Transcallosal Connectivity Changes from Infancy to Late Adulthood: An *Ex Vivo* Diffusion Spectrum Imaging Study of Macaque Brains

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Abstract

Interhemispheric communication plays a critical role to ensure normal brain functions in cognition and behavior. Since non-human primate (NHP) brains resemble most aspects of the human brain, a thorough knowledge of interhemispheric cortical connectivity changes in NHP brains throughout the developmental and aging periods may provide valuable insights for translational and clinical research. In this study, formalin-fixed rhesus monkey brains aged from 1 to 24 years were utilized to examine transcallosal connectivity changes using diffusion spectrum imaging (DSI). It was found that the transcallosal connectivity for most frontal cortical areas, including dorso- and ventro-lateral prefrontal, premotor, and motor cortices, demonstrated pronounced age-related alterations. However, such a pattern was less obvious in temporal, posterior parietal, and visual cortices. The DSI results reveal the age-related evolution pattern of transcallosal connectivity in various cortical areas of macaque brains from infancy to late adulthood, and may have implications for assessing the functional defects or alterations in the associated cortical areas during brain development and aging in humans.

Key words: aging; brain maturation; DSI; interhemispheric cortical connectivity; non-human primate; white matter tractography

Introduction

INTERHEMISPHERIC CONNECTIVITY PLAYS a crucial role in maintaining normal cognitive functions and behaviors. The interruption of interhemispheric connectivity can result in profound functional disorders in patients, including children and adults (Anderson et al., 2011; Dick et al., 2013; Knochel et al., 2012). A thorough knowledge of the progressive alteration of interhemispheric fiber connectivity during normal brain development and aging can provide valuable insights in understanding cognitive development or decline during the entire lifespan.

Since corpus callosum (CC) serves as a bridge to connect both cerebral hemispheres, most studies of interhemispheric connectivity focus on the CC structure directly (Luders et al., 2010; Nowicka and Tacikowski, 2011; van der Knaap and van der Ham, 2011; Wahl et al., 2007). Previous studies have demonstrated that interhemispheric connectivity is an important indicator of brain dysfunction in different stages

of human lifespan (Luders et al., 2010; Ota et al., 2006). Earlier resting-state functional magnetic resonance imaging (rsfMRI) studies have also demonstrated that the interhemispheric functional connectivity changes with age in humans (Tomasi and Volkow, 2012; Vergun et al., 2013). However, most studies were based on a comparison between different age groups, or with the assumption of linear relationship with age in development or degeneration stage of the brain (Makris et al., 2007; Tomasi and Volkow, 2012; Vergun et al., 2013). Due to the limited age range in each study, the actual trend or change can be different from one study to another, depending on its specific age coverage in the entire lifespan. In addition, the white matter maturation and degeneration is differentiated across the entire brain regions. Previous results have illustrated that the frontal lobe is lately matured compared with other regions and also, the age-related degeneration mostly occurs in the frontal brain (Lebel et al., 2008; Pfefferbaum et al., 2000; Sullivan and Pfefferbaum, 2006; Thompson and Nelson, 2001). Age-related

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alterations in brain white matter of non-human primates (NHPs) have been reported, but most studies either focused on limited brain areas or failed to offer comprehensive inter-hemispheric connectivity information for the whole brain (Chen et al., 2013; Peters and Sethares, 2002; Phillips and Sherwood, 2012).

Diffusion tensor imaging (DTI)-based fiber tractography has been applied to determine transcallosal interhemispheric connections between different cortical areas (Hofer and Frahm, 2006). However, DTI is limited to delineate the primary diffusion orientation based on the measurement of anisotropic water diffusion, and it is difficult to detect the crossing or touching fibers in an imaging voxel (Wiegell et al., 2000). For example, DTI-based fiber tracking usually shows the dorsal but not lateral cortical fibers from the anterior CC (Hofer and Frahm, 2006). Since homotopic interconnections exist between the hemispheres and also heterotopic interconnections linking functionally different cortices (Clarke and Zaidel, 1994; de Lacoste et al., 1985; Witelson, 1989), the DTI results might be biased due to the failure to detect crossing or touching fibers. In contrast, diffusion spectrum imaging (DSI) allows sufficient angular resolution and can be used to examine crossing fiber tracts in a single voxel (Wedeen et al., 2005). Therefore, DSI-based fiber tractography can provide a novel and unprecedented opportunity for studying complicated fiber connections *in vivo* or in postmortem studies (Granziera et al., 2009; Meng and Zhang, 2014; Schmahmann et al., 2007; Wedeen et al., 2005, 2008).

NHPs are highly similar to humans in anatomical structures, functional connections, and brain organizations (Hofer et al., 2008; Nakahara et al., 2007; Thiebaut de Schotten et al., 2012). Multiple similarities in fiber association connections have been reported in both human and macaque monkeys (Thiebaut de Schotten et al., 2012). Information of interhemispheric connectivity alteration with age in NHP brains may provide important implications for translational research in brain development and aging. In this study, the cortically specific changes of transcallosal connectivity were evaluated with formalin-fixed macaque brains from infancy to late adulthood using DSI tractography.

Materials and Methods

Animals

All procedures were approved and in compliance with the Institutional Animal Care and Use Committees (IACUC) of Emory University and the NIH guides for the care and use of laboratory animals. Twelve normal rhesus monkeys (*Macaca mulatta*) of both sexes (six female and six male animals) from 1 to 24 years old (Table 1) with no history of neurological disease or brain injury were utilized. The animals were euthanized by pentobarbital overdose and immediately intracardially perfused with saline followed by 10% buffered formalin. The whole brains were immersed in formalin and kept in a refrigerator for at least 1 month. These brain samples were collected from earlier projects in which the animals in the control groups were euthanized for research purpose or from the cohort of unassigned monkeys sacrificed due to the IACUC end point (such as illness or injury, etc). Each subject's usage and health history was evaluated by the veterinary staff in our facility to ensure the brain was healthy and intact before being recruited into this study.

TABLE 1. THE DEMOGRAPHIC INFORMATION OF THE MACAQUE BRAINS

No.	Sex	Age (years)
1	Female	1.4
2	Female	2.0
3	Male	3.1
4	Female	5.9
5	Male	6.4
6	Male	9.9
7	Female	10.3
8	Male	13.8
9	Female	14.1
10	Female	20.2
11	Male	22.3
12	Male	22.8

MRI experiments

The experiments were carried out on a Bruker Biospec 7.0T spectrometer (Bruker Biospin Corporation) that was equipped with a 12 cm-ID actively shielded gradient insert (400 mT/m). A 7 cm-ID quadrature volume coil was used for signal excitation and reception. The DSI pulse sequence was custom developed and implemented under the software Paravision 5.1. To reduce eddy current effect due to the demand of high *b*-values (Koch and Norris, 2000), double spin echo acquisition was applied on a 3D EPI sequence with parameters TE/TR=55 msec/500 ms, FOV=70×50×80 cm³, for 1 mm isotropic spatial resolution. Diffusion was encoded with 514 diffusion directions covering a full q-space 3D grid with a five radical grid size and *b*-value=40,000 sec/mm², and one B₀ image (*b*-value=0 sec/mm²). The total scan time of each brain sample was 45 h with two averages, yielding a signal to noise ratio (SNR) of around 45 in the B₀ image of the whole brain.

Data processing

Dorsolateral prefrontal cortex (dlPFC), ventrolateral prefrontal cortex (vlPFC), dorsal premotor cortex (dPMC), ventral premotor cortex (vPMC), primary motor cortex (PMC), somatosensory cortex (SSC), temporal cortex (TC), posterior parietal cortex (PPC), visual cortex (VC), and CC were selected based on a T₁-weighted macaque brain template by referring a rhesus monkey brain atlas (Saleem and Logothetis, 2006). The template was built with isotropic 0.5 mm spatial resolution from coregistered and averaged T₁-weighed images of adult macaque monkeys of both sexes in the Yerkes research center.

The cortical areas defined from the template were registered (with 12 DOF linear affine transformation) to the DSI images without diffusion gradients (B₀ images) using the FSL software (FMRIB; Oxford) (Jenkinson et al., 2012) (see Fig. 1 and the template in Fig. 2a). In order to examine the registration errors across ages from infancy to late adulthood, the images of monkey brain template were registered to the DSI B₀ images of each monkey brain, and the residual errors between two brain images were compared within three age stages (i.e., ≤5 years, >5 years but <15 years, and ≥15 years) with one-way ANOVA using the SPSS 22 software (SPSS, Inc.).

The white matter tracts were constructed using deterministic fiber tracking (Wedeen et al., 2008; Yeh et al., 2013) with the DSI-Studio software (<http://dsi-studio.labsolver.org>).

FIG. 1. Coregistration operation evaluation of macaque brains at different ages. **(a)** Images registered from the T_1 -weighted template to B_0 images (T_2 -weighted); **(b)** The differences between B_0 images and the corresponding registered images from the template (as shown in **a**). The residual signal intensity is mostly due to the contrast difference between the two images. The geometry of the difference images looks as similar as the images in **(a)**, indicating good coregistration operation; **(c–h)** CC and various cortical areas (the masks) determined from the template were registered to individual monkey brains (green color), with the registration information provided by registering the template to the B_0 images. CC, corpus callosum; dIPFC, dorsolateral prefrontal cortex; vIPFC, ventrolateral prefrontal cortex; dPMC, dorsal premotor cortex; vPMC, ventral premotor cortex; PMC, primary motor cortex; SSC, somatosensory cortex; PPC, posterior parietal cortex; TC, temporal cortex; VC, visual cortex.

Cortically transcallosal tractography for the interested cortical areas in both hemispheres was performed in the following two steps. First, the cortical area in the left hemisphere was selected as a seed, and then the CC was used as the waypoint where the fibers are crossing and the fibers terminate in the corresponding cortical area in the right hemisphere, by using 10,000 seeds or iterative fiber tracking numbers. Second, the same procedure was repeated but started with the cortical area in the right hemisphere as a seed. The proportion of the total fibers from

the two fiber tracking steps (20,000 tracking numbers in total), or the normalized cortical transcallosal fibers, was used for assessing the transcallosal connection strength for each cortical area. During the data processing, the cortical transcallosal connection strength was defined by calculating the relative values of the fiber numbers connecting different cortical regions through CC. The increased or reduced fiber numbers were associated to the changes of transcallosal connections between the hemispheric cortical areas in each brain.

FIG. 2. Demonstration of the transcallosal fiber tracts for various cortical areas in an adult monkey brain. (a) The sagittal view of a macaque T₁-weighted template used to define CC and cortical areas; Axial (b) and sagittal (c) view of the delineated transcallosal fibers, coded with different colors; (d–l) Illustration of the delineated transcallosal fibers crossing CC (light red color in the center of the picture d–l) and the associated cortical areas (light to blue color; from d to l: dIPFC, vIPFC, dPMC, vPMC, PMC, SSC, PPC, TC, and VC). The fiber tracking results are from a fixed adult macaque brain (~10 years old), overlaid on the DSI B₀ images. DSI, diffusion spectrum imaging.

The relationship between the connection strength and ages of the animals was examined by data fitting with Poisson and quadratic regression models, respectively, using custom-written Matlab scripts (MathWorks). Quadratic model provides a simple correlation with age (Allen et al., 2005; Lebel and Beaulieu, 2011), while Poisson model considers different change patterns during the entire lifespan (Lebel et al., 2010). The following equation was used for the Poisson model:

$$\text{Connection strength} = A * \text{age} * e^{-B * \text{age}} + C,$$

in which *A*, *B*, and *C* are the fitting parameters.

To test whether the fitting significance is, indeed, unlikely to occur by chance, permutation test was used in performing multiple comparisons. In the permutation test, each animal's age was randomly assigned to one of the connectivity measurements of all animals and, thus, one permuted data set was obtained; then, the corresponding correlation coefficient value (*r*) was calculated based on the permuted dataset fitted with Poisson or quadratic models. For 5000 permutations, 5000 correlation coefficient values were obtained (Manly,

1997). Then, the significance of the correlation of the original experimental data was determined based on the distribution of the 5000 correlation coefficient values calculated with the permuted datasets, with a significant level of $p < 0.05$.

Results

As demonstrated in Figure 1, a macaque brain template (T₁-weighted) was well coregistered to the DSI B₀ images (T2-weighted) of three animal subjects at very different ages (Fig. 1). The residual signal intensity in the difference images is mostly due to the contrast difference between the two images (Fig. 1b). The geometry of the difference images looks as similar as the registered images from the template, indicating good coregistration operation. The registration results of different brain areas in each subject were examined visually and confirmed (Fig. 1c–h). In addition, further quantitative tests indicated that there was no significant difference ($p = 0.41$, with a significance level of $p < 0.05$) in the residual registration errors for the brains at three age stages (i.e., ≤ 5 years, > 5 years but < 15 years, and ≥ 15 years).

The determined transcallosal fiber tracts for various cortical areas in an adult monkey brain (10 years old) were illustrated in Figure 2. As seen in Figure 2d–l, transcallosal fibers for different cortical areas across the whole brain in both dorsal and ventral orientations were successfully determined by DSI tractography.

The changing patterns of transcallosal fibers in different cortical areas of three representative monkey brains were demonstrated in Figure 3. The results indicate that the trans-

callosal connectivity keeps increasing before the middle age (i.e., ~13.8 years old), and then declines in the aging period (Figs. 3 and 4). Such change was more pronounced in the frontal lobes and also in SSC (Fig. 3a–f) but less obvious in PPC, temporal, and occipital lobes (Fig. 3g–i).

Statistics showed different results while fitting the progressive transcallosal connectivity changes with two different fitting models. As shown in Figure 4, the ages at which the transcallosal connectivity reached its maximum were earlier

FIG. 3. Changes of transcallosal fibers in various cortical areas across the whole brains with three different ages from infancy to late adulthood. Cortically transcallosal fibers for dIPFC (a), vIPFC (b), dPMC (c), vPMC (d), PMC (e), SSC, (f), PPC (g), TC (h), and VC (i) overlaid on the DSI B_0 images.

FIG. 4. Illustrations of Poisson and quadratic curve fittings of the transcallosal connectivity changes in different cortices of the monkey brain from infancy to late adulthood. The interested regions include dIPFC (a), vIPFC (b), dPMC (c), vPMC (d), PMC (e), SSC (f), PPC (g), TC (h), and VC (i). The star (*) indicates that the fitting is statistically significant ($p < 0.05$, after multiple-comparison correction) for the model (see details in Table 2).

with Poisson model than those with quadratic model (Fig. 4a–f, h, i). In addition, compared with Poisson model, quadratic model failed to delineate the early connectivity changes in PPC (Fig. 4g). As shown in Table 2, the p - and R -values fitted with Poisson model were, respectively, smaller and larger than those fitted with quadratic model, indicating that Poisson model was better than quadratic model for fitting the transcallosal connectivity changes during the lifespan. After multiple comparisons with permutation test, the results showed that the fitting significance took place in dIPFC, vIPFC, dPMC, vPMC, PMC, and TC with the Poisson model, while it was seen only in dIPFC and dPMC with the quadratic model. In addition, as shown in Figure 4, the transcallosal cortical connectivity in the frontal lobe of older adults decreased by about 50% of its maximum value, while such a reduction in temporal and visual cortices was only around 20%.

Discussion

In this study, DSI tractography was used to examine the progressive changes of the transcallosal connectivity of macaque brains from infancy to late adulthood. It was found that the

TABLE 2. FITTING RESULTS FOR THE TRANSCALLOSAL CONNECTIVITY OF VARIOUS CORTICAL AREAS WITH AGE USING TWO REGRESSION MODELS

Cortical regions	Poisson model			Quadratic model		
	Age (years) at peak	R	p	Age (years) at peak	R	p
dIPFC	8.1	0.89	0.0009*	11.5	0.81	0.01*
vIPFC	7.3	0.76	0.02*	10.6	0.75	0.03
dPMC	9.8	0.82	0.006*	12.6	0.81	0.01*
vPMC	10.2	0.82	0.007*	12.9	0.70	0.05
PMC	8.3	0.79	0.01*	11.6	0.72	0.04
SSC	7.7	0.62	0.11	10.8	0.61	0.12
PPC	4.6	0.67	0.07	8.6	0.56	0.19
TC	5.9	0.74	0.03*	–3.9	0.58	0.16
VC	6.3	0.66	0.07	9.4	0.46	0.34

*Fitting significance with the models was determined after multiple-comparison corrections with permutation test with a significant level of $p < 0.05$.

dIPFC, dorsolateral prefrontal cortex; dPMC, dorsal premotor cortex; PMC, primary motor cortex; PPC, posterior parietal cortex; SSC, somatosensory cortex; TC, temporal cortex; VC, visual cortex; vIPFC, ventrolateral prefrontal cortex; vPMC, ventral premotor cortex.

transcallosal connectivity for most frontal cortical areas, including dorso- and ventro-lateral prefrontal, premotor, and motor cortices, demonstrated pronounced alteration during brain development and aging. In contrast, such changes were much mitigated in temporal, PPC, and VC. The progressive changes with age follow the Poisson pattern. The DSI results reveal the region-specific changes of the cortical transcallosal connectivity in macaque brains throughout the lifespan.

DSI has numerous advantages over DTI in assessing the transcallosal white matter fibers, although DTI has well demonstrated its robustness and sensitivity in many preclinic and clinic studies (Hofer and Frahm, 2006; Hofer et al., 2008; Meng et al., 2014; Schmahmann et al., 2007). The ability of *in vivo* DSI tractography for determining the extensive transcallosal fibers across segmented CC has been demonstrated in adult macaque monkeys (Meng and Zhang, 2014). In contrast, *ex vivo* DSI provides improved SNR and spatial resolution, enabling a better detection of white matter bundles. Therefore, it could be utilized to assess the transcallosal connectivity of the different cortical areas in fixed monkey brains, and furthermore, to evaluate the temporal changes of the transcallosal connectivity in the lifespan.

Using DSI tractography, cortically transcallosal connection strength can be evaluated by calculating the fiber numbers connecting different cortical regions through CC. Such method has been exploited previously in evaluating the hippocampal network connections in rhesus monkeys (Koo et al., 2013). In addition, there are alternative measurements, such as zero-displacement probability and q-space inverse variance (Assaf et al., 2000; Wu et al., 2008), which can be used for evaluating diffusion process in the tissue as well.

The age-related changes were analyzed with two different regression models. The results showed that the Poisson model had advantage over the quadratic regression model (Fig. 4 and Table 2). Poisson model considers varying slopes for connectivity changes in both developmental and aging periods. In contrast, the quadratic regression model assumes even slopes across both the periods (Fjell et al., 2010), though the quadratic regression model provides a simple way to account for the correlated terms over most of the age range (Allen et al., 2005; Lebel and Beaulieu, 2011). As illustrated in Figure 4, the transcallosal connectivity for different cortical areas changed faster in the developmental period than in the aging period, suggesting that the neural fibers mature quickly during brain development but degenerate slowly during aging, in good agreement with previous studies (Lebel et al., 2010).

It has been reported that the whole brain white matter percentage increases after birth for approximately 5 years in macaque monkeys (Malkova et al., 2006), and the thickness of CC keeps increasing with age in developing macaque brains (Li et al., 2011). Previous DTI studies in human or NHP brain development have demonstrated that fractional anisotropy (FA) values of white matter fibers increase from infancy to the juvenile stage or young adulthood, showing a progressive maturation procedure in the central nervous system (Alexander et al., 2007; Hermoye et al., 2006; Huppi and Dubois, 2006; Yan et al., 2014b), though the white matter maturation progresses differently in different brain structures (Lebel and Beaulieu, 2011; Lebel et al., 2008). Obviously, the findings of the transcallosal connectivity changes from infancy to young adulthood are consistent with the increases in white matter volume, CC thickness,

and FA of most white matter fibers in the developing brain. In addition, previous studies in human and NHP brains have demonstrated that the white matter integrity decreases over time during aging (Chen et al., 2013; Yan et al., 2014a). It was also reported that the percentages of normal sheath profiles in prefrontal cortex and CC decreased dramatically in monkeys that were older than 20 years (Peters and Sethares, 2002). The earlier findings are in good agreement with the decreased connectivity observed in the transcallosal connectivity of elder macaque brains.

As seen in Figure 4 and Table 2, the transcallosal connectivity of the frontal lobe increased from 1 year old, reached a maximum at 7–10 years, and then significantly decreased after 15 years old when fitted with the Poisson model. Such changing patterns remain similar in most cortical areas, including dlPFC, vlPFC, dPMC, vPMC, PMC, and SSC (Fig. 4a–f). Specifically, decreasing transcallosal connectivity in the frontal cortex occurs about 1–3 years later than those in parietal, temporal, and occipital lobes (as fitted with Poisson model; Fig. 4g–i and Table 2). In addition, the transcallosal connectivity of the prefrontal, premotor, motor, and temporal cortices correlated significantly with age when fitted with the Poisson model, though there were less cortical areas whose transcallosal connectivity was significantly correlated with the quadratic model (Fig. 4 and Table 2). The temporal changes of transcallosal connectivity in the frontal lobe of monkey brain agree well with the previous results of late white matter maturation in the prefrontal cortex and the frontal lobe connectivity in humans (Lebel et al., 2008; Thompson and Nelson, 2001). Our results are also in good agreement with the finding that the areas of the anterior CC increased more slowly than those of the posterior CC in humans from 5 to 18 years old (Giedd et al., 1999). In this study, the elongated period of increasing interhemispheric connectivity in the frontal areas of developing brains would be attributed to the prolonging maturation of the cortices themselves and the neuronal pathways involved with the associated areas.

In the older adult monkeys, the transcallosal cortical connectivity in the frontal lobe decreased much more than that in the temporal and visual cortices. As shown in Figure 4, compared with most cortical areas in the frontal lobe, the connectivity for SSC, PPC, and VC was not significantly correlated with age by fitting with either the Poisson or quadratic model (Table 2). Although the connectivity for the TC significantly correlated with age when fitted with the Poisson model, the *p*-value ($p = 0.03$) was much larger than that in other areas whose connectivity significantly correlated with age. The finding that the aging effect is more prominent in the frontal lobe than that in the posterior brain regions, such as cortical areas in the occipital lobe, has been previously revealed by DTI (Pfefferbaum et al., 2000; Sullivan and Pfefferbaum, 2006). The heterogeneity of normal neuroanatomical degeneration was also demonstrated by volumetric measurement in adult human brains which were more than 22 years old, showing that the gray matter in the frontal lobe was the most strongly associated with aging, while that in the occipital lobe was the least associated with it (Allen et al., 2005). Our present results showed that interhemispheric connectivity changes over time were more pronounced in the frontal lobe, which was consistent with what were previously reported in humans (Allen et al., 2005; Pfefferbaum et al., 2000; Sullivan and Pfefferbaum, 2006).

Abnormal alterations in interhemispheric cortical connectivity might be associated with cognitive dysfunctions and abnormal behaviors in the lifespan. A previous rsfMRI study has demonstrated that decreased interhemispheric functional connectivity in sensorimotor cortex, superior temporal gyrus, and superior parietal lobule was relevant to functional defects in autism patients (Anderson et al., 2011). A decline of anterior white matter integrity was also found in elderly people with cognitive impairment (Teipel et al., 2010). Such cognitive disorders could be associated with the abnormal transcallosal connectivity in the relevant cortical regions. Since the life expectancy of macaque monkeys is about 25 years (Primate Info Net, <http://pin.primat.wisc.edu>), this study consists of macaques from 1 to 24 years old, resembling the human lifespan from infancy to late adulthood. The changing pattern of the connectivity in macaque brain may provide a valuable baseline reference in translational research for the functional defects or alterations in the associated cortical areas during development and aging of the human brain (Paus et al., 2008).

Conclusion

In this work, DSI tractography was used to evaluate the cortically specific changes of transcallosal connectivity across anterior-posterior brain lobes of formalin-fixed macaque brains from infancy to late adulthood. The changes were age-related and varied for different brain lobes. The similarity of the connectivity change patterns in both human and macaque brains suggests that the macaque monkey is a valuable model for translational research of the developmental and aging brain.

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Author Disclosure Statement

No competing financial interests exist.

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