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Factors moderating neuropsychological outcomes following mild traumatic brain injury: A meta-analysis

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Abstract

There continues to be debate about the long-term neuropsychological impact of mild traumatic brain injury (MTBI). A meta-analysis of the relevant literature was conducted to determine the impact of MTBI across nine cognitive domains. The analysis was based on 39 studies involving 1463 cases of MTBI and 1191 control cases. The overall effect of MTBI on neuropsychological functioning was moderate ($d = .54$). However, findings were moderated by cognitive domain, time since injury, patient characteristics, and sampling methods. Acute effects (less than 3 months postinjury) of MTBI were greatest for delayed memory and fluency ($d = 1.03$ and .89, respectively). In unselected or prospective samples, the overall analysis revealed no residual neuropsychological impairment by 3 months postinjury ($d = .04$). In contrast, clinic-based samples and samples including participants in litigation were associated with greater cognitive sequelae of MTBI ($d = .74$ and .78, respectively at 3 months or greater). Indeed, litigation was associated with stable or worsening of cognitive functioning over time. The implications and limitations of these findings are discussed. (*JINS*, 2005, *11*, 215–227.)

Keywords: Brain concussion, Head injury, Minor, Neuropsychological, Sequelae, Litigation

INTRODUCTION

Traumatic brain injury (TBI) is a leading cause of death and disability (Centers for Disease Control and Prevention, 2003). Each year an estimated 1.5 million people in the United States alone sustain a nonfatal brain injury (Sosin et al., 1996). Approximately 80% of these injuries are classified as mild (Kraus & Nourjah, 1988), involving only a brief loss or alteration of consciousness. Increasingly, mild traumatic brain injury (MTBI) has been recognized as a major public health concern with an annual worldwide incidence ranging from 100 to 550 per 100,000 (Andersson et al., 2003; Duus et al., 1991; Evans, 1992; Thornhill et al., 2000). The economic impact of MTBI is substantial, accounting for about 44% of the 56 billion dollar annual cost of TBI in the United States (Thurman, 2001).

Although it is clear that most patients suffer at least some acute cognitive difficulties, the nature and course of post-acute cognitive recovery remains an area of intense controversy. While most cases of MTBI recover completely within the first 3 months (Dikmen et al., 1986, 1995; Gentilini et al., 1985; Gronwall & Wrightson, 1974; Levin et al., 1987; Rutherford et al., 1979), a significant minority continue to report distressing symptoms for months (Alves et al., 1993; Dikmen et al., 1986; Hartlage et al., 2001; Powell et al., 1996) or years postinjury (Alexander, 1992; Deb et al., 1999; Hartlage et al., 2001). The prevalence of persistent symptoms varies across studies from 7–8% (Binder et al., 1997) to 10–20% (Alexander, 1995) to 33% (Rimel et al., 1981). Frequently these complaints involve a constellation of physical, emotional, and cognitive symptoms collectively known as postconcussion syndrome (PCS). Common

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symptom complaints include headaches, balance problems, dizziness, fatigue, depression, anxiety, irritability, and memory and attention difficulties, often without demonstrable structural changes to the brain (Eisenberg & Levin, 1989) or neuropsychological dysfunction (Dikmen et al., 1986; Levin et al., 1987). Some have suggested that persistent PCS reflects subtle neurological dysfunction beneath the detection threshold of routine diagnostic procedures such as computed tomography (CT), magnetic resonance imaging (MRI), and electroencephalography (EEG) conducted shortly after injury (Hayes & Dixon, 1994; Miller, 1996; Povlishock & Coburn, 1989). Others contend, however, that persisting symptoms are the result of psychological mechanisms such as poor coping styles (Marsh & Smith, 1995), emotional reactions to an adverse event (Bryant & Harvey, 1999), or expectations of symptoms that may occur following a MTBI (Mittenberg et al., 1992). While PCS has been recognized for at least the last few hundred years (Evans, 1992), the debate over the persistence of symptoms following MTBI in a minority of individuals has led to PCS being a particularly controversial diagnosis in the medical-legal arena.

Because objective evidence of cognitive impairment is part of the Diagnostic and Statistical Manual–4th Edition (DSM–IV) diagnostic criteria for PCS (American Psychiatric Association, 1994), documenting neuropsychological deficits is one approach used to help establish the validity of symptom complaints, particularly in the medical-legal arena. However, the extent to which neuropsychological impairment persists is controversial. Three meta-analytic reviews have been published on neuropsychological outcomes in MTBI. The first, by Binder and colleagues (1997), included only participants at least 3 months postinjury who had been selected due to a history of mild head trauma rather than symptom complaint (i.e., population-based or unselected samples). These authors calculated a total of 11 effect sizes from eight different studies and found the sample-size weighted overall effect to be quite small ($g = .07$). When effect sizes were calculated for specific neuropsychological domains, only attention had an effect size significantly greater than zero ($g = .17$).

In contrast, a subsequent meta-analysis by Zakzanis et al. (1999) included 12 studies. There is no indication regarding study selection criteria, other than MTBI. Thus, this study differed from the Binder et al.'s study (1997) by including both clinic-based/referred samples and the unselected samples of Binder and colleagues. An overall effect size was not reported. Instead, effect sizes were reported for specific neuropsychological tests and then for those tests grouped into seven cognitive domains. The results of this domain analysis revealed moderate to large effect sizes for all cognitive domains, with the largest for cognitive flexibility/abstraction ($d = .72$) and the smallest for manual dexterity ($d = .44$). However, it is impossible to know whether these larger effect sizes reflect the inclusion of more acutely injured participant samples, as time since injury was not specified, or reflect the inclusion of clinic-based samples.

A recent meta-analysis (Schretlen & Shapiro, 2003) attempted to clarify these disparate results by examining both MTBI studies and moderate-to-severe studies and including only population-based or unselected samples. Based on 15 studies, the overall neuropsychological effect size (d) for MTBI was .24, while the effect size for moderate/severe TBI was .74. These findings suggest that it was the inclusion of studies with clinic-based symptomatic participants that resulted in the larger effect sizes in the Zakzanis and colleagues (1999) meta-analysis. Further, these investigators grouped studies of MTBI into 4 time-since-injury intervals, $<$ 7 days, 7–29 days, 30–89 days, and $>$ 89 days, and found significant differences across these intervals ($d = .41$, .29, .08, and .04, respectively). The neuropsychological effect size associated with MTBI was not significantly different from zero by 30–89 days postinjury. However, these investigators did not report effect sizes by different neuropsychological domains, and it is certainly possible that some domains may show residual impairments not captured by the overall effect size [e.g., the Binder et al. (1997) findings of a significant effect size only for the attention/concentration domain].

The purpose of this study was to determine the magnitude of impairment in MTBI participants across multiple cognitive domains. Of primary interest was whether there are differences in effect sizes based on several dimensions: cognitive domain (e.g., attention, memory, etc.), time since injury, and the nature of the study participants (litigation *versus* clinic-based *versus* unselected samples).

METHOD

Search Strategy and Selection Criteria

Articles published between 1970 to March 2004 were identified through a literature search of online databases (PUBMED and PsychINFO). The search was limited to articles published in the English language using human participants. The key words were "cognition," "neuropsychological," "minor," "head injury," "brain injury," "mild," "traumatic brain injury," and "concussion." In addition, we examined the reference sections of previous meta-analyses, as well as the reference sections of retrieved empirical studies to locate additional studies. This was done to minimize the possibility of overlooking any studies missed in the computerized database searches.

To be included in the analysis, studies had to meet several criteria which were implemented to ensure a reasonably homogeneous set of studies and to allow for the calculation of effect sizes pertaining to the potential cognitive sequelae of MTBI. First, participants had to have sought medical attention for mild head injury. As such, studies of sports-related injuries were excluded due to the potential differences between participants in these types of samples (i.e., athletes usually do not seek medical attention at a facility but rather are assessed during and immediately after the sporting event). Also, those studies that did not suggest

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brain injury *per se* (i.e., whiplash) were excluded. Second, participants with mild head injury had to be compared to some control group. Although the definition of MTBI differed among studies, there had to be some attempt to define participants by level of severity. Those studies that did not separate their findings by severity level were excluded from the study. Third, participants had to be compared on cognitive measures, either clinically validated tests or experimental measures. Fourth, the studies had to include sufficient statistical information to allow for calculation of effect sizes. Fifth, participants had to be adults or adolescents, as children may have different cognitive sequelae following MTBI (Borg et al., 2004; Capruso & Levin, 1992). Finally, as we are interested in changes in cognitive functioning over time following MTBI, we only included studies that reported time since injury.

We examined a total of 133 studies from which 39, with a total of 41 effect sizes, met inclusion criteria (see asterisked studies in the reference section). Of note, the Levin et al.'s study (1987) contributed three separate effect sizes, as results were presented by three separate geographic sites. If multiple time points or multiple severity groups (within the context of MTBI) were presented, an average effect size was calculated. As Mangels et al. (2002) used the same participants as Levine et al. (1998), we only included the Mangels et al.'s study. Finally, although McAllister et al. (2001) used 6 participants and 8 controls from the McAllister et al. (1999) study, we considered these studies independent and therefore included an effect size for each. The 39 studies contributed a total of 1463 cases of MTBI and 1191 control cases. The basic characteristics of each of the included studies are displayed in Table 1, including the overall unweighted effect size (d) for each study. The frequency of various unweighted effect sizes are presented in a histrogram in Figure 1. The unweighted effect sizes were utilized to visually depict the most frequent effect sizes associated with MTBI independent of sample size. The severity of injury data for each study are presented in Table 2.

Cognitive Outcome Measures

The outcome measures were tests of cognitive performance for MTBI cases and controls. These tests were grouped into nine broad domains of functioning, based upon the typical grouping seen in the neurological and neuropsychological literature (Lezak, 1995; Spreen & Strauss, 1998). For experimental tasks (i.e., tasks not validated for clinical use), we relied upon the authors' domain assignment. Measures included within the nine domains are: *global cognitive ability*—Wechsler Adult Intelligence Scales (Wechsler, 1987a, 1997a), National Adult Reading Test (Nelson & Willison, 1991), and the General Neuropsychological Deficit Scale from the Halstead-Reitan Neuropsychological Test Battery (Reitan & Wolfson, 1993); *attention*—Trail Making Test-Part A (Reitan & Wolfson, 1985), Paced Auditory Serial Addition Task (Gronwall, 1977; Levin, 1983), Digit Span, Arithmetic, Digit Symbol, and the Letter-Number Sequencing subtest from the Wechsler Intelligence Scales (Wechsler, 1974, 1987a), Test of Everyday Attention (Robertson et al., 1994), Consonant Trigrams Test (Peterson & Peterson, 1959), Sentence Repetition Test (Meyers et al., 2000), Continuous Performance Test (Conners, 1995), simple and choice reaction time tasks, experimental tasks of selective attention, n-back tasks, attention subscale of the BNI Screen for Higher Cortical Function (Prigatano et al., 1995), Digit Span and Visual Span subtests from the Wechsler Memory Scales (Wechsler, 1987b, 1997b), serial addition by 3's, and the Seashore Rhythm Test (Reitan & Wolfson, 1993); *executive functioning*—Trail Making Test-Part B (Reitan & Wolfson, 1985), Stroop Color and Word Test interference score (Golden, 1978), Category Test from the Halstead-Reitan Battery (Reitan & Wolfson, 1993), and the Wisconsin Card Sorting Test (Heaton, 1981; Heaton et al., 1993); *fluency*—Controlled Oral Word Association Test (Benton & Hamsher, 1976), Ruff Figural Fluency Test (Evans et al., 1985), and semantic fluency (Goodglass & Kaplan, 1972); *memory acquisition*—learning trials or immediate recall trials from the following tests: California Verbal Learning Test (Delis et al., 1987), Benton Visual Retention Test (Benton, 1974), Wechsler Memory Scale (Wechsler, 1987b, 1997b), Selective Reminding Test (Buschke, 1973; Mattis & Kovner, 1978), Rey-Osterrieth Complex Figure (Osterrieth, 1944), Rey Auditory Verbal Learning Test (Schmidt, 1996), BNI Screen for Higher Cerebral Functions (Prigatano et al., 1995), Standardized Assessment of Concussion (McCrea et al., 1997), Continuous Recognition Memory (Hannay & Levin, 1988), and experimental word recognition tasks; *delayed memory*—delayed recall portions from the following tests: California Verbal Learning Test (Delis et al., 1987), Wechsler Memory Scales (Wechsler, 1987b, 1997b), Rey-Osterrieth Complex Figure (Osterrieth, 1944), Rey Auditory Verbal Learning Test (Schmidt, 1996), BNI Screen for Higher Cerebral Functions (Prigatano et al., 1995), Standardized Assessment of Concussion (McCrea et al., 1997), and the Mattis-Kovner Verbal Learning and Memory Test (Mattis & Kovner, 1978); *language*—Boston Naming Test (Kaplan et al., 1983), speech/language subscale of the BNI Screen for Higher Cortical Function (Prigatano et al., 1995), Speed and Capacity of Language Processing Test (Baddeley et al., 1992), and the Vocabulary and Similarities subtests from the Wechsler Adult Intelligence Scales (Wechsler, 1987a, 1997a); *visuospatial ability*—the Block Design, Picture Completion and Picture Arrangement subtests from Wechsler Scales (Wechsler, 1987a, 1997a), the visuospatial portions of the BNI Screen for Higher Cerebral Functions (Prigatano et al., 1995), the copy portion of the Benton Visual Retention Test (Benton, 1974), and the Rey-Osterrieth Complex Figure (Osterrieth, 1944); and *motor abilities*—finger tapping and name writing (Reitan & Wolfson, 1993).

Data Extraction and Statistical Analysis

Effect sizes were calculated using techniques espoused by Hunter and Schmidt (Hunter & Schmidt, 1990; Hunter et al.,

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Table 1. Characteristics of the 39 studies included in the meta-analysis

First author	Year published	Cognitive ability domain(s) examined	*n* MTBI	*n* Controls	MTBI age	Months since injury	Selection method	Mean effect size
Barrow	2003	FL	24	24	35.0	0.17	U	1.03
Bassett	1990	G, A, EX, FL, AQ, DM, L, V	19	29	15.3	0.75	U	.59
Bell	1999	A, EX, FL, AQ, DM, V,	20	20	38.7	12.00	L	.47
Bohnen	1992a	A, EX, AQ	18	9	29.45	6.03	U,C	.28
Bohnen	1992b	A	22	11	27.3	22.75	U,C	.36
Bohnen	1995	A, EX, AQ	22	11	27.3	22.75	U,C	.15
Borgaro	2003	A, DM, L, V	28	14	44.9	0.44	U	1.38
Brooks	1999	A, EX, FL, L	11	13	32.0	0.08	U	.94
Chen	2003	A,EX,FL,AQ,DM	5	5	34.4	16.6	C	.75
Cicerone	1997	A, EX	50	40	34.6	13.20	C	.49
Cicerone	2002	L	32	32	39.4	14.30	C	.20
Comerford	2002	AQ, DM, L	56	85	28.6	0.01	U	.76
Dikmen	1995	G, A, EX, AQ, DM, MO	161	121	28.9	12.00	U	.01
Dikmen	2001	G, A, EX, AQ	157	109	28.4	6.5	U	.12
Gentilini	1985	A, AQ	50	50	35.4	1.00	U	.17
Gentilini	1989	A	22	22	28.4	1.00	U	.66
Goldstein	2001	A, EX, FL, AQ, L	18	14	62.3	0.83	U	.36
Hugenholtz	1988	A	22	44	29.5	0.97	L	.51
Leininger	1990	A, EX, FL, AQ, DM, V	53	23	31.8	7.25	L	.62
Levin	1987	A, AQ, DM, V	155	56	23.1	0.25	U	.75
MacFlynn	1984	A	45	45		0.03	U	.98
Mangels	2002	A, EX, FL, AQ, DM, L	11	10	29.4	30.60	U	.20
Mathias	1999	A, EX, AQ, DM	27	27	34.7	2.92	U	.34
Mathias	2004	A, FL, AQ, DM	40	40	32.4	0.88	L	.52
McAllister	1999	A, EX, FL, AQ, DM	12	11	29.4	0.74	U	.11
McAllister	2001	A, FL	17	12	31.8	0.90	U	.64
Meyers	2001	A, DM	35	30	32.7	9.29	C,L	.47
Mutter	1994	L, V	12	12	29.3	0.30	U	.40
Parasuraman	1991	A	10	10	29.7	0.35	U	1.09
Ponsford	2000	G, A, AQ, L	84	53	26.4	1.63	U	.11
Potter	2002	G, A, EX, AQ, DM	24	24	31.4	9.79	C	.53
Raskin	1996	FL	17	22	42.3	38.87	C	.96
Raskin	1997	A, EX, AQ, DM, V	10	10	41.8	14.24	L	1.27
Reitan	1999	G	38	41	29.6	6.26	U,C	1.48
Ruffolo	2000	A, EX	62	49	35.9	21.20	C	.92
Shum	1990	A, MO	7	7	28.3	1.65	U	.67
Stuss	1989	A	22	22	29.5	0.07	U	2.35
Tiersky	1998	A, EX, AQ, DM, V	33	20	35.5	20.00	L	.92
Voller	1999	A, EX, AQ, DM	12	14	24.1	1.50	U	.64

Note. Cognitive Ability Domains: G = Global cognitive function, A = Attention, EX = Executive functions, FL = Fluency, AQ = Acquisition memory, DM = Delayed memory, L = Language, V = Visuospatial skill, MO = Motor function. Months Since Injury: mean number of months patients tested following injury; Selection Method: C = participants selected from clinic referrals and/or symptomatic sample, U = participants were recruited prospectively, were not selected based on symptomatology, and/or were unsymptomatic, L = litigation.

1982). Calculated from the data reported in each study was the effect-size estimate, *d* (i.e., the control group mean minus the TBI group mean, divided by the pooled standard deviation). Thus, *d* represents the standardized difference between the two groups within each study, with a positive effect size indicative of better performance by the control group. In studies where more than one dependent measure was present for a cognitive domain (e.g., multiple tests of fluency), an averaged effect size was calculated for the overall analysis to avoid one study dominating the results. For example, if a study had tests with both nonverbal and verbal fluency, these effect sizes were averaged to generate the overall effect size for fluency. For the effect sizes reported in this study, the averaged *d* values are weighted by each study's sample size. Finally, we identified potential outliers using funnel plots (Makdissi et al., 2001) and eliminated one effect size that was clearly an outlier. Funnel plots place emphasis on both sample size and deviancy of effect size.

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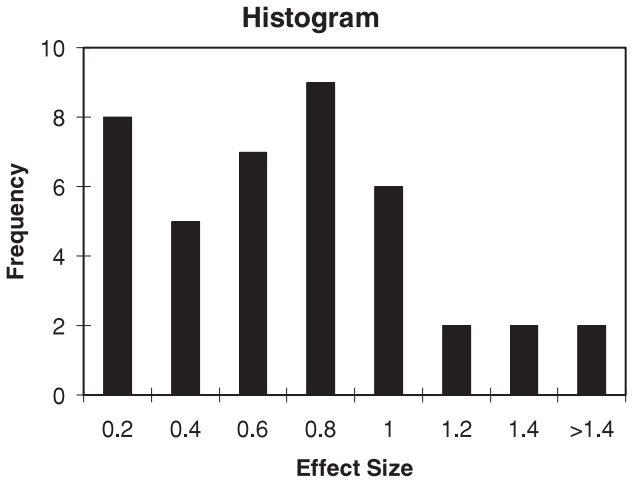

Fig. 1. Frequency of 41 unweighted effect sizes across 39 studies.

Moderator Variables

We also calculated the *Q* statistic to examine homogeneity of effect sizes across studies. The null hypothesis of homogeneity among obtained effect sizes suggests that the observed results represent a single population effect and differences among the obtained effect sizes are due to sampling error. If a significant *Q* value is observed, on the other hand, this indicates heterogeneity of results and potential moderator effects. *Q* is computed by dividing the variance of the sample-weighted *d* by the sampling error variance and this quantity is then multiplied by the number of data points or samples (see formula on page 428, Hunter & Schmidt, 1990). The *Q* statistic is evaluated on the chi-square distribution at $k - 1$ degrees of freedom, where *k* equals the total number of samples. If *Q* exceeds the upper-tail critical value of the chi-square distribution, then the null hypothesis of homogeneity is rejected and potential moderators of the effect size may be explored. We examined the influence of potential categorical moderating variables including cognitive domain, time since injury ($<$90 days *versus* $\geq$90 days) and selection context of the study participants (in litigation *versus* symptomatic/clinic-based *versus* unselected samples). Studies were coded as involving litigation if the authors mentioned that some or all participants were seeking compensation or were involved in litigation. Two studies that had only one litigating participant were not considered litigation studies. Clinic-based studies were coded as such if patients were specifically characterized as symptomatic or if patients were exclusively referred to long-term rehabilitation facilities. Unselected samples were coded as such if participants were recruited prospectively, if they were not selected based on symptomatology, and/or if the samples were unsymptomatic. If a study included more than one patient selection type (e.g., litigation and clinic-based), effect sizes were examined separately for each type. These moderator variables were first coded by a doctorate-level practicing neuropsychologist and independently re-coded by a neuropsychology postdoctoral fellow. Agreement was perfect for time since injury. Agreement on selection context and cognitive domain was good (*kappa* = .99 for both variables). In those instances where the raters disagreed, consensus was reached collectively.

RESULTS

Overall Effect Size

The overall effect (*d*) of MTBI on neuropsychological performance was 0.54 ($p < .05$) based on 39 studies, Q (40) = 5291, $p < .05$. The interrater reliability of this value was calculated using a Pearson's correlation (r = 1.00, $p < .0001$) between overall effect size calculations for each study as determined by two raters. Because null findings are typically not reported in the literature, meta-analyses are frequently criticized as containing a biased sample of all studies conducted. That is, meta-analyses reflect only statistically significant findings, while studies with null results remain unpublished and stored in a researcher's file drawer. To address this issue, we conducted a file-drawer analysis. Essentially, a file-drawer analysis estimates how many studies with null results would need to exist to render the effect size of the current meta-analysis trivial (Rosenthal, 1979). Results suggest that 172 unpublished studies with an effect size of $<$.1 would be needed to eliminate the overall effect size.

Overall Effect Sizes by Cognitive Domain

Effect sizes for the nine cognitive domains are displayed in Table 3. MTBI was associated with statistically significant deficits in all domains except motor functions (only two studies included motor functions). Most effect sizes were moderate to large (Cohen, 1988) with fluency and delayed memory having the largest overall effect sizes. Smallest overall effects were found on motor and executive measures.

As can be seen in Table 3, significant heterogeneity was apparent in all domains except motor functioning. We therefore examined the influence of several additional potential moderating variables in all domains except motor functioning. Potential moderators examined included time since injury and sample selection context (in litigation *versus* clinic-based sample *versus* unselected samples). These variables were selected for further investigation based on the MTBI literature and because the number of studies including these variables was generally sufficient to permit these additional analyses.

Time Since Injury

The results of the time-since-injury moderator analysis are presented in Table 4. In 7 of the 8 cognitive domains examined, the effect of MTBI on neuropsychological functions

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Table 2. Severity indices of the 39 studies included in the meta-analysis

First author	Year published	Neuroimaging findings	GCS	LOC	PTA	Other
Barrow	2003	3/21 had abnormal CT	13–15	≤30 min	≤24 hr	
Bassett	1990	12/19 had abnormal CT	13–15			all but 2 had no prior HI
Bell	1999	6/12 had abnormal CT or MRI		30% dazed-none 50% brief–15 min 20% 15–30 min		
Bohnen	1992a		15	<15 min	≤60 min	no skull fx, alc
Bohnen	1992b		15	<15 min	≤60 min	no skull fx, alc
Bohnen	1995		15	<15 min	≤60 min	no skull fx, alc
Borgaro	2003	14 abnormal CT/MRI, 14 normal	14.2			
Brooks	1999	either normal or small contusions	14.5			
Chen	2003	normal		0.50 min	0.87 hr	no previous HI, LD, or P
Cicerone	1997	normal	13–15	<30 min	< 1 hr	
Cicerone	2002		13–15	≤30 min	≤24 hr	no previous HI, LD, P no ADHD, neuro, narcotics
Comerford	2002		13–15			2.65 min
Dikmen[1]	1995			< 1 hr		
Dikmen[1]	2001	20% abnormal CT	14.4	71% < 1 hr 25% 1–24 hr 4% > 1 day	52% ≤24 hr 41% 1–13 days 7% ≥14 days	
Gentilini	1985		13–15	<20 min	<3 days in hospital, no neuro	
Gentilini	1989		13–15	<20 min	<3 days in hospital, no neuro	
Goldstein	2001	normal	13–15	<20 min		
Hugenholtz	1988			none		no hospital, no neuro
Leininger	1990		13–15	≤20 min		no deterioration in neuro
Levin	1987		14.8	≤20 min		no neuro
MacFlynn	1984				<24 hr	no alc
Mangels	2002	1/10 abnormal CT	14.5		7.2 days	no visual field defect, P, SA
Mathias	1999		14.8	≤20 min		no neuro, P, or SA
Mathias	2004	12 normal CT 2 normal MRI	14.7	20% 0 44% <1 min 36% 1–20 min		no neuro, P no English as 2nd language
McAllister	1999		13–15	≤30 min	≤24 hr	no P
McAllister	2001		13–15	≤30 min	≤24 hr	no P
Meyers	2001			9.72 min		
Mutter	1994	3/10 abnormal CT	14.6	≤20 min		≤24 hr in hospital, no HI,SA,P
Parasuraman	1991	1/8 abnormal CT	14.9	≤20 min		normal neuro, ≤48 hr in hospital No HI in last 6 months No alc or P
Ponsford	2000		13–15	<30 min	≤24 hr	≤24 hrs in hospital, no neuro
Potter	2002		13–15	11.02 min	2.16 min	no neuro
Raskin	1996	normal		0.42 min		no neuro, P, SA
Raskin	1997		13–15	≤30 min	≤24 hr	no P,SA,LD
Reitan	1999	9/20 abnormal		26% none 48% ≤5 min 26% 10–25 min		
Ruffolo	2000	normal		<20 min	<24 hr	
Shum	1990	at least 3/7 abnormal CT	14.9	≤10 min		
Stuss	1989			none		no hospital, no neuro, no alc
Tiersky	1998			≤30 min	≤24 hr	
Voller	1999	3/12 had abnormal MRI	15	6.7min	<1 hr	≤48 hr in hospital

Note. [1]In these studies the length of coma variable (LOC) = time to follow commands. Ranges are given unless mean values are reported; min = minutes, hr = hours; GCS = Glasgow Coma Scale; LOC = length of coma; PTA = length of posttraumatic amnesia; Other = other exclusionary criteria; fx = fracture, neuro = focal findings, P = psychiatric, HI = head injury, alc = alcohol, SA = substance abuse, LD = learning disability, ADHD = attention deficit/hyperactivity disorder.

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Table 3. Effect sizes for the nine cognitive domains

	Number of studies (*k*)	Sample size (controls)	Sample size (MTBI cases)	*d*	95% *CI*	*Q*
Global Cognitive Ability	6	377	483	.24*	.10–.37	281*
Attention	35	993	1266	.47*	.39–.56	3637*
Executive Functions	19	656	628	.21*	.10–.31	760*
Fluency	12	223	247	.77*	.58–.96	86*
Memory Acquisition	23	741	987	.35*	.25–.44	1477*
Delayed Memory	19	596	701	.69*	.58–.81	1733*
Language	9	262	271	.54*	.37–.72	100*
Visuospatial Skill	10	184	330	.57*	.40–.75	234*
Motor Functions	2	128	168	.16	−.07–.39	2

Note. *$p < .05$.

was an average of .23 standard deviation units less when measured postacutely (i.e., ≥90 days) relative to acutely (i.e., <90 days). In contrast, the visuospatial domain showed an increase in the effect size with greater time since injury. However, from Table 4, it is apparent that there is still significant heterogeneity across cognitive domains. We therefore conducted further moderator analyses based on sample selection context.

Sample Selection Context

Given that cognitive outcomes were clearly related to time since injury, subsequent moderator analyses of sample selection context were stratified on time since injury. As can be seen in Table 5, selection context clearly affected effect sizes. The effect sizes reported in Table 5 are independent (i.e., the clinic-based column does not contain litigation cases and the unselected sample column does not contain litigation or clinic-based cases). In order to be able to compare current findings with previous meta-analytic studies, Table 5 also presents overall effect sizes averaged across domains for the three different sample selection contexts.

Table 4. Moderator analyses—time since injury by cognitive domain

	<90 Days			≥90 Days		
Time since injury	*d*	(*k*)	*Q*	*d*	(*k*)	*Q*
Global	.29*	(4)	66.1*	.20*	(4)	60.6*
Attention	.53*	(21)	1244.5*	.32*	(17)	834.6*
Executive Functions	.21*	(7)	47.8*	.15*	(13)	476.8*
Fluency	.81*	(7)	36.4*	.71*	(5)	8.5
Memory Acquisition	.37*	(13)	488.5*	.23*	(12)	473.4*
Delayed Memory	.96*	(10)	464.4*	.40*	(9)	169.3*
Language	.64*	(7)	46.6*	.20	(3)	.1
Visuospatial Skill	.48*	(6)	97.4*	.73*	(4)	21.5*

Note. Values in columns represent average effect sizes, i.e., *d*. Values in parentheses represent the number of studies on which the average effect size is based.
*$p < .05$.

Studies with participants in litigation and studies with unselected samples had a similar overall effect size at <90 days ($d = .52$ *versus* .63, respectively). However, the average effect size associated with litigation increased from <90 days to an average of 13 months postinjury. This finding stands in marked contrast to the findings of studies using unselected samples in which the neuropsychological outcome of MTBI participants was equal to control participants by ≥90 postinjury ($d = .04$). There were no studies with clinic-based samples with outcomes <90 days postinjury, but clinic-based and litigation-based samples were essentially the same at ≥90 days postinjury ($d = .74$ and .78, respectively).

Litigation status also explains a discrepant finding with regard to time since injury seen in Table 4. Visuospatial skill was the only domain with an increasing effect size across time, but all visuospatial studies conducted at ≥90 days involved participants in litigation, while those studies conducted at < 90 days were all unselected samples.

When neuropsychological outcomes for the 8 cognitive domains were examined based on unselected samples, the largest acute effect sizes (<90 days since injury) were for fluency and delayed memory ($d = .89$ and 1.03, respectively). In contrast, studies of participants in litigation had similar acute effect sizes across cognitive domains (*d* ranging from .48 to .58), which generally increased across time (*d* ranging from .59 to .80 at ≥ 90 days). In an effort to determine if the larger litigation effect sizes could be explained by inadequate effort or malingering, litigation study effect sizes were compared based on the presence or absence of validity tests. Litigation studies that included effort screening had an average effect size of .50 ($p > .05$, $k = 2$, $Q = 0$, $p > .05$) while those that did not include effort screening had an average effect size of .66 ($p < .05$, $k = 5$, $Q = 17.6$, $p < .05$). These two effect sizes are homogenous, $Q = .91$, $p > .05$.

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Table 5. Moderator analyses—time since injury by cognitive domain by sample selection context

Cognitive domain (Time since injury)	Litigation-based studies			Clinic-based studies			Unselected sample studies		
	d	(*k*)	*Q*	*d*	(*k*)	*Q*	*d*	(*k*)	*Q*
Averaged Across Domains									
< 90 Days	.52*	(2)	0				.63*	(23)	1649.4*
≥ 90 Days	.78*	(6)	14.1*	.74*	(11)	410.9*	.04	(8)	49.3*
Global									
< 90 Days							.29*	(4)	66.1*
≥ 90 Days				1.32*	(2)	24.5*	−-.02	(2)	.1
Attention									
< 90 Days	.52*	(2)	.1				.53*	(19)	1125.5*
≥ 90 Days	.67*	(5)	30.8*	.74*	(8)	84.9*	.04	(8)	40.6*
Executive Functions									
< 90 Days							.21*	(7)	47.8*
≥ 90 Days	.59*	(5)	10.9*	.47*	(6)	75.2*	−.15	(5)	49.6*
Fluency									
< 90 Days	.58*	(1)					.89*	(6)	22.9*
≥ 90 Days	.59*	(2)	.7	.88*	(2)	.6	.98*	(1)	
Memory Acquisition									
< 90 Days	.53*	(1)					.35*	(12)	444.3*
≥ 90 Days	.78*	(4)	20.1*	.79*	(4)	3.2	.01	(6)	37.2*
Delayed Memory									
< 90 Days	.48*	(1)					1.03*	(9)	369.5*
≥ 90 Days	.80*	(5)	11.2*	.43*	(3)	15.6*	.07	(2)	.1
Language									
< 90 Days							.64*	(7)	46.6*
≥ 90 Days				.20	(1)		.21	(2)	.1
Visuospatial Skill									
< 90 Days							.48*	(6)	97.4*
≥ 90 Days	.73*	(4)	21.5*						

Note. The number of studies (*k*) in this table does not equal *k* in Table 4 due to certain studies contributing to >1 cell in this table (e.g., a study which presented data separately for unselected samples *versus* clinic-based sample selection).
*$p < .05$.

DISCUSSION

Our meta-analysis provides a more up-to-date and comprehensive review of the MTBI literature and includes more studies than previous meta-analyses of neuropsychological outcomes. In addition, we examined the effects of moderator variables, some of which have not been examined in prior studies. Results from those studies using unselected samples suggest that there is an effect of MTBI within the first 90 days with mild neuropsychological impairments across domains, but with specific and relatively large deficits in fluency (d = .89) and delayed memory recall (d = 1.03). However, this acute effect is essentially zero by 3 months postinjury, replicating the findings of Schretlen and Shapiro (2003). These findings extend the results of this prior meta-analytic study (Schretlen & Shapiro, 2003) by examining not only the overall effect size, but the effect sizes for specific cognitive domains. In the studies using unselected samples by 90 days postinjury, no individual cognitive domain was significantly different from zero, with the exception of fluency which was an outlier finding based on only one study (Mangels et al., 2002). Although not an outlier in other domains, within the fluency domain, this study produced results that were clearly different than other domains by 90 days postinjury. This study was atypical in that the MTBI group had an average of 7.2 days posttraumatic amnesia (PTA) which exceeds standard criteria for MTBI (American Congress of Rehabilitation Medicine, 1993). In addition, the sample size was quite small (n = 11 MTBI). Overall, however, the results of this meta-analysis suggest that for the MTBI unselected sample at large, there is full neuropsychological recovery by 3 months postinjury. This is consistent with literature suggesting that most cognitive deficits associated with MTBI resolve in the first 3 months (Dikmen et al., 1986, 1995; Gentilini et al., 1985; Gronwall & Wrightson, 1974; Levin et al., 1987; Rutherford et al., 1979).

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Moderator analyses demonstrated the importance of considering sample selection context when examining the cognitive sequelae of MTBI. Participants in litigation had an overall acute effect size ($d = .52$ at < 90 days since injury) comparable to unselected samples ($d = .63$). However, the acute neuropsychological profile of specific difficulties with fluency and delayed memory recall was not present for participants in the litigation-based samples. In addition, unlike participants in unselected samples, those in litigation do not improve with time and actually get worse. These findings are consistent with the literature suggesting that the effect of financial incentive on outcome following MHI is quite large (Binder & Rohling, 1996) and that sampling method (i.e., clinic-based *versus* unselected samples) is paramount (Binder et al., 1997; Dikmen et al., 1992).

It is tempting to attribute these neuropsychological litigation effects, particularly in the postacute phase (≥ 90 days postinjury), to test invalidity, symptom exaggeration, or malingering. However, moderator investigation of differential effect sizes when symptom validity indices were used in litigation-based studies failed to eliminate the findings (no validity screening $d = .50$; validity screening $d = .66$). In addition, in the postacute phase of recovery, participants in clinic-based samples had comparable moderate to large neuropsychological effect sizes to those of participants in litigation-based samples. The underlying cause of these ongoing cognitive difficulties in litigation and clinic samples is not clear from the current meta-analytic study. Further research will be necessary to determine whether this ongoing adverse effect is due to subtle and lasting brain dysfunction or to psychological factors such as secondary gain (Binder & Rohling, 1996), implicit beliefs or self-expectation (Mittenberg et al., 1992), poor coping styles (Marsh & Smith, 1995), emotional reactions to an adverse event (Bryant & Harvey, 1999), or other factors.

Our results suggest that the effect sizes reported in previous meta-analyses may be confounded by sampling context and time since injury. For example, Binder et al. (1997) reported an effect size for attention of $g = .17$. Our results suggest that this effect size is reduced to essentially zero by 3 months or greater when litigating and symptomatic participants are removed. Our time since injury findings are consistent with Schretlen & Shapiro (2003) in that effect sizes associated with MTBI decrease over time. However, these investigators did not report effect sizes by different neuropsychological domains. Our data suggest that the time since injury effect is generalizable across most cognitive domains. Performance on measures of global cognition, attention, executive functions, fluency, memory acquisition, delayed memory, and language was intact for individuals with MTBI at 3 months or more postinjury as compared with performance at less than 3 months postinjury.

There are several limitations to this study, some of which are inherent to conducting a meta-analysis. Differential criteria for establishing MTBI were averaged in this analysis. Previous research has demonstrated the importance of stringency in defining MTBI, as well as the importance of demographic variables (Dikmen et al., 2001), neither of which was investigated in this meta-analysis. Other potential moderators include "diagnosis threat" (Suhr & Gunstad, 2002) and psychiatric variables (Levin et al., 2001). Examining the effect of MTBI across many cognitive domains and across potential moderators necessarily entailed a small number of studies in some cells. So, for example, the effect sizes of MTBI on fluency ($d = .98$) or on language ($d = .21$) at 90 days or greater for unselected samples comes from only one and two studies, respectively. Clearly, more postacute studies using unselected samples in these domains are necessary. Other more frequently investigated domains (e.g., attention) probably reflect more stable findings. Furthermore, among the studies included in the analysis, few had information on all of the ability domains targeted. It should be noted that we obviously could only code studies as including litigating participants when the authors mentioned this variable. It is likely that some studies failed to exclude participants in litigation, particularly the clinic-based studies, but did not mention this in their study. As such, effect sizes associated with clinic-based samples may be artificially inflated. Finally, it was impossible to compare clinic-based *versus* unselected samples across time in this analysis, as clinic-based studies were exclusively conducted at greater than 90 days postinjury. Clearly, these variables are inextricably confounded with one another due to the lack of variability. As such, the effect sizes associated with these analyses may not reflect the actual amount of variance accounted for by time since injury and sample selection.

Finally, the Q values were still significant even after moderator analyses. Exceptions were global cognition at 90 days or greater, language at 90 days or greater, and delayed memory at 90 days or greater, all of which were comprised of only 1 to 3 studies. As Q is susceptible to artificial variance inflation when the number of studies is large (Hunter & Schmidt, 1990), it is difficult to know whether nonsignificant Q values were due to few studies, and in turn if the significant Q values were due to a greater number of studies. Also, as we were unable to control for potential artifacts (e.g., reliability of the neuropsychological measures), an inflation of Type I error is likely (Schmidt & Hunter, 2003). Therefore, there remain important as-yet-unidentified moderators.

Despite these limitations, this meta-analysis provides compelling evidence that MTBI has little to no effect on neuropsychological function by 3 months or greater postinjury in the MTBI population at large. Participants in litigation, on the other hand, remain stable or get worse with time. Further research is necessary to clarify these findings in certain, less-studied cognitive domains (e.g., motor functioning, language, etc.).

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