

ORIGINAL ARTICLE

Long-Term Cognitive Outcome in Moderate to Severe Traumatic Brain Injury: A Meta-Analysis Examining Timed and Untimed Tests at 1 and 4.5 or More Years After Injury

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ABSTRACT. Ruttan L, Martin K, Liu A, Colella B, Green RE. Long-term cognitive outcome in moderate to severe traumatic brain injury: a meta-analysis examining timed and untimed tests at 1 and 4.5 or more years after injury. *Arch Phys Med Rehabil* 2008;89(12 Suppl 2):S69-76.

Objectives: To examine long-term outcome of moderate to severe traumatic brain injury (TBI) on timed and untimed cognitive tests using meta-analysis.

Design: Meta-analysis examining outcome at 2 epochs, 6 to 18 months postinjury (epoch 1) and 4.5 to 11 years postinjury (epoch 2).

Setting: Data source was published articles (1966–2007) identified through electronic and manual search.

Participants: A total of 1380 subjects with moderate to severe TBI participated in the 16 studies meeting inclusion criteria.

Interventions: Not applicable.

Main Outcome Measures: Timed and untimed neuropsychologic tests with quantitative results (means, SDs, *t*, and *df* tests) from studies containing a healthy comparison group and a mean time since injury falling within 1 of the 2 epochs.

Results: Patient versus control weighted effect sizes were medium to large at epoch 1 for both untimed tasks ($r = -.46$; confidence interval [CI], $-.32$ to $-.65$) and timed tasks ($r = -.46$; CI, $-.35$ to $-.59$). At epoch 2, effect sizes were slightly smaller for untimed tasks ($r = -.38$; CI, $-.25$ to $-.60$) and timed tasks ($r = -.40$; CI, $-.32$ to $-.62$).

Conclusions: Patients showed robust, persisting impairments on both timed and untimed tests at recovery plateau (ie, 6–18mo postinjury) and many years later. These findings converge with previous studies, though using an alternative approach that obviates some of the methodologic problems of longitudinal studies, such as selective attrition.

Key Words: Brain injuries; Neuropsychology; Rehabilitation.

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ACCORDING TO THE World Health Organization, TBI will surpass many diseases as the major cause of disability (and death) by the year 2020, with approximately 10 million

people affected annually worldwide.¹ The magnitude of the problem is caused in large part by the persistence of cognitive impairments,²⁻¹⁰ which may cause decades of disability as a result of the young demographic that TBI afflicts.¹¹⁻¹⁴ In moderate and severe TBI, cognitive deficits are associated strongly with the ongoing disruption of social networks, employability, and return to work.¹⁵⁻¹⁷ Therefore, gaining an understanding of the long-term course of cognitive functioning is of marked clinical importance: knowing whether some or all cognitive functions show persisting deficits into the longer term would allow better prognostication, planning, and the likelihood of developing targeted prophylactic treatments; the last is particularly important given the small but growing number of findings that some people even show a regression of some cognitive functions over time.^{8,18-20} Because some research has demonstrated that information processing impairments may mediate the relationship between TBI severity and post-TBI adaptive functioning,²¹ in the present study, we compared performance at 2 subacute time points on timed versus untimed tests.

Prospective studies examining early cognitive recovery after moderate and severe injury^{2,22,23} have generally found that most recovery occurs within the first 6 to 18 months of injury^{2,23} and that some improvement may continue thereafter at a slower pace.^{8,24,25} There has been considerable variability in findings on the rate and pattern of recovery of different functions,^{22,26} with the exception of speed of processing, which shows the most consistent findings after moderate to severe TBI.²⁷⁻³⁷ Studies have shown a higher prevalence of compromise^{36,38,39} and slower speed and extent of recovery^{40,41} on timed versus untimed tests, suggesting that speed of processing is uniquely vulnerable to the effects of moderate and severe brain injury.

With regard to longer-term outcomes, prospective studies of long-term cognitive recovery are relatively few. As pointed out by Dikmen et al,⁴² longitudinal cognitive recovery studies have also contained significant methodologic limitations, with a follow-up period rarely exceeding 2 years, biased samples (eg, those referred for clinical care),¹⁹ and even in prospective, well defined samples, very high attrition rates.^{8,19,20} As well, test

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List of Abbreviations

CI	confidence interval
ES	effect size
GCS	Glasgow Coma Scale
LOC	loss of consciousness
PASAT	Paced Auditory Serial Addition Test
PTA	posttraumatic amnesia
TBI	traumatic brain injury
TSI	time since injury

batteries have often included only 1¹⁸ or 2 tests.⁴² As such, other approaches to studying long-term outcome are warranted.

Overall, long-term recovery studies have not yet shown clear-cut patterns of findings across tests,^{8,18,19} although persisting impairments to speed of processing seem to be a common thread across studies. Dikmen et al,⁴² who maintained an 80% retention rate (but with 60% of the sample in the mild TBI range), prospectively examined long-term outcome at 3 to 5 years postinjury on a test of verbal learning and recall, and on the PASAT, a challenging timed test of sustained attention requiring serial calculations.⁴³ Clinically impaired performances (2–3 SDs below average) were observed on the PASAT⁴³ at all degrees of severity. However, for verbal learning, clinically significant impairment was observed only at the most severe level of injury, and impairment was still only 1.35 deviations below average. Moreover, prior neurologic disorders were present in some patients, and therefore, even this level of impairment may have been an overestimate. Thus, definitive persisting deficits on the timed PASAT test were observed, while the persisting deficits in verbal learning were milder and more circumscribed.

Salmond et al⁴⁴ reported persistence of deficits across 2 time points a minimum of 6 months apart, ranging from 6 months postinjury to 3 years postinjury. While not explicitly mentioned, 6 of the 8 variables showing significant differences between patients and controls were timed variables, and of the variables showing no between-group differences, only 1 of 6 was a timed variable. These results, too, suggest that performance on timed variables may be more significantly affected in the longer term. These results are consistent with Spikman et al,⁴⁵ who examined 51 patients with TBI several years postinjury and whose findings underscored the persistence of impairments in speed of processing.

A small number of long-term outcome studies have also shown a regression in functioning over time. The finding does not appear to be attributable to age-related decline given the use of age-scaled normative data or age-matched control groups in studies. Again, clear patterns in the data have yet to emerge in this branch of research; also, methodologic weaknesses limit the inferences that can be drawn. In a 30-year follow-up study of 210 patients with TBI, Himanen et al¹⁹ observed slight cognitive decline in 56% of patients on learning, memory, visuospatial construction, and arithmetic, and improvement only in semantic memory. However, attrition was 70%, and the study sample was composed of patients specifically referred for neuropsychologic or neurologic follow-up and thus likely showed disproportionate impairments. Salmond⁴⁴ found a decline in their battery in spatial recognition only; however, interestingly, it was the latency (ie, timed) measure of spatial recognition on which the decline was observed. Finally, in a study of 182 people with mild to severe TBI carried out by Millis et al,⁸ 15.2% showed a decline, 22.1% showed improvement, and 62.2% were unchanged over a 5-year period. Although the authors reported that most improvement was observed on measures of cognitive speed, visuoconstruction, and verbal memory, it is of interest to note that 2 of the 3 tests showing the highest decline (grooved pegboard and Trail-Making Test Part B) were also timed tests. However, this study, too, had very high attrition (>90%), rendering the observations regarding patterns across tests somewhat tenuous.

Taken together, previous studies suggest that cognitive deficits—particularly speed of processing—may persist or even worsen in the longer term, but that a clear pattern of findings across functions has yet to be identified. One explanation for variability in findings, as Mathias and Wheaton²⁷ have pointed

out, is that past studies of recovery may be confounded by the conflation of timed with untimed tests,⁴⁶ whereby speed of processing deficits compromise performance on tests that are purportedly measuring other cognitive functions (eg, spatial recognition), but nonetheless contain a timed dependent measure.

In sum, cognitive processing is consistently impaired by moderate and severe TBI, and there is evidence that deficits persist into the longer term. However, the patterns of persisting deficits are uncertain to date, because of methodologic limitations of the relatively few studies undertaken, including the confounding of untimed cognitive processes (eg, memory) with timed dependent variables. Therefore, further research is warranted to disentangle the contribution of speed of processing from untimed tests as well as to examine speed of processing on its own.

The current study employed meta-analysis to examine the long-term cognitive recovery of timed and untimed processes at approximately 1 year postinjury and at greater than 4.5 years postinjury. We were interested in how patients performed toward the end of the early recovery period versus how they fared many years postinjury, long after therapies would have stopped for most patients⁴⁷ and after a return to prior role would have been attempted. Meta-analysis has the advantage of allowing integration of a collection of studies on a particular topic for the purpose of synthesizing the findings. The method calculates standardized mean differences or ESs (ie, the difference between 2 means relative to the pooled SD, resulting in a *z* score) to provide a common metric on which to compare studies, with higher ES reflecting stronger differences between groups than lower ES. Researchers have noted that meta-analysis can minimize errors and heighten understanding of neuropsychologically meaningful patterns in data by integrating the findings from multiple studies.^{48,49} To our knowledge, there are no published meta-analytic studies in moderate to severe TBI specifically examining the performances of people with TBI versus healthy controls on timed and untimed neuropsychologic tasks at 2 postinjury epochs.

METHODS

Literature Search and Study Selection

A comprehensive search of PsycINFO and Medline electronic databases was undertaken in order to identify published studies examining cognition and TBI. Key words used in the search included *brain injury*, *traumatic brain injury*, *TBI*, and *head injury*. These words were combined with *cognition*, *neuropsychology*, and *neurocognition*. Search constraints included articles published in English and those printed after 1966 (after the inception of the Medline database) and indexed up until June 2007. For all articles identified as relevant, a manual search of the articles' reference lists was conducted to see whether there were any cited works that were missed by the search engines.

Original studies were included in the meta-analysis if they met the following criteria: (1) neuropsychologic tasks were administered to patients with TBI who were reported to have sustained either moderate or severe nonpenetrating brain injuries (ie, GCS score <13, LOC >1h, and/or duration of PTA >1h); (2) the mean TSI was reported for patients with TBI that allowed classification of studies into 2 nonoverlapping epochs (epoch 1: mean TSI, 6–18mo; epoch 2: mean TSI, ≥4.5y); (3) the research design included a comparison group composed of healthy, age-matched control subjects; (4) study statistics amenable for conversion to conventional ESs that reflect group differences were available (these measures included group

means and SDs, *t*, and *df*); and (5) the cognitive tasks included in the study were adequately described so that a determination could be made about whether the cognitive task was timed or untimed. A test was classified as timed if the dependent variable was timed or if exposure to test material was timed, necessitating speeded processing. All classifications were agreed on by 3 experts in the field of neuropsychology.

The titles of articles and abstract content obtained in the literature search were perused for indications that the study met the inclusion criteria. Copies of the full text of these studies were obtained and the articles were reviewed to determine whether they met the inclusion criteria for the study. Each article was examined by a minimum of 2 of the coauthors to determine its eligibility for the meta-analysis, and a total of 16 appropriate studies were identified.

Data Collection

For each study included in the meta-analysis (table 1), the journal name, title, authors, and date of publication were recorded. Several sample characteristics were also noted, including sample size, mean age, mean education, and sex for patient

and control samples when available; plus, severity of brain injury, as measured by GCS, duration of PTA, and length of LOC for the patient group were recorded, as was TSI at testing.

For some studies, adjustments to the published data were required in order to allow inclusion of the data in the meta-analysis. For example, for longitudinal studies of recovery, in which patients were tested more than once, only data from the first occasion of testing were included (to avoid contaminating the results with practice effects). Also, if more than 1 neuropsychologic test was used to measure a cognitive domain within a study, the mean ES was used so that each study had only 1 ES estimate per grouping of tasks, timed or untimed. Also, in the case of separate articles conducted by the same authors in which participants overlapped substantially, the findings were combined and treated as 1 study.^{50,51}

All cognitive tasks and test variables were included in the meta-analytic database. Pooling of the numerous and various cognitive measures for purposes of analysis can raise methodologic and theoretical challenges because of the heterogeneity of test batteries across studies. For the purpose of this study, we were interested only in examining the global difference be-

Table 1: Demographic Details for the TBI and Control Groups: Injury Data for the TBI Group

Studies	TBI and Controls (n)	TBI (n)	Controls (n)	Mean Age TBI (y)	Mean Age Controls (y)	Mean YOE TBI	Mean YOE Controls	Mean TSI (mo)	Injury Severity (tests used for classification)
Untimed—Epoch 1									
Ariza et al ⁵⁸	40.0	20.0	20.0	25.6	25.4	11.4	12.0	6.0	Mod/Sev (GCS)
Dikmen et al ²²	395.0	274.0	121.0	28.9	31.2	12.0	12.0	12.0	Mod/Sev (GCS)
Formisano et al ⁵⁵	45.0	25.0	20.0	22.3	Matched	NA	NA	11.2	Sev (GCS)
Mathias et al ⁵²	50.0	25.0	25.0	28.6	28.4	11.8	12.0	7.0	Sev (GCS, LOC)
Salmond et al ⁴⁴	41.0	21.0	20.0	33.0	36.0	NA	NA	9.8	Sev (NA)
Mean untimed epoch 1	114.2	73.0	41.2	27.7	28.7	11.7	12.0	9.2	
Untimed—Epoch 2									
Larson et al ⁸³	50.0	26.0	24.0	40.7	35.9	13.9	13.8	110.0	Mod/Sev (GCS, LOC, PTA)
Schmitter-Edgecombe et al ⁵⁹	40.0	20.0	20.0	29.5	29.3	14.1	14.5	64.8	Sev (LOC)
Schmitter-Edgecombe et al ⁵⁴	54.0	27.0	27.0	32.4	32.6	14.0	14.4	60.0	Sev (GCS, LOC)
Schmitter-Edgecombe et al ⁵⁰	48.0	24.0	24.0	34.4	35.4	14.1	14.2	126.0	Sev (GCS, PTA)
Simpson et al ⁵³	40.0	20.0	20.0	32.4	32.2	14.3	14.8	72.0	Sev (GCS)
Vickery et al ⁵⁶	40.0	20.0	20.0	34.1	38.7	12.5	12.7	64.8	Sev (GCS, LOC)
Mean untimed epoch 2	45.3	22.8	22.5	33.9	34.0	13.8	14.1	63.4	
Mean epoch 1 and 2	76.6	45.6	31.0	31.1	31.6	13.1	13.4	38.8	
Timed—Epoch 1									
Ariza et al ⁵⁸	40.0	20.0	20.0	25.6	25.4	11.4	12.0	6.0	Mod/Sev (GCS)
Dikman et al ²²	395.0	274.0	121.0	28.9	31.2	12.0	12.0	12.0	Mod/Sev (GCS)
Formisano et al ⁵⁵	45.0	25.0	20.0	22.3	Matched	NA	NA	11.2	Sev (GCS)
Mathias et al ⁵²	50.0	25.0	25.0	28.6	28.4	11.8	12.0	7.0	Sev (GCS, LOC)
Periáñez et al ⁶⁴	313.0	90.0	223.0	34.6	38.9	12.9	13.3	12.5	Sev (GCS, PTA)
Spikman et al ⁶⁵	104.0	44.0	60.0	29.8	28.5	NA	NA	12.0	Sev (GCS, PTA)
Vakil et al ⁷³	52.0	25.0	27.0	27.0	25.4	NA	NA	4.9	Sev (GCS, LOC)
Mean timed epoch 1	142.7	71.9	70.9	28.1	30.3	12.0	12.3	9.4	
Timed—Epoch 2									
O’Keeffe et al ⁶²	36.0	18.0	18.0	31.3	32.9	NA	NA	38.6	Sev (GCS, PTA)
Park et al ⁶³	24.0	12.0	12.0	53.2	51.5	15.3	15.9	62.4	Sev (NA)
Schmitter-Edgecombe et al ⁵⁹	40.0	20.0	20.0	29.3	29.5	14.1	14.5	64.8	Sev (PTA)
Schmitter-Edgecombe et al ⁵⁰	48.0	24.0	24.0	34.4	35.4	14.1	14.2	126.0	Sev (GCS, PTA)
Simpson et al ⁵³	40.0	20.0	20.0	32.3	32.2	14.3	14.8	72.0	Sev (GCS)
Vickery et al ⁵⁶	48.0	23.0	25.0	34.1	38.7	12.5	12.7	61.7	Sev (GCS, LOC)
Mean timed epoch 2	39.3	19.5	19.8	35.8	36.7	14.0	14.4	51.4	
Mean epoch 1 and 2	95.0	47.7	47.3	31.7	33.2	13.1	13.5	28.8	

NOTE. Severity ratings are based on self-description of mean severity level provided by author of article. Abbreviations: LOC, loss of consciousness; Mod, moderate; NA, not available; YOE, years of education; Sev, severe.

tween timed and untimed neuropsychologic tests, so the various cognitive measures were simply divided into these 2 categories based on the researchers' specific knowledge of neurocognitive tests and/or as per the description provided in the original articles. A description of the individual cognitive variables that make up these 2 groups of tasks can be found in table 2. The studies were then further divided into the 2 nonoverlapping epochs. Epoch 1 was chosen to allow an examination of performances after the end of the acute recovery period and when most recovery would be expected to have occurred based on previous studies. Epoch 2 was selected to be nonoverlapping, and representative of chronic TBI. We selected a time point of 4 years postinjury as the earliest time point. Studies that met inclusion criteria ranged from a TSI of 4.5 to 10.6 years (see table 1 for studies included in each cognitive domain and epoch).

Magnitude of effect. A meta-analysis assumes that each study estimates real differences between groups. Combining several estimations thus yields a more veridical estimation of the real effect. Standardized ESs were initially computed for

each variable with adequate quantitative information (eg, mean ± SD). ESs were then averaged across studies. While the *d* statistic has been the most conventional meta-index previously used, a recent preference for correlational ES measures is notable in the literature.⁶⁶ As such, we used *r* values in our report. The *d* and *r* indices are interchangeable according to the relation $r = [d^2 / (d^2 + 4)]^{1/2}$ (assuming relatively equal sample sizes).⁴⁹ Whereas *d* is interpreted in terms of SD units (ie, mean difference/pooled SD), mean *r* values are interpreted in the same manner as typical correlation coefficients. In Cohen's⁴⁹ qualitative terms, mean *r*'s of .10, .20, and .50 can be considered small, medium, and large ESs, respectively, in behavioral-science research. The *r* values (weighted and unweighted) and CIs were calculated by first obtaining the Fisher *z*-transformed coefficients from the individual test comparisons within each study.⁶⁷

Weighted *r* values reported are corrected by sample size, thereby giving greatest weight to the studies with the most reliably estimated study ESs—those with the largest sample sizes.⁶⁸ Each mean weighted *r*² and SD was then used to

Table 2: Summary of Individual Untimed and Timed Cognitive Tests by Domain and Epoch

Untimed Tests	E 1	E 2	Timed Tests	E 1	E 2
Learning and Recall			Fluency		
AVLT Immediate Recall ⁵²	X		Controlled Oral Word Association ^{58,60}	X	
AVLT Delayed Recall ⁵²	X		Design Fluency ^{52,53,55-57,61}	X	
California Verbal Learning Test—Total ⁵³		X	Scanning		
California Verbal Learning Test—Trial 1 ⁵⁴		X	Digital cancellation ms ⁵³		X
California Verbal Learning Test—Trial 5 ⁵⁴		X	Digit cancellation hits ⁵³		X
California Verbal Learning Test Short-Delay ⁵⁴		X	Psychomotor		
Long Delay Free Recall ^{53,54}		X	Finger tapping—dominant ^{22,58,59}	X	
Prose Delayed Recall ⁵⁵	X		Grooved pegboard—dominant hand ⁵⁶		X
Related-Word Delayed Recall ⁵⁵	X		Finger tapping—nondominant ^{22,56,58,59}	X	X
Unrelated-Word Delayed Recall ⁵⁵	X		Name writing—dominant ²²	X	
WMS—Logical Memory ²²	X		Name writing—nondominant ^{22,58}	X	
WMS—Visual Reproduction ²²	X		Attention		
WMS—Logical Memory ^{22,51}	X	X	Dual Attention to Response Task ⁶²		X
WMS—Visual Reproduction ^{22,51}	X	X	PASAT (adapted) 1st Third ⁶³		X
WMS-III Word List Immediate Recall ⁵⁶		X	PASAT (adapted) 2nd Third ⁶³		X
WMS-III Word List Delayed Recall ⁵⁶		X	PASAT (adapted) 3rd Third ⁶³		X
WMS-III Word List Recognition ⁵⁶		X	Sustained Attention to Response Task—Fixed ⁶²		X
Selective Reminding Total Recall ²²	X		Sustained Attention to Response Task—Random ⁶²		X
Selective Reminding Total Delayed Recall ²²	X		Trail-Making Test Part A ^{22,52,53,58,64}	X	
Total Recall after 4-hour delay ²²	X		Word Reading/Naming		
Prospective Memory Focal Cue Hits ⁵¹		X	Stroop—color reading ²²	X	
Prospective Memory Peripheral Cue Hits ⁵¹		X	Stroop—word reading ²²	X	
Executive Function Tests			Stroop—color/word reading ^{53,65}	X	X
Raven's Progressive Matrices ⁵⁵	X		Executive		
WCST—Categories ^{53,54}		X	Trail-Making Test Part B ^{22,52,53,64}	X	
WCST—Errors ⁵²	X		Trail-Making Test Part B—A ^{51,64}	X	
WCST—Perseverations ^{53,54}		X	Trail-Making Test Part B:A Ratio ⁶⁴	X	
Category Test ^{22,55,57}	X		Trail-Making Test Part B-A/Trails A ⁶⁴	X	
Mental Efficiency					
Alphabet Span Test ⁵¹		X			
Seashore Rhythm Test ²²	X				
Visuospatial Skills					
Facial Recognition ⁵⁸	X				
Rey Figure Copy ⁵⁸	X				
Other					
Tactual Performance Test ²²	X				
WAIS—Full Scale Intelligence Quotient ^{51,53,59}		X			

Abbreviations: AVLT, Auditory Verbal Learning Test; WAIS, Wechsler Adult Intelligence Test; WCST, Wisconsin Card Sort Test; WMS, Wechsler Memory Scale.

Table 3: ES Summary Statistics for TBI Versus Control Groups on Untimed and Timed Cognitive Tasks at Epochs 1 and 2

Groups	k	n	Total Weighted <i>r</i> Score	CI _s	Total Unweighted <i>r</i> Score	Fail-Safe n	Coefficient of Robustness
Untimed cognitive tasks	12	895	-0.45	-0.36 to -0.57		34	-2.87
Overall					-0.47		
Epoch 1	5	323	-0.46	-0.32 to -0.65	-0.50	36	-1.83
Epoch 2	7	273	-0.38	-0.25 to -0.60	-0.44	70	-2.26
Timed cognitive tasks	13	1295	-0.45	-0.40 to -0.56	-0.49	88	-2.11
Overall					-0.52		
Epoch 1	7	1015	-0.46	-0.35 to -0.59	-0.48	54	-1.60
Epoch 2	6	280	-0.40	-0.32 to -0.62	-0.49	41	-1.44

compute 95% CIs for both the timed and untimed groups. Finally, the *r*² values were reconverted to *r* values.^{66,67} The 95% CI around the weighted *r* reflects the variability across studies and, if encompassing 0, indicates nonsignificant (*P*>.05) deviation of the mean ES from this null hypothesis value.

Note that, given the relatively small number of studies published in this area, the use of weighted *r* could disproportionately bias results based on a single study. Therefore, unweighted *r* values are also presented in order to provide the most comprehensive review possible.

In addition to the CIs, coefficients of robustness were calculated to compare the observed effects for robustness and homogeneity. Viewed as a “second-order effect size,”⁶⁹ the coefficients of robustness provides a common metric in order to compare average group ESs as they are standardized by their SDs.

Because of the potential for meta-analyses to be subject to publication biases—that is, the selective publication of significant results—fail-safe calculations were also conducted. A number of different methods have been proposed to deal with this issue. Consistent with our choice of the *r* measure of ES, we applied the Orwin method⁷⁰ that calculates the number of additional studies of null effect needed to reduce the average ES to a minimal size (ie, *r*=.10).^{49,71}

RESULTS

Participants

A total of 1380 participants from 16 studies were included in this meta-analysis: 694 people with moderate to severe TBI and 686 control participants. Demographic details for participants in the studies included in this analysis are summarized in table 1. Participants were similar in terms of their mean age and years of education. When the ages and educational levels were compared via *t* test, the TBI and control groups did not differ significantly (education, *t*₁₅=.55, *P*>.05; age, *t*₁₅=.76, *P*>.05), suggesting that these groups were overall well matched on these variables. Furthermore, participants in studies across both epochs, and across timed versus untimed tests, did not appear to differ in their demographic data and injury characteristics (see table 1). From among these publications, 13 studies had either similar numbers or a matched percentage of men in both TBI and control groups, 2 studies did not report the sex of participants in either group,^{63,72} 1 study reported only the sex of participants in the TBI group,⁷³ and 4 studies reported unequal numbers of men between the TBI and control groups. The overall percentage of men in the TBI group was 75.8, while overall percentage of men in the control group was 69.4. In terms of injury severity, the overall average GCS score

was 7.25, while average length of PTA was 53.23 days. Thus, participants were, overall, within the severe range of severity.

Untimed versus timed tests. Similar numbers of studies were used in each epoch for untimed and timed tests (untimed=5 studies in epoch 1, and 6 studies in epoch 2; timed=7 studies in epoch 1, and 6 studies in epoch 2).

Table 3 lists the ES differences (weighted *r*, unweighted *r*, CIs, coefficients of robustness, and fail-safe n) between patients with TBI and healthy controls for the 2 epochs organized by timed and untimed neuropsychologic tests.

The overall weighted *r* for each domain collapsed across the 2 epochs shows that patients with TBI performed worse than controls on both types of tests (table 3; untimed: weighted *r*=-.45, CI, -.36 to -.57; timed: weighted *r*=-.45, CI, -.40 to -.56). Examination of unweighted *r* yielded similar results.

For untimed tests, a moderate to large negative ES difference (weighted *r*) in both epochs (epoch 1: weighted *r*=-.46, CI, -.32 to -.65; epoch 2: weighted *r*=-.38 CI, -.25 to -.60) was observed. The negative ESs show that patients with TBI perform consistently worse than controls on untimed tests across these 2 points in the chronic TBI spectrum. Examination of unweighted *r* values yielded similar results. The overall CIs suggest that the results are reliable; the coefficient of robustness suggests the method of analysis is relatively robust to outliers and small departures from underlying assumptions.

Similarly, for timed tests, a moderate to large negative ES difference (weighted *r*) in both epochs (epoch 1: weighted *r*=-.46, CI, -.35 to -.59; epoch 2: weighted *r*=-.40; CI, -.32 to -.62) was noted. Like untimed cognitive tasks, the findings show that patients with TBI consistently performed worse than controls. Examination of unweighted *r* yielded a very similar pattern of findings from epoch 1 to 2.

DISCUSSION

To our knowledge, this is the first research synthesis that has examined untimed versus timed cognitive processing during 2 subacute periods after moderate to severe TBI. Very few longitudinal studies of recovery have examined recovery at this late postinjury phase; of these, most were plagued by significant attrition and likely sample bias. Consequently, a clear and definitive clinical picture of long-term outcome from moderate and severe TBI has remained elusive.

We observed robust residual cognitive deficits at both epochs, for both timed and untimed processing. In a meta-analytic study of subjects with moderate to severe TBI, Schretlen and Shapiro⁷⁴ noted large ESs when they explored earlier epochs than in our study (<6mo postinjury; >24mo postinjury). Our findings were compatible with these findings in that significant persisting cognitive impairments were observed during the chronic stages of recovery.

In the current study, we further characterized this picture by separately examining untimed versus timed cognitive processing across epochs, thus avoiding the potential confounding of untimed performances by impaired speed of processing. We observed moderate to large ESs at each epoch for untimed and timed tasks, indicating that significant cognitive impairments persist even when the dimension of speed of processing is parceled out from neuropsychologic tests encompassing verbal learning/recall, visuospatial learning/recall, prospective memory, executive functioning, mental efficiency, and visuospatial skills. These findings are consistent with those of a recent study³⁸ finding that deficits in divided attention, executive functions, and long-term memory were better explained by a primary deficit in working memory than a deficit in speed of processing per se at approximately 1.5 years after brain injury.

That cognitive deficits persist even in the absence of any speed of processing requirement suggests that patients with TBI, their families, and the health care professionals that work with them should be prepared to implement compensatory strategies and accommodations for a wide variety of deficits into the long term in order to facilitate functioning and improve quality of life. These efforts are of particular import given the negative impact of persistent cognitive deficits post-TBI (eg, economic toll, increased psychologic distress such as depression/suicide, psychosocial dysfunction, marital/family/social network breakdown) and may be guided by findings linking specific cognitive deficits to functional outcome (eg, Rassovsky et al²¹ found that speed of information processing but not verbal memory mediated the relationship between TBI severity and post-TBI adaptive functioning).²¹

Further, more fine-grained research is needed to characterize primary, underlying persisting deficits and possible differences across neuropathologic, demographic, or psychosocial subgroups. It is also needed in order to uncover more subtle chronic changes that may exist, such as the clinically and scientifically important possibility of postrecovery cognitive decline. Animal^{75,76} and human studies^{77,78} have suggested that the brain may atrophy after initial injury and that cognitive functioning, too, may show a decline for some people in some domains after an initial normalized period of recovery.^{8,19,20} For example, Till et al²⁰ found that approximately 1 (27%) in 4 adults with moderate to severe TBI demonstrated some degree of cognitive decline between the first year of recovery and 2 to 5 postinjury. Ng et al⁷⁹ found visible interval changes on structural magnetic resonance imaging (read by expert neuroradiologists) over the same time period, including increased gliosis, increased white matter signal intensities, and tissue loss.

Persisting cognitive impairments may also leave some people vulnerable to a downward spiral of neuroplasticity with negative consequences analogous to that proposed by Mahncke et al^{80,81} in association with aging. Turner and Green⁸² have argued that chronic TBI, with its endogenous and exogenous changes similar to those observed in normative aging (eg, cognitive impairment, loss of employment, reduced opportunities for social contact), fosters conditions for negative plasticity.

Study Limitations

It should be noted that our literature search was limited to articles published in English, and that it is possible that unpublished studies with nonsignificant findings were excluded from the current meta-analysis. It is also possible that the search terms used were not exhaustive, resulting in the omission of relevant articles. Recruitment methods of the included studies were not assessed (eg, subjects may have been enrolled because they were symptomatic or had experienced particularly good or

poor recoveries), and this too could potentially contribute to outcome heterogeneity.

The ultimate quality of a meta-analysis is guided by the quality of included primary studies. Mathias and Wheaton²⁷ describe a number of factors that must be included within TBI studies in order to allow appropriate evaluation of individual studies and integration of studies in the form of meta-analyses. Future authors are advised to include those factors cited and to examine neuropsychologic recovery course separately for timed and untimed tasks. One limitation of the primary studies—which in turn produced limitations in the current meta-analysis—is that they did not quantify the percentage of variance accounted for by speed of processing versus other mental processes. Because the tests used in the studies eligible for inclusion at epoch 1 differed from those in epoch 2, direct comparisons across the epochs should be made with caution.

Another reason comparisons across epochs must be made conservatively is that there may be differences in the samples that would influence the results. For example, clinical or demographic factors (eg, persisting symptoms, socioeconomic status, education) could carry greater influences on the probability of participating in a long-term follow-up study than an earlier study; studies conducted early postinjury are often incorporated into routine clinical care, and thus factors such as family support, socioeconomic status, and severity of injury are less likely to influence participation. In this regard, we found that years of education were slightly higher in epoch 2 than epoch 1 in the current study, suggesting that those available for or interested in participating in a neuropsychologic study many years postinjury might be better educated than those who did not participate. A mitigating factor for this concern, however, is that the disparity in education from epoch 1 to epoch 2 was the same for timed and untimed tests. Therefore, any biases as a function of TBI may have influenced the 2 test types similarly. Another mitigating factor is that severity of injury was highly similar across test type and epochs, with most studies including patients in the severe range of injury on average, and a few made up of patients in the moderate-to-severe range.

Additional factors that may be worthwhile to include in future studies and were not evaluated in our study include the presence of chronic pain symptoms, affective status, and symptom validity performance. Issues such as chronic pain and affective status are additional factors associated with TBI that could influence an individual's neuropsychologic test performance, resulting in potential decline and/or fluctuation over time. Future work incorporating these factors would enrich our current knowledge regarding TBI recovery course and possible moderators.

CONCLUSIONS

People with moderate to severe TBI exhibit wide-ranging neuropsychologic deficits in both the acute and chronic phases of recovery. Relative to healthy controls, people with moderate to severe TBI were impaired on both timed and untimed neuropsychologic tasks at 2 chronic postinjury epochs: at or shortly after recovery plateau, and much later, at 4.5 or more years postinjury. These results, using meta-analysis, converge with and provide further specificity to the relatively small number of previous longitudinal studies of cognitive deficits in chronic TBI.

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