Magnetic resonance imaging markers reflect cognitive outcome after rehabilitation in children with acquired brain injury

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Abstract: PURPOSE To test markers from conventional and diffusion Magnetic Resonance Imaging (MRI) as possible predictors of cognitive outcome following rehabilitation therapy in children with acquired brain injury (ABI). METHODS Twenty-one children (10 boys, mean age 11.6 years, range 7.1-19.4) with stroke or traumatic brain injury underwent MRI including Diffusion Tensor Imaging (DTI) before admission to the rehabilitation centre. The conventional images were scored according to a standardised injury scoring system, and mean Fractional Anisotropy (FA) was determined within the Corpus Callosum (CC), as this structure is hypothesised to play an important role in cognition. Both conventional MRI injury scores and mean FA of the CC and its sub-regions were compared with standard functional cognitive outcome scores. Relationships between MRI indices and cognitive outcome scores were assessed using multiple regression and receiver operating characteristic (ROC) analyses. RESULTS A backwards regression analysis revealed that the mean FA of the CC body and genu and the supratentorial injury score appear to represent the best predictors of outcome, together with the age at rehabilitation and time in rehabilitation. In the ROC analysis, the mean FA values of the CC body and genu and the infratentorial injury score provided the highest sensitivity, while the mean FA of the CC splenium showed the highest specificity for outcome. CONCLUSIONS The conventional MRI injury scores and DTI metrics from the CC reflect cognitive outcomes following rehabilitation. Neuroimaging methods such as MRI with DTI may therefore provide important markers for cognitive recovery after brain injury.

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Magnetic resonance imaging markers reflect cognitive outcome after rehabilitation in children with acquired brain injury

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ABSTRACT

Purpose: To test markers from conventional and diffusion Magnetic Resonance Imaging (MRI) as possible predictors of cognitive outcome following rehabilitation therapy in children with acquired brain injury (ABI).
Methods: Twenty-one children (10 boys, mean age 11.6 years, range 7.1–19.4) with stroke or traumatic brain injury underwent MRI including Diffusion Tensor Imaging (DTI) before admission to the rehabilitation centre. The conventional images were scored according to a standardised injury scoring system, and mean Fractional Anisotropy (FA) was determined within the Corpus Callosum (CC), as this structure is hypothesised to play an important role in cognition. Both conventional MRI injury scores and mean FA of the CC and its sub-regions were compared with standard functional cognitive outcome scores. Relationships between MRI indices and cognitive outcome scores were assessed using multiple regression and receiver operating characteristic (ROC) analyses.
Results: A backwards regression analysis revealed that the mean FA of the CC body and genu and the supratentorial injury score appear to represent the best predictors of outcome, together with the age at rehabilitation and time in rehabilitation. In the ROC analysis, the mean FA values of the CC body and genu and the infratentorial injury score provided the highest sensitivity, while the mean FA of the CC splenium showed the highest specificity for outcome.
Conclusions: The conventional MRI injury scores and DTI metrics from the CC reflect cognitive outcomes following rehabilitation. Neuroimaging methods such as MRI with DTI may therefore provide important markers for cognitive recovery after brain injury.

1. Introduction

Acquired brain injury (ABI), such as traumatic brain injury (TBI) or stroke, can cause a broad spectrum of cognitive dysfunctions, including problems with memory, learning, perception, and executive functions (working memory, attention, cognitive inhibition, problem solving [1]). The injury can produce a disruption in various brain networks, and the lesion characteristics, including type and extent of injury, play an important role in the recovery of cognitive function. Outcome is also affected by the combination of therapies performed, and in children and adolescents, the developmental stage additionally affects the course of recovery, resulting in a high variability in outcome following rehabilitation therapy. There is therefore a need to optimize individual therapies by exploiting cerebral plasticity and recovery mechanisms [2,3]

Neuroimaging methods, such as magnetic resonance imaging (MRI), are frequently used for the diagnosis and assessment of the extent of injury following stroke or TBI. Within the acute stroke setting, standardised neuroradiological scoring systems like the Alberta Stroke Program Early Computed Tomography Score (ASPECTS) for the assessment of early computed tomography (CT) images, help to predict the functional outcome [4]. However, while MRI offers higher sensitivity relative to CT for detecting minor strokes [5] or white matter (WM) injury in patients with TBI [6], only a few studies have assessed the accuracy of standardised MR injury scoring for the prediction of cognitive outcome following ABI, particularly in children [7].

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Advanced MRI techniques, such as diffusion tensor imaging (DTI), have been shown to provide useful tools for detecting areas of axonal remodelling associated with WM reorganisation, as well as areas of injury [8,9]. To identify predictors for cognitive impairment, tractography analyses have largely focused on microstructural changes within the Corpus Callosum (CC), as changes within the CC have been related to impairment of cognitive functions [10,11]. In children, abnormal callosal development can lead to deficits in functional connectivity that are related to impairments in specific cognitive domains, showing that the CC plays an important role in the development of cognition [12].

Previous studies have identified DTI markers as possible predictors for motor [13–16] and cognitive outcomes [11,17,18] following ABI [19]. Nevertheless, few studies have combined DTI markers with injury scores from conventional MRI, and to date no studies have examined the link between conventional MRI and DTI indices, and cognitive outcomes after therapy within the paediatric population. Since children and adolescents have a higher risk for ABI (particularly TBI [20]), possibly resulting in a disruption of cognitive development at an early age [21], predictors of cognitive outcome after rehabilitation would provide a necessary first step towards the optimisation of tailored therapies aiming to improve cognitive outcomes.

In this study, we aim to test a set of markers from MRI that could serve as predictors of cognitive outcome following rehabilitation therapy in children and adolescents with ABI. Based on the neurophysiology of the CC [11], we hypothesised that the fractional anisotropy (FA) of the CC will correlate positively with cognitive outcome scores. Further, we expected that MR injury scores will correlate inversely with outcome scores.

2. Materials and methods

2.1. Patient recruitment

Data from 21 children with ABI treated at the University Children's Hospital Zurich were used in this study (including a subset previously reported by Ressel et al., [13,23]). Inclusion criteria for this retrospective study were: (1) stroke or TBI, (2) 3 T MRI and DTI data from the scanner at the University Children's Hospital Zurich, (3) MRI and DTI before admission to the rehabilitation centre, (4) availability of functional outcome (Functional Independence Measure for Children or WeeFIM) and neuropsychological test scores from the rehabilitation centre of the University Children's Hospital Zurich, (5) age over 7 years (due to the cognitive development), (6) written consent from the parents and, if older than 14 years, from patients. Ethical approval was obtained from the ethical committee of the canton of Zurich. Patient and MRI characteristics are given in Table 1.

2.2. Magnetic resonance imaging

Structural MRI measurements were performed with a 3 T scanner (Signa HD.xt/MR750, General Electric Healthcare, Milwaukee, WI, USA). The clinical MRI protocol included anatomical axial T1-weighted (repetition time = 600 ms, echo time = 18 ms, slice thickness = 4 mm, voxel resolution = 1 × 1 × 4 mm) and T2 weighted fast spin-echo images in 3 planes (repetition time = 5000 − 6000 ms, echo time = 112 ms, slice thickness = 3 mm, voxel resolution = 0.5 × 0.5 × 3 mm), coronal FLAIR images (repetition time = 9000 ms, echo time = 120 ms, slice thickness 4 mm, voxel resolution = 0.6 × 0.9 × 4 mm), as well as DTI data collected with a pulsed gradient-spin-echo sequence with an echo planar imaging (EPI) readout (field-of-view, 240 mm, TR 6000 ms, mean TE 89.5 ms (range 76.5–98.4 ms), slice thickness 3 mm, acquisition matrix 128 × 128, reconstructed matrix size 256 × 256, reconstructed voxel resolution 0.94 × 0.94 × 3 mm^3). Seven patients were scanned with a DTI protocol incorporating 21 gradient directions, while 14 patients were imaged with a 35 gradient direction protocol (see Table 1).

As described in detail by Ressel et al. [23], data analysis was performed using the FMRIB Software Library (FSL, Oxford, UK; Smith et al. [24,25]). The FSL processing pipeline included masking of the DTI images with the Brain Extraction Tool (BET), correcting for eddy current artefacts with eddy-correct, and fitting a diffusion tensor model at each voxel with DTIFIT. The FA maps for each patient were then normalised to Montreal Neurological Institute (MNI) space. The CC and its substructures (Genu [GCC], Body [BCC], Splenium [SCC]) were selected as regions of interest, which are hypothesised to play an important role in cognition [12]. Tract selection was achieved using the Johns Hopkins University white-matter template (see Fig. 1), and data from the mean FA of the CC, GCC, BCC, and SCC were exported for further statistical analysis.

2.3. Radiological scoring

A neuroradiologist with 2 years of experience scored the brain injuries from structural MRI measurements, using the standardised scoring system described by Shiran et al. [26]. This scoring system for supratentorial lesions includes the following 4 domains: the number of affected lobes, volume and type of WM injury, grey matter damage, and major WM tract injury. Each domain (excluding WM volume loss) has a dichotomous score with 0 indicating that the structure appears normal and 1 indicating the presence of a lesion. WM volume loss was assessed by measuring the width of the WM on each side of the brain (see Fig. 2 for an example), and comparing the affected side with the unaffected side. A score of 0 is assigned for no volume loss, 1 for a mild (less than 40 %) loss in volume, 2 for a moderate (40–60 %), and 3 for a severe (greater than 60 %) decrease of volume. Shiran et al. [26] performed at least 3 measurements, which they averaged. In our study we performed 6 measurements in 10 cases, 5 measurements in 3 cases, 4 measurements in 2 cases, and 3 measurements in 6 cases.

A separate dichotomous score was performed for infratentorial lesions. In this score, 0 points represents a normal structure and 1 point was assigned for lesions in the following structures: pons, midbrain, medulla oblongata, each cerebellar hemisphere, and vermis.

An additional score for the CC and its subregions (GCC, BCC, and SCC) was also assigned and consisted of a dichotomous score for each subregion with 0 points representing a normal appearance and 1 point for any pathology within this structure.

2.4. Rehabilitation strategies and outcome measures

All patients underwent a multimodal rehabilitation therapy program including amongst others physiotherapy and occupational therapy. In addition, 17 patients received neuropsychology to improve cognitive functioning, 16 patients received speech and language therapy, and 12 patients participated in one-to-one or group sports therapy. All patients attended school during their time in the rehabilitation centre.

To assess the motor and cognitive outcome of the patients, professional caregivers and nurses assessed the Functional Independence Measured for children (WeeFIM) routinely for all patients [27]. The WeeFIM contains 18 items covering the subscales self-care, mobility, and cognition, which can be assessed by observing a child's daily life performance and scored according to criterion standards. For this study, we focused on the cognition subscale with 5 items (comprehension, expression, social interaction, problem solving and memory; Fig. 3). Furthermore, we were particularly interested in the WeeFIM memory item, because it incorporates aspects of both episodic memory (i.e. the ability to remember past events) and prospective memory (i.e. the ability to remember to carry out intended actions), which is relevant for many daily life activities.

The German version of the Wechsler Intelligence Scale for Children (WISC-IV [22]) was also administered during the patients' stay in the rehabilitation centre or, in N = 3 cases, after discharge from the

Table 1
Patient and MRI characteristics.

	Patient characteristics			MRI Characteristics	
Patient number	Gender	Age at rehabilitation (years)	Time in rehabilitation (days)	DTI protocol	Time after injury (days)
Stroke (n = 8)					
1	f	19.39	11	21 Dir	288
2	f	13.92	129	35 Dir	12
3	m	11.41	38	21 Dir	1
4	m	16.39	24	21 Dir	54
5	m	14.13	220	21 Dir	46
6	m	10.05	78	21 Dir	*
7	f	10.90	129	35 Dir	7
8	m	11.41	78	35 Dir	8
Average		13.45	88.38		83.50
SD		3.18	69.19		117.08
TBI (n = 13)					
1	f	10.81	50	21 Dir	50
2	f	11.92	144	21 Dir	6
3	f	9.48	118	35 Dir	4
4	f	9.27	189	35 Dir	3
5	f	7.75	135	35 Dir	92
6	f	7.15	25	35 Dir	14
7	m	10.43	175	35 Dir	86
8	m	7.60	22	35 Dir	5
9	m	13.25	365	35 Dir	81
10	m	10.19	44	35 Dir	1
11	m	10.41	106	35 Dir	144
12	f	13.28	52	35 Dir	9
13	f	15.54	105	35 Dir	2
Average		10.54	117.69		38.23
SD		2.46	92.6		47.46
Total (n = 21)					
Average		11.65	106.52		55.48
SD		3.04	83.86		81.59

Abbreviations: *Dir* directions, *DTI* Diffusion tensor imaging, *f* female, *m* male, *SD* standard deviation, *TBI* Traumatic brain injury, *perinatal stroke.

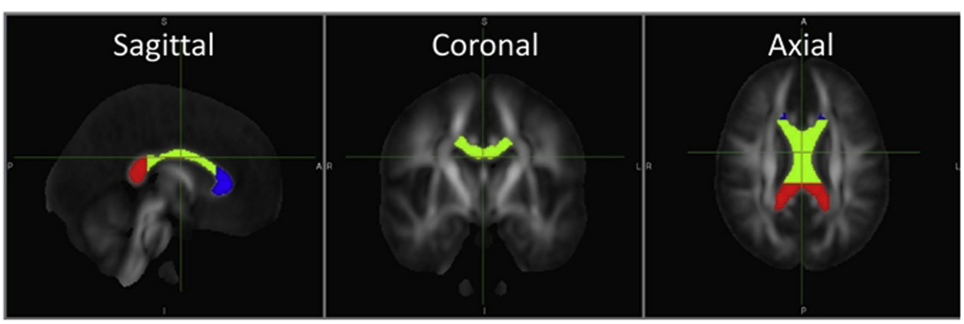

Fig. 1. Example of regions of interest used in the DTI analyses. The corpus callosum and its substructures genu (blue), body (green), splenium (red) were automatically defined from the FMRIB software library software using the Johns Hopkins University white-matter template.

rehabilitation centre by experienced neuropsychologists. It is a widely used neuropsychological test which provides information about intelligence, attention, memory, perception, language, and other higher cognitive functions. For the present study, four index scores were used: verbal comprehension, perceptual reasoning, working memory, and processing speed.

2.5. Statistics

Statistical analyses were performed using SPSS (version 20, IBM Corp., Armonk, NY). To test for normality of the data, the Shapiro-Wilk test was performed.

A multiple regression model (backward method) was used to identify the best predictors of cognitive outcome from the MRI markers. The WeeFIM and WISC-IV cognitive outcomes after rehabilitation were selected as the dependent variables, while the following variables were used as the independent variables: Age at rehabilitation, time in rehabilitation, time of MRI after injury, mean FA (GCC, BCC, SCC), supratentorial injury scores (bilateral), infratentorial injury scores, CC injury scores, WM volume width (sum), WM volume loss (percentage).

The sensitivity, specificity, and area under the curve (AUC) of the DTI measures (mean FA) and MRI injury scores were calculated with a receiver operating characteristic (ROC) analysis. Patients were classified as having a good outcome if their WeeFIM cognitive scores after rehabilitation were greater than 30. A healthy 7 year old child should score the maximal score of 7 on each of the 5 items (comprehension, expression, social interaction, problem solving and memory). As scores of 6 and 7 indicate independence, a total score above 30 should indicate that the child is on average independent. The ROC analysis was performed for each of the FA measures and injury scores, as well as with a new predictor variable generated from a binary logistic regression analysis with the following FA measures and injury scores as covariates:

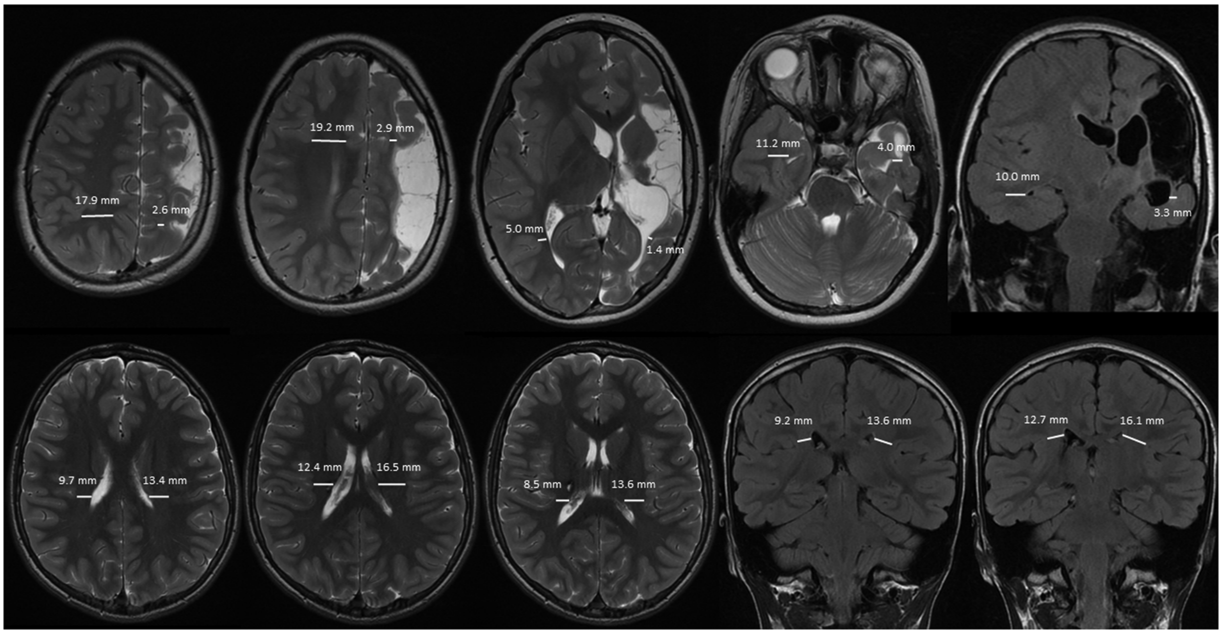

Fig. 2. Axial T2-weighted fast spin echo and coronal FLAIR images from two patients with a left MCA stroke (top) and a focal haemorrhage (bottom), to illustrate the measurements of the width of the white matter and the degree of WM loss (top panels: WM loss: 78 %, WM loss score = 3, bottom panels: WM loss = 28 %, WM loss score = 1).

mean FA (GCC, BCC, SCC), supratentorial injury scores (bilateral), infratentorial injury score, WM volume width (sum), WM volume loss (percentage).

3. Results

3.1. Patient characteristics

Patient demographics are provided in Table 1, together with details regarding the DTI protocol used for data acquisition. All patients suffered from a form of acquired brain injury, consisting of either stroke (total N = 8; ischemic stroke: N = 4 (including one perinatal stroke). haemorrhagic stroke: N = 4), or traumatic brain injury (N = 13). While all DTI data were acquired before rehabilitation, a large variability in the timing of MRI after injury was present, with 12 scans performed within 14 days after injury, and 9 performed in the chronic phase, over 40 days post-injury (see Table 1 for details). One patient had multiple strokes over a period of 9 months, in this case the time from injury to MRI was calculated from the most recent stroke (Table 1).

The mean FA values within the CC, GCC, BCC, and SCC are listed in Table 2, together with the supratentorial and infratentorial injury scores, the CC injury scores, and the degree of WM loss. The WeeFIM and WISC-IV scores obtained from each patient during their rehabilitation stay are listed in Table 3. Results from the Shapiro-Wilk test for normality of the FA values, MRI injury scores, and cognitive outcome scores are given in appendix A.

3.2. Multiple regression analyses

Multiple regression analysis for the WeeFIM cognitive outcome as the dependent variable revealed a significant model ($p = 0.001$, $R = 0.871$, adjusted $R^2 = 0.673$) in which the following variables remained in the model: Age at rehabilitation (standardised $\beta = 0.895$, $p < 0.001$), mean FA BCC (standardised $\beta = 0.631$, $p = 0.003$), mean FA GCC (standardised $\beta = -0.636$, $p = 0.002$), supratentorial (bilateral) injury scores (standardised $\beta = -0.532$, $p = 0.017$), and time in

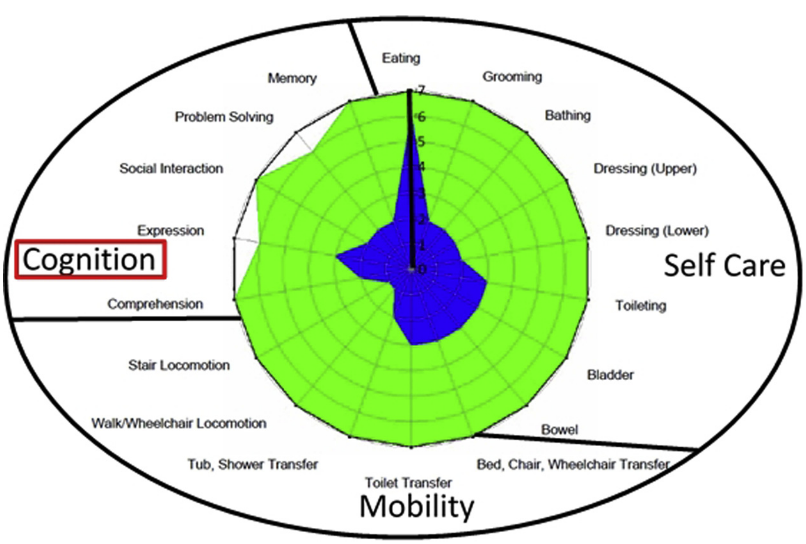

Fig. 3. Individual example of Functional Independence Measure for Children (WeeFIM) measurements at admission and discharge. The patient experienced a traumatic brain injury (male, 10 years old, 175 days between admission and discharge of Rehabilitation). Shown are WeeFIM scores for each item at admission (blue) and at discharge (green) from the rehabilitation centre. The cognition subscale used in the analyses is marked in red.

Table 2
Mean fractional anisotropy and radiological injury scores.

Patient number	Mean FA				Supratentorial injury score			Infratentorial injury score	CC Injury score	Mean WM width (mm)		WM volume loss§	
	CC	GCC	BCC	SCC	Left	Right	Bilateral			Left	Right	%	Score
Stroke (n = 8)													
1	0,44	0,40	0,49	0,46	15	0	15	0	0	23,83	32,12	30,14	1
2	0,42	0,46	0,43	0,37	6	0	6	0	1	12,93	15,20	14,93	1
3	0,51	0,47	0,52	0,55	3	5	8	4	0	10,67	10,67	0,00	0
4	0,27	0,26	0,39	0,19	11	9	20	0	3	18,37	15,60	18,84	1
5	0,46	0,43	0,44	0,50	12	0	12	0	0	13,87	13,62	24,83	1
6	0,31	0,29	0,39	0,27	18	0	18	0	0	2,70	12,65	78,66	3
7	0,40	0,35	0,38	0,47	14	0	14	0	0	10,78	15,33	29,68	1
8	0,49	0,46	0,47	0,53	4	0	4	0	0	14,64	10,50	28,28	1
Average	0,41	0,39	0,44	0,42	10,38	1,75	12,13	0,50	0,50	13,47	15,71	28,17	1,13
SD	0,08	0,08	0,05	0,13	5,48	3,41	5,72	1,41	1,07	6,14	6,93	22,75	0,83
TBI (n = 13)													
1	0,51	0,46	0,45	0,59	2	3	5	0	0	2,10	2,10	0,00	0
2	0,40	0,38	0,29	0,50	10	7	17	5	2	2,83	8,93	68,31	3
3	0,46	0,41	0,49	0,50	3	0	3	0	0	15,98	15,98	0,00	0
4	0,50	0,46	0,56	0,50	5	5	10	3	1	11,55	9,80	15,15	1
5	0,49	0,46	0,49	0,51	0	0	0	1	0	16,90	16,90	0,00	0
6	0,45	0,42	0,50	0,44	2	0	2	0	0	6,50	6,20	4,62	0
7	0,39	0,41	0,27	0,44	10	0	10	0	1	6,77	13,08	48,24	2
8	0,50	0,48	0,54	0,50	0	0	0	3	0	10,67	10,67	0,00	0
9	0,36	0,29	0,42	0,38	3	3	6	0	2	21,83	21,83	0,00	0
10	0,55	0,52	0,53	0,60	0	0	0	0	0	7,77	7,77	0,00	0
11	0,40	0,40	0,32	0,46	5	5	10	0	1	8,40	8,40	11,55	1
12	0,31	0,27	0,34	0,33	5	0	5	1	0	9,70	9,70	0,00	0
13	0,39	0,39	0,37	0,39	6	4	10	0	0	8,88	10,18	0,00	0
Average	0,44	0,41	0,43	0,47	3,92	2,08	6,00	1,00	0,54	9,45	10,62	11,37	0,54
SD	0,07	0,07	0,10	0,08	3,38	2,53	5,16	1,63	0,78	6,59	6,60	21,79	0,97
Total (n = 21)													
Average	0,43	0,40	0,43	0,45	6,38	1,95	8,33	0,81	0,52	11,24	12,88	17,77	0,76
SD	0,07	0,07	0,08	0,10	5,26	2,82	6,06	1,54	0,87	6,99	7,55	23,15	0,94

rehabilitation (standardised β = -0.371, p = 0.017).

Since the time from injury and MRI was not significant in the regression model, this model was recalculated after excluding the time from injury to MRI in the initial model (enabling the inclusion of a stroke patient with perinatal stroke), resulting in a significant model ($p < 0.001$, R = 0.901, adjusted $R^2 = 0.750$) in which the following variables remained: Age at rehabilitation (standardised β = 0.830, $p < 0.001$), mean FA BCC (standardised β = 0.623, p = 0.001), mean FA GCC (standardised β = -0.577, p = 0.001), supratentorial (bilateral) injury scores (standardised β = -0.544, p = 0.004), and time in rehabilitation (standardised β = -0.314, p = 0.016).

Multiple regression analysis for the WISC scores as the dependent variable revealed a trend for verbal comprehension (p = 0.055, R = 0.719, adjusted $R^2 = 0.373$) in which the following variables remained in the model: Supratentorial (bilateral) injury scores (standardised β = -0.911, p = 0.021), WM volume loss percentage (standardised β = 0.759, p = 0.046), and time of MRI after injury (standardised β = -0.500, p = 0.049).

Multiple regression analysis for the WISC working memory scores as the dependent variable revealed a significant model ($p < 0.001$, R = 0.991, adjusted $R^2 = 0.961$) in which the following variables remained in the model: Time of MRI after injury (standardised β = -0.850, $p < 0.001$), supratentorial (bilateral) injury scores (standardised β = -0.778, $p < 0.001$), WM volume loss percentage (standardised β = 1.394, $p < 0.001$), mean FA SCC (standardised β = -0.604, p = 0.001), mean FA GCC (standardised β = 0.522, p = 0.001), infratentorial injury scores (standardised β = -0.286, p = 0.007), and CC injury scores (standardised β = -0.297, p = 0.011).

Multiple regression analysis for the WISC processing speed scores as the dependent variable revealed a significant model (p = 0.009, R = 0.780, adjusted $R^2 = 0.530$). The following variables remained in the model: Age at rehabilitation (standardised β = 0.717, p = 0.005) and time in rehabilitation (standardised β = -0.435, p = 0.055).

For perceptional reasoning, the model was not significant.

3.3. Receiver operating characteristic (ROC) analysis

The results of the ROC-analysis are listed in Table 4. For the predictor variable generated from a binary logistic regression analysis model of the FA measures and injury scores, both the sensitivity and specificity for outcome were 79 %, with an AUC of 0.796 for the full group, 0.917 for the stroke subgroup, and 0.750 for the TBI subgroup.

For the individual FA measures and injury scores, in the whole group (n = 21), the mean FA within the BCC and the infratentorial injury score provided the highest sensitivity, whereas the mean FA within the SCC showed the highest specificity. In the stroke subgroup, all FA measures and injury scores, apart from the percentage of WM volume loss, demonstrated high (100 %) specificity, but the percentage of WM volume loss provided the highest sensitivity for the outcome. In the TBI subgroup, the mean FA within the SCC provided the highest specificity, while the mean FA within the GCC and the infratentorial injury score provided the highest sensitivity.

4. Discussion

In the present study, we investigated the relationship between MRI indices, including injury scores from conventional MRI as well as microstructural WM changes of the CC assessed with DTI, and cognitive outcomes following ABI in children. We found that the degree of supratentorial injury and WM loss together with the FA within the CC appear to represent the best MRI-based predictors of outcome, but the age at rehabilitation and time in rehabilitation also influence cognitive recovery significantly. Specifically, patients tend to have better cognitive outcomes if they are older and spend less time in rehabilitation, but

Table 3
Functional Independence Measure for Children (WeeFIM) and Wechsler Intelligence Scale for Children (WISC-IV) scores.

	WeeFIM at discharge of rehab								WISC-IV scores					
Patient number	WeeFIM time after		Cognition	Comprehension	Expression	Social Interaction	Problem Solving	Memory	Neuropsychological test time after		Verbal comprehension	Perceptual reasoning	Working memory	Processing speed
	injury (days)	start of rehab (days)							injury (days)	start of rehab (days)				
Stroke (n = 8)														
1	850	11	35	7	7	7	7	7	–	–	–	–	–	–
2	154	129	35	7	7	7	7	7	67	42	97	108	102	103
3	779	38	33	7	7	6	6	7	–	–	–	–	–	–
4	566	24	31	6	6	7	6	6	–	–	–	–	–	–
5	271	220	31	7	5	6	6	7	124	73	83	106	80	–
6	645	78	19	5	7	2	2	3	–	–	–	–	–	–
7	144	129	25	7	6	5	4	3	81	66	77	67	90	76
8	87	78	35	7	7	7	7	7	63	54	130	119	117	103
Average	437.00	88.38	30.50	6.63	6.50	5.88	5.63	5.88	225.57	68.00	96.75	100.00	97.25	94.00
SD	307.86	69.19	5.73	0.74	0.76	1.73	1.77	1.81	320.52	23.82	23.70	22.73	15.95	15.59
TBI (n = 13)														
1	61	50	35	7	7	7	7	7	–	–	–	–	–	–
2	38	144	32	7	6	6	6	7	778	763	92	77	87	–
3	136	118	30	7	6	7	5	5	77	59	109	100	96	94
4	200	189	21	4	4	4	4	5	76	65	87	96	90	83
5	145	135	32	6	7	6	6	7	104	95	95	92	62	50
6	41	25	23	5	4	6	4	4	59	44	–	–	–	74
7	207	175	33	7	6	7	6	7	134	104	90	117	80	79
8	37	22	27	6	6	5	5	5	43	28	81	86	96	100
9	395	365	23	4	6	5	3	5	252	223	55	63	56	–
10	73	44	35	7	7	7	7	7	88	59	103	112	93	97
11	125	106	27	7	7	4	4	5	411	395	–	–	–	86
12	64	52	33	7	6	7	6	7	62	50	101	104	96	100
13	116	105	34	7	7	6	7	7	46	35	90	115	84	111
Average	126.00	117.69	29.61	6.23	6.07	5.92	5.38	6.00	182.23	160.00	90.30	96.20	84.00	87.40
SD	99.47	92.6	4.89	1.16	1.04	1.11	1.32	1.15	208.69	217.05	14.88	17.33	14.31	17.26
Total (n = 21)														
Average	244.48	106.52	29.95	6.38	6.24	5.90	5.48	5.95	197.40	132.94	92.14	97.29	87.79	88.92
SD	251.11	83.86	5.10	1.02	0.94	1.34	1.47	1.40	245.76	185.46	17.09	18.18	15.46	16.50

Abbreviations: *SD* standard deviation, *TBI* Traumatic brain injury.

Table 4
Results from the ROC analysis for the full group of all patients, and within the stroke and TBI subgroups.

Patient group	Predictors	Sensitivity	Specificity	AUC
All Patients (n = 21)				
	Mean FA SCC	0.500	1.000	0.653
	Mean FA BCC	0.857	0.429	0.592
	Mean WM width (sum)	0.429	0.857	0.577
	Mean FA GCC	0.857	0.429	0.571
	Mean FA CC	0.643	0.571	0.571
	CC injury score	0.714	0.429	0.556
	% WM Volume loss	0.500	0.714	0.551
	WM volume loss score	0.500	0.571	0.536
	Supratentorial injury score (bilateral)	0.429	0.714	0.526
	Infratentorial injury score	0.857	0.286	0.500
Stroke (n = 8)				
	Mean FA GCC	0.833	1.000	0.917
	% WM Volume loss	0.833	1.000	0.917
	Mean FA BCC	0.833	1.000	0.833
	Mean FA CC	0.833	1.000	0.833
	Mean WM width (sum)	0.667	1.000	0.833
	WM volume loss score	1.000	0.500	0.792
	Supratentorial injury score (bilateral)	0.667	1.000	0.750
	Mean FA SCC	0.500	1.000	0.667
	CC injury score	0.333	1.000	0.667
	Infratentorial injury score	0.167	1.000	0.583
TBI (n = 13)				
	Mean FA GCC	0.875	0.600	0.725
	Mean FA SCC	0.625	1.000	0.675
	CC injury score	0.750	0.600	0.663
	Mean WM width (sum)	0.750	0.600	0.625
	% WM Volume loss	0.750	0.600	0.600
	Mean FA BCC	0.625	0.600	0.550
	Infratentorial injury score	0.875	0.400	0.538
	WM injury score	0.750	0.400	0.525
	Mean FA CC	0.500	0.800	0.525
	Supratentorial injury score (bilateral)	0.625	0.600	0.500

Outcome was defined from the WeeFIM cognition outcome at discharge from rehabilitation, using a cut-off at 30 Abbreviations: *FA* Fractional anisotropy, *ROC* Receiver operating characteristic, *TBI* Traumatic brain injury, *WeeFIM* Functional Independence Measure for Children, *AUC* area under the curve, *BCC* Body Corpus Callosum, *CC* Corpus Callosum, *GCC* Genu Corpus Callosum, *SCC* Splenium Corpus Callosum, *WM* White Matter.

the latter factor is likely to reflect a lower severity of the underlying injury, or a result of a better post-injury recovery. Patients also tend to have better cognitive outcomes if they have higher FA values within the body of the CC, higher WM volumes, and lower injury scores. These results support the utility of MRI measures as predictors for cognitive outcome in patients with ABI, and highlight in particular the importance of the CC for cognitive function, thus adding to the growing body of knowledge, which describes the role of the CC in cognition.

Of the injury scores derived from the conventional MR images, infratentorial injury appears to provide the best sensitivity, but it showed a relatively low specificity for cognitive outcome within the whole group of patients, while the WM volume (assessed from measurements of the width of the WM) provided better specificity, but a lower sensitivity. Among the FA measures, mean FA within the SCC provided the highest combined sensitivity and specificity in the entire group, but due to the heterogeneity of the patient group, the optimal markers for outcome may differ between stroke and TBI subgroups. Indeed, in the stroke subgroup, the percentage of the WM volume loss appears to provide the highest combined sensitivity and specificity (together with the FA within the GCC), with an AUC of 0.92. In the TBI subgroup, mean FA within the SCC and GCC appear to provide the highest combined sensitivity and specificity, but in general the AUC values were lower. However, by combining FA measures and injury scores into a single predictor variable, sensitivity and specificity could be improved.

As mentioned in the introduction, the CC plays an important role in cognition and memory networks within the brain [18]. Degeneration of GCC and SCC are associated with an age-related decline in cognitive performance [28]. Within the CC, alterations in the GCC and BCC may underlie neurocognitive impairment in children with TBI, as a lower FA calculated over clusters including the CC was associated with lower WISC-IV-scores and poorer functional outcome. [11]. Data from the present study support this view, showing that in general, disruption of the CC due to ABI can predict cognitive outcome. However, given the multifactorial nature of brain injury and recovery following ABI, injury to structures outside the CC also appear to play an important role in the recovery of cognitive function. The injury scores from conventional MRI, particularly the supratentorial score, and degree of WM volume loss represent indices of more widespread damage to structures outside the CC, and may therefore provide an important, complementary marker for the risk of poor cognitive outcome. These injury scores are easily obtained within a clinical setting, and, together with the FA values, may provide important biomarkers enabling the development of individualised therapies to improve cognitive outcomes following ABI.

Concerning the WeeFIM, it is important to note that the subcategories included in the cognition subscale (comprehension, expression, social interaction, problem solving and memory) are used to measure the general health and functional independence of patients with just one score for each item (1 for total assistance to 7 for complete independence). Nevertheless, studies have shown significant associations between more detailed measures of neuropsychological performance and WeeFIM scores for daily cognitive functions [29]. In the present study, the apparent link between the FA in the CC, injury scores, and the cognitive and memory subcategories of the WeeFIM is supported by a link between CC FA, injury scores, and the working memory and processing speed subscales of the WISC-IV.

4.1. Limitations

Due to the retrospective nature of the present study, the sample size, the heterogeneity, and the wide range in age within the group of patients could neither be selected nor controlled. In addition, two patient subgroups were included in the analysis (namely, stroke and TBI patients), which increased the heterogeneity of the sample. A larger sample size would enable the subdivision of the sample in stroke and TBI subgroups, as well as in different age subgroups to investigate the impact of these variables on recovery with regard to brain maturation [30]. The recovery could also include regeneration and/or reorganisation of the tracts due to rehabilitation, but obviously spontaneous recovery could also play an important role [3]. The time of the MRI scan and the time of outcome assessments following rehabilitation after the injury also could not be controlled. Nevertheless, we tried to adjust for the influence of these confounders by including the variables age, time of MRI after injury, and time of functional outcome or neuropsychological tests after injury in the analyses.

The use of a multiple regression model enabled the assessment of the impact of a number of different variables (in the form of mean FA measurements, injury scores, and other demographic and clinical variables) in a single analysis for each outcome score, limiting the need for multiple statistical comparisons. However, one limitation of this method is that results can be confounded by collinearity between the independent variables. Collinearity diagnostics revealed that three of the variables which remained significant in the model between the WeeFIM score and the independent variables (specifically the FA in the BCC and GCC and the supratentorial injury score) showed condition numbers between 11 and 28, although their variance inflation factor values ranged between 1.640 and 2.080. While condition numbers above 30 are often used as a cutoff for a critical degree of collinearity, condition numbers above 10 can also be problematic [31], which may explain the negative beta value for the FA in the GCC in this model. Using the WISC-IV as the outcome variable (e.g. for working memory), the beta value for the FA within the GCC was positive (and associated with a condition number below 5), but other variables like the CC lesion score and the percentage of WM loss showed high levels of collinearity (condition numbers 26 and 38, respectively), which may explain the positive beta value for the WM loss in that analysis. Therefore, given the apparent collinearity between some variables, these results should be considered with caution until they can be replicated in a larger sample.

For the present study, only the WeeFIM and the WISC-IV scores could be used, and due to the presence of neurological deficits (e.g. aphasia), some of the subtests of the WISC-IV could not be performed in all patients. Other additional tests or assessments performed in the rehabilitation centre could not be included due to their small sample size, and the analysis did not take into account the cognitive abilities before injury, since no standardised scores for the baseline cognitive abilities were available.

A further technical limitation is that the measurements were acquired with two different DTI gradient sampling schemes (incorporating 21 and 35 directions, n = 9 and n = 16, respectively). Due to the small sample size and the retrospective nature of this study, it was not possible to perform additional subgroup analyses for the different sampling schemes. Nevertheless, previous studies have shown that FA becomes insensitive to the number of sampling directions for schemes incorporating more than 20 directions [32], and therefore, the FA derived from the two different schemes should be comparable. The supratentorial injury scoring protocol was developed for a different pediatric patient group (specifically children with cerebral palsy), and validated for motor rather than cognitive outcomes. However, for the present study this quantitative scoring system was supplemented by additional scores for the degree of injury to the corpus callosum specifically, as well as the degree of infratentorial injury. Considering these limitations, the findings of the present study should be considered as a first indication of the usefulness of MRI markers for cognitive outcome after rehabilitation in children with acquired brain injury. Larger studies are needed, with sufficient power to compare between subgroups of patients and identify the main factors governing recovery in each subgroup.

5. Conclusion

Neuroimaging methods like DTI combined with radiological scoring may provide important biomarkers for the degree in recovery of cognitive functioning after brain injury.

CRediT authorship contribution statement

Volker Ressel: Conceptualization, Methodology, Investigation, Visualization, Formal analysis, Funding acquisition, Writing - original draft. **Daphne Berati:** Investigation, Visualization, Writing - review & editing. **Carla Raselli:** Investigation, Writing - review & editing. **Karin Birrer:** Investigation, Writing - review & editing. **Raimund Kottke:** Investigation, Visualization, Writing - review & editing. **Hubertus JA van Hedel:** Conceptualization, Formal analysis, Supervision, Funding acquisition, Writing - review & editing. **Ruth O'Gorman Tuura:** Conceptualization, Methodology, Supervision, Writing - review & editing.

Declaration of Competing Interest

The authors declare that they have no conflict of interest.

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Appendix A. Tests for Normality

The Shapiro-Wilk test showed normally distributed values for mean FA values in the CC ($p = 0.488$), GCC ($p = 0.523$), BCC ($p = 0.055$), and SCC ($p = 0.127$). The Shapiro-Wilk test showed normally distributed values for bilateral supratentorial injury scores ($p = 0.352$), and mean WM width ($p = 0.169$). The Shapiro-Wilk test showed non-normally distributed values for bilateral infratentorial injury scores ($p < 0.001$), the percentage of WM loss ($p < 0.001$), the score for WM loss ($p < 0.001$), and CC scores ($p < 0.001$). The Shapiro-Wilk test showed a normal distribution of the WISC values in verbal comprehension ($p = 0.431$), perceptual reasoning ($p = 0.339$), working memory ($p = 0.506$), and processing speed ($p = 0.099$). Also, it showed a non-normal distribution of the WeeFIM values for cognition ($p = 0.008$), comprehension ($p < 0.001$), expression ($p < 0.001$), social interaction ($p = 0.001$), problem solving ($p = 0.009$), and memory ($p < 0.001$).

References

[1] T. Babikian, R. Asarnow, Neurocognitive outcomes and recovery after pediatric TBI: meta-analytic review of the literature, Neuropsychology 23 (3) (2009) 283–296.
[2] N. Takeuchi, S. Izumi, Rehabilitation with poststroke motor recovery: a review with a focus on neural plasticity, Stroke Res. Treat. 2013 (2013) 128641.
[3] R.J. Nudo, Recovery after brain injury: mechanisms and principles, Front. Hum. Neurosci. 7 (887) (2013).
[4] L.D. Alexander, J.A. Pettersen, J.J. Hopyan, D.J. Sahlas, S.E. Black, Long-term prediction of functional outcome after stroke using the Alberta Stroke Program Early Computed Tomography Score in the subacute stage, J. Stroke Cerebrovasc. Dis. 21 (8) (2012) 737–744.
[5] F. Moreau, N. Asdaghi, J. Modi, M. Goyal, S.B. Coutts, Magnetic resonance imaging versus computed tomography in transient ischemic attack and minor stroke: the more you see the more you know, Cerebrovasc. Dis. Extra 3 (1) (2013) 130–136.
[6] J.P. Coles, Imaging after brain injury, Br. J. Anaesth. 99 (1) (2007) 49–60.
[7] E.A. Wilde, E.D. Bigler, J.V. Hunter, M.A. Fearing, R.S. Scheibel, M.R. Newsome, J.L. Johnson, J. Bachevalier, X. Li, H.S. Levin, Hippocampus, amygdala, and basal ganglia morphometrics in children after moderate-to-severe traumatic brain injury, Dev. Med. Child Neurol. 49 (4) (2007) 294–299.
[8] Q. Jiang, Z.G. Zhang, M. Chopp, MRI evaluation of white matter recovery after brain injury, Stroke 41 (10 Suppl) (2010) S112–3.
[9] L.K. Sztriha, R.L. O'Gorman, M. Modo, G.J. Barker, S.C. Williams, L. Kalra, Monitoring brain repair in stroke using advanced magnetic resonance imaging, Stroke 43 (11) (2012) 3124–3131.
[10] E.L. Dennis, T. Babikian, C.C. Giza, P.M. Thompson, R.F. Asarnow, Diffusion MRI in pediatric brain injury, Childs Nerv. Syst. 33 (10) (2017) 1683–1692.
[11] M. Königs, P.J. Pouwels, L.W. Ernest van Heurn, R. Bakx, R. Jeroen Vermeulen, J. Carel Goslings, B.T. Poll-The, M. van der Wees, C.E. Catsman-Berrevoets, J. Oosterlaan, Relevance of neuroimaging for neurocognitive and behavioral outcome after pediatric traumatic brain injury, Brain Imaging Behav. 12 (1) (2018) 29–43.
[12] L.B. Hinkley, E.J. Marco, A.M. Findlay, S. Honma, R.J. Jeremy, Z. Strominger, P. Bukshpun, M. Wakahiro, W.S. Brown, L.K. Paul, A.J. Barkovich, P. Mukherjee, S.S. Nagarajan, E.H. Sherr, The role of corpus callosum development in functional connectivity and cognitive processing, PLoS One 7 (8) (2012) e39804.
[13] V. Ressel, R. O'Gorman Tuura, I. Scheer, H.J.A. van Hedel, Diffusion tensor imaging predicts motor outcome in children with acquired brain injury, Brain Imaging Behav. 11 (5) (2017) 1373–1384.
[14] C. Ma, A. Liu, Z. Li, X. Zhou, S. Zhou, Longitudinal study of diffusion tensor imaging properties of affected cortical spinal tracts in acute and chronic hemorrhagic stroke, J. Clin. Neurosci. 21 (8) (2014) 1388–1392.
[15] Y. Kusano, T. Seguchi, T. Horiuchi, Y. Kakizawa, T. Kobayashi, Y. Tanaka, K. Seguchi, K. Hongo, Prediction of functional outcome in acute cerebral hemorrhage using diffusion tensor imaging at 3 T: a prospective study, AJNR Am. J. Neuroradiol. 30 (8) (2009) 1561–1565.
[16] W. Yuan, S.K. Holland, V.J. Schmithorst, N.C. Walz, K.M. Cecil, B.V. Jones, P. Karunanayaka, L. Michaud, S.L. Wade, Diffusion tensor MR imaging reveals persistent white matter alteration after traumatic brain injury experienced during early childhood, AJNR Am. J. Neuroradiol. 28 (10) (2007) 1919–1925.
[17] M. Kinoshita, M. Nakada, H. Okita, J. Hamada, Y. Hayashi, Predictive value of

fractional anisotropy of the arcuate fasciculus for the functional recovery of language after brain tumor resection: a preliminary study, Clin. Neurol. Neurosurg. 117 (2014) 45–50.
[18] G.E. Strangman, T.M. O'Neil-Pirozzi, C. Supelana, R. Goldstein, D.I. Katz, M.B. Glenn, Fractional anisotropy helps predicts memory rehabilitation outcome after traumatic brain injury, NeuroRehabilitation 31 (3) (2012) 295–310.
[19] L.A. Boyd, K.S. Hayward, N.S. Ward, C.M. Stinear, C. Rosso, R.J. Fisher, A.R. Carter, A.P. Leff, D.A. Copland, L.M. Carey, L.G. Cohen, D.M. Basso, J.M. Maguire, S.C. Cramer, Biomarkers of stroke recovery: consensus-based core recommendations from the stroke recovery and rehabilitation roundtable, Neurorehabil. Neural Repair 31 (10-11) (2017) 864–876.
[20] P.S. Pinto, A. Poretti, A. Meoded, A. Tekes, T.A. Huisman, The unique features of traumatic brain injury in children. Review of the characteristics of the pediatric skull and brain, mechanisms of trauma, patterns of injury, complications and their imaging findings–part 1, J. Neuroimaging 22 (2) (2012) e1–e17.
[21] R.J. Forsyth, Back to the future: rehabilitation of children after brain injury, Arch. Dis. Child. 95 (7) (2010) 554–559.
[22] D. Wechsler, The Wechsler Intelligence Scale for Children—fourth Edition, Pearson, London, 2003.
[23] V. Ressel, Scheer I. van Hedel HJA, R. O'Gorman Tuura, Comparison of DTI analysis methods for clinical research: influence of pre-processing and tract selection methods, Eur Radiol Exp 2 (1) (2018) 33.
[24] S.M. Smith, M. Jenkinson, M.W. Woolrich, C.F. Beckmann, T.E. Behrens, H. Johansen-Berg, P.R. Bannister, M. De Luca, I. Drobnjak, D.E. Flitney, R.K. Niazy, J. Saunders, J. Vickers, Y. Zhang, N. De Stefano, J.M. Brady, P.M. Matthews, Advances in functional and structural MR image analysis and implementation as FSL, NeuroImage 23 (S1) (2004) S208–S219.
[25] S.M. Smith, M. Jenkinson, H. Johansen-Berg, D. Rueckert, T.E. Nichols, C.E. Mackay, K.E. Watkins, O. Ciccarelli, M.Z. Cader, P.M. Matthews, T.E. Behrens, Tract-based spatial statistics: voxelwise analysis of multi-subject diffusion data, NeuroImage 31 (2006) 1487–1505.
[26] S.I. Shiran, M. Weinstein, C. Sirota-Cohen, V. Myers, D. Ben Bashat, A. Fattal-Valevski, D. Green, M. Schertz, MRI-based radiologic scoring system for extent of brain injury in children with hemiplegia, AJNR Am. J. Neuroradiol. 35 (12) (2014) 2388–2396.
[27] M.E. Msall, K. DiGaudio, B.T. Rogers, S. LaForest, N.L. Catanzaro, J. Campbell, F. Wilczenski, L.C. Duffy, The functional independence measure for children (WeeFIM). Conceptual basis and pilot use in children with developmental disabilities, Clin. Pediatr. (Phila) 33 (7) (1994) 421–430.
[28] S.N. Lockhart, C. DeCarli, Structural imaging measures of brain aging, Neuropsychol. Rev. 24 (3) (2014) 271–289.
[29] T. McBride, Neuropsychological scores and WeeFIM cognitive ratings of children with traumatic brain injury: a brief report, Brain Inj. 29 (7-8) (2015) 951–954.
[30] T. Babikian, T. Merkley, R.C. Savage, C.C. Giza, H. Levin, Chronic aspects of pediatric traumatic brain injury: review of the literature, J. Neurotrauma 32 (23) (2015) 1849–1860.
[31] J.H. Kim, Multicollinearity and misleading statistical results, Korean J. Anesthesiol. 2019 (July 15) (2019), https://doi.org/10.4097/kja.19087.
[32] D.K. Jones, The effect of gradient sampling schemes on measures derived from diffusion tensor MRI: a Monte Carlo study, Magn. Reson. Med. 51 (4) (2004) 807–815.