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Selective increase in posterior corpus callosum thickness between the age of 4 and 11 years

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ABSTRACT

Establishing an efficient functional and structural connectivity between the two cerebral hemispheres is an important developmental task during childhood, and alterations in this development have accordingly been linked to a series of neurodevelopmental and pediatric disorders. The corpus callosum, the major white-matter structure connecting the hemispheres, has been shown to increase in size throughout the three first decades of life. However, behavioral studies indicate that adult-like performance levels of functional hemispheric interaction are already reached during middle and late childhood. Thus, here we specifically examine the structural development of the corpus callosum during the functionally relevant time period by for the first time (a) selectively addressing prospective childhood development and (b) analyzing a sample in which also younger children are well represented. Corpus callosum anatomy was assessed from 732 T1-weighted MRI datasets acquired from 428 children (213 boys, 215 girls) aged of 4.1 and 10.9 years, of which 304 were scanned at two time points. Regional callosal thickness was determined from an outline-based segmentation of the mid-sagittal cross-sectional surface area. Linear-mixed model analyses revealed a significant increase in thickness with age (effect size: up to 15% explained variance) equivalent to a growth in callosal thickness of up to 0.19 mm per year in the posterior corpus callosum. The age effect was found to be stronger in posterior segments (i.e., splenium) than in other callosal subregions. Also, the age effect was found to be comparable between boys and girls, and was detected irrespective of whether developmental or individual differences in overall brain size where accounted for or not. Our results demonstrate a selective increase in posterior corpus-callosum thickness during middle and late childhood. Since axons crossing the midline in the splenium mainly connect occipital and parietal cortices, the accentuated posterior growth might reflect the onset of a posterior-to-anterior moving maturation wave in cortical development known to take place in the same time period.

Introduction

The establishment and optimization of functional and structural connectivity between the two cerebral hemispheres can be seen as an important developmental task during childhood. Congenital failure to develop inter-hemispheric axons, as e.g. in cases of partial or complete agenesis of the corpus callosum, is associated with delayed and hampered interhemispheric integration (e.g., Bayard et al., 2004; Ocklenburg et al., 2015) and slowing of executive processing (Marco et al., 2012). Also, alterations during maturation of the corpus callosum have been linked to pediatric disorders or developmental disabilities, including attention/hyperactivity disorder (e.g., Gilliam et al., 2011, Dramsdahl et al., 2012) and dyslexia (e.g., von Plessen et al., 2002). These observations related to an altered callosal development also emphasize the importance of gaining a better understanding of the typical development of the corpus callosum during childhood. Thus, the aim of the present study was to examine the macrostructural development of the corpus callosum, with particular focus on middle to late childhood (4 to 11 years). This age period is of special relevance since a series of behavioral studies indicates substantial changes in functional interhemispheric interaction (Banich and Brown, 2000). The quality of bimanual motor coordination (Marion et al., 2003) and hemispheric-visuomotor integration (Chicoine et al., 2000), interhemispheric-

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transfer time (Brizzolara et al., 1994; Hagelthorn et al., 2000), magnitude of the bilateral visual field advantage (Banich et al., 2000; Hagelthorn et al., 2000), interhemispheric integration of auditory information (Westerhausen et al., 2010), as well as the incidence of mirror movements (Mayston et al., 1999) have been demonstrated to reach adult-like performance levels in this age period.

Although the corpus callosum is known to rapidly grow in size especially in the first two to three years of life (Clarke et al., 1989; Garel et al., 2011; Rakic and Yakovlev, 1968) the results of a series of important developmental structural magnetic resonance imaging (sMRI) studies indicate that the midsagittal corpus callosum increases during childhood and adolescence (e.g., Chavarria et al., 2014; De Bellis et al., 2001; Ganjavi et al., 2011; Giedd et al., 1999; Giedd et al., 1996; Keshavan et al., 2002; Lenroot et al., 2007; Luders, Thompson, & Toga, 2010; Rauch and Jinkins, 1994; Thompson et al., 2000) and also well into the third decade of life (Prendergast et al., 2015; Pujol et al., 1993). From this, one might assume that the corpus callosum also grows within the above defined age period of interest. However, to fully evaluate these previous findings, the age distribution of the analyzed samples needs to be considered. In all previous studies that included participants from the respective age period the group of youngest children (below the age of 5 years) was not represented well, and rather represented only a small proportion of the study sample. All previous studies also included a substantial amount of adolescents and young adult participants (upper age ranging from late teens to late twenties). As a result, the statistical results were representative mostly for older children, adolescents, and partly young adults. For example, although showing a continuous increase in corpus callosum thickness during childhood and adolescence, Luders et al. (2010a, 2010b) found statistically significant differences only when the youngest age group (5- to 6-year-olds) was compared with the oldest age group (17- to 18-year-olds).

The aim of the present mixed cross-sectional and longitudinal study was to, for the first time, (a) selectively address middle to late childhood development (4 to 11 years) without additionally including older participants, and (b) utilize an appropriate sample size also for younger children. Since previous studies have reported a pronounced thickness increase in posterior than anterior parts of the corpus callosum in combined childhood and adolescence samples (Giedd et al., 1996; Luders et al., 2010b), the present study also tests whether these regional differences are observable in children as well. Furthermore, the present study aims to examine corpus callosum development under consideration of the participant's sex as well as of the relation to the parallel growth in total brain volume. More specifically, two previous studies found sex differences in the developmental trajectories of the corpus callosum, with boys showing a faster increase as compared to girls when analyzing a combined childhood and adolescence sample (De Bellis et al., 2001; Luders et al., 2010b). However, it can be speculated that the observed sex differences in corpus callosum might be driven mainly by the adolescent subsample. Recent studies show that especially during adolescence sex differences in the brain anatomy are formed, likely driven by the hormonal changes during puberty (e.g., Ahmed et al., 2008; Bramen et al., 2011; Paus et al., 2010). Following this reasoning, developmental sex differences during childhood could be expected to be small, if present at all. Also, childhood and adolescence are characterized by an ongoing increase in overall brain size (De Bellis et al., 2001; Lenroot et al., 2007) and brain maturation (Ostby et al., 2009; Tamnes et al., 2010a). In the adult brain, corpus callosum size is positively related to measures of brain volume (Bermudez and Zatorre, 2001; Jancke et al., 1997) and the growth in corpus callosum might be seen secondary to the overall volumetric brain increase during childhood. However, since earlier studies indicate that childhood growth of the corpus callosum is stronger than it would be expected from growth in brain size (Rauch and Jinkins, 1994), it is predicted that even after considering brain size, an increase in callosal size should be observed during childhood in the present study.

Table 1
Sample characteristics.

Age group	N	% girls	% Oslo	% rh	Mean age (s.d.) in years
4 to 5	46	47.8	95.7	84.8	4.67 (0.25)
5 to 6	131	50.4	91.6	90.1	5.55 (0.27)
6 to 7	175	50.9	85.7	91.4	6.51 (0.26)
7 to 8	132	50.0	70.5	88.6	7.51 (0.29)
8 to 9	121	55.4	51.2	92.6	8.46 (0.28)
9 to 10	74	55.4	24.3	90.5	9.39 (0.29)
10 to 11	53	50.9	32.1	88.7	10.44 (0.25)
Total	732	51.6	68.9	90.2	7.30 (1.61)

Notes. N = number of observations (including first and second measuring point), % girls = percentage of girls; % Oslo = percentage of data from the Oslo site; % rh = percentage right-handed; s.d. = standard deviation.

Material and methods

Participants

Participants were recruited via the Norwegian Mother and Child Cohort Study (MoBa) conducted by the Norwegian Institute of Public Health, which aimed to obtain a representative sample for the Norwegian population (Magnus et al., 2006). For the present study, MoBa participants living in greater Oslo and Trondheim area were invited to participate in the present magnetic resonance imaging (MRI) study. The resulting study sample consisted of 428 children (213 boys, 215 girls) of which 124 underwent MRI once and 304 (141 boys, 163 girls) underwent it twice, so that a total number of 732 observations were included in the present analyses. The datasets are from participants covering an age range from 4.1 to 10.9 years (including first and second time point of measuring; see Table 1 for details regarding the age distribution) with a mean age of 7.30 years (standard deviation, s.d.: ±1.61 years). MRI was conducted at two imaging sites located in Oslo (Rikshospitalet) and Trondheim (St. Olav's Hospital), respectively, so that 504 datasets were collected in Oslo and 228 in Trondheim. While at both sites the sex distribution of the datasets was comparable (52.2% girls in Oslo, and 50.4% girls in Trondheim, Fisher's Exact test, $p = 0.68$), the mean age at scanning was higher in Trondheim (8.50 ± 1.39 years) than in Oslo (6.76 ± 1.40 years; $t_{730} = 15.7$, $p < 0.001$). Furthermore, 45 of the children (24 boys, 21 girls, and 10.5% of the total sample) were identified by their parents as non-right handed, of whom 27 (12 boys, 15 girls) also had MRI at the second time point, so that 72 datasets (across time points) stem from non-right handed children.

The final number of subjects resulted after excluding 43 of original 775 datasets (5.5%) due to the following exclusion criteria: A history of any injury or disease known to affect the function of the central nervous system function, including neurological or psychiatric illness, or moderate to severe head trauma. Further, low birth weight (less than 2500 g) served as exclusion criterion. All relevant information was obtained at time of first MRI by asking the parent by using a customized questionnaire. Also excluded were datasets for which the structural MRI images did not pass quality control (see next MRI acquisition section).

The research project was approved by the Regional Committee for Medical and Health Research Ethics (REK southeast, number 2010/2359). For all children, written informed consent was obtained from a parent, and the children themselves gave oral consent.

MRI acquisition

MRI was performed at two imaging facilities, one in Oslo and one in Trondheim. Both sites used a 1.5 Tesla Siemens Avanto scanner, with the same head coil type (12-channel) and same pulse sequences for data acquisition. For all scans, a T1-weighted MPRAGE sequence (repetition time, TR = 2400 ms; echo time, TE = 3.61 ms; inversion time,

TI = 1000 ms; flip-angle of 8 degrees) with 160 sagittal slices (thickness: 1.2 mm) with a 192 × 192 scan matrix in a field of view of 240 × 240 mm^2 was used. The image resolution was 1.25 × 1.25 × 1.20 mm^3. Data acquisition was done using parallel imaging technique (iPAT, GRAPPA factor 2) acquiring multiple (between 2 and 4) T1 volumes in a short scan time (4 min 18 s per volume). This allowed for selecting the volume of best imaging quality which then was used in the analyses. The quality rating was based on visual inspection and performed by two experienced examiners (D.A.R., S.K.K.). Datasets of low quality, e.g. due to movement artefacts, were excluded.

Determining regional corpus callosum thickness

Image pre-processing and statistical analysis steps were performed using routines written in MATLAB (MathWorks Inc., Natick, MA, USA). First, in order to achieve approximate spatial alignment between individual images, all images were coregistered to a customized (child) T1-template (in MNI space) using rigid-body transformations with Statistical Parametric Mapping (SPM12, www.fil.ion.ucl.ac.uk/spm/software/spm12/) routines (Wellcome Department of Cognitive Neurology, London, UK). It should be noted that the rigid-body transformation only resulted in a re-orientation not in a deformation of the volume, so that the absolute and relative size measures were not affected by the coregistration step. Then, the resulting images were segmented with SPM12 to obtain white-matter images in native space (resampled to 1 mm isovoxels). In an automatic procedure the mid-sagittal slice was selected and the corpus callosum identified on the white-matter images. The resulting mid-sagittal corpus callosum segmentations were visually inspected and compared to the raw T1-image, and when necessary manually corrected (e.g., by removing white matter voxels belonging to the fornix) to correctly capture the corpus callosum. The total number of voxels of the such determined callosal cross-section was extracted as estimate of the mid-sagittal surface area (in mm^2), and used for statistical analysis. The total midsagittal corpus callosum area varied between 216 and 720 mm^2 (mean 416 ± 68 mm^2) across participants and time points.

In preparation of the regional callosal thickness analysis, the segmented mid-sagittal slice was interpolated to a 0.33 × 0.33 mm^2 in-plane resolution in order to obtain a higher sampling density for the determination of the callosal outline and exported for further analyses. Regional thickness was then determined based on an outline/surface-based segmentation approach (for similiar approaches see Clarke et al., 1989; Luders et al., 2006; Walterfang et al., 2009). An outline of the corpus callosum was created by removing all non-border voxels from the segmented corpus callosum, and the voxels representing the tip of the rostrum and the base of the splenium were identified in a semi-automatic procedure. The tip of the rostrum was defined as the posterior-most voxel of the in-bend rostrum in the anterior half of the corpus callosum. The base of the splenium was defined as the ventral-most voxel in the posterior corpus callosum. These points were used to separate the outline of the corpus callosum into a "lower" (connecting the points along the ventral border of the corpus callosum) and an "upper" outline (connecting the points along the dorsal border). The midline between upper and lower outline – calculated as mean between upper and lower outline sampled at 60 support points spaced equidistantly on the two outlines – served as basis for calculating the thickness measures. Further, the 60 midline support points were resampled to achieve equidistance along the midline. The number of 60 points was chosen as a compromise between the previously used 29 to 100 points (cf. Clarke et al., 1989; Luders et al., 2006) since it was found to provide a sufficiently high number of sampling points to capture the structure of corpus callosum, while at the same time it does not inflate the number of statistical tests excessively. Callosal thickness was then determined orthogonal to the midline at these resampled support points, by calculating the distance between the point of intersection of the orthogonal with the upper and the lower outline, respectively. Thus, for each subject and observation, 60 thickness measures were obtained and used for statistical analysis. Mean corpus callosum outline across all 732 observations can be found in Fig. 1. A frequently utilized scheme for analyzing corpus callosum anatomy is based on subdividing the mid-sagittal surface area based on geometrical rules into sub-regions (Witelson, 1989). For example, relative to its anterior-posterior extension the corpus callosum has been divided into "thirds" defining genu, truncus, and splenium, respectively (see also Fig. 1). The here adopted thickness-measurement approach was preferred of the geometrical subdivision since it promises (a) to be less dependent on the curvature of the corpus callosum which varies between individuals (Clarke et al., 1989; Luders et al., 2006) and (b) a better regional specificity (e.g., here 60 versus 3–5 resolution elements in the conventional approach).

Estimation of total intracranial volume

Developmental increase in total brain size will also affect the development of callosal size and thickness measures. Thus, in order to be able to analyze the effect of brain size on the observed callosal measures, we used the T1-weighted images to also obtain an estimation of the total intracranial volume (TIV) of each individual/scan. TIV was estimated using the automated segmentation routines ("tissue volumes" utility) provided with SPM12. This method has been shown to provide highly valid estimates of TIV when related to "gold standard" of manual segmentation (Hansen et al., 2015; Malone et al., 2015). This approach defines TIV as the total volume within the cranium, including forebrain, midbrain, hindbrain, and cerebellum, as sum over grey matter, white

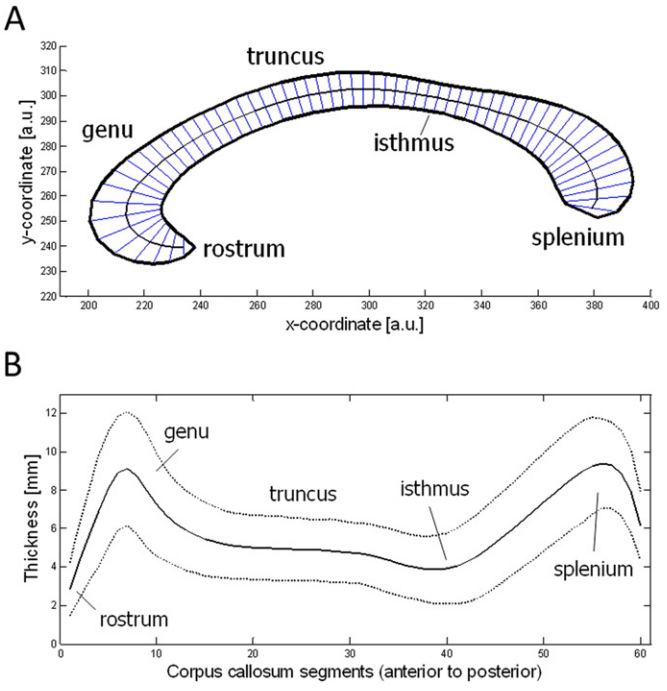

Fig. 1. Average mid-sagittal outline and thickness measures of the corpus callosum across all observations (N = 732). Panel (A) shows the outline of the corpus callosum (anterior = left, posterior right), the midline between upper and lower outline, as well as the 60 segment lines placed orthogonal to the midline representing the (mean) thickness measures. The panel also indicates the anatomical names for the callosal subregions: rostrum, the inward-bend, beak-like tip in the anterior part; genu, the anterior corpus callosum which often defined as the anterior third relative to the anterior-posterior extent of the corpus callosum; truncus, or mid-body of the structure (or middle third; cf. Witelson, 1989); isthmus, the narrowing posterior to the truncus; and the splenium, the bulbous posterior sections (often defined as posterior fifth). Panel (B) shows the mean thickness (solid line) and 95% confidence limits (dotted lines) for the 60 callosal segments from anterior to posterior and across all 732 observations.

matter, and CSF tissue classes. The inferior boarder of the cerebellum is used as inferior limit for the estimation of TIV. The present data was acquired as sagittal images, so that all relevant brain regions including the cerebellum were part of all image volumes, allowing for a reliable estimation of TIV. TIV varied between 1103 and 2009 ml (mean 1412 ± 122 ml).

Statistical analysis

The regional thickness analysis consisted of two main statistical analyses: first, a linear mixed-effects model was calculated to address (for each of the 60 callosal thickness measures) the development of the corpus callosum, as well as possible developmental sex differences (analysis 1). In general, linear-mixed effect models allow integrating cross-sectional and longitudinal data and estimate common developmental trajectories (Verbeke and Molenberghs, 2009). The model included the predictors of interest: Age (centered), Sex, and interaction of Age and Sex (as fixed effects): In order to account for the repeated-measure nature in a huge proportion of the sample different intercepts with regard to Subjects were also included in the model (random effects). A random intercept model was fitted since an explorative analysis had shown no significant improvement in model fit in a model using both random intercept and slope fitting. Additionally, the predictor Site (Trondheim vs. Oslo) was included to account for possible differences resulting from using different MR scanners, an approach which can be deemed appropriate in aggregate studies with no discrepancies in scanning platforms and scanning sequence (Chen et al., 2014). Second, in order to address the possible confounding effect of brain size the first model was extended by including TIV as additional predictor/covariate (analysis 2).

To analyze the growth of the total midsagittal callosal area comparable linear mixed-effects models were calculated as for the regional analysis: the first analysis containing predictors for Age (centered), Sex, and the interaction of Age and Sex (fixed effects), as well as allowing for different intercepts between Subjects (as random effects). In a second analysis, TIV was included as additional predictor. Analogue to the regional analysis, both analyses also included the predictor Site as covariate of non-interest.

All analyses were conducted using restricted maximum likelihood estimations (using a full covariance matrix; Cholesky parameterization), and the models were fitted using the "fitlme" functions provided with MATLAB. For regional tests, significance thresholds were adjusted using Bonferroni-Holm procedure to achieve type I error rate adjustment to $\alpha = 0.05$ (within the corpus callosum). To test for regional differences in the effect of Age on callosal thickness, post-hoc pair-wise slope comparisons were conducted between the 60 segments using t-tests. Effect size was calculated as proportion of explained variance (ω^2), defined as the increase in explained variance in the present model relative to the same model without the variable in question. For all effects a "just detectable effect size" (sensitive power analysis) of $\omega^2 = 0.02$ was determined using G*Power (www.gpower.hhu.de), that is, the existence of population effects larger than 2% explained variance can be excluded with a power of 0.80 (Cohen, 1988). This estimation was based on the regional analysis using the most conservative Bonferroni-Holm correction (i.e., resulting when no significant effect at any callosal segment was found) so that a test-wise α of $0.05/60 = 0.00083$ threshold was the basis for this calculations. For tests allowing for a more liberal α correction, high sensitivity/power for even smaller effect sizes can be assumed.

The inclusion of the factors Age, Sex, and TIV, followed the aims of the present study as outlined in the Introduction. However, the effects of other variables were considered in explorative analyses. First, a possible non-linear effect of age was considered, by including age squared and the interaction of age squared with sex as additional predictors; and secondly the effect of handedness, introducing the predictor Handedness (right handed vs. non-right handed participants) and the interaction of Age and Handedness. These extended models were directly compared with the original models (with and without TIV as predictor) in order to assess model-fit improvement for any of the callosal thickness measures using likelihood ratio, LR, test based on the maximized log-likelihood model fit statistics.

Results

Analysis of regional callosal thickness

Not accounting for differences in TIV, a significant positive effect of Age was found in the splenium of the corpus callosum (all $\omega^2 > 0.05$; see Fig. 2, upper right panel). The strongest association was located in segment 59 in the splenium ($\beta = 0.19$; $t_{727} = 6.57$, $p < 0.0001$, $\omega^2 = 0.15$) indicative of a fitted average growth of 0.19 mm per year (see Fig. 3). Post-hoc inter-regional comparisons revealed that the slope for the effect of Age on thickness was significantly steeper in the posterior segments compared to all middle and anterior segments (see Fig. 4, left panel). Additionally, the corpus callosum was found to be thicker in boys than girls, with significant differences located along the entire corpus callosum (for all significant effects $\omega^2 > 0.005$; see Fig. 2 upper left panel). The largest Sex difference was found in the genu of the corpus callosum (segment 17; $\beta = -0.44$, $t_{727} = -5.50$, $p < 0.0001$, $\omega^2 = 0.01$) representing 0.44 mm thicker corpus callosum in boys than in girls. Furthermore, the analysis did not provide any indication for an interaction of Sex and Age (all $\omega^2 < 0.02$, Fig. 2, lower left panel). For matter of completeness, the analysis also revealed a small but significant effect of Site in the genu sub-region, with smaller average measures in the Oslo compared to the Trondheim sample (maximum effect in segment 9; $\beta = -0.71$, $t_{727} = -4.61$, $p < 0.0001$, $\omega^2 = 0.01$, see Supplementary Fig. 1).

Including TIV as covariate did not substantially alter the effect of Age. A positive association of Age and thickness was found in the splenium sub-region (Fig. 5, upper right panel), with an increase of 0.18 mm per year representing the maximum effect found again in segment 59 ($\beta = 0.18$; $t_{726} = 6.38$, $p < 0.0001$, $\omega^2 = 0.14$, Fig. 3B). Also here post-hoc analyses revealed that the slope of the Age effect was steeper in posterior compared to anterior and middle regions of the corpus callosum (Fig. 4, right panel). However, including TIV affected the Sex effect, that is, no sex differences were found in the corpus callosum (all $\omega^2 < 0.02$; see Fig. 5, upper left panel), while significant positive associations of TIV with callosal thickness were detected throughout rostrum, genu, and truncus (for all significant effects $\omega^2 > 0.01$; Fig. 5, lower right panel). The strongest effect of TIV was found in the genu (segment 11) where an increase in TIV by 100 ml was associated with an increase in callosal thickness by 0.34 mm ($\beta = 3.38$; $t_{726} = 8.04$, $p < 0.0001$, $\omega^2 = 0.05$). No significant interaction of Sex and Age was detected (all $\omega^2 < 0.02$; Fig. 5, lower left panel). Finally, the Site effect was significant in the genu (maximum effect in segment 9; $\beta = -0.69$, $t_{726} = -4.72$, $p < 0.0001$, $\omega^2 = 0.02$, see Supplementary Fig. 1).

The explorative analyses did neither for considering Age squared nor Handedness reveal substantial improvement in model fit for any of the thickness segments. Direct comparison of the extended with the original models were non-significant for the inclusion of Age squared (all $p > 0.07$; all $\chi^2_{LR} < 14.7$, df = 2) and Handedness predictors (all $p > 0.46$; all $\chi^2_{LR} < 6.31$, df = 2).

Analysis of total midsagittal corpus callosum size

The total corpus callosum was found to be positively associated with Age ($\beta = 9.16$; $t_{727} = 9.36$, $p < 0.0001$, $\omega^2 = 0.25$) indicating an increase of about 9 mm^2 in midsagittal area per year. Also, a significant Sex effect was detected ($\beta = -35.75$; $t_{727} = -6.10$, $p < 0.0001$, $\omega^2 = 0.002$) with the corpus callosum being larger in boys than girls. Beyond this neither the Sex by Age interaction ($\beta = 0.57$; $t_{727} = 0.43$; $p = 0.67$; $\omega^2 < 0.001$)

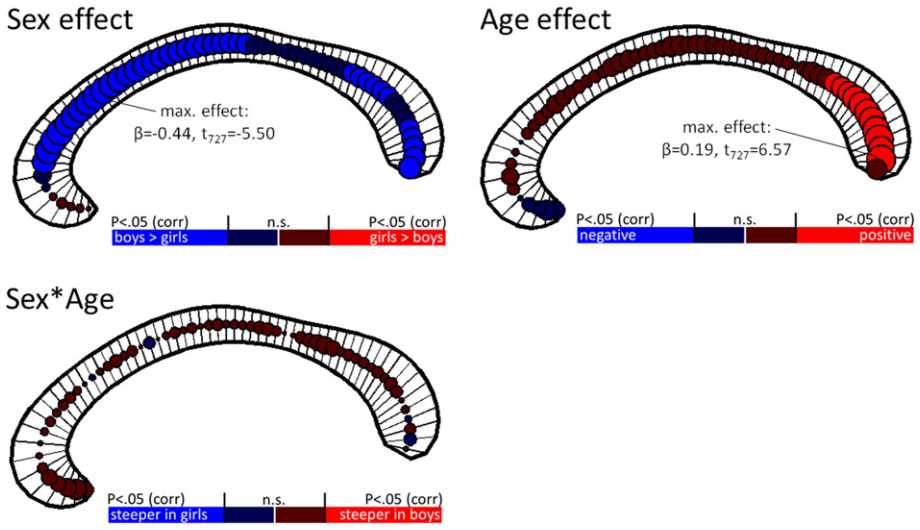

Fig. 2. Results of regional callosal thickness (Analysis 1), including the effects of Sex (upper left), Age (upper right), and the interaction of Sex and Age (lower left). The magnitude of the respective effect is indicated by a circle at each of the 60 callosal segments, whereby the size of the circle codes the size of the t-value for the significant test of the corresponding predictor. The color codes the sign of the effect (red = positive, blue = negative), with significant tests being indicated by lighter colors than non-significant tests. Across the corpus callosum, significance thresholds were adjusted using Bonferroni-Holm procedure to achieve alpha adjustment to 5%. Note: the anterior part of the corpus callosum is on the left side of each panel.

nor the main effect of Site yielded significance ($\beta = -7.29$; $t_{727} = -1.11$; $p = 0.27$; $\omega^2 < 0.001$).

The effect of Age remained also when including TIV as a covariate ($\beta = 8.08$; $t_{726} = 8.12$, $p < 0.0001$, $\omega^2 = 0.21$) reflecting an area increase of 8 mm^2 per year. Also after the inclusion of TIV, boys were found to have a larger corpus callosum than girls ($\beta = -22.14$; $t_{726} = -3.75$, $p = 0.0001$, $\omega^2 = 0.027$). TIV itself also was a significant predictor, whereby an increase in TIV by 100 ml was associated with an increase in callosal area of 118 mm^2 ($\beta = 118.65$; $t_{726} = 6.74$, $p < 0.0001$, $\omega^2 = 0.03$). Again neither the interaction of Sex and Age ($\beta = 0.39$; $t_{726} = 0.29$; $p = 0.77$; $\omega^2 < 0.001$) nor the effect of Site were significant ($\beta = -7.68$; $t_{726} = -1.23$; $p = 0.22$; $\omega^2 < 0.001$).

As for the regional thickness analysis, also for total area, neither considering Age squared nor Handedness revealed substantial improvement in model fit: Comparing the extended models with the original models was neither significant for the inclusion of Age squared (all $p > 0.13$; all $\chi^2_{LR} < 3.97$, df = 2) nor for the inclusion of Handedness predictors (all $p > 0.48$; all $\chi^2_{LR} < 11.24$, df = 2).

Discussion

A significant and selective increase in thickness of the splenium of the corpus callosum between the age of 4 and 10 years was demonstrated by for the first time utilizing a large sample in which also younger children are well represented. Although also the total midsagittal area of the corpus callosum was found to increase in this age period, the regional thickness analysis indicates that this overall effect is mainly driven by segments located in the posterior corpus callosum. The

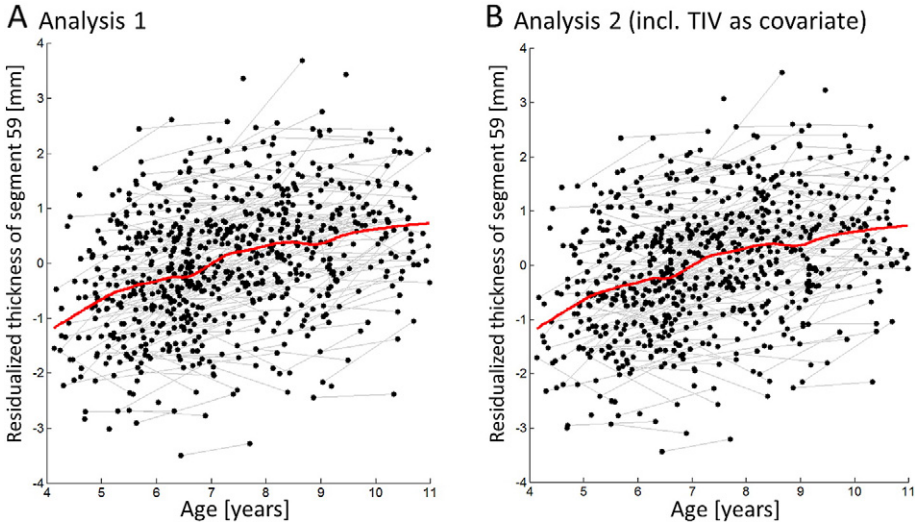

Fig. 3. Relation between callosal thickness and Age at the location of the maximum effect in analysis 1 (A) and analysis 2 (B; i.e. with total intracranial volume, TIV, as covariate). In both analyses the maximum effect was found in segment 59 located in the splenium of the corpus callosum. The association is presented as spaghetti scatter plot with measures of the same participant being connected by grey lines. To be more intuitive, the x-axis shows the participants' age in years although the actual analysis was done using age as mean-centered variable. The y-axis represents the thickness as measured in segment 59 residualized for all other effects included in the respective design (see Statistical analysis section). The red line represents locally weighted scatterplot smoothing of the prediction.

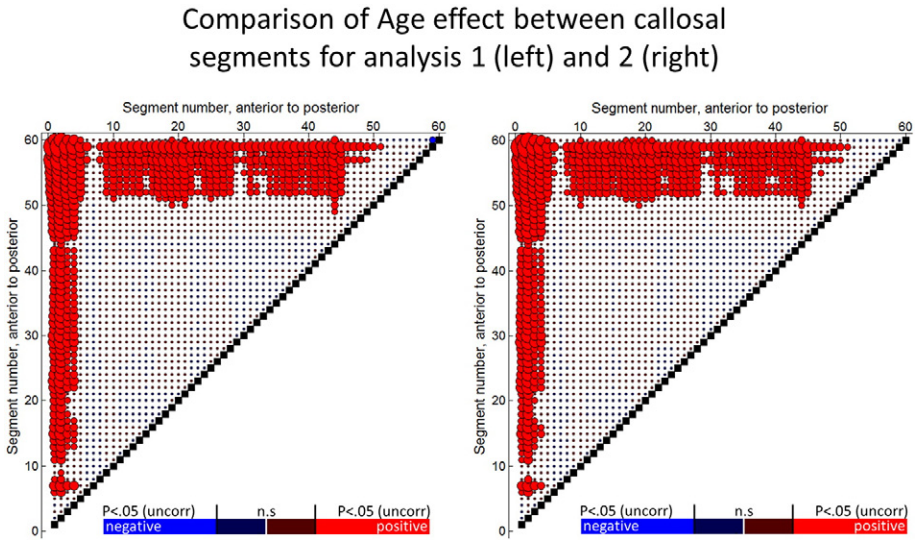

Fig. 4. Post-hoc test for differences in the magnitude of the Age effect between callosal segments for analysis 1 (left) and analysis 2 (right; i.e. with TIV as covariate). The matrix plots show the (non-redundant) statistical comparison in the slope of the Age effect between all segments, with the size of the circle indicating the corresponding t-value, and its color the direction of the effect (red = positive, blue = negative). The upper horizontal "band" of significant slope differences in both graphs, shows that the posterior segments (about segment 51 to 59) have a steeper slope than most of the anterior and middle callosal segments. The vertical "band" of significant slope differences, shows that most segments in the middle and posterior segment differ from anterior slopes.

callosal segment which revealed the strongest effect (15% variance explained by age) was located in the splenium and showed an average thickness growth of 0.19 mm per year. In this, the present findings extend the results of earlier studies which report comparable growth pattern but only in samples which also included adolescents or young adults (Chavarria et al., 2014; De Bellis et al., 2001; Ganjavi et al., 2011; Garel et al., 2011; Giedd et al., 1999; Giedd et al., 1996; Keshavan et al., 2002; Lenroot et al., 2007; Luders et al., 2010b; Rauch and Jinkins, 1994; Thompson et al., 2000). The revealed structural development also adds to the interpretation of the results of a series of behavioral studies suggesting an ongoing maturation of interhemispheric interaction in middle and late childhood, both in quality of information transfer (e.g., Brizzolara et al., 1994; Hagelthorn et al., 2000; Westerhausen et al., 2010) as well as in the interhemispheric coordination of processing (e.g., Chicoine et al., 2000; Marion et al., 2003). It further shows that the age effect on callosal thickness persists (in comparable effect size) when differences in TIV are accounted for. Thus, also in middle to late childhood posterior callosal growth does not just reflect the increase in overall brain size (De Bellis et al., 2001; Lenroot et al., 2007) but rather seems to be driven by additional maturation effects of the interhemispheric connections (see also Rauch and Jinkins, 1994). Furthermore, callosal growth was found to be linear (see Fig. 3) and supplementary analyses showed that models including potential quadratic effects of age did not improve the model fit substantially. While the current results confirm most of the previous studies showing a positive linear association between age and corpus callosum anatomy across childhood and adolescence (De Bellis et al., 2001; Ganjavi et al., 2011; Giedd et al., 1996; Luders et al., 2010b), it also might be taken to indicate that elsewhere reported nonlinear relationships (Giedd et al., 1999; Lenroot et al., 2007) were likely due to reduction in growth

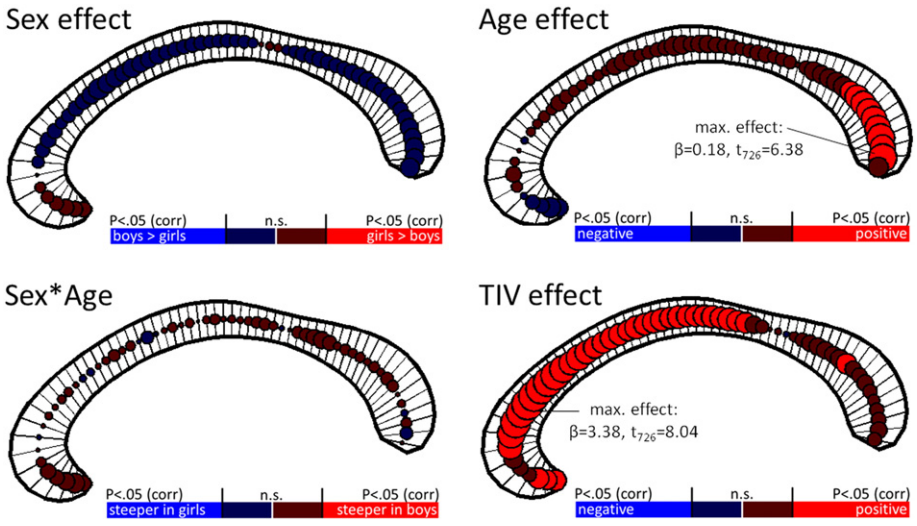

Fig. 5. Results for regional callosal thickness (analysis 2), including the effects of Sex (upper left), Age (upper right), the interaction of Sex and Age (lower left), and total intracranial volume (TIV, lower right). The respective effect is visualized by a circle at each of the 60 segments of the corpus callosum, with significant tests being indicated by lighter colors than non-significant tests. Bonferroni-Holm procedure was applied to achieve alpha adjustment to 5%. The anterior corpus callosum is on the left side of each panel.

rate in the also included adolescents rather than a non-linear association already during childhood. Related, the absence of non-linear/quadratic effects also suggests that the observed growth or slope of the association is constant across the examined age period, so that no regional acceleration or decelerations in growth were observed in the examined age period (given the test power analysis effects larger than 2% explained variance can be excluded). Thus, no substantial temporal differences in progress of macrostructural maturation of the corpus callosum are apparent in the age range between 4 to 11 years.

However, in line with previous studies (Giedd et al., 1996; Luders et al., 2010b; Thompson et al., 2000) the present findings confirm regional differences in the maturation of the corpus callosum also in children. Not only was the effect size found to be largest in the posterior segments, also did direct comparisons between the slopes reveal significantly steeper slopes for the Age effect in posterior compared to anterior and middle corpus callosum segments (Fig. 4). Luders et al. (2010a, 2010b) interpreted the stronger posterior growth in their sample, in relation to a posterior-to-anterior moving maturation wave in cortical development, in which the maturation of occipital and parietal cortices, precedes frontal and temporal cortex maturation (e.g., Amlien et al., 2016; Gogtay et al., 2004; Sowell et al., 2004; Tamnes et al., 2010a; Tamnes et al., 2010b). Given the topographical organization of the corpus callosum – that is, occipital and parietal regions are interconnected through the posterior corpus callosum, while frontal regions are connected through the anterior corpus callosum (Schmahmann and Pandya, 2006) – the development of the corpus callosum can be predicted to follow a similar posterior-to-anterior gradient of maturation. The here observed posterior callosal age effect during childhood might thus be seen to reflect the onset of this wave, and should be followed by a pronounced anterior development in adolescence (as shown in Luders et al., 2010b).

Summarizing the above, corpus callosum development shows a phase of rapid overall callosal growth during infancy and early childhood (Clarke et al., 1989; Garel et al., 2011; Rakic and Yakovlev, 1968) until an age of approximately 3 years. This initial phase appears to be followed by an anterior-posterior-anterior maturation pattern during childhood and adolescence. That is, an accentuated increase in thickness of the anterior corpus callosum between 3 to 6 years (Thompson et al., 2000) which is followed by a pronounced maturation of the posterior sections between the age of 4 and 11 years (as shown in the present study), and by a second accentuated anterior maturation during late adolescence (Luders et al., 2010b, see also Giedd et al., 1999; Lenroot et al., 2007). Beyond this, gross-anatomical development of the corpus callosum likely extends well into adult age (Prendergast et al., 2015; Pujol et al., 1993)." On a microstructural level, axon pruning, through retraction or degeneration, results in continuous reduction in the number of callosal axons during infancy, but is paralleled by formation of myelin sheaths around the remaining axons (Innocenti and Bressoud, 2003). The increase in axon myelination is thought to result in a net increase in callosal size despite the progressive axon loss (e.g., Clarke et al., 1989). Also during the here examined childhood period (as well as during later adolescence and young adult age), increase in myelination appears to be the likely microstructural substrate of the observed macrostructural increase. This notion is supported by diffusion-tensor imaging studies showing increase in callosal fractional anisotropy during childhood and adolescence (e.g., Krogsrud et al., 2016; Lebel et al., 2008; Rollins et al., 2010; Snook et al., 2007). Crucially, the increase in anisotropy appears to be mainly driven by a reduction in radial diffusion, i.e. diffusion orthogonal to the main fiber direction (e.g., Krogsrud et al., 2016; Rollins et al., 2010), which is likely indicative for an increased in myelination of the axons (Song et al., 2002).

The selective posterior growth of the corpus callosum during childhood appeared to be general, in as much as no indication for developmental sex differences was found. That is, the interaction of Age and Sex (with good power/sensitivity) was non-significant in all callosal segments independent of whether TIV was considered as covariate or not. In this, the present results replicate several previous studies (Giedd et al., 1999; Giedd et al., 1996; Lenroot et al., 2007). Two other studies, however, indicated slope differences by calculating separate regression analyses for boys and girls, with boys showing steeper slopes than girls (De Bellis et al., 2001; Luders et al., 2010b). Both studies do not provide a direct test for slope differences and it is not clear if apparent difference would also be statistically significant. Also, both studies included adolescents and young adults so that the observed interaction between age and sex might have been driven by the older participants in the sample. Adolescence, with the onset of puberty, is associated with dramatic hormonal alterations which have been associated with sex differences in brain development (Ahmed et al., 2008; Bramen et al., 2011; Paus et al., 2010). Also for the corpus callosum, differences in callosal thickness have been indicated to be related to the progression in pubertal development (Chavarria et al., 2014), so that a differential development between the sexes during adolescence might appear likely. Nevertheless, considering childhood alone, the present study did not indicate any developmental differences in the corpus callosum between boys and girls.

Sex might not only be related to developmental differences with age but also to mean differences in callosal anatomy independent of age. Since the report of sex differences in the corpus callosum by DeLacoste-Utamsing and Holloway (1982), sexual dimorphism in the adult corpus callosum have been frequently examined both at the macrostructural (e.g., Bermudez and Zatorre, 2001; Jancke et al., 1997; Luders et al., 2006; Luders et al., 2014; Westerhausen et al., 2004) and microstructural (with diffusion-tensor imaging) level (e.g., Westerhausen et al., 2011a; Westerhausen et al., 2004). Meta-analytical evidence indicates that the absolute size of the corpus callosum is larger in adult males than females (Bishop and Wahlsten, 1997; Smith, 2005), while this difference disappears (e.g. Bishop and Wahlsten, 1997; Luders et al., 2014) or is even reversed (Bermudez and Zatorre, 2001) once sex differences in brain size are accounted for. However, in the latter case the sex effect is usually small, explaining not more than 1% of variance (Smith, 2005). Considering the developing corpus callosum, several studies did not find sex differences, neither with (Lenroot et al., 2007) nor without considering brain size as covariate (De Bellis et al., 2001; Garel et al., 2011). However, two larger studies provide results similar to what is known from adult samples, namely that an overall main effect of sex with larger (anterior) callosal areas in boys vanishes (Giedd et al., 1999) or reverses (Ganjavi et al., 2011) after brain size was included as covariate. Notably, both studies included children and adolescents in their sample, studying an age range between 4 and 18 and between 6 and 18 years, respectively. The present study demonstrates a similar pattern in a child sample: a slightly, but significantly thicker corpus callosum in boys compared to girls, both in total callosal area and in regional thickness (maximum variance explained $<3\%$). While the difference on regional thickness measures statistically vanishes once TIV was included as covariate, for total callosal area the effect was found to persist. Of note, for the regional thickness analysis the effect the Sex effect remains (although not significantly) negative almost throughout the entire corpus callosum, that is, larger callosal thickness in boys, even after TIV inclusion (see Fig. 5, upper left panel). Thus, in contrast to the adult pattern, male participants also after accounting for brain size differences appear to have a larger corpus callosum than female participants. Since studies typically find a reversion of the effect in older aged developing samples (Ganjavi et al., 2011) and adult samples (Bermudez and Zatorre, 2001; Smith, 2005) a developmental sex effect might occur beyond the here examined age range. As also indicated above, hormonal changes during puberty have been shown to foster the emergence of sexual dimorphisms during adolescence (Ahmed et al., 2008). However, the present lack of a significant interaction of Sex and Age, at least supports the notion that the age effects are stable within the present age range from 4 to 11 years. In summary, like for the adult corpus callosum, once accounted for brain size, the sexual dimorphism in children is small.

In the present sample, we did not find any indications for differences in callosal thickness or callosal growth as a function of handedness. Handedness is a frequently discussed factor when addressing structural differences in the corpus callosum. Non-right handed adult participants are frequently reported to exhibit larger mid-sagittal corpus callosum area than right-handed individuals (e.g., Habib et al., 1991; Tuncer et al., 2005; Witelson, 1989), although not consistently (e.g., Jancke et al., 1997; Luders et al., 2010a; Westerhausen et al., 2004). However, the present findings are in line with Luders et al. (Luders et al., 2010b), who also did not find any handedness-related corpus callosum differences in a developing sample. It has to be noted, however, that the present handedness assessment was based on parents' information about their children's handedness, and thus might not yield as valid classification as more elaborated questionnaires or behavioral measures that are traditionally used in handedness research (Peters, 1995). Also, it has been proposed that callosal size in adults is not linked to left- or right- handedness in itself, but rather to the degree of difference between left- and right-hand preference (Luders et al., 2010a), information which is unfortunately not available for the present sample. Future studies addressing callosal handedness effects in children might benefit from a more refined handedness assessment.

In order to achieve an as big sample size as possible the present study utilized data from two MR imaging facilities equipped with the same hardware and using the same pulse sequences for data acquisition. Nevertheless, a significant effect of scanning site was found, reflecting smaller measures of corpus callosum thickness in three genu segments in the Oslo as compared to the Trondheim sample. Previous studies show that scanner effects on sMRI measures might results from a number of factors, including differences in homogeneity of the static magnetic field or in imaging-gradient nonlinearity (Jovicich et al., 2006), which also here are possible candidates for explaining the differences between the sites (despite scanner type/built and head coil were the same at both sites). It cannot be excluded, however, that the site difference could also at least partly be due to “true” differences in callosal anatomy resulting from the on average higher age of the Trondheim sample (see Participants section). In any case, using Site as covariate in the analysis, should have accounted for scanner effects given that scanner equipment and imaging sequence were the same at both sites (Chen et al., 2014). Thus, it is the authors belief, that the here observed effects of Age, Sex, or TIV on callosal thickness are not substantially affected by scanner effects.

In conclusion, the present study indicates a linear increase in thickness especially in the splenium of the corpus callosum during the childhood period of 4 to 11 years. Sex effects, both on absolute size as well as on developmental trajectories in this period appear to be small, and for regional thickness measures negligible, once brain size differences are accounted for. It appears likely that these structural changes are the anatomical substrate of changes in the functional interaction between the hemispheres which can be observed in the same time period (e.g., Brizzolara et al., 1994; Chicoine et al., 2000; Hagelthorn et al., 2000). Given the present findings, interhemispheric integration especially in visual (Westerhausen et al., 2006) and auditory processing (Westerhausen et al., 2009) should be affected since axons running through the splenium interconnect sensory and high-order visual and auditory cortices in occipital, parietal, and temporal lobe regions (Schmahmann and Pandya, 2006). While initial findings support the notion of such association of structural and functional development in children and adolescents (Kurth et al., 2013; Westerhausen et al., 2011b), it remains for future studies to systematically address this structure-function association during childhood development. Furthermore, considering the topography of callosal axons within the corpus callosum, the accentuation of the age effect in the posterior corpus callosum between the 4 and 11 years likely reflects the posterior-to-anterior moving maturation wave in cortical development observed in the same time period (e.g., Amlien et al., 2016; Gogtay et al., 2004; Sowell et al., 2004; Tamnes et al., 2010a; Tamnes et al., 2010b).

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