Published in final edited form as:

Pediatr Radiol. 2015 July ; 45(8): 1189–1197. doi:10.1007/s00247-015-3298-8.

Periventricular hyperintensity in children with hydrocephalus

S. Hassan A. Akbari,

Department of Neurological Surgery St. Louis Children's Hospital, Washington University School of Medicine, St. Louis, MO, USA

David D. Limbrick Jr.,

Department of Neurological Surgery St. Louis Children's Hospital, Washington University School of Medicine, St. Louis, MO, USA; Department of Pediatrics St. Louis Children's Hospital, Washington University School of Medicine, St. Louis, MO, USA

Robert C. McKinstry,

Department of Radiology St. Louis Children's Hospital, Washington University School of Medicine, St. Louis, MO, USA

Mekibib Altaye,

Division of Biostatistics and Epidemiology Cincinnati Children's Hospital, Cincinnati, OH, USA

Dustin K. Ragan,

Department of Pediatrics St. Louis Children's Hospital, Washington University School of Medicine, St. Louis, MO, USA

Weihong Yuan,

Department of Pediatric Radiology Cincinnati Children's Hospital, Cincinnati, OH, USA

Francesco T. Mangano,

Department of Pediatric Neurological Surgery Cincinnati Children's Hospital, Cincinnati, OH, USA

Scott K. Holland, and

Department of Pediatric Radiology Cincinnati Children's Hospital, Cincinnati, OH, USA

Joshua S. Shimony

Department of Radiology St. Louis Children's Hospital, Washington University School of Medicine, St. Louis, MO, USA; Mallinckrodt Institute of Radiology Washington University School of Medicine 510 S. Kingshighway Blvd. St. Louis, MO 63110, USA

Abstract

Background—Magnetic resonance images of children with hydrocephalus often include a rim of hyperintensity in the periventricular white matter (halo).

Objective—The purpose of this study was to decide between the hypothesis that the halo is caused by cerebrospinal fluid (CSF) flow during the cardiac cycle, and the alternate hypothesis that the halo is caused by anatomical changes (stretching and compression of white matter).

J. S. Shimony shimonyj@mir.wustl.edu.

Conflicts of interest None

Materials and methods—Participants were selected from a multicenter imaging study of pediatric hydrocephalus. We compared 19 children with hydrocephalus to a group of 52 controls. We quantified ventricle enlargement using the frontal-occipital horn ratio. We conducted qualitative and quantitative analysis of diffusion tensor imaging in the corpus callosum and posterior limb of the internal capsule. Parameters included the fractional anisotropy (FA), mean diffusivity, axial diffusivity and radial diffusivity.

Results—The halo was seen in 16 of the 19 children with hydrocephalus but not in the controls. The corpus callosum of the hydrocephalus group demonstrated FA values that were significantly decreased from those in the control group ($P=4\cdot10^{-6}$), and highly significant increases were seen in the mean diffusivity and radial diffusivity in the hydrocephalus group. In the posterior limb of the internal capsule the FA values of the hydrocephalus group were higher than those for the control group ($P=0.002$), and higher values in the hydrocephalus group were also noted in the axial diffusivity. We noted correlations between the diffusion parameters and the frontal-occipital horn ratio.

Conclusion—Our results strongly support the hypothesis that the halo finding in hydrocephalus is caused by structural changes rather than pulsatile CSF flow.

Keywords

Periventricular hyperintensity; Hydrocephalus; Diffusion tensor imaging; Fractional anisotropy; Magnetic resonance imaging; Children

Introduction

Hydrocephalus is a common pediatric disorder often resulting from congenital malformations, hemorrhage, tumors, infection or spinal dysraphism. The disorder affects up to 1 per 1,000 live births [1] and is present in roughly one-third of all central nervous system abnormalities [2, 3]. It has been reported that each year 45,000 to 50,000 pediatric patients have shunt surgery, with an overall cost of approximately \$2.0 billion [4]. It is thought that hydrocephalus occurs when the normal balance of cerebrospinal fluid (CSF) production and absorption is disturbed [5]. Treatment options for hydrocephalus include shunting procedures with ventricular drain, and endoscopic third ventriculostomy. Despite these treatment options, in-hospital mortality for hydrocephalus has been reported to be 2.6%, versus 0.4% for non-hydrocephalus pediatric patients [4]. This study separated rate of death from shunt-related admissions (including initial placement, malfunction and shunt-related infection), from rate of death from non-shunt-related causes.

The optimal imaging modality for hydrocephalus is MRI. MRI can provide anatomical as well as CSF flow information that can help predict the success of interventional procedures [6].

Children with hydrocephalus have a variety of changes notable on MRI, including dilatation of the ventricles, especially the temporal horns of the lateral ventricles, CSF flow voids [6], effacement of the cortical sulci, and in severe cases subependymal edema (transependymal flow) in the white matter adjacent to the frontal and occipital horns [7]. It has also been noted that children with hydrocephalus often have a rim of hyperintensity in the lateral

periventricular white matter, best seen on MRI with fluid-attenuated inversion recovery (FLAIR) [6] or diffusion imaging (Fig. 1). A continuous rim, or halo, can be seen in up to 51% of children with hydrocephalus and is possibly more common in obstructive hydrocephalus [8]. There are two hypotheses as to the cause of this hyperintensity. During systole, an increase in vascular volume leads to a shift of CSF flow from the intracranial ventricular system and subarachnoid spaces to the cisterns and foramen magnum, a process that is reversed during diastole [6]. These shifts in CSF flow with the cardiac cycle have been shown to be substantial in size [9] and may be linked to the rim of periventricular hyperintensity noted on MRI in children with hydrocephalus. Another hypothesis is that the hyperintensity in the periventricular white matter is caused by anatomical changes from hydrocephalus. Specifically, surrounding white matter structures may become compressed (corona radiata and internal capsule) or stretched (corpus callosum) as the ventricles increase in size.

Fractional anisotropy (FA) maps, calculated from diffusion tensor imaging (DTI), may be helpful in differentiating these hypotheses. FA defines the extent of diffusion asymmetry in a particular area of interest. Elevated FA implies a common direction and coherence of fibers in a particular region of interest, while a decrease of FA implies a loss in fiber coherence. FA can also be understood in terms of the difference between the axial diffusivity along the fiber direction and the radial diffusivity perpendicular to it. If periventricular white matter hyperintensity is caused by cardiac pulsations, there should be no change in the extent of anisotropy in these white matter structures. If, however, periventricular white matter hyperintensity is caused by structural changes, the value of FA could increase or decrease in the periventricular white matter because compression and stretching of fibers secondary to increased ventricular size could lead to changes in fiber coherence.

The purpose of this study was to assess whether periventricular hyperintensity in children with hydrocephalus is secondary to anatomical changes within the periventricular white matter or secondary to CSF pulsation from the cardiac cycle.

Materials and methods

Subject characteristics

All participants were selected from an ongoing multicenter, prospective, longitudinal imaging study of pediatric hydrocephalus. Cincinnati Children's Hospital Medical Center (CCHMC) and St. Louis Children's Hospital (SLCH) were the sites of recruitment and institutional review board approval was obtained at both institutions. Participants' parents gave consent when enrolled into the study according to institutional review board guidelines at both institutions. Nineteen children with hydrocephalus (8 from SLCH, 11 from CCHMC) and 52 control subjects (48 from CCHMC, 4 from SLCH) were recruited for this study between December 2009 and November 2013. All children presented with symptoms related to congenital hydrocephalus and required surgical diversion of CSF. Children with brain anomalies other than hydrocephalus were excluded (e.g., Chiari II with myelomeningocele, intraventricular hemorrhage from prematurity, traumatic brain injury, cerebral palsy, cortical dysplasia, and other neurological disorders that affect brain white matter integrity).

Magnetic resonance/diffusion tensor image acquisition

MRI with DTI data were obtained prior to hydrocephalus treatment and were acquired on 1.5-T MRI scanners (GE Signa; GE Healthcare, Milwaukee, WI, and Siemens Avanto; Siemens Healthcare, Erlangen, Germany). Children all underwent a high-resolution T1-W anatomical scan with either a 3-D inversion recovery prepared spoiled gradient recalled (SPGR) sequence on the GE scanners (repetition time [TR]/echo time [TE]/inversion time [TI] 11.9/5/300 ms; ASSET 2 [array spatial sensitivity encoding technique]) or a 3-D magnetization-prepared rapid gradient echo (MP-RAGE) sequence on the Siemens scanner (TR/TE/TI 1,900/2.78/1,100 ms; flip angle 15 degrees; IPAT 2 [integrated parallel acquisition techniques]). The geometric specifications for T1-weighted images were as follows: orientation sagittal; field of view 256×256 mm; matrix 256×256; voxel size 1×1×1 mm. DTI acquisition was performed using a single-shot diffusion-weighted echo planar imaging (EPI) sequence with diffusion weighted images (DWIs) acquired in 15 non-collinear directions (TR/TE 9,400/93.2 ms; field of view 240×240 mm; acquisition matrix 96×96; voxel size 2.5×2.5×2.5 mm; ASSET or IPAT factor 2; b=1,000 s/mm²; number of averages 2).

DTI fractional anisotropy images were qualitatively reviewed for the presence of a halo (Fig. 1). The presence of the halo in a child was confirmed on transverse FA images if it was seen on more than half of the slices in which the ventricles were seen. MRI images derived from DTI were quantitatively reviewed and included: FA maps (Fig. 1), mean diffusivity maps (Fig. 1), axial diffusivity, radial diffusivity, and directionally encoded color maps (Fig. 2).

Quality control for diffusion imaging

The compatibility of MRI data acquired from different scanners at two research sites was established at the beginning of the study and was maintained rigorously throughout the study to assure the stability of scanner performance in geometric measurement, DTI measurement and signal-to-noise ratio [10]. Measurements were compared annually across the two sites using a standard phantom and a traveling human phantom.

Diffusion tensor imaging (DTI)

DTI data processing was performed using DTIStudio 3.02 software (Johns Hopkins University, Baltimore, MD) [11]. The images were corrected for head motion and eddy current artifact in the preprocessing. Diffusion tensor was calculated using the standard method and was used to create fractional anisotropy, mean diffusivity, and directionally encoded color maps [12]. FA and mean diffusivity maps were analyzed for presence of a periventricular halo in any of the slices of the data set using DTIStudio. Directionally encoded color maps were used to assess periventricular white matter fiber orientation in the hydrocephalus group versus control group. Images were compared between the groups for fiber orientation and intensity [11].

Further analysis of DTI parameters was conducted using Analyze (Mayo Clinic, Rochester, MN). FA values in the posterior limb of the internal capsule were obtained using bilateral regions of interest on the slice inferior to the point at which the internal and external

capsules merge to form the corona radiata and in anterior-posterior alignment with the genu of the internal capsule. Values were averaged between the hemispheres, and the DTI parameter values in the posterior limb of the internal capsule were plotted against age in months at the time of the scan. An additional region of interest was selected in the genu of the corpus callosum. These DTI parameter values in the corpus callosum were also plotted against age at the time of the scan.

Frontal-occipital horn ratio

The frontal-occipital horn ratio is a common measure of ventricular size used to evaluate the degree of ventricular dilatation [13]. The frontal-occipital horn ratio was measured on a transaxial slice in the middle of the brain with maximal ventricular dimension.

Statistical analysis

To address the differential distribution of age in the two groups, we followed the methods of Mukherjee et al. [14], conducting a non-linear regression of FA with age (t) using all data points and formulas of the form $FA = A - B \exp(-Ct)$, with A , B and C being estimated constants that describe the developmental trajectory of the DTI parameters. The resulting residual variation in FA after removing the effect of age was then used in group comparison. Statistical analyses were performed using a Student t -test for continuous variables. Linear regression was performed between the diffusion parameters and the frontal-occipital horn ratio. All computations were performed using MATLAB (version R2012a; MathWorks, Natick, MA). All tests were two-sided unless otherwise specified, and a $P < 0.05$ was used to indicate a significant effect.

Results

The average age at time of scan for the hydrocephalus group ($n=19$) was 30.2 ± 57.9 months (range 1 day to 16.2 years) and for the control group ($n=52$) it was 25.9 ± 30.9 months (range 9 days to 11.2 years). There was no statistically significant difference between the groups ($P=0.29$).

The average frontal-occipital horn ratio for the control group was 0.29 ± 0.03 , and for the hydrocephalus group it was significantly higher at 0.52 ± 0.09 . Within the hydrocephalus group, five children were classified as having mild ventriculomegaly (frontal-occipital horn ratio < 0.45), six as moderate and eight as severe (frontal-occipital horn ratio > 0.55).

The halo was best visualized on the FA maps (Fig. 1), and in 16 out of 19 children with hydrocephalus the halo was present along the margins of the lateral ventricles on all slices in which the ventricles were visualized. The three children with hydrocephalus without a halo were from the mild ventriculomegaly group. No halo was seen in any of the controls. We also used the mean diffusivity maps to exclude the presence of surrounding edema, which would manifest as a rim of hyperintensity on the mean diffusivity maps. No children with hydrocephalus were found to have periventricular rims of hyperintensity on their mean diffusivity maps to suggest edema. Control subjects also had no evidence of a periventricular halo on mean diffusivity (Fig. 1).

Directionally encoded color maps were qualitatively analyzed and they showed decreased intensity of the right-to-left crossing fibers in the corpus callosum in children with hydrocephalus compared to controls (Fig. 2). These fibers demonstrated shifting of direction from medio-lateral to more supero-inferior fiber orientations from the draping of the corpus callosum over the enlarged ventricles. There was also blunting of color signal intensity in the periventricular white matter across all children with hydrocephalus.

Results of DTI values versus age at time of scan are shown for the corpus callosum in Fig. 3 and for the posterior limb of the internal capsule in Fig. 4. The parameters for the nonlinear estimated best fit curve are provided in Table 1. Further analysis was performed on the deviation of the DTI values from the estimated maturation curves (Table 1). In the corpus callosum the FA values of the hydrocephalus group were highly significantly decreased from those in the control group ($P=4 \cdot 10^{-6}$), and highly significant increases were seen in the mean diffusivity and radial diffusivity in the hydrocephalus group. In the posterior limb of the internal capsule the FA values of the hydrocephalus group were higher than those for the control group ($P=0.002$), and higher values in the hydrocephalus group were also noted in axial diffusivity.

Linear regression plots between the diffusion parameters and the frontal-occipital horn ratio are presented in Fig. 5. The coefficient of determination R^2 values and the corresponding P -values for these regressions are presented in Table 1. Significant regressions for the corpus callosum were seen in FA, mean diffusivity and radial diffusivity. In the posterior limb of the internal capsule the only significant regression was with axial diffusivity.

Discussion

It has been shown that enlarged ventricles in hydrocephalus often lead to periventricular white matter injury [15]. Many children with hydrocephalus have an observed periventricular rim of hyperintensity on FLAIR and FA images (Fig. 1). The hyperintensity may be segmental around the ventricle or may form a complete periventricular rim [8]. In the pediatric population, this may be the result of architectural changes within the periventricular white matter or potentially an artifact secondary to pulsatile CSF flow. This study addresses these two hypotheses.

Our results suggest that the periventricular hyperintensity seen on MRI in children with hydrocephalus is a result of architectural changes in the periventricular white matter caused by ventricular dilation and either white matter compression (in the posterior limb of the internal capsule) or stretching (in the corpus callosum). The changes observed using directionally encoded color maps, especially the changes in fiber orientation and the change in signal intensity, strongly suggest an architectural change resulting in periventricular white matter hyperintensity. These findings are not suggestive of pulsatile CSF flow, which would not be expected to affect the directionally encoded color.

Additionally, qualitative evaluation of our directionally encoded color maps suggests that the children with more severe hydrocephalus have greater changes in the directionally encoded color image. This can be explained by structural changes but would not be expected

if the halo were caused by pulsatile CSF flow. The mean diffusivity maps do not demonstrate periventricular halos on any slices in either the hydrocephalus or control groups. The lack of signal change on the mean diffusivity maps excludes the presence of subependymal or transependymal CSF flow in our group, which would cause a uniform elevation in the mean diffusivity value, which we did not see in our data.

Because FA is age-dependent [16, 17], excluding age factor yields a more accurate comparison of differences between the groups. We used exponential formulas to describe the non-linear changes of FA with age [14] to correct for the age factor in our data. Our results show a highly statistically significant difference in FA between the hydrocephalus and the control groups in the corpus callosum and a significant change in the posterior limb of the internal capsule in the opposite direction. Stretching of the corpus callosum over the dilated ventricles would cause a relative thinning of the numerous cellular membranes, leading to a relative increase in radial diffusivity and mean diffusivity, which we clearly observed, and thus a decrease in FA values.

Compression of the posterior limb of the internal capsule secondary to ventricular dilation would cause a relative decrease in the extra-cellular space and an increase in crowding and alignment among the fibers of the posterior limb of the internal capsule, which would lead to increased coherence in the fiber tracts, resulting in elevated FA and axial diffusivity. The plausibility of the explanation in regard to the stretching and crowding of the tissue is strengthened by the results from the linear regression analysis between the DTI values and the frontal-occipital horn ratio (Fig. 5 and Table 1), which shows significance in the DTI parameters that are most significantly different between the groups and would be most affected by stretching and crowding. If the CSF pulsation were the main cause of periventricular hyperintensity a similar change would be expected in both the posterior limb of the internal capsule and the corpus callosum, which we do not see, and thus these results further support the architectural change hypothesis.

Of note, 16 of 19 children with hydrocephalus had FA periventricular halos on all slices along the lateral ventricles. This further supports the hypothesis that architectural changes are the cause of the periventricular hyperintensity. Had the halos been caused by CSF pulsation, they would likely not be seen on all slices of a single child's MRI, but rather only in areas with strong CSF pulsation.

Additionally, pulsatile motion of the CSF and the adjacent subependymal parenchyma is known to cause variable signal attenuation in diffusion imaging [18] that tends to reduce the FA, which would contradict the finding in the posterior limb of the internal capsule in our hydrocephalus group.

Some caveats should be considered in the interpretation of our findings. First, this is a small sample size of children with periventricular hyperintensity on MRI, and the research study was not designed to specifically address the etiology of MRI periventricular hyperintensity in hydrocephalus. Although there was no statistically significant difference in the ages between the groups ($P=0.29$), there were more control subjects among the older age groups. This difference stems from the typical age in which children with hydrocephalus present

with symptoms to the hospital. In children DTI values change rapidly and predictably as a function of age, so a correction for age was performed, and this represents a more accurate comparison of values between the groups. Another consideration is that none of our images was acquired with cardiac gating. Cardiac gating has been described as a method for reduction of the effect of pulsatile CSF flow, but at the cost of increased scanning time, which may not be realistic in our study population [18]. However, our results were consistent throughout all image slices for each hydrocephalus subject, making it unlikely that pulsatile CSF flow affected our analysis.

Despite these limitations, the results of our study strongly suggest that periventricular hyperintensity on MR images of children with hydrocephalus is caused by structural changes rather than secondary to CSF pulsation. Directions to further address this issue could include using cardiac gating in image acquisition, assuming this could be done without excessively extending the study length. Structural changes could then be assessed in the absence of potential CSF pulsation artifact. Additionally, quantitative measures similar to those presented in our study could be obtained in children before and after CSF diversion procedures to assess for degree of change after treatment.

Conclusion

Our results strongly support the hypothesis that periventricular hyperintensity on MRI in pediatric patients with hydrocephalus is caused by structural changes in the periventricular white matter rather than pulsatile cerebrospinal fluid flow.

Acknowledgments

This work was supported by an R01 grant from the National Institutes of Health/National Institute of Neurological Disorders and Stroke (NIH/NINDS). The authors would like to acknowledge the critical efforts of the clinical research coordinators, Deanna Mercer and Sarah Simpson, and research assistant Akila Rajagopal.

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Fig. 1.

Axial fractional anisotropy images in a 26-month-old boy with hydrocephalus (**a**) and a 48-month-old male control (**b**) at the level of region-of-interest selection. Mean diffusivity images in hydrocephalus (**c**) and control (**d**) patients demonstrate no periventricular white matter hyperintensity. Arrows in (**a**) point to the halo. Sample regions of interest are marked on (**a**) and (**b**)

Fig. 2. Directionally encoded color images in a 26-month-old boy with hydrocephalus (**a, c**) and a 48-month-old male control (**b, d**) in transverse (**a, b**) and coronal (**c, d**) planes demonstrate decreased intensity of crossing fibers of the corpus callosum (*pink, red*) and increased

intensity of supero-inferior fibers (*blue*) in the lateral periventricular white matter in the boy with hydrocephalus vs. the control patient

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Fig. 3.

Diffusion tensor imaging parameter values in the corpus callosum plotted as a function of age for the group with hydrocephalus (*red circles*) and normal controls (*black circles*). The black curves are an estimate of the parameter change with age. **a, b** The fractional anisotropy values (**a**) in children with hydrocephalus are lower than those in controls ($P=4\cdot 10^{-6}$) and the mean diffusivity values (**b**) in children with hydrocephalus are higher than those in the controls ($P=2\cdot 10^{-8}$). **c, d** These changes are driven by the significantly larger radial diffusivity values (**d**) in the hydrocephalus group ($P=3\cdot 10^{-9}$); the axial diffusivity values (**c**) are not statistically different ($P=0.097$)

Fig. 4.

Diffusion tensor imaging parameter values in the posterior limb of the internal capsule plotted as a function of age for the group with hydrocephalus (*red circles*) and normal controls (*black circles*). The black curves are an estimate of the parameter change with age.

a, b The fractional anisotropy values (**a**) in children with hydrocephalus are higher than those in controls ($P=0.002$), but the mean diffusivity values (**b**) are no different between children with hydrocephalus and controls ($P=0.23$). **c** The fractional anisotropy changes are driven by the significantly larger axial diffusivity values in children with hydrocephalus ($P=4 \cdot 10^{-5}$). **d** The radial diffusivity values are not different between groups ($P=0.19$)

Fig. 5.

Linear regression plots between diffusion parameters and the frontal-occipital horn ratio.

The dependent parameters are: (a) corpus callosum fractional anisotropy, (b) corpus callosum mean diffusivity, (c) corpus callosum radial diffusivity, and (d) posterior limb of the internal capsule axial diffusivity. Pearson R values and *P*-values are presented in Table 1. Only plots with significant values are presented

Table 1

Non-linear regression analysis for comparison of diffusion parameter values between hydrocephalus and control groups in the corpus callosum (CC) (Fig. 3) and in the posterior limb of the internal capsule (PLIC) (Fig. 4)

Parameter	A, B, C of age-correction curve ^a	Mean deviation controls	Mean deviation hydrocephalus	Age-corrected <i>P</i> -value	R ² (Fig. 5) ^b	R ² <i>P</i> -value (Fig. 5) ^b
CC FA	0.67 (0.03) 0.36 (0.03) 0.13 (0.05)	0.03 (0.08)	-0.09 (0.11)	4·10 ⁻⁶ **	0.34	0.009*
CC MD	0.82 (0.03) -0.74 (0.05) 0.14 (0.03)	-0.05 (0.09)	0.15 (0.18)	2·10 ⁻⁸ **	0.36	0.007*
CC AD	1.54 (0.04) -0.59 (0.06) 0.10 (0.03)	-0.014 (0.14)	0.06 (0.22)	0.097	0.20	0.052
CC RD	0.47 (0.04) -0.84 (0.06) 0.18 (0.05)	-0.07 (0.12)	0.20 (0.20)	3·10 ⁻⁹ **	0.35	0.008*
PLIC FA	0.67 (0.03) 0.26 (0.03) 0.06 (0.03)	-0.021 (0.06)	0.04 (0.07)	0.002**	0.05	0.36
PLIC MD	0.76 (0.01) -0.40 (0.02) 0.24 (0.04)	-0.004 (0.04)	0.02 (0.08)	0.23	0.17	0.08
PLIC AD	1.38 (0.02) -0.30 (0.05) 0.39 (0.08)	-0.03 (0.08)	0.08 (0.12)	4·10 ⁻⁵ **	0.28	0.02*
PLIC RD	0.45 (0.02) -0.44 (0.03) 0.18 (0.04)	0.006 (0.07)	-0.02 (0.1)	0.19	0.09	0.21

^a Age correction of the parameters uses the generic formula $Parameter = A - B \exp(-Ct)$, with *A*, *B* and *C* being estimated constants. For estimation of the fractional anisotropy (FA), *B* is positive, and for the estimation of the mean diffusivity (MD), axial diffusivity (AD) and radial diffusivity (RD) the *B* is negative. Standard deviation values are in parentheses. Units for *A* and *B*: for FA, dimensionless; for MD, AD, RD: 10⁻³mm²/s. Units for *C*: month⁻¹

^b The last two columns present the coefficient of determination R² and the *P*-value for the linear regression between the respective diffusion parameter and the frontal-occipital horn ratio. The significant correlations are presented in Fig. 5

* *P*<0.05

** *P*<0.005