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Diffusion tensor imaging of the brainstem in children with achondroplasia

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Abstract

Aim—The aims of this study were to compare, using diffusion tensor imaging (DTI) of the brainstem, microstructural integrity of the white matter in children with achondroplasia and age-matched participants and to correlate the severity of craniocervical junction (CCJ) narrowing and neurological findings with DTI scalars in children with achondroplasia. This study also aimed to assess the potential role of fibroblast growth factor receptor type 3 on white matter microstructure.

Method—Diffusion tensor imaging was performed using a 1.5T magnetic resonance scanner and balanced pairs of diffusion gradients along 20 non-collinear directions. Measurements were obtained from regions of interest, sampled in each pontine corticospinal tract (CST), medial lemniscus, and middle cerebellar peduncle, as well as in the lower brainstem and centrum semiovale, for fractional anisotropy and for mean, axial and radial diffusivity. In addition, a severity score for achondroplasia was assessed by measuring CCJ narrowing.

Result—Eight patients with achondroplasia (seven males, one female; mean age 5y 6mo, range 1y 1mo–15y 1mo) and eight age- and sex-matched comparison participants (mean age 5y 2mo, range 1y 1mo–14y 11mo) were included in this study. Fractional anisotropy was lower and mean diffusivity and radial diffusivity were higher in the lower brainstem of patients with achondroplasia than in age-matched comparison participants. The CST and middle cerebellar peduncle of the participants showed increases in mean, axial, and radial diffusivity. Fractional anisotropy in the lower brainstem was negatively correlated with the degree of CCJ narrowing. No differences in the DTI metrics of the centrum semiovale were observed between the two groups.

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Supporting information

The following additional material may be found online.

Interpretation—The reduction in fractional anisotropy and increase in diffusivities in the lower brainstem of participants with achondroplasia may reflect secondary encephalomalacic degeneration and cavitation of the affected white matter tracts as shown by histology. In children with achondroplasia, DTI may serve as a potential biomarker for brainstem white matter injury and aid in the care and management of these patients.

Achondroplasia is a skeletal dysplasia and is the most common form of disproportionate short stature in children. It has been found to be caused by two recurrent mutations in the gene encoding fibroblast growth factor receptor type 3 (*FGFR3*) in over 95% of affected individuals.¹ *FGFR3* has multiple functions, including regulating linear bone growth, and its mutations consequently have a detrimental effect on longitudinal growth.¹ It is also important in craniofacial development and, therefore, mutations in this gene cause abnormal cartilage formations and premature fusion of synchondroses. The diminished growth of the skull base leads to narrowing of the craniocervical junction (CCJ) and foramen magnum, which can lead to cervicomedullary compression. Cervicomedullary compression, seen in 35% of patients, is the most serious neurological complication.² It may result in cervical cord compression and manifest as spasticity and hyperreflexia. Finally, the family of fibroblast growth factors (FGFs) has been shown to play a role in the normal development and differentiation of oligodendrocytes and is potentially involved in abnormal white matter myelination in mice.³

Diffusion tensor imaging (DTI) is an advanced magnetic resonance imaging (MRI) technique that allows in vivo evaluation of the microstructure and integrity of white matter tracts.^{4,5} The sensitivity of DTI is high enough to detect white matter abnormalities and it is, therefore, a suitable technique to study white matter changes that may result in secondary to chronic cervicomedullary compression in achondroplasia.^{6,7}

The aims of this study were to compare, using DTI of the brainstem, the microstructural integrity of the white matter in children with achondroplasia and age-matched participants and to correlate the severity of CCJ narrowing and neurological findings with DTI scalars. We also aimed to assess the potential role of *FGFR3* on white matter microstructure. We hypothesized that white matter integrity would be altered in children with achondroplasia and that there would be a negative correlation between fractional anisotropy values and the degree of CCJ narrowing as well as neurological impairment. We also hypothesized that the mutant *FGFR3* gene could cause abnormal white matter myelination in children with achondroplasia.

METHOD

Participants

The inclusion criteria for this study were (1) a confirmed diagnosis of achondroplasia (imaging and/or genetic findings), (2) availability of DTI data before neurosurgical decompression and without artifacts enabling a high-quality DTI post processing, and (3) age at MRI of 18 years or younger. Data from eligible patients were obtained through an electronic search of our pediatric neuroradiology database covering the period between 1 September 2010 and 31 December 2012.

In this period, magnetic resonance images were acquired in 13 children with achondroplasia in our tertiary pediatric hospital. Out of 13 patients, eight fulfilled the inclusion criteria. Five patients were excluded because of the absence of presurgical DTI data or limiting motion artifacts.

Demographic data and detailed information about neurological features in the patients were collected by a review of the clinical histories. Hyperreflexia and clonus, identified as being signs of upper motor lesions involving descending motor pathways, were classified as present or absent.

Age- and sex-matched comparison participants were selected from our pediatric magnetic resonance database using three criteria (1) normal brain anatomy, (2) absence of neurological disorders, and (3) availability of DTI raw data.

Because of the retrospective nature of this study and absence of risk involved with this study, a consent waiver was provided by the institutional review board.

Conventional imaging analysis

The severity of achondroplasia was evaluated using sagittal and axial T1-weighted images at the level of the CCJ. A similar measurement to that described by Brühl et al.⁸ was used. The length of the clivus (from the tip of the dorsum sellae to the basion) and the diameter of the spinal canal at the level of the second cervical vertebral body were measured in the sagittal plane. The transverse diameter of the foramen magnum was measured in the axial plane. Moreover, the basal (nasion–tip of dorsum sellae–basion) and Welcker (nasion–tuberculum sellae–basion) angles were measured in a sagittal plane (Fig. 1). Based on the results of Brühl et al.,⁸ the severity of CCJ narrowing was graded using five parameters and points: (1) length of the clivus (<25mm=0 points, 25mm=1 point), (2) sagittal diameter of the spinal canal at the middle of C2 (>9mm=0 points, 9mm=1 point), (3) transverse diameter of the foramen magnum (>18mm=0 points, 18mm=1 point), (4) basal angle (<130°=0 points, 130°=1 point), and (5) Welcker angle (>103°=0 points, 103°=1 point). One point was given to each measurement or parameter representing increasing severity of narrowing at the CCJ, ranging from a minimum total of 0 to a maximum total of 5 points.

Diffusion tensor imaging

All MRI studies were performed on a 1.5T scanner (Siemens Avanto, Erlangen, Germany) using our standard departmental protocol including three-dimensional T1- and axial T2-weighted images, an axial fluid-attenuated inversion recovery (FLAIR) sequence, as well as a single-shot spin echo, echo planar axial DTI sequence with diffusion gradients along 20 non-collinear directions. An effective high b -value of 1000s/mm² was used for each of the 20 diffusion-encoding directions. We performed an additional measurement without diffusion weighting ($b=0$ s/mm²). For the acquisition of the DTI data, the following parameters were used: repetition time (TR)=7100ms, echo time (TE)=84ms, slice thickness=2.5mm, field of view (FOV)=240 × 240mm and matrix size=192 × 192. Parallel imaging iPAT=2 with GRAPPA (generalized auto-calibrating partial parallel acquisition

reconstruction) was used. The acquisition was repeated twice to enhance the signal-to-noise ratio.

Diffusion tensor imaging analysis

Patients' DTI data were transferred to an off-line workstation for further postprocessing using DtiStudio, DiffeoMap and RoiEditor software (available at www.MriStudio.org). The raw diffusion-weighted images were first co-registered to one of the least diffusion-weighted images and corrected for eddy current and participant motion using a 12-mode affine transformation. The following maps were generated: fractional anisotropy, vector, color-coded fractional anisotropy, and mean, axial, and radial diffusivity. After rigid transformation to an age-appropriate template for adjustment of position and rotation of images, regions of interest (ROIs) were drawn manually, centered within the bilateral pontine corticospinal tract (CST), medial lemniscus, and middle cerebellar peduncle (Fig. 2). Two additional ROIs were placed in the bilateral centrum semiovale. The DTI analysis was focused on these well-defined tracts that can be measured in a reproducible fashion. In addition, these fiber tracts were evaluated based on their location, as they were expected to be at risk for chronic injury in achondroplasia. For the identification of each structure, axial color-coded fractional anisotropy maps were used in comparison with the MRI atlas by Oishi et al.⁹ Each ROI was drawn as large as possible in the axial plane, taking care not to include cerebrospinal fluid (CSF) along the margin of the structure on color-coded images. An additional ROI was drawn at the level of the lower brainstem covering the entire lower brainstem in the axial plane (Fig. 2). For each analyzed structure, three different ROIs were placed on contiguous magnetic resonance slices and the average fractional anisotropy and mean, axial, and radial diffusivity values were calculated. The same post-processing was performed twice by the first author (with an interval of 4wk between evaluations) and once by the second author in order to assess the intra- and interrater reliability of image analysis.

Statistical analysis

Generalized linear mixed effects models were used to calculate intraclass correlation coefficients (ICCs), which were then used to evaluate intra- and interrater reliability. Good intra- and interrater reliability were defined, a priori, as a lower 95% confidence limit for ICCs of not more than 0.75. To compare age as a variable, to analyze the DTI scalars between the groups, as well as to compare DTI scalars of the patients with neurological findings, paired *t*-tests were used.

Spearman's rank correlation was performed to correlate DTI scalars with the severity of CCI narrowing and the patients' age. Analyses were performed using SAS software, version 9.3 (SAS Institute, Inc., Cary, NC, USA). All tests were two-sided and observed differences were considered statistically significant if *p* value was less than 0.05. No adjustment was made for multiple comparisons.

RESULTS

Participants

The study comprised eight participants (seven males, one female; mean age 5y 6mo, range 1y 1mo–15y 1mo) with achondroplasia and eight comparison participants matched for age (mean 5y 2mo, range 1y 1mo–14y 11mo) and sex. The median age at presurgical MRI of the patients was 4 years 10 months and median age at MRI of the comparison participants was 5 years 6 months. Patients and comparison participants did not differ for age ($p=0.64$). Clonus was present in three individuals and hyperreflexia in two individuals (Table SI, online supporting information). No data on gait function were available.

Conventional imaging analysis

The severity of CCJ narrowing is shown in Table SI. Four participants had a total score of severity of 3, three had a total score of 2, and one had a total score of 1, according to the measurements adapted from Brühl et al.⁸

Diffusion tensor imaging analysis

Intrarater and interrater reliability for the ROI analysis-based approach were excellent, with lower 95% confidence limits of ICC values of between 0.85 and 1 and between 0.92 and 1 respectively. Since we obtained high ICC values, the DTI scalars derived by the first analysis performed by the first author were utilized in subsequent analysis.

The DTI scalars for the patients and the comparison participants are summarized and compared in Table I. The study group demonstrated a decrease in fractional anisotropy in the lower brainstem ($p<0.01$). No difference was observed in fractional anisotropy in the other six regions ($p>0.05$). In all regions, mean diffusivity was higher in patients than in comparison participants ($p<0.05$). Axial diffusivity was increased in the patient group in all regions except the lower brainstem. Radial diffusivity was also increased in patients in all regions except the bilateral medial lemniscus. In the bilateral centrum semiovale, no differences were observed in DTI metrics between patients and comparison participants.

The results of the correlation between DTI scalars and severity of CCJ narrowing are summarized in Table SII (online supporting information). A higher severity score was correlated with a decrease in fractional anisotropy values ($p<0.05$) in the lower brainstem (Fig. 3). No correlation was found between fractional anisotropy values and severity of CCJ narrowing for the other six regions. A decrease in radial diffusivity in the left medial lemniscus and an increase in radial diffusivity in the right medial lemniscus correlated with a high severity score ($p=0.01$ and $p=0.045$). No correlation was found between the DTI metrics and patient age or between the presence of hyperreflexia and clonus and DTI scalars of the CST or lower brainstem.

DISCUSSION

Achondroplasia is a skeletal dysplasia affecting the entire musculoskeletal system and causing secondary multisystemic complications resulting in high rates of morbidity and mortality.^{10–12} The multiple manifestations of achondroplasia present with different

symptoms and clinical findings at different ages.¹³ CCJ narrowing is one of the first manifestations of achondroplasia in children and is responsible for the high infant mortality rate (up to 7.5%) associated with achondroplasia, which may also cause chronic compression of the brainstem and cervical spinal cord.^{14,15} A detailed assessment of the CCJ, brainstem, and spinal cord, including careful neurological history taking and examination, neuroimaging, and polysomnography, is, therefore, mandatory in every infant with achondroplasia, as recently recommended by the American Academy of Pediatrics.^{16,17}

Neuroimaging evaluation may be performed by computed tomography (CT) or MRI and focuses mostly on bony structures and CSF circulation.⁸ CT with thin cuts and bone windows may allow an accurate assessment of the size of the foramen magnum.¹⁶ The disadvantage of CT, however, is the lack of high-resolution soft tissue characterization of the brainstem and cervical cord and the inherent higher sensitivity of children to the short- and long-term side effects of radiation. Assessment by MRI offers excellent soft tissue contrast and allows a quantitative morphological assessment of the neuronal structures with simultaneous application of measurements of distances and angulations at the CCJ.⁸ Brühl et al.⁸ found that the foramen magnum, basal angle, and Welcker angle were significantly smaller than in age-matched comparison participants. Moreover, MRI may add 'functional' and dynamic data about the CSF flow and venous drainage utilizing phase-contrast imaging.^{8,18,19} Today, the advanced neuroimaging assessment of the musculoskeletal structures and CSF flow in achondroplasia provides morphologic and 'functional' data, whereas the evaluation of the brain tissue (brainstem and spinal cord) is still rather simple, with purely qualitative assessment of the signal intensity.^{8,20} An intramedullary hyperintense signal on T2-weighted images was reported in about 80% of the study group and it is most likely that it represents myelomalacia or cavity formation.^{8,21} Histological examination of the spinal cord lesions in achondroplasia showed gliosis and cystic myelomalacia, as seen in the hyperextension type of spinal cord injury.²²

We applied DTI to quantify microstructural changes in the brainstem and cerebellar white matter tracts in children with achondroplasia. We did demonstrate that there was a decrease in fractional anisotropy values in the lower brainstem, confirming our first hypothesis. The decrease in fractional anisotropy reflects alteration of, or impaired, white matter microstructural integrity; however, this is a rather non-specific measure on its own.²³ It is likely that the marked increase in radial diffusivity and mean diffusivity in the lower brainstem along with the reduction in fractional anisotropy reflects direct injury to the brainstem white matter tracts compared with the limited increase in mean diffusivity observed in secondary white matter degeneration.^{5,24} The differences in the changes in diffusion properties in primary and secondary white matter changes reflect underlying microstructural differences in the two conditions. Incongruent or even anti-parallel movements of the lower brainstem and spinal cord above and below the narrowed CCJ may induce microtrauma with secondary encephalomalacic degeneration and cavitation of the affected white matter tracts.⁸ T2-hyperintense CSF-filled microcavities result in increased content of unhindered isotropic water diffusion. Accordingly, it is most likely that the pathomechanism of injury of the white matter tracts in the lower brainstem is mechanical, secondary to the compression of the brainstem by the abnormally formed bones at the CCJ. Possibly, the chronic mechanical injury may lead to irreversible vascular injury and

subsequent brainstem injury. White matter changes are not limited to the lower brainstem and were also seen at the pontine level in the CST, medial lemniscus, and middle cerebellar peduncle. An increase in all diffusivities, with no difference in fractional anisotropy between patients and comparison participants, was found in the bilateral CST and middle cerebellar peduncle and may reflect demyelination or dysmyelination with increased water or edema in the extracellular space. On conventional T2-weighted images, these white matter tracts usually demonstrate normal signal intensity in achondroplasia.⁸ This once again emphasizes that the sensitivity of DTI in detecting white matter changes is higher than that of conventional MRI sequences.

In order to test our second hypothesis we graded the CCJ narrowing according to Brühl et al.⁸ to determine a severity score. Confirming our hypothesis, fractional anisotropy in the lower brainstem was negatively correlated with the severity of achondroplasia (r value -0.717 , $p=0.045$), while fractional anisotropy in other regions did not correlate with the CCJ narrowing severity score. Only the correlation between lower brainstem fractional anisotropy and CCJ narrowing severity score may, most likely, be explained by the anatomical proximity of the lower brainstem and foramen magnum. Our result matches the correlation between intramedullary lesions and CCJ narrowing, as reported on conventional MRI.⁸ Moreover, Spearman's rank correlation revealed a positive correlation between radial diffusivity in the right CST and the severity score, as well as a negative correlation between axial diffusivity in the left medial lemniscus and the severity score. The clinical significance of these correlations is unclear.

No correlation was found between clinical signs of CST involvement and DTI scalars in the CST and lower brainstem. This lack of correlation may be explained by the small number of patients and the retrospective nature of this study. Interestingly, a similar lack of correlation between neurological abnormalities and MRI findings, including impairment of the CSF flow and narrowing of venous outlets, was previously reported.⁸ Our data suggest that DTI may depict changes in the microstructure of major white matter tracts before clinical symptoms become apparent.

In mice, the family of FGFs including ligands and receptors, is implicated in numerous cellular processes such as white matter development and myelination. FGF receptors 1–3 are expressed in the embryonic forebrain, which includes regions overlapping with ventral sites of oligodendrocyte progenitor generation.²⁵ Impaired or deficient functional development of oligodendrocyte progenitors into mature myelin-producing cells is expected to result in abnormal white matter myelination. DTI is a suitable neuroimaging technique for quantifying abnormal white matter integrity, for example in genetic white matter diseases.⁶ The bilateral centrum semiovale is an ideal location to assess white matter microstructure in achondroplasia because it is unlikely that it represents a region that would be altered by mechanical injury secondary to skull base abnormalities. We did not find differences in DTI metrics between patients and the comparison participants. These findings do not support the hypothesis that *FGFR3* causes abnormal white matter myelination in children with achondroplasia. Our results are in agreement with a recent study providing evidence that *Fgfr1* and *Fgfr2*, but not *Fgfr3*, have critical functions in the regulation of oligodendrocyte progenitor generation from the embryonic mouse forebrain.³

We are aware of limitations to our study, including the small number of patients, the retrospective nature of the study, the lack of comprehensive clinical information, the absence of blinding to the patients' diagnosis during the DTI postprocessing, and the ROI-based analysis, which is dependent to a greater extent on the investigator. Nevertheless, intra- and interrater reliability were high for regions and measured DTI scalars.

CONCLUSION

We have shown that, in children with achondroplasia, DTI may quantify brainstem white matter changes that correlate with the severity of CCJ narrowing. Reduction in fractional anisotropy and increase in all diffusivities may reflect secondary encephalomalacic degeneration and cavitation of the affected white matter tracts as shown by histology. DTI allows one to quantify tissue alterations in patients with achondroplasia, potentially identify suitable patients for therapeutic suboccipital decompression, and monitor treatment response. Future studies with larger numbers of patients are needed to further assess the role of DTI in routine presurgical evaluation and surveillance of children with achondroplasia.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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ABBREVIATIONS

CCJ	Craniocervical junction
CST	Corticospinal tract
DTI	Diffusion tensor imaging
FGF	Fibroblast growth factor
FGFR3	Fibroblast growth factor receptor type 3
ROI	Region of interest

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What this study adds

- We found decreased fractional anisotropy in the lower brainstem of children with achondroplasia, indicating a loss of white matter microstructural integrity.
- Quantitative DTI changes of brainstem white matter correlated with the severity of CCJ narrowing in pediatric achondroplasia.

Figure 1.

Midsagittal T1- (a) and axial T2-weighted (b) images of a 15-year-old male with achondroplasia showing the measurements we performed (1) length of the clivus (tip of the dorsum sellae–basion), (2) sagittal diameter of the spinal canal at the middle of C2, (3) transverse diameter of the foramen magnum (basion–opisthion), (4) basal angle (nasion–tip of dorsum sellae–basion), and (5) Welcker angle (nasion–tuberculum sellae–basion).

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Figure 2.

Axial color-coded fractional anisotropy maps (a–c) and axial fractional anisotropy maps (d–f) at the level of the pons and lower brainstem, showing the position of the regions of interest covering the bilateral corticospinal tract (CST), medial lemniscus (ML), and middle cerebellar peduncle (MCP), as well as all the lower brainstem in a male ages 2 years and 6 months with achondroplasia.

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Figure 3.

Scatterplots showing changes in fractional anisotropy (FA) and mean (MD), axial, (AD) and radial diffusivity (RD) at the level of the lower brainstem in relation to the degree of craniocervical junction (CCJ) narrowing in children with achondroplasia. Fractional anisotropy values are significantly lower in children with a higher degree of CCJ narrowing, while mean, axial, and radial diffusivity values did not differ between patients depending on the degree of CCJ narrowing.

Differences in diffusion tensor imaging parameters of brainstem, cerebellar and supratentorial regions comparing children with achondroplasia and comparison participants

Table 1

	Patients		Comparison participants		<i>p</i> ^a	
	Mean	SD	Mean	SD		
Centrum semiovale right	Fractional anisotropy	0.372	0.055	0.373	0.044	0.99
	Mean diffusivity (×10 ⁻³ mm ² /s)	1.039	0.087	1.036	0.067	0.89
	Axial diffusivity (×10 ⁻³ mm ² /s)	1.468	0.127	1.458	0.105	0.49
	Radial diffusivity (×10 ⁻³ mm ² /s)	0.844	0.114	0.830	0.115	0.44
Centrum semiovale left	Fractional anisotropy	0.365	0.090	0.362	0.046	0.91
	Mean diffusivity (×10 ⁻³ mm ² /s)	1.031	0.088	1.025	0.084	0.81
	Axial diffusivity (×10 ⁻³ mm ² /s)	1.453	0.096	1.448	0.101	0.65
	Radial diffusivity (×10 ⁻³ mm ² /s)	0.841	0.111	0.831	0.116	0.15
Corticospinal tract right	Fractional anisotropy	0.505	0.105	0.485	0.109	0.67
	Mean diffusivity (×10 ⁻³ mm ² /s)	0.995	0.131	0.737	0.077	<0.01
	Axial diffusivity (×10 ⁻³ mm ² /s)	1.568	0.310	1.126	0.063	<0.01
	Radial diffusivity (×10 ⁻³ mm ² /s)	0.715	0.124	0.543	0.114	<0.01
Corticospinal tract left	Fractional anisotropy	0.470	0.096	0.489	0.077	0.63
	Mean diffusivity (×10 ⁻³ mm ² /s)	0.999	0.047	0.718	0.060	<0.01
	Axial diffusivity (×10 ⁻³ mm ² /s)	1.545	0.203	1.097	0.086	<0.01
	Radial diffusivity (×10 ⁻³ mm ² /s)	0.729	0.065	0.524	0.083	<0.01
Medial lemniscus right	Fractional anisotropy	0.597	0.106	0.540	0.071	0.11
	Mean diffusivity (×10 ⁻³ mm ² /s)	0.991	0.054	0.766	0.139	<0.01
	Axial diffusivity (×10 ⁻³ mm ² /s)	1.750	0.143	1.297	0.139	<0.01
	Radial diffusivity (×10 ⁻³ mm ² /s)	0.604	0.122	0.532	0.059	0.07
Medial lemniscus left	Fractional anisotropy	0.597	0.106	0.541	0.059	0.20
	Mean diffusivity (×10 ⁻³ mm ² /s)	0.982	0.076	0.794	0.095	<0.01
	Axial diffusivity (×10 ⁻³ mm ² /s)	1.725	0.112	1.337	0.145	<0.01
	Radial diffusivity (×10 ⁻³ mm ² /s)	0.607	0.129	0.523	0.085	0.10
Middle cerebellar peduncle right	Fractional anisotropy	0.740	0.053	0.717	0.046	0.11

	Patients		Comparison participants		
	Mean	SD	Mean	SD	<i>p</i> ^a
Middle cerebellar peduncle left	Mean diffusivity (×10 ⁻³ mm ² /s)	0.922	0.056	0.695	<0.01
	Axial diffusivity (×10 ⁻³ mm ² /s)	1.909	0.092	1.404	<0.01
	Radial diffusivity (×10 ⁻³ mm ² /s)	0.427	0.074	0.344	<0.01
	Fractional anisotropy	0.755	0.061	0.722	0.14
	Mean diffusivity (×10 ⁻³ mm ² /s)	0.934	0.079	0.698	<0.01
	Axial diffusivity (×10 ⁻³ mm ² /s)	1.969	0.128	1.417	<0.01
	Radial diffusivity (×10 ⁻³ mm ² /s)	0.415	0.104	0.333	0.01
	Fractional anisotropy	0.317	0.080	0.454	0.01
	Mean diffusivity (×10 ⁻³ mm ² /s)	1.184	0.159	0.999	0.02
	Axial diffusivity (×10 ⁻³ mm ² /s)	1.632	0.410	1.508	0.36
Lower brainstem	Radial diffusivity (×10 ⁻³ mm ² /s)	0.955	0.056	0.732	<0.01

^a *p* values from two-tailed paired *t*-test; statistically significant differences are bold.