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Normal volumetric and T1 relaxation time values at 1.5 T in segmented pediatric brain MRI using a MP2RAGE acquisition

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Abstract

Objectives This study introduced a tailored MP2RAGE-based brain acquisition for a comprehensive assessment of the normal maturing brain.

Methods Seventy normal patients (35 girls and 35 boys) from 1 to 16 years of age were recruited within a prospective monocentric study conducted from a single University Hospital. Brain MRI examinations were performed at 1.5 T using a 20-channel head coil and an optimized 3D MP2RAGE sequence with a total acquisition time of 6:36 min. Automated 38 region segmentation was performed using the MorphoBox (template registration, bias field correction, brain extraction, and tissue classification) which underwent a major adaptation of three age-group T1-weighted templates. Volumetry and T1 relaxometry reference ranges were established using a logarithmic model and a modified Gompertz growth respectively.

Results Detailed automated brain segmentation and T1 mapping were successful in all patients. Using these data, an age-dependent model of normal brain maturation with respect to changes in volume and T1 relaxometry was established. After an initial rapid increase until 24 months of life, the total intracranial volume was found to converge towards 1400 mL during adolescence. The expected volumes of white matter (WM) and cortical gray matter (GM) showed a similar trend with age. After an initial major decrease, T1 relaxation times were observed to decrease progressively in all brain structures. The T1 drop in the first year of life was more pronounced in WM (from 1000–1100 to 650–700 ms) than in GM structures.

Conclusion The 3D MP2RAGE sequence allowed to establish brain volume and T1 relaxation time normative ranges in pediatrics.

Key Points

- *The 3D MP2RAGE sequence provided a reliable quantitative assessment of brain volumes and T1 relaxation times during childhood.*
- *An age-dependent model of normal brain maturation was established.*
- *The normative ranges enable an objective comparison to a normal cohort, which can be useful to further understand, describe, and identify neurodevelopmental disorders in children.*

Keywords Gray matter · White matter · Reference values · Neurodevelopmental disorders · Pediatrics

Baptiste Morel and Gian Franco Piredda contributed equally to this work.

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Abbreviations

CSF Cerebrospinal fluid
GM Gray matter
UNI Uniform
WM White matter

Introduction

Maturation of the human central nervous system begins in utero and continues through adolescence, with the most dramatic changes occurring in the first few years of life. Similar patterns of brain development among individuals have been identified, which involve—among others—the myelination of white (WM) and gray matter (GM) tissues, axonal pruning, gyrification of the brain cortex, and an increase in brain size [1]. Developmental delay and other neurological disorders have been associated with an atypical spatiotemporal maturation of brain tissues [2]. For instance, although being a key component in the interpretation of pediatric brain MRI studies, the estimation of GM and WM volumes remains mainly subjective and qualitative in clinical practice, with moderate performance [3]. In addition, the interpretation of signal intensities is still challenging, as shown, for example, in the WM of neonatal brain MRI exams [4]. A quantitative characterization of normal brain maturation in children using MRI is thus of major interest.

Automated methods for volumetric brain segmentation and quantitative MR imaging developed in adults have to be adapted to young subjects due to the "inverted" different brain parenchyma contrasts before 2 years of age [5] and the anatomical differences with adult data, which in turn required the establishment of new templates [6]. Nowadays, several methods exist to longitudinally study quantitative volumetric data for various brain structures, mainly in adults [7–9], in pediatrics [10–12], or in neonates [13]. Brain structure parcellation in children relies on morphological [12], statistical [14], or quantitative MR-based [7, 15, 16] approaches. However, limited sample sizes of patients were employed during the first few years of life.

Previous studies also measured relaxation times for several specific brain structures (basal ganglia, GM, WM, hippocampus, among others) but only recruiting cohorts with limited age ranges and never for entire childhood [15, 17–22]. In addition, sequences with long acquisition times are often needed, rendering them impractical for daily clinical practice.

The aim of our study was to automatically assess the brain volumetry and T1 relaxometry with a clinical practical sequence, based on a pediatric optimized MP2RAGE sequence [23]. The MP2RAGE sequence was already validated in adult neuroradiology to investigate pathologies such as Alzheimer's disease [9] or anorexia-related atrophy [24]. A high reproducibility would be interesting for a longitudinal study for individuals. MP2RAGE sequence has proven to have a high repeatability for the segmentation of every region, particularly for subcortical structures [25] and for the T1 relaxation time [26]. The MP2RAGE sequence thus may constitute a promising imaging technique to help analyze brain maturation in a pediatric population, yet the rapid morphological and microstructural tissue changes occurring during development necessitate the adaptation of the MR sequence parameters as well as dedicated post-processing to reduce potential errors and minimize bias.

The innovation was to adapt three age-group templates for the pediatric brain segmentation to obtain detailed anatomy, morphometry, and T1 relaxometry information of main structures. As an application, we determined the normal ranges of brain volumes and T1 relaxation times in vivo depending on age.

Material and methods

Study population

A prospective monocentric study was conducted recruiting 70 consecutive children from a single University Hospital between January 2017 and November 2019 with an original indication of an isolated headache without neurological symptoms that showed a spontaneously favorable evolution. Normal clinical follow-up was at least for 1 year. The study population was composed of 35 males and 35 females (see detailed demographics in Supplementary Material Fig. S1). Three age groups were defined: from 1 to 2 years (10 subjects), 2 to 8 years (37 subjects), and 8 to 16 years (23 subjects). Approval was received by the local Ethics Committee in Human research (RNI-2017-093). All the children's parents gave informed consent.

Clinical exclusion criteria for this study were identified pathologies in the brain, prior intracranial operation, known developmental delay in language or motor domains, autism spectrum disorder, chronic epilepsy, significant prematurity (younger than 34 weeks GA at delivery), significant macrocephaly (head circumference > 97th percentile), significant microcephaly (head circumference < 3rd percentile), hydrocephalus, suspected or proven genetic abnormalities, and genetic dispositions known to be involved in abnormal brain development. Imaging exclusion criteria were motion or susceptibility artifacts on the UNI MP2RAGE volume. Artifacts were ruled out independently by two observers.

Image acquisition

All patients were scanned at 1.5 T (MAGNETOM Aera, Siemens Healthcare) using a 20-channel head coil without general anesthesia. Intrarectal pentobarbital (5 mg/kg) has

been delivered in children requiring sedation. Whole-brain imaging was achieved with the MP2RAGE sequence using acquisition parameters tailored to pediatric applications (spatial resolution = 1.33 × 1.33 × 1.25 mm^3, FOV = 256 × 240 mm^2, TI_1/TI_2 = 600/2000 ms, flip angles = 5–6°, TR = 5000 ms, TA = 6:36 min).

Image processing

Automated brain segmentation was performed using the MorphoBox prototype [9] which underwent a major adaptation of its templates. Three age-appropriate T1-weighted templates were generated for each age group including ten subjects aged 1–2 years, 37 subjects aged 2–8 years, and 23 subjects aged 8–16 years. The considered T1-weighted contrast was obtained by multiplying the INV_2 and UNI images to remove the salt-and-pepper noise outside the head and in proximity of cortical GM structures [27]. Templates were built using an iterative method, requiring N non-linear registrations [28, 29] to be performed at each iteration, where N is the number of normal subjects. A voxel-wise average across subjects was used as an initial reference target volume. This target volume was updated after each iteration by a voxel-wise average across the N registered volumes. A total of 38 anatomical classes (10) were drawn by a pediatric neuroradiologist on the three resulting templates and consensus was obtained with two other neuroradiologists according to the standard anatomical nomenclature (27). These templates were included in the MorphoBox pipeline, substituting the adult template described in [9, 24]. Apart from this change, the MorphoBox pipeline was used in its original form to segment the 70 pediatric subjects automatically. Volumes and average T1 relaxation values were then calculated over each segmentation mask.

Qualitative segmentation validation assessment

A qualitative segmentation validation was performed independently by two experts (7 and 8 years of experience) who checked the quality of each individual segmentation. The validation procedure consisted of verifying the following criteria:

i) Assessment of image quality,
ii) Assessment of movement artifacts,
iii) Assessment of errors in intracranial volume segmentation: checking whether the intracranial volume is correctly segmented, i.e., no skull is included, and no brain parenchyma is excluded from the segmented brain region;
iv) Assessment of appropriate anatomic coverage: the tissue segmentation was overlaid onto the MP2RAGE image to verify that the boundaries between WM, GM, and CSF corresponded to actual tissue boundaries in the image contrast.

The parcellation of the brain was verified by visually comparing the subjects' individual brain parcellation to the parcellation of the template.

Normative data modeling

Reference ranges accounting for the normal evolution of brain volumes (V) with age were established for each region ($\mathbf{r}$) using a logarithmic model

$$E\{V(\mathbf{r})\} = \beta_0(\mathbf{r}) + \beta_1(\mathbf{r}) * \log(\text{age})$$

with β_0 being the model intercept and β_1 the coefficient pertaining to the age effect.

A modified Gompertz growth model was used to establish reference ranges for T1 values:

$$E\{T_1(\mathbf{r})\} = \beta_0(\mathbf{r}) e^{e^{-\beta_1(\mathbf{r})*\text{age}} - \beta_2(\mathbf{r})*\text{age}}$$

with β_0 corresponding to the transition of T1 between two different growth states, β_1 the growth rate during the fast development in the first years of life, and β_2 the growth rate during the following slower development. A Shapiro-Wilk test was employed in both cases to investigate whether fitting residuals were normally distributed. Resulting p values smaller than 0.05 were considered to reject normality after Bonferroni's correction for multiple comparisons.

Results

Image processing

A reduction of blurriness and enhanced definition of tissue boundaries were observed after each iteration during the template creation in each age group (see Fig. S2 in the Supplementary Material).

Using these age-appropriate templates, brain segmentation was successfully achieved in all 70 normal subjects according to the quality assessment defined in the "Material and methods" section. Axial slices of the acquired MP2RAGE T1-weighted images and T1 maps, along with the corresponding segmentation masks, for five subjects with different ages are shown in Supplementary Material Fig. S3.

Development of brain volumes

Normal evolution during development of various brain structures is reported in Figs. 1, 2, 3, and 4.

The total intracranial volume increased rapidly between 12 and 24 months, then with a slower and progressively smaller

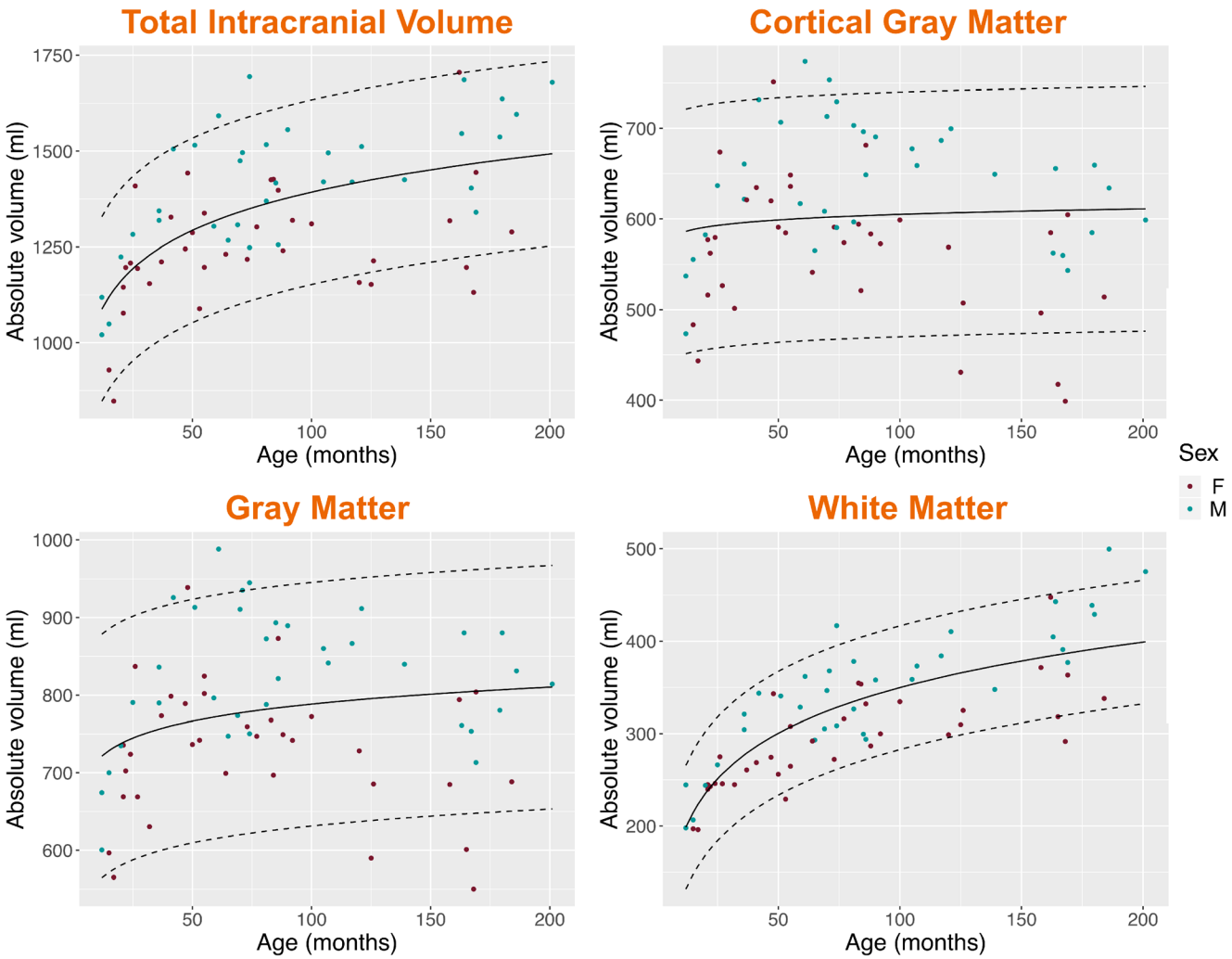

Fig. 1 Normal evolution from 1 to 16 years of age of the total intracranial volume, cortical gray matter, whole gray matter, and white matter volumes

rate, reaching a value of approximately 1400 mL in early adolescence (Fig. 1). A continuous increase throughout the age range of the study population was observed also for the WM volume, reaching a value of 400 mL in adolescence (Fig. 1). Lobe-wise, a slightly more accentuated increase of frontal lobe WM volume was observed with respect to other lobes (Fig. 2). The GM volume (including deep and cortical GM) increased rapidly during the first 24–48 months of life as well, yet with an overall change that is less evident than that of WM and mostly driven by the expansion of the temporal lobe GM (Fig. 2). A maximum absolute volume of cortical GM of 600 mL is reached between 4 and 5 years of age.

Basal ganglia volumes were estimated to vary from 35 mL at 1 year of life to around 60 mL at 16 years. Thalami volume was found to change from 10 to 19 mL. Hippocampus volume was estimated to vary from 3.5 to 7 mL. Cerebellum GM volumes were from 80 to 140 mL and WM from 10 to 25 mL. Corpus callosum volume undergoes a slow increase from 1 to 2.5 mL. Brainstem volumes were estimated to enlarge from 15 to 40 mL (Fig. 3).

Values of intraventricular CSF volume demonstrated relative stability throughout childhood. Lateral ventricle volumes were estimated to vary between 5 and 30 mL, the third ventricle between 2 and 5 mL, and the fourth ventricle from 1 to 4 mL (Fig. 4).

Residuals of the established models were found to be distributed normally for all brain regions.

Evolution of relaxation times

The normal evolution of T1 relaxation times for the segmented structures along development is reported in Figs. 5 and 6.

After an initial major decrease of T1 between 12 and 24 months of life, a steady and less rapid decrease was observed in all brain structures. The T1 drop in the first year of life was more pronounced in WM than in GM structures (Fig. 5), most likely due to the myelination of WM. Throughout the development of brain tissues with age, T1 values were found to decrease from 1400–1500 to 1100–1200 ms in cortical GM structures and from 1000–1100 to

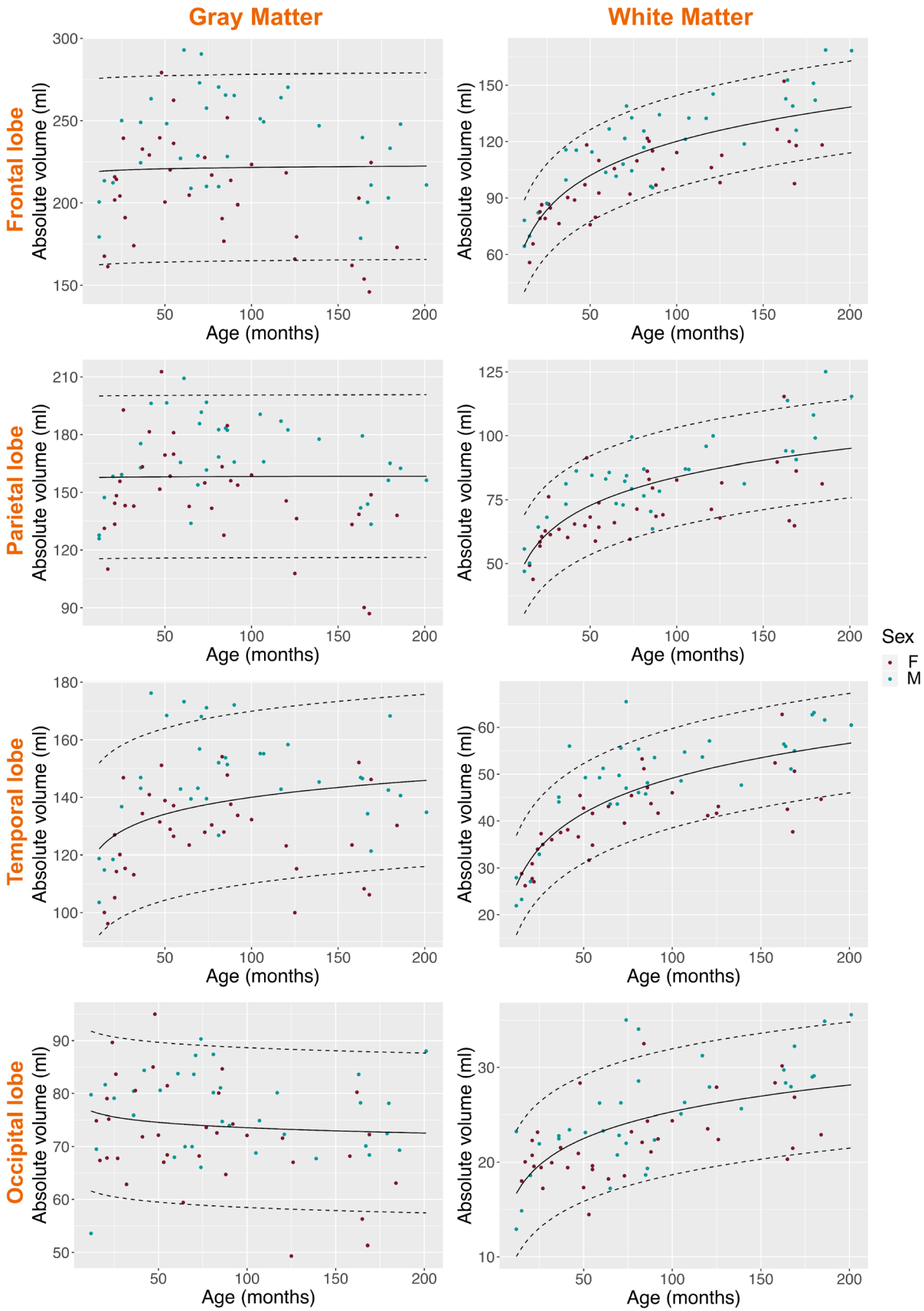

Fig. 2 Normal evolution from 1 to 16 years of age of the cortical gray matter and white matter volumes with respect to brain lobes

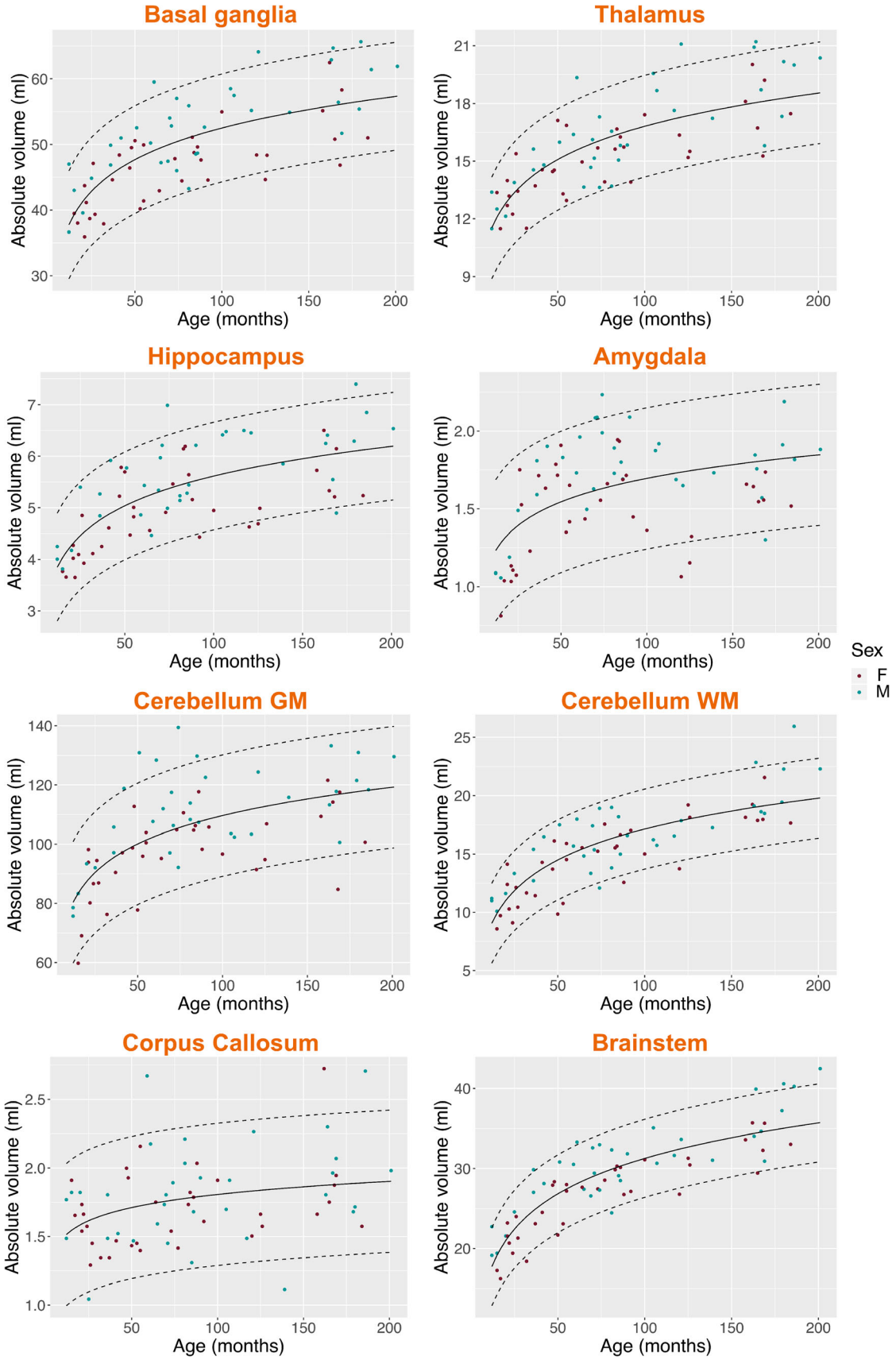

Fig. 3 Normal evolution from 1 to 16 years of age of the basal ganglia, thalamus, hippocampus, amygdala, cerebellum gray matter (GM) and white matter (WM), corpus callosum, and brainstem volumes

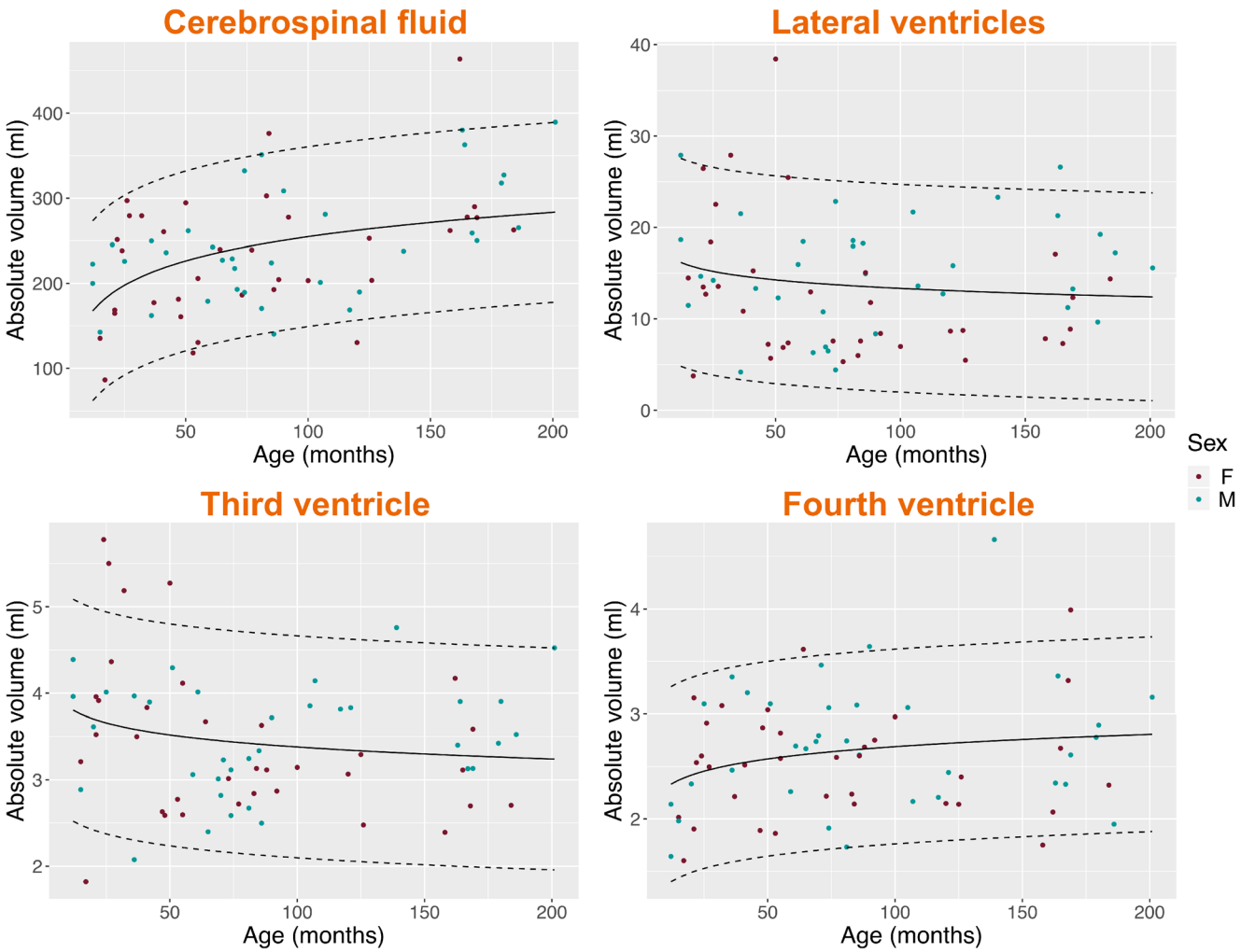

Fig. 4 Normal evolution from 1 to 16 years of age of the cerebrospinal fluid, lateral ventricle, third ventricle, and fourth ventricle volumes

650–700 ms in WM structures (Fig. 6). In other subcortical structures, T1 values were found to decrease from 1200 to 900 ms in the basal ganglia and thalamus and from 1100 to 850 in the brainstem.

Residuals of the established models were found to be normally distributed for all brain regions expect for occipital WM, cerebellum, amygdala, and brainstem.

Discussion

This study introduced a framework of an optimized MR sequence and subsequent image processing to automatically measure regional volumes and T1 relaxation times in 38 brain structures in children. The segmentation of the template instead of the segmentation of each subjects was efficient and provided reliable data with the segmentation algorithm adapted from the adult. Reference courses of these quantitative measurements in the 1-to-16-year age range were established and found to be similar to trends observed in previous studies.

An automated quantitative brain segmentation that enables longitudinal tracking and comparison with normative reference ranges of brain volumes is of major interest [15]. As many diseases lead to focal parenchymal abnormalities that would not be detected by whole-brain volumetric analysis alone, the possibility to analyze brain structures both in their entirety and region-wise is desirable. To that end, the findings of this study will be most advantageous in the assessment of diffuse and focal disease processes.

Considering the main brain structures, the volumes obtained with the automated segmentation in this study were in full accordance to previously reported data [7, 14–16, 30], especially with the study conducted by Courchesne et al [16] and the NIH MRI study of normal brain development [30]. The latter reported a rapid increase in the first 24 months, then with a progressively smaller and slower rate, reaching a value of 1400 mL in early adolescence, which was also found here. Similarly, the WM converged to a volume value of 400 mL in early adolescence, comparing well with the 475 mL reported in the NIH cohort [30].

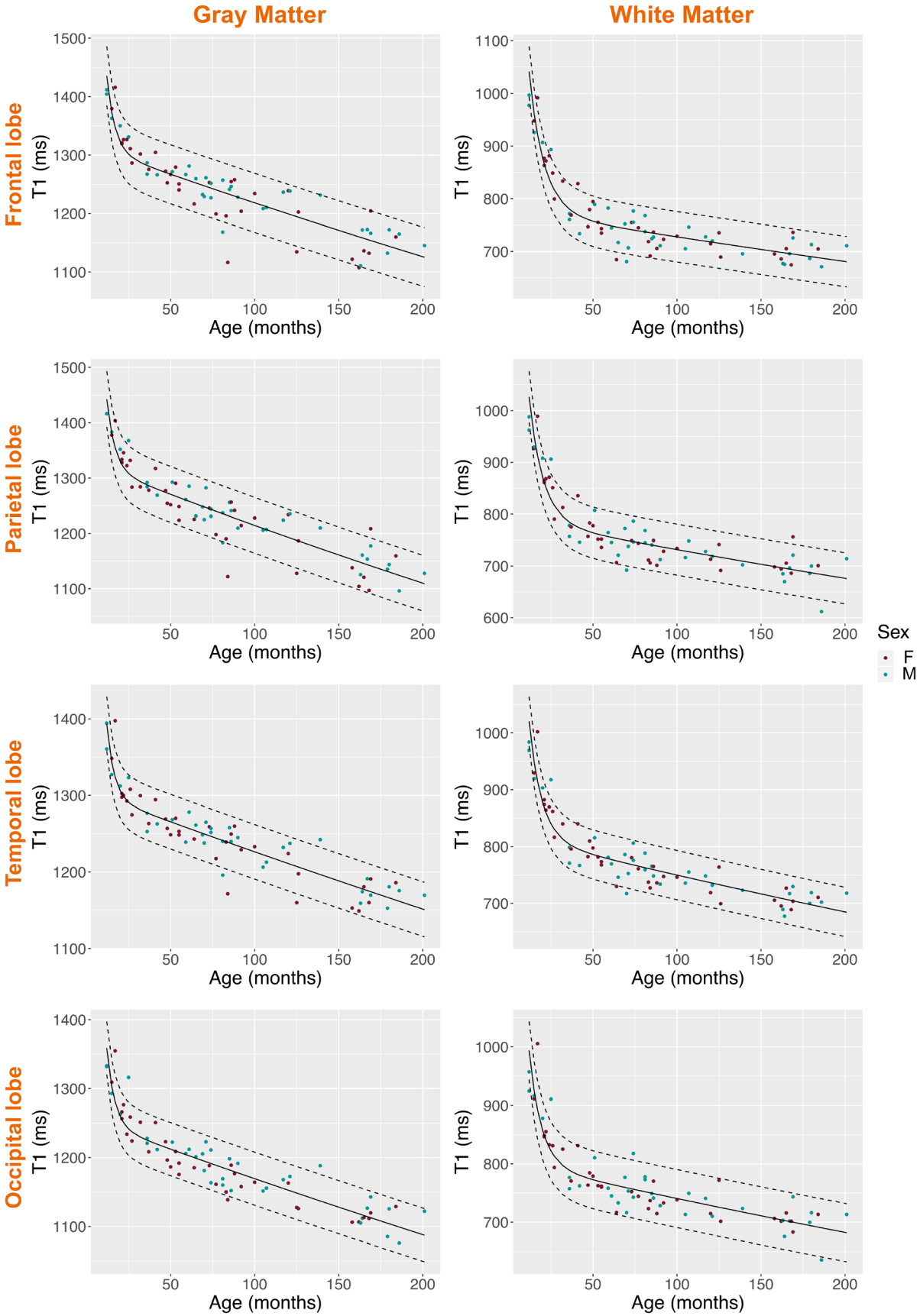

Fig. 5 Normal evolution from 1 to 16 years of age of the cortical gray matter and white matter T1 relaxation times depending on brain lobes

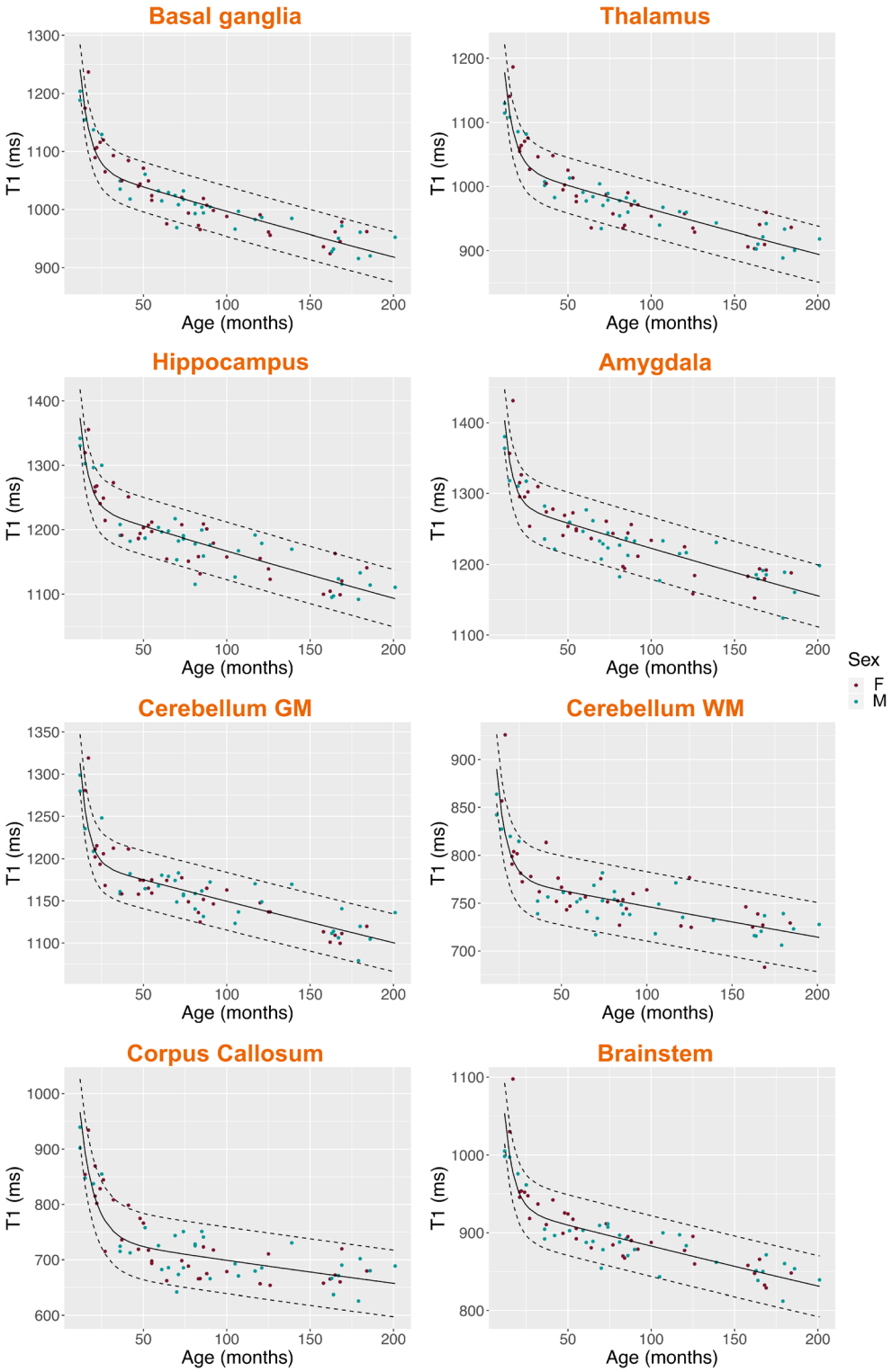

Fig. 6 Normal evolution from 1 to 16 years of age of the basal ganglia, thalamus, hippocampus, amygdala, cerebellum gray matter (GM) and white matter (WM), corpus callosum, and brainstem T1 relaxation times

A maximum absolute volume of GM of 800 mL was found to be reached between 4 and 5 years of age, much earlier than in the study conducted by McAllister et al, yet similar to what was shown by Serai et al and to the value of 787 mL reported in the NIH cohort [30]. Of note, a gradual decline throughout the teenage years was not observed as previously shown [15]. These small discrepancies could be explained partially by the employed segmentation algorithm: the delineation of the boundaries between GM and WM could slightly vary. In this context, it is important to note that the descriptive terms "gray matter" and "white matter" can be misleading when used to describe the brain parenchyma, as axons and myelin exist

within GM structures, and neurons are present in WM on the microscopic level.

Further analysis focused on more detailed parcellation of subcortical structures (basal ganglia, thalami, corpus callosum, and cerebellum, among others) whose volumes were confirmed to increase during childhood. When comparing these specific brain structures, volumes obtained in our study were found very similar to those reported in the NIH cohort [30].

The normative range values might be relevant to explore the volumetric data further in patients with microcephaly and macrocephaly and distinguish the affected brain structures better. Obtaining these data in pediatric patients with focal epilepsy in context of focal cortical dysplasia might help in screening and determining the pathological area and its impact on the total or lobar brain volumes, as it has been studied in adults [31, 32]. Volumetric data would also be helpful in the follow-up of patients with hydrocephaly.

The employed MP2RAGE sequence has the additional advantage of providing T1 relaxometry maps for the assessment of microstructural changes related to brain maturation. A rapid decrease of T1 values was observed between 12 and 24 months of life, with a subsequent steady yet less rapid progression in all lobes and the supra- and infratentorial brain structures. This drop in T1 was more pronounced in WM than in GM structures, most likely due to myelination processes occurring in WM tissues [33]. The initial high water content of the brain is indeed progressively replaced by myelin. The reported expected T1 values of GM and WM were found to be in the same range as previously reported. For example, T1 values in the parietal WM were between 700 and 1000 ms, in accordance with values estimated in previous studies, 833 ms in the study conducted by Chen et al [34] and between 800 and 1000 ms in the study by Eminian et al [17].

The characterization of healthy brain maturation that has emerged would be helpful for further assessment of a variety of neurodevelopmental disorders as deviations from normal growth trajectories [35]. Age-related changes in T1 relaxation time have been described by location in GM and WM in healthy adults [26]. Additionally, it would be useful during the interpretation of "morphologically normal" brain MRI images during exploration of focal epilepsy or mental retardation [3]. The fact that two metrics (volumetry and T1 relaxometry) can be combined to characterize a given brain region should give additional specificity to the comparison: volumetry thereby measuring brain growth and T1 relaxometry probing the tissue microstructure at the same time. T1 relaxation cartography may help to identify biomarker of retard of myelination better or depict metabolic pathologies. The determination of volume and T1 relaxation times of brain structures only reflected a partial aspect of the MR-based brain tissue characterization. More advanced techniques as MR fingerprinting (MRF) are currently being developed to quantify multiple tissue properties simultaneously (T1, T2, magnetization transfer, among others) [36, 37]. However, even though the recent integration of parallel imaging and deep learning–based reconstruction techniques can reduce acquisition time (~7 min in adults), MRF acquisitions are not yet established in pediatric clinical use [38].

The proposed "three in one" has the advantage of being fast, accurate, and reproducible, but may possibly give slightly less accurate results than a careful manual delineation of the structures of interest. The same subjects were used for both building the templates and getting the regional values, which could have led to improve our segmentation results. It also has influenced the building of the template with a heterogeneity of the number of subject in each age group. Although respectable, the sample size of 70 normal subjects was smaller in comparison with those used for the development of the CDC growth charts or in head circumference [39]. Larger sample sizes may well define percentiles with appropriate precision particularly for the outlying percentiles [40]. Moreover, our normal subjects were only representative of a sample of our regional population of mainly Caucasian people. So, the established normative ranges will probably have to be adapted to a population with different genetic traits and/or environmental/epigenetic exposures [41, 42].

It should be noted that we have not performed a repeatability study on a pediatric cohort to characterize the stability of the used analyses. This was considered prohibitive as MRI exams are considerably more stressful for children than for adults [43]. Nonetheless, the employed morphometric algorithm with the adult template has been used in multiple research studies and is well characterized in terms of performance and quality metrics. A repeatability study was published [44]. A complementary test-retest reproducibility has shown a high reliability for every region [25]. Brain volumetry repeatability has shown a high reproducibility and MP2RAGE was the most reliable for subcortical structures [25]. The more channel coil used, the better the reliability is. Finally, results must be confirmed by a larger prospective multi-centric study to validate the possibility of extending the use of the established norms to different centers. Corresponding norms at higher field strengths (e.g., 3 T MRI) should be established as T1 values naturally differ with field strength.

White matter changes were observed to be remarkable and fast during the first 2 years of age. This phenomenon suggests that the anatomical templates used for segmentation should probably be split by semester or trimester to adapt to this fast development better. This especially concerns the segmentation and determination of T1 values of the termination areas of myelination.

A clinical evaluation to assess the performance of the established framework for the detection and characterization of different brain pathologies is currently ongoing.

Conclusion

An optimized 3D MP2RAGE acquisition was proposed, which was used to establish a fully automated processing pipeline to create an age-dependent model of volumetric and T1 value changes between 1 and 16 years of age based on a large pediatric cohort of normal subjects. This objective assessment of brain evolution during childhood provided by this framework might help to further identify, describe, and understand neurodevelopmental disorders in children.

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Compliance with ethical standards

Guarantor The scientific guarantor of this publication is Baptiste Morel.

Conflict of interest BM, JPC, CT, CD, and DS declare that they have no competing interest. GFP, TH, BM, and TK are fulltime employees of Siemens Healthcare AG Switzerland. The other authors have nothing to disclose.

Statistics and biometry GF Piredda and B Maréchal have significant statistical expertise. No complex statistical methods were necessary for this paper.

Informed consent Approval was received from the local Ethics Committee in Human research (RNI-2017-093). All the children's parents gave written informed consent.

Ethical approval Approval was received from the local Ethics Committee in Human research (RNI-2017-093).

Methodology
- prospective
- observational
- performed at one institution

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