REVIEW ARTICLE (META-ANALYSIS)


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Abstract

Objective: To undertake a systematic review and meta-analysis of the relationship between microstructural damage and cognitive function after hospitalized mixed-mechanism (HMM) mild traumatic brain injury (mTBI).

Data Sources: PsycInfo, EMBASE, and MEDLINE were used to find relevant empirical articles published between January 2002 and January 2016.

Study Selection: Studies that examined the specific relationship between diffusion tensor imaging (DTI) and cognitive test performance were included. The final sample comprised previously medically and psychiatrically healthy adults with HMM mTBI.

Data Extraction: Specific data were extracted including mTBI definitional criteria, descriptive statistics, outcome measures, and specific results of associations between DTI metrics and cognitive test performance.

Data Synthesis: Of the 248 original articles retrieved and reviewed, 8 studies met all inclusion criteria and were included in the meta-analysis. The meta-analysis revealed statistically significant associations between reduced white matter integrity and poor performance on measures of attention (fractional anisotropy [FA]: $d = -0.413$, $P < .001$; mean diffusivity [MD]: $d = -0.407$, $P = .001$), memory (FA: $d = -0.347$, $P < .001$; MD: $d = -0.568$, $P < .001$), and executive function (FA: $d = -0.246$, $P < .05$), which persisted beyond 1 month postinjury.

Conclusions: The findings from the meta-analysis provide clear support for an association between in vivo markers of underlying neuropathology and cognitive function after mTBI. Furthermore, these results demonstrate clearly for the first time that in vivo markers of structural neuropathology are associated with cognitive dysfunction within the domains of attention, memory, and executive function. These findings provide an avenue for future research to examine the causal relationship between mTBI-related neuropathology and cognitive dysfunction. Furthermore, they have important implications for clinical management of patients with mTBI because they provide a more comprehensive understanding of factors that are associated with cognitive dysfunction after mTBI.

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Mild traumatic brain injury (mTBI) constitutes an estimated 70% to 90% of all traumatic brain injuries and has an incidence of 100 to 300 per 100,000; it is associated with a significant burden of care for the individual and broader community. Although there has been considerable focus on mTBI in professional athletes and military veterans, because of differences in the biomechanical forces of injury, this research is not necessarily generalizable to most individuals with mTBI—those with hospitalized mixed-mechanism (HMM) injuries, which most commonly result from motor vehicle collisions and falls. Early autopsy-based histologic studies in HMM populations demonstrated that mTBI causes diffuse axonal injury (DAI) and microhemorrhages. Until recently, however, it was not possible to examine microstructural pathology in vivo because of the insufficient sensitivity of computed tomography and conventional magnetic resonance imaging (MRI). Consequently, earlier researchers were not able to...
Diffusion tensor imaging and cognitive function in mild TBI

List of abbreviations:

- DAI diffuse axonal injury
- DTI diffusion tensor imaging
- FA fractional anisotropy
- HMM hospitalized mixed-mechanism
- MD mean diffusivity
- MRI magnetic resonance imaging
- mTBI mild traumatic brain injury

Determine directly whether there is a relationship between mTBI-related structural neuropathology and mTBI-related dysfunction, in particular cognitive impairment.

Technological advances and improved sensitivity of MRI techniques have enabled researchers to examine microstructural neuropathology in vivo for the first time. Within mTBI research, diffusion tensor imaging (DTI) is commonly used to examine the structural integrity of white matter tracts, thereby providing a means of investigating DAI in vivo. Changes in DTI markers of underlying pathology—specifically reduced fractional anisotropy (FA) and increased mean diffusivity (MD)—are indicative of reduced white matter integrity and are typically found within long-coursing white matter tracts after mTBI. In addition to revealing such microstructural damage in vivo after mTBI, these technological advances have enabled researchers to investigate the in vivo association between mTBI-related structural neuropathology and cognitive dysfunction.

Given the microstructural damage that results from mTBI, it is logical that injury-related neuropathology will likely cause cognitive difficulties. Indeed, during the early acute period, which commonly describes the first 7 days postinjury, cognitive dysfunction in the domains of processing speed, attention, memory, and executive function is frequently found after mTBI. Findings such as reduced processing speed and impaired attention after mTBI are logically consistent with the effect of diffuse damage on white matter networks, which affects inter- and intrahemispheric integration and transfer of information. Similarly, impaired memory and executive dysfunction after mTBI are logically consistent with the damage to white matter tracts connecting frontal and temporal regions that occurs in HMM mTBI, since these are areas critically involved in both memory and executive control. To date, these well-known associations between normally functioning cognitive and neuroanatomic networks have been appropriately used to underpin clinical interpretation and management of individuals with HMM mTBI. Importantly, however, they do not provide evidence that microstructural damage demonstrably affects cognitive function after HMM mTBI.

Early studies retrospectively linked cognitive impairments experienced beyond the early acute period after mTBI to findings of microscopic pathology revealed at autopsy. More recently, studies of neurologic conditions, including moderate to severe TBI, have demonstrated that damage to white matter tracts disrupts network connectivity, which in turn detrimentally affects cognitive function. Functional neuroimaging techniques have also revealed changes in patterns of brain activation and cerebral blood flow during performance of cognitive tasks within mTBI populations, thereby further reinforcing the idea that there is a relationship between cognitive impairment and damage to brain microstructure.

All of these findings provide indirect support for a relationship between injury-related structural neuropathology and cognitive dysfunction after mTBI. They do not provide direct evidence of such a relationship, however. While histopathologic evidence is needed to demonstrate a direct association between mTBI-related neuropathology and cognitive dysfunction after mTBI, use of advanced structural neuroimaging techniques enables us to examine this relationship in vivo. Demonstration of a clear association between DTI markers of underlying neuropathology and cognitive dysfunction is important because it will contribute to the ongoing debate in the literature regarding the etiology of cognitive dysfunction after mTBI, which is commonly attributed to pre-morbid psychological and environmental factors rather than injury-related neuropathology. Support for a clear association between cognitive function and mTBI-specific neuropathology will allow clinicians and researchers to more fully understand the factors that influence recovery trajectories and long-term outcome after mTBI and should result in improved patient management, treatment, and prognosis.

Because of the recency of the aforementioned advances in neuroimaging techniques, investigation of the in vivo relationship between structural neuropathology and cognitive dysfunction is a relatively nascent field of mTBI research. Researchers in this area have examined structural neuropathology at a range of time points after mTBI and have reported a variety of results; this has resulted in a lack of consensus regarding whether there is indeed a relationship between structural neuropathology and cognitive function beyond the early acute period after mTBI. Despite the high incidence of HMM mTBIs, researchers have also largely focused on specific mTBI subsamples (eg, sports-related concussion), which have lower incidence rates than HMM mTBI. In light of these factors, it is timely to direct research attention to individuals with HMM mTBIs and develop a consensus understanding of the findings to date.

This article aims to undertake a systematic review and meta-analysis of the relationship between microstructural damage and cognitive function after HMM mTBI, beyond the early acute period (>7d). The review seeks to address the following questions: (1) Are changes in DTI metrics associated with variations in performance on cognitive tests after mTBI? (2) If they are, which cognitive domains are associated with change in DTI metrics and to what extent?

Methods

Protocol and registration

The systematic review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines. The protocol was not registered before commencement.

Search strategies and selection criteria

A search was conducted using PsycInfo, EMBASE, and MEDLINE using the keywords “mild traumatic brain injury,” “magnetic resonance imaging,” “MRI,” and “cognition” (appendix 1 shows the full electronic search strategy). Additional articles were identified from the reference lists of related empirical and review articles.

Strict inclusion criteria (table 1) were used to obtain a precise estimate of the effect size of any relationship between measures of...
white matter integrity and cognition. Inclusion and exclusion criteria ensured that cognitive measures were of sufficient psychometric quality to facilitate collation and comparison of results between studies. Additionally, the period of the search was restricted because of previously raised concerns about the poor methodological quality and considerable limitations of mTBI research conducted or published before 2002.

Data collection
From each eligible study, specific data were extracted and subsequently cross-checked by the authors. Data included descriptive statistics (ie, participant sample size, age, time since injury), mTBI definition criteria (ie, Glasgow Coma Scale score, duration of loss of consciousness and posttraumatic amnesia), information relating to outcome measures (ie, neuroimaging, cognitive tests, classification of cognitive tests by domain), and specific results examining the relationship between DTI metrics and cognitive test performance. The authors of eligible studies were contacted with requests for additional results and comparisons that were conducted.

To ensure consistency, for each study, the classification of cognitive tests by domain was cross-checked and, where necessary, reclassified according to the most commonly accepted neuropsychological domains. The principal summary measure used in analyses was the correlation coefficient between FA, MD, and performance on each cognitive test, converted to the Fisher $z$ scale. Comprehensive Meta-Analysis version 3.0 software was used for the meta-analysis. Since each eligible study included several measures of the same cognitive domain, a synthetic effect size was computed to combine the effect across outcomes as per the recommendations of Borenstein. That is, for each study, the Fisher $z$ statistic for the correlation between measures of each cognitive domain and DTI metric was combined. The synthetic effect size was calculated using Comprehensive Meta-Analysis software and cross-checked by manual calculation.

Assessment of risk and bias
The quality of individual studies was assessed according to the recommendations of Viswanathan et al and The Cochrane Collaboration for the assessment of bias within intervention studies, as no such standards exist for observational epidemiologic studies. Each study was examined for bias relating to (1) selection of participants, (2) attrition, (3) methodological differences between patient and control groups (ie, detection bias), and (4) selective outcome reporting (ie, reporting bias). Methods used to investigate whether there was bias between studies are outlined in the Results section.

Results
Study selection
A total of 382 records were identified by searching databases and reference lists of relevant articles, of which 248 remained after removal of duplicates (fig 1). Titles and abstracts were screened to identify studies that examined both white matter damage and cognition after mTBI; 214 articles did not meet inclusion criteria and were excluded, with 36% of these examining neither cognition nor white matter integrity. Of the remaining 34 full-text articles, a further 26 were excluded (see fig 1 for exclusion reasons). A total of 8 studies were included in the quantitative synthesis.

Characteristics of included studies
The 8 studies included in the meta-analysis yielded a total of 220 participants with mTBI and 176 controls aged between 18 and 60 years. While all studies included a healthy control group to compare neuroimaging and cognitive test findings between groups, no correlational analyses were conducted between cognitive test performance and DTI findings within the control...
groups. Consequently, control group data were not included in these meta-analyses. Characteristics of the mTBI participants and the studies are detailed in Table 2. Three of the 8 studies were longitudinal, while the remaining 5 used a matched case-control design (see Table 2). When approached, the authors of 1 study provided additional results that were included in the meta-analyses.

### Determination of risk and bias

#### Within individual studies

Because recruitment methods and participant characteristics were comparable across all studies, the risk of selection bias was classified as "low." The risk of attrition was classified as "low" in 13 of the 3 longitudinal studies that examined attrition bias, and "unclear" in the remaining 2 studies. All 8 studies used valid and reliable measures of cognition according to Lezak and Strauss et al., and there were no differences in outcome assessment between groups. The risk of detection bias was classified as "low" in 2 studies that included blinding of the neuroimaging outcome assessment and the neuropsychological assessment. Blinding was not reported in the remaining 6 studies, making the risk of bias "unclear." All studies reported prespecified outcomes, making the risk of reporting bias "low."

#### Across studies

Visual inspection of funnel plots for the meta-analyses suggested an absence of publication bias. This was further supported by calculation of Egger’s test of the intercept and the Begg and Mazumdar rank correlation test, which revealed nonsignificant P values for both FA and MD. Rosenthal’s “fail-safe N” values for FA and MD were 86 and 94, respectively, which suggest that inclusion of additional studies in the meta-analyses would have been unlikely to nullify the observed effects. With the use of Duval and Tweedie’s trim-and-fill method, the best estimate of the unbiased effect size for FA was .188, compared with .274 for the observed effect size. Including imputed studies resulted in a small shift in the point estimate of the effect size, which suggests that the impact of bias is trivial. For MD, there was no change in the point estimate of the effect size of .354, which again suggests that the impact of bias is trivial.

#### Results of individual studies

**DTI outcome measures: mTBI versus control groups**

Seven of the 8 studies conducted neuroimaging less than 1 month postinjury (see Table 2). Compared with controls, 5 studies found that during this period, participants with mTBI had a significantly lower FA in specified regions of interest.
while 3 studies found participants with mTBI had a significantly higher MD. One of the studies found FA to be higher in the mTBI group compared with controls, while another study did not report group-level differences in FA.

Of the 8 studies, 1 study conducted neuroimaging 1 month postinjury, while a further 2 studies conducted follow-up neuroimaging more than 1 month after injury. Relative to controls, FA was significantly lower in participants with mTBI more than 1 month postinjury, while MD was significantly higher.

Cognitive outcome measures: mTBI versus control groups

Five of the 8 studies conducted a cognitive assessment less than 1 month postinjury. Of these, 3 studies found that participants with mTBI performed more poorly on cognitive testing compared with controls. The differences were statistically significant on measures of processing speed, attention, language, working memory, memory, and executive function. Differences in performance on cognitive testing between participants with mTBI and controls were not significant in 1 study and were not reported in another.

Three of the 8 studies conducted their cognitive assessment more than 1 month postinjury. Similarly, the 3 longitudinal studies conducted a follow-up cognitive assessment more than 1 month postinjury. Of these 6 studies, did not examine between-group differences in cognitive test performance; the remaining 4 studies found that participants with mTBI performed more poorly on cognitive testing relative to controls. The differences were statistically significant on measures of processing speed, attention, visuospatial function, language, memory, and executive function.

Meta-analyses

As previously described, no studies compared the relevant neuroimaging metrics and cognitive performances in their control groups. Consequently, the meta-analyses were restricted to the mTBI groups. A random-effects model was used to minimize heterogeneity between studies.

Variation in the interval between injury and neuroimaging was minimized by including neuroimaging results from the baseline assessments of all 8 studies. Neuroimaging was conducted less than 1 month postinjury in 7 of the 8 studies (see table 2). To avoid examining cognition in the early acute period (<7d postinjury), results from the follow-up, rather than baseline, cognitive assessment of the 3 longitudinal studies were included in the meta-analysis. Thus, all cognitive assessments were conducted more than 1 week after injury, with 5 of the 8 studies conducting cognitive assessments more than 3 months postinjury.

Results of meta-analyses across all time points

Six of the 8 studies examined the relationship between FA and general cognition. General cognition refers to the combined effect sizes for comparisons between measures of all cognitive domains, including the additional domains of language, response speed, and spatial function, and DTI metrics across all studies. Six studies also examined the relationship between MD and general cognition. Statistically significant effect sizes were found for the associations between general cognition and both FA ($d = .274, P < .001$) and MD ($d = .354, P < .05$), as indicated by the diamond in figures 2 and 3.

The effect sizes for the relationship between DTI metrics and each cognitive domain are presented in table 3. Unlike the cognitive domains of attention, memory, and executive function, only 1 study reported results for the association between processing speed and FA, which consequently could not be meta-analyzed. Only 2 studies reported results for the relationship between processing speed and MD, and the meta-analysis found no association between the two. In contrast, poor performance on measures of attention and memory function was significantly associated with reduced FA and increased MD. Poor performance on measures of executive function was significantly associated with reduced FA.

Results of meta-analyses as a function of time point

Some studies conducted cognitive assessments many months postinjury. Consequently, the studies were divided into 2 groups to examine whether the observed effect sizes changed as a function of time postinjury. The 2 time points, referring to less than and greater than 1 month postinjury, were denoted by $t1$ and $t2$, respectively. Five studies conducted cognitive testing at $t1$ and 5 conducted cognitive testing at $t2$.

Statistically significant effects were found for the relationship between general cognition and FA at both $t1$ ($d = .247, P < .05$) and $t2$ ($d = .292, P < .05$). General cognitive function was also significantly associated with MD at both $t1$ ($d = -.304, P < .05$) and $t2$ ($d = -.264, P < .05$). The effect sizes for the relationships between FA, MD, and individual cognitive domains at $t1$ and $t2$ are presented in table 4.

A medium effect size was found for the relationship between increased MD and reduced processing speed at $t1$, which was statistically significant. This relationship could not be examined at $t2$ because only 1 study included results for the association. At both $t1$ and $t2$, poor performance on measures of attention was significantly associated with reduced FA and increased MD; effect sizes were small to medium. For memory function, no significant associations were found for either FA or MD at $t1$. In contrast at $t2$, a small-to-medium statistically significant effect size was found for the association between poor memory function and reduced FA; a medium and statistically significant effect size was found for MD. For executive function, no significant association was found with FA at $t1$, while a small effect size that was approaching significance was found at $t2$.

Discussion

This systematic review and meta-analysis provides the first unequivocal evidence of an in vivo association between markers of underlying injury-related neuropathology and cognitive dysfunction more than 7 days after HMM mTBI. The associations were statistically significant for the combined results across all cognitive domains (ie, general cognition), and within the specific domains of attention, memory, and executive function, for all time points combined. Attention and memory were most strongly associated with both DTI metrics, with significant effect sizes being small to medium for these domains. A small but statistically significant effect was also found for executive function but only with the FA metric.

The meta-analyses more specifically revealed that reductions in attention, memory, and executive function were reliably associated with markers of greater structural neuropathology after mTBI. Although these results are consistent with the
<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>mTBI Criteria</th>
<th>Mechanism of Injury (n)</th>
<th>MRI (tesla)</th>
<th>DTI Metrics</th>
<th>Cognitive Domains and Tests Used</th>
<th>Time Point</th>
<th>n Age (y)</th>
<th>Education (y)</th>
<th>Time Postinjury to Neuroimaging</th>
<th>Time Postinjury to Cognitive Testing</th>
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<tr>
<td>Grossman et al, 2013</td>
<td>Longitudinal</td>
<td>ACRM</td>
<td>MVC (2) FA 3.0 MD</td>
<td>Processing speed&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Baseline 20 34.8±10.7 10 37.8±9.3 Follow-up 15.2±1.87 14.5±1.19</td>
<td>1mo: 22.1±15.4d (range, 5–54d)</td>
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<td>Holli et al, 2010</td>
<td>Matched case-control</td>
<td>WHO</td>
<td>Not reported 1.5 FA ADC</td>
<td>Processing speed&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Baseline 26 38.8±13.6</td>
<td>&lt;3wk</td>
<td>8.9d (range, 5–14d)</td>
<td>&lt;6mo</td>
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<td>Kumar et al, 2009</td>
<td>Matched case-control</td>
<td>GCS 13–15 LOC &lt;20min</td>
<td>Not reported 1.5 FA MD</td>
<td>Processing speed&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Baseline 22 27.45±7.39 13.14±2.46</td>
<td>&lt;21d: 12.5±5.40d (range, 2–20d)</td>
<td>&lt;21d: 11.75±4.97d (range, 4–20d)</td>
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<td>Mayer et al, 2010</td>
<td>Matched case-control</td>
<td>ACRM</td>
<td>MVC (6) FA 3.0 MD</td>
<td>Processing speed&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Baseline 17 33.44 4.05d (range, 1–10d)</td>
<td>N/A</td>
<td>&lt;24h of MRI</td>
<td>6mo</td>
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<td>Miles et al, 2008</td>
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<td>ACRM</td>
<td>Not reported 1.5 FA MD</td>
<td>Processing speed&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Baseline 43 32.4</td>
<td>&gt;1mo: 16.9d (range, 1–53m)</td>
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<td>Niogi et al, 2008</td>
<td>Independent groups</td>
<td>GCS 13–15 PTA (presence of)</td>
<td>Not reported 3.0 FA ADC</td>
<td>Processing speed&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Baseline 61 27.07±8.55 11.52±1.94</td>
<td>10.01±4.26h (range, 0–23h)</td>
<td>6.05±12.0mo</td>
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<td>Veeramuthu et al, 2015</td>
<td>Longitudinal</td>
<td>GCS 13–15 LOC &lt;30min</td>
<td>MBC vs MVC (30) FA MD</td>
<td>Processing speed&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Baseline 25 32.5±10.4 12.84±3.05</td>
<td>1mo: 32.08±3.62d (range, 26–40d)</td>
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<tr>
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<td>Matched case-control</td>
<td>GCS 13–15 Symptoms of neurologic dysfunction</td>
<td>Not reported 3.0 FA MD</td>
<td>Processing speed&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Baseline 20 34.8±10.7 10 37.8±9.3 Follow-up 15.2±1.87 14.5±1.19</td>
<td>1mo: 22.1±15.4d (range, 5–54d)</td>
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NOTE: Values are mean ± SD or as otherwise indicated.
Abbreviations: ACRM, American Congress of Rehabilitation Medicine; ADC, apparent diffusion coefficient; GCS, Glasgow Coma Scale; LOC, loss of consciousness; MBC, motor bike collision; MVC, motor vehicle collision; N/A, not applicable; PTA, posttraumatic amnesia; WHO, World Health Organization.

a Symbol digit modality test.
b Wechsler Adult Intelligence Scale-III/IV Digit Span Subtest.
c Trail Making Test A.
d Trail Making Test B.
e California Verbal Learning Test-II.
f Rey Complex Figure Test.
g Wechsler Adult Intelligence Scale-III Letter-Number Sequencing Test.
h Stroop Test.
i Rey Auditory Verbal Learning Test.
j Four Word Short-Term Memory Test.
k Cambridge Neuropsychological Test Automated Battery Paired Associates Learning Subtest.
l Number Connection Test A.
m Figure Connection Test A.
n Wechsler Adult Intelligence Scale-P/III/IV Digit-Symbol/Coding Subtest.
o Wechsler Adult Intelligence Scale-P Picture Arrangement Subtest.
p Wechsler Adult Intelligence Scale-P Object Assembly Subtest.
q Number Connection Test B.
r Figure Connection Test B.
s Wechsler Adult Intelligence Scale-P/IV Block Design Test.
t Wechsler Adult Intelligence Scale-P Picture Completion Subtest.
u Grooved Pegboard.
v Paced Auditory Serial Addition Task.
w Wechsler Adult Intelligence Scale-III/IV Arithmetic Subtest.
x Wisconsin Card Sort Test.
y Controlled Oral Word Association Test.
z Headminder Cognitive Stability Index.
aaa Weinberg Visual Cancellation Test.
abb Rusk Institute of Rehabilitation Medicine Similarities.
acc Prioritization Test form A and B.
ad Will Temperament Test.
aae Attention Network Task.
aaf Neuropsychological Assessment Battery-Screening Attention tests (Digits Forward, Digits Backward, Numbering and Lettering).
aag Neuropsychological Assessment Battery-Screening Visuospatial tests (Design Construction, Visual Discrimination).
aah Neuropsychological Assessment Battery-Screening Language tests (Naming, Auditory comprehension).
aai Neuropsychological Assessment Battery-Screening Memory tests (Shape learning immediate and delayed recognition, Story immediate recall and delayed recall).
aaj Neuropsychological Assessment Battery-Screening Executive Function tests (Word generation, Mazes).
ak Wechsler Adult Intelligence Scale-IV Similarities Subtest.
al Wechsler Adult Intelligence Scale-IV Vocabulary Subtest.
am Wechsler Adult Intelligence Scale-IV Information Subtest.
an Wechsler Adult Intelligence Scale-IV Matrix Reasoning Subtest.
ao Wechsler Adult Intelligence Scale-IV Visual Puzzles Subtest.
ap Wechsler Adult Intelligence Scale-IV Symbol Search Subtest.
known theoretical impact of DAI on attention, memory, and executive function after mTBI, they represent the first clear support for a relationship between reduced white matter integrity and cognitive dysfunction in vivo. This is important because it challenges the argument that cognitive dysfunction after mTBI can be fully explained by premorbid psychological and environmental factors. These findings therefore enable clinicians and researchers to have confidence that there is a real association between structural neuropathology and cognitive function beyond the early acute period after mTBI. This will result in more confident and consistent clinical decision-making and will factually underpin future empirical studies. The current findings also demonstrate that we now have a reliable technique to examine the relationship between in vivo mTBI-related structural neuropathology and cognitive dysfunction after HMM mTBI. This provides an avenue for future researchers to examine whether associations between specific cognitive domains and specific white matter tracts exist within HMM mTBI samples, and whether there is a causal relationship between neuropathologic injury severity and variation in cognitive recovery after mTBI. It also enables investigation of the relationship between structural neuropathology and cognition at the level of the individual patient. Thus, this finding provides an avenue for substantial progress to be made in both research and clinical care for patients with mTBI.

It is noteworthy that evidence of a direct relationship between markers of underlying structural neuropathology and cognition was found despite using a sample of only previously medically and psychiatrically healthy adults. That is, the finding cannot be attributed to preexisting factors, including previous mTBI or premorbid psychiatric factors such as depression. Additionally, the linear relationship between greater injury-related neuropathology and poorer performance on cognitive testing, which was demonstrated in this study, strongly supports the notion that mTBI occurs on a spectrum of structural neuropathologic severity, which is in turn associated with a spectrum of cognitive dysfunction. Together, these key findings provide good evidence that premorbidly healthy patients with a first-ever mTBI who are demonstrating more severe cognitive dysfunction are also more likely to be experiencing more severe structural neuropathology. Clinical awareness of this association is important because it has the potential to affect the individual clinical management of these types of patients.

Importantly, the relationship between in vivo measures of neuropathology and cognition was not overly dependent on time.
postinjury. As previously described, this relationship was examined both within and beyond 1 month postinjury. The overall observed effect sizes were comparably small and statistically significant at both time points when comparing associations for general cognition and attention. In contrast, for memory and executive function, a stronger association was found beyond 1 month compared to within 1 month postinjury. The finding of an association between reduced white matter integrity and poor cognitive function less than 1 month postinjury is not surprising, given that indirect evidence of a detrimental effect of mTBI on cognition is strongest for the acute period.9,14 Yet the current findings revealed associations between at least 1 metric of structural neuropathology and performance on measures of attention, memory, and executive function well beyond 1 month postinjury. Thus, in contrast to previously reported changes in DTI metrics in the months after injury, which are likely associated with functional changes in neurometabolism,41-43 the current findings suggest that a relationship between in vivo measures of structural neuropathology and cognitive function persists in the later stages of recovery. This has important implications for future research seeking to understand cognitive dysfunction in individuals who demonstrate atypical recovery.

Given that a decrease in processing speed is one of the most reliable consequences of mTBI,9,18,44,45 it seems surprising that no association was found between processing speed and white matter integrity for the combined data across all time points. A statistically significant association was only found for data obtained less than 1 month postinjury. Given that associations were found for other typically affected cognitive domains using the combined data across all time points, closer consideration of the processing speed finding is worthwhile and suggests that it may be due to methodological issues that were not applicable for other cognitive domains. Specifically, only a small number of studies (n = 2) investigated processing speed and yielded a small total participant sample (n = 37), making the power of this meta-analysis very limited. Further studies examining the possible relationship between processing speed and white matter integrity are clearly warranted.

| Table 3 | Effect sizes (d) and statistical significance for relationships between white matter integrity and cognition grouped by cognitive domain and DTI metric |
|-----------------|------------------|------------------|-----------------|-----------------|-------|-----------------|
| Cognitive Domain | DTI Metric | No. of Studies | No. of Total mTBI Participants | d | 95% CI |
| Processing speed | FA | 1 | 12 | -.187 | -.897 to .794 |
| Processing speed | MD | 2 | 37 | -.413 | .214 to .757 |
| Attention | FA | 4 | 90 | -.407 | -.596 to -.175 |
| Attention | MD | 3 | 68 | .347 | .171 to .502 |
| Memory | FA | 4 | 119 | .568 | -.710 to -.381 |
| Memory | MD | 3 | 74 | -.246 | .013 to .453 |
| Executive function | FA | 3 | 77 | .375 | .214 to .538 |
| Executive function | MD | 1 | 12 | .319 | .187 to .453 |

Abbreviations: CI, confidence interval.  
* P<.05.  
† P<.001.  
‡ Could not be evaluated by use of meta-analytic methods because only 1 study included the results for the specific comparison.

| Table 4 | Effect sizes and statistical significance for relationships between white matter integrity and cognition grouped by cognitive domain, DTI metric, and time postinjury |
|-----------------|------------------|------------------|-----------------|-----------------|-------|-----------------|
| Cognitive Domain | DTI Metric | Time Point | No. of Studies | No. of Total mTBI Participants | d | 95% CI |
| Processing speed | FA | t1 | 1 | 17 | -.573 | -.772 to -.269 |
| Processing speed | MD | t2 | 1 | 12 | .336 | .096 to .539 |
| Attention | FA | t1 | 3 | 69 | -.319 | -.571 to -.013 |
| Attention | MD | t2 | 3 | 68 | .444 | .219 to .625 |
| Memory | FA | t1 | 2 | 39 | -.407 | -.596 to -.175 |
| Memory | MD | t2 | 3 | 97 | .123 | -.214 to .434 |
| Executive Function | FA | t1 | 2 | 39 | .405 | .217 to .584 |
| Executive Function | MD | t2 | 3 | 74 | -.375 | -.709 to .097 |

Abbreviations: CI, confidence interval; t1, <1 month postinjury; t2, >1 month postinjury.  
* P<.05.  
† P<.001.  
‡ Could not be evaluated by use of meta-analytic methods as only 1 study included the results for the specific comparison.
In light of the strong theoretical rationale for a robust relationship between structural neuropathology and cognition, the effect sizes for the associations between measures of white matter integrity and cognition may seem surprisingly small. Again, the likely explanation for this is methodological. Differences in cognitive and neuroimaging measures were noted between studies, which include differences in measures of cognitive function, strength of MRI scanners, specifics of DTI sequences, and regions of interest examined. Additionally, individual studies used different methods to examine reduced white matter integrity (eg, tract-based spatial statistics or region-of-interest analysis in a priori—determined regions) and to collate DTI findings before conducting correlational analyses (eg, within a specific area of a white matter tract or across an entire tract). These methodological differences are potential sources of heterogeneity that could have affected the overall effect size found. First, differences in the psychometric properties of cognitive tests could have reduced the ability to detect poor performance; second, differences in neuroimaging characteristics could have affected the estimation of DAI. The use of DTI itself may have limited the ability to identify larger effect sizes. While DTI is a significant advance relative to prior structural imaging techniques, it has limited sensitivity and may therefore have led to underestimation of the extent of white matter damage after mTBI.

Collectively, these methodological differences may have affected the size of the associations found between DTI metrics and cognition in individual studies, and thereby affected the overall effect size of the meta-analysis. In particular, outcome measures such as cognitive tests and DTI metrics are continuous and involve a process of standardization. As a result, they are associated with a degree of measurement error. This error reduces the strength and size of associations found in individual studies, which secondarily affects the results of the meta-analysis. Importantly, however, the impact of this error is to attenuate the magnitude of the effect sizes in the meta-analyses, and thus the meta-analytic effect sizes could not have been erroneously inflated in this study.

While interstudy variation in cognitive assessment and neuroimaging characteristics may have contributed to the finding of small effect sizes, these differences are unlikely to have altered the direction of the effect. Inspection of the forest plots of the meta-analyses (see figs 2 and 3) reveals that the effect sizes of associations between DTI markers and specific cognitive domains consistently fall to the same side of zero, even in those studies where the associations were nonsignificant. Therefore, any impact on effect sizes because of interstudy variation would not have resulted in an alteration to the direction of the effect. The reliability of the observed effect sizes in this meta-analysis was further supported by the results of sensitivity analyses that were conducted to more fully investigate the consequences of interstudy variations in methodology. Sensitivity analyses revealed that the effect sizes remained small (FA: $d = .245 - .325$; MD: $d = -.213$ to $-.344$) when the influence of each study was separately removed from the meta-analyses. The resultant associations remained statistically significant for FA ($P < .05$), and were significant or trending toward significance for MD ($P = .002 - .122$). This indicates that all studies were exerting comparable levels of influence on the meta-analyses. Collectively, these further investigations provide strong support for the finding that there is a reliable association between markers of underlying neuropathology and cognitive dysfunction after HMM mTBI.

In addition to the findings of the meta-analysis, this systematic review provides insights into the methodological quality of existing studies that have implications for future research. The search revealed that there continues to be considerable variability in the definition of mTBI, which is highly problematic when trying to compare results between studies. In addition, many existing studies have examined specific mTBI samples, such as professional athletes and military veterans, while others have included HMM mTBI in broader TBI samples. All of these groups differ from the more common HMM mTBIs in terms of the biomechanical forces of injury, and trajectory of neuropathologic and cognitive recovery. Finally, only a very small number of studies, each with small sample sizes, have examined the specific relationship between DAI and cognition after mTBI. Thus, to more fully understand the relationship between pathology and cognitive dysfunction after mTBI, it will be important to study large samples from homogeneous, well-defined patient populations.

**Study limitations**

As previously described, the limitations of this meta-analysis result primarily from the small number of eligible studies and resultant small number of associations examined by multiple studies. Despite using a random-effects model to minimize heterogeneity, variance may have resulted from methodological differences between studies. These include the interval between injury, neuroimaging, and cognitive testing, and characteristics of both neuroimaging and cognitive measures. Other limitations include those common to all studies with a small sample size: low statistical power and wide confidence intervals surrounding both the calculated effect sizes and variance. Despite this, the findings from these individual studies are remarkably consistent, and the use of meta-analytic methods to collate existing data does allow meaningful interpretation of the relationship between white matter integrity and cognition.

**Conclusions**

The findings of this systematic review and meta-analysis demonstrate clearly for the first time that DTI markers of underlying neuropathology are reliably associated with cognitive function after mTBI. This is the first technique that has successfully enabled researchers to measure the in vivo relationship between structural neuropathology and cognitive function after mTBI. As such, this represents an important advance in our attempts to understand the consequences of mTBI. The current findings are consistent with the known impact of DAI on cognition and provide clear support for an association between markers of reduced white matter integrity and poor performance on measures of attention, memory, and executive function, which persists beyond 1 month postinjury. While it is apparent that further research is needed, this study demonstrates that mTBI-related neuropathology is an important component in understanding cognitive dysfunction both within and beyond the first month postinjury. Furthermore, having demonstrated that in vivo markers of underlying neuropathology are reliably associated with performance on measures of cognitive function, these findings provide a basis for future research to investigate the extent to which structural neuropathology has a causal relationship with cognitive dysfunction after mTBI, particularly in those individuals who do not follow the “normal” recovery trajectory.
**Supplier**

a. Comprehensive Meta-Analysis version 3.0 software; Biostat, Inc.

**Keywords**

Brain concussion; Cognitive dysfunction; Diffusion tensor imaging; Magnetic resonance imaging; Neuropathology; Rehabilitation

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**Appendix 1 Full Electronic Search Strategy**

1. mild traumatic brain injur*.mp. [mp = title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]
2. exp Magnetic Resonance Imaging/
3. (Magnetic Resonance Imaging or MRI).mp. [mp = title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]
4. 2 or 3
5. 1 and 4
6. cogniti*.mp. [mp = title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]
7. exp Cognition/
8. 6 or 7
9. 5 and 8
10. limit 9 to (yr = “2002 -Current” and (“all adult (19 plus years)” or “young adult (19 to 24 years)” or “adult (19 to 44 years)” or “young adult and adult (19–24 and 19–44)” or “middle age (45 to 64 years)” or “middle aged (45 plus years)” or “all aged (65 and over)” or “aged (80 and over)”))
11. limit 10 to article

**References**


