A Meta-Analysis of Neuropsychological Outcome After Mild Traumatic Brain Injury: Re-analyses and Reconsiderations of Binder et al. (), Frencham et al. (), and Pertab et al. ()

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A Meta-Analysis of Neuropsychological Outcome After Mild Traumatic Brain Injury: Re-analyses and Reconsiderations of Binder et al. (1997), Frencham et al. (2005), and Pertab et al. (2009)

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The meta-analytic findings of Binder et al. (1997) and Frencham et al. (2005) showed that the neuropsychological effect of mild traumatic brain injury (mTBI) was negligible in adults by 3 months post injury. Pertab et al. (2009) reported that verbal paired associates, coding tasks, and digit span yielded significant differences between mTBI and control groups. We re-analyzed data from the 25 studies used in the prior meta-analyses, correcting statistical and methodological limitations of previous efforts, and analyzed the chronicity data by discrete epochs. Three months post injury the effect size of −0.07 was not statistically different from zero and similar to that which has been found in several other meta-analyses (Belanger et al., 2005; Schretlen & Shapiro, 2003). The effect size 7 days post injury was −0.39. The effect of mTBI immediately post injury was largest on Verbal and Visual Memory domains. However, 3 months post injury all domains improved to show non-significant effect sizes. These findings indicate that mTBI has an initial small effect on neuropsychological functioning that dissipates quickly. The evidence of recovery in the present meta-analysis is consistent with previous conclusions of both Binder et al. and Frencham et al. Our findings may not apply to people with a history of multiple concussions or complicated mTBIs.

Keywords: Traumatic brain injury; Meta-analysis; Post concussion; Effect size calculations.

INTRODUCTION

Large-scale epidemiological studies have demonstrated that traumatic brain injury (TBI) is a common occurrence in the United States and throughout the world (see Kraus & Chu, 2005, for an epidemiological review). The most common severity is mild traumatic brain injury (mTBI), accounting for approximately 75% of all TBIs (Langlois et al., 2003). The average incidence of mTBI was estimated to be 503 per 100,000 in the United States (Bazarian et al., 2005), although this likely is an underestimate, as it is based on emergency department visits only. Many individuals...
who suffer an mTBI do not seek treatment (Demakis & Rimland, 2010) or are not treated emergently.

Some believe that there is controversy regarding neuropsychological outcome of mTBI, with a few studies suggesting the possibility of prolonged deficits after three months (e.g., Bohnen, Twijnstra, & Jolles, 1993; Hugenholtz, Stuss, Stethem, & Richard, 1988). Most have found substantial recovery within 3 months, if not sooner (e.g., Echemendia, Putukian, Macklin, Julian, & Shoss, 2001; Macciocchi, Barth, Wayne, Rimel, & Jane, 1996; for review see Carroll et al., 2004).

What controversy remains regarding mTBI recovery may be due to the enormity of the literature that has addressed the issue, which includes multiple methodological and conceptual challenges. For instance, there are differing diagnostic criteria for mTBI; many studies rely on self-report of symptoms without medical or neurological verification, and patients often have complicating pre-existing or co-morbid psychological factors and diagnoses. The context in which the evaluation takes place is also important as exaggeration or frank malingering is common among cases in litigation (see Iverson, 2005; Putnam, Millis, & Adams, 1996; Ruff & Jamora, 2009, for reviews). In short, many individual studies have been done on the neuropsychological outcome of mTBI, and they vary considerably in their samples, assessment procedures, and research design or methodology.

Meta-analytic reviews can provide strong evidence on any medical or behavioral outcome (Clarke, Hopewell, & Chalmers, 2007; Glasziou, Sheppard, & Brassey, 2010; Schmidt, 1992). The number of published meta-analytic studies in medical fields has grown enormously (Colford, 2001). Meta-analytic reviews of the neuropsychological outcome of mTBI have been particularly important in shaping opinions on this topic, especially reviews of outcomes after mTBI in adults. A popular text on the topic by McCrea (2008) concluded, after reviewing the available meta-analytic and other neuropsychological outcome studies, that there was strong evidence of complete recovery of neuropsychological ability soon after mild traumatic brain injury in adults. Yet this conclusion remains contentious for some investigators (e.g., Iverson, 2010). The initial meta-analysis of outcomes following mTBI in adults was conducted by Binder, Rohling, and Larrabee (1997). Three of the six authors on the current paper were the authors of the original paper (MLR, LEB, & GJL). Binder et al. included eight published papers with 11 total samples and compared those with mTBI at least 3 months post injury to controls. Binder et al. (1997) focused on prospective and quasi-prospective samples recruited because of a history of mTBI and excluded clinical samples; that is, samples recruited because they were symptomatic. Quasi-prospective samples were composed of participants with a history of mTBI in studies of another clinical condition, for example, a study of the effect of mTBI in people seropositive for HIV (Bornstein et al., 1993). Binder et al. found that (a) across all neuropsychological domains those with mTBI performed slightly below controls (effect size1 = -0.07), and (b)

1 For the sake of consistency, in this paper a negative effect size indicates better performance by the control group than the mTBI group, regardless of the definition of negative effect size in previous studies. Some previously published papers, including Binder et al. (1997), defined effect sizes in the reverse direction. For example, Binder et al. (1997) reported an effect size of -0.07 showed a negligible superiority of controls over mTBI cases, but in the present paper, the same effect size is reported as -0.07.
the largest effect size differences were found on measures of Attention/Concentration and Memory Acquisition (both effect sizes = -0.17 with only Attention/Concentration statistically significant). These authors concluded that the average effect of mTBI on neuropsychological functioning was “undetectable” (Binder et al., 1997, p. 428). However, at the time of this initial meta-analytic review published in 1997, the sample sizes were small.

The issue of exclusion of clinical studies of mTBI when performing meta-analytic outcome studies is important (Dikmen & Levin, 1993). The justification for excluding clinical, non-prospective studies is that clinical studies have self-selected participants who will have symptoms and objective neuropsychological deficits that may be for reasons other than a history of mTBI, and are wrongly attributed to mTBI. People may have subjective complaints similar to what is seen in postconcussive syndrome, such as memory loss, headaches, and dizziness, for many reasons; the symptoms of postconcussive syndrome are nonspecific. For example, people in litigation for psychological injuries or physical injuries that did not involve their heads (Iverson, King, Scott, & Adams, 2001; Lees-Haley & Brown, 1993) commonly report symptoms that are considered postconcussive. Patients suffering from clinical depression endorse symptoms similar to those seen in postconcussive syndrome quite frequently (Iverson, 2006; Suhr & Gunstad, 2002), as do people reporting acute stress (Gouvier, Cubic, Jones, Brantley, & Cutlip, 1992). A history of learning disabilities or attention deficit hyperactivity disorder may also result in neuropsychological complaints persisting into adulthood (Mapou, 2008). The rates of endorsement of symptoms of postconcussive syndrome by healthy normal people are also quite high (Iverson & Lange, 2003; Sawchyn, Brulot, & Strauss, 2000). Another reason for excluding clinical studies from meta-analytic reviews of outcome is that people are biased reporters of their pre-injury levels of postconcussive symptoms, tending to rate themselves as less symptomatic than do people with no history of head injury (Gunstad & Suhr, 2004; Hilsabeck, Gouvier, & Bolter, 1998). In summary, symptoms that seemingly are diagnostic of postconcussive syndrome or of mTBI often are associated with non-head injury factors.

Participants can also have objective neuropsychological abnormalities for many reasons; objective abnormalities, like symptoms, are nonspecific. Objective neuropsychological abnormalities may represent a variant of normal cognition; the prevalence of low scores in normative samples is higher than what often may be believed by some clinicians (Binder, Iverson, & Brooks, 2009). Low scores may also be a product of suboptimal motivation (Boone, 2007; Larrabee, 2007). Developmental learning disabilities persisting into adulthood (Mapou, 2008) are another source of neuropsychological abnormalities. One study (Greiffenstein & Baker, 2003) showed that in cases of claimed postconcussive syndrome, low neuropsychological scores were predicted by low high school grades, suggesting that the participants’ low scores were developmental rather than acquired due to mTBI. In a direct comparison, the effect size of clinical studies of mTBI was significantly larger than the effect size of non-clinical studies (Belanger, Curtiss, Demery, Lebowitz, & Vanderploeg, 2005). Thus there are many reasons why non-prospective, clinical studies are likely to spuriously inflate the influence of mTBI on cognition and, as concluded by Dikmen and Levin (1993), clinical...
samples, “do not allow attributions of the problems observed to the effects of head injury” (p. 33).

In 2005 Frencham, Fox, and Maybery performed a follow-up meta-analysis, including studies that had been published since Binder et al. (1997) had published their findings. Frencham et al. examined acute effects as well as the residual neuropsychological deficits caused by mTBI. Like Binder et al., Frencham et al. included only prospective studies or samples recruited because of a history of mTBI and not simply those who complained of symptoms following an mTBI. Post injury, they found a significant effect due to mTBI of −0.33 during the acute phase of recovery (i.e., within 3 months). The magnitude of this effect shrank across time to non-significance, equaling just −0.11 in the post acute phase of recovery (i.e., after 3 months). The largest effect size difference was for measures grouped into the Speed of Processing domain. There was a significant negative correlation between time since injury and the overall effect size ($r = −0.47$), indicating that the effect of mTBI diminished over time. Frencham et al. called for more research on the issue of possible enduring neuropsychological effects, with a focus on considering specific neuropsychological domains and utilizing neuropsychological measures that are the most sensitive to cognitive deficits associated with mild TBI.

Other meta–analytic reviews have also found evidence that adults who experienced mTBIs can expect full recovery within three months of their injury. See Table 1 for a summary of the various studies reviewed below, which also illustrates the recovery curve for neuropsychological ability following an mTBI. For example, Belanger et al. (2005) found, collapsing across all time intervals, an effect size of −0.54. After 3 months the overall effect size for clinical studies, whose participants essentially were self-recruited because of symptoms, was −0.74. However, in the prospective studies, results from individual neuropsychological domains failed to show persisting abnormalities after 3 months and was only −0.04.

Schretlen and Shapiro (2003) conducted a meta-analysis of patient samples to compare the effects of mTBI to that of a moderate to severe TBI. They found evidence of persisting neuropsychological problems only in the moderate-to-severe TBI groups. During the acute period, defined as being 7 days post injury, they found an overall effect of mTBI on cognition of −0.41. For the period between 7 to 30 days, this effect of impairment on cognition shrank to −0.29, and for the period between 30 to 89 days, the effect was only −0.08. Finally, 89 days or more following injury, the overall effect of mTBI on cognition was non-significant and in a positive direction at 0.04. These authors concluded, “…cognitive test performance was

Table 1. Summary of previously published meta-analyses examining the effect of mTBI on cognitive functioning across time

<table>
<thead>
<tr>
<th>Author(s)</th>
<th>0–7 days</th>
<th>8–30 days</th>
<th>15–92 days</th>
<th>&gt;93 days</th>
<th>Ln Reg R</th>
<th>All epochs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Binder et al. (1997)</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>−0.07</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Schretlen et al. (2004)</td>
<td>−0.41</td>
<td>−0.29</td>
<td>−0.08</td>
<td>0.04</td>
<td>0.42</td>
<td>−0.46</td>
</tr>
<tr>
<td>Frencham et al. (2005)</td>
<td>−0.33</td>
<td>−0.52</td>
<td>−0.24</td>
<td>−0.08</td>
<td>0.43</td>
<td>−0.31</td>
</tr>
<tr>
<td>Belanger et al. (2007)</td>
<td>−0.52</td>
<td>−0.42</td>
<td>−0.24</td>
<td>−0.08</td>
<td>0.43</td>
<td>−0.31</td>
</tr>
<tr>
<td>Pertab et al. (2009)</td>
<td>−0.42</td>
<td>−0.42</td>
<td>−0.24</td>
<td>−0.08</td>
<td>0.43</td>
<td>−0.31</td>
</tr>
</tbody>
</table>
essentially indistinguishable from that of matched controls by one month post injury” (2003, p. 346). Similarly, Belanger and Vanderploeg (2005) examined neuropsychological outcome after sports concussions and found full recovery within 7 to 10 days for all neuropsychological domains with delayed memory recovering a few days later than other domains.

In summary, these five meta-analytic studies all found that mTBI has negligible effects on neuropsychological functioning in the long term. With the exception of Binder et al. (1997), who did not study acute effects, each of these studies also clearly demonstrated an acute effect of mTBI followed by gradual to rapid recovery.

Recently, Pertab, James, and Bigler (2009) re-analyzed the studies included in Binder et al. (1997) and Frencham et al. (2005). Their intent was to determine whether a subgroup of mTBI patients had a significantly poorer outcome than the majority of the sample. In attempting to detect such a subgroup they planned to re-analyze the data as a function of: (1) method of injury; (2) diagnostic criteria employed; (3) type of neuropsychological assessment tool employed; and (4) whether symptomatic or non-symptomatic mTBI participants were assessed separately. However, they found an insufficient amount of data to analyze method of injury, diagnostic criteria employed, and symptomatic status. Like prior meta-analytic researchers, Pertab et al. found a non-significant effect size for the greater than 3 months time period, collapsed across type of assessment tool. However, Pertab et al. found that the chi-squared test for heterogeneity was significant, supporting the presence of variable outcome as a function of assessment tool employed and suggesting to them the presence of clinically significant lasting negative effects on a subset of neuropsychological measures. They suggested that such effects might be obscured when only the overall effect was examined.

Our understanding of individuals’ neuropsychological outcomes following mTBI is greatly informed by meta-analytic procedures. There are, however, several limitations to the prior studies reviewed previously. First, all prior published analyses adopt a fixed-effects model, which assumes that the obtained effect sizes were sampled from the same population and the only type of error was random error (i.e., whether an individual study was selected for inclusion). Given the enormous variability in participants included in the various studies examined, along with a host of other factors (e.g., recruitment procedures, mTBI etiology, litigation status, instruments employed, time post injury), this assumption probably cannot be met. In addition to random error there are likely random differences between studies for which a source might not be identified. Thus, a random effects model is more likely to be accurate for modeling the effects of mTBI (see Lipsey & Wilson, 2001). We use a random effects model in our analyses, which to our knowledge had not been used by any of the authors of the prior meta-analyses on this topic.

The second limitation of the prior meta-analyses of mTBI concerns how the statistical procedures addressed chronicity effects. Binder et al. (1997) were only interested in post-acute effects (i.e., 3 months or more post injury) and did not include studies that examined patients who were in acute stages of mTBI recovery. This limitation does not permit a full understanding of recovery process. Moreover, while the other two studies included acutely injured participants, there were limitations in the methods used to analyze the relationship between
neuropsychological impairment and time post injury. Pertab et al. (2009) merely assessed effect size differences between studies in the acute and sub-acute stages of recovery (i.e., less than 3 months) and post-acute or chronic stages of recovery (i.e., equal to or greater than 3 months). Frencham et al. (2005) computed only the correlations between effect sizes and time post mTBI. While these approaches are statistically defensible, they are not likely to be as useful to the typical clinician. Knowing the effect size of mTBI across time post injury (e.g., ≤7 days, 8 to 30 days, 31 to 92 days, and ≥ 3 months) is more important for understanding recovery post injury and for clinical decision making (Schretlen & Shapiro, 2003). These outcomes are presented in the current paper.

The Pertab et al. (2009) meta-analysis contained additional limitations and errors, some of which we detected only through examination of the database that they provided to us (Personal communication, Jon Pertab, October 2009). Although the stated goal of Pertab et al. was to perform a re-analyses of the data found in Binder et al. (1997) and Frencham et al. (2005), they chose to include only 18 of the original 25 studies (72%) analyzed by both Binder et al. and Frencham et al. Specifically, they examined just 29 of the 48 available samples (60%). They also examined only 285 of the 527 available effect sizes (54%). Finally, of the calculations they completed, their results included only 1348 of the possible 4881 participants across all studies (28%). Finally, in the several studies in which a within-participants design was employed, with participants being assessed at various times post injury, Pertab et al. collapsed all epochs into a single time-frame. It is unclear to us how they computed time post injury in such studies. Considering the evidence reviewed above of significant acute neuropsychological effects followed by recovery (Belanger et al., 2005; Belanger & Vanderploeg, 2005; Frencham et al. 2005; Schretlen & Shapiro, 2003), in the current review we deemed it essential to separate acute from chronic effects.

Summarizing, our goal in the current meta-analysis was to re-analyze studies used in our prior meta-analysis (Binder et al., 1997) and the meta-analysis of Frencham et al. (2005), the stated goal of Pertab et al. (2009). However, we wanted to do so in a way that addressed the limitations described above. Namely, rather than a fixed effects model we used a random effects model. We tracked neuropsychological recovery with four clinically meaningful times post injury. We computed separate effect sizes for each time-point post injury in studies that evaluated participants over multiple time points.

**METHOD**

**Study selection**

All articles in the Binder et al. (published before 1994) and the Frencham et al. (published between 1994 to 2003) studies were included in the current meta-analysis (n = 25). In both of these published studies inclusion criteria were based on Binder et al.’s initial criteria: (1) participants included based on history of mTBI versus symptomatology; (2) inclusion of descriptive statistics so that effect sizes could be calculated or, if these were not available, effect sizes could be estimated based on the
relevant statistics; (3) participant attrition rate under 50%; (4) exclusion of participants with moderate or severe TBI; and (5) adult participants. We limited included studies to those examined in the earlier published meta-analytic reviews rather than including more recent studies that met other inclusion criteria because we are responding to the arguments of Pertab et al. (2009) and they had adopted this same strategy. Our goal was to make our results directly comparable to their results.

**Effect size calculation**

Effect sizes were computed for each test by (a) dividing the difference between the control group and mTBI group performance by the pooled standard deviation; (b) weighting by the inverse of each study’s sample variance so that larger samples had a relatively larger effect on the overall effect size (Lipsey & Wilson, 2001, p. 36); and (c) correcting for small n or samples with less than 20 participants (Hedges, 1981). These are the same procedures adopted by Pertab et al. (2009), as noted in their introduction. In cases where there were multiple evaluations post injury of the mTBI group (e.g., Echemendia et al., 2001, conducted evaluations at 2 hours, 2 days, 1 week, and 1 month after mTBI), we calculated an effect size at each epoch, which is not the same procedure that was followed by Pertab et al. If the control group was not evaluated at each epoch, we used the performance of the control group at the initial assessment as the basis of comparison. Effect sizes were grouped across four epochs post injury: (1) <7 day; (2) 8–30 days; (3) 31–92 days; and (4) >93 days. In addition, effect sizes were grouped into the following neuropsychological domains based on a consensus of the current authors: (a) Verbal Memory, (b) Visual Memory, (c) Working Memory, (d) Executive Functioning, (e) Processing Speed, (f) Verbal Comprehension, and (g) Perceptual Reasoning. These domains differ slightly from those used in the prior meta-analyses, but nonetheless they identify key neuropsychological domains of functioning. Across all domains, a negative effect size indicates worse performance by the mTBI group as compared to the control group.

**Meta-analytic model and statistics**

As noted above, we used a random effects rather than a fixed effects meta-analytic model (Hedges & Vevea, 1998). Using the model, we estimated effect sizes using an additive combination of a fixed parameter (i.e., the true effect size) as well as a random study parameter, which estimates the random fluctuations in the true effect size across studies due to design variations. For each of the four epochs, we computed a $Q$ statistic with an approximate chi-square distribution with $k - 1$ degrees of freedom to test the homogeneity null hypothesis that all the effect sizes are similar within the period. A significant effect would mean that the effect sizes are heterogeneous and, ideally, moderator analyses would be performed to account for this variability.
RESULTS

Across the 25 examined studies there were 48 samples with a total of 2828 mTBI participants and 2053 controls. As shown in Table 2 there were no significant demographic differences between mTBI and control participants across studies. Consistent with our inclusion criteria, participants with mTBI experienced an average loss of consciousness (LOC) that was relatively brief (10.2 minutes) and post-traumatic amnesia (PTA) that was relatively short (18.9 minutes), with an estimated Glasgow Coma Score (GCS) upon presentation to medical personnel that was relatively high (14.6).

As shown in Table 3 the overall effect size across all epochs and neuropsychological domains was $-0.28$. On average, mTBI participants performed about one quarter of a standard deviation worse than controls on neuropsychological testing collapsed across all epochs. However, there were differences across the epochs with the largest effect size evident for the <7-days post injury epoch ($d = -0.39$) and smallest effect size evident for the <3 months post injury epoch ($d = -0.07$). Only the effect size differences in the first two epochs, which covered the time just following injury up to 30 days post injury, were reliably different from zero ($p < .05$). The homogeneity testing within each epoch was non-significant, indicating that the effect sizes were homogenous and that further moderator testing was not necessary. Thus these data show no evidence of the existence of an impaired subgroup of impaired mTBI patients, as was postulated by Pertab et al. (2009).

As was true of the overall effect size for the aggregated neuropsychological measures, within the neuropsychological domains, the negative effect of mTBI also diminished over time, as shown in Tables 4 and 5. In these analyses the effect sizes for Verbal and Visual Memory domains immediately post injury are relatively large ($d = -0.56$ & $-0.66$, respectively). Furthermore, across epochs the three domains with the most sensitivity to the effects of mTBI were Verbal memory, Working Memory, and Visual Memory. However, 3 months post injury Verbal Memory improved to a negligible effect size equal to $-0.10$ and Visual Memory improved even more to a positive 0.03. Working Memory showed the most impairment with a small but significant effect size of $-0.19$ at 3 months post injury. These measures of

<p>| Table 2. Demographic and injury severity measures for available analyzed data |
|---------------------------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|</p>
<table>
<thead>
<tr>
<th></th>
<th>mTBI $M$</th>
<th>mTBI $SD$</th>
<th>Control $M$</th>
<th>Con $SD$</th>
<th>$p$</th>
<th>$d$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total sample</td>
<td>48</td>
<td>2834</td>
<td>2057</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sample size average</td>
<td>48</td>
<td>59.0</td>
<td>67.2</td>
<td>42.9</td>
<td>47.4</td>
<td>.0066</td>
</tr>
<tr>
<td>Age (years)</td>
<td>43</td>
<td>25.1</td>
<td>7.2</td>
<td>25.9</td>
<td>7.8</td>
<td>.65</td>
</tr>
<tr>
<td>Education (years)</td>
<td>39</td>
<td>12.6</td>
<td>1.3</td>
<td>12.5</td>
<td>1.2</td>
<td>.63</td>
</tr>
<tr>
<td>Sex (% male)</td>
<td>43</td>
<td>73.4</td>
<td>20.9</td>
<td>74.3</td>
<td>19.2</td>
<td>.83</td>
</tr>
<tr>
<td>LOC (minutes)</td>
<td>17</td>
<td>10.2</td>
<td>15.8</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>GCS</td>
<td>5</td>
<td>14.6</td>
<td>0.4</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PTA (minutes)</td>
<td>11</td>
<td>18.9</td>
<td>54.5</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

LOC = loss of consciousness; GCS = Glasgow Coma Scale; PTA = post-traumatic amnesia.
Table 3. Random effects model summary data for each epoch collapsed across cognitive domains

<table>
<thead>
<tr>
<th>Summary</th>
<th>d</th>
<th>SE</th>
<th>K</th>
<th>M Days Post-Inj</th>
<th>mTBI n</th>
<th>Con n</th>
<th>Total n</th>
<th>Low 95% CI</th>
<th>High 95% CI</th>
<th>Z</th>
<th>p for Z</th>
<th>Q</th>
<th>p for Q</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group 1 &lt; 7 days</td>
<td>-0.39</td>
<td>0.06</td>
<td>16</td>
<td>3</td>
<td>1598</td>
<td>1090</td>
<td>2688</td>
<td>-0.50</td>
<td>-0.27</td>
<td>6.54</td>
<td>&lt;.0001</td>
<td>16.65</td>
<td>.34</td>
</tr>
<tr>
<td>Group 2 =8–30 days</td>
<td>-0.32</td>
<td>0.08</td>
<td>12</td>
<td>24</td>
<td>457</td>
<td>339</td>
<td>796</td>
<td>-0.47</td>
<td>-0.17</td>
<td>4.19</td>
<td>&lt;.0001</td>
<td>8.34</td>
<td>.68</td>
</tr>
<tr>
<td>Group 3 =31–92 days</td>
<td>-0.14</td>
<td>0.11</td>
<td>4</td>
<td>58</td>
<td>281</td>
<td>160</td>
<td>441</td>
<td>-0.35</td>
<td>0.06</td>
<td>1.35</td>
<td>.0885</td>
<td>2.73</td>
<td>.43</td>
</tr>
<tr>
<td>Group 4 &gt;93 days</td>
<td>-0.07</td>
<td>0.07</td>
<td>16</td>
<td>234</td>
<td>492</td>
<td>464</td>
<td>956</td>
<td>-0.20</td>
<td>0.06</td>
<td>1.04</td>
<td>.1492</td>
<td>5.68</td>
<td>.98</td>
</tr>
<tr>
<td>All epochs</td>
<td>-0.28</td>
<td>0.04</td>
<td>48</td>
<td>80</td>
<td>2828</td>
<td>2053</td>
<td>4881</td>
<td>-0.35</td>
<td>-0.21</td>
<td>7.59</td>
<td>&lt;.0001</td>
<td>46.13</td>
<td>.51</td>
</tr>
</tbody>
</table>
Table 4. Summary data from random effects model collapsed across all epochs and presented by cognitive domain

<table>
<thead>
<tr>
<th>Cognitive Domain</th>
<th>Wt</th>
<th>M</th>
<th>d</th>
<th>SE</th>
<th>K</th>
<th>mTBI n</th>
<th>Con n</th>
<th>Total N</th>
<th>95% CI Lower</th>
<th>95% CI Upper</th>
<th>Z</th>
<th>p for Z</th>
<th>Q</th>
<th>p for Q</th>
</tr>
</thead>
<tbody>
<tr>
<td>Verbal Memory</td>
<td>-0.35</td>
<td>0.07</td>
<td>34</td>
<td>1927</td>
<td>1666</td>
<td>3593</td>
<td></td>
<td></td>
<td>-0.49</td>
<td>-0.21</td>
<td>-4.97</td>
<td>&lt;.0001</td>
<td>39.75</td>
<td>.19</td>
</tr>
<tr>
<td>Working Memory</td>
<td>-0.33</td>
<td>0.05</td>
<td>38</td>
<td>1907</td>
<td>1211</td>
<td>3118</td>
<td></td>
<td></td>
<td>-0.42</td>
<td>-0.24</td>
<td>-7.13</td>
<td>&lt;.0001</td>
<td>34.92</td>
<td>.57</td>
</tr>
<tr>
<td>Visual Memory</td>
<td>-0.31</td>
<td>0.11</td>
<td>15</td>
<td>484</td>
<td>366</td>
<td>850</td>
<td></td>
<td></td>
<td>-0.52</td>
<td>-0.10</td>
<td>-2.92</td>
<td>.0018</td>
<td>10.56</td>
<td>.72</td>
</tr>
<tr>
<td>Executive Functioning</td>
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<td>0.07</td>
<td>16</td>
<td>1232</td>
<td>1037</td>
<td>2269</td>
<td></td>
<td></td>
<td>-0.35</td>
<td>-0.08</td>
<td>-3.08</td>
<td>.0010</td>
<td>13.28</td>
<td>.58</td>
</tr>
<tr>
<td>Verbal Comprehension</td>
<td>-0.17</td>
<td>0.13</td>
<td>11</td>
<td>370</td>
<td>347</td>
<td>717</td>
<td></td>
<td></td>
<td>-0.42</td>
<td>0.08</td>
<td>-1.35</td>
<td>.0885</td>
<td>7.84</td>
<td>.64</td>
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<tr>
<td>Perceptual Reasoning</td>
<td>-0.16</td>
<td>0.07</td>
<td>14</td>
<td>275</td>
<td>210</td>
<td>485</td>
<td></td>
<td></td>
<td>-0.30</td>
<td>-0.02</td>
<td>-2.19</td>
<td>23.00</td>
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<tr>
<td>Processing Speed</td>
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<td>0.06</td>
<td>32</td>
<td>2413</td>
<td>1659</td>
<td>4072</td>
<td></td>
<td></td>
<td>-0.27</td>
<td>-0.04</td>
<td>-2.72</td>
<td>.0033</td>
<td>20.65</td>
<td>.92</td>
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<tr>
<td>ALL DOMAINS</td>
<td>-0.28</td>
<td>0.04</td>
<td>48</td>
<td>2828</td>
<td>2053</td>
<td>4881</td>
<td></td>
<td></td>
<td>-0.35</td>
<td>-0.21</td>
<td>-7.59</td>
<td>&lt;.0001</td>
<td>46.13</td>
<td>.51</td>
</tr>
</tbody>
</table>
Working Memory were classified as measures of Attention/Concentration in our previous work (Binder et al., 1997).

**DISCUSSION**

The purpose of this meta-analysis was to re-analyze data that led Pertab et al. (2009) to draw conclusions that were different from the conclusions drawn by Binder et al. (1997) and Frencham et al. (2005). We sought to improve on these prior meta-analyses while retaining comparability across studies. Specifically, we used a random effects meta-analytic model. We partitioned effects sizes into clinically meaningful time-frames post injury while computing separate effect sizes at each epoch for studies that evaluated neuropsychological functioning at multiple time points. We found that, averaging across all neuropsychological domains and epochs, mTBI resulted in a relatively small effect size ($d = -0.28$, significantly different from zero). Effect sizes significantly diminished over time, from the largest at less than 7 days post injury ($d = -0.39$, which is significantly different from zero) to the smallest at greater than 3 months post injury ($d = -0.07$, which is not significantly different from zero). This latter pattern was consistent across domains, although there were initially larger effect sizes for the memory domains.

Our study had some limitations. We included only the outcome studies that were analyzed in the meta-analyses of interest but we skipped the most recent studies. Some prospective studies (e.g., Dikmen, Machamer, Winn, & Temkin, 1995) tested mTBI participants repeatedly and comparison participants once, possibly producing practice effects in the mTBI participants that might underestimate the true effect of the injury. Future meta-analytic reviews should address this issue. Our findings may not apply to people who sustain numerous concussions, such as professional athletes in some sports (Wall et al., 2006). We would not apply our conclusions as readily to cases of complicated mTBI (Williams, Levin, & Eisenberg, 1990); that is, cases complicated by lesions shown by brain scans or unequivocal neurological abnormalities such as hemiplegia.

Similar to the prior meta-analyses our findings indicate that, averaging across all epochs, mTBI results in a relatively small effect on neuropsychological functioning. The effect size of $-0.28$ across all time intervals between mTBI and control conditions is consistent with the small effect sizes described above.
participants and controls, equivalent to approximately one quarter of a standard deviation, would be very difficult to detect reliably on standard neuropsychological instruments. For instance, if the effect size difference actually was slightly larger, \( d = -0.30 \), the two sample distributions would have 79% overlap (see Zakzanis, 2001); 79% of the scores obtained by the mTBI participants would fall within the distribution of scores obtained by the controls. Considering the high frequency of low test scores in normative samples (Binder et al., 2009), the corresponding classification statistics, such as sensitivity (i.e., the accuracy of detecting mTBI as mTBI) and specificity (i.e., accuracy of detecting controls as not having experienced an mTBI) would be low. Similarly, even if the largest effect size is evaluated \( d = -0.39 \) for within 7 days post injury, the overlap percentage is still a relatively high 73%. Small differences such as these would be difficult to detect reliably on a case-by-case basis. The effect sizes for Verbal and Visual Memory and Verbal Comprehension were larger within the first 7 days post injury, making these differences somewhat easier to detect. The diagnostic problem of overlap between controls and mTBI patients is much worse after 3 months when neuropsychologists are often asked to assess mTBI patients to address the question of permanent neuropsychological deficits. The effect size difference at or after 3 months post injury of \( -0.07 \) is indistinguishable from zero (i.e., non-significant effect). Our meta-analytic findings are consistent with recent non-quantitative reviews including a best-evidence synthesis on prognosis after mTBI (Carroll et al., 2004) and a broad literature review on this topic (Iverson, 2005). More importantly, our findings are consistent with other published meta-analytic reviews cited above and listed in Table 1.

It has been contended that meta-analytic reviews could obscure permanent or long-term effects of mTBI in a subgroup that might be especially vulnerable (Pertab et al., 2009; see also Iverson, 2010). This supposition was presented hypothetically and graphically in the Pertab et al. meta-analysis. Our work indicates that that a highly impaired, but undetected, subgroup of mTBI patients of any appreciable size is unlikely to exist. First, individual research studies include participants who compose samples of larger populations. Statistical comparisons between samples can result in Type I error, incorrectly rejecting a null hypothesis of no differences between groups that truly exists in the larger population; or Type II error, incorrectly failing to find a significant difference between the two sample groups that truly exists in the population. If individual studies failed to show significant differences between control and mTBI samples that truly existed in the larger populations of normal and mTBI patients because the studies lacked statistical power, then meta-analytic studies have a greater chance of finding the true population differences than individual studies (Glasziou et al., 2010; Schmidt, 1992). For example, in some cases, low-powered individual studies of various medical topics have failed to show differences, while meta-analytic studies of the same topics have revealed significant results (Glasziou et al., 2010).

If there were an mTBI subgroup of any appreciable size that remained impaired on neuropsychological tests more than 3 months post injury, then methodologically correct meta-analytic studies should have a greater chance than the individual outcome studies of finding differences between the mTBI groups and the control groups. The differences between subgroups should result in a statistically
significant difference in the meta-analysis. However, to date six meta-analytic reviews, including the present one, found no evidence of a significant difference. Only Pertab et al. (2009) found a long-term significant impact of mTBI and we assert that their conclusion was spurious, based on incorrect methodology and statistics.

While the above findings are clear about the expected neuropsychological outcome post injury from an mTBI, it remains possible that there are a small number of outliers with poor neuropsychological outcomes after mTBI. Before concluding that an individual has long-term or permanent neuropsychological deficits caused by mTBI, complicating factors such as poor effort or malingering, significant pain or fatigue, psychological distress, and pre-morbid condition (e.g., learning disability or attention deficit/hyperactivity disorder) need to be ruled out. Careful attention must also be given to the prevalence of low scores on large test batteries of normative samples. Given the small, non-significant effect sizes 90 days or more after mTBI, the magnitude and/or the prevalence of permanent neuropsychological deficits must be very low. If the error rate of neuropsychological diagnosis of mTBI calculated from combining false positives and false negatives exceeds the base rate frequency of permanent neuropsychological deficits, then using the base rates for diagnosis will be more accurate than using neuropsychological testing (Gouvier, 1999). Low-frequency events of small magnitude can be detected only with a diagnostic strategy that inevitably yields far more false positive diagnostic errors than true positive diagnoses (Gouvier, Hayes, & Smiroldo, 1998; Meehl & Rosen, 1955; Wiggins, 1973). Hence clinicians who diagnose brain injury 3 months or more after an mTBI will likely be wrong.

The results generated by the current study have additional clinical implications. Our random effects model generated a table showing a notable pattern of neuropsychological recovery over time. The table will allow clinicians to provide better predictions of recovery post injury for their patients than did the prior meta-analyses. Our findings point to initial mild neuropsychological impairment immediately after the injury. This effect is likely due to physiological changes at the cellular level, in what has been termed a neurometabolic cascade (see Iverson, 2005), which results in time-limited but reversible neuronal dysfunction shortly after the trauma.

A second finding is that an mTBI appears to impair initially verbal and visual memory preferentially. Given that the Processing Speed domain was not as affected, the effect for memory does not appear to be simply due to slowed processing or task time demands. Rather, it may be that brain regions that support memory processing (i.e., the temporal lobe and related medial temporal lobe structures, and/or orbitofrontal cortex) are more vulnerable to the initial effect of mTBI. The ability to form and later retain new memories is thus compromised, at least relative to other domains. This would be consistent with patient complaints regarding memory problems immediately after the injury (e.g., see Lundin, De Boussard, Edman, & Borg, 2006; Ponsford et al., 2000). However, this effect was transient, as the effect sizes for memory are similar to the other domains after 1 month. These findings can be used to reassure patients who may experience some immediate symptoms but are not likely to have long-term problems related to their mTBI.
REFERENCES


