年龄对大脑结构偏侧性的影响研究

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摘 要 因方法学的不同，年龄对大脑偏侧性变化的影响还存在一些争议。本研究基于高分辨磁共振结构图像，利用多参数模型分析了人脑衰老过程中偏侧性的改变情况。研究共纳入 205 例被试，按年龄分为 7 个小组。每名被试的磁共振 T1 加权图像用 Freesurfer 软件进行前期处理，并计算大脑皮层 34 个功能区域的形态学特征，包括表面积、平均沟回指数、皮层厚度、皮层下白质体积。用多参数分析方法整合 4 种特征信息对每组大脑的偏侧性进行评估，同时将具有显著性的 *P* 值映射到脑模板上用于可视化。结果表明，随着年龄增加，大脑偏侧性出现全局性的下降，其中以顶叶、枕叶下降最为明显。偏侧性保留或反转的区域主要集中于和高级认知水平相关的区域，这提示大脑在正常衰老过程中可能存在代偿机制以应对认知功能的损伤。该研究为理解神经行为、神经生理疾病提供了新的视角。

关键词 大脑偏侧性；正常衰老；多参数分析；磁共振影像

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Age Effect on Structural Hemispheric Asymmetry Revealed by Multivariate Model

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Abstract Age dependence on the hemispheric asymmetry alteration remains inconclusive partially due to the diversity of methodology. In this study, a multivariate model was applied to evaluate the evolution of the structural hemispheric asymmetry during healthy aging based on magnetic resonance imaging data. The T1-weighted images from 205 subjects were retrieved and categorized into 7 age groups. The morphological features including the surface area, mean curvature index, cortical thickness, and subjacent white matter volume in 34 regions of interest were calculated. The multivariate analysis was then performed on each age group to investigate the composite effect of the four features on asymmetry alterations. The *P* values were finally mapped onto a FreeSurfer template for visualization. Global reduction of hemispheric laterality was identified with a worse decline in parietal and occipital lobes as age advances. Reservation and left-right shift of laterality were vastly detected in the high-level cognition-related regions, which may imply a compensatory mechanism of healthy brain counteracting the age-associated functional impairment. The age dependence on the hemispheric asymmetry may embed mechanisms that underlie the behavioral and cognitive declination

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associated with age related neuropsychological diseases.

Keywords hemispheric lateralization; healthy aging; multivariate analysis; magnetic resonance imaging

1 Introduction

Hemispheric asymmetry evolves in the process of structural and functional maturation of human brain. Although the mechanism of lateralization is not fully established, mounting evidences have shown that regional hemispheric asymmetries undergo dynamic changes during the life span[1].

Two models were concerned with the age-related variations of cerebral laterality: the right hemi-aging model and the hemispheric asymmetry reduction in old adults (HAROLD) model. The right hemi-aging hypothesis proposes that functions attributed to the right hemisphere are affected to a greater degree than those to the left hemisphere in age-related cognitive decline[2,3]. One of the findings supporting this hypothesis was that verbal function is largely age-invariant whereas visuospatial function showed substantial age-associated decline[4]. Weller and Latimer-Sayer[5] also reported that left-hand (right hemisphere) abilities of the sensory-motor task decreases more rapidly with age than that of the right hand (left hemisphere). However, the right hemi-aging model is primarily based on behavioral rather than neurobiological evidences, which may be biased due to the complexity of different tasks. The HAROLD model states that, under similar conditions, prefrontal cortex (PFC) activity tends to be less lateralized in older than in younger adults[6]. Functional neuroimaging along with electrophysiological and behavioral evidences in the domains of episodic memory encoding and retrieval, semantic memory retrieval, working memory, perception and inhibitory control were observed to support the HAROLD model[7-11]. Evidence for the HAROLD model has been more consistent than that for the right hemi-aging model. However, other brain regions apart from PFC, where asymmetry alterations may also occur, are not included in HAROLD. Our previous study demonstrated that hemispheric asymmetry experienced region-specific alterations with laterality shift in part of the limbic system at late life in comparison to young subjects[12], indicating that the age effect on the cerebral morphology is beyond a general tissue atrophy with more complicated events associated with compensatory and protective mechanisms of brain evolution involved.

Previous structural studies on cerebral lateralization mainly focused on an independent morphological variable, ignoring the interaction among indices that leads to discrepant outcome between analyses[13-15]. Multivariate model, instead, surmounts the drawback of univariate model in lateralization evaluation, especially in some neurological diseases where abnormalities tend to occur in various aspects of neuron across different brain regions. The multivariate analysis was validated as more comprehensive and reliable measure in compensation of univariate by taking into account the effects of all variables in characterizing brain morphology[12].

In this study, we explored the effect of aging on cerebral structural lateralization using a multivariate

model based on high resolution anatomic magnetic resonance (MR) images. Study of the trajectories of cerebral laterality evolution would be helpful in better understanding the mechanisms of brain aging, providing a baseline for researches in psychology and psychiatry in which laterality could be the substrate of the diseased brain.

2 Materials and methods

2.1 Subjects

Data of a total of 205 right-handed healthy subjects aged from 20 to 89 years were retrieved from the Open Access Series of Imaging Studies（OASIS, http://www.oasis-brains.org/）database. The OASIS study was approved by IRB of the Washington University in St. Louis. All subjects and if applicable, their legal representatives, gave written informed consent prior to the collection of clinical and imaging data. The dataset follows the rigor establishment with careful quality control, detailed documentation, and full anonymization prior to data analysis. Approval for public sharing of the anonymized data was obtained.

Nondemented subjects aged over 40 years in the database were all selected except for the ones who demonstrate abnormally large lateral ventricles and those who failed in the following image processing. Subjects between 20-39 years old were randomly selected with matched gender. All subjects were screened to rule out psychiatric and neurological conditions that might contribute to dementia but typical variation of advanced aging was included. Subjects were categorized into 6 groups for the evaluation of age-related asymmetry alteration. The demographic information was summarized in Table 1.

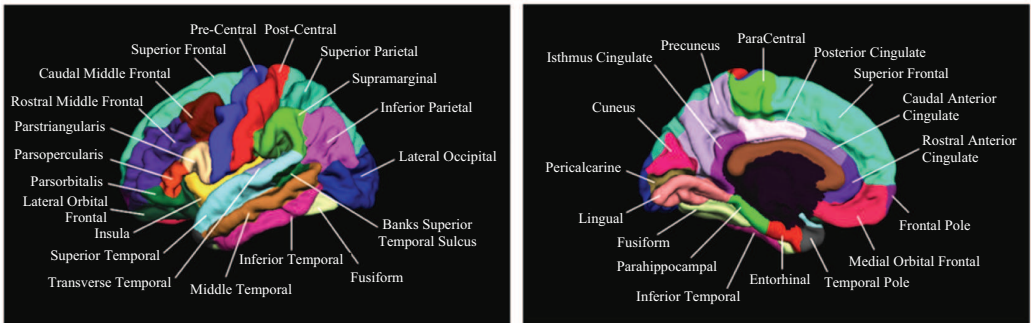
Table 1　Summary of the demographic information of subjects

Groups	Age range	Number of subjects (male/female)	Mean age ± std
1	20-39	38 (16/22)	30.54 ± 6.68
2	40-49	37 (16/21)	45.58 ± 2.74
3	50-59	39 (17/22)	54.36 ± 3.03
4	60-69	27 (9/18)	64.56 ± 3.15
5	70-79	35 (10/25)	74.37 ± 2.35
6	80-89	29 (7/21)	85.07 ± 3.31

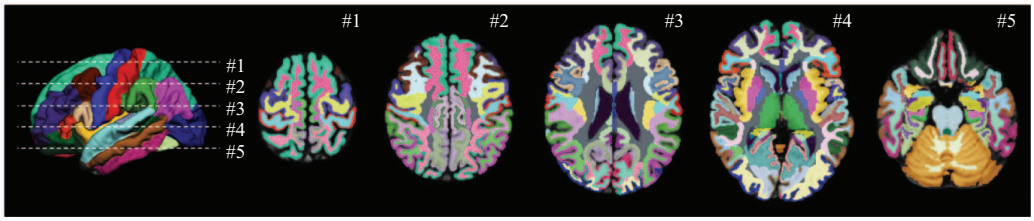
2.2 Image processing

T1 weighted images（T1WI）were retrieved from the OASIS database for each of the subjects who were scanned on a 1.5 T Siemens MR imaging system with the MP-RAGE sequence. The typical imaging parameters were TR 9.7 ms, TE 4.0 ms, FA 10°, thickness 1.25 mm, and resolution 1.0 mm×1.0 mm×1.25 mm.

FreeSurfer software（version 5.0.0, http://surfer.nmr.mgh.harvard.edu/）was used to calculate morphological variables based on the T1WI of the entire brain for each subject. Images were first intensity normalized, skull stripped, aligned to the Talairach space, and segmented into gray matter（GM）, white matter（WM）, and cerebrospinal fluid（CSF）. A construction of cortical surface and WM surface was performed followed by the inflation of the folded surfaces, topology correction, and projection to the standard spherical coordinate system defined by FreeSurfer brain atlas that enables automated anatomical parcellation of cerebral cortex into 34 gyral-based regions of interest（ROI）[16-18] and subjacent white matter ROIs for both hemispheres of each subject[19,20]（Fig. 1）. Surface area, mean curvature index, and thickness, along with corresponding white matter volume of each ROI were calculated as morphological variables for each hemisphere[20-22].



(a)



(b)

Fig. 1 Cortical parcellation of 34 ROIs (a) and corresponding white matter segmentation (b)

(The morphological indices, including surface area, mean curvature index, thickness, and subjacent white matter volume were then calculated for each ROI of each hemisphere)

2.3 Lateralization measurement and statistical analysis

Statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS 17.0, SPSS Corp., Chicago, IL, USA). Multivariate analysis of covariance (MANCOVA) was conducted to test the compositive morphological differences between left and right hemispheres for each group with assumption that asymmetry alteration on each ROI was independent. Surface area, curvature index, cortical thickness, and subjacent WM volume were introduced as collective response variables in MANCOVA. Subject gender and age were introduced as covariates. Multiple-comparison correction was performed across ROIs in all analyses to control the false discovery rate (FDR) at a significance level of 0.05. The P values were then mapped onto a FreeSurfer template for visualization. The lateralization index of significantly asymmetric regions with $P<0.05$ (corrected) was defined as $LI=\sum_i (L_i-R_i)/(L_i+R_i)$, $(i=1,\cdots,4)$, where L_i and R_i were the mean value across subjects of the ith variable for the left and right hemisphere, respectively. $LI>0$ indicates a leftward asymmetry and $LI<0$ indicates a rightward asymmetry. Results were finally mapped onto a cortical surface of left hemisphere for visualization. Lateralization index changing rate (ΔLI) was calculated across aging by $\Delta=(LI_{j+1}-LI_j)/LI_j$, where j denotes the jth age group.

3 Results

From young to elder, the overall number of ROIs with significant hemispheric asymmetry reduced in regions including the lateral parietal and occipital areas, the medial frontal and posterior cingulated gyri, the precentral gyrus, the superior and caudal

middle frontal gyri, the middle temporal gyrus, the lingual gyrus, and the temporal pole (Fig. 2). Laterality was mostly preserved in the prefrontal cortex and temporal lobe relative to the parietal and occipital lobe where hemispheric asymmetry was vastly lost during aging. The postcentral gyrus and precuneus showed no asymmetry throughout the entire age range. Laterality shift occurred as early in 40s in the entorhinal cortex and as late in 80s in the paracentral lobule, from the right side to the left.

The changing rates of lateralization index with a mean value higher than 2% were plotted in colored curves (Fig. 3). Two peaks were observed at age 40s and 70s with the maximum changing rate up to 50% and 20%, respectively. Laterality varied the most in medial orbitofrontal gyrus, entorhinal cortex and frontal pole for age 40s, and in middle frontal gyrus, cuneus and postcentral gyrus for age 70s.

4　Discussion

Lateralization offers crucial benefit to increase

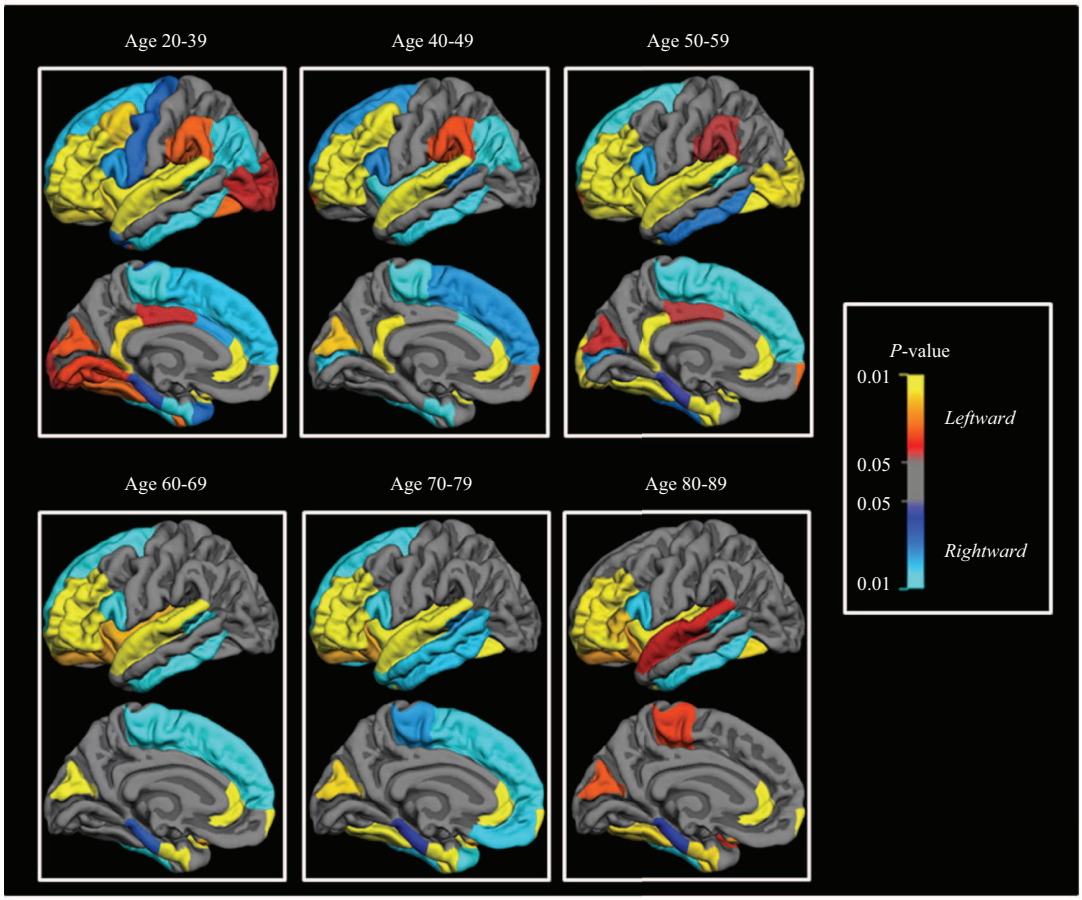


Fig. 2　Hemispheric asymmetry in each age group

(Hemispheric asymmetries significantly reduced during aging with the most impaired regions located in the posterior cerebrum including the parietal and occipital lobe. Lateralization reversion was found in the entorhinal cortex and paracentral lobule from right hemisphere to the left as early in age 40s and as late in age 80s. Color bar in red-yellow denotes leftward lateralization, while blue-cyan denotes rightward lateralization)

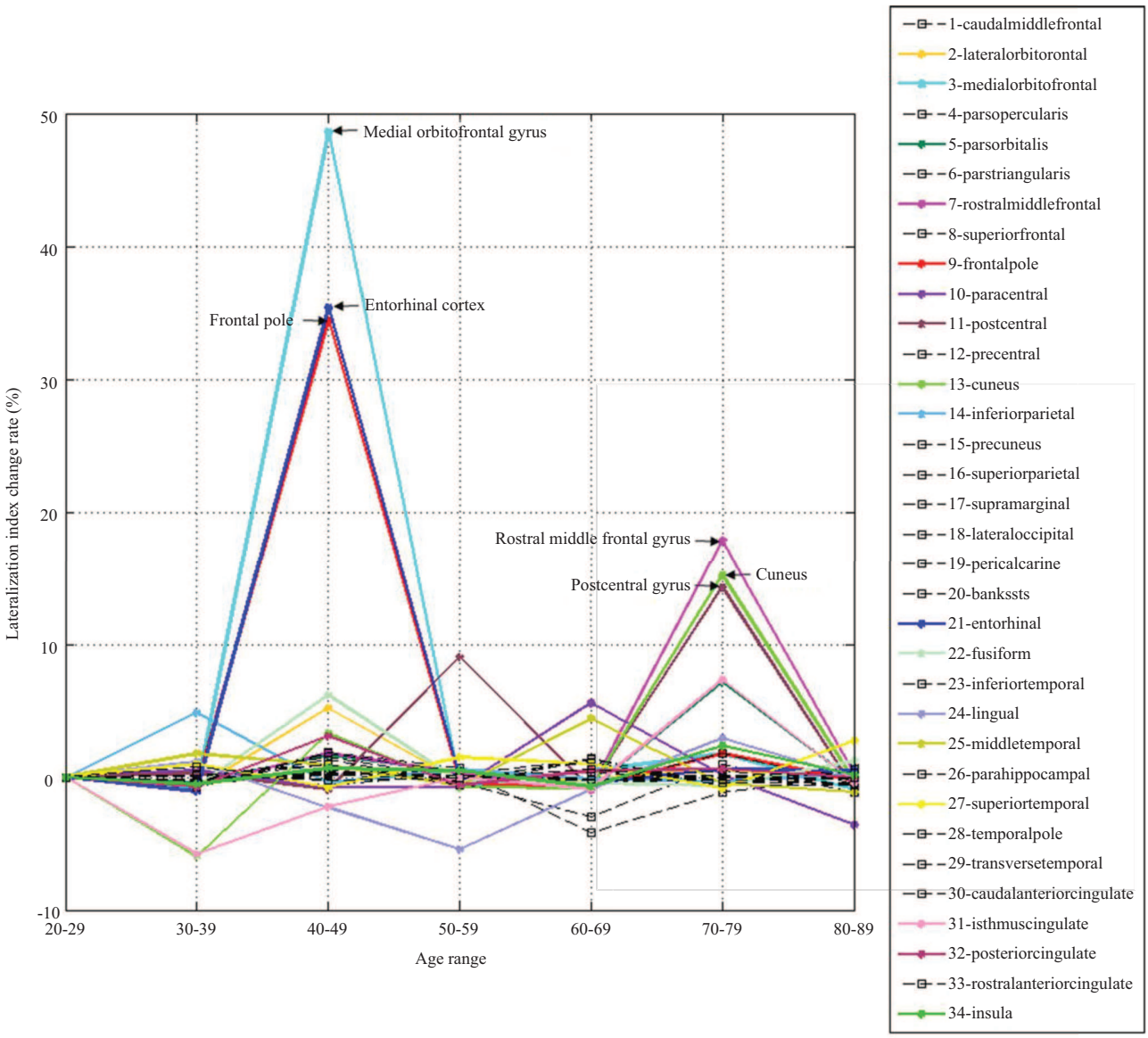


Fig. 3 The changing rate of lateralization index (Δ*LI*) across aging was illustrated for each of the 34 ROIs

(Those with pronounced variation (mean ＞ 2%) were plotted with colored curves. Two peaks were presented respectively at age 40s and age 70s, indicating a significant increase of lateralization index at the corresponding age range in comparison with the previous range)

the efficiency of information processing, whereby functional specialization of one hemisphere leaves the other to better coordinate different tasks. In addition, dominance by one hemisphere is thought to be a way of avoiding the simultaneous initiation of contradictory responses in organisms with laterally placed eyes[23]. Previous research agreed that cerebral asymmetry reduced during aging which is consistent with the functional degeneration[2,3,6], despite the discrepancy on location and areas between studies.

4.1 Asymmetry reduction and reservation during aging

Reduction of the hemispheric asymmetry with aging was confirmed in the current MANCOVA

study. Tissue atrophy, loss of neuronal bodies and dysmorphology of neurons may affect the central nervous system as a whole, or highly confined to specific regions[24]. In this study asymmetry reduction was mainly identified in regions associated with visual processing, language processing, emotional response and decision making. Laterality reduction in these areas may partially account for the slower reaction time, declined visual acuity, and degenerative language construction ability frequently seen in aged individuals. Lateralization was relatively preserved in prefrontal cortex and temporal lobe where advanced cognitive function including episodic memory, object recognition, and spatial navigation are performed. As it has been reported that the prefrontal cortices and temporal volumes were more significantly affected upon aging[25], the retained hemispheric asymmetry may serve as a mechanism for the brain to minimize the functional losses due to tissue atrophy by preserving lateralization during aging procedure.

Hemispheric asymmetry experiences dynamic adjustment in adaption to the cerebral aging, injury or neurological disorders, which enables brain being shaped and reshaped across an entire lifespan based on the intrinsic property of neuroplasticity[26-28]. Park and Reuter-Lorenz[27]proposed that the brain builds protective “scaffolds” in response to the age-related neural insults of brain shrinkage, decreased white matter integrity, and decreased dopamine receptors to shore up declining structures whose function has become noisy, inefficient, or both. There has been broad evidence in postmortem data as well as in in-vitro study suggesting that neuroplasticity in older animals and human occurs in the form of neurogenesis or synaptic modulation and can result from both increased cognitive and physical engagement[29-31].

4.2 Laterality reversion during aging

Laterality reverse from right hemi dominance to the left was observed in the entorhinal cortex and paracentral lobule during aging, roughly in accordance with the right hemi-aging model[2,3] which has been verified by behavioral studies in the domains of cognitive, affective and sensorimotor processing. However, the hypothesis remains controversial due to the differences in methodology. The multivariate structural analysis in the current study may support the model in terms of neuro-morphological basis. Nevertheless, the hemispheric asymmetry in these areas was still preserved rather than vanished to compensate the regressive functional capacity.

It is also noteworthy that laterality shift occurred as early in age 40s as seen in this study in areas of the entorhinal cortex which has been suggested to be a hub in a widespread network for memory and navigation. The laterality shift in this region may be the substrate of a process of functional optimization during brain maturation in line with the development of mental abilities that peak around age 46[32]. Reverse occurred in areas of paracentral lobule in age 80s is more likely to be an aging-induced adjustment in response to brain degeneration. While some cerebral structures fight back in response to degeneration by successfully reserving or converting hemispheric asymmetry, others were compelled to sustain age-related decline.

4.3 Phased variation of lateralization index

Another finding in this study was that life-span

asymmetry evolution is regionally heterochronic rather than with a constant pattern. Regions such as the broca's area, supramarginal gyrus, precentral gyrus, and anterior cingulated gyrus underwent a mild variation of lateralization from young adulthood to elderly, while other regions including the medial orbitofrontal gyrus, entorhinal cortex, frontal pole, rostral middle frontal gyrus, cuneus, and postcentral gyrus experienced two remarkable peaks at specific age ranges (as shown in Fig. 3). As the lateralization index changing rate ΔLI was defined as the normalized difference between LI_{j+1} and LI_j, where j denotes the jth age range, a notable spike of ΔLI indicates a large increase of lateralization at the corresponding stage compared to the earlier one. The change rates of lateralization index in certain regions, for example, the insula, cuneus, posterior cingulated gyrus, lingual gyrus, and paracentral lobule, fluctuated around zero, implying that not all the asymmetry trajectories over aging were monotonic. Although the mechanism remains unknown, the emergence of brain lateralization was assumed to be the interaction of genetic, hormonal, and environmental modulation. The pattern of brain asymmetry at certain age range is believed to be an integrated result of a dynamic equilibrium of multiple biochemical, metabolic, and mechanical forces and events. Animal studies have revealed that protein Fgf8[33] and prenatal exposure to sex hormone[34] modulate cerebral asymmetric development in terms of the degree and direction of lateralization. Schaafsma et al.[35] showed that pre-, peri- and post-natal environmental factors including light exposure, body posture, parental handedness as well as social pressures are important in the development of lateralization.

Two apexes were observed in the change rates of lateralization index in age 40s (49%) and 70s (18%), respectively. The apex at age 40s involves regions of the medial orbitofrontal gyrus, entorhinal cortex and frontal pole, where high level cognitive performance including reasoning and memory are functioned, while the apex of age 70s involves areas of the rostral middle frontal gyrus, cuneus and postcentral gyrus, where basic sensorimotor functions such as senses and movement are concerned. It was reported that cognitive performances in problem solving and reasoning ability, spatial ability, as well as short term memory undergo a general drop beyond mid-40s[36], which is highly relevant with the observation in the current study that the ROIs related to the aforementioned cognitive capacity demonstrated a remarkable increment of lateralization in age 40s. There is a steeper decline in cognitive functions associated with basic living after age 70s partially due to the neuronal loss in the brain, however, the decrement does not become functionally significant as those owing to diseases[37]. Asymmetry reservation or strengthening may substrate the process that helps slow down and compensate functional declines.

The pattern of lateralization changes also provides a way to reveal the normal brain evolution over aging. Thompson et al.[38] have once reported that the last brain regions to develop in childhood- areas involved in more advanced functions- are the first to degenerate in dementia; and the earliest developing brain regions- areas controlling vision and sensation- are spared until the very late stages of Alzheimer's disease. This mode of brain degradation may also be applied to the healthy aging process, where prefrontal and temporal cortices associated with high level cognitive performance are the most

vulnerable, followed by the parietal and occipital lobes that are more responsible for the basic sensorimotor functions[25,38]. However, the difference between healthy aging and dementia was that the healthy brain may start up a protective or self-improved lateralization mechanism to compensate functional loss. Lack of such a mechanism may lead to neurological problems that may accelerate brain degeneration or pathological changes[12].

4.4 Limitations

There are several limitations in this study. Out of the 205 subjects, the number of subjects in each age group is small. In addition, unequal male and female subjects were included with the number of males being smaller than that of females in all groups. Cross-sectional analysis may also raise issues on demographic and health-related variations which are likely to affect brain asymmetries.

5 Conclusions

Age poses substantial effect on the cerebral structural lateralization revealed with multivariate analysis indexed by cortical surface area, curvature, thickness, and subjacent white matter volume. Hemispheric asymmetry reduced during healthy aging with the most impaired areas located in the parietal and occipital lobe. Laterality reservation and left-right reversion observed in the high-level cognitive-related regions may indicate a compensatory mechanism of healthy brain in reaction to aging-associated functional decline. Lack of the reservation and reversion of the regional laterality may be associated with demented disorders such as Alzheimer's disease. Investigation of aging effects on hemispheric asymmetry may facilitate the understanding of brain-behavior relations, the neural underpinnings of cognition, and the identification of abnormality in neurological and psychiatric diseases.

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