Automatic measurements of the corpus callosum in the follow-up of preterm children: Methodology and validation

Jaime Simarro[1,2,*], Manuel Lubián[4], Bahram Jafrasteh[3], Simón Lubián[3,4], Thibo Billiet[1], Els Ortibus[2,5,†] and Isabel Benavente-Fernández[3,4,6,†]

[1]*Research and Development, icometrix, Leuven, Belgium*

[2]*Department of Development and Regeneration, KU Leuven, Leuven, Belgium*

[3]*Biomedical Research and Innovation Institute of Cádiz (INiBICA) Research Unit, Puerta del Mar University Hospital, Cádiz, Spain*

[4]*Division of Neonatology, Department of Paediatrics, Puerta del Mar University Hospital, Cádiz, Spain*

[5]*Department of Pediatric Neurology, UZ Leuven, Belgium*

[6]*Area of Paediatrics, Department of Child and Mother Health and Radiology, Medical School, University of Cádiz, Cádiz, Spain*

Abstract

Brain injury in preterm infants is associated with a high risk of neurodevelopmental disability. One of the most frequent forms of brain injury is white matter injury. The largest white matter structure is the corpus callosum and measurements of this structure have been associated with white matter volume. Consequently, quantification of the corpus callosum could provide an insight into the white matter injury related to preterm birth. However, manual measurements require an experienced rater, are highly time-consuming and suffer from high inter- and intra-rater variability.

In this paper, we present an automated method for measuring the corpus callosum on T1-weighted images of children, and we evaluate the model in terms of accuracy performance. Automatic measurements of the anterior area, posterior area and length of the corpus callosum have a good intraclass correlation coefficient while relatively low absolute error compared to the same measurement performed manually by an expert child neurologist.

Keywords

MRI quantification, follow-up of preterm infant, corpus callosum, white matter injury

1. Introduction

Brain injury in preterm infants is associated with a high risk of neurodevelopmental disability [1]. White matter injury (WMI) is one of the most frequent forms of brain injury in this population [2]. It includes a spectrum of lesions from periventricular leukomalacia (PVL) to a diffuse pattern of WMI [2]. WMI is associated with adverse neurodevelopmental outcomes, for

DETERMINED 2022: Neurodevelopmental Impairments in Preterm Children — Computational Advancements, August 26, 2022, Ljubljana, Slovenia

*Corresponding author.

† EO and IBF are Joint Senior Authors.

jaime.simarro@icometrix.com (J. Simarro)

example, around 10 % of infants with very low birth weight (those born with 1500g or less) that develop PVL later exhibit cerebral palsy and 50% have cognitive and behavioral deficits [3].

The corpus callosum (CC) is the largest white matter (WM) structure and has a key role in interhemispheric functional connectivity [4]. As a result of the importance of this brain structure, the CC is defined as a region of interest in several assessment tools of brain abnormality in preterm infants[5] and children [6]. In addition, this WM structure is associated with WM volume in children with cerebral palsy [7].

Consequently, quantification of this structure could provide an insight into the WM injury related to preterm birth. In spite of the potential of manual quantification of CC [8, 9], these manual measurements require an experienced rater, are highly time-consuming and suffer from high inter- and intra-rater variability [10].

In contrast, artificial intelligence-based software for analysing magnetic resonance images (MRI) has proven to be highly successful in boosting accuracy and increasing time efficiency. In a systematic literature review, Cover et al. summarized the methods for segmentation and parcellation of CC divided in model-based, region-based, thresholding and machine learning [10].

A semi-automatic segmentation tool via constrained elastic deformation of flexible Fourier contour model was applied to a pediatric dataset [11]. Despite the high reliability of the method segmenting the CC (test-retest intra-class correlation coefficient of 0.99), user interaction is required to correct the automatic segmentation. The development of a fully automatic tool for quantification of CC in pediatrics is delayed significantly due to considerable challenges such as partial volume effect, intensity inhomogeneity, extremely variable anatomy, and image artifact (e.g. ghost artifact).

In this study, we aim to overcome these challenges and propose a novel methodology that automatically quantifies the CC and its subregions. Moreover, we will evaluate the performance of these measurements compared with those obtained by manual segmentation.

2. Dataset and methods

2.1. Dataset

The dataset is composed of 65 MRI scans from patients that had been admitted at the Neonatal Intensive Care Unit after being born preterm. These scans were performed during the follow-up of these children at 8 years of age.

Table 1: Demographics of the dataset

# Patients	65
Sex Female (%)	36 (55.3%)
Age (min-max)	8.48 (6.37-10.25) years
Gestational Age at birth (min-max)	29.6 (24.0-34.0) weeks
Birth Weight (min - max)	1325 (550 - 2345) g
Birth Weight<1500g (%)	48 (73.8%)

T1-weighted (T1w) images were acquired at the Hospital Puerta del Mar, Cadiz, using a Siemens Symphony 1.5T MRI system with two different scanning parameters (repetition time = 1910 ms, echo time = 3.5 ms, flip angle = 15 degrees, voxel, size = $1x1x1$ mm3) and (repetition time = 2200 ms, echo time = 3.25 ms, flip angle = 8 degrees, voxel, size = $0.5x0.5x1$ mm3). Two scans were

excluded due to low image quality. Table 1 summarizes the main demographic characteristics of this population.

2.2. MRI analysis

Automatic quantification of the CC from a T1w image was performed in several steps. Figure 1 illustrates the steps proposed in this algorithm. Below, we describe the different steps in detail.

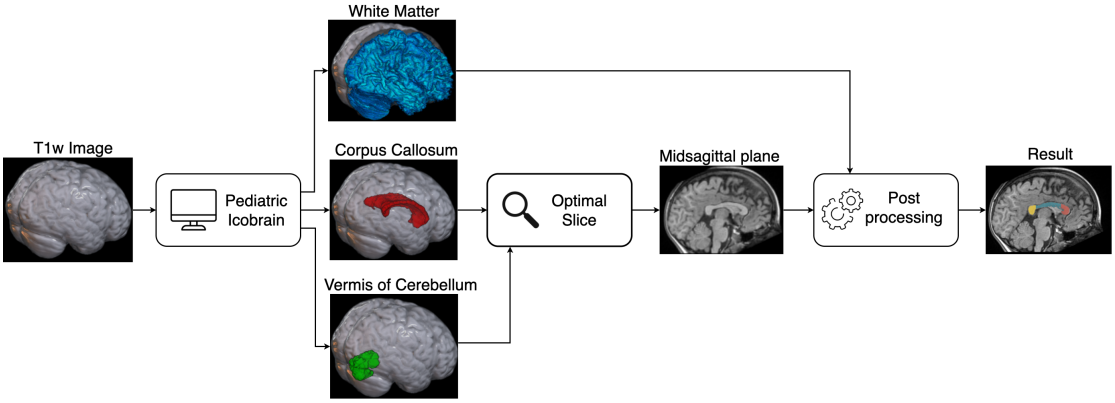

Figure 1: Main processing steps of the pipeline to obtain the automatic measurements of the corpus callosum

2.2.1. Pediatric icobrain

Pediatric icobrain is a model optimized for the pediatric population that is based on the medical device software of icobrain adult pipeline. In summary, the icobrain adult pipeline works as follows: After skull stripping, bias correction and atlas to image registration, the T1w image is segmented optimizing a Gaussian Mixture Model that considers the image intensity, the spatial prior knowledge, the intensity nonuniformities and the spatial consistency [12]. As icobrain is an adult-based pipeline, it was modified to be used for pediatric patients by including age-specific pediatric atlases [13, 14] . Automated segmentation of WM, CC and vermis of the cerebellum was performed on the T1w MR scans using the Pediatric Icobrain model.

2.2.2. Selection of the Optimal Slice

CC is well defined in the 2D midsagittal plane. However, this structure can not be defined in the axial plane and coronal plane since there is not a discontinuity in the WM tracks. Therefore, structural measurements of the CC are performed in the midsagittal plane.

Midsagittal plane is the sagittal slice in which the 4th ventricle and the vermis of the cerebellum are maximally visible. Taking into consideration these prior anatomical landmarks, we used the $argmax$ algorithm to select the midsagittal plane as the sagittal slice with maximum area of vermis.

$$\underset{x}{argmax}\, f(x) := \{x : f(s) \leq f(x) for\, all\, s\, \in X\} \tag{1}$$

where $f(x)$ denotes the amount of the vermis in an x sagittal slice and X the complete set of the sagittal slices.

Alignment with the horizontal axis. As there is considerable heterogeneity in the CC orientation within healthy brains, mainly following the orientation of the brainstem, expert readers typically align all the CC by manually defining the anterior and posterior points of the CC. The proposed algorithm takes advantage of the morphology of the CC to mimic this manual process. Firstly, the contour of the segmentation was fitted to an ellipse. The major axis of the ellipse represents the maximal anterior-posterior distance of the CC and therefore, it can be used to rotate and align all the images (see Figure 2). Alignment of all the images using the CC anterior-posterior axis facilitates the visual interpretation of the parcellation while enhancing the explainability of the algorithm.

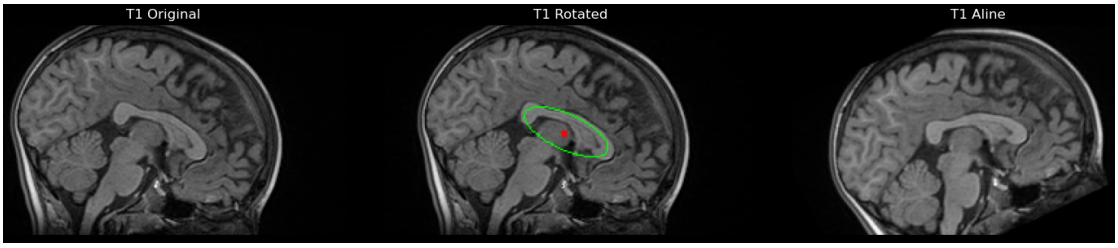

Figure 2: Midsagittal plane of T1-weighted image. Note how the corpus callosum is aligned with the horizontal axis by capturing the anterior-posterior axis of this structure with an ellipse fitting.

2.3. Post-processing

Several post-processing steps were conducted in order to fine-tune the segmentation of the CC.

Prior Anatomical Knowledge of the CC defines WM as the only tissue in this structure. Consequently, this anatomical knowledge was forced into the CC segmentation.

Smoothing of the contours. Alignment of the CC requires a rotation and therefore, an interpolation (bilinear), producing noisy sharp edges in the contour of the CC (which does not represent the anatomy of the structure). This noise was removed using a morphological operation of opening.

$$CC \circ K = (CC \ominus K) \oplus K \tag{2}$$

where $\circ$ denotes the morphological operation of opening, which is just an erosion [1] $\ominus$ followed by a dilation [2] $\oplus$, K denotes a $2x2$ kernel.

[1] Erosion. The value of the output pixel is the minimum value of all pixels in the neighborhood defined by the kernel.
[2] Dilation. The value of the output pixel is the maximum value of all pixels in the neighborhood defined by the kernel.

Largest connected component. CC appears in the midsagittal plane as a single component. However, in some patients the CC is over-segmented, capturing another WM structure, the fornix. The selection of the largest connected component (i.e. the CC) removed the unconnected segmentation of the fornix. This step has the potential limitation of removing an unconnected region of the CC mask, although, as consequence of the robust pediatric icobrain pipeline were atlas to image registration is used, there are no cases with an unconnected CC mask.

Equidistant parcellation and area computation The subdivision of the CC into smaller regions, such as rostrum, genu, body and splenium, is known as parcellation [10]. Our parcellation is based on the study by Park et al. [4], which was also used in prior manual segmentation. The subdivision in 3 sub-regions is proposed in this work in order to be easily reproducible in the clinical setting. In our model, a longitudinal division of 5 equidistant regions was computed. These regions were then clustered as follows: the anterior region, including the rostrum and genu; the central region, including the 2nd, 3er and 4th equidistant regions of the body of the CC; and the posterior region, including the splenium. The anterior-posterior length was also computed.

2.4. Statistical methodology

Accuracy can be defined as the degree of closeness of measurements of a quantity (e.g. area of the CC) to that quantity's actual value. In most cases, this actual value will not be known and, therefore, the accuracy is assessed by comparing the measurements produced by the algorithm, with reference values (ground truth), in this case, produced by an independent child neurologist.

Intraclass correlation coefficient (ICC) computes the reliability of measurements of two raters (i.e. manual and automatic). We selected the two-way random-effects model with absolute agreement. Interpretation of ICC follows the well-known guidelines presented in [15].

Mean absolute error (MAE) is a measure of errors between automatic and manual quantification of the regions.

$$MAE = \frac{\sum_{i=1}^{n} |y_i - \hat{y}_i|}{n} \tag{3}$$

where n denotes the number of patients, y_i the measurement of the manual expert and $\hat{y}_i$ the automatic measurement.

3. Results

3.1. Quantitative analysis

The ICC (CI 95%) performance of the algorithm is not uniform in all the measurements, ranging from 51.23 (2.03-74.06) for the central region to 94.77 (85.86 - 97.53) in the measurement of the length. Automatic measurements of the anterior area and length show a good ICC with the manual measurements with a relatively low percentage of mean absolute error (i.e. <10%). A

more detailed description of this inter-rater reliability experiment can be seen in Figure 3 and Table 2.

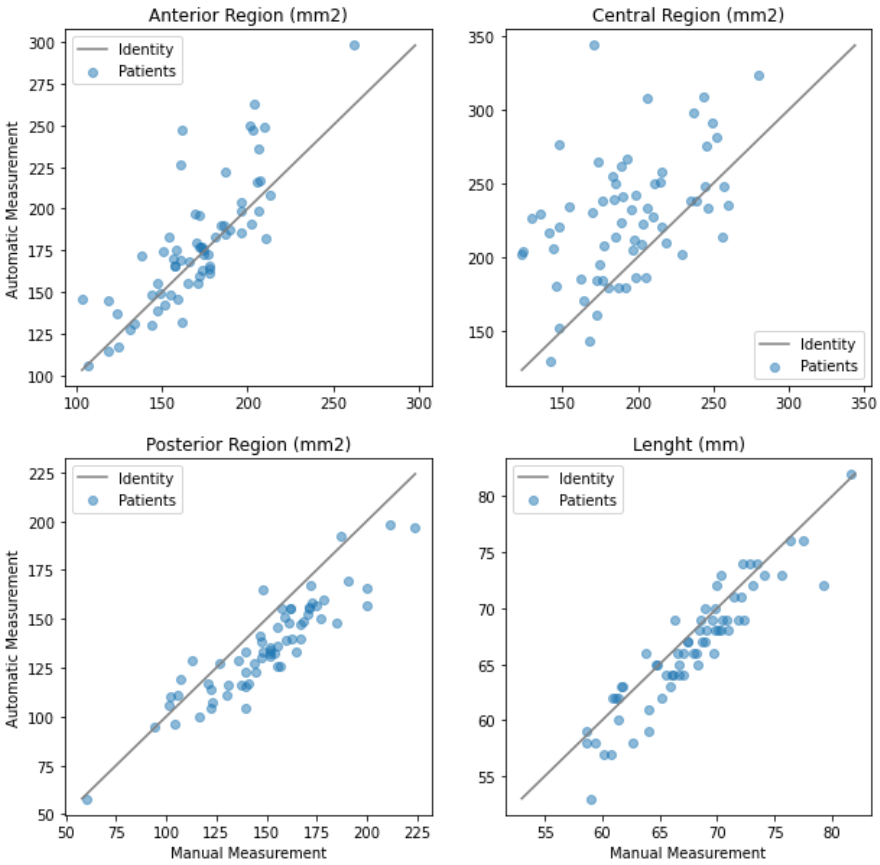

Figure 3: Scatter plots illustrating the corpus callosum quantification compared to the manual quantification of an expert child neurologist.

Table 2
Accuracy of the automatic measurements compared with expert manual quantification. The reference for the Mean Absolute Error is the manual measurement

Region	ICC (CI 95%)	Mean Absolute Error (%)
Anterior	86.48 (76.25 - 92.08)	16.33 mm2, (9,61%)
Central	51.23 (2.03 - 74.06)	40.83 mm2, (21,12%)
Posterior	88.12 (20.34 - 96.11)	16.40 mm2, (10,94%)
Length	94.77 (85.86 - 97.53)	1.89mm, (2,79%)

The central region has a mean absolute error higher than 20%. As illustrated in Figure 4, measurements in this region have a non-zero difference due to an overestimation of the automatic method.

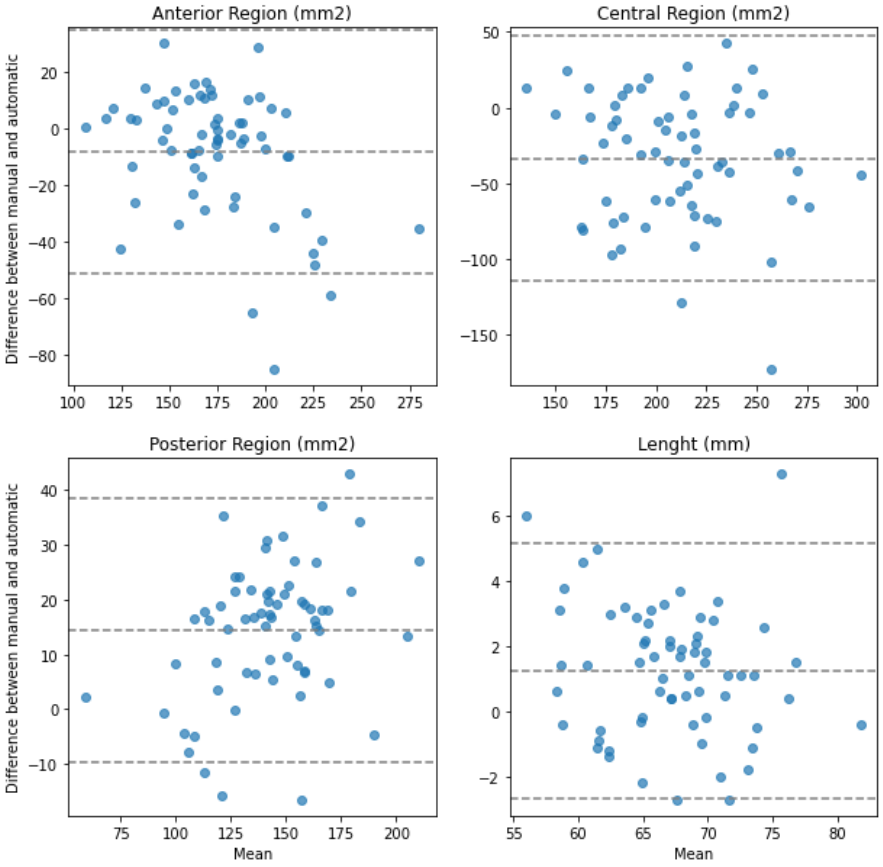

Figure 4: Bland–Altman plot of the corpus callosum measurements. Horizontal lines represent the average difference and the 95% limits of agreement (i.e. average difference ± 1.96 standard deviation of the difference).

3.2. Qualitative analysis

Figure 5 illustrates the automatic parcellation of the CC in three patients. We can observe an accurate segmentation in patients A and B. In contrast, in patient C, there is prominent thinning of the CC producing an extreme variability from the healthy anatomy and consequently, an inaccurate quantification (see red circle in Figure 5).

4. Discussion and conclusions

In this paper, we presented a preliminary evaluation of the proposed automatic method. Results seem to be in line compared with other proposed methods, although direct comparison is not possible as no other work computes the same region of interest.

Measurements of the anterior area and length of the CC have a good ICC while relatively low absolute error compared to manual measurement of an expert child neurologist. In the posterior region, the ICC is high although the poor level of reliability of 95% confident interval should be

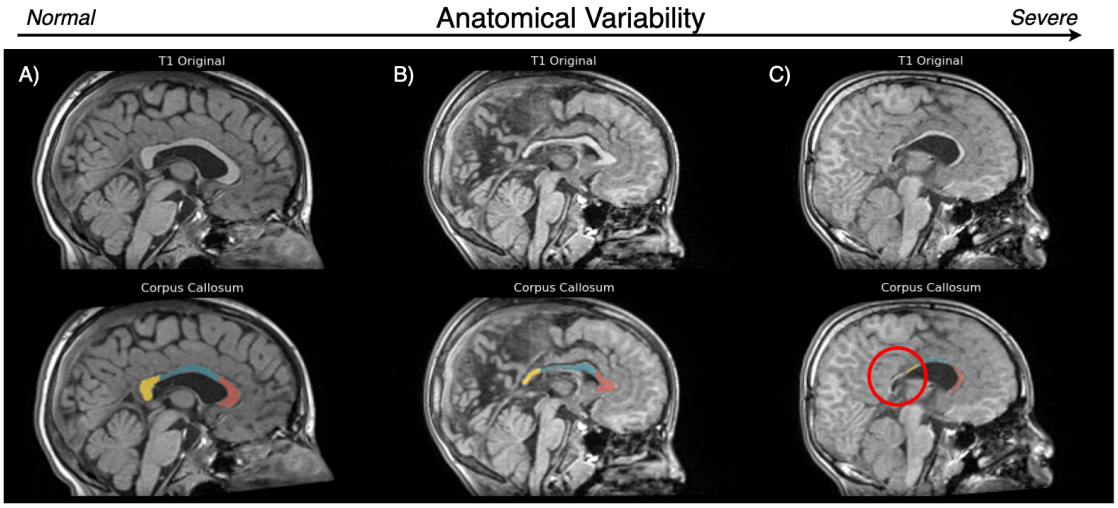

Figure 5: Illustration of the corpus callosum parcellation for several anatomical variabilities.

further studied. These promising results allow a quantitative and objective future investigation of the relationship between the anatomy of the CC and white matter injury related to preterm birth.

In contrast, the automatic measurement of the area of the central region of the CC shows a high error with respect to the manual measurement. This overestimation of the area is consequence of the over-segmentation of the CC including the fornix in this central region. Segmentation of CC without including the fornix is a complex task as both structures are similar and proximal [10].

We have been able to show that the methodology has the potential to properly handle the main challenges in pediatric quantification of the CC (e.g. intensity heterogeneity, minor image artifact). However, in some cases where there is extremely variable anatomy (i.e. prominent thinning of the CC) the algorithm under-segments this structure, proving an even lower volume quantification. Nevertheless, this low volume quantification also highlights the volume abnormality.

The methodology will be further improved in order to face the mentioned challenges. The pediatric icobrain block could be updated with a more advance supervised learning methodology (i.e. deep convolutional neural networks) which will allow to remove consistent errors, such as the over-segmentation of the fornix or under-segmentation in cases with extremely variable anatomy, by adding new training cases [16]. Moreover, the current turn-around-time of 30 minutes could be potentially improved by removing the computationally expensive registrations. In addition, the performance of the model could be further validated in a multi-center study and the reliability could be assessed in a test-retest study. After these improvements and additional validations, we will investigate the relationship of the CC measurement with the clinical outcome and WM volume.

Acknowledgments

The PARENT project has received funding from the European Union's Horizon 2020 research and innovation program under the Marie Sklodowska-Curie Innovative Training Network 2020. Grant Agreement N 956394.

References

[1] J. J. Volpe, H. C. Kinney, F. E. Jensen, P. A. Rosenberg, The developing oligodendrocyte: key cellular target in brain injury in the premature infant, International Journal of Developmental Neuroscience 29 (2011) 423–440.

[2] M. Guillot, S. P. Miller, The dimensions of white matter injury in preterm neonates, in: Seminars in Perinatology, volume 45, Elsevier, 2021, p. 151469.

[3] J. J. Volpe, Cerebral white matter injury of the premature infant-more common than you think, Pediatrics 112 (2003) 176–176.

[4] H.-J. Park, J. J. Kim, S.-K. Lee, J. H. Seok, J. Chun, D. I. Kim, J. D. Lee, Corpus callosal connection mapping using cortical gray matter parcellation and dt-mri, Human brain mapping 29 (2008) 503–516.

[5] H. Kidokoro, J. J. Neil, T. E. Inder, New mr imaging assessment tool to define brain abnormalities in very preterm infants at term, American Journal of Neuroradiology 34 (2013) 2208–2214.

[6] S. Fiori, A. Guzzetta, K. Pannek, R. S. Ware, G. Rossi, K. Klingels, H. Feys, A. Coulthard, G. Cioni, S. Rose, et al., Validity of semi-quantitative scale for brain mri in unilateral cerebral palsy due to periventricular white matter lesions: Relationship with hand sensorimotor function and structural connectivity, NeuroImage: Clinical 8 (2015) 104–109.

[7] A. Panigrahy, P. D. Barnes, R. L. Robertson, L. A. Sleeper, J. W. Sayre, Quantitative analysis of the corpus callosum in children with cerebral palsy and developmental delay: correlation with cerebral white matter volume, Pediatric radiology 35 (2005) 1199–1207.

[8] I. S. Gousias, A. D. Edwards, M. A. Rutherford, S. J. Counsell, J. V. Hajnal, D. Rueckert, A. Hammers, Magnetic resonance imaging of the newborn brain: manual segmentation of labelled atlases in term-born and preterm infants, Neuroimage 62 (2012) 1499–1509.

[9] J. Piven, J. Bailey, B. J. Ranson, S. Arndt, An mri study of the corpus callosum in autism, American Journal of Psychiatry 154 (1997) 1051–1056.

[10] G. Cover, W. G. Herrera, M. P. Bento, S. Appenzeller, L. Rittner, Computational methods for corpus callosum segmentation on mri: A systematic literature review, Computer methods and programs in biomedicine 154 (2018) 25–35.

[11] C. Vachet, B. Yvernault, K. Bhatt, R. G. Smith, G. Gerig, H. C. Hazlett, M. Styner, Automatic corpus callosum segmentation using a deformable active fourier contour model, in: Medical Imaging 2012: Biomedical Applications in Molecular, Structural, and Functional Imaging, volume 8317, SPIE, 2012, pp. 79–85.

[12] H. Struyfs, D. M. Sima, M. Wittens, A. Ribbens, N. P. de Barros, T. Vân Phan, M. I. F. Meyer, L. Claes, E. Niemantsverdriet, S. Engelborghs, et al., Automated mri volumetry as a

diagnostic tool for alzheimer's disease: Validation of icobrain dm, NeuroImage: Clinical 26 (2020) 102243.
[13] T. Vân Phan, D. M. Sima, C. Beelen, J. Vanderauwera, D. Smeets, M. Vandermosten, Evaluation of methods for volumetric analysis of pediatric brain data: the childmetrix pipeline versus adult-based approaches, NeuroImage: Clinical 19 (2018) 734–744.
[14] T. Vân Phan, D. Sima, D. Smeets, P. Ghesquière, J. Wouters, M. Vandermosten, Structural brain dynamics across reading development: A longitudinal mri study from kindergarten to grade 5, Human Brain Mapping 42 (2021) 4497–4509.
[15] T. K. Koo, M. Y. Li, A guideline of selecting and reporting intraclass correlation coefficients for reliability research, Journal of chiropractic medicine 15 (2016) 155–163.
[16] L. Henschel, S. Conjeti, S. Estrada, K. Diers, B. Fischl, M. Reuter, Fastsurfer-a fast and accurate deep learning based neuroimaging pipeline, NeuroImage 219 (2020) 117012.