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Elayne Joe April 12, 2022

Time-Varying Lateralization of Infant White Matter Tracts and the Development of the Corpus Callosum

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Abstract

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By Elayne Joe

Background: The corpus callosum (CC) is the largest white matter structure in the brain that influences interhemispheric connectivity and, subsequently, lateralization. However, exactly how the CC influences lateralization and how this relationship emerges in infancy remains unclear. Understanding how the CC develops in relation to lateralization in the typically-developing infant is critical since developmental disorders, such as autism spectrum disorder, dyslexia, and congenital sensorineural hearing loss, have been linked to atypical lateralization in the brain and altered callosal morphology. Thus, this project explores how CC development is associated with the development of lateralization of infant white matter tracts in the first 6 months of life.

Methods: Diffusion MRI data were collected at up to 3 time points between birth and 6 months in $N = 78$ typically-developing infants. Template-based probabilistic tractography delineated left and right masks for 7 bilateral white matter structures, in addition to the whole-brain, that were selected due to the presence of significant lateralization during infancy. These include the arcuate fasciculus (AF), anterior thalamic radiation (ATR), fornix (Fx), inferior fronto-occipital fasciculus (IFOF), inferior longitudinal fasciculus (ILF), and pyramidal tract from the motor (PTM) and sensorimotor (PTS) cortices. Trajectories of lateralization indices were fit using Functional Principal Components Analyses, and associations between lateralization and fractional anisotropy of the CC splenium (CCs), body (CCb), and genu (CCg) were explored using Functional Linear Regression.

Results: Significant associations were found between the IFOF and CCs, ATR and CCs, ATR and CCb, PTM and CCb, whole-brain and CCb, and whole-brain and CCg. For the CCs and CCb, CC development and lateralization were positively correlated in the earlier days of infancy and negatively correlated towards the end of the first 6 months of life, whereas this trend was reversed for the CCg.

Discussion: The relationships between CC development and lateralization development were found to be time-varying, indicating that CC development is both positively and negatively associated with lateralization. By studying this relationship within typically-developing infants, our findings may provide a point of comparison for atypical developmental processes, especially early in development, which may have implications for earlier diagnostic criteria in developmental disorders.

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Table of Contents

Introduction

The corpus callosum (CC) is the major white matter structure in the brain that connects the two cerebral hemispheres and facilitates the transfer of information between both homotopic and heterotopic cortical areas (Witelson, 1989). In the adult brain, callosal fibers are believed to mediate interhemispheric connectivity (Wahl et al., 2007) and, subsequently, play significant roles in functional lateralization (Hervé et al., 2013), especially in relation to handedness (Beaulé et al., 2012) and language (Putnam et al., 2008). This is further supported by studies of patients who have undergone callosotomy who are incapable of integrating lateralized higher-level cognitive and linguistic functions (Gazzaniga, 2000; Bloom & Hynd, 2005; Johnston et al., 2008; van der Knaap & van der Ham, 2011). However, the exact mechanism through which the CC exerts its influence on lateralization is not yet fully understood.

Within the current literature, two main theories exist in an attempt to explain the role of the CC in lateralization. The excitation theory suggests that, when one hemisphere is stimulated during specific tasks, the CC integrates this information in order to activate the unstimulated homotopic regions in the other hemisphere (Yazgan et al., 1995). Evidence for this hypothesis is given by studies showing a negative correlation between CC size and behavioral laterality in dichotic listening tasks, in addition to the right ear advantage in split-brain patients, both of which show a reduction in the number of callosal fibers and connected callosal fibers, respectively, associated with increased laterality (Yazgan et al., 1995; Hausmann et al., 2005). This is because fewer callosal fibers would cause the CC to be less effective when activating the unstimulated hemisphere, leading to increased lateralization. In contrast, others propose an inhibitory theory for lateralization, in which the CC inhibits one hemisphere during specific tasks, allowing the other hemisphere to specialize in that given function (Cook, 1984; Karbe et

al., 1998). This theory is supported by the right ear advantage seen in dichotic listening, indicating that the CC blocks signals from auditory stimuli to the right hemisphere, which leads to a left hemisphere, or right ear, dominance (Westerhausen & Hugdahl, 2008). Furthermore, decreased callosal density seen in old age is associated with decreased inhibition of the opposing hemisphere during simple motor task performances (Langan et al., 2010). This is due to the fact that fewer callosal fibers cause the CC to be less effective when inhibiting the less dominant hemisphere, which leads to a reduction in lateralization and decrease in efficiency during lateralized tasks. However, due to the strong evidence for both theories, it has been suggested that the role of the CC in lateralization may be more complex than initially anticipated and may include a nuanced interplay between excitatory and inhibitory influences (Bloom & Hynd, 2005; Schulte & Müller-Oehring, 2010; Häberling, Badzakova-Trajkov, & Corballis, 2011).

Some previous studies have found evidence supporting both an excitatory and inhibitory function of the CC in lateralization (Clarke & Zaidel, 1994), indicating that these two theories are not mutually exclusive. Rather, hemispheric lateralization may involve a dynamic and possibly simultaneous interaction of both excitatory and inhibitory influences from the CC depending on the functions required by a given task. For example, less complex behavioral tasks, such as phonetic discrimination tasks, may be more efficiently conducted within a single dominant hemisphere without interference from the other (Belger, 1993). In this case, it may be more advantageous for the CC to play an inhibitory role in functional lateralization. In contrast, interhemispheric collaboration, in which the CC exerts an excitatory influence, may increase the brain's capacity for information processing by allowing for a dispersal of processing load across hemispheres and, subsequently, may be more advantageous during computationally demanding tasks (Banich, 1995). Furthermore, these different strategies applied by the brain during various

behavioral tasks may be related to structural variations of cerebral lateralization and the microstructure of the CC (Doron & Gazzaniga, 2008). For example, for certain regions of the brain that specialize in less computationally complex functions, a reduced need for interhemispheric transmission may be reflected through a decrease in connectivity and fiber size in the parts of the CC that connect these regions.

Since it still remains unclear exactly how the CC influences hemispheric lateralization, this mechanism may be better understood by studying how lateralization develops in the infant brain and determining whether the development of the CC plays a role. Structural and functional lateralization are hallmarks of the infant brain (Bisiacchi & Cainelli, 2021) and play critical roles in language and other higher-level cognitive tasks, which are believed to be related to CC development (Molfese, Freeman, & Palermo, 1975; Brooks & Obrzut, 1981). For instance, in healthy preterm infants, Baldoli et al. (2014) found that the transition from bilateral temporal activation patterns during linguistic stimuli to leftward lateralized activations was correlated to improved scores in neurodevelopmental assessments of locomotor development, language processing, and other behavioral outcomes over time. In a study of infants at high and low risk for autism spectrum disorder (ASD), greater leftward lateralization of white matter tracts was associated with improved results in expressive and receptive language skills (Liu et al., 2018). Furthermore, atypical lateralization and callosal morphology during infancy have been linked to adverse neurodevelopmental outcomes (Peterson et al., 2003; Counsell et al., 2008; Ghassabian et al., 2012; Thompson et al., 2012) and the emergence of developmental disorders, such as ASD (Wolff et al., 2015; Liu et al., 2018), dyslexia (Langer et al., 2017; Thiede et al., 2019), and congenital sensorineural hearing loss (Wang et al., 2019). Therefore, understanding how the brain develops and lateralizes in typically-developing infants, especially with the input from

interhemispheric connectivity provided by the CC, may offer a point of comparison for atypical developmental processes. However, despite its scientific and clinical significance, no previous studies have examined the relationship between the development of the CC and lateralization within the context of the first 6 months of life, a period marked by rapid brain growth (Holland et al., 2014), in a prospective longitudinal study.

Thus, this project examines how the development of the CC is associated with structural lateralization of the infant brain within the first 6 months of life. In order to study these associations, Functional Principal Components Analysis (FPCA) was used to build the trajectories of the lateralization indices (LIs) (Dubois et al., 2016), used to quantify hemispheric asymmetry, of 7 bilateral white matter pathways, including the arcuate fasciculus (AF), anterior thalamic radiation (ATR), fornix (Fx), inferior fronto-occipital fasciculus (IFOF), inferior longitudinal fasciculus (ILF), and pyramidal tract from the motor (PTM) and sensorimotor (PTS) cortices, and the whole-brain in addition to mapping the development of the splenium (CCs), body (CCb), and genu (CCg) of the CC during the first 6 months of life. White matter structures of interest were selected due to the presence of significant lateralization during infancy. Functional Linear Regression (FLR) was used to explore the associations between the development of the CC and the LIs of the white matter structures and how they change throughout infancy. Based on previous literature, we hypothesized that the maturation of the CC is associated with the lateralization of white matter tracts in the infant brain, and the direction of this relationship will indicate whether this association is in line with the excitation or inhibition theories.

Methods

Participants

Infants in this study were typically-developing controls enrolled in a prospective longitudinal study of infants at high and low risk for autism spectrum disorder (ASD). Infants were considered typically-developing if they were born at full-term (mean gestational age = 38.6 weeks, *SD* = 1.98 weeks), had no family history of ASD first, second, or third degree relatives, no developmental delays in first degree relatives, no pre- or perinatal complications, no history of seizures, no known medical conditions or genetic disorders, and no hearing loss or visual impairment. Infants who had contraindication for MRI were not allowed to participate. The Emory University Institutional Review board approved the research protocol for this study.

Data were acquired at up to three pseudo-random time points between birth and 6 months (Figure 1). Pseudo-random sampling, a non-uniform sampling design in which data were not collected at regular fixed intervals, makes use of a key feature of Functional Data Analysis/Principal Analysis by Conditional Expectation (FDA/PACE): the number of data points that a single infant contributed could be sparse so long as the data points from the whole sample homogeneously covered the covariance surface (0-6 months) (Yao et al., 2005a; Yao et al., 2005b). This feature provides a statistical advantage since some infants did not provide usable data at each testing session either due to a missed session or failure to fall asleep. Additionally, pseudo-random sampling has the advantage of providing estimates of growth trajectories at all time points between birth and 6 months (unlike typical uniform sampling designs that require interpolation to infer information between fixed time points) (Yao et al., 2005a; Yao et al., 2005b). A total of 81 infants were scanned at 135 time points completed between 10 and 210 days of age. In 16 out of 135 scans, infants woke up before the diffusion scan was completed. If

less than 6 volumes of diffusion weighted images were collected (the minimum number of volumes required for estimating diffusion tensor and tensor-based metrics) (Basser, Mattiello, & LeBihan, 1994) ($N = 4$) or if eddy current distortion correction could not be performed ($N = 2$), the data were excluded. The final sample for this study included 78 participants, of which 47 were male and 31 were female, scanned at 126 time points. The racial/ethnic distribution of subjects was 70.5% White - not Hispanic/Latino, 7.7% White - Hispanic/Latino, 5.1% Black - not Hispanic/Latino, 2.6% Black - Hispanic/Latino, 1.3% Native American/Alaskan Native, 2.6% Mixed Race - not Hispanic/Latino, 2.6 % other - Hispanic/Latino, and 2.6% unknown.

MRI Data Acquisition

All infant scans were acquired at Emory University's Center for Systems Imaging Core on a 3T Siemens Tim Trio ($N = 26$) or a 3T Siemens Prisma ($N = 52$) scanner, using a 32-channel head coil. All infants were scanned during natural sleep, using procedures similar to those described in Shultz & Vouloumanos (2010). First, in order to promote natural sleep, infants were rocked, swaddled and/or fed. After they fell asleep, the infants were placed in a custom-made pediatric bed. To reduce and mask the scanner noise to <70 dBA, two safeguards were put in place: 1) infant sound attenuating headphones that played white noise and enabled real-time monitoring of in-ear sound levels during the session and 2) an acoustic hood that was placed in the MRI bore. Two experimenters were present throughout the scan process to monitor in-ear noise and the infant's state through a camera that was mounted on the head coil. If the infant woke up or the noise level exceeded 70 dBA, the scan was stopped.

Diffusion MRI data from the Tim Trio scanner were acquired using a multiband (Feinberg et al., 2010; Moeller et al., 2010) sequence with the following parameters: repetition time (TR) of 6200 ms, echo time (TE) of 74 ms, a multiband factor of 2 combined with parallel

imaging (GRAPPA) with an acceleration factor of 2, a field-of-view (FOV) of 184×184, image matrix of 92×92, b value of 0/700 s/mm2, spatial resolution of 2 mm isotropic, and 61 diffusion directions, 56 slices covering the whole-brain. An extra 6 averages of b0s were collected to improve the signal-to-noise ratio (SNR) of the baseline diffusion MRI signal. The total scan time for the diffusion MRI sequence was 7 minutes 26 seconds.

Diffusion MRI data from the Prisma scanner were acquired using a multiband sequence with the following parameters: repetition time (TR) of 2330 ms, echo time (TE) of 86.6 ms, a multiband factor of 4 without parallel imaging acceleration, a field-of-view (FOV) of 184×184, image matrix of 106×106, b value of 0/700 s/mm2, spatial resolution of 1.75mm isotropic, and 89 diffusion directions, 68 slices covering the whole-brain. An extra 6 averages of b0s were collected to improve the signal-to-noise ratio (SNR) of the baseline diffusion MRI signal. The total scan time for the diffusion MRI sequence was 3 minutes 58 seconds. Another repetition with b = 2000 s/mm2 and 90 diffusion directions was collected, but was not used in the current study.

For diffusion imaging protocols on both scanners, b0 images were acquired in the opposite phase encoding direction (posterior-to-anterior) for removing susceptibility-related distortion in diffusion (Andersson, Skare, & Ashburner, 2003).

Data Preprocessing

FSL (6.0.03) and in-house MATLAB (R2016b, MathWorks Inc. 2016) code were used to preprocess infant data. Data were preprocessed by correcting inter-volume motion artifacts, removing susceptibility distortion using the “topup” function in FSL, and eddy-current distortion and motion correction using FSL’s “eddy” tool (Andersson & Sotiropoulos, 2016). Weighted

least squares estimators were used to estimate diffusion MRI parameters (Koay et al., 2006; Veraart et al., 2013).

Image Registration

All infant brain images were aligned to a common space using tensor-based registration described in Zhang et al. (2006; 2007). In addition to providing orientation information about white matter microstructure, tensor maps differ from T1- and T2-weighted images by maintaining white and gray matter signal intensity differences over the first postnatal months, which provides more detailed mapping of features between infants (Zhang et al., 2006; Zhang et al., 2007; Pecheva et al., 2017). Multilevel registration was used to align infant brain images to a cohort-specific template (Guimond, Meunier, and Thirion, 2000; Zhang et al., 2006).

Fiber Tractography of Infant White Matter Pathways

Whole-brain tractography was seeded from the whole-brain white matter mask (mean fractional anisotropy, FA>0.15) and performed using Fiber Assignment by Continuous Tracking (FACT) (Mori et al., 1999; Cook et al., 2006) in Camino (http://camino.cs.ucl.ac.uk/). After all possible streamlines representing white matter connectivity in the infant brain were constructed, 9 major bilateral white matter pathways, including the arcuate fasciculus (AF), anterior thalamic radiation (ATR), cingulum (Ci), fornix (Fx), inferior fronto-occipital fasciculus (IFOF), inferior longitudinal fasciculus (ILF), pyramidal tract from the motor (PTM) and sensorimotor (PTS) cortices, and uncinate fasciculus (UF), in addition to the corpus callosum (CC) were delineated using TrackVis (Mori et al., 2002; Dubois et al., 2006; Catani et al. 2008; Li et al., 2010; Perani et al., 2011; Wolff et al., 2012). Seed regions were determined for each white matter tract using infant anatomical atlases, and all fiber bundles passing through a seed region were tracked, with some constraints depending on the bundles. The tracking was performed by following the

orientation of the tensor first eigenvector through each individual voxel. The present study focuses on 7 bilateral white matter pathways of interest, including the AF, ATR, Fx, IFOF, ILF, PTS, and PTM, and their relationship to the CC since these tracts demonstrated significant lateralization during infancy.

Additionally, the CC was divided into 3 subsections using methods similar to those outlined in Dubois et al. (2006). The anterior portion, referred to as the genu (CCg), was defined as the connection pathway between the frontal lobes while the posterior portion, referred to as the splenium (CCs), was defined as the region connecting the occipital and parietal lobes. Any other fibers in between these two regions were defined as part of the body (CCb) of the CC.

White matter integrity in each tract was quantified using fractional anisotropy (FA), which is a Diffusion Tensor Imaging (DTI) scalar value between 0 and 1 that measures the coherence of water diffusion within each voxel (Soares et al., 2013). Higher FA values are interpreted as greater fiber integrity due to an increase in coherence of the direction of water diffusion and is believed to reflect increased axon density, fiber packing density, and myelination (Friedrich et al., 2020). For whole-brain white matter composition, a white matter mask was used to distinguish white and gray matter, and FA values were computed for each voxel and averaged within each hemisphere. Lateralization of each tract and within the whole-brain was quantified using a lateralization index (LI), which was computed from the equation, $(L\text{-}R)/(L+R)$, where L denotes the mean FA value of the left tract and R denotes the mean FA value of the right tract (Dubois et al., 2016).

Harmonization of Data Collected on Siemens Trio and Prisma Scanners using ComBat

Infant data collected on Siemens Trio and Prisma 3T scanners were harmonized using ComBat, which is a regression-based harmonization technique that models additive and

multiplicative site/scanner effects within each voxel (Johnson, Li, & Rabinovic, 2007). An FA mask (FA>0.05) was applied to each infant's tensor map in template space and all voxels within the FA mask were input into the ComBat model. White matter tract masks were then multiplied with the FA mask to ensure that only harmonized voxels were included in regression analyses. Data harmonization was performed for each DTI metric separately using ComBat software (https://github.com/Jfortin1/ComBatHarmonization) in MATLAB.

Data Analysis

Developmental windows of significant difference were determined by bootstrapped 95% simultaneous confidence bands. FDA/PACE, more specifically Functional Principal Components Analysis (FPCA), was used to construct individual growth curves and analyze changes in FA and LI over time (Yao et al., 2005a; Yao et al., 2005b). Using FDA allowed us to bypass limitations that are associated with traditional growth curve modeling by modeling statistical variation in scaling and in developmental timescale and by empirically creating curve shapes. The PACE component of this method of analysis allowed for the mapping of developmental trajectories of FA despite missing data points, a near inevitability in longitudinal studies of infants. FPCA growth curves were created for the LIs of the white matter structures of interest and FA of the subsections of the CC. Functional linear regression (FLR), a type of linear regression adapted for the case in which predictors and response variables are trajectories, was used to test for associations between the white matter LIs, the response trajectory, and CC development, the predictor trajectory. To test the significance of the regression relationship, a regression parameter surface, or beta topography, was built for each association, and a quasi-functional coefficient of determination (*Quasi-*R^2) and its resulting p-value were calculated. A *Quasi-*R^2 test statistic is similar to a standard R^2 value in that it describes what percentage of variability in the dependent

variable is explained by the model. However, a *Quasi-*R^2 is a more conservative measure since it is corrected based on error within the sample.

Results

Using FPCA, LI curves were constructed for all 9 bilateral white matter pathways (Figure 2) and the whole-brain (Figure 3). Significant lateralization was found in 7 white matter tracts, including the AF, ATR, Fx, IFOF, ILF, PTM, and PTS, in addition to the whole-brain. 4 of these tracts demonstrated time-varying lateralization, in that lateralization changed over time. For example, the AF demonstrated significant leftward lateralization between 41 - 91 days (Figure 2A), and the Fx also showed significant leftward lateralization between 160 - 200 days (Figure 2D). Meanwhile, the ATR was significantly rightward lateralized between 103 - 182 days (Figure 2B), and the PTS also showed significant rightward lateralization between 31 - 200 days (Figure 2H). In contrast, the IFOF (Figure 2E) and PTM (Figure 2G) demonstrated consistent leftward lateralization across all 200 days, and the ILF (Figure 2F) and whole-brain (Figure 3) were consistently rightward lateralized from 0 - 200 days. No lateralization was seen in the Ci (Figure 2C) or UF (Figure 2I).

FPCA was also used to construct the FA trajectories of the different sections of the CC, and we found that the CCb exhibited the highest FA values, followed by the CCg and then CCs, respectively (Figure 4). Additionally, the CCb and CCg appear to have a greater change in FA over time, indicating that these regions are developing rapidly during this time period and are not yet fully mature. In comparison, the CCs appears to have a flatter slope, indicating that development is occurring slower and that this region is more mature.

The 7 white matter structures that showed lateralization and the white matter composition of the whole-brain were used in our FLR analyses in order to determine whether white matter lateralization is associated with development of the CC. Associations were explored between the LIs of these 7 white matter structures, in addition to the white matter composition of the

whole-brain, and the 3 sections of the CC for a total of 24 associations (Table 1). Of these 24 associations, 6 had significant *Quasi-*R^2 values ($p < 0.05$): 1) IFOF and CCs, 2) ATR and CCs, 3) ATR and CCb, 4) PTM and CCb, 5) whole-brain and CCb, and 6) whole-brain and CCg. Only the whole-brain and CCg association survived Bonferroni correction for multiple comparisons ($p < 0.0021$).

Beta topographies were used to visualize time-specific associations between trajectories of LIs and CC development. A significant association between the LI of the IFOF and FA values of the CCs was found with a *Quasi-*$R^2 = 0.04$ and $p = 0.021$. The shape of the beta topography indicates that higher FA values in the CCs at 160 - 200 days were associated with higher LI values, which indicate increased lateralization, in the IFOF at 40 - 60 days (Figure 5). A significant association between the LI of the ATR and FA values of the CCs was found with a *Quasi-*$R^2 = 0.04$ and $p = 0.049$. The shape of the beta topography indicates that higher FA values in the CCs at 0 - 40 days and 120 - 200 days were associated with lower LI values, which indicate increased lateralization, in the ATR at 30 - 60 days (Figure 6).

A significant association between the LI of the ATR and FA values of the CCb was found with a *Quasi-*$R^2 = 0.04$ and $p = 0.041$. The shape of the beta topography indicates that higher FA values in the CCb at 150 - 200 days were associated with lower LI values, which indicate increased lateralization, at 60 - 100 days and higher LI values, which indicate decreased lateralization, at 180 - 200 days in the ATR (Figure 7). A significant association between the LI of the PTM and FA values of the CCb was found with a *Quasi-*$R^2 = 0.09$ and $p = 0.017$. The shape of the beta topography indicates that higher FA values in the CCb at 0 - 60 days were associated with higher LI values, which indicate increased lateralization, at 60 - 100 days and lower LI values, which indicate decreased lateralization, at 180 - 200 days in the PTM (Figure

8). A significant association between the LI of the whole-brain and FA values of the CCb was found with a *Quasi-*R^2 = 0.07 and p = 0.035. The shape of the beta topography indicates that higher FA values in the CCb at 100 - 200 days were associated with lower LI values, which indicate increased lateralization, at 60 - 120 days and higher LI values, which indicate decreased lateralization, at 180 - 200 days in the whole-brain (Figure 9).

A significant association between the LI of the whole-brain and FA values of the CCg was found with a *Quasi-*R^2 = 0.1 and p = 0.002. The shape of the beta topography indicates that higher FA values in the CCg at 40 - 200 days were associated with higher LI values, which indicate decreased lateralization, at 70 - 120 days and lower LI values, which indicate increased lateralization, at 180 - 200 days in the whole-brain (Figure 10).

Table 2 shows a summary of all results. Associations with the CCs typically occurred earlier in infancy at 30 - 60 days of tract development and were positively correlated with lateralization, which supports the inhibition theory. Associations with the CCb showed a positive correlation with lateralization at 60 - 120 days and a negative correlation with lateralization at 180 - 200 days, which indicates support for the inhibition theory earlier in development before transitioning to support for the excitation theory toward the end of the first 6 months of life. In contrast, the association with the CCg demonstrated a negative correlation with lateralization at 70 - 120 days and a positive correlation with lateralization at 180 - 200 days, which supports the excitation theory earlier in development and the inhibition theory toward the end of the first 6 months of life.

Discussion

The present study examined the relationship between the development of the CC and the development of lateralization in 7 infant white matter structures in addition to the whole-brain. Specifically, we investigated the hypothesis that the maturation of the CC is associated with the lateralization of infant white matter tracts and that this association is time-varying, meaning that the association could be positive at certain time points and negative at other time points. In alignment with our hypothesis, we found that there is, in fact, a relationship between FA within the different subsections of the CC and LIs of various white matter structures and that this association is time-varying, indicating that CC development is both positively and negatively correlated with structural lateralization at different time points.

Since we found both positive and negative correlations between CC development and infant white matter tract lateralization, this provides evidence to support both the inhibitory and excitatory theories of the CC's role in hemispheric lateralization. A positive correlation, in which lateralization increases as CC development increases, supports the inhibition theory by indicating that increased maturation of the CC allows the CC to more effectively inhibit the less dominant hemisphere during lateralized tasks, leading to increased lateralization (Cook, 1984; Karbe et al., 1998). In contrast, a negative correlation, in which lateralization decreases as CC development increases, supports the excitation theory by suggesting that increased maturation of the CC allows the CC to more effectively activate the unstimulated hemisphere during lateralized tasks, leading to decreased lateralization (Yazgan et al., 1995).

The first 6 months of life is a critical period of infant brain development marked by rapid structural growth of the brain (Holland et al., 2014) and significant increase in myelination and fiber organization of the CC (Barkovich & Kjos, 1988). Specifically, the CC has been shown to

develop posteriorly to anteriorly (Deoni et al., 2012) with different maturational patterns in different subsections of the CC (Deoni, et al., 2011). Our results appear to validate these developmental trends since the timing of associations between CC development and lateralization were consistent within subsections of the CC, but the timing of the associations between subsections differed. Specifically, associations between LIs and the CCs were found earlier than those with the CCb or CCg, indicating that the earlier maturation of the CCs, in comparison to the CCb and CCg, may be linked to earlier development of lateralization in certain white matter tracts.

For the CCs, a positive correlation between CCs development and ATR and IFOF lateralization was found relatively early in development at 30 - 60 days and 40 - 60 days, respectively. This positive correlation shows support for an inhibitory function of the CCs in early development of lateralization. In particular, the ATR is associated with visuospatial working memory later in infancy (Short et al., 2013), which demonstrates a rightward lateralization (Nagel et al., 2013), while the IFOF is associated with non-verbal semantic language processing in adolescence (Almairac et al., 2015), which demonstrates a leftward lateralization (Balsamo, Xu, & Gaillard, 2006). The development of structural lateralization in these tracts early in infancy may be a precursor for functional lateralization related to these tracts later in development. Furthermore, while visuospatial working memory is rightward lateralized, verbal working memory is leftward lateralized in adolescence (Nagel et al., 2013), possibly indicating an inhibitory role of the CC in line with our results, such that both hemispheres can specialize in certain functions without interference from the other. Although it was surprising that the lateralization of the ATR, which is located near the anterior portion of the brain, was associated with the development of the CCs, which connects regions in the posterior portion of

the brain, visuospatial working memory has been linked to activation in the occipito-temporal structures and parietal cortex of the brain (Zimmer, 2008).

The associations between ATR, PTM, and whole-brain lateralization and CCb development were time-varying. Positive correlations were typically found earlier in development, at approximately 60 - 120 days, in comparison to negative correlations, which all occurred at 180 - 200 days. This indicates that the CCb exerts inhibitory influences earlier in infancy and excitatory influences closer to the end of the first 6 months of life. Thus, our results may suggest that earlier inhibitory influences of the CCb allow for early establishment of hemispheric dominance patterns and later excitatory influences of the CCb allow for greater interhemispheric transmission for more complex functions. These findings are especially interesting in the context of the functions of the PTM and CCb. For example, the PTM consists of fibers associated with motor control of the face, head, and neck (Northam et al., 2019) and has been linked to the asymmetric tonic neck reflex (ATNR) in newborns (Sarnat, 2003). The ATNR is a postural reflex found in infants within the first 90 days of life, in which the infant demonstrates neck and body movements in one direction (Gesell, 1938), most commonly with a preference toward the right (Liederman & Coryell, 1981), which indicates a leftward hemispheric lateralization. This behavior and the timing of its presence in infancy is consistent with our results of a leftward lateralization of the PTM, with this lateralization being positively correlated with increased CCb development at 60 - 100 days. As the ATNR in infants begins to subside, infants begin to gain increased control over their own movements, a more complex behavior, which approximately coincides with the timing of a more excitatory role of the CCb observed in our data. Furthermore, the CCb is involved in the midline integration of auditory, visual, and somatosensory information later on in life, which is a complex function that is

believed to require greater interhemispheric connectivity (Aboitiz et al., 1992a; Aboitiz et al., 1992b). Thus, this would explain the trend toward an excitatory role of the CCb in lateralization that we see in our results at 180 - 200 days.

In contrast, the association between whole-brain lateralization and CCg development shows an almost inverse developmental pattern compared to the associations of the CCb. CCg development was negatively correlated to whole-brain lateralization during the earlier days of infancy at 70 - 120 days and positively correlated toward the end of the first 6 months of life at 180 - 200 days, indicating that the CCg may initially play an excitatory function in lateralization before switching to an inhibitory function later in infancy. These conflicting results may be due to two potential reasons: 1) The CCg is the last part of the CC to mature (Deoni et al., 2012), which may lead to a delayed or differential developmental pattern for the CCg, relative to the more mature CCb and CCs (Deoni et al., 2011). 2) The CCg connects the frontal lobes involved in higher-order cognitive functions (Otero & Barker, 2013), which may require a different developmental pattern due to the difference in computational complexity compared to the functions of the CCb and CCs (Deoni et al., 2011; Deoni et al., 2012). In this case, it may be possible that early development of the frontal lobe requires rapid interhemispheric transfer facilitated by an excitatory function of the CCg. Once the frontal lobe becomes slightly more mature, then processing can be fine-tuned through the establishment of lateralization offered by an inhibitory function of the CCg.

Our results appear to be consistent with previous literature on the developmental timeline of the CC, in which the CC matures posteriorly to anteriorly and different subsections of the CC demonstrate different maturational patterns (Deoni et al., 2011; Deoni et al., 2012). Additionally, we found that the development of the 3 subsections of the CC were associated with the

development of lateralization in various white matter structures, which may indicate potential links to certain infant behaviors. However, we did not find significant associations between CC development and lateralization of the AF, Fx, ILF, or PTS.

Implications

Although the role that the CC plays in the development of hemispheric lateralization is not yet fully understood, the results of the present study help to elucidate this relationship during a critical period of rapid brain development in infancy. While functional lateralization is influenced by several factors (Bisiacchi & Cainelli, 2021), exploring structural lateralization and how it develops in the infant brain may provide insight into hemispheric dominance patterns and the lateralization of function. Specifically, the microstructure and connectivity of the CC may reflect the role that the CC plays in lateralization and interhemispheric communication. For instance, callosal fibers that are larger in diameter and more heavily myelinated, as indicated by higher FA values, may connect regions that require greater interhemispheric collaboration due to specializing in more complex functions (Doron & Gazzaniga, 2008).

In addition to supporting previous literature on the maturational patterns of the CC, our results show that CC development is significantly associated with the development of structural lateralization in the brain while suggesting potential links to lateralization of behavior in the typically-developing infant. Furthermore, atypical morphology in the CC is often associated with atypical hemispheric lateralization and behavior, both of which can contribute to the emergence of developmental disorders, such as ASD (Liu et al., 2018; Wolff et al., 2015), dyslexia (Langer et al., 2017; Thiede et al., 2019), and congenital sensorineural hearing loss (Wang et al., 2019). Thus, by characterizing how the CC and lateralization should develop in the typically-developing infant, our findings may provide a point of comparison for atypical developmental processes,

especially early in development, which may have implications for earlier diagnostic criteria in these developmental disorders.

Limitations and Future Directions

One limitation of this study was the lack of clarity in interpreting associations with whole-brain lateralization. For example, although we found a significant association between the development of the CCg and the lateralization of the whole-brain, we did not find an association between the development of the CCg and the lateralization of any of our white matter pathways of interest. As this study focused only on a subset of white matter tracts in the brain, but the exploration of whole-brain white matter encompasses additional tracts that were not delineated for this study, these additional tracts could be driving the associations found between whole-brain lateralization and development of the CCg. Future studies could explore associations in white matter tracts not included in this study, such as the superior longitudinal fasciculus, to further explore the role of the CCg in lateralization.

Additionally, the lack of significant associations with the AF were surprising since previous studies have found atypical development of the CC to be associated with atypical lateralization in the AF network (Adibpour et al., 2018; Hinkley et al., 2016). A potential reason for this may be due to the fact that we divided the CC into 3 subsections in order to account for the difference in maturity between the posterior and anterior regions of the CC. However, we did not account for how certain white matter tracts span across the entire brain, posteriorly to anteriorly, potentially washing out possible relationships between development of the subsections of the CC and lateralization. Future work can account for these larger tracts by dividing them into subsections similar to those of the CCs, CCb, and CCg. This would control

for the size of these tracts and the fact that these white matter tracts are also developing posteriorly to anteriorly (Deoni et al., 2011).

Lastly, although the present study only maps the development of the CC and lateralization throughout the first 200 days of life, the infant brain, and especially the CC, continues to grow significantly throughout the rest of infancy (Keshavan et al., 2002). We also found several significant results in the 180 - 200 day time period, but those associations may continue well beyond the time after which we stopped collecting data, especially associations involving regions of the brain that are less developed, such as the CCg. Thus, future research may want to consider exploring the relationship between CC development and lateralization throughout the first couple years of life in order to better understand how lateralization is established from birth to adolescence.

Tables and Figures

Table 1. P-values derived from testing the significance of *Quasi-*R^2. These values denote significant associations between different sections of the CC and various white matter structures of interest. * indicates $p < 0.05$. ** indicates $p < 0.0021$ using Bonferroni correction for multiple comparisons

	CCs	**CCb**	**CCg**
AF	0.626	0.706	0.549
ATR	0.049*	0.041*	0.547
Fx	0.541	0.377	0.211
IFOF	0.021*	0.238	0.124
ILF	0.126	0.235	0.086
PTM	0.305	0.017*	0.076
PTS	0.414	0.309	0.841
Whole-Brain	0.506	0.035*	0.002**

Table 2. Timings of positive and negative associations. Results were in support for the excitation theory when lateralization decreased as CC development increased, and results were in support for the inhibition theory when lateralization increased as CC development increased.

	Support for Excitation Theory	**Support for Inhibition Theory**
IFOF and CCs	N/A	40 - 60 days
ATR and CCs	N/A	30 - 60 days
ATR and CCb	180 - 200 days	60 - 100 days
PTM and CCb	180 - 200 days	60 - 100 days
Whole-Brain and CCb	180 - 200 days	60 - 120 days
Whole-Brain and CCg	70 - 120 days	180 - 200 days

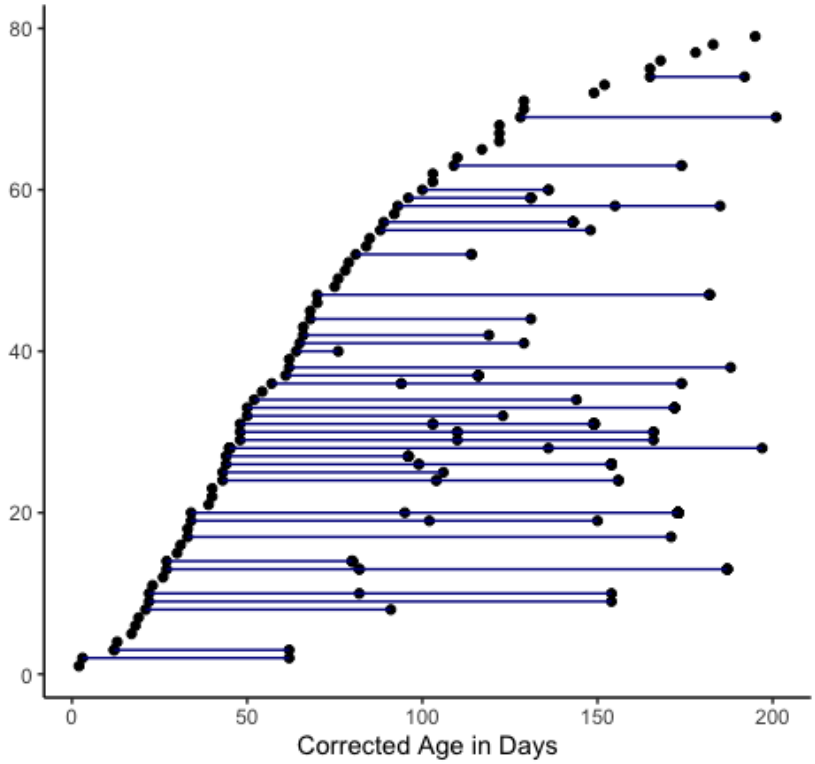

Figure 1. Pseudo-random sampling design for MRI data collection. Each row represents MRI visits for a single participant with the black circle marking the age, adjusted for gestational age, in days at the time of data collection.

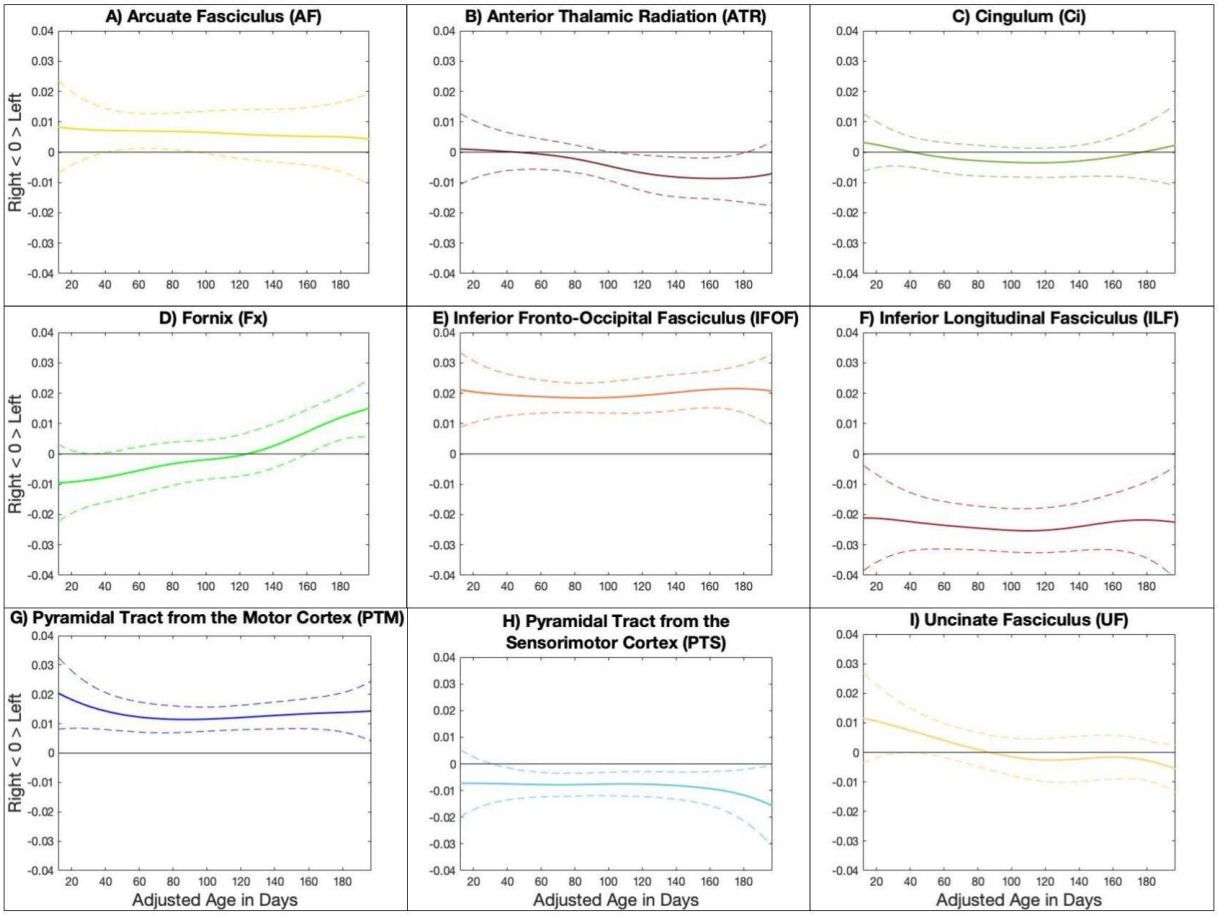

Figure 2. LIs of all 9 bilateral white matter pathways over the first 200 days of life. Bolded lines represent mean LIs over time, and dashed lines represent bootstrapped 95% simultaneous confidence bands. **A)** The AF demonstrates significant leftward lateralization between 41 - 91 days. **B)** The ATR demonstrates significant rightward lateralization between 103 - 182 days. **C)** The Ci demonstrates no significant lateralization. **D)** The Fx demonstrates significant leftward lateralization between 160 - 200 days. **E)** The IFOF demonstrates significant leftward lateralization between 0 - 200 days. **F)** The ILF demonstrates significant rightward lateralization between 0 - 200 days. **G)** The PTM demonstrates significant leftward lateralization between 0 - 200 days. **H)** The PTS demonstrates significant rightward lateralization between 31 - 200 days. **I)** The UF demonstrates no significant lateralization.

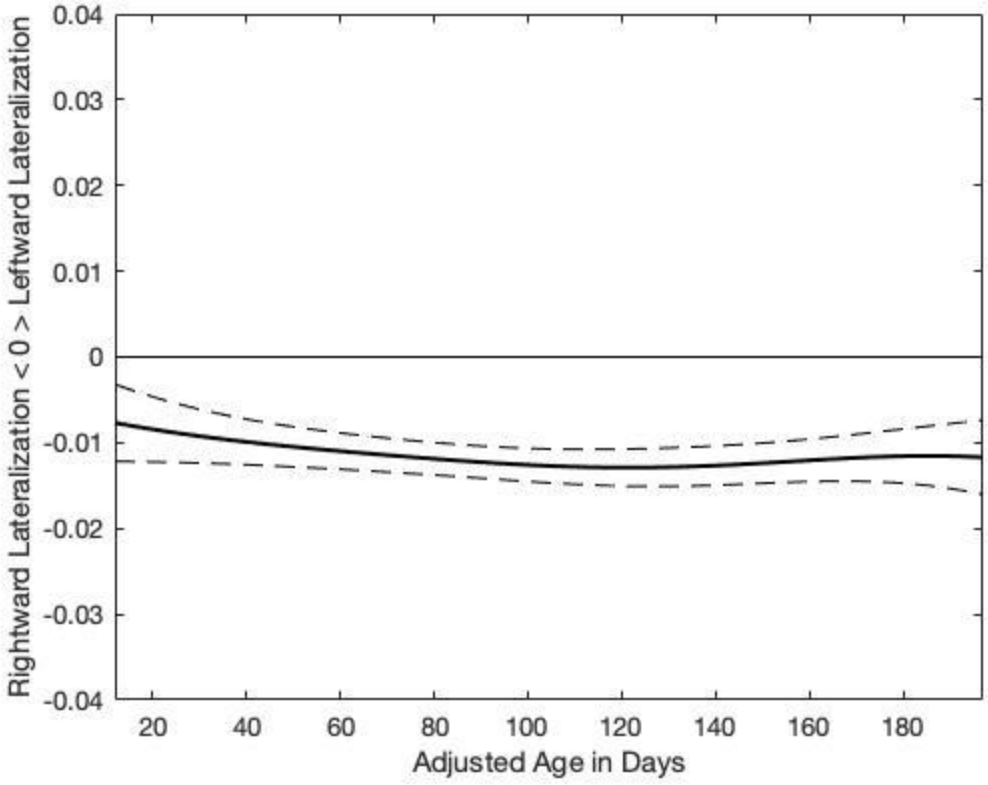

Figure 3. LI of the whole-brain over the first 200 days of life. The bolded line represents the mean LI over time, and the dashed lines represent bootstrapped 95% simultaneous confidence bands. Significant rightward lateralization is seen between 0 - 200 days.

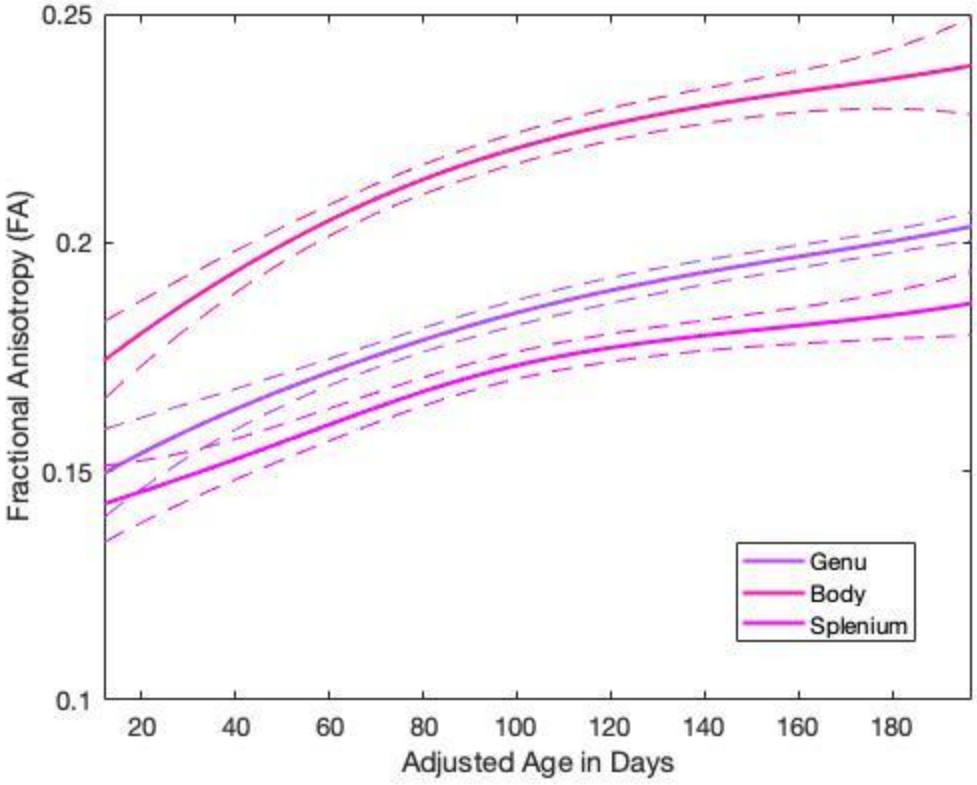

Figure 4. FA of the CC over the first 200 days of life. The bolded line represents the mean FA over time, and the dashed lines represent bootstrapped 95% simultaneous confidence bands.

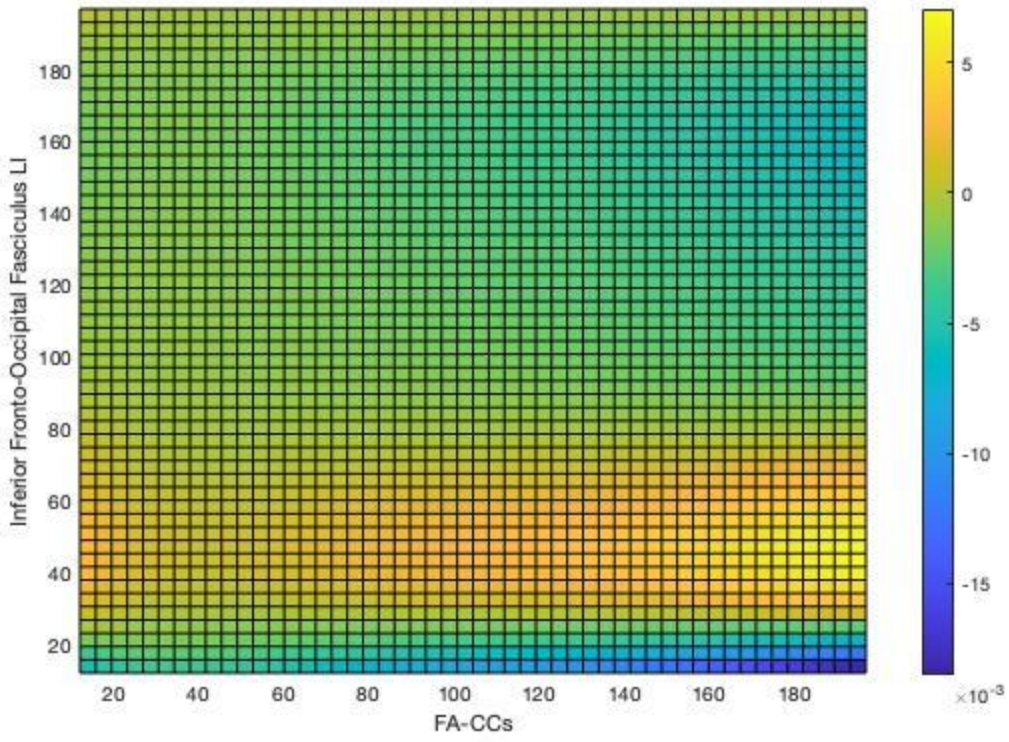

Figure 5. Beta topography of the IFOF and CCs association. The x-axis tracks the development of the CCs FA over the first 200 days of life, and the y-axis tracks the development of the IFOF LI over the first 200 days of life. Warmer colors indicate a positive association between FA and LI while cooler colors indicate a negative association between FA and LI. A significant association between the LI of the IFOF and FA values of the CCs was found with a *Quasi-*R^2 = 0.04 and $p = 0.021$. The shape of the beta topography indicates that higher FA values in the CCs at 160 - 200 days were associated with higher LI values, which indicate increased lateralization, in the IFOF at 40 - 60 days.

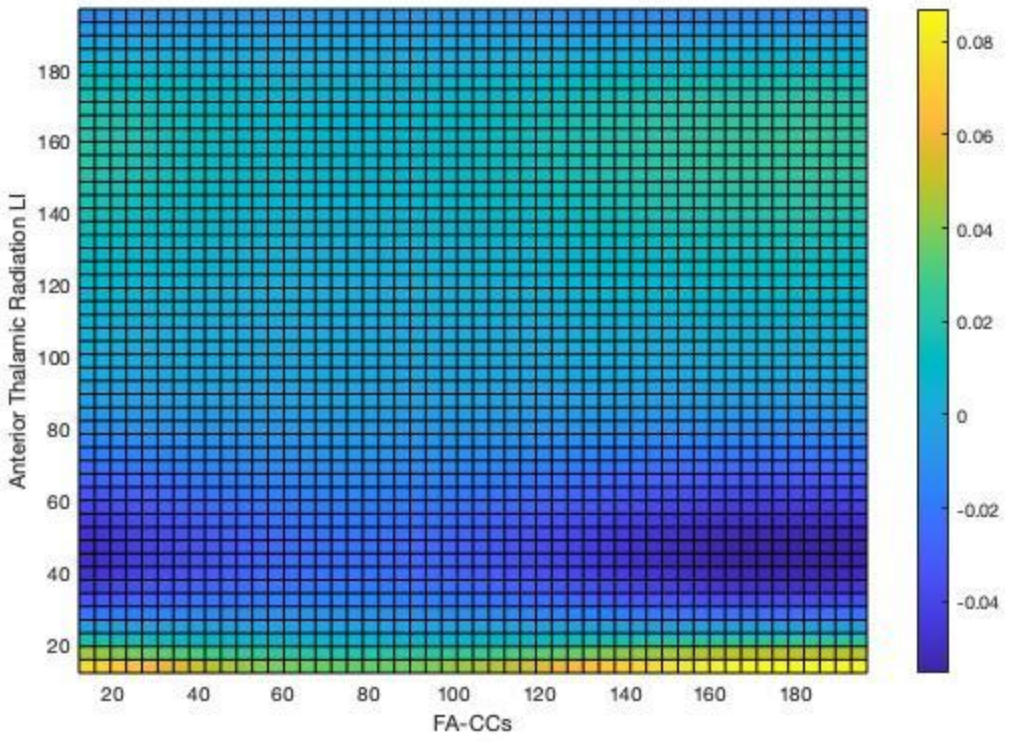

Figure 6. Beta topography of the ATR and CCs association. The x-axis tracks the development of the CCs FA over the first 200 days of life, and the y-axis tracks the development of the ATR LI over the first 200 days of life. Warmer colors indicate a positive association between FA and LI while cooler colors indicate a negative association between FA and LI. The shape of the beta topography indicates that higher FA values in the CCs at 0 - 40 days and 120 - 200 days were associated with lower LI values, which indicate increased lateralization, in the ATR at 30 - 60 days.

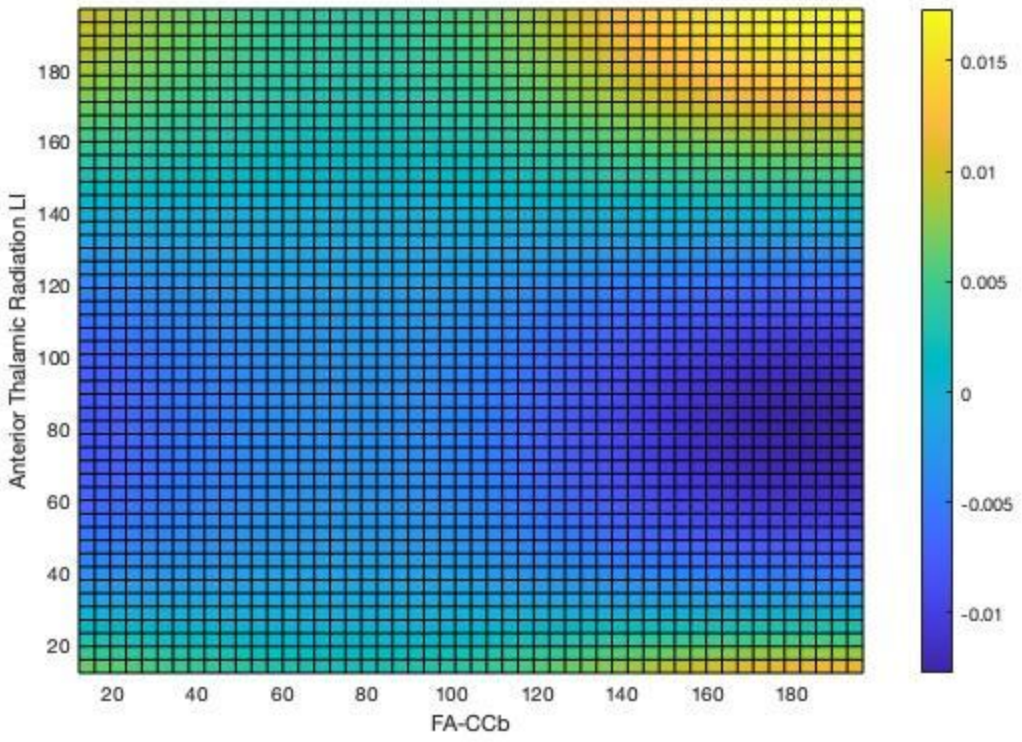

Figure 7. Beta topography of the ATR and CCb association. The x-axis tracks the development of the CCb FA over the first 200 days of life, and the y-axis tracks the development of the ATR LI over the first 200 days of life. Warmer colors indicate a positive association between FA and LI while cooler colors indicate a negative association between FA and LI. The shape of the beta topography indicates that higher FA values in the CCb at 150 - 200 days were associated with lower LI values, which indicate increased lateralization, at 60 - 100 days and higher LI values, which indicate decreased lateralization, at 180 - 200 days in the ATR.

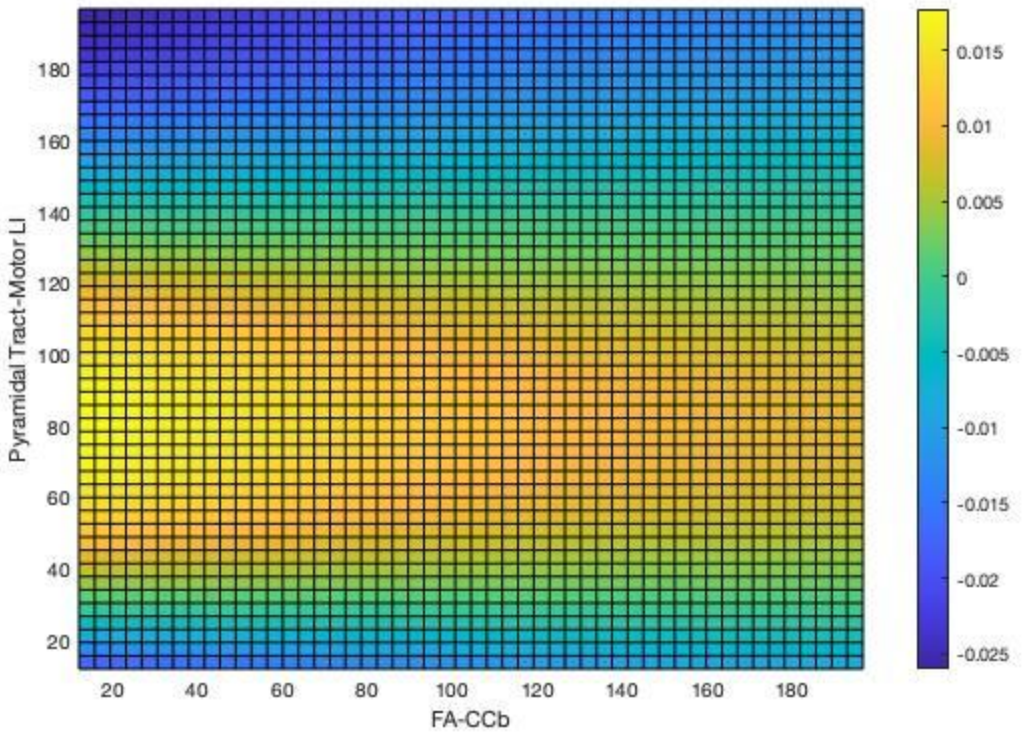

Figure 8. Beta topography of the PTM and CCb association. The x-axis tracks the development of the CCb FA over the first 200 days of life, and the y-axis tracks the development of the PTM LI over the first 200 days of life. Warmer colors indicate a positive association between FA and LI while cooler colors indicate a negative association between FA and LI. A significant association between the LI of the PTM and FA values of the CCb was found with a *Quasi-*R^2 = 0.09 and $p = 0.017$. The shape of the beta topography indicates that higher FA values in the CCb at 0 - 60 days were associated with higher LI values, which indicate increased lateralization, at 60 - 100 days and lower LI values, which indicate decreased lateralization, at 180 - 200 days in the PTM.

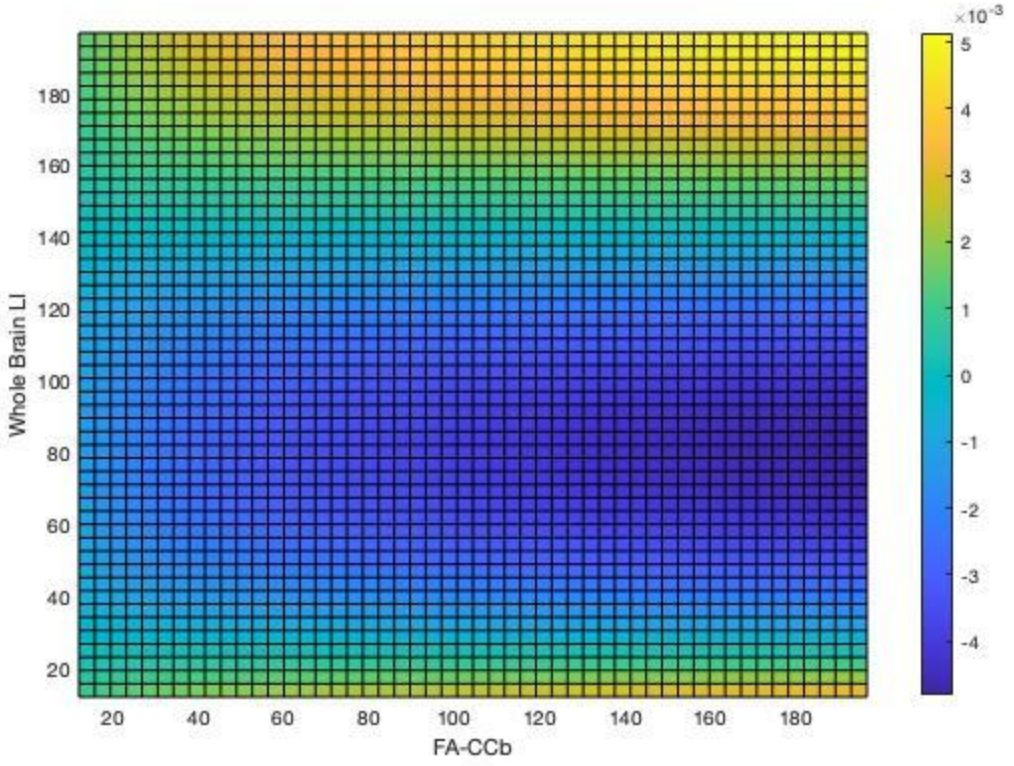

Figure 9. Beta topography of the whole-brain and CCb association. The x-axis tracks the development of the CCb FA over the first 200 days of life, and the y-axis tracks the development of the whole-brain LI over the first 200 days of life. Warmer colors indicate a positive association between FA and LI while cooler colors indicate a negative association between FA and LI. A significant association between the LI of the whole-brain and FA values of the CCb was found with a *Quasi-*R^2 = 0.07 and p = 0.035. The shape of the beta topography indicates that higher FA values in the CCb at 100 - 200 days were associated with lower LI values, which indicate increased lateralization, at 60 - 120 days and higher LI values, which indicate decreased lateralization, at 180 - 200 days in the whole-brain.

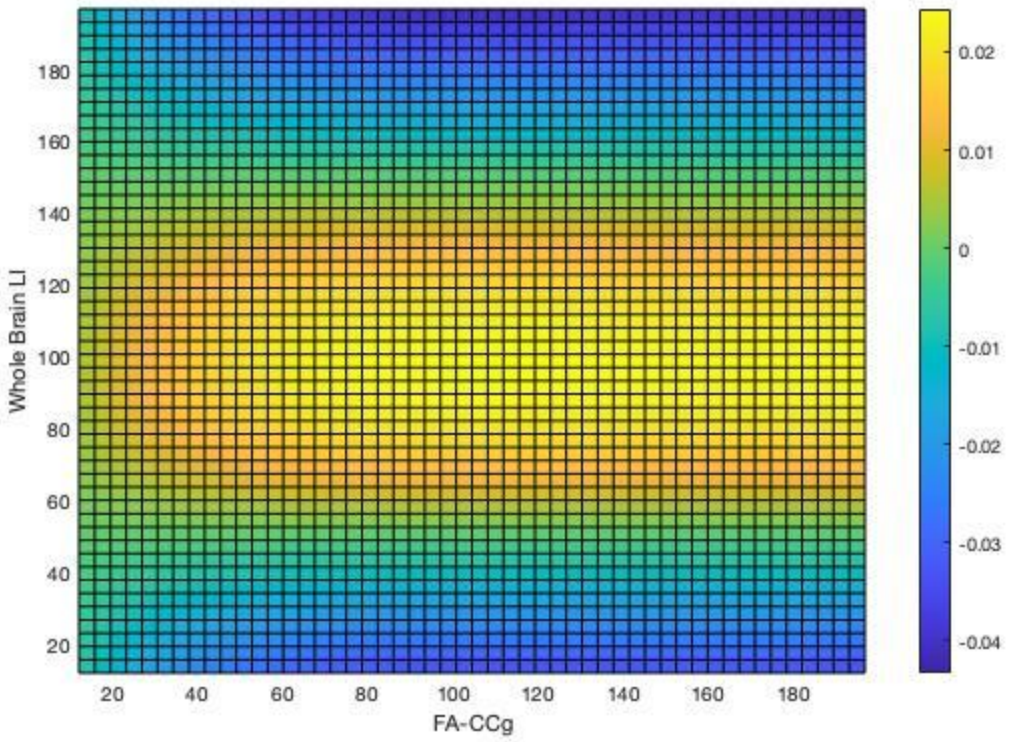

Figure 10. Beta topography of the whole-brain and CCg association. The x-axis tracks the development of the CCg FA over the first 200 days of life, and the y-axis tracks the development of the whole-brain LI over the first 200 days of life. Warmer colors indicate a positive association between FA and LI while cooler colors indicate a negative association between FA and LI. A significant association between the LI of the whole-brain and FA values of the CCg was found with a *Quasi-*R^2 = 0.1 and p = 0.002. The shape of the beta topography indicates that higher FA values in the CCg at 40 - 200 days were associated with higher LI values, which indicate decreased lateralization, at 70 - 120 days and lower LI values, which indicate increased lateralization, at 180 - 200 days in the whole-brain.

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