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Research Paper

# A Diffusion Tensor Imaging Analysis of Frontal Lobe White Matter Microstructure in Trigonocephaly Patients

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ABSTRACT

*Background:* Children with trigonocephaly are at risk for neurodevelopmental disorders. The aim of this study is to investigate white matter properties of the frontal lobes in young, unoperated patients with metopic synostosis as compared to healthy controls using diffusion tension imaging (DTI).
*Methods:* Preoperative DTI data sets of 46 patients with trigonocephaly with a median age of 0.49 (interquartile range: 0.38) years were compared with 21 controls with a median age of 1.44 (0.98) years. White matter metrics of the tracts in the frontal lobe were calculated using FMRIB Software Library (FSL). The mean value of tract-specific fractional anisotropy (FA) and mean diffusivity (MD) were estimated for each subject and compared to healthy controls. By linear regression, FA and MD values per tract were assessed by trigonocephaly, sex, and age.
*Results:* The mean FA and MD values in the frontal lobe tracts of untreated trigonocephaly patients, younger than 3 years, were not significantly different in comparison to controls, where age showed to be a significant associated factor.
*Conclusions:* Microstructural parameters of white matter tracts of the frontal lobe of patients with trigonocephaly are comparable to those of controls aged 0-3 years.


## Introduction

Trigonocephaly, caused by prenatal closure of the metopic suture, is the second most common form of single-suture craniosynostosis.[1] The presentation of metopic synostosis is highly variable and ranges from a mild phenotype to a severe phenotype with the classic wedge-shaped skull, depending on when the suture closes during gestation. Children with metopic synostosis are at risk for neurocognitive disorders, such as behavioral problems and delays in speech and language development.[2,3]

Ethics approval statement: The Ethics Committee of the Erasmus Medical Center approved this prospective imaging study (METC-2018-124). We conformed to the statement of the Declaration of Helsinki. The manuscript is in line with the Recommendations for the Conduct, Reporting and Editing and Public of Scholarly Work in Medical Journals and aim for the inclusion of representative human populations (sex, age, and ethnicity) as per those recommendations.

Patient consent statement: The Ethics Committee of the Erasmus Medical Center approved this prospective imaging study in patients with trigonocephaly (METC-2018-124), which is part of ongoing work at the Dutch Craniofacial Center involving protocolized care, brain imaging, clinical assessment, data summary, and evaluation.

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Patients with moderate and severe phenotypes undergo surgical correction of the frontal bones and supraorbital rims, with the aim to prevent potential restriction of brain development, to reduce the risk of raised intracranial pressure, and to improve esthetic outcomes. However, the functional indication for surgical intervention has been under debate. Recent studies have shown that the percentage of patients with trigonocephaly with preoperative papilledema as a sign of intracranial hypertension is negligible (<2%).[4] In addition, preoperatively patients with trigonocephaly show a normal intracranial volume similar to that of healthy age-matched controls.[5] Furthermore, cerebral blood flow of the frontal lobes in unoperated patients with trigonocephaly up to the age of 18 months is not significantly different from control patients as shown with arterial spin labelling-magnetic resonance imaging (MRI).[6] Finally, the triangular shape of the forehead tends to improve over time, although it is not known to what extend this self-correction occurs.

To date, the exact underlying pathophysiology of metopic synostosis and its relation with neurocognitive disorders is unclear. There are two predominant theories on the relation between metopic synostosis and potential altered neurodevelopment. One theory states that metopic synostosis is part of a bone malformation of the frontal bones which in turn leads to mechanical restriction of brain development.[7] The second theory proposes an intrinsic brain anomaly in which the exerted pressure by the frontal lobes as driving force of suture patency is failing.[5,7-9] In line with the latter theory, previous studies have demonstrated that the frontal intracranial volume is smaller in patients with trigonocephaly than in controls and that neurodevelopmental disorders occur in both unoperated patients with a mild trigonocephaly phenotype as well as in operated patients with a severe phenotype.[2,3,5] In addition, recent studies have shown an overlap in genetic mutations between patients with trigonocephaly and patients with neurodevelopmental disorders.[10-12] These findings suggest that aberrant neural development, especially of the frontal lobe, is caused by an inborn brain problem, rather than mechanical restriction.

Insight into the microarchitecture of the white matter of the unoperated brain could improve our understanding of the pathophysiology of metopic synostosis and its relation to altered neural development. MRI with diffusion tension imaging (DTI) can be used to investigate the white matter microarchitecture by analyzing white matter tracts. Recent studies have shown that the microstructure of white matter tracts may be altered in some types of craniosynostosis.[13-17] However, to date, there have been no studies on the microstructure of the white matter in patients with isolated metopic synostosis. Therefore, the aim of this study is to investigate the white matter properties of the frontal lobe in unoperated patients with metopic synostosis as compared to healthy controls using DTI measurements. Based on the early development of white matter structures and on the higher prevalence of neurodevelopmental disorders in patients with trigonocephaly, we hypothesize that the white matter microstructure of the frontal lobe is altered early in life.[4,5]

## Material and Methods

We conducted a prospective cohort study, which was approved by the Institutional Research Ethics Board at the Erasmus University Medical Center, Rotterdam, the Netherlands (MEC-2018-124). This study is part of ongoing work at the Dutch Craniofacial Center involving protocolized care, brain imaging, and clinical assessment.

### *Subjects*

Patients were included between 2018 and 2020. We included all unoperated patients with nonsyndromic trigonocephaly, for whom a surgical correction was considered and for whom three-dimensional diffusion-weighted MRI and T1-weighted MRI scans of the brain were available. We considered patients with a genetic variant (n = 3) of unknown significance as patients with nonsyndromic trigonocephaly. Patients with known pathogenic mutations (e.g., 9p deletion syndrome, Down syndrome, Jacobsen syndrome) or patients born prematurely were excluded from this study. Controls were identified from a historic hospital MRI database of children who had undergone MRI brain studies for clinical reasons between 2010 and 2020. Patients were considered a control if any cerebral and/or skull pathology was absent. Scans of potential controls were reviewed by an expert pediatric radiologist and a neurosurgeon to ensure the absence of any cerebral pathology and/or skull pathology. MRI brain scans of insufficient quality due to motion artefacts were excluded (n = 4).

### *MRI acquisition*

All brain MRI data were acquired with a 1.5-Tesla unit (General Electric Healthcare, Milwaukee, Wisconsin), including a three-dimensional T1-weighted fast-spoiled gradient-recalled sequence and a DTI sequence. DTI was obtained using a multirepetition single-shot echo-planar sequence with a slice thickness of 3 mm without a gap. Images were obtained in 25 of 35 gradient directions with the following parameters: b-value: 1000s/mm$^2$; repetition time: 15,000 ms; time to echo: 82.1 ms; field of view: 240 × 240 mm$^2$; and matrix size: 128 × 128, resulting in a voxel size of 1.8 × 1.8 × 3.0 mm$^3$. Both groups underwent deep sedation or anesthesia during the MRI procedure using sevoflurane or propofol.

### *White matter tracts of the frontal lobe*

Major white matter tracts coursing completely or partially through the frontal lobe were analyzed: the anterior thalamic radiation (ATR), cingulate gyrus part of the cingulum (CGC), unicate fasciculus (UNC), the forceps minor (FMI), and the inferior fronto-occipital fasciculus (IFO). Tracts of the left and right hemisphere were analyzed separately as previous studies have shown regional asymmetry between hemispheres.[18] Assuming mechanical restriction of the frontal lobe would not affect the occipital lobe, we also assessed the forceps major (FMA). The FMA locates in the occipital region and therefore served as a subject-specific control tract. As an additional measure, we assessed the ratio of FMI/FMA between patients and controls.

### *DTI metrics*

The white matter metrics derived from DTI, voxel by voxel, are mathematically estimated based on three mutually perpendicular eigenvectors, whose magnitude is given by three corresponding eigenvalues. These eigenvalues are used to generate quantitative maps of fractional anisotropy (FA), the derivation of mean diffusivity (MD), radial diffusivity (RD), and axial diffusivity (AD). As the FA, MD, RD, and AD equations are mathematically coupled, we first investigated FA and MD before analyzing the impact of the radial and axial measures of diffusivity. FA represents the amount of diffusional asymmetry in a voxel, which is presented from 0 (infinite isotropy) to 1 (infinite anisotropy). The MD is measured in mm$^2$/sec.

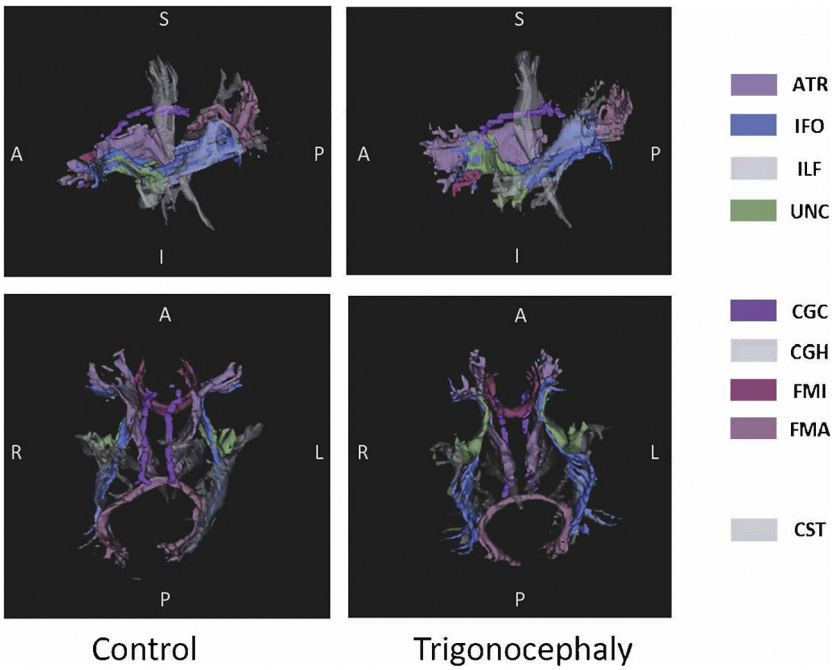


**FIGURE 1.** Tractography of the representative patient and control. The tracts used in this study are depicted as colored tracts. These tracts include the anterior thalamic radiation (ATR), the inferior fronto-occipital fasciculus (IFO), uncinate fasciculus (UNC), cingulate gyrus part of the cingulum (CGC), the forceps minor (FMI), and the forceps major (FMA). The gray tracts were not used in this study and include the inferior longitudinal fasciculus (ILF), the hippocampal gyrus–associated cingulum (CGH), and the corticospinal tract (CST). In each column, the left and superior views of the tracts are shown.

*Data processing*

The image processing was performed with the use of the FMRIB Software Library (FSL), version 6.0.0, created by the Analysis Group, FMRIB, Oxford, UK (ref).[19] First, the images were modified in a preprocessing step to exclude nonbrain tissue and then to correct for artifacts induced by eddy currents and for translations and/or rotations resulted from head motion. The resulting transformation matrices were used to rotate the gradient direction table to account for rotations applied to the data. The diffusion tensor was fitted at each voxel, and common scalar metrics were subsequently computed.

Second, fully automated probabilistic tractography was performed as described by de Groot et al. on each subject's diffusion data set, using the FSL plugin AutoPtx.[20] The results of the probabilistic tractography were normalized to a scale from 0 to 1 using the total number of successful seed-to-target attempts. Next, we thresholded each pathway, using previously established values (ATR: 0.002, CGC: 0.01, IFO: 0.01, FMA: 0.005, FMI: 0.01, UNC: 0.01; de Groot et al., 2015). Nonzero mean DTI scalar measures were computed within each tract. Average fractional anisotropy and mean diffusivity values were then computed for each fiber bundle.[21]

*Quality control*

Quality control was performed by visually inspecting each tract for each subject (by BL, with 4 years of diffusion MRI experience). If tracts were segmented inadequately, the subject was excluded from this study. Two representative subjects, one patient with trigonocephaly and one control, are shown in Fig 1.

*Statistical analysis*

Statistical analysis was conducted using R Studio (version 4.0.3).[22] Continuous data are presented as mean and standard deviation or as median and interquartile range (IQR), depending on whether the data are being distributed normally or not. Categorical data are presented as counts. Per tract histograms, boxplots and the Shapiro-Wilk test were used to confirm FA and MD were approximately normally distributed. Parametric statistics were used after establishing that the distribution of the data did not violate assumptions of normality. If a normal distribution was violated, several transformations were investigated. If this transformation did not improve the normal distribution, the untransformed data were used.

FA and MD values in each of the chosen tracts were investigated by box plots and scatterplots. Subsequent linear regression models were used to further examine the FA values and MD values, with patient/control, sex, and age as independent variables. Sex and age have previously been shown to affect FA and MD values.[18,23-28] $\beta$-Coefficients were calculated (stats package) for each regression. Affected tracts would be further investigated by assessing the diffusivity values AD and RD. The FMA was assessed as a control tract to further validate our results; we compared the FA FMI/FMA ratio between patients and controls and the MD FMI/FMA ratio between patients and controls using a $t$ test. The Bonferroni correction was conducted, and a $P$-value $< 0.0025$ ($P$-value $= 0.05/20$) was considered statistically significant. The effect of age on FA and MD between patients with trigonocephaly and controls was investigated using effect plots.

As an additional analysis, we created subgroups based on age categories, to further correct for any effect due to age. Because of the low number of patients and controls, this is enclosed in Supplemental Table 1.

## Results

*Characteristics*

Fourty-six patients with trigonocephaly with a median age of 0.49 years (IQR: 0.38) and twenty-one control subjects with a

**TABLE 1.**
Descriptives

| Descriptives | Trigonocephaly | Controls |
|---|---|---|
| n MRI | 46 | 21 |
| F: M | 12:34 | 14:07 |
| Median age (IQR) | 0.49 (0.38) | 1.44 (0.98) |

Abbreviations:
F = Female
IQR = Interquartile range
M = Male
MRI = Magnetic resonance imaging

median age of 1.44 years (IQR: 0.98) were included in this study as presented in Table 1.

*Fractional anisotropy*

By linear regression, we found no significant effect of trigonocephaly or gender on FA values of the investigated white matter tracts (Table 2). The effect of age was significant for all tracts, including the control tract FMA ($P < 0.0025$). The FA FMI/FMA ratio between patients and controls did not show a significant difference ($P = 0.79$) as well. We visualized the effect of age on increase of the FA value per tract in patients compared to controls, using scatterplots and effect plots (Fig 2) to correct for the age difference between the patient and control group, which confirmed again the nonsignificant difference between patients with trigonocephaly and controls.

*Mean diffusivity*

The results of the linear regression on values of MD of the analyzed white matter tracts are shown in Table 2, showing the effect of trigonocephaly, age, and gender on the MD values. No significant difference in the MD values was found in the frontal lobe tracts comparing patients to controls. The effect of gender was not significant on the MD values in the different tracts. The effect of age was significant for the left ATR, left and right CGC, FMI, left and right IFO, and the left UNC ($P < 0.0025$). The effect of age was significant in the reference tract FMA as well. Assessing the MD FMI/FMA ratio between patients and controls showed no significant difference ($P = 0.77$). Using scatterplots and effect plots for all tracts, the MD in time (age in years) is visualized for patient and controls (Fig 2). It shows the decrease of MD in time and the nonsignificant difference between patients and controls.

As there was no significant difference in both FA and MD values of patients as compared to controls, we did not further investigate the diffusivity values RD and AD. An additional analysis to further correct for age with the 21 oldest patients compared to the 21 controls showed no significant difference between patients with trigonocephaly and controls (Supplemental Table 1).

*RD and AD*

In the supplemental figure (Supplemental Figure 1), the scatterplots of RD and AD are depicted.

## Discussion

In this report, we present, to our knowledge, the first study on automated DTI in patients with trigonocephaly aged 0 to 3 years. Based on the increased prevalence of neurodevelopmental disorders in patients with trigonocephaly, we hypothesized that white matter tracts of the frontal lobe of patients with trigonocephaly would be abnormal from early life onward.[2,29-31] In this study, we did not detect a significant difference in the FA or MD values of frontal lobe tracts in young patients with trigonocephaly as compared to controls. A second reason could be that a difference between patients with trigonocephaly and controls could not be shown because the effect was masked by a large age difference between groups.

The exact underlying pathophysiology of metopic synostosis is unclear, with two dominant hypotheses, namely an inborn brain disorder causing the metopic suture to close prematurely vs mechanical restriction in which the closed metopic suture causing impaired development of the frontal lobe.[5,7-9] In line with the theory that trigonocephaly is an inborn brain disorder, recent studies have shown that some genetic mutations found in patients with trigonocephaly overlap with patients with developmental delay disorders.[10-12] This suggests that aberrant neural development, especially of the frontal lobe, is associated with metopic synostosis. Previous studies have demonstrated that neurodevelopmental disorders occur in both unoperated patients with a mild trigonocephaly phenotype as well as in operated patients with a severe phenotype.[2,3] Mechanical restriction seems unlikely, as surgical intervention has not been proven to improve neurocognitive outcomes and the percentage of intracranial hypertension in patients with trigonocephaly is negligible.[2-4]

Several studies have investigated the associations between neurocognitive disorders and trigonocephaly. Studies focused on different aspects of neurocognitive development, including IQ, behavior, autism, and characteristics of attention deficit hyperactivity disorder, oppositional deficit dyperactivity Disorder, or conduct disorder.[2,29-31] These studies strongly suggest that there is an increased risk for patients with trigonocephaly to develop neurocognitive disorders.

Twenty-one to thirty-one percent of patients with trigonocephaly have an IQ < 80-85 as compared to ≤16% of the norm group.[2] Translating these numbers to our cohort would mean a subset, of 9 to 14 patients of this cohort, would be affected. Although a previous study in preterm neonates used DTI as a predictive tool to assess neurocognitive functioning later in life,[32] our study may have missed the subtle effect of only a subgroup of neurocognitively affected patients with trigonocephaly. However, if we assess the raw data, we cannot distinguish an outlying subgroup of patients with trigonocephaly. It is difficult to assess neurocognitive function and (mild) disorders in neurodevelopment at the age of the patients included in the study (<3 years). Future studies should further assess DTI in older patients with trigonocephaly and its relation with neurocognitive function.

To our knowledge, only one study has investigated DTI in metopic synostosis in a small sample of patients. Cabrejo et al used DTI to investigate combined sagittal and metopic synostosis patients (n = 5) and found an increased FA value in the cingulate tract of these patients as compared to isolated sagittal synostosis patients (N = 5).[14] However, they did not investigate isolated metopic synostosis, nor did they include normal controls. In contrast to this study, we did not find a significant difference in the cingulate tract or other tracts in patients with metopic synostosis as compared to controls.

Our study has several limitations. Currently, large cohort studies and standardized DTI values and thresholds in healthy infants and young children are missing. In addition, DTI depends on many technical variables, such as the type of scanner used and the amount of diffusion encoding directions. This makes it impossible to compare the values in our study to other pediatric DTI studies. In addition, in this study, we have chosen to use tract-based technology rather than a region-of-interest or whole-brain voxel-based approach. A region-of-interest approach could perhaps be valuable

**TABLE 2.**
Linear Regression on FA and MD With the Independent Variables Age, Trigonocephaly, and Gender With a Bonferroni Correction (0.05/20 = 0.025)

| Linear Regression | FA | | | | | MD | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Estimate | Std. Error | CI 2.5% | CI 97.5% | *P* Value | Estimate | Std. Error | CI 2.5% | CI 975% | *P* Value |
| ATR L | | | | | | | | | | |
| Intercept | 0.25 | 0.01 | 0.23 | 0.26 | 0 | 1.12 | 0.02 | 1.07 | 1.16 | 0 |
| Age (years) | 0.03 | 0.00 | 0.02 | 0.04 | 0 | −0.07 | 0.01 | −0.09 | −0.04 | <0.0025 |
| Trigonocephaly | 0.01 | 0.01 | 0.00 | 0.02 | 0.05 | 0.01 | 0.02 | −0.03 | 0.05 | 0.71 |
| Gender (male) | −0.01 | 0.00 | −0.02 | 0.00 | 0.09 | −0.01 | 0.02 | −0.04 | 0.03 | 0.75 |
| ATR R | | | | | | | | | | |
| Intercept | 0.24 | 0.01 | 0.23 | 0.26 | 0 | 1.10 | 0.02 | 1.05 | 1.14 | 0 |
| Age (years) | 0.03 | 0.00 | 0.02 | 0.04 | 0 | −0.07 | 0.01 | −0.09 | −0.04 | <0.0025 |
| Trigonocephaly | 0.01 | 0.01 | 0.00 | 0.02 | 0.08 | 0.01 | 0.02 | −0.03 | 0.04 | 0.76 |
| Gender (male) | 0.00 | 0.00 | −0.01 | 0.01 | 0.43 | 0.00 | 0.01 | −0.03 | 0.03 | 0.86 |
| CGC L | | | | | | | | | | |
| Intercept | 0.26 | 0.01 | 0.23 | 0.29 | 0 | 1.09 | 0.02 | 1.05 | 1.13 | 0 |
| Age (years) | 0.05 | 0.01 | 0.04 | 0.07 | <0.0025 | −0.08 | 0.01 | −0.10 | −0.06 | <0.0025 |
| Trigonocephaly | 0.01 | 0.01 | −0.01 | 0.04 | 0.22 | 0.02 | 0.02 | −0.01 | 0.06 | 0.21 |
| Gender (male) | −0.01 | 0.01 | −0.03 | 0.01 | 0.25 | 0.00 | 0.01 | −0.02 | 0.03 | 0.86 |
| CGC R | | | | | | | | | | |
| Intercept | 0.24 | 0.01 | 0.21 | 0.27 | 0 | 1.11 | 0.02 | 1.07 | 1.16 | 0 |
| Age (years) | 0.05 | 0.01 | 0.03 | 0.06 | <0.0025 | −0.09 | 0.01 | −0.11 | −0.06 | <0.0025 |
| Trigonocephaly | 0.01 | 0.01 | −0.01 | 0.03 | 0.40 | 0.02 | 0.02 | −0.02 | 0.06 | 0.45 |
| Gender (male) | −0.01 | 0.01 | −0.03 | 0.01 | 0.47 | 0.00 | 0.02 | −0.04 | 0.03 | 0.84 |
| FMI | | | | | | | | | | |
| Intercept | 0.33 | 0.01 | 0.30 | 0.36 | 0 | 1.21 | 0.02 | 1.16 | 1.25 | 0 |
| Age (years) | 0.09 | 0.01 | 0.07 | 0.10 | 0 | −0.10 | 0.01 | −0.13 | −0.08 | <0.0025 |
| Trigonocephaly | 0.01 | 0.01 | −0.02 | 0.03 | 0.49 | 0.01 | 0.02 | −0.03 | 0.05 | 0.58 |
| Gender (male) | 0.00 | 0.01 | −0.02 | 0.02 | 0.87 | −0.01 | 0.02 | −0.04 | 0.03 | 0.72 |
| IFO L | | | | | | | | | | |
| Intercept | 0.27 | 0.01 | 0.26 | 0.29 | 0 | 1.15 | 0.02 | 1.10 | 1.20 | 0 |
| Age (years) | 0.04 | 0.00 | 0.03 | 0.05 | 0 | −0.08 | 0.01 | −0.10 | −0.05 | <0.0025 |
| Trigonocephaly | 0.00 | 0.01 | −0.01 | 0.02 | 0.81 | 0.05 | 0.02 | 0.00 | 0.09 | 0.04 |
| Gender (male) | −0.01 | 0.01 | −0.02 | 0.00 | 0.15 | −0.01 | 0.02 | −0.04 | 0.03 | 0.73 |
| IFO R | | | | | | | | | | |
| Intercept | 0.27 | 0.01 | 0.25 | 0.28 | 0 | 1.15 | 0.02 | 1.10 | 1.20 | 0 |
| Age (years) | 0.05 | 0.00 | 0.04 | 0.06 | 0 | −0.08 | 0.01 | −0.11 | −0.06 | <0.0025 |
| Trigonocephaly | 0.00 | 0.01 | −0.01 | 0.02 | 0.56 | 0.04 | 0.02 | 0.00 | 0.08 | 0.07 |
| Gender (male) | −0.01 | 0.01 | −0.02 | 0.00 | 0.20 | 0.01 | 0.02 | −0.03 | 0.04 | 0.68 |
| UNC L | | | | | | | | | | |
| Intercept | 0.25 | 0.01 | 0.24 | 0.26 | 0 | 1.09 | 0.02 | 1.06 | 1.13 | 0 |
| Age (years) | 0.04 | 0.00 | 0.03 | 0.05 | 0 | −0.06 | 0.01 | −0.08 | −0.04 | <0.0025 |
| Trigonocephaly | 0.01 | 0.01 | 0.00 | 0.02 | 0.06 | 0.02 | 0.02 | −0.01 | 0.05 | 0.11 |
| Gender (male) | −0.01 | 0.00 | −0.02 | 0.00 | 0.02 | 0.00 | 0.01 | −0.03 | 0.02 | 0.82 |
| UNC R | | | | | | | | | | |
| Intercept | 0.25 | 0.01 | 0.23 | 0.26 | 0 | 1.10 | 0.02 | 1.07 | 1.14 | 0 |
| Age (years) | 0.04 | 0.00 | 0.03 | 0.05 | 0 | −0.07 | 0.01 | −0.09 | −0.05 | <0.0025 |
| Trigonocephaly | 0.01 | 0.01 | 0.00 | 0.02 | 0.20 | 0.02 | 0.01 | 0.00 | 0.05 | 0.09 |
| Gender (male) | 0.00 | 0.01 | −0.01 | 0.01 | 0.50 | 0.00 | 0.01 | −0.02 | 0.02 | 0.99 |
| FMA | | | | | | | | | | |
| Intercept | 0.31 | 0.01 | 0.28 | 0.33 | 0 | 1.17 | 0.03 | 1.11 | 1.24 | 0 |
| Age (years) | 0.05 | 0.01 | 0.04 | 0.07 | <0.0025 | −0.09 | 0.02 | −0.12 | −0.05 | <0.0025 |
| Trigonocephaly | −0.01 | 0.01 | −0.03 | 0.01 | 0.32 | 0.01 | 0.03 | −0.04 | 0.07 | 0.59 |
| Gender (male) | 0.00 | 0.01 | −0.01 | 0.02 | 0.60 | 0.01 | 0.02 | −0.04 | 0.05 | 0.77 |

Abbreviations:
ATR = Anterior thalamic radiation
CGC = Cingulate gyrus part of the cingulum
CI = Confidence interval
FA = Fractional anisotropy
FMA = Forceps major
FMI = Forceps minor
IFO = Inferior fronto-occipital fasciculus
MD = Mean diffusivity
UNC = Uncinate fasciculus

to assess specific local differences. In addition, we obtained controls from a historic cohort of subjects who had undergone an MRI brain scan for clinical reasons. Next, we were unable to fully match the age of patients and controls. Myelination development is greatest during the first years of life, and small differences in age affect FA and MD. However, we did not have enough statistical power to subdivide our cohort into groups of 0-1, 1-2, and 2+ years.

In line with this, we observed a significant effect of age on the FA and MD values in both patients and controls. Although we did an additional analysis between patients and controls of similar age in the supplemental table, we were still not able to find any statistically significant difference between patients and controls. Finally, the trigonocephaly cohort consists of 81% male patients, whereas the control group consists of 36% males. However, by linear

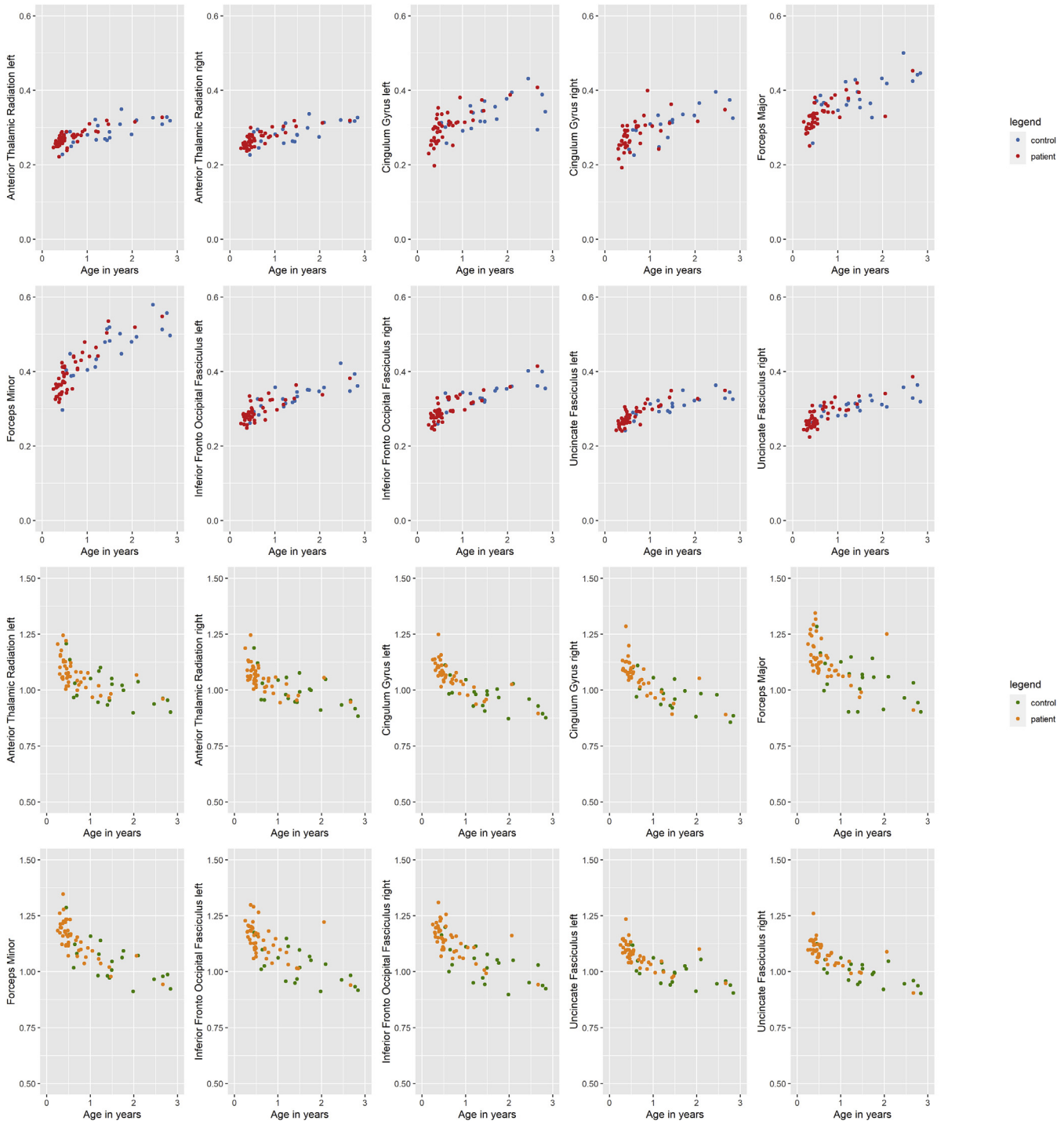


**FIGURE 2.** Scatterplots of FA (scalar value ranging between 0 and 1) and MD ($mm^2$/sec). FA, fractional anisotropy; MD, mean diffusivity.

regression, sex has demonstrated no significant impact on the FA or MD values.

*Future perspectives*

In this study, we could not identify a significant difference between the main white matter tracts of the frontal lobe in young patients with trigonocephaly and controls. However, one could argue that the potential mechanical restriction of the metopic synostosis and/or intrinsically affected white matter is too subtle to measure/not yet measurable with DTI or arterial spin labelling on this age. We investigated whole tracts as a parameter of white matter microstructure in patients with trigonocephaly. Insight into other brain structures than white matter microstructure, for example, by volumetric analysis of global or regional gray and white matter structures or cortical microstructure analysis, might improve our understanding of the pathophysiology of metopic synostosis and its possible relation to altered neural development. For the future, the comparison of brain properties of older operated patients with trigonocephaly with brain properties of older

nonoperated patients with trigonocephaly could give more information about the substrate of the cognitive and behavioral issues and the added value of surgery.

## Conclusion

In conclusion, microstructural parameters of white matter tracts of the frontal lobe of patients with trigonocephaly are comparable to those of controls aged 0-3 years. No difference in FA or MD of the frontal lobe white matter microstructure in trigonocephaly was found.

## Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.pediatrneurol.2022.04.003.

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