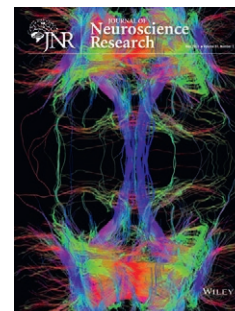


RESEARCH ARTICLE

Diffusion kurtosis imaging in mild traumatic brain injury and postconcussional syndrome

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Abstract

Aims of this study were to investigate white matter (WM) and thalamus microstructure 72 hr and 3 months after mild traumatic brain injury (TBI) with diffusion kurtosis imaging (DKI) and diffusion tensor imaging (DTI), and to relate DKI and DTI findings to postconcussional syndrome (PCS). Twenty-five patients (72 hr = 24; 3 months = 23) and 22 healthy controls were recruited, and DKI and DTI data were analyzed with Tract-Based Spatial Statistics (TBSS) and a region-of-interest (ROI) approach. Patients were categorized into PCS or non-PCS 3 months after injury according to the ICD-10 research criteria for PCS. In TBSS analysis, significant differences between patients and controls were seen in WM, both in the acute stage and 3 months after injury. Fractional anisotropy (FA) reductions were more widespread than kurtosis fractional anisotropy (KFA) reductions in the acute stage, while KFA reductions were more widespread than the FA reductions at 3 months, indicating the complementary roles of DKI and DTI. When comparing patients with PCS ($n = 9$), without PCS ($n = 16$), and healthy controls, in the ROI analyses, no differences were found in the acute DKI and DTI metrics. However, near-significant differences were observed for several DKI metrics obtained in WM and thalamus concurrently with symptom assessment (3 months after injury). Our findings indicate a combined utility of DKI and DTI in detecting WM microstructural alterations after mild TBI. Moreover, PCS may be associated with evolving alterations in brain microstructure, and DKI may be a promising tool to detect such changes.

KEYWORDS

brain concussion, diffusion tensor imaging, magnetic resonance imaging, postconcussion syndrome

*These authors contributed equally.

Significance

Patients with mild traumatic brain injury (TBI) were assessed with diffusion tensor imaging (DTI) and diffusion kurtosis imaging (DKI) 72 hr and 3 months after injury and compared with healthy controls. Differences in white matter microstructure were found between the groups, both with DKI and DTI on both time points, but different patterns of alteration were detected with the two methods. Moreover, in patients with postconcussional syndrome we found indications of evolving alterations in several DKI metrics in WM and thalamus 3 months after injury when compared with patients without symptoms and healthy controls. Thus, our findings suggest that the combined use of DTI and DKI may prove to be a promising biomarker after mild TBI.

1 | INTRODUCTION

Diffusion tensor imaging (DTI) is more sensitive in detecting microstructural tissue damage after mild traumatic brain injury (TBI) than conventional imaging tools such as computer tomography (CT) and clinical magnetic resonance imaging (MRI) (Yuh et al., 2014). However, DTI has produced mixed findings in mild TBI patients (Shenton et al., 2012) and a review showed approximately equal number of studies reporting increased versus decreased fractional anisotropy (FA) in a wide range of white matter (WM) areas during the first 3 months after mild TBI (Dodd, Epstein, Ling, & Mayer, 2014).

Diffusion kurtosis imaging (DKI), which is a newer diffusion technique based on the non-Gaussian diffusion of water, is considered to better reflect diffusion in biological tissues, especially in brain areas with high tissue heterogeneity such as gray matter (Glenn, Helpert, Tabesh, & Jensen, 2015; Steven, Zhuo, & Melhem, 2014; Wu & Cheung, 2010; Yu et al., 2017). Hence, DKI has the potential to provide a distinct microstructural contrast in comparison with the DTI parameters. To date, few studies have investigated DKI in patients with mild TBI (Grossman et al., 2012, 2013; Lancaster et al., 2016; Stokum et al., 2015), focusing on the most common DKI metrics; mean kurtosis (MK), axial kurtosis (AK), and radial kurtosis (RK). In these studies, lower MK and increased AK have been reported in WM and thalamus in patients with mild TBI compared with healthy controls both in the acute, semi-acute (within 1 month), and the chronic (≥ 6 months) phase, and differences in DKI were demonstrated in the absence of DTI abnormalities. In line with this, DKI, but not DTI findings, have been associated with hippocampal and cortical astrogliosis in an animal mild TBI study (Zhuo et al., 2012). These studies support the view that DKI can be more sensitive to the pathology underlying mild TBI than DTI.

The findings of lower MK in the thalamus are especially interesting and are in line with studies on moderate and severe TBI (Anderson, Wood, Bigler, & Blatter, 1996; Maxwell et al., 2004). Given its reciprocal connections to the entire cerebral cortex, the thalamus could play an important role in understanding the pathology of mild TBI and predicting its outcome (Grossman & Ingles, 2016).

More recently, kurtosis fractional anisotropy (KFA) and mean kurtosis tensor (MKT) metrics have been proposed. In the same way that the anisotropy of the diffusion tensor is described by the scalar FA, KFA is mathematically analogous to FA, and reflects the anisotropy of the kurtosis tensor (Hansen & Jespersen, 2016):

$$KFA = \frac{\|W - \bar{W}I^{(4)}\|_F}{\|W\|_F}$$

where W is the kurtosis tensor and $I^{(4)}$ is the fully symmetric, rank 4 isotropic tensor defined by its components:

$$I_{ijkl}^{(4)} = \frac{1}{3} (\delta_{ij}\delta_{kl} + \delta_{ik}\delta_{jl} + \delta_{il}\delta_{jk})$$

KFA differs from the above-mentioned DKI measures in depending solely on the kurtosis tensor and not on the diffusion tensor. The kurtosis and diffusion tensors are distinct physical quantities that reflect different aspects of the diffusion dynamics, and as a consequence, they can vary independently and portray distinct physiological and structural processes. This new kurtosis metric could therefore potentially further increase the sensitivity of DKI for detecting hitherto unidentified brain injury in mild TBI. Indeed, it has been demonstrated in rats and in a healthy volunteer that KFA offers distinct and complementary microstructural contrast when compared with DTI parameters, particularly in areas with near orthogonal fiber arrangements such as the superior corona radiata and centrum semiovale, and in deep brain structures such as the thalamus consisting of both white and gray matter where FA indicates anisotropy close to zero (Glenn et al., 2015; Hansen & Jespersen, 2016). MKT on the other hand, was proposed as an alternative way of calculating MK, but with a shorter acquisition and post-processing time (Hansen, Lund, Sangill, & Jespersen, 2013). Like MK, MKT also quantifies the degree of deviation from Gaussian diffusion, but compared to MK, which is based on knowledge of both the diffusion and kurtosis tensors, MKT is based only on the trace of the kurtosis tensor (Glenn et al., 2015; Hansen et al., 2013). MK is the average over the sphere (or diffusion directions) of the kurtosis $K(n)$:

$$MK = \bar{K} = \frac{1}{4\pi} \int_{S_2} K(\hat{n}) d\hat{n} = \frac{1}{4\pi} \int_{S_2} \frac{\bar{D}^2}{D(\hat{n})^2} W(\hat{n}) d\hat{n}$$

While MKT is the average of the kurtosis tensor $W(n)$:

$$MKT = \bar{W} = \frac{1}{4\pi} \int_{S_2} W(\hat{n}) d\hat{n} = \frac{1}{5} Tr(W)$$

In a recent study, higher MKT was found in the thalamus in patients with mild TBI compared with healthy controls at 2 weeks, but not at 3 months after injury (Naess-Schmidt et al., 2017). The additional value of KFA and MKT compared with MK, RK, and AK has, however, not been evaluated in mild TBI or any other patient groups.

Mild TBI is generally associated with good outcome, but some patients suffer from persistent symptoms such as headache, sleep problems, fatigue, irritability, and forgetfulness weeks and months after injury (Carroll et al., 2014; Cassidy et al., 2014). When these symptoms last longer than 3 months, they are classified as post-concussional syndrome (PCS) (World Health Organization, 1993). Though clearly associated with factors such as pre-injury mental health, as well as post-injury anxiety and early neuropsychological deficits (Silverberg et al., 2015), PCS is also hypothesized to be mediated by an impact to the brain itself (Messe et al., 2011), and research has been directed toward identifying biological markers predictive of PCS. Clinical MRI is often negative in mild TBI, and no consistent associations between traumatic findings and PCS have been reported (Silverberg et al., 2015). There is some evidence of the predictive value of different DTI metrics obtained in the sub-acute phase (>1-month post-injury) for PCS (Messe et al., 2011; Yuh et al., 2014), but the value of very early MRI has not been studied. Furthermore, ongoing postconcussion symptoms have been associated with alterations in DTI metrics in several studies (Bouix et al., 2013; Dean, Sato, Vieira, McNamara, & Sterr, 2015; Smits et al., 2011), but findings are mixed (Lange et al., 2015; Waljas et al., 2014) and the results remain inconclusive. Interestingly, reduced MK in the thalamus has been associated with objective cognitive impairment in TBI (Grossman et al., 2012, 2013). In contrast, no indication of an alteration in MKT in the thalamus was found in a study of patients with extensive postconcussions symptoms (Naess-Schmidt et al., 2018).

The aims of this longitudinal study were: (a) to study WM and thalamus microstructure as described with DTI and DKI in patients 72 hr and 3 months after mild TBI and in healthy controls; and (b) to compare DKI and DTI metrics in PCS patients, non-PCS patients, and healthy controls in the acute phase and at 3 months. A broad range of DKI and DTI metrics were extracted and analyzed with Tract-based spatial statistics (TBSS) and a region-of-interest (ROI) approach in WM and the thalamus.

2 | MATERIALS AND METHODS

2.1 | Study population

Patients were prospectively recruited during 18 weeks between September 2013 and January 2014 from a regional Level 1 Trauma Center (St. Olavs Hospital) in Trondheim, Norway. During the last 6 weeks of this period, patients were also recruited from Trondheim municipal emergency clinic. Patients presenting with possible TBI were identified by review of patient lists, and through daily contact with the neurosurgical department. Subsequently, the patients were approached and evaluated for inclusion.

TBI was defined as an alteration in brain function, or other evidence of brain pathology, caused by an external force (Menon et al., 2010). We used the proposed criteria from WHO Collaborating Centre for Neurotrauma Task Force on Mild TBI (Holm, Cassidy, Carroll, & Borg, 2005) to classify the TBI as mild, which is Glasgow Coma Scale (GCS) score at presentation to the hospital 13–15, any loss of consciousness (LOC) < 30 min, and post-traumatic amnesia (PTA) < 24 hr. Exclusion criteria were (a) below 18 or above 60 years of age, (b) not speaking Norwegian, (c) presence of severe psychiatric disease, severe somatic disease or drug abuse, (d) history of complicated mild, moderate, or severe TBI or other diseases associated with brain pathology, (e) late presentation to the hospital (>96 hr), and (f) contraindications for MRI. Patients were included in the data analysis if they had the 3-month outcome evaluation and at least one MRI.

After the study period, CT referrals from the whole inclusion period were reviewed in order to evaluate the completeness of the patient cohort. A total of 201 patients between 18 and 60 years had an acute CT due to head trauma during the 18-week inclusion period (Figure 1). Of these, 99 patients did not meet the inclusion criteria. Of the 102 patients with mild TBI, 30 patients met the exclusion criteria, 9 patients refused participation, 17 patients could not be reached, and 21 patients had been treated at the municipal emergency clinic before the start of recruitment from this unit. With that, 25 patients were recruited via CT referrals. In addition, five patients without head CT were included, all from the municipal emergency clinic. Five of the 30 included patients did not have the 3-month outcome evaluation and were omitted from the data analysis. Hence, the final sample comprised 25 mild TBI patients, 12 men and 13 women (Figure 1, Table 1). Of these patients, 24 had acute MRI (mean time to MRI = 69 hr; range = 261) and 23 had the 3-month MRI (mean time to MRI = 82 d; range = 43). Twenty-two patients completed both scans. In addition, a convenience sample consisting of 22 healthy control subjects, 10 men and 12 women, matched with regard to age, sex, and education were recruited from the hospital and university staff, as well as patients' and academic staff members' families, colleagues, and friends. Healthy controls were scanned twice (mean time between MRI = 98 d, range = 28) with the same MRI protocol as the patients with mild TBI. All control subjects underwent the first scanning during the last half of 2014, with the last follow-up scan performed in March 2015. The healthy controls were free of psychiatric disease, drug abuse, severe somatic disease, or other diseases associated with brain pathology, and did not have a history of complicated mild, moderate, or severe TBI.

2.2 | Demographic and injury-related variables

Information about demographics, somatic disease, and substance abuse was collected with a semi-structured interview. Pre-injury psychiatric history was assessed with the MINI International Neuropsychiatric Interview (M.I.N.I.) (Sheehan et al., 1998) by a clinical psychologist (R.H.K) or a medical doctor (C.E. or T.S.). Both patients and healthy controls received the semi-structured

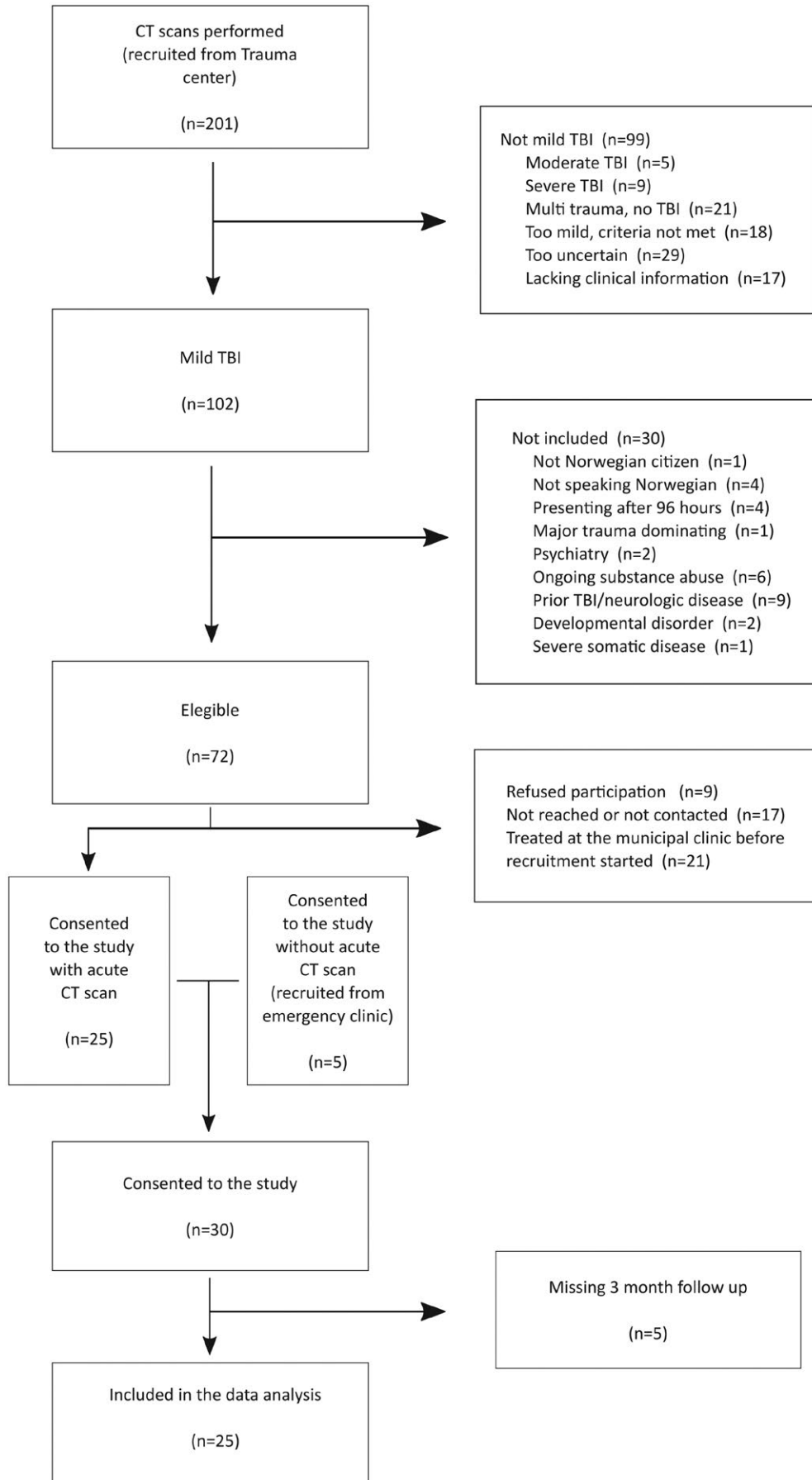


FIGURE 1 Flow chart of the patient evaluation process

TABLE 1 Demographic and clinical characteristics of mild TBI patients with and without PCS and healthy controls

	All mild TBI (n = 25)	PCS (n = 9)	Non-PCS (n = 16)	HC (n = 22)	p-value	
					Mild TBI vs. HC	PCS vs. Non-PCS
Age (years, mean ± SD)	32.7 ± 13.0	25.0 ± 10.0	37.0 ± 12.8	34.5 ± 8.7	0.574	0.017
Education (years, mean ± SD)	14.9 ± 3.1	12.6 ± 1.4	16.2 ± 3.0	15.7 ± 2.2	0.303	<0.001
Sex (n male)	12	5	7	10	0.861	0.571
Injury mechanism (n)						
Fall	12	4	8			
Traffic accidents	8	2	6			
Violence	1	1	0			
Other	4	2	2			
GCS score (n Na/13/14/15)	2/2/2/19	0/1/1/7	2/6/1/7			0.791
LOC (n yes/no/unknown)	12/5/8	4/3/2	8/2/6			
LOC duration (n)						
<5 min	8	3	5			
5–15 min	1	0	1			1.000
Unknown duration	3	1	2			
PTA (n yes/no/unknown)	24/0/1	9/0/0	15/0/1			
PTA duration (n)						
<1 hr	20	7	13			
1–23 hr	4	2	2			0.572
Unknown duration	1	0	1			
Traumatic CT findings (n)	5	1	4			
Traumatic MRI findings (n)	6	2	4			
Hospitalization (n)	18	5	13			

Abbreviations. PCS: postconcussional syndrome; HC: healthy controls; GCS: Glasgow Coma Scale; LOC: loss of consciousness; PTA: post-traumatic amnesia. *P*-values in bold indicate statistical significance.

interview and the M.I.N.I. For the mild TBI patients, the injury-related variables GCS score, duration of LOC and PTA, the external cause of injury and findings on head CT and clinical MRI (obtained at time of DKI) were gathered from medical records and patient interviews.

2.3 | Postconcussional syndrome evaluation

Three months after the injury, patients received the Rivermead Postconcussion Symptom Questionnaire (RPSQ) (King, Crawford, Wenden, Moss, & Wade, 1995) and the three last questions from the British Columbia Postconcussion Symptom Inventory (BC-PSI) (Iverson, Zasler, & Lange, 2007). On the RPSQ, respondents were asked to rate 16 symptom complaints on a 5-point scale (0 to 4), where 0 = “not experienced at all,” 1 = “no more of a problem compared with before the accident,” 2 = “a mild problem,” 3 = “a moderate problem,” and 4 = “a severe problem.” On the three last questions from BC-PSI respondents were asked questions related to changes in alcohol tolerance, worrying about symptoms, and self-perception of having a brain damage. Questions were rated on a scale from 1 to 5, where 1 = “not at all” and 5 = “very severe problem.”

2.4 | PCS case assignment

Patients were categorized into a PCS or non-PCS group 3 months after injury according to the ICD-10 research criteria for PCS (World Health Organization, 1993). ICD-10 criteria C1 (unpleasant sensations and pains), C2 (emotional changes), C3 (subjective cognitive symptoms), and C4 (insomnia) were assessed with the RPSQ (C1 = question 1–4, 6, 13–15; C2 = question 7–9, 16; C3 = question 10–12, and C4 = question 5). A given criterion was considered fulfilled if 1 or more questions within a specific domain were rated as 2 (a mild problem) or higher. The three last questions from the BC-PSI were designed to comply with criteria C5 (reduced tolerance to alcohol) and C6 (preoccupation with symptoms and fear of permanent brain damage). The criteria were considered satisfied if the question addressing them was rated 3 (“somewhat”) or higher. In accordance with ICD-10, patients exhibiting 3 or more of the criteria C1 to C6 were classified as PCS cases.

2.5 | Magnetic resonance imaging

MRI was performed on a 3T Siemens Skyra system (Siemens Healthcare, Erlangen, Germany) with a 32-channel head coil. The DKI

sequence was a single-shot balanced-echo EPI sequence acquired in 30 non-collinear directions with 3 b -values ($b = 0$, $b = 1,000$ and $2,000$ s/mm²) with the following parameters: TR 8,800 ms, TE 95 ms, FOV 240 × 240 mm, slice thickness 2.5 mm, acquisition matrix 96 × 96, giving isotropic voxels of 2.5 mm. Sixty transversal slices with no gaps were acquired, giving full brain coverage. Five images without diffusion weighting (b_0) were acquired to increase signal-to-noise ratio. To correct for image distortion, two additional b_0 images were acquired with opposite phase encoding polarity (Andersson, Skare, & Ashburner, 2003).

In addition to the DKI sequence, the scan protocol consisted of a series of clinical MRI sequences (3D T1-weighted-MPRAGE, Diffusion-weighted imaging, 3D T2 space, 3D T2-weighted FLAIR, 3D T2-weighted SWI, and T2-weighted turbo spin echo sagittal). One experienced neuroradiologist (K.A.K) and one resident in radiology (J.X.) examined the images and reported the findings by consensus based on standard neuroradiological procedures. There were no scanner upgrades in the time period for the data collection.

2.6 | Magnetic resonance imaging data processing and analysis

The fMRIB Software Library (FSL: <http://www.fmrib.ox.ac.uk/fsl>) and Diffusion Kurtosis Estimator (DKE: <http://academicdepartments.musc.edu/cbi/dki/dke.html>) were used for image analysis. Non-brain tissue was removed with the Brain Extraction Tool (BET, FSL). Artifacts due to eddy currents and movements were corrected with eddy (FSL), which simultaneously models the effects of diffusion eddy currents and movements on the image. Correction of the susceptibility-induced off-resonance field artifacts were done by topup (FSL), a tool for estimating and correcting susceptibility-induced distortions (Andersson et al., 2003). Data were collected with reversed phase-encode blips, resulting in pairs of images with distortions going in opposite directions. From these pairs, the susceptibility-induced off-resonance field was estimated using a method similar to that described in (Andersson et al., 2003) as implemented in FSL (Smith et al., 2004), and the two images were combined into a single corrected one.

DKI and DTI model fitting was performed using DKE and parametric maps were calculated for FA, mean diffusivity (MD), radial

diffusivity (RD), axial diffusivity (AD), KFA, MK, MKT, RK, and AK (Tabesh, Jensen, Ardekani, & Helpert, 2011).

Using TBSS (FSL) (Smith et al., 2006), voxel-wise statistical analysis were carried out on the skeletonized DKI and DTI maps using the Randomize algorithm (Winkler, Ridgway, Webster, Smith, & Nichols, 2014) to test for group differences. Randomize carries out permutation-based testing and inference by using threshold-free cluster enhancement with a correction for multiple comparisons (Nichols & Holmes, 2002). The corrected p -maps were used and statistical threshold for all the analyses was $p < 0.05$. Age and sex were included in the main design matrix.

In addition to voxel-wise comparisons, 5 WM ROIs were chosen due to their susceptibility to injury after mild TBI (Niogi & Mukherjee, 2010) and defined by the intersection of the ICBM-DTI-81 white-matter labels atlas (Mori et al., 2008) and the WM skeleton. Both the ICBM atlas and the WM skeleton were given in MNI space. The ROIs were the genu, body, and splenium of the corpus callosum and the anterior limb of internal capsule bilaterally. Additionally, 3 × 3 × 3 voxel (0.42 cm³) ROIs were drawn (R.H. K. and J.X.) on axial slices bilaterally in the thalamus on each subject's FA image. Thalami were identified by three surrounding landmarks in the axial plane; the splenium of corpus callosum, the posterior limb of internal capsule, and the cerebral midline (Figure 2). All ROIs were chosen prior to the onset of the study. For all white and gray matter ROIs, mean FA, MD, AD, RD, KFA, MK, MKT, AK, and RK were calculated with FSL.

Both in the TBSS and ROI analysis, group differences were tested for the acute mild TBI ($n = 24$) versus healthy controls at time point 1 ($n = 22$), 3-month mild TBI ($n = 23$) versus healthy controls at time point 2 ($n = 22$), acute MRI in PCS ($n = 9$) versus non-PCS ($n = 15$) and healthy controls ($n = 22$), and 3-month MRI in PCS ($n = 8$) versus non-PCS ($n = 15$) and healthy controls ($n = 22$). Pairwise comparisons were also performed between the first and second images of the controls in both the TBSS and ROI analyses.

2.7 | Statistical analysis

Differences in age and education between groups were analyzed with Welch's t tests (Moser & Stevens, 1992). Chi-squared test was used to compare the variables sex, GCS score, LOC and PTA between groups. Fisher's Exact test was used when the expected cell values were below 5. Differences in ROI derived diffusion

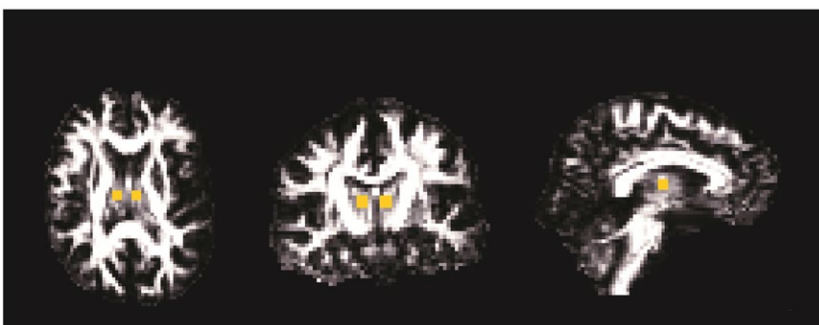


FIGURE 2 Example of placement of the thalamus ROIs in three planes and the surrounding landmarks (internal capsule, splenium of corpus callosum, and the cerebral midline) on the FA image of one mild TBI patient

metrics between patients and healthy controls were analyzed with Welch's *t* tests, which performs better than Student's *t* test when sample sizes and variances are unequal between groups. Uncorrected *p*-values ($\alpha = 0.05$), as well as *p*-values after controlling the false discovery rate (FDR) with the Benjamini-Hochberg method (Benjamini & Hochberg, 1995) were reported. Degrees of freedom was rounded to the next integer. Differences between PCS patients, non-PCS patients, and healthy controls were analyzed with Analysis of Covariance (ANCOVA) with age as covariate. Uncorrected *p*-values from the ANCOVA were reported ($\alpha = 0.05$), as well as FDR-corrected *p*-values. Uncorrected *p*-values for the group-wise comparisons (PCS vs. non-PCS, PCS vs. HC, non-PCS vs. HC) were also reported. The descriptive statistical analyses of the demographic and injury-related variables were performed in SPSS v. 22 (IBM Corp, 2013), and the analyses of the diffusion metrics in the ROIs were performed in R (R Core Team, 2015).

3 | RESULTS

3.1 | Demographic and injury-related variables

Mean age in the mild TBI group was 32.7 years, length of education was 14.9 years, and 48% were male (Table 1). There were no statistically significant differences between patients and healthy controls with regard to age, sex, or education. Fall (48%) was the most common cause of injury, followed by traffic accidents (32%). The majority of patients had a GCS score of 15 at presentation (74%). Forty-eight percent had a witnessed period of LOC, all but one below 5 min. PTA was present in 96%, and the duration was <1 hr for 83% of the patients. Head CT was performed in 88% of the patients, and demonstrated intracranial findings in five patients (23%).

Six patients had intracranial traumatic findings on MRI (frontal and temporal cerebral contusions and microhemorrhages, frontal and temporal microhemorrhages, multiple microhemorrhages in all four lobes, frontal contusion and subdural hemorrhage, subdural hemorrhage, and frontal contusion). None of the patients had microhemorrhages in the internal capsule, corpus callosum, or thalamus.

Eighteen (72%) of the patients with mild TBI were hospitalized due to: Brain CT findings ($n = 5$), motor vehicle accident ($n = 2$); living situation ($n = 4$); facial fractures ($n = 1$); unilateral pupil dilatation due to contusion of the eye ($n = 1$); mild TBI occurring during a hospital admission for orthopedic surgery ($n = 1$); and GCS score < 15 or loss of consciousness > five minutes ($n = 4$). For seven of these patients, MRI was performed while they were hospitalized. Ten patients had intravenous transfusion as part of acute care ($\leq 1,000$ ml crystalloids). For these ten patients, time from infusion to acute MRI was >20 hr for one patient, ~32 hr for one patient, and ~48 hr for eight patients.

3.2 | Diffusion metrics in WM and thalamus: Mild TBI versus healthy controls

The TBSS analyses of the acute MRI revealed lower KFA and FA and higher RD in patients compared with controls (Figure 3). Reduced

KFA and FA were detected in the following tracts: genu of corpus callosum, cerebellar peduncle, internal capsule, corona radiata, and superior fronto-occipital fasciculus. Additionally, the mild TBI group had lower FA in the external capsule and stria terminalis. There was a substantial voxel-wise overlap between KFA and FA in the acute phase (#vox 1449), but FA was lower in a larger number of voxels (#vox 5020) compared with KFA (#vox 3104). Higher RD was only evident in the right anterior corona radiata. No significant differences were found in MD or in any of the other DTI or DKI metrics. On the 3-month MRI, patients had lower KFA (#vox 25820) and FA (#vox 25199) in the same regions as in the acute MRI, as well as several additional regions (Figure 3), including the posterior thalamic radiation bilaterally. The number of overlapping voxels with KFA and FA reductions was still substantial (#vox 14146). No significant differences were seen in any of the other DTI or DKI metrics at 3 months.

With regard to the ROI analyses, alterations were seen for both DKI and DTI metrics in the acute phase and 3 months after injury, but the effects were not statistically significant after FDR correction (Table 2).

The pairwise comparisons did not reveal any statistically significant differences in the diffusion metrics between the two time points in the control subjects for both the TBSS and the ROI analyses.

3.3 | Postconcussional syndrome

Nine out of 25 patients (36%) met the criteria for PCS 3 months after injury. PCS patients were significantly younger ($p = 0.017$) and less educated ($p = 0.0005$) than non-PCS patients (Table 1). Otherwise, no significant differences were found.

3.4 | Diffusion metrics in WM and thalamus: PCS, non-PCS, and healthy controls

The TBSS analyses of the acute and 3-month MRI did not reveal any statistically significant differences in DKI or DTI metrics between PCS and non-PCS patients.

Table 3 presents the means and standard deviations of the ROI-derived diffusion metrics for PCS patients, non-PCS patients, and healthy controls. Unadjusted means are presented, since age effects were not statistically significant in any of the ANCOVAs. Statistically significant group effects before FDR correction are presented together with *p*-values after correction. There were no group differences in any of the DKI or DTI metrics on the acute MRI after correction.

Three months after injury, that is, concurrent with symptom assessment, differences were found for several DKI/DTI metrics with near statistically significant corrected *p*-values from the ANCOVA. For RK and MK in the internal capsule and thalamus, as well as for MKT and AK in the thalamus, group-wise comparisons demonstrated lower values in PCS patients compared with non-PCS patients, as well as when compared with healthy controls. PCS patients had lower FA in the internal capsule and lower MKT in the internal

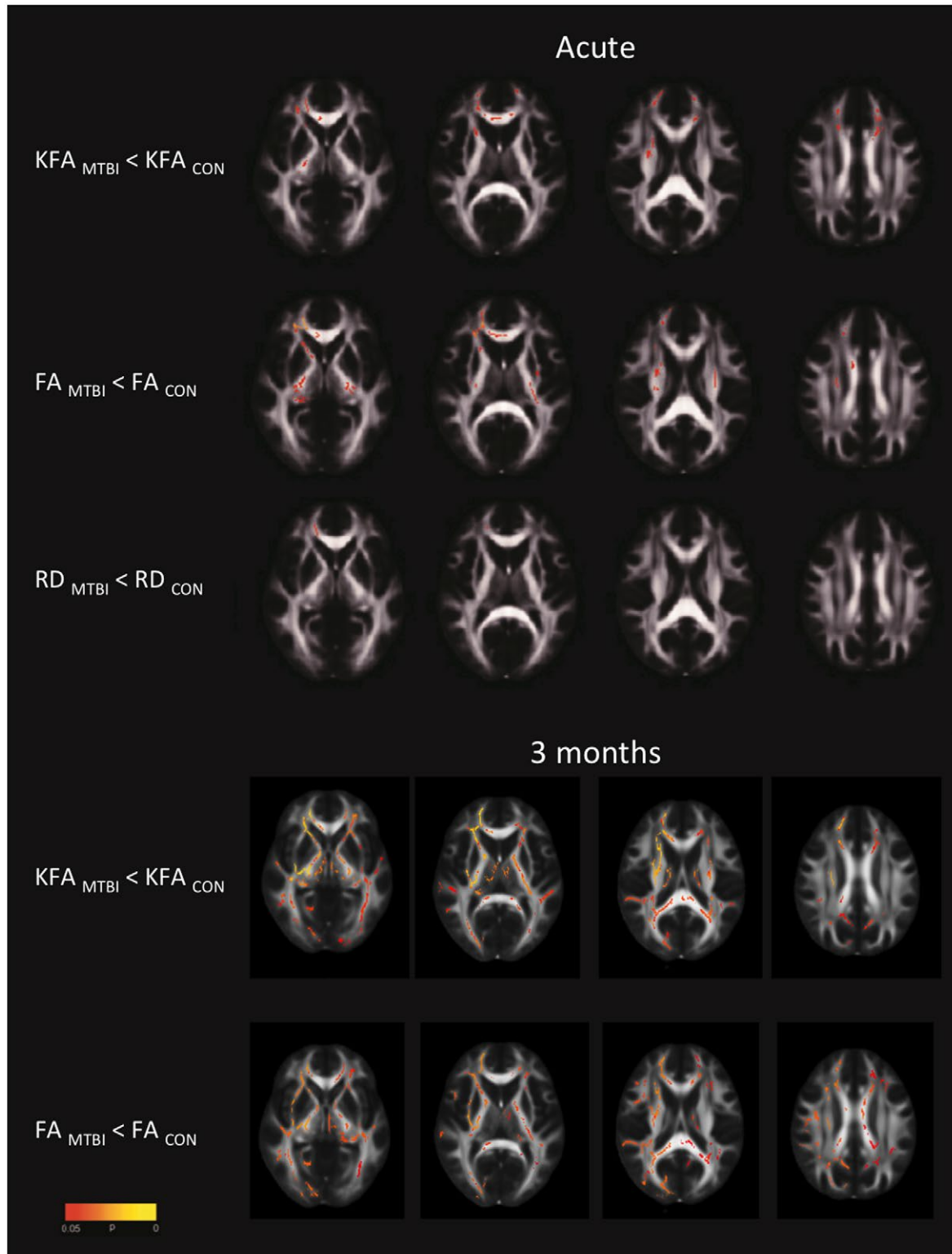


FIGURE 3 TBSS analyses comparing mild TBI (MTBI) patients and healthy controls (HC) corrected for differences in sex and age. Threshold-free cluster enhancement was used to correct for multiple comparisons and the statistical threshold for all the analyses was set to $p < 0.05$. Statistically significant differences in KFA, FA, and RD between patients and healthy controls were found on the acute MRI, while differences in KFA and FA were found on the 3-month MRI.

TABLE 2 Summary data with uncorrected and corrected *p*-values for selected ROIs and diffusion metrics: Healthy controls and patients with mild TBI

	HC			MTBI			t (df)	Uncorr.	P-FDR		
	N	Mean	SD	N	Mean	SD					
Acute	FA	Int. Cap. R	22	0.533	0.019	24	0.519	0.019	2.39 (43)	0.021	0.332
	FA	CC Splenium	22	0.708	0.023	24	0.693	0.023	2.20 (44)	0.033	0.352
	MK	Int. Cap. L	22	1.229	0.042	24	1.203	0.045	2.08 (44)	0.044	0.352
	KFA	CC Genu	22	0.548	0.021	24	0.534	0.026	2.04 (43)	0.047	0.352
	RK	Int. Cap. L	22	1.935	0.084	24	1.865	0.079	2.92 (43)	0.006	0.329
	RK	Thalamus R	22	1.176	0.054	24	1.124	0.077	2.68 (41)	0.010	0.329
	RK	Int. Cap. R	22	2.013	0.079	24	1.955	0.085	2.40 (44)	0.021	0.332
3-month	FA	Int. Cap. R	22	0.533	0.024	23	0.518	0.018	2.23 (39)	0.031	0.350
	KFA	Thalamus L	22	0.333	0.034	23	0.312	0.034	2.09 (43)	0.043	0.350
	KFA	CC Splenium	22	0.561	0.023	23	0.547	0.022	2.14 (42)	0.038	0.350
	AK	Thalamus L	22	0.817	0.062	23	0.780	0.053	2.12 (41)	0.040	0.350
	AK	Thalamus R	22	0.806	0.054	23	0.772	0.046	2.27 (41)	0.029	0.350
	RK	Int. Cap. L	22	1.919	0.091	23	1.863	0.077	2.21 (41)	0.033	0.350

Abbreviations: HC: healthy controls; MTBI: patients with mild traumatic brain injury; SD: standard deviation; t (df): t statistics (degrees of freedom); P-FDR: *p*-values corrected for false discovery rate with the Benjamini-Hochberg procedure; RK: radial kurtosis; FA: fractional anisotropy; MK: mean kurtosis; KFA: kurtosis fractional anisotropy; CC: corpus callosum; Int. Cap.: anterior limb of the internal capsule. *P*-values in bold indicate statistical significance.

TABLE 3 Summary data with uncorrected and corrected *p*-values for selected ROIs and diffusion metrics: Healthy controls, non-PCS patients, and PCS patients

	HC		PCS-		PCS+		<i>p</i> -values						
	Mean	SD	Mean	SD	Mean	SD	Uncorr. P-ANCOVA	P-FDR	Uncorr. PCS vs. non-PCS	Uncorr. PCS vs. HC	Uncorr. non-PCS vs. HC		
							<i>F</i> (<i>df1</i> , <i>df2</i>)						
Acute	KFA	0.548	0.021	0.525	0.027	0.548	0.017	4.98 (2,44)	0.011	0.360	0.022	0.997	0.005
	MK	1.229	0.042	1.212	0.047	1.187	0.038	3.23 (2,44)	0.050	0.522	0.160	0.016	0.248
	RK	1.176	0.054	1.133	0.088	0.110	0.055	3.92 (2,44)	0.028	0.522	0.412	0.016	0.060
	RK	2.013	0.079	1.971	0.080	1.929	0.093	3.54 (2,44)	0.038	0.522	0.232	0.013	0.130
	RK	1.935	0.084	1.883	0.077	1.834	0.077	5.29 (2,44)	0.009	0.360	0.158	0.003	0.060
3-month	FA	0.533	0.024	0.524	0.019	0.509	0.012	3.83 (2,44)	0.030	0.171	0.114	0.008	0.199
	MK	1.223	0.004	1.213	0.052	1.169	0.024	6.12 (2,44)	0.005	0.083	0.018	0.003	0.463
	MK	1.229	0.033	1.227	0.051	1.182	0.029	5.34 (2,44)	0.009	0.083	0.013	0.006	0.868
	MK	0.992	0.049	0.981	0.066	0.925	0.025	5.04 (2,44)	0.011	0.087	0.019	0.004	0.534
	MK	0.998	0.038	0.998	0.041	0.954	0.026	4.65 (2,44)	0.015	0.106	0.011	0.007	0.999
	MKT	1.112	0.029	1.105	0.046	1.075	0.027	3.70 (2,44)	0.033	0.175	0.059	0.016	0.586
	MKT	1.094	0.031	1.091	0.042	1.062	0.027	3.24 (2,44)	0.049	0.229	0.063	0.027	0.751
	MKT	0.978	0.049	0.966	0.064	0.910	0.022	5.35 (2,44)	0.009	0.083	0.018	0.003	0.468
	MKT	0.981	0.040	0.977	0.041	0.936	0.027	4.22 (2,44)	0.022	0.136	0.021	0.008	0.769
	AK	0.817	0.062	0.800	0.052	0.743	0.034	5.27 (2,44)	0.009	0.083	0.022	0.002	0.367
	RK	1.919	0.091	1.891	0.080	1.811	0.035	5.56 (2,44)	0.007	0.083	0.029	0.002	0.304
	RK	2.013	0.086	2.005	0.087	1.902	0.059	5.72 (2,44)	0.006	0.083	0.007	0.002	0.791
	RK	1.158	0.045	1.169	0.049	1.107	0.030	5.42 (2,44)	0.008	0.083	0.003	0.008	0.470

Note. Summary data and *p*-values for healthy controls (*n* = 22); non-PCS patients (*n* = 15); PCS patients acute MRI (*n* = 9); PCS patients 3-month MRI (*n* = 8); *p*-values < 0.05 are presented in boldface. Abbreviations: HC: healthy controls; *F*: *F*-statistics; *df*: degrees of freedom; P-FDR: *p*-value corrected for false discovery rate with the Benjamini-Hochberg procedure; RK: radial kurtosis; KFA: kurtosis fractional anisotropy; MK: mean kurtosis; FA: fractional anisotropy; MKT: mean kurtosis tensor; AK: axial kurtosis; CC: corpus callosum; Int. Cap.: anterior limb of the internal capsule. *P*-values in bold indicate statistical significance.

capsule compared with healthy controls, but for the latter metrics, no differences were seen when comparing PCS and non-PCS patients. No differences in any metrics were seen when comparing non-PCS patients and healthy controls at 3 months.

4 | DISCUSSION

This study demonstrated DKI and DTI alterations in WM in the acute stage and 3 months after mild TBI. No association was found between the DKI and DTI metrics in the acute stage and later development of PCS, while several DKI metrics obtained in WM and thalamus concurrently with symptom assessment (i.e., 3 months after injury) were different in patients with PCS compared with patients without PCS and to healthy controls.

In our study, both DKI and DTI alterations were demonstrated in WM on the acute and 3-month MRI. However, the pattern of altered voxels seen between time points in TBSS analyses suggests that DKI should be regarded as complementary to DTI rather than redundant metrics of diffusion anisotropy (Glenn et al., 2015; Steven et al., 2014). The newly proposed DKI metric KFA appeared particularly sensitive in depicting WM microstructural changes 3 months after mild TBI, probably due to its dependence only on the kurtosis tensor, which is considered to better reflect diffusion in biological tissues compared with the diffusion tensor (Hansen & Jespersen, 2016).

The reductions in FA probably indicates changes in WM integrity and axonal damage (Basser, 1995), while the relationship between the DKI metrics and the pathophysiological damage in mild TBI patients is poorly understood. There are however evidence that gives us reason to believe that DKI is more sensitive to changes in areas of more complex tissue microstructure compared with DTI. Studies supporting this view have demonstrated that MK and RK strongly correlated with neurite density in the caudate putamen in mice, while FA was only found to correlate moderately, indicating that DKI is more sensitive to changes in areas of complex WM microstructure such as areas with crossing fibers (Irie et al., 2017). Other studies have shown that MK could reflect neuronal shrinkage (Wu & Cheung, 2010), changes in axonal and myelin density (Fieremans, Jensen, & Helpert, 2011) and astrogliosis (Zhuo et al., 2012). However, KFA is a novel technique, and further research is needed in order to validate the microstructural correlates for KFA.

In contrast to previous research where correction for multiple comparisons was performed (Grossman et al., 2012, 2013), we did not find statistically significant differences in the DKI metrics in the thalamus when comparing all patients with mild TBI and healthy controls. Another, more recent study (without corrections for multiple comparisons) found changes of MKT in the thalamus at 2 weeks after injury which were normalized after 3 months (Naess-Schmidt et al., 2017). These alterations were characterized by *higher* MKT, in contrast to the previously mentioned studies where lower MK was found, after a less uniform timespan. Seemingly, most of the patients in the studies of Grossman et al. were symptomatic at the time they were examined, so the studies may not be fully comparable to our study or to the study of Naess-Schmidt et al., which did not indicate

an evolution of microstructural changes in the thalamus over time after mild TBI.

On the 3-month MRI, we found a notable trend toward lower DKI metrics, MK and RK in the internal capsule in patients with PCS when compared with those without PCS and healthy controls. For the DTI metrics, a similar trend was found, with lower FA in the internal capsule in PCS patients compared with healthy controls. Several previous studies have investigated the association between DTI and PCS, and our finding of lower FA is in line with some of these (Bouix et al., 2013; Dean et al., 2015; Fakhran & Alhilali, 2014; Messe et al., 2011; Niogi, Mukherjee, Ghajar, Johnson, Kolster, Sarkar et al., 2008; Niogi, Mukherjee, Ghajar, Johnson, Kolster, Lee et al., 2008; Smits et al., 2011; Yuh et al., 2014). In contrast, other studies have failed to demonstrate a relationship between DTI and PCS when comparing patients with and without postconcussional symptoms (Lange et al., 2015; Waljas et al., 2014).

Moreover, we found a tendency toward lower RK and MK in the thalamus, in PCS patients compared with non-PCS patients and healthy controls on the 3-month MRI. In previous studies (Grossman et al., 2012, 2013), lower MK has been found in the thalamus in the mild TBI group with cognitive deficits compared with patients without deficits. Although the association between measures of cognition and self-reported symptoms (PCS) is unclear, we believe that our results support these previous findings. Another recent study, on the other hand, did not find any association between MKT in the thalamus and postconcussional symptoms (Naess-Schmidt et al., 2018). With regard to the DTI metrics, the differences were limited to FA in the internal capsule, hence suggesting that DKI may be better suited to detect alterations associated with ongoing PCS. There is a growing body of research pointing toward the special role of the thalamus in relation to outcome after mild TBI (Grossman & Inglesse, 2016). Given the extensive reciprocal connectivity between thalamus and the cerebral cortex, our findings of reduced tissue complexity in thalamus could help explain the globalized nature of PCS symptoms. Furthermore, there is evidence of thalamo-cortical involvement in headache (Kuner, 2010), sleep disturbances (Saper, Scammell, & Lu, 2005), and fatigue (McCormick, 1999), symptoms commonly reported after mild TBI (Carroll et al., 2014). Given these findings, further outcome research focusing on the thalamus after mild TBI, especially in relation to PCS is warranted (Grossman & Inglesse, 2016).

The abnormalities that appeared concurrently with symptom assessment in patients with PCS, were not present in the acute MRI. Hence, these may be evolving during the persistence of symptoms in these patients. Given the lack of meaningful differences in the acute phase between patients with and without PCS, we found no support for a role of early DKI or DTI metrics as predictive markers for postconcussion symptoms after mild TBI.

4.1 | Strengths and limitations

A particular strength of this study is that MRI was performed both very early, and also concurrent with the outcome assessment, with uniform intervals between the examinations.

Moreover, there was almost no loss to follow-up for the second evaluation. Furthermore, in order to increase the sensitivity to detect microstructural alterations after mild TBI, this study combined the use of voxel-wise and ROI-based analyses. However, there are several limitations of this study, of which the small sample size is the most important. A small study is particularly vulnerable to variability in the data that are not accounted for, for instance due to inevitable fluctuations on the MR scanner with time, and consequently on the diffusion metrics, which could have a large impact on the results. First, we applied a large number of regions of interests and a large number of metrics from both DTI and DKI in order to explore these for the benefit of future larger studies. The large number of comparisons increased the probability of making type I errors, while the correction we made, increased the risk of type II errors in the DKI and DTI analyses in this study with a relatively small sample size. The results from the ROI-based analyses should therefore be viewed as exploratory and interpreted with caution. Second, we included also patients with visible lesions in the head CT or the clinical MRI examination. Due to the limited sample size, we were not able to study this group separately. Future larger studies should investigate the significance of such macroscopic damage to brain tissue further. Importantly, though, none of these lesions were located in the chosen ROIs. Three patients had microhemorrhages visible on SWI. This may have influenced the diffusion parameters due to the distortion effects of iron from the microhemorrhages (Moen et al., 2016). Again, the small number of patients with microhemorrhages made the comparison of patients with and without microhemorrhages infeasible. Finally, the patients with PCS were younger than the patients without PCS. Adjusting for age may not be fully compensating for this unfortunate imbalance in age when comparing these two groups. We believe, however, that the risk of drawing erroneous conclusions would have been larger if the PCS group had been the older one.

4.2 | Conclusion

The combined use of DKI and DTI may facilitate the detection of microstructural changes in WM following mild TBI in the acute and subacute phase. With regard to PCS, we found no evidence for a predictive value of early DKI or DTI, but a notable trend toward alterations in the DKI metrics in WM and thalamus in the 3-month MRI in patients with ongoing PCS. Our findings suggest that DKI may be a promising biomarker after mild TBI, and possibly help to elucidate the underlying pathophysiology of PCS.

DECLARATION OF TRANSPARENCY

The authors, reviewers, and editors affirm that in accordance to the policies set by the Journal of Neuroscience Research, this manuscript presents an accurate and transparent account of the study being reported and that all critical details describing the methods and results are present.

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CONFLICT OF INTEREST

The authors have no conflicts of interest to declare.

AUTHOR CONTRIBUTIONS

All authors had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. *Conceptualization*, R.H.K., A.K.H., A.V., T.S., and L.E.; *Methodology*, R.H.K. and L.E.; *Investigation*, R.H.K., C.E., H.K.M., A.K.H., T.S., and L.E.; *Formal Analysis*, R.H.K. and L.E.; *Resources*, R.H.K., C.E., H.K.M., A.K.H., T.S., and L.E.; *Writing—Original Draft*, R.H.K., C.E., T.S., and L.E.; *Writing—Review and Editing*, R.H.K., C.E., H.K.M., A.K.H., A.V., T.S., and L.E.; *Visualization*, R.H.K. and L.E.; *Supervision*, T.S. and L.E.; *Funding Acquisition*, T.S., A.K.H., A.V., and L.E.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Transparent Science Questionnaire for Authors.

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