

RESEARCH PAPER

Diffusion tensor imaging studies of mild traumatic brain injury: a meta-analysis

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ABSTRACT

Objectives To assess the possibility that diffusion tensor imaging (DTI) can detect white matter damage in mild traumatic brain injury (mTBI) patients via systematic review and meta-analysis.

Methods DTI studies that compared mTBI patients and controls were searched using MEDLINE, Web of Science, and EMBASE, (1980 through April 2012).

Results A comprehensive literature search identified 28 DTI studies, of which 13 independent DTI studies of mTBI patients were eligible for the meta-analysis. Random effect model demonstrated significant fractional anisotropy (FA) reduction in the corpus callosum (CC) ($p=0.023$, 95% CIs -0.466 to -0.035 , 280 mTBIs and 244 controls) with no publication bias and minimum heterogeneity, and a significant increase in mean diffusivity (MD) ($p=0.015$, 95% CIs 0.062 to 0.581 , 154 mTBIs and 100 controls). Meta-analyses of the subregions of the CC demonstrated in the splenium FA was significantly reduced ($p=0.025$, 95% CIs -0.689 to -0.046) and MD was significantly increased ($p=0.013$, 95% CIs 0.113 to 0.950). FA was marginally reduced in the midbody ($p=0.099$, 95% CIs -0.404 to 0.034), and no significant change in FA ($p=0.421$, 95% CIs -0.537 to 0.224) and MD ($p=0.264$, 95% CIs -0.120 to 0.438) in the genu of the CC.

Conclusions Our meta-analysis revealed the posterior part of the CC was more vulnerable to mTBI compared with the anterior part, and suggested the potential utility of DTI to detect white matter damage in the CC of mTBI patients.

INTRODUCTION

Mild traumatic brain injury (mTBI) is one of the most controversial neurologic injuries, as there is no obvious biological marker. Diffusion tensor imaging (DTI) has been considered as a potential biomarker in mTBI patients with otherwise normal neuroimaging,¹ as it can detect white matter microstructure changes. The most commonly used scalar invariant derived from DTI is fractional anisotropy (FA), which quantifies the orientation and integrity of white matter tracts. A decrease in FA may indicate axonal degradation and discontinuities with excess water between tracts or in perivascular spaces, which may also occur in mTBI.²

In the field of DTI studies of mTBI patients, the corpus callosum (CC) has been repeatedly investigated. Because a number of neuroimaging studies of moderate and severe traumatic brain injury demonstrated that the CC was one brain region that consistently experiences some of the largest amounts of deformation of any brain region,^{3–5}

and DTI studies demonstrated decreased FA in the CC.^{6,7} Further, both linear and angular acceleration may damage callosal fibers, which may lead to microstructural changes that can be identified in neuroimaging studies, particularly DTI.⁸ In addition, postmortem studies revealed histological lesions in the CC (reviewed in refs^{9,10}).

Although a number of DTI studies with mTBI patients have investigated brain damage, they yielded inconsistent results. While some studies reported an increase or no change in FA following mTBI,¹¹ other studies reported a significant reduction in FA.¹²

Thus, we hypothesised that the microstructure brain damage in mTBI patients can be detected by DTI; moreover, we hypothesised that also mTBI patients show similar location and direction of microstructure brain damage to that with moderate to severe traumatic brain injury, that is, FA is reduced in the CC and IC in mTBI patients. To investigate the hypotheses, we carried out a systematic review of the literature of DTI studies of mTBI patients and conducted a meta-analysis of DTI studies of mTBI patients, and have located a priori-defined region of interest (ROI). Although we have a hypotheses, we do not confine ROI in the CC and IC, but performed a meta-analysis wherever it was possible, for the entire brain, to examine whether DTI can be a biomarker of mTBI.

METHODS**Systematic review****Data sources**

DTI studies that examined the FA of mTBI patients compared with control subjects were obtained through the computerised databases of MEDLINE, Web of Science and EMBASE. The search terms used in the systematic screening were ‘brain injury’, ‘axonal injury’ and ‘trauma’, which were also combined with the terms ‘tensor’, ‘TBSS’, ‘tract-based spatial statistics’ (TBSS) and ‘tractography’. Two reviewers (YA and RI) performed independent screenings of the titles and abstracts of the studies to identify relevant studies to be included. Reference lists of included articles were also examined to search additional studies to be included.

Whole brain voxel-based analysis and ROI analysis

There are two major different approaches to examine microstructure damage from DTI data. The first one is the voxelwise whole brain analysis (WBA), such as voxel-based analysis (VBA)¹³ or TBSS¹⁴ approaches. Typically, they only provide details of areas that are significantly different



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between groups. The other one is ROI analysis, including that which utilised tractography for the definition of ROI.¹⁵ They do not investigate globally, but provide values of ROIs even when there was no significant difference.

In the current review, we performed systematic screening of DTI studies of mTBI, and we divide studies into two sections, based on the difference in the approach. Voxel-based global approaches, such as VBA studies and TBSS studies, were assigned to the section on WBA studies. A priori-defined local approaches, such as ROI studies and tractography studies, were sorted as ROI studies.

Selection criteria for database

We sought articles for database (1) in peer-reviewed journals between 1980 and April 2012, and (2) which studied brain DTI in mTBI patients compared with a control group. The literature search was performed without language restrictions.

Meta-analysis

Heterogeneity of WBA studies

There are two kinds of WBA studies, TBSS and VBA. As they differ from each other in the process of registration and smoothing,^{14 16} results from these different studies are not unifiable. Further, though reliable methods of meta-analysis of VBA have already been established,^{17 18} a reliable method of meta-analysis of TBSS has rarely been introduced. Thus, we can conduct a meta-analysis of only VBA studies.

As described below, the current systematic review yielded only five VBA studies whose thresholds completely differ with each other, which is not suitable and sufficient to conduct a meta-analysis. Thus, we will conduct a meta-analysis of ROI studies in the current work.

Meta-analysis of ROI studies

Selection of studies for meta-analysis

In addition to selection criteria for the database, we further imposed the following criteria for inclusion into the meta-analysis: (1) studies that utilised tractography or ROI methods; (2) studies included that reported sufficient data to allow for effect-size calculations; (3) had recruited more than three participants for each group and (4) reported no detectable change in the ROI by conventional imaging such as MRI and CT. To ensure the meta-analysis was sufficiently powered, brain region values were included if there were two or more studies reporting more than three datasets with sufficient data in total. If studies did not report sufficient data, we emailed the corresponding author to obtain further information. In cases where the author did not respond, we excluded the study from our analysis.

Data extraction

To perform the meta-analyses, we defined a standardised mean difference (SMD) as the effect-size statistic, which is defined as the difference between the mean of the experiment group and that of the comparison group divided by the pooled SD.¹⁹ In the current meta-analyses, the mean of DTI values in mTBI patients was subtracted from those in the control groups in each ROI, respectively, and divided by the pooled SD of both. Meta-analysis of Observational Studies in Epidemiology guidelines for conducting and reporting meta-analysis of observational studies were followed.²⁰

Statistical analysis

All meta-analyses were performed using the Comprehensive Meta-Analysis version 2 software (©2006, Biostat, Inc., Engle-

wood, New Jersey, USA). Standardised mean difference was calculated and used for the effect sizes. For meta-analysis, a single-effect size was computed from one comparison. In studies that used multiple ROIs from a single region, for example, the CC, the weighted average effect size was calculated. In studies that reported DTI values in the left and right hemispheres,^{21–23} we calculated the mean of two effect sizes from the left and right hemispheres and integrated it in the analysis.

In studies that compared three groups, such as one control and two mTBI groups, the number of participants in the control group was divided into two groups to avoid duplicate counting.^{24 25}

Furthermore, to perform sensitivity analysis of the CC, the datasets were assigned into three groups according to the CC location: genu, midbody and splenium. We employed random effect models for all the meta-analyses to minimise the potential heterogeneity between studies, such as variation in location of ROI, number of excitation (NEX) and b factor. We focused on five major DTI-derived invariants, including FA, apparent diffusion coefficient (ADC), mean diffusivity (MD), axial diffusivity (AD), and radial diffusivity. We performed a meta-analysis of the invariants of which more than three studies have been reported.

Sensitivity analysis

We performed a one-way sensitivity analysis to test the robustness of the results from the meta-analysis by excluding one dataset at a time. By doing this, we can assess whether any single dataset is responsible for the result.

Further, the effect of potential confounders were tested by sensitivity analysis in specified subgroups excluding studies with potential confounds. These potential confounds included comorbid psychiatric disorders, such as post-traumatic stress disorder, medication or substance misuse, including alcohol and field strength of MR scanner. In studies that did not mention the existence of major psychiatric disorder, we recognised them as the studies without major psychiatric disorder.

Meta-regression analysis

The meta-analysis revealed significant differences between mTBI patients and control individuals with a sufficient number of datasets.²⁶ To investigate the effect of possible modifiers or abnormalities, we performed meta-regression analyses to examine the relationship between mean duration of time between the point of injury and imaging, male ratio, and the mean age and SMD for the FA values in the whole CC and splenium. The regression was examined using the Comprehensive Meta-Analysis 2 software.

Assessment of between-study heterogeneity

Between-study heterogeneity was assessed using the I^2 statistics. Thresholds for the interpretation of I^2 were based on previous studies suggesting that 0% to 50% represents mild heterogeneity, 50% to 75% moderate heterogeneity, and 75% to 100% considerable heterogeneity.

Publication bias

Publication bias was assessed qualitatively by visual inspection of funnel plots, and quantitatively by linear regression analysis. Based on previous literature, this calculation was tested with datasets of at least 10.²⁶ A significance difference ($p < 0.10$) suggested the studies were heterogeneous.²⁵

Data synthesis

Twenty demographic, clinical and methodological variants, including the number of participants, number of male participants,

mean age, diagnostic criteria of mTBI, psychiatric comorbidity, medication and substance misuse, strength of magnetic field (Tesla), b factor, number of excitation, echo time (TE), repetition time, type of values reported by the study and main findings were extracted for both, WBA and ROI studies and, additionally, four and one characteristics of imaging were obtained for WBA and ROI studies, respectively, as shown in online supplementary tables 1-1 and 1-2. The datasets, participants, mean differences, 95% CI, Z-value, p value, and I² score are shown in table 1.

RESULTS

Study selection for database

The literature search produced 592 articles, of which 68 DTI studies were identified as potential candidates for the database. Twenty studies were excluded because they included data from moderate and severe traumatic brain injury, which could not be separated from the mTBI data. Seven studies were discarded because they were review articles or did not report original data. Six studies were excluded because they did not compare mTBI patients with control subjects. Two studies were not DTI studies. Two studies were not included in the database due to overlap of data.^{27 28} Thus, 28 studies were included in the database. Among these 28 studies, 10 studies utilised whole brain voxelwise analysis and were included in the WBA section, whereas 19 studies were assigned to the ROI section, and are shown in online supplementary tables 1–1, and 1-2. The process of study selection is shown in figure 1.

Study selection for meta-analyses

From the 19 studies in the section on ROI studies, three studies were excluded because they did not report sufficient data to calculate effect size.^{29–31} Two studies were excluded because they located the ROI only in the fornix and cingulum.^{32 33} As only two studies with two datasets reported DTI values from the cingulum with sufficient data to calculate effect size, and one reported DTI values from fornix, cingulum and fornix were excluded from the meta-analysis.

Additionally, one study was discarded because it utilised an original statistical analysis with percentile approach, as it was unable to calculate an effect size.³⁴ Therefore, 13 studies were included in the meta-analysis.^{12 21–25 35–41}

Characteristics of included studies

Section of WBA studies

Nine studies involving 189 mTBI patients and 154 controls were identified in this section.^{2 11 34 41–47} Five utilised the TBSS

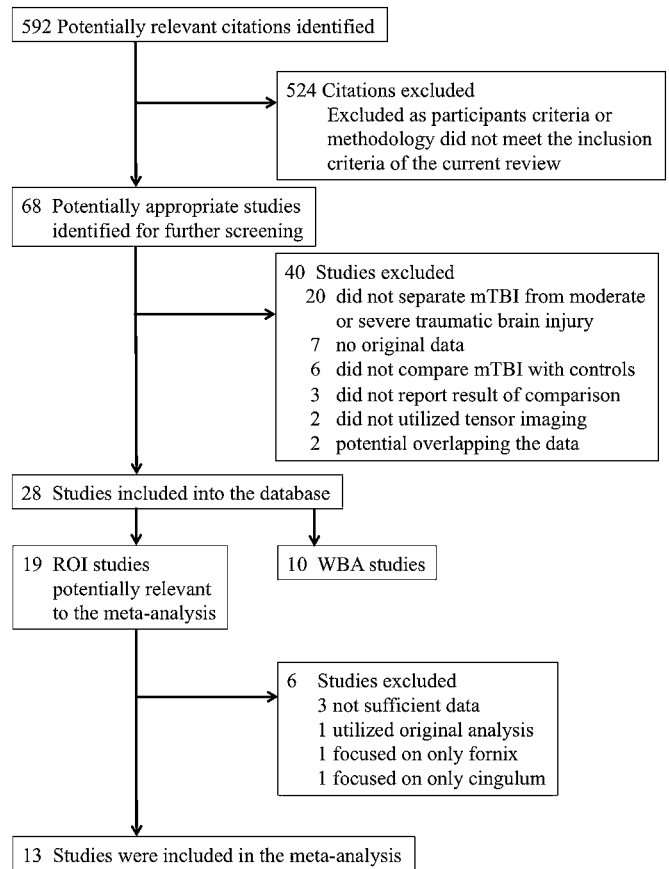


Figure 1 Process of study selection.

approach,^{41 43 45–47} whereas five^{2 11 34 42 44} adopted the voxel-based WBA. Thresholds adopted in these studies differ considerably; one utilised quantile analysis,³⁴ five studies^{41 43 45–47} adopted threshold at p<0.05 and one² at p<0.01 multiple comparison corrected, the other did not correct multiple comparison. Eight^{2 11 34 41–43 46 47} utilised a 3-T scanner and two^{44 45} used a 1.5-T scanner. Although the included studies demonstrated inconsistent results, three TBSS studies^{41 43–45} with the same threshold did not reveal any significant difference in FA values between mTBI patients and controls, whereas one study demonstrated diffuse FA reduction.⁴⁷ (online supplementary table 1-1)

Table 1 Meta-analysis by tract and value

Group	Invariant	Number of datasets	N*1	N*2	Lower 95% CI	Upper 95% CI	Z-value	p Value	Heterogeneity I square (%)	Publication bias	
CC	FA	15	280	244	-0.466	-0.035	-2.274	0.023	27.153	0.684	
	ADC	3	39	35	-0.391	1.886	1.287	0.198	82.682	NA	
	MD	6	154	100	0.062	0.581	2.425	0.015	0.000	NA	
Genu of CC	FA	12	248	218	-0.537	0.224	-0.805	0.421	72.933	0.535	
	ADC	3	39	35	-0.313	2.869	1.574	0.115	89.874	NA	
	MD	4	132	88	-0.120	0.438	1.117	0.264	0.000	NA	
Midbody of CC	FA	9	197	156	-0.404	0.034	-1.651	0.099	4.188	NA	
	Splenium of CC	FA	15	280	244	-0.689	-0.046	-2.238	0.025	65.870	0.610
		ADC	3	39	35	-0.928	2.564	0.918	0.358	91.997	NA
IC	FA	MD	6	154	100	0.113	0.950	2.490	0.013	53.164	NA
		FA	8	117	105	-0.317	0.478	0.397	0.691	46.970	NA
		CR	3	41	57	-0.564	0.272	-0.684	0.494	0.000	NA

N*1: number of patients of mTBI, N*2: number of control subjects.

ADC, apparent diffusion coefficient; CC, corpus callosum; CR, corona radiata; FA, fractional anisotropy; IC, internal capsule; MD, mean diffusivity

Section of ROI studies

Thirteen studies with 15 independent comparisons, 280 mTBI patients and 244 controls were included in the meta-analysis.^{12 21–25 35–41} Twelve patients were recruited, whose GCS score ranged from 13 to 15.^{12 21–25 35–40} Seven^{12 21 22 25 35 37 40} utilised a 1.5-T MRI scanner and six^{23 24 36 38 39 41} used a 3-T MRI scanner. All investigated FA value, whereas three examined ADC^{22 40 41} and four examined MD.^{24 25 37 38} Two reported AD and radial diffusivity.^{35 37} The duration between the event and scan ranged from three 3 days¹² to eight 8 years.³⁷ Nine out of 13 studies recruited mTBI patients without past history of major psychiatric problems,^{21–23 25 35 36 39–41} the remaining four studies did not mention any history of major psychiatric problems among mTBI patients.

Meta-analysis of DTI measures in the CC and IC of mTBI patients

Corpus callosum

Thirteen studies with 15 datasets that recruited 280 mTBI patients and 244 controls were integrated in the meta-analytical differences in FA value in the CC, and showed a significant FA decrease in mTBI patients ($p=0.023$) without heterogeneity and no publication bias (Table 1, figure 2).^{12 21–25 35–41} Three studies with 39 mTBI patients and 35 controls demonstrated no significant difference in ADC values ($p=0.198$) (table 1).^{22 40 41} Finally, four studies with six independent datasets involving 154 mTBI patients and 100 controls revealed a significant increase in MD in mTBI patients ($p=0.015$) without heterogeneity (table 1).^{24 25 37 38}

Genu of the corpus callosum

Eleven studies with 12 datasets involved 248 mTBI patients, and 215 controls were integrated using a random effect model, and demonstrated no significant difference between mTBI and controls in FA value in the genu of the CC ($p=0.450$) (Table 1, online supplementary figure 1).^{12 21–23 25 36–41} Three studies with 39 mTBI patients and 35 controls demonstrated no significant differences in ADC values ($p=0.115$) (table 1).^{22 40 41}

while three studies with four comparison groups showed no significant changes in MD ($p=0.264$) (table 1).^{27 37 38}

Midbody of the corpus callosum

In nine studies which recruited 197 mTBI patients and 156 controls, a marginal reduction in FA values was observed in the midbody of the CC ($p=0.099$) (Table 1, online supplementary figure 2).^{12 23 35–41}

Splenium of the corpus callosum

Thirteen studies with 15 datasets with 280 mTBI patients and 244 controls revealed a significant reduction in FA values in mTBI patients ($p=0.025$) without publication bias and moderate heterogeneity (Table 1, online supplementary figure 3).^{12 21–25 35–41} Three studies with 39 mTBI patients and 35 controls revealed no significant differences in ADC values ($p=0.358$) (table 1).^{22 40 41} A significant increase in MD ($p=0.013$) was demonstrated in mTBI patients using the random effect model in four studies with six independent datasets involving 154 mTBI patients and 100 controls with moderate heterogeneity (table 1).^{24 25 37 38}

Internal capsule

Six studies^{12 21–25} with seven datasets involving 117 mTBI patients and 105 controls demonstrated no significant difference in FA values in the IC ($p=0.691$) (table 1).

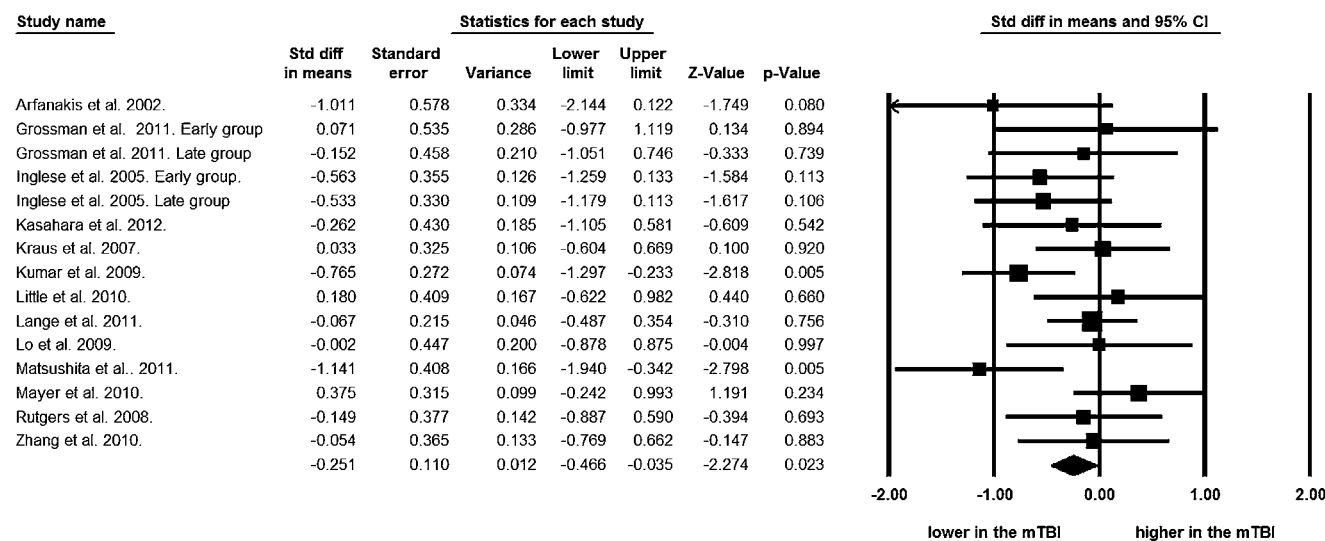
Corona radiata

Three studies^{12 36 39} with 41 mTBI patients and 57 controls were integrated in the meta-analysis, and demonstrated no significant FA reduction ($p=0.494$) (table 1).

Sensitivity analyses

To test the robustness of the findings, that the FA value is significantly reduced and MD is significantly increased in the whole CC and the splenium of the CC in mTBI patients, a one-way sensitivity analysis of each meta-analysis was performed. In

Meta-analysis of FA in the whole CC



FA was significantly reduced in mTBI patients.

Figure 2 Forest plot of FA in the CC Standardised mean differences (SMD) for FA measures in the CC between mTBI patients and control subjects. The forest plot displays SMD and 95% confidential intervals.

the CC, all the one-way sensitivity analyses preserved a marginal reduction of FA with 12 out of 15 replicating a significant reduction of FA (online supplementary table 2), while five out of six analyses replicated a significant MD increment (online supplementary table 2). In the splenium of the CC, all the one-way sensitivity analyses preserved a marginal reduction of FA with 12 out of 15 replicating a significant reduction of FA, while four out of six analyses replicated a significant MD increment (online supplementary table 2).

Sensitivity analysis performed in the specified-subgroups without major psychiatric problems demonstrated significant FA reduction in the whole CC ($p=0.019$) and splenium ($p=0.016$), and MD increase in the whole CC ($p=0.042$) and splenium ($p=0.026$) (online supplementary table 3). Sensitivity analysis of studies with a 1.5-T scanner also preserved significant FA reduction in the whole CC and splenium ($p<0.001$, $p=0.003$) and MD increment in the whole CC and splenium ($p=0.011$, $p=0.022$) (online supplementary table 3). On the other hand, sensitivity analyses of studies without medication or substance misuse did not show significant difference in FA or MD in the whole CC and splenium (online supplementary table 3).

Meta-regression

To investigate the effect of FA reduction in the whole CC and splenium of mTBI patients, we conducted meta-regressions with three potential modifiers; duration of time between the point of injury, male ratio, and imaging and mean age of participants. Meta-regression analysis revealed no significant effect of duration of time ($p=0.83$), male ratio ($p=0.70$) and mean age ($p=0.38$) on reduction of FA in the whole CC in mTBI patients. However, the mean age of mTBI patients had a marginally significant effect on reduction of FA in the splenium ($p=0.06$) (figure 3), but no significant effect of male ratio ($p=0.31$), and duration of time ($p=0.46$) (online supplementary table 4).

DISCUSSION

To the best of our knowledge, this is the first meta-analysis of DTI studies of mTBI patients to demonstrate significantly



Figure 3 The relationship between effect size for FA and age of study participants. The effect size from each comparison of VOIs is plotted by the mean age of mTBI patients. The line of best fit shows a gradual but substantial decrease of FA.

reduced FA and significantly increased MD in the CC compared with controls, without publication bias and with no heterogeneity. In addition, a subanalysis based on the subregions of the CC demonstrated a significant decrease of FA and significant increase of MD in the splenium, a marginal reduction of FA in the midbody and no changes in FA and MD in the genu of the CC. The viability of the FA reduction and increase in MD in the whole CC and splenium were examined by a one-way sensitivity analysis of each meta-analysis. Sensitivity analyses further demonstrated that these findings were preserved in specified subgroups with studies without psychiatric disorders.

Of the types of DTI studies, the hypothesis-free, whole brain analyses, such as VBA or TBSS approaches are useful to investigate the overall changes in white matter, rather than specific white matter tracts or areas.^{13 14} In contrast, the other type of DTI study, the ROI analysis, which investigates a priori-defined region or tractography, is useful to investigate specific tracts and defined ROI, and report invariances derived from tensor imaging. Thus, selecting DTI studies with a priori-defined design analysis is rational when we have an a priori hypothesis that DTI in the CC may be the potential tool to detect microstructure damage in the white matter following mTBI.

The significant FA reduction demonstrated by our meta-analysis suggests the potential diagnostic ability of DTI in mTBI patients. Our findings have provoked the assumption that previous studies were unable to demonstrate significant differences because of the small number of participants and varying duration after trauma.

In keeping with the findings of a previous study that reported unmyelinated axons in the CC after animal TBI,⁴⁸ we found that a reduced FA value indicates differences in cellular membrane integrity, fiber myelination, fiber diameter and directionality in the CC after mTBI. The CC is the main fiber tract that connects the hemispheres and is topographically organised. The genu of the CC represent fibers from the prefrontal cortex; the midbody is composed of fibers from the premotor, motor, parietal and superior temporal cortex; and the splenium represents fibers from the inferior temporal and occipital cortex. There are some possible reasons why the CC is vulnerable to mTBI. First, the CC is a very organised area of the brain, with axons predominantly oriented in one direction, is inherently anisotropic and has higher FA values compared with less organised areas of white matter. Second, as the CC connects both hemispheres, external accelerational forces at a lateral or oblique-lateral angle of rotation can cause injury to the CC.⁴⁹ In addition, the CC has been recognised as a region frequently injured by shear strain,⁵⁰ as shown in victims of shaken baby syndrome.^{51 52}

The meta-analysis clearly demonstrated selective FA reduction in the posterior part of the CC, such as it reached significance in the splenium and a marginal difference in the midbody, as well as selective MD increases in the splenium. MD is another invariant that is often reported in DTI studies, which is a measure of the average molecular diffusion independent of any tissue directionality and is affected by cellular size and integrity.¹ Results, such as lower FA and higher MD, imply that the posterior part of the CC is more vulnerable to injury than the anterior part like the genu. The vulnerability of the posterior part of the CC compared with the anterior part has been repeatedly reported by imaging studies of brain injury.^{50 53 54} One MRI study reported that 80% of CC injury was distributed in the posterior part in patients with a moderate to severe TBI.^{55 56} Though the mean age of the included studies was limited, ranging from 27 to 42, it had a marginally significant effect on the FA reduction in the splenium ($p=0.06$). Although we are unable to offer a compelling

explanation for this relationship, it may potentially be due to age-related changes in white matter maturity. Previous studies have reported that FA is increased during childhood and adolescence, and reaches its peak value at around age 30, then gradually decreases.⁵⁶ An external trauma may accelerate the loss of FA. To test this relationship, a large-scale original study is required.

There are a number of clinical and methodological confounds that may effect the result. For example, sexual dimorphism of the CC in DTI has been reported.⁵⁷ Although meta-regression showed no significant relation between male ratio and effect size, male ratio was not available from all the studies. Thus, the finding should be interpreted with caution. Medication and substance misuse also influence results.⁵⁸ Though no studies reported participants of substance misuse, some studies did not clarify that they excluded individuals with substance abuse, and sensitivity analysis excluding them did not show significant difference. Thus, the potential effect of medication or substance abuse is not completely assessed. With regard to strength of magnetic field, although sensitivity analysis with studies which utilised a 1.5-T scanner preserved the findings, sensitivity analysis with a 3-T scanner did not show significance. As microstructure damage is more detectable in stronger magnetic field, this result is against the hypothesis.

Limitation

Our study, however, does have several methodological considerations and limitations that must be acknowledged. Due to the nature of a meta-analysis, we can make statistical analysis only at the level of studies, with no way of confirming that the mTBI participants of the included studies actually exhibited the findings presented. We found considerable heterogeneity between studies that may attribute to methodological issues. Some of the included studies utilised a 1.5-T MR scanner, while others used a 3-T. In addition, the NEX, b factor and number of directions are considerably different. Although we employed a random effect model to tolerate heterogeneity, the different methodologies integrated from these studies may be criticised. Although we conducted a comprehensive literature search and meta-analyses of the CC, IC and corona radiata, there is the possibility that other brain areas could also present white matter changes that were not investigated in this meta-analysis.⁵⁹

In addition, we cannot deny the probable existence of the data we could not find. Further, though we have demonstrated significant FA reductions in the CC of mTBI patients with a large effect size, the large total number of participants could help the small differences reach significance. Additionally, it has been repeatedly reported that mTBI patients were at risk of developing mental health problems, such as depression and substance misuse, versus those mental health problems that are common among individuals who have mTBI.⁶⁰ And it is widely known that those mental health problems alter DTI values.⁶¹ Although sensitivity analysis with studies without major psychiatric disorders preserved the significance of the findings, due to lack of sufficient number of studies that investigated mental health problems among mTBI patients, it was impossible to examine whether the DTI change demonstrated any result from pure injury or was related to psychological problems that may be the cause and sequel of injury.

Finally, it is a pivotal point that diagnostic tools of mTBI are changing. Almost all the included studies recruited patients with a GCS scored between 13 and 15, however, there has been a recent argument on the definition of mTBI, and whether it should include patients with a GCS score of 13.⁶²

CONCLUSION

In conclusion, our findings from this meta-analysis of DTI studies of mTBI patients clearly demonstrate a significant FA reduction in the CC without publication bias and heterogeneity. The results provide strong evidence that DTI can detect microstructural damage in the white matter of mTBI patients, highlighting its potential utility in clinical settings.

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Contributors YA and RI performed study screenings independently. In the case of discrepancies, a consensus was reached by means of discussion with the third reviewer (HS). YA performed all the data extraction and computation of effect size twice to avoid error. RI also performed data extraction and computation of the effect sizes independently. YA wrote the paper. RI, MG, NY, and HS took part in writing the paper.

Competing interests None.

Provenance and peer review Not commissioned; externally peer reviewed.

Data sharing statement Dr KH and Dr KK had let us share SD of FA values in their study. Dr AM had let us share mean and SD of FA values in their study.

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Supplementary table 1-1. Summary of included WBA-DTI studies

Study	Character of participants							Character of imaging											Main findings (Compared with controls)							
	Trauma group		Comparison group			GCS score	Duration after trauma (weeks)	prior	Post	Medication Substance misuse	T	b	TR/TE (ms)	NEX	Number of direction	value					Type of whole brain analysis	Software	Threshold	Multiple comparison correction		
N ^{*1}	males	mean age y.o	N ^{*2}	males	mean age											yes	no	yes	no	yes					no	yes
Bazarian et al. 2007	6	NA	NA	6	NA	NA	13-15	within 0.43	NA	yes	no	3	700	4800/91	NA	NA	○	x	x	x	x	voxel based analysis	SPM	Quantile analysis	no	FA is reduced in the AIC and increased in the posterior CC
Chu et al. 2010	10	4	15.7	10	4	15.7	15	0.386	no	yes	NA	3	1000	6318/51	2	30	○	○	x	x	○	voxel based analysis	SPM2	p < 0.001 (for ADC)	no	FA was increased in thalamus
Cubon et al. 2011	10	5	19.7	10	5	20.4	13-15	NA	no	yes	NA	3	1000	10000/95	3	60	○	x	○	x	x	TBS	FSL	p < 0.05	corrected	No significant difference in FA.
Henry et al. 2011	16	16	22.1	8	NA	22.8	15	0.488	no	yes	no	3	700	2500/3.83	NA	NA	○	x	x	x	x	voxel based analysis	SPM8	p < 0.003	no	FA increased in dorsal CST and in the CC
Lipton et al. 2008	17	8	NA	10	NA	NA	13-15	NA	NA	NA	no	1.5	1000	NA	NA	25	○	x	○	x	x	voxel based analysis	FSL	p < 0.005	no	FA was reduced in OFA, IC, CC,

STG

Lipton et al. 2009	20	9	33.4	20	9	34.2	13-15	NA	NA	yes	NA	3	1000	3800/88	NA	32	○	x	○	x	x	voxel based analysis	FSL	p < 0.01	corrected FDR	FA was decreased in the DLPFC
Messe et al. 2011	23	17	30.6	23	11	30	13-15	2.457	no	yes	no	1.5	1000	5300/110	3	26	○	x	x	x	x	TBS S	FSL	p < 0.05	corrected TFCE	No significant difference in FA. FA is decreased in the CC, IC, CR, SS, ES, Cg, Fx, UF, SLF.
Messe et al. 2012	53	35	35.5	40	28	36.3	13-15	NA	no	yes	no	3	1000	10000/87	NA	50	○	x	○	○	○	TBS S	FSL	p < 0.05	corrected TFCE	FA was reduced in the IFOF
Smit et al. 2010	19	10	26	12	8	28	13-15	4.371	NA	yes	no	3	1000	14200/68.9	NA	25	○	x	x	x	x	TBS S	FSL	p < 0.05	corrected FDR	No significant difference in the FA.
Zhang et al. 2010	15	NA	21.3	15	NA	20.8	15	4.3	no	no	NA	3	NA	6500/93	NA	NA	○	○	x	x	x	TBS S	FSL	p < 0.05	corrected	

N*1: number of patients of mild traumatic brain injury, N*2: number of controls subjects. *3: behavioral symptoms were characterized as confusion, delirium, restlessness, irritability and dizziness. *4: symptoms were assessed using Neurobehavioral Symptom Inventory Somatic complaint. Abbreviation: ROI: region of interest, TBSS: Tract-Based Spatial Statistics, GCS: Glasgow coma scale, NEX: number of excitation, TE: echo time, TR: repetition time, FA: fractional anisotropy, ADC: apparent diffusion coefficient, MD: mean diffusivity, RD: radial diffusivity, AD: axial diffusivity, TFCE: Threshold-Free Cluster Enhancement, AIC: anterior internal capsule, CST: cortico-spinal tract, OFA: orbitofrontal area, STG: superior temporal gyrus, DLPFC: dorsolateral prefrontal cortex, IC: internal capsule, CR: corona radiata, SS: sagittal stratum, ES: external capsule, Cg: cingulum, Fx: fornix, SLF: superior longitudinal fasciculus, UF: uncinate fasciculus, IFOF: inferior fronto-occipital fasciculus

Supplementary table 1-2. Summary of included ROI-DTI studies

Study	Character of participants								Character of imaging											Main findings (Compared with controls)			
	Trauma group			Comparison group			GC S score	Duration after trauma (weeks)	prior	post	Medication	Substance misuse	Tesla	b factor	TR/TE (ms)	NE X	Number of direction	value					Location of ROIs other than CC
N ^{*1}	males	mean age y.o.	N ^{*2}	males	mean age	Psychiatric disorder												F	AD	M	A	R	
Arfankis et al. 2002	5	3	35.6	10	5	28.9	13-15	NA	no	NA	NA	1.5	1001	4500/71	4	23	o	x	x	x	x	AIC, PIC, EC	FA was reduced in the AIC, PIC, EC and CC.
Bazarian et al. 2007	6	NA	NA	6	NA	NA	13-15	within 0.43	NA	yes	no	3	700	4800/91	NA	NA	o	x	x	x	x	AIC, PIC, EC	No significant difference.
Geary et al. 2010	40	17	34.53	35	16	32.54	NA	275.08	no	yes	no	3	750	NA	NA	28	o	x	x	x	x	ACR, PCR, EC, Cg, fMin, fMaj, IFOF, SLF, SS thalamus	FA was reduced in the SLF, SS, UF.
Grossman et al. 2011	22	14	38.2	14	9	36.5	13-15	9.36/202.8	NA	no	no	3	NA	9090/93	NA	NA	o	x	o	x	x	IC, CS	FA was reduced in the IC.
Inglese et al. 2005	46	29	36	29	15	35	13-15	0.6/296.4	no	NA	NA	1.5	1000	5000/100	4	6	o	x	o	x	x	IC, CS	FA was reduced in the CC and IC.
Kasahara et al. 2012	10	7	39.1	12	10	23	13-15	291.2	no	NA	no	1.5	1000	5400/99	1	60?	o	x	x	o	o	50 ROIs	No significant difference.
Kraus et al. 2007	20	8	35.85	18	7	32.83	13-15	428.0	no	NA	no	3	750	5200/81	2	27	o	x	x	x	x	ACR, PCR, CST, Cg, fMin, fMaj, IFOF, SLF, EC, SS	FA was reduced in CST, SS, SLF.

Kumar et al. 2009	26	NA	34.25	33	22	32.1	13-15	1.3	NA	behavioral symptoms ^{*3}	NA	1.5	1000	8000/100	8	10	o	x	o	o	o	no	FA was reduced in the genu and splenium of CC.
Lange et al. 2011	60	43	30.8	34	25	37.1	13-15	6.7	no	NA	no	3	1000	5600/75	NA	16	o	x	o	x	x	no	No significant difference.
Little et al. 2010	12	NA	31.2	12	NA	30.8	13-15	222.0	no	NA	no	3	1000	5000/64	8	27	o	x	x	x	x	ACR, PCR, fMin, fMaj, thalamus	FA was reduced in the ACR, PCR, fMaj, and CC.
Lo et al. 2009	10	5	38.16	10	5	44	13-15	383.8	no	cognitive impairment	no	1.5	1000	8700/89	1	25	o	o	x	x	x	IC, Pons	FA was reduced in the IC and CC.
Matsushita et al. 2011	9	NA	39.3	27	13	42.9	13-15	0.5	NA	NA	NA	1.5	1000	10060/87	NA	6	o	x	x	x	x	CR, IC, FWM, OWM	No significant difference.
Mayer et al. 2010	21	NA	27.45	20	NA	26.81	13-15	1.8	no	emotional, cognitive, somatic symptoms ^{*4}	no	3	800	9000/8400	1	30	o	x	x	x	x	SCR, SLF, UF, CR, IC	FA was reduced in the SCR, UF, IC, CC, and CR.
Miles et al. 2008	16	11	33.44	29	14	35	13-15	0.6	no	yes	no	1.5	1000	5000/100	4	6	o	x	o	x	x	CS, IC	FA was reduced in the ROIs.
Niogi et al. 2008	43	28	32.4	23	17	29.9	13-15	67.6	no	yes	no	3	1000	14000/63	NA	55	o	o	x	x	x	UF, ACR, ILF, Cg, SLF	FA was reduced in the ROIs.
Rutgers et al. 2008	24	NA	34	10	7	37	13-15	22.0	NA	NA	no	1.5	1000	5700/110	NA	25	o	o	x	x	x	no	FA was reduced in the

Wu et al. 2010	1 2	6	15. 3	1 1	6	15. 8	15	0.4	no	NA	NA	3	100 0	63180/ 51	NA	30	○	○	x	x	x	Cg	genu of CC. ADC was reduced in the Cg.
Yallampalli et al. 2010	1 1	5	15. 09	1 1	5	15. 82	15	NA	no	NA	no	3	NA	63180/ 51	2	30	○	○	x	x	x	Fx	FA in the fornix was higher.
Zhang et al. 2010	1 5	NA	21. 3	1 5	NA	20. 8	15	4.3	no	no	NA	3	NA	6500/9 3	NA	NA	○	○	x	x	x	hippocampus	No significant difference.

N*1: number of patients of mild traumatic brain injury, N*2: number of controls subjects. *3: behavioral symptoms were characterized as confusion, delirium, restlessness, irritability and dizziness. *4: symptoms were assessed using Neurobehavioral Symptom Inventory Somatic complaint. Abbreviation: ROI: region of interest, GCS: Glasgow coma scale, NEX: number of excitation, TE: echo time, TR: repetition time, FA: fractional anisotropy, ADC: apparent diffusion coefficient, MD: mean diffusivity, RD: radial diffusivity, AD: axial diffusivity, AIC: anterior internal capsule, PIC: posterior internal capsule, EC: external capsule, ACR: anterior corona radiata, PCR: posterior corona radiata, Cg: cingulum, fMin: forceps minor, fMaj: forceps major, IFOF: inferior fronto-occipital fasciculus, SLF: superior longitudinal fasciculus, UF: uncinata fasciculus, SS: sagittal stratum, CS: centrum semiovale, CST: cortico-spinal tracts, CR: corona radiata, SCR: superior corona radiata, FWM: frontal white matter, OWM: occipital white matter

Supplementary table 2. One-dataset-removed sensitivity analysis

FA							
ROI	Removed datasets	Z-value	Effect size p-value	ROI	Removed datasets	Z-value	Effect size p-value
Whole CC	Arfanakis et al. 2002.	-2.055	0.040	Splenium	Arfanakis et al. 2002.	-2.109	0.035
	Grossman et al. 2011. Early group	-2.293	0.022		Grossman et al. 2011. Early group	-2.283	0.022
	Grossman et al. 2011. Late group	-2.194	0.028		Grossman et al. 2011. Late group	-2.196	0.028
	Inglese et al. 2005. Early group.	-1.960	0.050		Inglese et al. 2005. Early group.	-1.842	0.065
	Inglese et al. 2005. Late group	-1.945	0.052		Inglese et al. 2005. Late group	-1.840	0.066
	Kasahara et al. 2012.	-2.136	0.033		Kasahara et al. 2012.	-2.206	0.027
	Kraus et al. 2007.	-2.350	0.019		Kraus et al. 2007.	-2.330	0.020
	Kumar et al. 2009.	-1.751	0.080		Kumar et al. 2009.	-1.977	0.048
	Lange et al. 2011.	-2.275	0.023		Lange et al. 2011.	-2.094	0.036
	Little et al. 2010.	-2.425	0.015		Little et al. 2010.	-2.263	0.024
	Lo et al. 2009.	-2.275	0.023		Lo et al. 2009.	-2.325	0.020
	Matsushita et al. 2011.	-1.991	0.046		Matsushita. 2011.	-1.856	0.063
	Mayer et al. 2010.	-2.913	0.004		Mayer et al. 2010.	-2.561	0.010
Rutgers et al. 2008.	-2.187	0.029	Rutgers et al. 2008.	-2.194	0.028		
Zhang et al. 2010.	-2.256	0.024	Zhang et al. 2010.	-2.284	0.022		
MD							
Whole CC	Grossman et al. 2011. Early group	2.637	0.008	Splenium	Grossman et al. 2011. Early group	2.874	0.004
	Grossman et al. 2011. Late group	2.403	0.016		Grossman et al. 2011. Late group	2.389	0.017

Inglese et al. 2005. Early group.	1.953	0.051	Inglese et al. 2005. Early group.	2.282	0.022
Inglese et al. 2005. Late group	2.042	0.041	Inglese et al. 2005. Late group	1.914	0.056
Kumar et al. 2009.	2.038	0.042	Kumar et al. 2009.	2.230	0.026
Lange et al. 2011.	2.210	0.027	Lange et al. 2011.	1.942	0.052

Abbreviations; FA: fractional anisotropy, MD: mean diffusivity, ROI: region of interest, CC: corpus callosum

Supplementary table 3. Results from sensitivity analyses

Region	Value	Specified criteria	Number of studies	Number of datasets	95% CI lower	95% CI upper	Z-value	p-value
the whole CC	FA	No psychiatric comorbidity	9	11	-0.460	-0.041	-2.342	0.019
		No substance misuse	8	9	-0.219	0.240	0.090	0.928
		1.5 tesla scanner	7	8	-0.821	-0.302	-4.247	< 0.001
	MD	No psychiatric comorbidity	3	5	0.012	0.612	2.038	0.042
		No substance misuse	2	3	-0.188	0.530	0.934	0.350
		1.5 tesla scanner	2	3	0.110	0.861	2.532	0.011
splenium of the CC	FA	No psychiatric comorbidity	9	11	-0.917	-0.094	-2.410	0.016
		No substance misuse	8	9	-0.242	0.217	-0.107	0.915
		1.5 tesla scanner	7	8	-1.235	-0.244	-2.924	0.003
	MD	No psychiatric comorbidity	3	5	0.073	1.139	2.230	0.026
		No substance misuse	2	3	-0.062	0.659	1.621	0.105
		1.5 tesla scanner	2	3	0.130	1.646	2.296	0.022

Abbreviations: CC: corpus callosum, FA: fraction anisotropy, MD: mean diffusivity

Supplementary table 4. Meta-regression of FA

Whole CC				
Modifier	Separate dataset	Intercept	Slope	p-value
duration	14	-0.32	0.00	0.61
male ratio	9	0.05	-0.44	0.70
age	14	0.34	-0.02	0.32
Splenum of CC				
duration	13	-0.26	0.00	0.42
male ratio	9	0.33	-1.16	0.31
age	11	2.07	-0.07	0.03

Abbreviations; FA: fraction anisotropy, CC: corpus callosum