index	Design	Control	Subsample	Injury	Wechsler Scale	GCS measure	LOC measure	PTA measure	NOS	GCS	LOC	PTA	TPI	Age	Age Injury	Males	Education
												(1-9)	(15-3)	(*d*)	(*d*)	(*y*)	(*y*)	(*y*)	(%)	(*y*)
	Total	**859**									**Mean**	**4.5**	**14.2**	**0.0**	**0.4**	**1.7**	**26.6**	**23.0**	**60.4**	**11.6**
											SD	**1.6**	**0.3**	**0.0**	**0.2**	**1.8**	**14.0**	**13.2**	**27.4**	**2.0**
[1]	Mod	46	F P V	L	C	-	TBI	WISC-III/WPPSI-R	Admission	-	-	7	10.3	-	-	1.2	5.7	4.5	62	-
[45]	Mod	43	P V	CS	-	-	HI	WISC-III	-	-	-	3	10.6	-	-	4	10.9	7	61	-
[34]	Mod	14	P V	CS	-	-	HI	WISC-R	Stable GCS	-	-	4	9.9	-	-	2.4	10	7.6	-	-
[46]	Mod	19	F	CS	-	EI	TBI	WISC-IV	Admission	-	-	3	10.6	-	-	3.2	12.6	9.4	68	-
[37]	Mod	9	V & P	CS	-	Children	CHI	WISC/WAIS	Admission	-	-	3	-	0.5	-	2.9	11.7	8.8	-	-
[4]	Mod	18	F P V	L	-	-	TBI	WISC-R	Admission	Days to GCS = 15	Pro (TPP)	2	11.2	-	-	0.8	11.6	10.8	67	-
[47]	Mod	17	F P V	CS	C	-	HI	WISC-R/-III	Admission	Days to GCS = 9	-	5	10.6	-	-	3.2	14.9	11.9	47	-
[48]	Mod	20	F	CS	-	TOPS	TBI	WASI	Lowest	-	-	4	6.5	-	-	0.7	14	13.5	38	-
[48]	Mod	21	F	CS	-	IRC	TBI	WASI	Lowest	-	-	4	10.5	-	-	0.9	14.5	13.7	58	-
[49]	Mod	14	F	CS	C	-	TBI	WISC-IV/WAIS-III	Lowest	-	-	5	12.3	-	-	0.7	15.1	14.4	36	-
	Mod									***Child Sample***	**Mean**	**4.0**	**10.3**	**0.5**	**-**	**2.0**	**12.1**	**10.2**	**54.6**	
											SD	**1.4**	**1.6**	**-**	**-**	**1.3**	**2.9**	**3.3**	**12.6**	
[50]	Mod	115	F	CS	-	-	HI	WPPSI/WISC-R/WAIS	6h GCS	-	-	4	9.6	-	-	1.8	21.6	19.8	75	-
[51]	Mod	18	F P V	CS	-	-	TBI	WAIS-III	-	-	-	3	11.9	-	-	2	28.1	26.1	61	-
[52]	Mod	30	F P V	CS	-	Control TBI	TBI	WAIS-III/WAIS-R	-	-	-	2	-	0.09	3.3	2	33.6	31.3	70	12.52
[53]	Mod	107	F P V	CS	-	-	TBI	Wechsler	-	-	-	2	-	0.13	-	0.8	34.1	33.3	79	11.6
	Mod									***Adult Sample***	**Mean**	**2.8**	**10.8**	**0.1**	**3.3**	**1.7**	**29.4**	**27.6**	**71.3**	**12.1**
											SD	**1.0**	**1.6**	**0.0**	**-**	**0.6**	**5.8**	**6.0**	**7.8**	**0.7**
	Total	**491**									**Mean**	**3.5**	**10.1**	**0.2**	**3.3**	**2.1**	**17.4**	**15.3**	**62.8**	**12.1**
											SD	**1.4**	**1.5**	**0.2**	**-**	**1.1**	**9.6**	**9.9**	**12.4**	**0.7**

						Study Methodology								Injury Characteristics				Demographics			
Ref	Severity	*n*	IQ Index	Design	Control	Subsample	Injury	Wechsler Scale	GCS measure	LOC measure	PTA measure	NOS	GCS	LOC	PTA	TPI	Age	Age Injury	Males	Education
												(1-9)	(15-3)	(*d*)	(*d*)	(*y*)	(*y*)	(*y*)	(%)	(*y*)
[1]	Severe	31	F P V	L	C	-	TBI	WISC-III/WPPSI-R	Admission	-	-	7	5.1	-	-	1.3	5.9	4.7	61	-
[17]	Severe	16	F P V	L	-	Early injury	HI	WISC-R/WPPSI-R	Lowest 24h	Days to GCS = 8	Orientation	4	5.3	9.2	14.6	2.0	7.7	5.7	58	-
[37]	Severe	15	P V	CS	-	Children	CHI	WAIS	Admission	-	-	3	-	21	-	1.1	8.6	7.5	-	-
[54]	Severe	14	F	CS	C	Children	TBI	WASI	Admission	-	-	6	8.3	-	-	3.9	9.1	5.2	57	-
[34]	Severe	5	P V	CS	-	-	HI	WISC-R	Stable GCS	-	-	4	5.4	-	-	2.4	10.0	7.6		
[35]	Severe	23	F P V	CS	OC	-	TBI	WISC-R	Lowest	Obey commands	-	5	5.3	17.9	-	2.0	10.7	8.71	75	-
[55]	Severe	23	F P V	CS	-	-	TBI	WISC	Admission	-	-	3	5.3	-	-	4.1	10.7	6.6	57	4.2
[56]	Severe	76	V	CS	-	-	TBI	WISC-III	Admission	-	-	4	5.9	-	-	1.0	11.1	10.1	61	-
[57]	Severe	20	F P V	CS	C	-	TBI	WISC-R	-	-	-	4	-	15.8	50.5	1.7	11.1	9.6	70	-
[58]	Severe	36	F	CS	C	-	TBI	WISC-III	Lowest	-	Westmead	6	6.7	16.8	26.5	4.3	11.3	6.6	67	-
[4]	Severe	26	F P V	L	-	-	TBI	WISC-R	Admission	Days to GCS = 15	Pro (TPP)	2	5.5	25.2	54.2	0.8	11.6	10.8	67	-
[59]	Severe	17	F P V		SC	-	HI	WISC-R	Admission	-	-	5	8.8	6	-	3.4	11.9	8.3	67	-
[46]	Severe	9	F	CS	-	PI	TBI	WISC-IV	Admission	-	-	3	6.7	-	-	3.4	12.3	9.17	78	-
[17]	Severe	20	F P V	L	-	Late injury	HI	WISC-R. WPPSI-R	Lowest 24h	Days to GCS = 8	Orientation	4	5.2	7.8	18	2.0	12.8	10.8	58	-
[60]	Severe	151	F	CS	C	-	TBI	WISC-III	Lowest 24h	-	-	7	8.0	-	-	0.7	12.9	12.2	58	-
[61]	Severe	40	F P V	CS	-	TBI baseline	TBI	WISC-R/WAIS-R	-	-	-	4	-	21.1	-	0.6	13.9	13.4	75	6
[54]	Severe	14	F	CS	C	Adolescents	TBI	WASI	Admission	-	-	6	6.5	-	-	4.9	14.3	9.4	86	-
[47]	Severe	16	F P V	CS	C	-	HI	WISC-II/ WISC-R	Admission	Days to GCS = 9	-	5	6.1	10.1	-	5.3	15.0	9	47	-
[61]	Severe	25	F P V	CS	-	C baseline	TBI	WISC-R/WAIS-R	-	-	-	4	-	20.6	-	0.8	15.5	13.5	64	5.7
[37]	Severe	14	P V	CS	-	Adolescents	CHI	WAIS	Admission	-	-	3	-	28.3	-	0.6	17.5	16.9	-	-
[62]	Severe	19	F P V	CS	C	-	TBI	WAIS	Admission	-	-	5	5.9	-	-	9.4	8.6	18.1	86	-
[20]	Severe	16	F P V	L	-	-	TBI	WISC	-	-	-	4	-	17.6	-	6.8	18.8	11.8	39	-
[23]	Severe	20	P V	L	-	WAIS	TBI	WAIS	Admission	-	-	4	5.0	16	69	9.7	22.3	12.2	65	-
[24*]	Severe	16	P V	L	-	Not RE	TBI	WAIS-R	Admission	-	-	4	-	-	107.8	1.7	24.5	22.8	62	11.8
	Severe									***Child Sample***	**Mean**	**4.4**	**6.2**	**16.7**	**48.7**	**2.8**	**13.0**	**10.1**	**63.6**	**6.9**
											SD	**1.3**	**1.2**	**6.5**	**33.0**	**2.3**	**4,4**	**4.0**	**10.6**	**3.3**

	Study Methodology											Injury Characteristics				Demographics			
Ref	Severity *n*	IQ Index	Design	Control	Subsample	Injury	Wechsler Scale	GCS measure	LOC measure	PTA measure	NOS	GCS	LOC	PTA	TPI	Age	Age Injury	Males	Education
											(1-9)	(15-3)	(*d*)	(*d*)	(*y*)	(*y*)	(*y*)	(%)	(*y*)
[63]	Severe 16	F	CS	C	Young	TBI	WAIS-III	Admission	-	-	4	5.4	-	22.1	6.1	24.7	18.6	94	-
[24]	Severe 19	P V	L	-	RE	TBI	WAIS-R	Admission	-	-	4	-	-	28	1.2	25.7	24.5	79	13.1
[25]	Severe 27	F	L	-	-	TBI	WAIS-R	-	-	-	4	-	20.1	-	1.3	25.9	24.6	67	11.9
[23]	Severe 19	F P V	CS	-	RTS	TBI	WAIS-R	-	-	-	3	-	11.3	-	3.1	27.0	23.9	85	-
[64*]	Severe 44	F P V	CS	-	-	CHI	WAIS-III	-	-	GOAT	4	-	45.3	110.5	0.9	27.4	26.5	71	11.7
[65]	Severe 14	V	CS	C	-	CHI	WAIS-R	Lowest	Retro (records)	-	5	5.2	-	-	4.2	27.4	23.2	71	12.9
[25]	Severe 52	F	L	-	-	TBI	WAIS-R	-	-	-	4	-	4.3	-	1	25.1	24.1	73	11.8
[66]	Severe 63	P V	CS	-	-	TBI	WAIS-R	-	-	-	3	-	31.9	-	3.4	28.2	24.8	83	12.9
[67]	Severe 66	F	CS	-	-	TBI	WAIS-R	-	Retro (records)	-	4	-	13.3	-	3.9	28.4	24.6	-	13.4
[68]	Severe 64	F P V	CS	-	-	CHI	WAIS-R	Admission	-	-	3	8.4	-	-	1.9	29.0	27.2	52	12.7
[69*]	Severe 20	F	CS	C	-	CHI	WAIS-R	-	-	Retro	4	-	-	125	5.4	29.3	23.9	70	14.1
[70]	Severe 55	F	CS	-	-	CHI	WAIS-R	-	-	-	2	-	-	67.5	7.4	29.3	21.9	79	-
[71]	Severe 44	F	CS	-	-	TBI	WASI	Admission	-	Westmead	4	7.1		47.9	>5.0	29.6	-	85	11.6
[72]	Severe 78	F	CS	-	-	TBI	WAIS-R	Admission	-	Retro	3	8.9	-	23.7	2.9	29.8	29.7	81	-
[73]	Severe 71	P V	CS	-	-	CHI	WAIS-R	-	-	-	4	-	-	36.1	1.4	31.5	30.1	79	11.4
[74]	Severe 30	F P V	CS	-	-	TBI	WAIS-R	-	-	-	3	-	26.2	-	3.9	31.6	27.7	77	-
[67]	Severe 28	F	CS	-	-	TBI	WAIS-R	-	Retro (records)	-	4	-	23.6	-	5.3	32.4	27.1	-	12.7
[75]	Severe 11	F P V	CS	-	-	HI	WAIS	-	-	-	2	-	79.8	-	5.4	34.7	29.3	82	-
[76]	Severe 118	F P V	CS	-	-	CHI	WAIS-III	-	-	-	4	8.4	-	17.3	2.9	35.5	32.6	71	-
[77*]	Severe 24	F	CS	C	-	CHI	WAIS-R	Interview	-	Retro	5	-	34.4	74.8	10.6	35.6	25.3	83	14.0
[78]	Severe 35	F	CS	-	-	TBI	WAIS-R	-	-	-	2	-	8.9	74.5	0.7	36.1	35.4	80	-
[79]	Severe 25	F P V	CS	-	No RTS	TBI	WAIS-R	-	-	-	3	-	9.8	-	3.1	37.0	33.9	85	-
[12]	Severe 29	F	CS	-	-	TBI	WAIS-III	Admission	-	-	4	8.4	-	-	-	38.2	-	72	12.8
[80]	Severe 76	F P V	CS	-	-	TBI	WAIS-R	-	-	-	3	-	14	-	14.1	38.6	24.9	83	11.9
[81]	Severe 60	F	CS	C	-	TBI	WAIS-III	Lowest 24h	-	Westmead	7	7.4	-	26.3	10.6	42.0	31.4	55	12.1
[63]	Severe 16	F	CS	C	Old	TBI	WAIS-III	Admission	-	-	4	4.7	-	62.5	3.8	44.4	40.6	88	-

Study Methodology												Injury Characteristics				Demographics			
Ref	Severity	*n*	IQ Index	Design	Control	Subsample	Injury	Wechsler Scale	GCS measure	LOC measure	PTA measure	NOS	GCS	LOC	PTA	TPI	Age	Age Injury	Males	Education
												(1-9)	(15-3)	(*d*)	(*d*)	(*y*)	(*y*)	(*y*)	(%)	(*y*)
Severe										***Adult Sample***	**Mean**	**3.7**	**7.1**	**24.9**	**55.1**	**4.4**	**31.7**	**27.3**	**76.9**	**12.6**
											SD	**1.0**	**1.6**	**20.3**	**34.7**	**3.4**	**5.3**	**4.9**	**9.7**	**0.8**
Total	**1766**										**Mean**	**4.0**	**6.5**	**20.6**	**52.8**	**3.6**	**22.9**	**18.9**	**70.8**	**11.4**
											SD	**1.2**	**1.4**	**15.1**	**33.4**	**3.0**	**10.6**	**9.8**	**12.0**	**2.8**
Total TBI severity groups	**3116**										**Mean**	**4.1**	**9.8**	**11.9**	**31.3**	**2.9**	**22.9**	**19.2**	**66.6**	**11.5**
											SD	**1.4**	**3.6**	**15.3**	**36.3**	**2.6**	**11.6**	**2.6**	**17.7**	**2.4**

Note. C = healthy controls; CHI = closed head injury; COAT = Children's Orientation and Amnesia Test; CS = cross-sectional; EI = excellent integration; F = full-scale intelligence quotient; GCS = Glasgow Coma Scale; GOAT = Galveston Orientation and Amnesia Test; HI = head injury; L = longitudinal; LOC = loss of consciousness; MMI = mild memory impairment; Mod = moderate; n = sample size; NOS = Newcastle-Ottawa Scale quality score; OC = orthopedic controls; OGMS = orientation group monitoring system; P= performance intelligence quotient; PI = poor integration; pro = prospective; PTA = post-traumatic amnesia; RE = re-employed; Ref = reference; retro = retrospective; S = severe memory impairment; TOPS = 'TOPS' subgroup; SC = sibling controls; TBI = traumatic brain injury; TPI = time post-injury; TPP= time, place and person; V = verbal intelligence quotient; WAIS = Wechsler Adult Intelligence Scale; WASI = Wechsler Abbreviated Scale for Intelligence; Westmead = Westmead PTA Scale; WISC = Wechsler Intelligence Scale for Children; WPPSI = Wechsler Preschool and Primary Scale of Intelligence.

*Studies excluded for comparisons between the subacute and chronic phase groups.

INJURY SEVERITY

GCS SCORES

The forty-seven studies that reported GCS scores differed in the time of administration of the GCS (also see Table 1). Twenty-five studies measured GCS scores at admission to the hospital. Furthermore, six studies reported the post-resuscitation GCS score, three studies reported the lowest score measured during hospitalization, three studies reported the lowest GCS score measured in the first 24 hours of admission, two studies reported the GCS score at 6 hours and 24 hours post-injury, respectively and one study reported the earliest stable GCS score. Seven studies did not report the time of administration.

LOC DURATION

Twenty-seven studies reported LOC duration. Of these, eleven studies defined LOC duration as the time between injury and resolution of coma (not further specified. Furthermore, five studies defined LOC duration as the time between injury and the ability to obey simple verbal commands, three studies defined LOC duration as the time between injury and attainment of a GCS score of 15, 9 or 8. Eight studies did not provide a LOC duration definition.

Six studies recorded LOC duration prospectively, of which five studies applied the GCS and one study used clinical observations. Another five studies recorded LOC duration retrospectively, of which four studies used medical records and one study used self-reports to estimate LOC duration. Sixteen studies did not report the methodology of LOC duration measurement.

PTA DURATION

Twenty-nine studies reported PTA duration. Of these, four studies defined post-traumatic amnesia as the period between regaining consciousness and the recovery of orientation in time, place and person and/or awareness of activities of daily life. In line with the original definitions by Russel & Smith (1961), six studies defined PTA duration as the interval between injury and the recovery of orientation in time, place and person and/or awareness of daily activities. Nineteen of the studies that reported PTA duration did not provide any definition of PTA duration.

Twelve studies reported prospective recordings of PTA duration. Four of these studies used unstandardized clinical judgments of orientation in time, place and person, whereas eight studies applied the standardized Westmead PTA scale, Galveston Orientation and Amnesia Test, Child Orientation and Amnesia Test or Orientation Group Monitoring System. Six studies reported retrospective recordings of PTA duration, of which one estimated PTA

duration using McMillan's structured interview and five studies used hospital notes and self-reports on post-injury orientation and/or amnesia. Eleven studies did not provide any information on the methodology of PTA measurement.

GROUP COMPARABILITY

To investigate comparability of the TBI severity groups, the mild, moderate and severe TBI groups were compared on age, age at injury, gender ratio, years of education, TPI, GCS score and NOS study quality score (see Table 1). In the subacute phase of recovery, there were no significant differences between the TBI severity groups (*t*s ≤ 1.9, *p*s ≥ .10), except for longer TPI in the severe group than the mild TBI group ($t(38) = -2.1$, $p = .048$). There were also no significant differences between the TBI severity groups in the chronic phase (*t*s ≤ 1.5, *p*s ≥ .13), except for longer TPI in the severe TBI group as compared to the mild as well as moderate TBI groups (*t*s ≥ 3.5, *p*s ≤ .001). In addition, the moderate TBI group had a significant younger age at testing compared to the mild TBI group ($t(34.0) = 2.1$, $p = .046$). A large but non-significant difference in PTA duration was identified between the severe TBI groups in the subacute phase (M = 34.7, SD = 28.9) and chronic phase (M = 52.8, SD = 33.4). We matched these groups on injury severity during analyses comparing TPI groups, by excluding four studies from the chronic phase group (references 24, 64, 72-73 in Supporting Information), in order to prevent effects of injury severity to confound the analysis of recovery. As a result of the TBI severity classification procedure, the mild, moderate and severe TBI groups showed progressively lower GCS scores in the in the subacute phase group as well as the chronic phase group (*t*s ≥ 5.9, *p*s ≤ .001).

As differences in demographic variables between the TPI groups could confound interpretation of recovery effects, we also assessed TPI group comparability. The subacute phase and the chronic phase groups were compared on age, age at injury, gender, years of education, GCS score and NOS study quality score, separately for the mild, moderate and severe TBI groups. For none of the variables of interest a significant difference was obtained between the subacute phase and the chronic phase in the mild TBI group (*t*s ≤ 1.6, *p*s ≥ .13), the moderate TBI group (*t*s ≤ 0.9, *p*s ≥ .41) and the severe TBI group (*t*s ≤ 1.3, *p*s ≥ .20). As a result of the classification procedure for TPI, there was a significant higher TPI in the chronic phase as compared to the subacute phase for all TBI severity groups (*t*s ≥ 4.1, *p*s ≤ .001).

PUBLICATION BIAS

Fail-safe n values reflecting robustness of effect sizes for the influence of publication bias, indicated that the effect of *mild TBI* on FSIQ in the chronic phase was robust, whereas the effect on VIQ in the chronic phase was not robust (Table 2). Effect sizes in the *moderate TBI* group were not robust to the influence of publication bias according to the fail-safe n values. Fail-safe n values in the s*evere TBI* group indicated robust effect sizes. No funnel plot asymmetry was found in the effect sizes in the mild, moderate or severe TBI groups, except for VIQ of the moderate TBI group in the chronic phase of recovery. There were no associations between the magnitude of effect sizes and sample size or study quality. These results indicate that it is unlikely that publication bias meaningfully influenced the reported effect sizes for the mild, moderate and severe TBI groups, with the single exception of VIQ impairments in the chronic phase after moderate TBI.

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