


Developmental Curves of the Paediatric Brain Using FLAIR MRI Texture Biomarkers

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Abstract

Purpose: Analysis of FLAIR MRI sequences is gaining momentum in brain maturation studies, and this study aimed to establish normative developmental curves for FLAIR texture biomarkers in the paediatric brain. **Methods:** A retrospective, single-centre dataset of 465/512 healthy paediatric FLAIR volumes was used, with one pathological volume for proof-of-concept. Participants were included if the MRI was unremarkable as determined by a neuroradiologist. An automated intensity normalization algorithm was used to standardize FLAIR signal intensity across MRI scanners and individuals. FLAIR texture biomarkers were extracted from grey matter (GM), white matter (WM), deep GM, and cortical GM regions. Sex-specific percentile curves were reported and modelled for each tissue type. Correlations between texture and established biomarkers including intensity volume were examined. Biomarkers from the pathological volume were extracted to demonstrate clinical utility of normative curves. **Results:** This study analyzed 465 FLAIR sequences in children and adolescents (mean age 10.65 ± 4.22 years, range 2–19 years, 220 males, 245 females). In the WM, texture increased to a maximum at around 8 to 10 years, with different trends between females and males in adolescence. In the GM, texture increased over the age range while demonstrating a local maximum at 8 to 10 years. Texture had an inverse relationship with intensity in the WM across all ages. WM and edema in a pathological brain exhibited abnormal texture values outside of the normative growth curves. **Conclusion:** Normative curves for texture biomarkers in FLAIR sequences may be used to assess brain maturation and microstructural changes over the paediatric age range.

Résumé

Objectif : L'analyse de séquences FLAIR (*fluid-attenuated inversion recovery*) en IRM gagne en importance dans les études sur la maturation du cerveau. La présente étude a visé à établir des courbes de développement normatives du cerveau de l'enfant en matière de biomarqueurs de texture FLAIR. **Méthodes :** Un ensemble de données rétrospectives et unicentriques de 512 séquences FLAIR chez des enfants sains a été recensé, et 465 séquences ont été analysées. Une séquence de sujet présentant une affection a été analysée à titre de preuve de concept. Les séquences de participants ont été incluses si un neuroradiologiste confirmait qu'elles ne présentaient aucune caractéristique à signaler. Un algorithme automatisé de normalisation de l'intensité a été utilisé en vue de standardiser l'intensité du signal FLAIR entre les différents appareils d'IRM et les différents patients. Les biomarqueurs de texture FLAIR ont été extraits de la substance grise (GM), de la substance

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blanche (WM), de la substance grise profonde et des régions corticales de la substance grise. Des courbes de percentile particulières au sexe ont été rapportées et modélisées pour chaque type de tissu. Les corrélations entre la texture et les biomarqueurs établis, y compris le volume d'intensité, ont été examinées. Les biomarqueurs de la séquence du sujet présentant une affection ont été extraits afin de démontrer l'utilité clinique des courbes normatives. **Résultats :** Dans le cadre de cette étude, 465 séquences FLAIR chez des enfants et des adolescents (âge moyen 10.65 ± 4.22 ans, intervalle 2-19 ans, 220 de sexe masculin, 245 de sexe féminin) ont été analysées. Il a été observé que la texture de la substance blanche augmente pour atteindre un maximum vers 8-10 ans; les tendances sont différentes entre les deux sexes à l'adolescence. Il a également été observé que la texture de la substance grise augmente avec l'âge, et présente un maximum localisé à 8-10 ans. Dans le cas de la substance blanche, la texture présente une relation inverse avec l'intensité, et ce, peu importe l'âge. Le cerveau du sujet souffrant d'une affection a présenté des valeurs de texture anormales, soit en dehors des courbes de croissance normatives, dans les régions de la substance blanche et d'un œdème. **Conclusion :** Les courbes normatives des biomarqueurs de texture dans les séquences FLAIR peuvent être utilisées pour évaluer la maturation du cerveau et les changements structuraux à l'échelle microscopique chez l'enfant.

Keywords

magnetic resonance imaging, biomarkers, pediatrics, growth charts

Introduction

Abnormal brain development in children is seen in various diseases and disorders, including autism spectrum disorder, attention deficit/hyperactivity disorder, and epilepsy.¹ Maturation curves can be used to identify children with typical, delayed, or abnormal brain development. Normative maturation trajectories have been established for various MR imaging sequences in the paediatric age range.²⁻⁴ However, FLAIR sequences, although a mainstay of brain imaging, have limited information on maturation trajectories because signal intensities vary across MRI scanners and sequences. This work applies the FLAIR signal intensity standardization algorithm presented in a previous study⁵ to overcome this variability. FLAIR signal intensities have shown to be related to lipid and water content⁶ and may serve as indicators of maturation-related structural brain development.

Previous studies have shown that FLAIR texture parameters, which measure regional fluctuations in signal intensity, are related to cognition and robustly discriminate between neurodegenerative diseases in adults.^{7,8} FLAIR texture was correlated to MD and FA in adult populations, indicating that FLAIR texture is related to water content and diffusion.^{7,8} We hypothesize that FLAIR texture biomarkers can add value to maturation curves of the paediatric brain as they may provide supplementary information on tissue microstructure.

Percentile reference curves are standard tools describing the normal range of a parameter with respect to age. In clinical practice, physicians use percentile curves to evaluate measured values of patients. Comparing measurements to a reference standard aids in quantifying abnormalities against normative values. A limited set of percentile curves exist for paediatric parameters related to neurodevelopment, including brain volume, cortical thickness, total surface area, and head circumference.⁹⁻¹¹ The World Health Organization (WHO) publishes internationally accepted growth curves for children

younger than 5 years, including head circumference reference values for age and sex.⁹ A study by Zhang et al quantified annual changes of cortical thickness and subcortical volume of developing children between 1 and 6 years old using growth curve models.¹⁰ Lastly, Bethlehem et al aggregated 123 984 MRI scans between 115 days post-conception to 100 years of age. This provided brain curves over the human lifespan for regional volumes, mean cortical thickness, and total surface area which identified previously unreported neurodevelopmental milestones.¹¹

In this work, we aimed to assess a novel texture biomarker from T2-weighted FLAIR MR imaging in individuals 2 to 19 years of age without structural abnormalities to establish age- and sex-specific normative developmental curves.

Materials and Methods

Data

This study was approved by the local institutional review boards of a large Canadian university and hospital. Due to the retrospective nature of the study, informed consent was waived by the local research ethics board (2021-430-3). T2-weighted FLAIR and 3D T1-weighted MRI sequences were acquired in the clinical setting. All brain MRIs were reported as unremarkable by a paediatric neuroradiologist (M.W.). Imaging was acquired across MRI scanners from two vendors (Achieva, Philips Healthcare; Magnetom Skyra, Siemens), at field strengths of 1.5 T or 3 T. FLAIR sequences had section thicknesses of 3 to 5 mm and in-plane voxel dimensions of 0.6 to 1 mm, and TR, TI, and TE of 7 to 10 s, 2.3 to 2.9 s, and 85 to 150 ms respectively. 3D T1-weighted sequences had section thickness of 1 to 2 mm, in-plane voxel dimension of 1 mm, and TR, TE, and flip angle of 6 to 10 ms, 2 to 5 ms, and 7° to 15°, respectively.

Image Processing

FLAIR volumes were registered to the T1 space using the Advanced Normalization Tools symmetric normalization,¹² bias field-corrected,¹³ and intensity normalized.^{5,14} FreeSurfer Version 7.2¹⁵ was used to segment WM and GM regions on 3D T1-weighted images, and the masks were verified by a paediatric neuroradiologist (M.W.). GM subregions, deep GM (dGM), and cortical GM (cGM) were also segmented and verified. Segmentations were used to mask the respective regions of the FLAIR images and biomarkers were extracted from each region.

The texture biomarker extraction pipeline is demonstrated in Figure S1. FLAIR texture was investigated to measure the amount of local variations in signal intensity in a small window and a modified version of the microstructural marker in Bahsoun et al⁷ was used. For each slice, a local texture metric was computed as the average difference in signal intensity between the central window pixel and its neighbouring pixels (Supplementary Equation (1)). For regions with heterogeneous texture, there are rapid fluctuations in signal intensity and a large variation which result in a large value for texture. In smooth regions, the intensities are similar to one another, resulting in small variations and texture values. To analyze fine texture, the texture volume was Otsu thresholded¹⁶ and only the low amplitude variations were considered.⁷ The fine texture volumes were then masked per region to analyze texture in the WM and GM (cGM/dGM) regions separately. To maximize signal, as in Bahsoun et al,⁷ each regional texture volume was voxel-wise averaged across slices to yield mean 2D texture maps for GM, WM, dGM, and cGM. The median value of each regional texture map was taken as the final texture biomarker of the region.

FLAIR signal intensity and volume biomarkers were also extracted from each region investigate the correlations between texture and the 2 clinically established biomarkers. The FreeSurfer segmentations were used to mask the respective regions and the FLAIR signal intensity was obtained by computing the mean standardized FLAIR signal intensities per region. The volume biomarker was computed by summing up the voxels in each region and multiplying by the voxel resolution. To consider differences in head size, volumes were normalized by the intracranial volume (ICV).

Statistical Analysis

ANOVA was used to investigate differences in texture biomarker means between age groups with a significance level of $P < .05$. Growth curves were fitted using Generalized Additive Models for Location, Scale, and Shape (GAMLSS). Pearson's correlation analyses were performed to investigate relationships between the texture biomarker and signal intensity and volume per tissue, with significance level set at $P < .05$.

The GAMLSS model was used as the standard for creating percentile curves according to the WHO.¹⁷ It uses P-spline functions for estimating the mean, variance, skewness, and

Table 1. Cohort Summary.

Age range (y)	N	% Female
2-4	35	42.9
4-6	44	43.2
6-8	48	37.5
8-10	65	58.5
10-12	77	46.8
12-14	71	53.5
14-16	71	69.0
16-18.2	54	59.3

kurtosis distribution parameters of the measured variable with respect to age.^{18,19} As in the methods in Nagy et al,²⁰ all possible GAMLSS distributions were evaluated using the Akaike Information Criterion (AIC) estimator. The distribution with the lowest AIC score was chosen as the best fit model. The best-fit model was further verified through the model residuals—a model is well fit if the residuals are standard normal, or linear on its Q-Q plot. Percentile curves were plotted according to WHO standards, showing centiles 3, 15, 50, 85, and 97.²¹ Growth curves were modelled by tissue type and sex.

Proof-of-Concept Using Pathological Data

To examine the clinical applicability of the proposed growth curves in detecting abnormal neurodevelopment, a pre-operative MRI of a 15-year-old with a paediatric low-grade glioma was analyzed as proof-of-concept of real-world diagnostic and monitoring utility. We extracted texture and intensity biomarkers from the normal appearing white matter (NAWM) and the edema region surrounding the tumour, and plotted the biomarkers on the normative WM growth curves.

Results

Axial FLAIR and sagittal 3D T1-weighted FLAIR sequences of 512 children between 2 and 19 years of age were included in the study. Forty-seven data sets with marked registration errors and poor segmentation masks were excluded, leading to a final data set of 465 FLAIR and T1-weighted sequences (mean age of 10.65 years and 220/245 male/female split), summarized in Table 1.

FLAIR Biomarker Extraction

Summary statistics of the biomarkers extracted from the paediatric MRI are shown in Tables S1 to S3. The mean 2D texture maps of the GM, WM, cGM, and dGM of different ages are shown in Figure 1. ANOVA tests demonstrated significant differences ($P < .01$) in texture biomarker means between age groups for all tissue regions (Table S1). Boxplots showing the difference in texture biomarkers over the paediatric age range can also be found in Figure S2.

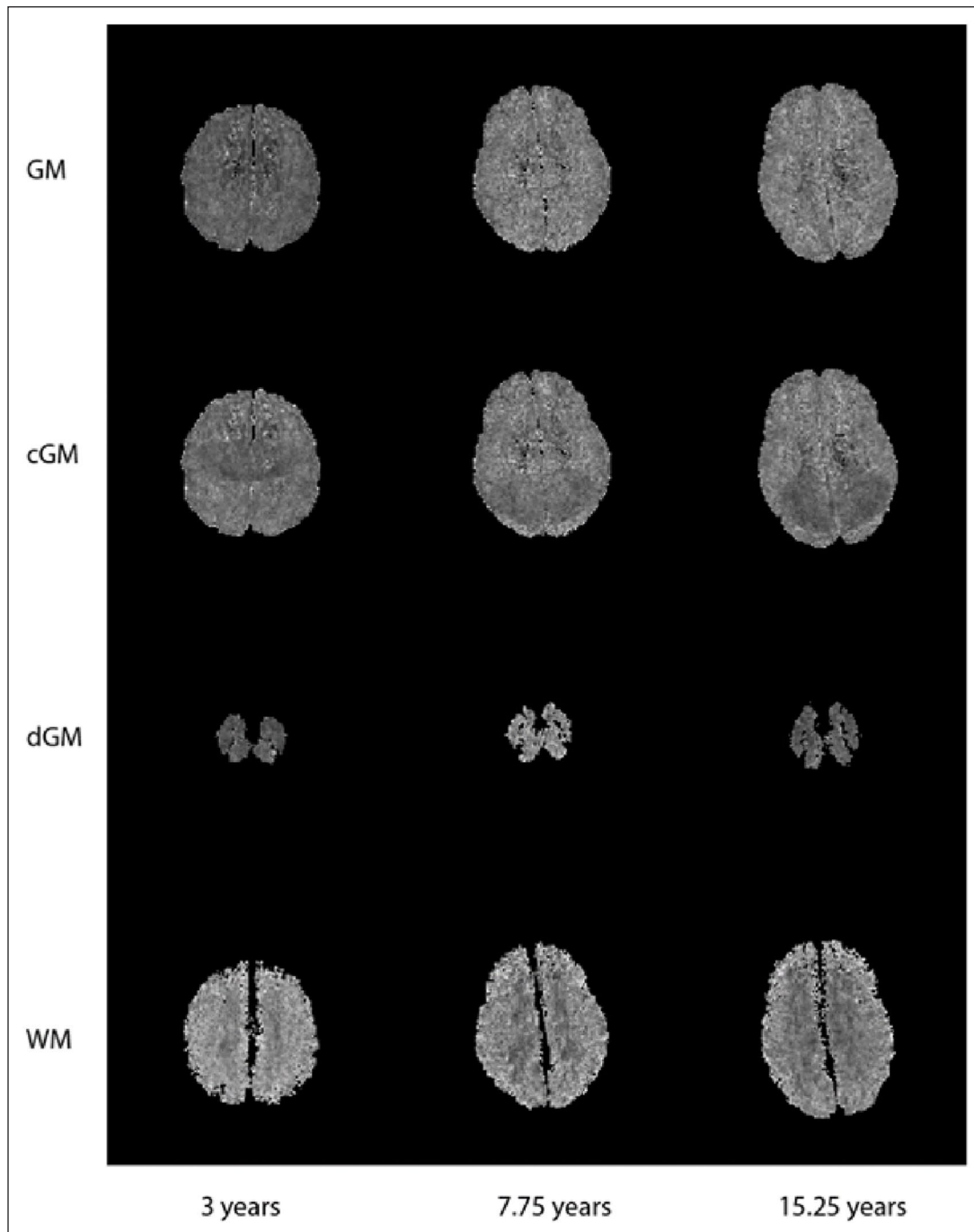


Figure 1. Sample mean 2D texture maps of the GM, cGM, dGM, and WM of different ages.

Note. GM=grey matter; cGM=cortical grey matter; dGM=deep grey matter; WM = white matter.

Growth Curves

GAMLSS growth curves were developed for the texture biomarker of each region. The parameters found for the best fit models are shown in Table S4. All residuals were found to be standard normal distributions in the proposed models, and the corresponding residual plots can be found in Figure S3. The final texture growth curves of girls and boys for GM and WM are shown in Figure 2. Plots for the entire population sample along with cGM and dGM curves are shown in Figures S4

and S5. For completeness, and examination of the pathological case, the WM intensity growth curve results are also shown in Figure S6 and Table S5.

For WM tissue regions, the texture feature demonstrated a maximum “roughness” at approximately 10 years of age for both girls and boys. The WM texture for girls demonstrated a slight constant decrease after 10 years, while boys demonstrated an increasing texture trend in adolescence after 14 years of age. In GM, FLAIR texture increased with age for

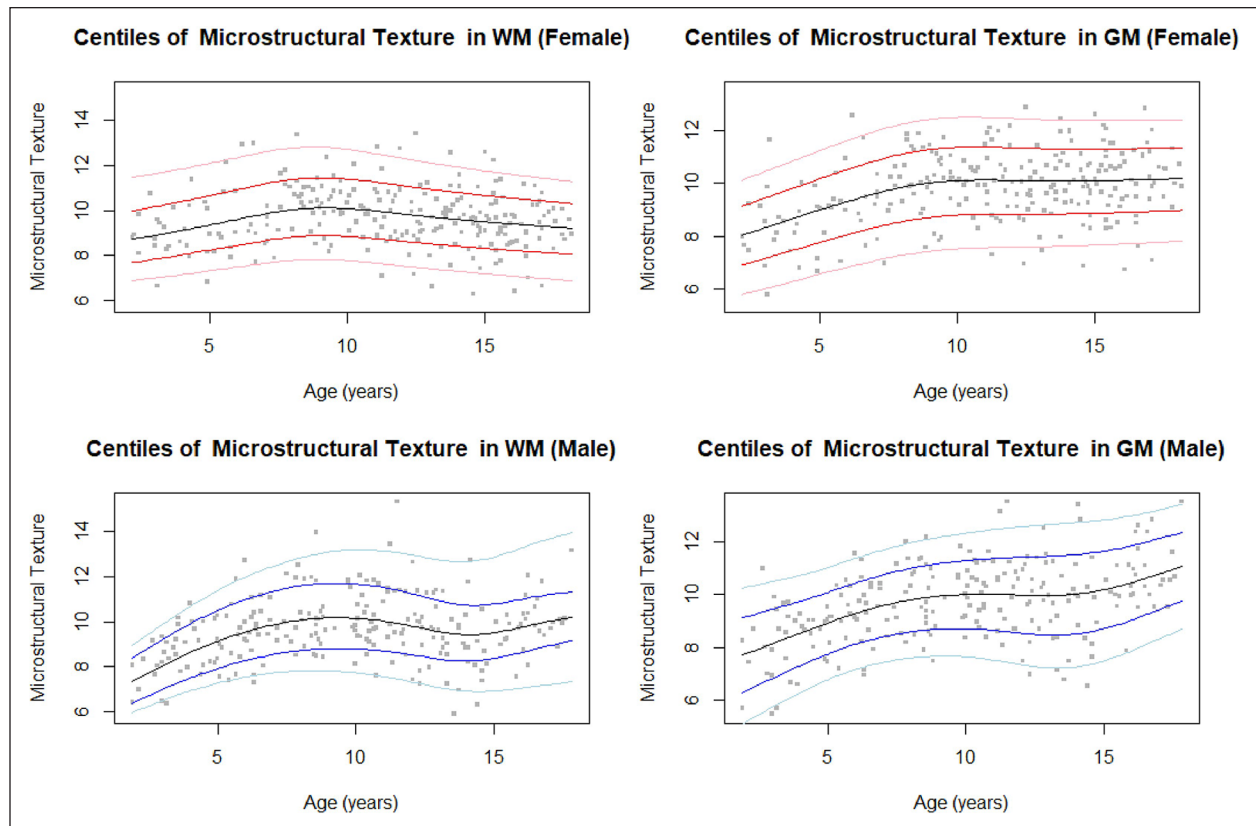


Figure 2. Centiles (3, 15, 50, 85, 97) for FLAIR microstructural texture biomarker from GM and WM in girls (top) and boys (bottom). Note. GM = grey matter; WM= white matter.

both boys and girls, with a peak around 10 years of age. As was found in a previous study,⁵ the patterns of the GM closely resembled those of the cGM, with dGM showing slightly different patterns. The dGM texture curve in females was relatively constant, while the dGM texture curve in males demonstrated slight increase in texture with age.

Figure S7 demonstrates images of a paediatric low-grade glioma with biomarkers from the surrounding edema and the NAWM to demonstrate proof of concept. The texture of the edema falls around the 85th percentile on the WM curve, while the NAWM demonstrated a texture value outside of the normative curves, 0.308 lower than the 1st percentile for that age (Figure 3, Tables 2 and 3). On the intensity growth curve, the edema demonstrated abnormally high signal intensity, while the NAWM intensity was around the 85th centile (Figure S6).

Texture, Signal Intensity, and Volume/ICV Correlations

To further analyze the relationship of texture biomarkers with respect to signal intensity and volume, Pearson's correlation tests were performed as seen in Figure S8. Tabulated results are found in Tables S6 and S7. Texture was strongly negatively correlated ($P < .001$) with signal intensity in the WM and dGM regions for all age groups. Only the 2 to 6 year age

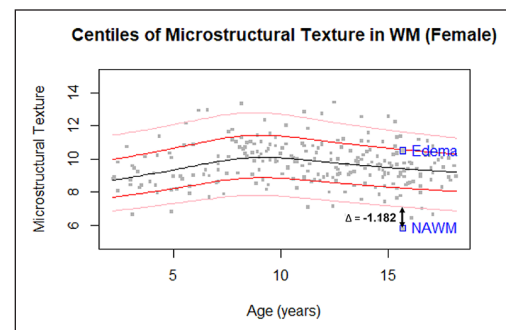


Figure 3. Centiles (3, 15, 50, 85, 97) for FLAIR microstructural texture biomarker from WM in girls with texture from the edema and NAWM regions of the pathological volume annotated. Note. NAWM = normal appearing white matter.

group for GM and 2 to 6 and 10 to 14 year age groups for cGM showed significant ($P < .05$) correlations between texture and signal intensity. cGM texture showed significant ($P < .05$) negative correlations with volume in 2 to 6, 6 to 10, and 10 to 14 year age groups. In the WM region only the 10 to 14 year age group showed significant ($P < .05$) negative correlations with volume. Interestingly, in the dGM, the 14 to 18 year age group showed a significant ($P < .05$) positive correlation between texture and volume.

Table 2. Distance of Pathological Tissue Texture From the Closest Percentile.

Pathological tissue	Age, sex	Closest percentile	Normal texture percentile value	Pathological texture value	Distance from closest percentile
Edema	15.67, F	85th	10.653	10.518	-0.135
NAWM	15.67, F	3rd	7.015	5.833	-1.182

Table 3. Distance of Pathological Tissue Texture From the Closest Minimum/Maximum Percentile (1st or 99th Percentiles).

Pathological tissue	Age, sex	Closest min/max percentile	Normal texture percentile value	Pathological texture value	Distance from closest min/max percentile
Edema	15.67, F	99th	12.264	10.518	-1.746
NAWM	15.67, F	1st	6.141	5.833	-0.308

Discussion

We used FLAIR texture of the brain to develop normative growth curves for children over the paediatric age range. Growth curves for the brains of normal children have strong clinical utility, as they can be used to quantitatively monitor neurodevelopment of children, and to assess pathological disease. We analyzed a novel FLAIR texture biomarker in 465 children and adolescents between 2 and 19 years of age.

In the WM, we found the FLAIR texture marker to increase from 2 to 19 years of age, with nonlinear trajectories. Texture increased to around 10 years of age, and then slightly decreased in adolescence while remaining higher than in early years. Low values for FLAIR texture indicate the WM region to have locally smooth (homogeneous) characteristics, while higher values indicate localized roughness (rapid fluctuations of signal intensity in a smaller window or heterogeneity). Previous studies have shown FLAIR texture and signal intensity to be related to water content, with strong correlations to mean diffusivity (MD), and to a lesser degree the organization of tissue, with moderate correlations to fractional anisotropy (FA).^{7,8} Therefore, signal intensity, and fluctuations in signal intensity as measured by the proposed FLAIR texture marker, may be related to tissue organization and presence of water.

Texture in the WM across age groups was found to be significantly different over the paediatric age range, with texture having a strong negative correlation with signal intensity in all age groups. The texture marker increased to a maximum at approximately 10 years of age, consistent with biphasic patterns across the age range found in previous studies.⁵ These results also agree with existing diffusion tensor imaging (DTI) studies in 2- to 10-year-old children that demonstrated an increase in FA and corresponding decrease in MD.²² Studies have shown that there is high water content in the WM at 2 years of age which decreases with myelination.²³ This is represented as an increase in FLAIR texture within this age range, suggesting that FLAIR texture may be capturing increased edge information related to myelination of fibre tract axons. After the age of 10 years, FLAIR texture decreased

slightly. Studies have shown that axonal maturation occurs in this age range, when axonal bundles begin to thicken, and the lipid components increase.²⁴ This may indicate that FLAIR biomarkers also capture the process of axonal thickening and packing, in which FLAIR texture demonstrates more homogeneity with higher lipid content.

When assessing girls and boys separately, the texture marker for girls decreased after 10 years, while it reached a local peak around 10 years of age and increased again at around 14 years in boys. It has been found that boys aged 5 to 18 years demonstrate greater variance and rates of increase in WM volume compared to girls,²⁵ which may be a source of the difference in texture trends between sexes. Additionally, studies have found axonal thickening and density to increase around puberty,²⁴ which occurs earlier for girls than for boys, and which may also contribute to the observed difference in trends at the 14-year mark.

As a proof-of-concept, we assessed the biomarkers from a 15-year-old girl with paediatric low-grade glioma. The signal intensity and texture in the edema and NAWM regions were computed and compared to the WM normative curves for females. The edema had abnormally high signal intensity and relatively normal texture values, while the NAWM showed abnormally low texture and normal signal intensity. Abnormally low texture in the NAWM may be related to reduced myelination, less tightly packed axons, and more leakage of interstitial fluid in a pathological brain.²⁶ In contrast, the signal intensity of the NAWM falls within the normative curve, suggesting the texture marker may provide additional information on tissue microstructure and injury. Interestingly, the edematous region falls in the 85th percentile of the normative WM texture curve, which suggests compared to the average subject at this age, there is more heterogeneity in this tissue region. These findings demonstrate the potential utility of normative growth curves and the proposed texture biomarker.

The biomarkers in the GM followed the same trends as the cGM, since cGM is the dominant volume in the GM region. cGM texture of the whole sample increased over the paediatric age. Interestingly, texture was only negatively

correlated to intensity in the 2 to 6 and 10 to 14 year age groups. Conversely, texture in the cGM was strongly negatively correlated to volume in all but the 14 to 18 year age group. Previous studies have found GM volume and cortical thickness reduction from childhood through adolescence due to neuronal pruning.²⁷ Additionally, compaction from WM myelination causes GM density to increase while volume decreases with age.²⁷ As Ribeiro et al²⁸ had found a significant correlation between neuronal density and gyrification in the GM, increase in FLAIR texture may be related to cortical folding, as the local signal intensity variations captured by the texture marker would increase for more complex surfaces.

For females, a steep increase in GM texture was seen from 2 to 10 years, after which texture remained relatively constant. For males, there was a continuous increase in texture across the entire age range. This corresponds to existing studies which found faster cortical maturation in females than in males, possibly corresponding to age differences at puberty.^{29,30} Texture in the dGM increased slightly over the age range for the whole sample and was strongly inversely correlated to signal intensity. Interestingly, texture in the dGM also demonstrated a significant positive correlation with volume in the 14 to 18 year age group. This may be related to myelination of the basal ganglia, which differs from the development of cortical GM.

There are several limitations of our study. First, while the sample size of the whole group is large and well-distributed over the age range, the ratio of boys to girls varies between age groups, which could make growth curves more susceptible to outliers. Another limitation pertains to the analysis of GM and WM tissues as global regions. While this is useful for constructing growth curves as a proof-of-concept, studies have found different GM and WM regions vary in their developmental trends. Future work will need to investigate parcellations of each region further. Further, DTI imaging would have been useful in correlating the proposed FLAIR biomarkers with validated tissue integrity such as MD and FA, but these sequences were unavailable for our sample. Future work may benefit from the acquisition of DTI for further investigation of the FLAIR biomarkers. Lastly, larger cohorts of pathological volumes should be investigated in future work, to validate the clinical relevance of the proposed texture biomarkers and growth curves in abnormal neurodevelopment tracking and disease detection, beyond the proof-of-concept in this work.

This study proposes a set of developmental curves created using novel FLAIR texture biomarkers to assess neurodevelopment in children and adolescents. The texture biomarker assesses local signal intensity fluctuations, which may reflect microstructural changes. In the WM, texture demonstrated an inverse relationship with intensity, which may be reflective of myelination, axonal packing, and water content. In the GM, texture was found to increase continually demonstrating an inverse relationship with volume. NAWM and edema in a pathological brain exhibited abnormal texture values outside

of the normative growth curve range, demonstrating the clinical utility of biomarker growth curves. In contrast to previous studies that focused primarily on intensity standardization and biomarkers,⁵ this work introduces a novel FLAIR texture measure and growth curves, providing additional insight into microstructural tissue development beyond intensity-based approaches.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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Supplemental Material

Supplemental material for this article is available online.

References

1. Parenti I, Rabaneda LG, Schoen H, Novarino G. Neurodevelopmental disorders: from genetics to functional pathways. *Trends Neurosci.* 2020;43:608-621.
2. Kızıldağ B, Düşünceli E, Fitoz S, Erden I. The role of classic spin echo and FLAIR sequences for the evaluation of myelination in MR imaging. *Diagn Interv Radiol.* 2005;11:130-136.
3. Murakami JW, Weinberger E, Shaw DWW. Normal myelination of the pediatric brain imaged with fluid-attenuated inversion-recovery (FLAIR) MR imaging. *AJNR Am J Neuroradiol.* 1999;20:1406-1411.
4. Ganzetti M, Wenderoth N, Mantini D. Whole brain myelin mapping using T1- and T2-weighted MR imaging data. *Front Hum Neurosci.* 2014;8:671.
5. Chan K, Ghazvanchahi A, Rabba D, et al. Brain maturation patterns on normalized FLAIR MR imaging in children and adolescents. *AJNR Am J Neuroradiol.* 2023;44(9):1077-1083. doi:10.3174/ajnr.A7966
6. Maillard P, Carmichael O, Harvey D, et al. FLAIR and diffusion MRI signals are independent predictors of white matter hyperintensities. *AJNR Am J Neuroradiol.* 2013;34:54-61.
7. Bahsoun M-A, Khan MU, Mitha S, et al. FLAIR MRI biomarkers of the normal appearing brain matter are related to cognition. *Neuroimage Clin.* 2022;34:102955.
8. Chan K, Fischer C, Maralani PJ, Black SE, Moody AR, Khademi A. Alzheimer's and vascular disease classification using regional texture biomarkers in FLAIR MRI. *Neuroimage Clin.* 2023;38:103385.
9. WHO. Head circumference for age. 2004. Accessed November 1, 2023. <https://www.who.int/tools/child-growth-standards/standards/head-circumference-for-age>
10. Zhang H, Li J, Su X, et al. Growth charts of brain morphometry for preschool children. *Neuroimage.* 2022;255:119178.

11. Bethlehem RAI, Seidlitz J, White SR, et al. Brain charts for the human lifespan. *Nature*. 2022;604:525-533.
12. Avants BB, Tustison NJ, Song G, Cook PA, Klein A, Gee JC. A reproducible evaluation of ANTs similarity metric performance in brain image registration. *Neuroimage*. 2011;54:2033-2044.
13. Gennatas ED, Avants BB, Wolf DH, et al. Age-related effects and sex differences in gray matter density, volume, mass, and cortical thickness from childhood to young adulthood. *J Neurosci*. 2017;37:5065-5073.
14. Reiche B, Moody AR, Khademi A. Pathology-preserving intensity standardization framework for multi-institutional FLAIR MRI datasets. *Magn Reson Imaging*. 2019;62:59-69.
15. Fischl B, Dale AM. Measuring the thickness of the human cerebral cortex from magnetic resonance images. *Proc Natl Acad Sci USA*. 2000;97:11050-11055.
16. Otsu N. A threshold selection method from gray-level histograms. *IEEE Trans Syst Man Cybern*. 1979;9:62-66.
17. Cole TJ, Stanoevic S, Stocks J, et al. Age- and size-related reference ranges: a case study of spirometry through childhood and adulthood. *Stat Med*. 2009;28:880-898.
18. Stasinopoulos DM, Rigby RA. Generalized additive models for location scale and shape (GAMLSS) in R. *J Stat Softw*. 2008;23:1-46.
19. Dinga R, Frazz CJ, Bayer JMM, Kia SM, Beckmann CF, Marquand AF. Normative modeling of neuroimaging data using generalized additive models of location scale and shape. Preprint. doi:10.1101/2021.06.14.448106
20. Nagy P, Kovacs E, Moreno LA, et al. Percentile reference values for anthropometric body composition indices in European children from the IDEFICS study. *Int J Obes*. 2014;38:S15-S25.
21. Canadian Pediatric Endocrine Group. WHO growth charts for Canada. 2014. Accessed October 28, 2023. <https://cpeg-gcep.net/content/who-growth-charts-canada>
22. Lebel C, Deoni S. The development of brain white matter microstructure. *Neuroimage*. 2018;182:207-218.
23. Fadeel SRA, Montasser MM, Etaby AN, Darweesh RM. The role of diffusion weighted magnetic resonance imaging in assessment of normal myelination in infantile brain. *Alex J Med*. 2015;51:271-276.
24. Genc S, Raven EP, Drakesmith M, et al. Novel insights into axon diameter and myelin content in late childhood and adolescence. *Cereb Cortex*. 2023;33:6435-6448.
25. Schmithorst VJ, Holland SK, Dardzinski BJ. Developmental differences in white matter architecture between boys and girls. *Hum Brain Mapp*. 2007;29:696-710.
26. Friedrich M, Farrher E, Caspers S, et al. Alterations in white matter fiber density associated with structural MRI and metabolic PET lesions following multimodal therapy in glioma patients. *Front Oncol*. 2022;12:998069.
27. Tustison NJ, Avants BB, Cook PA, et al. N4ITK: improved N3 bias correction. *IEEE Trans Med Imaging*. 2010;29:1310-1320.
28. Ribeiro PFM, Ventura-Antunes L, Gabi M, et al. The human cerebral cortex is neither one nor many: neuronal distribution reveals two quantitatively different zones in the gray matter, three in the white matter, and explains local variations in cortical folding. *Front Neuroanat*. 2013;7:28.
29. Lenroot RK, Gogtay N, Greenstein DK, et al. Sexual dimorphism of brain developmental trajectories during childhood and adolescence. *Neuroimage*. 2007;36:1065-1073.
30. Mutlu AK, Schneider M, Debbané M, Badoud D, Eliez S, Schaer M. Sex differences in thickness, and folding developments throughout the cortex. *Neuroimage*. 2013;82:200-207.