Longitudinal Change of Cortically Transcallosal Connectivity in Macaque Monkeys Revealed by Diffusion Spectrum Imaging Tractography

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TARGET AUDIENCE Neuroscientists, MRI physicists

INTRODUCTION The interhemispheric connectivity changes during development and aging could be accompanied with behaviour alterations and psychiatric disorders. As non-human primates (NHPs) brains mimic most aspects of human brains, the knowledge of the interhemispheric connectivity alterations with age in NHP brains may provide important implications for human functional and behavioural alterations in translational research [1]. Diffusion spectrum imaging (DSI) tractography can provide a novel and unprecedented opportunity for studying complicated brain fiber connections [2]. 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.

METHODS 12 normal macaque monkeys (6 female and 6 male) from 1 to 24 years old, 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. These samples were collected from prior projects in which animals in the control groups were euthanized for the research purpose or from the cohort of unassigned monkeys sacrificed due to the Institutional Animal Care and Use Committees (IACUC) end point. The experiments were carried out on a Bruker Biospec 7.0T spectrometer equipped with a 12cm actively-shielded gradient (400 mT/m). The DSI pulse sequence was custom-developed and implemented under the software Paravision 5.1. Double spin echo acquisition was applied on a 3D EPI sequence with parameters TE/TR = 55/500 ms, 3D matrix size = 70×50×80 for 1 mm isotropic spatial resolution. Diffusion was encoded with 514 diffusion directions covering full 3D q-space grid with 5 radical grid size and maximum b value = 40000 s/mm^2, and one B_0 image (b value = 0 s/mm^2). The cortical areas, including dorsolateral prefrontal cortex (dlPFC), ventrolateral prefrontal cortex (vlPFC), temporal cortex (TC) and visual cortex(VC) and corpus collosum (CC) defined from a template were registered to the B_0 images using the FSL software (FMRIB, Oxford). The white matter tracts were reconstructed using DSI-Studio software (http://dsi-studio.labsolver.org) [3]. Cortically transcallosal tractography for the interested areas in both hemispheres was performed in the following two steps. Firstly, the cortical area in the left hemisphere was selected as a seed, and then 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. Secondly, the same procedure was repeated but started with the cortical area in the right hemisphere as a seed. The proportion of the total fiber numbers from the two fiber tracking steps (20,000 tracking numbers) was used for assessing regionally transcallosal connectivity strength for each cortical area. The connectivity strength with respect to age was fitted with the Poisson model [4]: connectivity strength = $A*age*e^{-B*age} + C$, where A, B and C are the model terms. The fitting significance was determined after FDR multiple comparison corrections (q = 0.05).

RESULTS Transcallosal fibers for different cortices from the anterior to posterior brain lobes including both dorsal and ventral orientations were determined by DSI tractography (Fig.1). Significant fitting results between the connectivity strength and age were found in dlPFC ($p < 0.001$), vlPFC ($p = 0.02$) and TC ($p = 0.03$) but not VC ($p = 0.07$) (Fig. 2). The age for the peak connectivity strength in dlPFC and vlPFC were similar (i.e., > 7 years) but later than that in TC and VC (i.e., < 6.5 years). In addition, the connectivity change range in the anterior cortices (i.e., both dlPFC and vlPFC) was much larger than that in the posterior cortices (i.e., TC and VC).

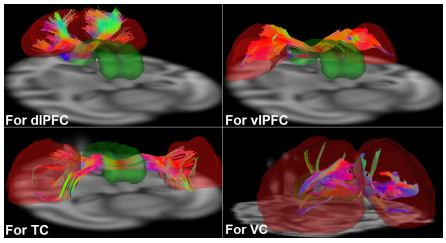

Figure 1. Transcallosal fibers for various cortical areas (red color) through CC (green color).

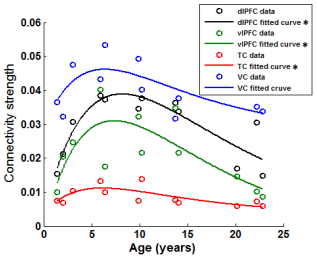

Figure 2. Changes of the transcallosal connectivity strength with age for various cortical areas. The star (*) means fitting significance ($p < 0.05$) after FDR correction.

DISCUSSIONS In the present study, transcallosal connectivity changes of cortical areas were found to be differential in the anterior-posterior brain lobes of macaque monkeys. The fitting curve showed fast developing but slow degenerating periods. The temporal changes of transcallosal connectivity in the frontal lobe of monkey brain agrees well with the previous results of late white matter maturation in the prefrontal cortex and the frontal lobe connection, and the slower maturation in anterior than posterior corpus callosum in human [5-6]. In addition, the results showed that the interhemispheric connectivity changes over age were more pronounced in the frontal lobe, which was consistent with the findings in aging human [7]. The similarity of the connectivity change pattern in both human and macaque brains suggests that macaque is a valuable model for translational research of developmental and aging brain.

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