



2019

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### Recommended Citation

Lin Shi, Peipeng Liang, Andy Li et al. Visualizing the neuroanatomical changes in Han Chinese adulthood: A pseudo-longitudinal study based on age-related large-scale statistical Chinese brain atlases. *Brain Science Advances* 2019, 5(2): 106-116.

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This research article is available in Brain Science Advances: <https://tsinghuauniversitypress.researchcommons.org/brain-science-advances/vol5/iss2/6>

# Visualizing the neuroanatomical changes in Han Chinese adulthood: A pseudo-longitudinal study based on age-related large-scale statistical Chinese brain atlases

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## ARTICLE INFO

**Received:** 24 April, 2019

**Revised:** 18 May, 2019

**Accepted:** 28 May, 2019

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## KEYWORDS

age-related statistical brain atlas, magnetic resonance imaging, pseudo-longitudinal study, brain maturation and ageing

## ABSTRACT

**Objective:** Understanding how brain changes over lifetime provides the basis for new insights into neurophysiology and neuropathology. In this study, we carried out a pseudo-longitudinal study based on age-related Chinese brain atlases (i.e., Chinese2020) constructed from large-scale volumetric brain MRI data collected in normal Han Chinese adults at varying ages.

**Methods:** In order to quantify the deformation and displacement of brains for each voxel as age increases, optical flow algorithm was employed to compute motion vectors between every two consecutive brain templates of the age-related brain atlas, i.e., Chinese2020.

**Results:** Dynamic age-related neuroanatomical changes in a standardized brain space were shown. Overall, our results demonstrate that brain inward deformation (mainly due to atrophy) can appear in adulthood and this trend generally accelerates as age increases, affecting multiple regions including frontal cortex, temporal cortex, parietal cortex, and cerebellum, whereas occipital cortex is least affected by aging, and even showed some degree of outward deformation in the midlife.

**Conclusion:** Our findings indicated more complicated age-related changes instead of a simple trend of brain volume decrease, which may be in line with the recently increasing interests in the age-related cortical complexity with other morphometry measures.

## 1 Introduction

Understanding how brain structure changes

over lifetime provides the anatomical basis for neurophysiology and the identification of its pathologies. In particular, with the high prevalence

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of dementia and other aging-associated diseases, it is in great demand to understand how the brain anatomy changes during aging. Age-related brain volume change typically follows an inverted-U trajectory, which increases in earlier ages, reaches a plateau in middle age and decreases gradually in elderly period [1–4]. Converging evidences suggested that age-related brain structural changes are complicated and region-dependent [5]. Visualizing the age-related neuroanatomical changes in an intuitive way with the high spatial resolution is potentially helpful for a comprehensive understanding of dynamic brain structural changes.

In this study, we propose to investigate the morphological details of brain aging using optical flow algorithm [6] on our 4D Chinese brain atlas, i.e., Chinese2020 [7] (Fig. 1). Optical flow has been applied to intraoperative MRI images to study the detailed brain shift before and after the dura opening [8], but has not been used to study morphological changes in a group atlas basis.

Brain atlas provides a standardized space for precise spatial positioning. It was Talairach who first proposed a 3D detailed brain coordinate system, known as Talairach space [9], which lays the basis for modern 3D brain mapping. Thereafter, a series of statistically population-based brain templates were constructed to extend the applicability of brain atlas to represent the brain in a group level [10–13]. Many spatio-temporal brain atlases were proposed to reflect the brain development in fetal, neonatal and pediatric stages [15–17], leaving much room for further studies in adult brain aging. Proposed in 2015, statistical Chinese brain atlas is the largest scale brain templates for Chinese population [7], and a series of age-related brain atlases were constructed in that study covering the ages of 20 to 75.

From the point of acquisition, longitudinal data collected at multiple stages for the same cohort

of subjects over time is valuable in reflecting age-related evolvement [4, 5, 18–23]. However, the feasibility of large-scale study is very low if not impossible due to difficulty in arranging long-term MR scans while maintaining a sufficient sample size with inconsistent scanning conditions. Therefore, we employed a pseudo-longitudinal study of brain development across lifespan from our constructed age-related template, i.e., Chinese2020, which serves as a feasible alternative to a longitudinal study. This is also the first pseudo-longitudinal study based on the largest collection of normal Chinese subjects' brain MR images.

## 2 Methods

### 2.1 Materials

The Chinese2020 templates were applied in this study to measure the brain morphological changes in aging [7]. The Chinese2020 templates were built on MRI scans of 2020 healthy adults across 24 Chinese provinces recruited from 15 hospitals. Pre-processing techniques including automatic noise estimation method and intensity normalization method were designed to improve the image quality and image profiles of different subjects obtained from different scanners for constructing the high-resolution brain templates. Twelve templates were generated spanning ages 20–75 with a 5-year interval by inter-subject registration. In order to make the brain templates more smoothly developed along the age axis, we adopted the kernel regression strategy to construct the time-varying brain templates. Eventually a whole population brain template was generated from the 12 templates through non-rigid registration. The templates constructed at a 5-year age interval are shown in Fig. 1A. In analogy, the ageing course of a man is illustrated in Fig. 1B. Methods for templates construction and any

associated references are available in our recent works [7].

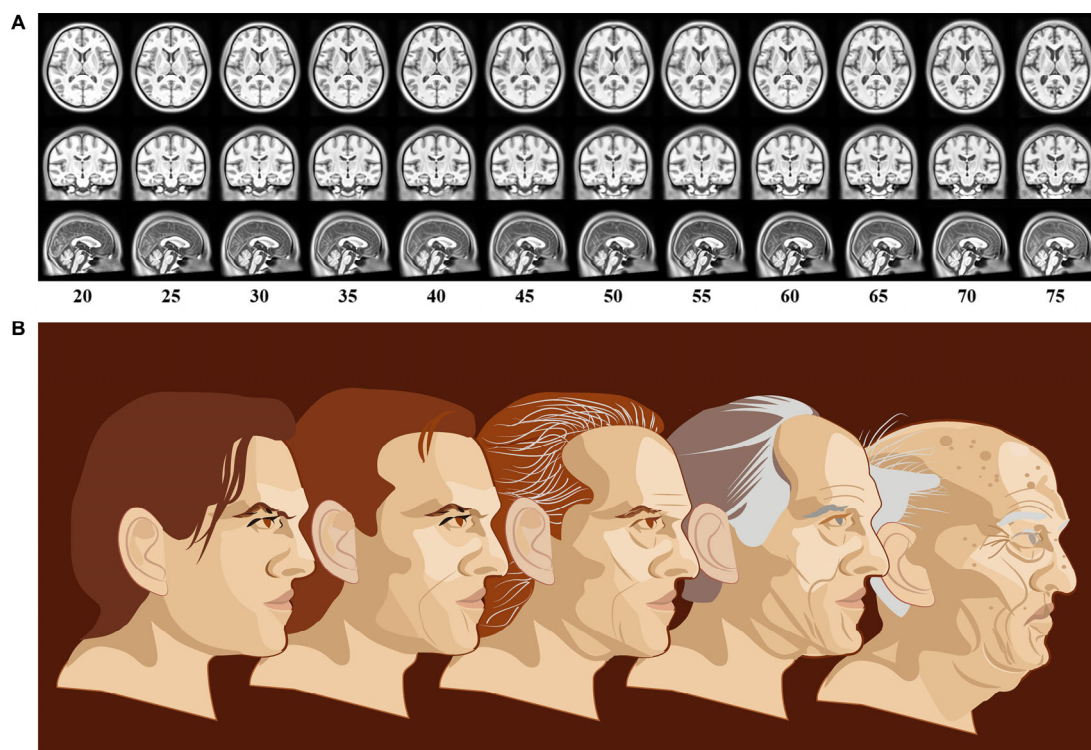
## 2.2 Methods for brain change quantification

In order to objectively evaluate the development of brain along the age axis, tensor-based optical flow algorithm was employed using variational methods to quantify the deformation and displacement of brains for each voxel [6]. Optical flow is a computer vision technique that represents the apparent motion in a series of images at different time points. The direction and magnitude of optical flow at each voxel can be represented by the direction and length of each arrow. In this study, motion vectors are estimated between every two consecutive brain templates of the spatial temporal brain atlas Chinese2020. First, color motion field was computed for all voxels to show both the direction and magnitude of all deformation between adjacent age groups, where the direction is encoded by the color and the magnitude is represented by the color intensity.

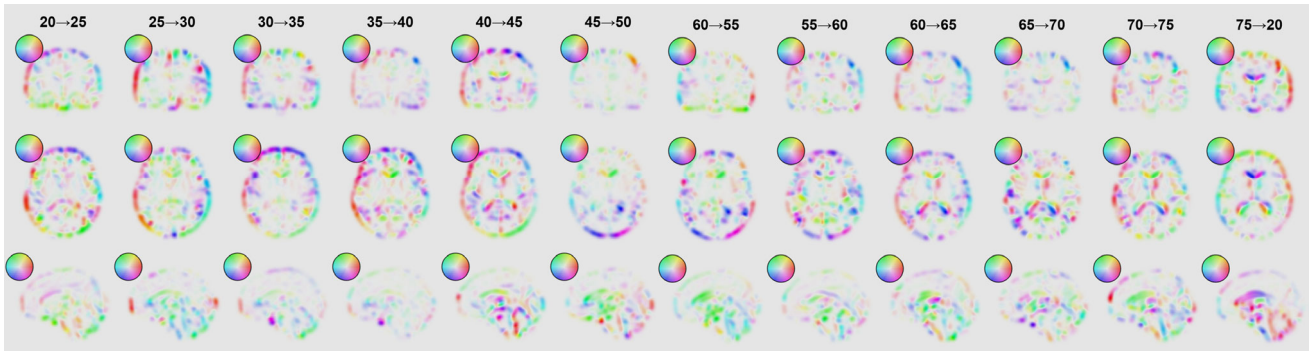
Second, in order to better visualize the effective deformation field, vector motion field was obtained by identifying motion vectors that satisfy the magnitude threshold of 0.07, and was overlaid onto the brain templates (of the younger age group), which enables further examination of our findings in relation to different brain regions.

## 3 Results

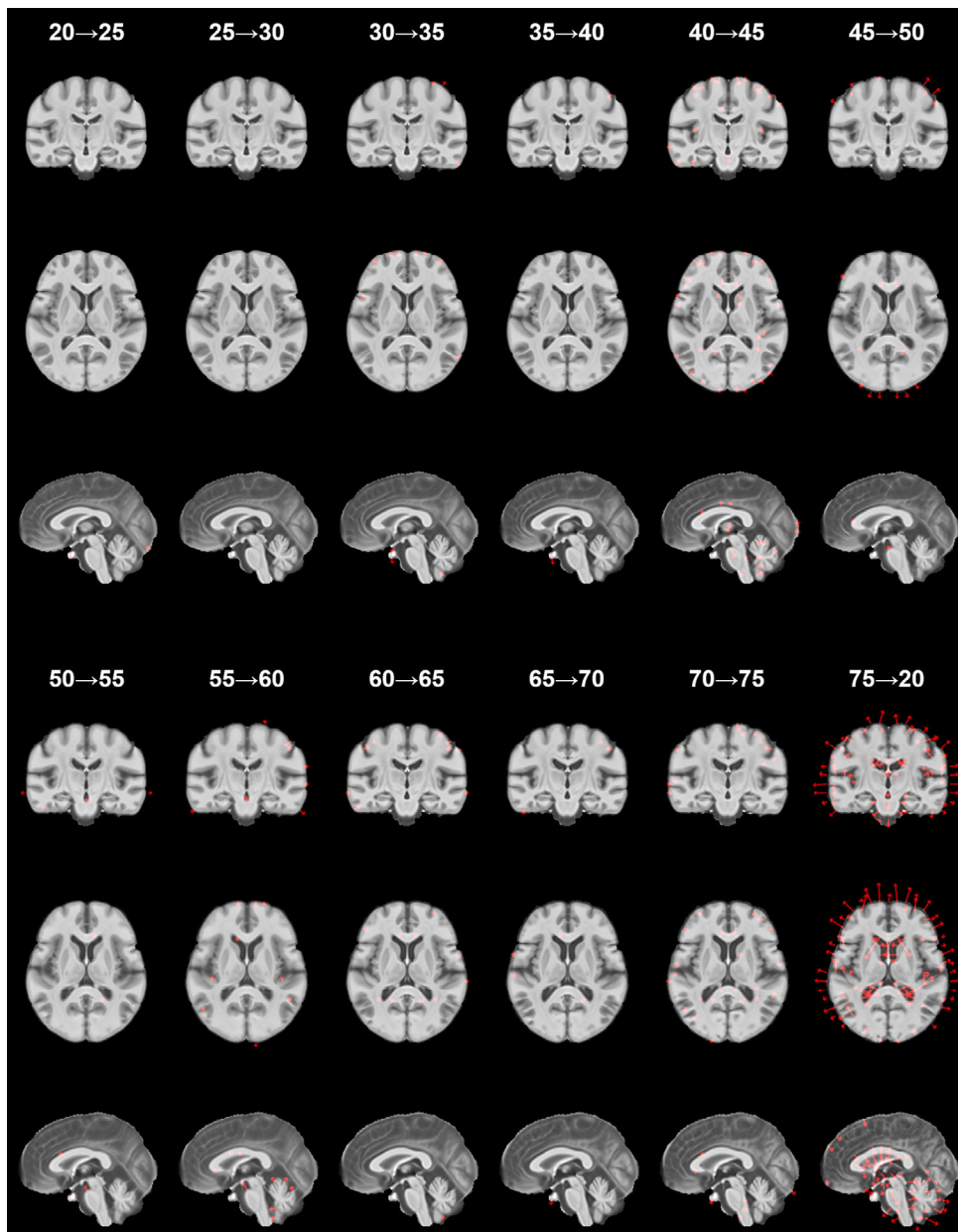
Figure 1A illustrated the constructed brain templates Chinese2020 used in our analysis, which has a total of 12 brain templates ranging from the age 20 to 75 at a 5-year interval. To observe the Chinese population-based brain deformation over the time course of aging, vector motion field and color motion field were computed using optical flow algorithm for all pairs of adjacent age groups. To summarize the results along all three axes, color motion field and motion vector field results at the cursor slice position (91, 109, 91) were shown in Figs. 2 and 3, respectively. In



**Fig. 1** The final Chinese brain template Chinese2020. (A) Templates for different age groups ranging from 20 to 75 years old. (B) Simulation cartoon of the aging course of a person.



**Fig. 2** Brain deformation in terms of color motion field in coronary, axial and sagittal views from the age 20 to age 75 using optical flow algorithm at the cursor slice position (91, 109, 91).



**Fig. 3** Brain deformation in terms of vector motion field in coronary, axial and sagittal views from the age 20 to age 75 using optical flow algorithm at the cursor slice position (91, 109, 91).

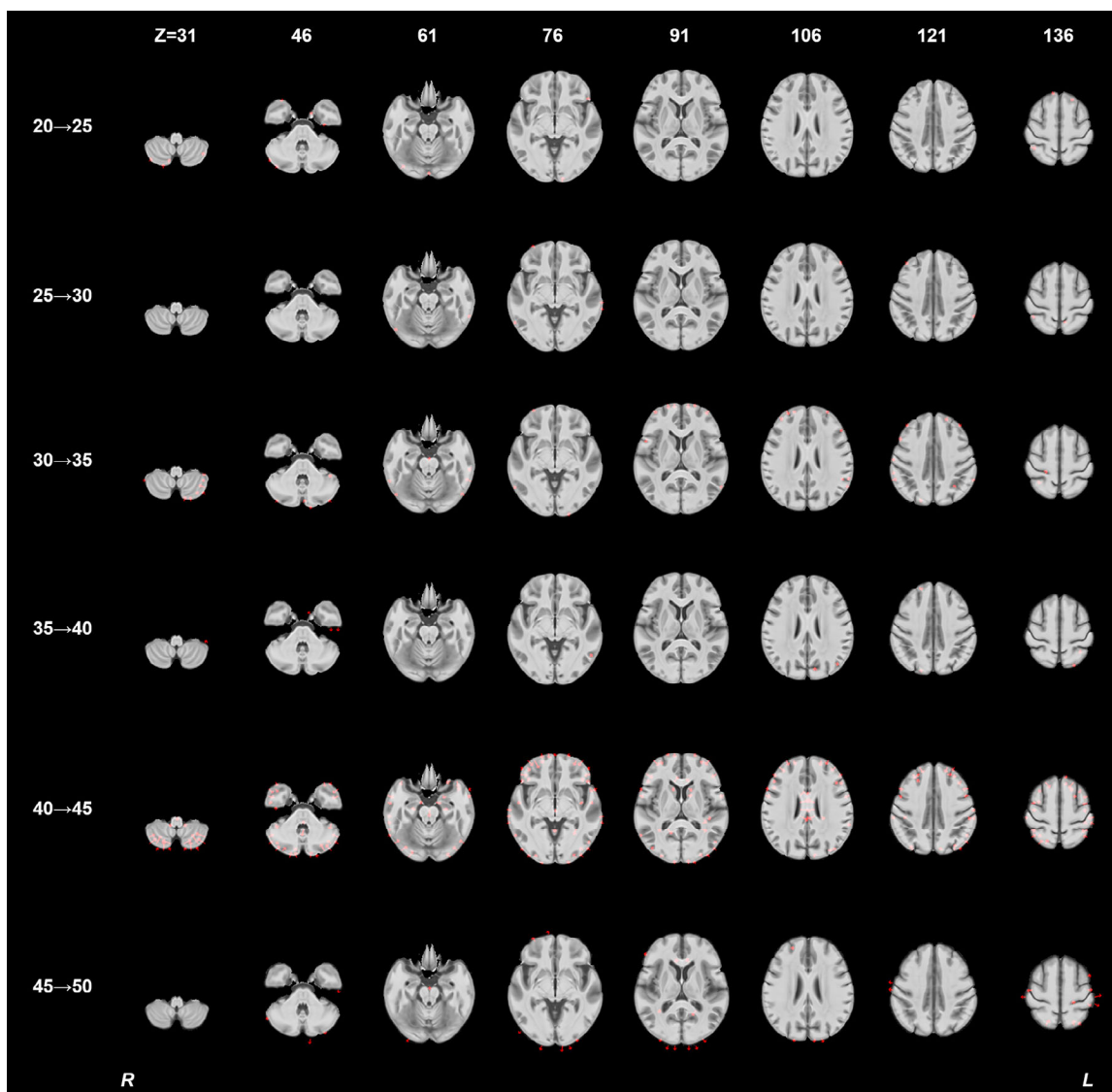
addition, a more detailed result from axial view at slice position  $Z = 31, 46, 61, 76, 91, 106, 121, 136$  was shown in Figs. 4 and 5, which depicts the brain deformation in terms of vector motion field from 20 to 50 years old and from 50 to 75 years old, respectively.

#### 4 Discussion

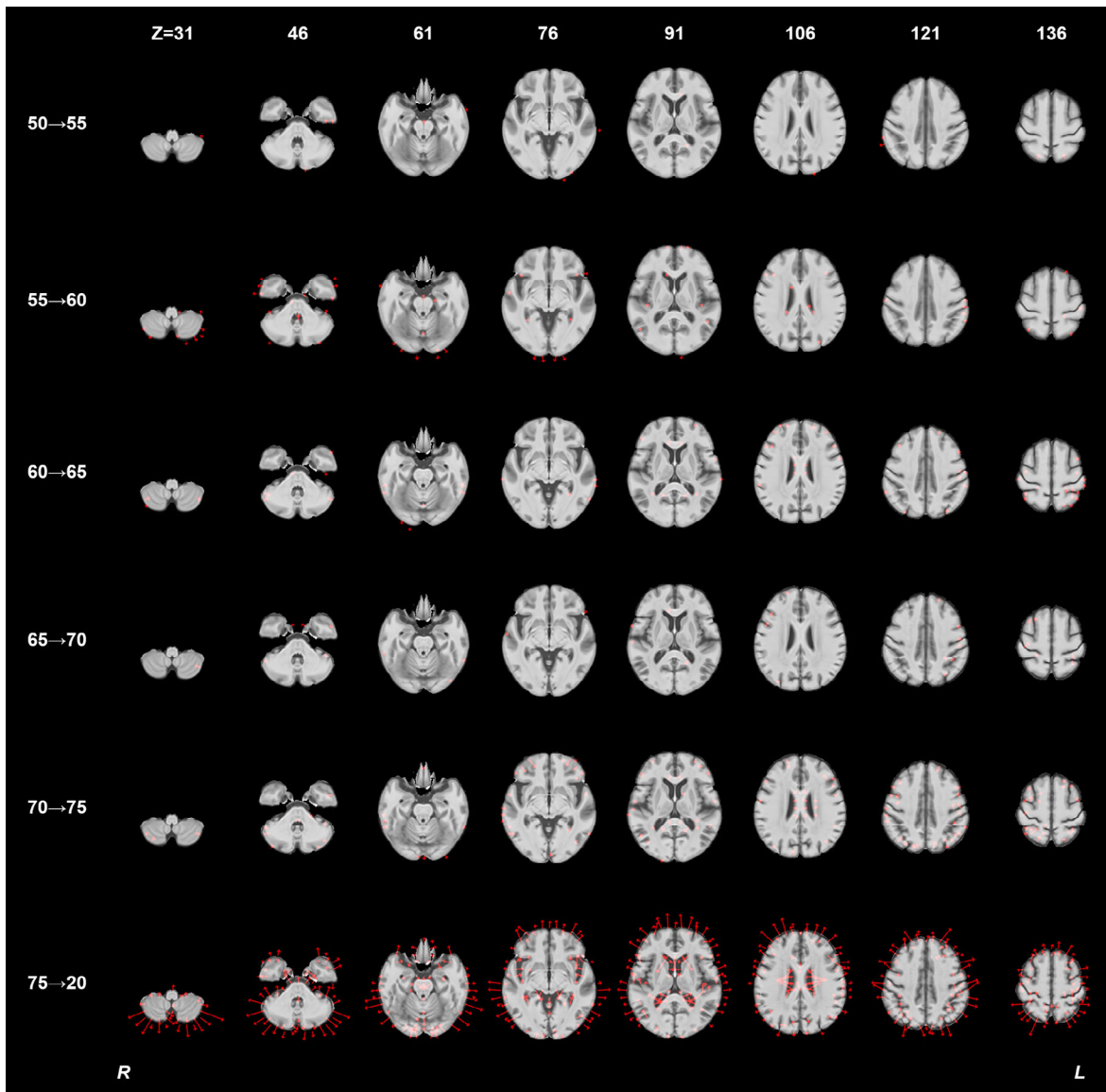
In this study, we provide a novel 4D visualization of the brain aging process across life span. This visualization is based on a standard tem-

plate space to portray convergent morphometric changes at population level, and a series of brain structural changes were found to be associated with advancing age.

Considering the weakness of the longitudinal data as addressed in introduction, the pseudo-longitudinal strategy may provide a more “flexible” visualization of brain aging changes. Based on the pseudo-longitudinal data, a spectrum of temporally continuous brain images can be reconstructed to approximate the real brain aging structural changes. In this manner, the temporal



**Fig. 4** Brain deformation in terms of vector motion field with more details in axial view from 20 to 50 years old using optical flow algorithm.



**Fig. 5** Brain deformation in terms of vector motion field with more details in axial view from 50 to 75 years old using optical flow algorithm.

details can be fully preserved. Besides, this visualization can reflect the average tendency of change at a population level and will not be biased toward individual variability, since it is in a standard template space based on a sufficiently large cohort. Moreover, except for some quantitative comparisons results which are usually the primary findings in longitudinal study, such as decreased grey matter volume, the pseudo-longitudinal visualization could present more geometric information related to brain aging.

The current knowledge on brain aging is still quite limited. From the temporal perspective, previous longitudinal studies of lifetime brain structure changes are comparatively rare. The longitudinal data set cannot address age-related brain differences spanning several decades [24], and the temporal resolution is quite limited since the data were usually collected in several scattered time points. From the spatial perspective, there have been evidences that age-related brain changes were not uniform across the hemisphere



and thought to be locally nonlinear [24], while most previous findings were based on the region-of-interest (ROI) analysis to emphasize the linear trends of changes, leaving the regional variability unexplored [5, 24]. Therefore, to preserve the full spatial and temporal information, in this study we provided a 4D description of age-related brain changes in a template space based on large-scale cross-sectional brain structural data. With this description, continuous and detailed changes can be presented in both domains of time and space.

Previous brain aging morphometric studies were generally confined within the quantitative findings such as decreased prefrontal grey matter volume, while some geometric features may be comparatively disregarded. Several interesting findings could be noticed based on our 4D visualization. When examining the vector motion field results generated from the optical flow algorithm in the axial plane (Figs. 4 and 5), deformation of anatomical structures is found to continue through adulthood and into old ages. For instance, brain inward deformation can already be seen during early adulthood (age 20–35). In particular, inward deformation during age 30–35 is relatively notable as compared to age 20–25 and age 25–30 in frontal cortex, temporal cortex, parietal cortex and cerebellum. In addition, ventricular outward deformation appeared to emerge in middle age (age 40–45, age 45–50, and age 50–55), and persist into old age (age 60–65, age 65–70, and age 70–75). Surprisingly, inward deformation of lateral ventricle, as well as outward deformation in cerebellum and occipital cortex can be observed during age 55–60. However, if we consider midlife (age 40–60) deformation as a whole, it still maintained an overall ventricular outward deformation and cerebellar inward deformation because the deformation in these two regions during age 40–45 has outweighed the opposing changes during age 55–60. As for

occipital cortex, it appeared to have greater outward deformation (age 45–50 and age 55–60) than inward deformation (age 40–45) in midlife. Moreover, we found that extensive brain inward deformation can already be observed during age 40–45 prior to older age transition during age 70–75, although brain inward deformation is still greater in late life when we examine the changes in longer duration (age 40–55 versus age 60–75). Overall, our results demonstrate that brain inward deformation can appear in adulthood and generally accelerate with increasing age, affecting multiple regions including frontal cortex, temporal cortex, parietal cortex, and cerebellum, whereas occipital cortex is least affected by aging and even showed some degree of outward deformation in midlife.

When comparing our findings to those of other studies, although it is widely pointed out that the parietal and occipital lobes are generally constant in the term of volume over life [3, 5, 25], our results have shown a prominent inward deformation in parietal cortex and a reciprocating deformation in occipital cortex at some point in the lifetime. This finding may be in line with the recently increasing interests on the age-related cortical complexity with more advanced morphometry measures [26–29], which indicated more complicated age-related changes instead of a general trend of decrease as suggested by volume. However, these previous studies may not cooperate well to provide consistent findings based on limited age window or small sample size, commonly tens of subjects. Further studies on the structural complexity of brain cortex may be investigated in future to add more novel findings.

On the other hand, it is noteworthy to mention that not all our deformation field results were indicative of the degree of brain atrophy, for the reason that large brain deformation alone is not a direct indicator for brain atrophy, where the

latter one involves an expansion in cerebrospinal fluid (CSF) relative to brain parenchyma. Thus, it could merely reflect the regional volume change if the deformation field is located within brain parenchyma (grey matter and white matter). In addition, the observations of brain changes in template level may also be confounded by the population distribution for constructing brain templates. Future longitudinal study could further investigate the finding of these pseudo-longitudinal results.

## 5 Conclusion

Our results implicated more complicated age-related brain structural changes rather than a general trend of decrease in volume alone, which may be consistent with recent studies on the age-related cortical complexity. Additional studies on longitudinal brain changes could further validate the results of this pseudo-longitudinal study. The potential impacts of this study lie in several aspects. First, investigation on the age-related brain morphological changes will help to answer the questions about how brain develops and degenerates. Besides, understanding how the brain structure changes in healthy individuals will help to provide a normal standard for future observing pathological changes of the brain. In summary, compared with previous static brain atlases, this work provides a time-varying reference that is more valuable and comprehensive to reflect the physiological aging process.

## Acknowledgments

The work described in this paper was supported by grants from the Innovation and Technology Commission (Project Nos. GHP-025-17SZ and GHP/028/14SZ) of the Hong Kong Special Administrative Region, Shenzhen Science and Technology Innovation Committee (Project No.

CYZZ20160421160735632), Beijing Nova Program (No. 2016000021223TD07), Capacity Building for Sci-Tech Innovation-Fundamental Scientific Research Funds (No. 19530050157, No. 19530050184), and the Beijing Brain Initiative of Beijing Municipal Science & Technology Commission.

## Conflict of Interests

Lin Shi is the director of BrainNow Research Institute. Yishan Luo is the R&D manager of BrainNow Research Institute. Andy Li is the research assistant intern of BrainNow Research Institute. Raymond Wong is the research assistant of BrainNow Research Institute. Lening Li is the director of Shenzhen SmartView MedTech Limited.

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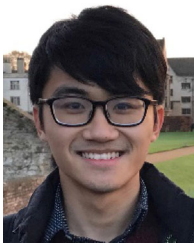
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