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The construction of MRI brain/head templates for Chinese children from 7 to 16 years of age

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ABSTRACT

Population-specific brain templates that provide detailed brain information are beneficial to both structural and functional neuroimaging research. However, age-specific MRI templates have not been constructed for Chinese or any Asian developmental populations. This study developed novel T1-weighted average brain and head templates for Chinese children from 7 to 16 years of age in two-year increments using high quality magnetic resonance imaging (MRI) and well-validated image analysis techniques. A total of 138 Chinese children (51 F/87 M) were included in this study. The internally and externally validated registrations show that these Chinese age-specific templates fit Chinese children's MR images significantly better than age-specific templates created from U.S. children, or adult templates based on either Chinese or North American adults. It implies that age-inappropriate (e.g., the Chinese56 template, the US20–24 template) and nationality-inappropriate brain templates (e.g., U.S. children's templates, the US20–24 template) do not provide optimal reference MRIs for processing MR brain images of Chinese pediatric populations. Thus, our age-specific MRI templates are the first of the kind and should be useful in neuroimaging studies with children from Chinese or other Asian populations. These templates can also serve as the foundations for the construction of more comprehensive sets of nationality-specific templates for Asian developmental populations. These templates are available for use in our database.

A brain MRI template provides a standard reference for assessment of brain structure and function (Ashburner and Friton, 1999; Roland and Zilles, 1994). Advances in understanding of the structure, function, and development of human brain would be facilitated with the availability of population-specific MRI templates in neuroimaging research. The most commonly used templates (e.g., the Talairach and Tournoux stereotaxic atlas, Talairach and Tournoux, 1988; the MNI-305, Collins et al., 1994; Joshi et al., 2004; the ICBM-152; Mazziotta et al., 2001) were created using adult participants from Western European or North American populations (see Mandal et al., 2012, for a review). These templates created with North American adult MRIs have been found to be inappropriate for use with brain images from children (see Richards and Xie, 2015 for a review). Tang et al. (2010) constructed the first average Chinese MRI template with 56 Chinese adult males. The Chinese adult brain template should not be recommended for use with Chinese children because using age-inappropriate MRI references would cause significantly more deformations of the brain tissues (Wilke et al., 2008; Yoon et al., 2009). Thus, the current study developed novel age-specific average MRI brain and head templates for Chinese children and adolescents spanning between 7 years and 16 years in 2-year intervals. We assessed whether registrations based on these Chinese age-specific templates would fit Chinese children's MR images significantly better than age-appropriate templates based on U.S. children, or adult templates based on either Chinese or U.S. adults.

Age-appropriate templates are recommended for scientific research targeted on developmental populations. Yoon et al. (2009) compared the tissue distributions obtained from normalizing an 8-year-old child's brain with an age-specific template (i.e., a template constructed based on 8-year-old children) and with an adult

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template. They found that normalization with the age-specific template led to significantly different tissue distributions than normalization with the adult template. Several brain and head MRI templates have been constructed based on North American pediatric populations ranging from infancy (e.g., Altaye et al., 2008; Shi et al., 2010, 2011; Sanchez et al., 2012b) to childhood and adolescence (e.g., Fonov et al., 2011; Sanchez et al., 2012a; Wilke et al., 2002, 2008), and over the entire lifespan (Richards et al., 2015; Richards and Xie, 2015). These age-specific templates were created to resolve the limitation of using adult references for brain images from pediatric populations.

It is important to use population-specific brain templates for MR images from Asian participants or patients. Significant differences have been shown between Caucasian and Asian brain features, such as size, shape, AC–PC distance, and brain structure volumes (Lee et al., 2005; Tang et al., 2010; Xie et al., 2014). Therefore, people have constructed average MRI templates for Chinese and Korean adults (Lee et al., 2005; Tang et al., 2010). Lee et al. (2005) found that a standard Korean brain template created based on Korean adults was 10% shorter in length, 9% shorter in height, and 1% greater in width compared to the ICBM-152 brain template. Similarly, Tang et al. (2010) found the Chinese adult template (Chinese56) created with 56 right-handed Chinese males was shorter in length and height and greater in width than the ICBM-152. Tang et al. (2010) also tested the registration of Chinese adults' MR images to the Chinese56 template in comparison with the ICBM-152 template. They found that use of the Chinese56 template led to significantly less deformation in shape and size than the ICBM-152 template. These studies imply that brain-imaging research with Chinese participants should consider using nationality-appropriate templates.

Differences in brain developmental trajectories have been found between Chinese and North American children and adolescents (Guo et al., 2007; Xie et al., 2014). Xie et al. (2014) compared brain development between Chinese and U.S. children from 8 to 16 years of age using structural MRI techniques. Results revealed both morphological and volumetric differences in brain development between these two nationalities. Chinese children's brains and heads were shorter in length and height and wider than those of U.S. children. Moreover, there were significant differences in cortical gray matter (GM) and white matter (WM) intensity between Chinese children and their U.S. peers. Developmental trajectories of cerebral volume, GM, and several key brain structures (e.g., fusiform gyrus, lingual gyrus, middle and superior temporal gyri, orbitofrontal gyrus, superior frontal gyrus) were also shown to be distinct between these two populations. A crucial implication of these findings is that brain and head templates created from North American children are not representative of Asian developmental populations. It has been found that the use of the ICBM-152 template with Chinese adults led to significantly greater deformation and reduced consistency compared with the use of a nationality-specific template (Tang et al., 2010). It is very likely that the use of templates created from North American children with MRIs of Chinese children will lead to the similar consequences. Therefore, the creation of age-specific templates for Asian infants, children, and adolescents would be necessary for research examining brain anatomy and activation in these pediatric populations and in facilitation of accurate medical diagnoses.

The current study was designed to create Chinese age-specific MRI brain templates used for scientific research with Chinese pediatric populations. We constructed five sets of T1-weighted average MRI brain and head templates for Chinese children and adolescents spanning 7–16 years of age. We constructed the templates in two year increments for five different age groups: 7–8 years, 9–10 years, 11–12 years, 13–14 years, and 15–16 years. Methods for template construction (e.g., nonlinear registration and transformation, iterative routines) that have been utilized and proven by others (Fonov et al., 2011; Sanchez et al., 2012a,b) were used to guide the current study. We assessed whether registrations based on these Chinese age-specific templates would fit Chinese children's MR images significantly better than nationality-inappropriate templates based on U.S. children, or adult templates based on either Chinese or U.S. adults. We predicted that the use of Chinese age-specific templates with Chinese children's MRIs would result in significantly less deformation and more consistency between original and transformed images than the use of other age- or nationality-inappropriate templates.

Table 1
Demographic Information for the Five Chinese Age Groups.

Group name	Age range	Total N	Gender (#female)
Chinese8Years	7–8	20	3
Chinese10Years	9–10	22	4
Chinese12Years	11–12	37	13
Chinese14Years	13–14	39	18
Chinese16Years	15–16	20	13
Total		138	51

1. Materials and methods

1.1. Participants

The MR images for the average MRI templates were collected from 138 children and adolescents ranging from 7 through 16 years of age (51 F/87 M). Participants were recruited from the local community in Chengdu, Sichuan province, China. They were scanned in the Huaxi MR Research Center (HMRRC) at the West China Hospital of Sichuan University. A multidisciplinary team, comprised of psychiatrists, neurologists, psychologists, and radiologists, examined the participants. Individuals were excluded if they had a history of neurological or psychiatric disorders, current or past substance abuse or psychoactive drugs. The MRI images were evaluated by a neuroradiologist as showing no reportable neurological abnormalities. Participants were divided into five age groups by two year increments and each group was labeled with the older age in the interval: Chinese 8 (7–8 years), 10 (9–10 years), 12 (11–12 years), 14 (13–14 years), and 16 (15–16 years). Two-year increments were chosen based on developmental changes documented in a study with Chinese children and adolescents that also utilized two-year intervals (Xie et al., 2014). These time windows also allowed us to achieve sufficient numbers in each age group while minimizing variability associated with age. See Table 1 for more detailed participant information including the number of subjects in each age group and gender.

Age-related U.S. child templates used for comparison were created from images that were collected at the McCausland Center for Brain Imaging (MCBI; Sanchez et al., 2012a) and matched-age, M/F control participants from the Autism Brain Imaging Data Exchange database (ABIDE; Di Martino et al., 2014). There were five age-related templates for 8, 10, 12, 14, and 16 years, respectively. All U.S. participants were healthy, without a history of previous neurological or psychiatric illness. A summary of these U.S. participants and databases could be found in Richards and Xie (2015) and Richards et al. (2015).

The Institutional Review Board (IRB) of West China Hospital in Sichuan University and University of South Carolina approved this study and the MRI scanning with children and adolescents. A consent form to obtain written consent from participants' parent(s) on behalf of the children and adolescents enrolled was proposed and approved by the IRB, together with the study protocol. The written consent form was obtained from all of the parent(s) on behalf of the children and adolescents enrolled in this study.

We randomly selected two males and two females from each Chinese group (i.e. 20 subjects in total were selected) as "external test" participants. Two healthy males and two females were randomly selected from the ABIDE database at each age as U.S. external participants. Their brain images were not included in the construction of the U.S. templates.

1.2. MRI data acquisition

The Chinese children's MRIs were collected from two MRI scanners in an MR research center affiliated with a university, located in a midwestern province of China. The majority of the subjects ($N = 113$) were scanned using a 3.0 T Siemens Trio Scanner. High-resolution 3-dimensional T1-weighted images were acquired using a MPRAGE sequence with the following parameters: TR/TE/TI = 1900/2.26/900 ms, Flip angle = 9°, 176 axial slices with thickness = 1 mm, axial FOV = 25.6 cm × 25.6 cm and data matrix = 256 × 256. The remaining 25 subjects were scanned with a 3.0T GE SIGNA MRI scanner. High-resolution 3-dimensional T1-weighted images were acquired using a spoiled gradient recalled (SPGR) sequence with the following parameters: TR/TE = 8.5/3.4 ms, Flip angle = 12°, 156 axial slices with thickness = 1 mm, axial FOV = 24 cm × 24 cm and data matrix = 512 × 512. These 25 subjects' scans were transformed to 1 mm × 1 mm × 1 mm isotropic resolution. Thus, all Chinese MRIs had 1 mm × 1 mm × 1 mm isotropic resolution.

The age-related U.S. children's MRI data was collected at the MCBI on a Siemens Medical System 3T Trio with a 3D T1-weighted MPRAGE RF-spoiled rapid flash scan in the sagittal plane with the following parameters: TR = 2,250 msec, TE = 4.52 ms, flip angle = 9°, FoV = 256 mm × 256 mm, matrix size = 1 mm × 1 mm × 1 mm (the sagittal dimension of the T1W ranged from 160 to 212 slices). The scans had sufficient FoV to cover from the top of the head down to the neck. More information about the MRI acquisition procedures can be found in Sanchez et al. (2012a); also see Richards and Xie (2015) and Richards et al. (2015). The ABIDE files came from the LONI site (loni.UCLA.edu) in compressed NIFTI format. They were done as MPRAGE scans, on a 3.0 T strength scanner, with slice thickness of 1.0–1.3 mm and sufficient FoV to cover down to the bottom of the brain (Di Martino et al., 2014). The MR images of the U.S. children from both the MCBI and ABIDE datasets were 3.0 T scans with high image quality. The combination of these images has been used to create age-appropriate templates for U.S. children (Sanchez et al., 2012a; Richards et al., 2015).

1.3. File preparation

The MR images were prepared for processing in three steps. First, the brains were extracted from the whole-head MRI volume using FSL computer programs. An automated batch script using FSL tools (Smith et al., 2004; Woolrich et al., 2009) completed this task with the following actions: registered the head to the ICBM-152 head template; transformed the ICBM-152 brain mask inversely to the participant space; used this mask to get a preliminary brain; used betsurf to get a binary skull mask; used the skull mask to delineate a second preliminary brain; used bet2 to extract the brain from the second preliminary brain mask for the final brain (Jenkinson et al., 2005). The use of betsurf and bet2 together followed standard FSL procedures. Each brain image was visually inspected for accuracy and some of the bet2 variables (e.g., fractional intensity threshold) were adjusted in order to get a well-formed brain volume (Jenkinson et al., 2005). Second, the individual participant MRI volumes were classified into GM, WM, and CSF. The FSL FAST (Zhang et al., 2001) procedure was used to segment the T1W scans without prior classification volumes. This method resulted in a set of partial volume estimates (PVE) of GM, WM, and CSF, for each participant's MRI volume. Third, we adjusted intensity variations that occur in the MRI scans. Bias field inhomogeneity was corrected with a N4 bias field correction procedure (Avants et al., 2011; Tustison et al., 2010). The MRI voxels with partial volume estimates of 1.0 in the GM segments were averaged to determine the average voxel intensity for GM. The scan was then renormed with this value to have a value of 100. Therefore, the GM intensity had an average value of 100 for all MRIs. Identical procedures were used in Sanchez et al. (2012a,b).

1.4. Construction of age-specific templates

Chinese age-specific MRI average templates were constructed with the iterative routines used in Sanchez et al. (2012a,b); also see Fonov et al. (2011), Yoon et al. (2009), and Guimond et al. (2000), for examples of similar iterative routine). The whole-head and brain-extracted MRI volumes were performed separately to provide both head and brain templates. Both linear and nonlinear registrations were used in the construction of templates for one age-specific group. The steps used in the construction of a template (brain or head) for one age-specific group are illustrated in Fig. 1. The initial step of the iterative procedure was to construct a tentative average (Fig. 1, "A_0") based on a rigid rotation (FLIRT 6 parameter linear registration and transformation; Jenkinson and Smith, 2001) to the MNI-152 adult template (ICBM-152 defined in Joshi et al., 2004; Mazziotta et al., 2001). Each participant's original MRI was then non-linearly registered to this tentative average template ($\mathbf{A_0}$) and transformed in size and orientation using the "Advanced Normalization Tools" (ANTS; Avants et al., 2008, 2011). The registered/transformed MRI images were averaged to get the A_n template. This template (A_n) then became the next reference template for the registration. This average procedure was iteratively applied separately for each of the study ages, and separately for the head and brain volumes. A gross resolution (50 × 0 × 0) with 50 steps maximum at 8 mm resolution began the first non-linear template registration. The second non-linear step was with 4 mm medium resolution (50 × 50 × 0 iterations), and the final steps with 1 mm fine resolution (50 × 50 × 50). The root mean square (RMS) difference between intensity values of successive average reference models (e.g., A_2 vs A_1; A_3 vs A_2) was calculated. The iterative procedure was finished until the successive RMS values reached and stayed a minimum. Information regarding the outcome of the iterative process for templates construction is shown in Supplemental Fig. 1, which illustrates the change in age-specific template fits with each successive iteration. The final reference model is the "age-specific" template.

1.5. Comparison of image registrations using different brain templates

We compared the consistency of brain morphological features between the original MR images of children participants and the transformed images after the registration to these four types of templates: (1) nationality-appropriate child template; (2) nationality-inappropriate child template; (3) Chinese56 adult template; (4) US20–24 adult template. We used Tang et al. (2010) procedure and calculated morphological features (length, width, height, width/length, height/length, width/height) on the original MRI brain images, and on transformed images. This comparison shows the size of the transformation needed to modify the original MR into the template space. The FSL procedure, fslstats (FSLUTILS, Smith et al., 2004; Woolrich et al., 2009), was used to find the minimum ROI surrounding the brain for the original MRI and the four transformed brains. The measures of length, width, and height came from the ROI size (cf procedure in Tang et al., 2010).

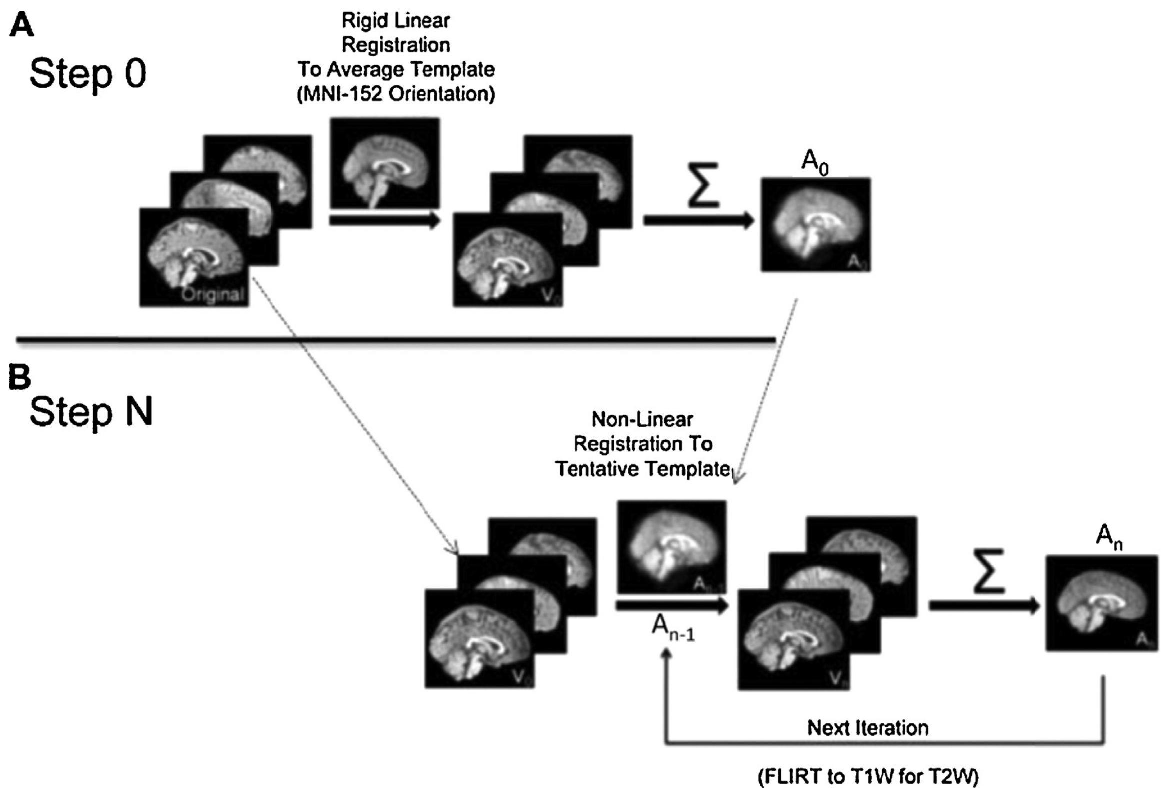

Fig. 1. The pipeline for age-specific template creation. (A) In Step 0, the rigid registration occurred using FLIRT (Jenkinson and Smith, 2001) to the MNI brain with 6 DOF, with an output that was the same volume size as the original. Rigidly registered brains (V_0) were averaged to create a rough template (A_0). This template was used as the first guide in Step N. (B) With each iteration of Step N, the rigidly registered brains were nonlinearly registered to an iterative average (A_{n-1}) and transformed and then averaged to create a new average (A_n) for the next iteration.

The consistency tests were done separately for internal and external test participants. For the internal tests, the MRI images making up the Chinese and U.S. (MCBI; Sanchez et al., 2012a) templates were registered into those four types of brain templates using the linear (12-dof Affine) transformation. In the external consistency test, we only tested Chinese external participants. Test brain templates were created with the same average procedures used to create the Chinese age-specific templates, but without the external test participants.

We also compared the characteristics of the linear and non-linear registration results, suggesting the changes of brain images occurred during these registration processes. First, we examined the sagittal, coronal, and axial scale values obtained from the linear (12-dof affine) registration process to estimate the changes of the brain shape and size during the registration. The values centered at 1.0 and represent the amount of linear change needed to transform the participant MRI into the average MRI template for that dimension (e.g., sagittal, coronal, or axial). Second, we examined the deformation/warp parameters obtained from the non-linear (ANTS) registration process by summing the sagittal, coronal, and axial distances found in the deformation matrices. This sum quantifies the amount of displacement needed to move a voxel location from the original MR image to the average MRI template to meet the registration criteria. These assessments of the linear and non-linear registration process were performed with both internal and external participants.

1.6. Comparison of tissue segmentation using different brain templates

We evaluated the impact of using nationality-appropriate brain templates on segmentation by doing tissue segmentation for Chinese participants using Chinese or U.S. child templates for priors. The brain images of the Chinese participants were registered with non-linear methods to the age-appropriate Chinese and U.S. child templates. The average segmented priors from the average MRI templates (Richards et al., 2015; Richards and Xie, 2015) were transformed to the participant space and used as priors for two widely used software tools, the FSL FAST (Zhang et al., 2001) and the SPM Unified Segmentation (Ashburner and Friston, 2005). The resulting segmented volumes were then used in a voxel-based volumetric analysis for the Chinese participants across ages. We evaluated the effect of using nationality-appropriate and nationality-inappropriate templates on the volumetric changes of GM and WM over development. Note that these methods are similar to those used in Xie et al. (2014) to analyze Chinese and U.S. child volumetric development.

1.7. Statistical methods

Mixed-design ANOVAs were performed for the statistical analyses of these data. Age and nationality were analyzed as between-subject variables while the type of reference templates used for registration was analyzed as a within-subject variable. Multiple comparisons and post hoc tests were Bonferroni corrected.

2. Results

2.1. Novel MRIs database created for Chinese developmental populations

The database consists of five age-specific MRI templates for Chinese children from 7 to 16 years of age in two year increments, with both T1W brain and head templates included. They are

Table 2
Comparison of the morphological features (length, width, height, W/L, H/L, and H/W) between the U.S. and Chinese children templates.

Measurement	Age	U.S. templates	CN templates	U.S. minus CN
Length (mm)	8	163	154	9
	10	168	154	14
	12	168	168	0
	14	171	166	5
	16	169	159	10
Width (mm)	8	133	138	−5
	10	129	140	−11
	12	134	138	−4
	14	131	140	−9
	16	131	134	−3
Height (mm)	8	132	131	1
	10	132	134	−2
	12	130	143	−13
	14	136	142	−6
	16	132	131	1
W/L	8	0.82	0.9	−0.08
	10	0.77	0.91	−0.14
	12	0.8	0.82	−0.02
	14	0.77	0.84	−0.07
	16	0.78	0.84	−0.06
H/L	8	0.81	0.85	−0.04
	10	0.79	0.87	−0.08
	12	0.77	0.85	−0.08
	14	0.8	0.86	−0.06
	16	0.78	0.82	−0.04
H/W	8	0.99	0.95	0.04
	10	1.02	0.96	0.06
	12	0.97	1.04	−0.07
	14	1.04	1.01	0.03
	16	1.01	0.98	0.03

loosely oriented to the ICBM-152 volume. Partial volume estimates and binary-segmented images were also created for each template using the FSL FAST (Zhang et al., 2001) segmentation method. These Chinese age-specific templates represent the average brain and head size for each age group.

Mid-sagittal and axial slices for each age-specific T1W brain and head templates are respectively demonstrated in Figs. 2 and 3. These two figures also include the Chinese56 and the US20–24 adult templates for comparison. The axial slices are at the AC–PC level for each age-specific T1W brain and head. The cortical and subcortical anatomy is pictured in both figures. All templates appear to be consistent in regards to level of detail and clarity. The gradual change in head and brain sizes is noticeable, and they appear to be smaller than the Chinese56 adult templates.

Chinese child templates created in the current study showed different global features than the age-related U.S. templates. Table 2 shows the comparison of the global features between the Chinese and U.S. (Sanchez et al., 2012a) children templates. The Chinese child templates were shorter, wider, and higher than the U.S. age-related templates. In addition, Chinese and U.S. child templates showed different 3-dimentinal ratios (W/L, H/L, and H/W). The ratios of width:length and height:length of the Chinese child templates were closer to one than those of the U.S. child templates. It means that the shape of the Chinese templates is more spherical (i.e., rounder) than the U.S. templates.

The results of GM tissue classification for these age-specific Chinese templates are shown in Fig. 4. The axial slices are demonstrated at the AC–PC level. The GM is shown bright and the relative dark regions consist of WM and other matters (e.g. the CSF).

2.2. Comparison of the consistency between original and transformed images

We compared the consistency of brain shape and size between the original brain images to four different types of average templates including the nationality-appropriate child templates, nationality-inappropriate child template, Chinese56 adult template, and the US20–24 adult template. In the internal test, mixed-design ANOVAs were performed to analyze the morphological characteristics (length, width, height) as a function of template/reference type and age for Chinese and U.S. participants. Results showed a significant main effect of template type on the transformed brain length (F (3, 400) = 5563.95, $p < .0001$), width (F (3, 400) = 8373.11, $p < .0001$), and height (F (3, 400) = 1424.69, $p < .0001$) for the Chinese participants. For the U.S. participants, there was also a main effect of template type on transformed brain length (F (3, 135) = 2579.91, $p < .0001$), width (F (3, 135) = 3931.42, $p < .0001$), and height (F (3, 135) = 1976.22, $p < .0001$). Multiple comparisons (Bonferroni corrected) showed the differences between these characteristics of transformed images and those of the original images. Table 3 shows the results from these comparisons. As expected from the construction of the average MRI, the participant and their age-appropriate/nationality-appropriate template was non-significantly different in all cases. Conversely, the nationality-inappropriate templates and the adult templates were significantly different in nearly all cases for the Chinese children participants. Larger changes in brain size were required to register the Chinese or U.S. children's images into the nationality-inappropriate child templates or adult templates.

We examined the same consistency tests for the external test participants. A mixed-design ANOVA was performed to analyze 6 characteristics as a function of template type and age for Chinese external participants. There was a significant main effect of template type on brain length (F (3, 45) = 719.44, $p < .0001$), width (F (3, 45) = 1021.75, $p < .0001$), height (F (3, 45) = 158.51, $p < .0001$), width:length (F (3, 45) = 461.36, $p < .0001$), height:length (F (3, 45) = 468.81, $p < .0001$), and height:width (F (3, 45) = 93.96, $p < .0001$). Table 4 includes the difference between the original participant MRI and the four transformed MRIs, collapsed over age. There was a difference in length between the Chinese test participants and the Chinese children templates, otherwise, these size parameters were not significantly different. Conversely, the original participant MRI was significantly different from the U.S. child template, the Chinese56 template, and US20–24 template, for nearly all features. Moreover, the transformed brain images of the Chinese test participants into the U.S. (child and adult) templates were greater in length, and smaller in width and height compared with their original brain images (Table 4), suggesting that the Chinese children's brain may be generally shorter, wider, and taller than the U.S. child and adult templates created from North U.S. populations. Registration using the Chinese56 adult template as the reference, however, led to the expansion of the original images in the coronal (length) and sagittal (width) directions. The ratios of width:length, height:length, and height:width were also significantly different between the original images and the registered images into the age- or nationality-inappropriate templates, meaning the shape of the brain differed between the Chinese participants' brain and the U.S. children and both adult templates.

2.3. Comparison of the linear registration parameters

We assessed the scale values that represent the change of shape and size in the original images that occurred in the linear (12-dof Affine) transformation process. Fig. 5 shows the mean scale values for both Chinese and U.S. participants after registration to the nationality-appropriate and nationality-inappropriate brain

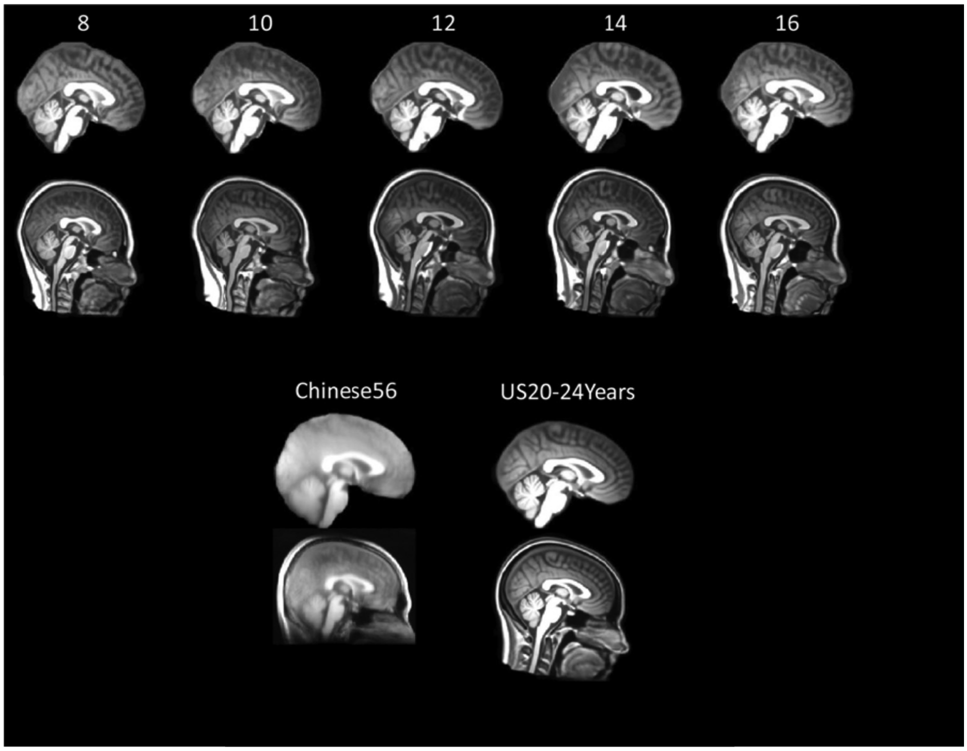

Fig. 2. Sagittal slices for the Chinese children brain and head templates.

templates in the internal validation tests. The average values were close to 1.0 across the five groups for registering the participant's brain image to its nationality-appropriate template (i.e., Chinese children to Chinese age-specific brain templates, U.S. children to U.S. age-specific templates). In contrast, the values for registration with nationality-inappropriate brain templates were significantly different from 1.0 for all three dimensions across all five age groups. The sagittal scale had to be decreased for the Chinese participants to

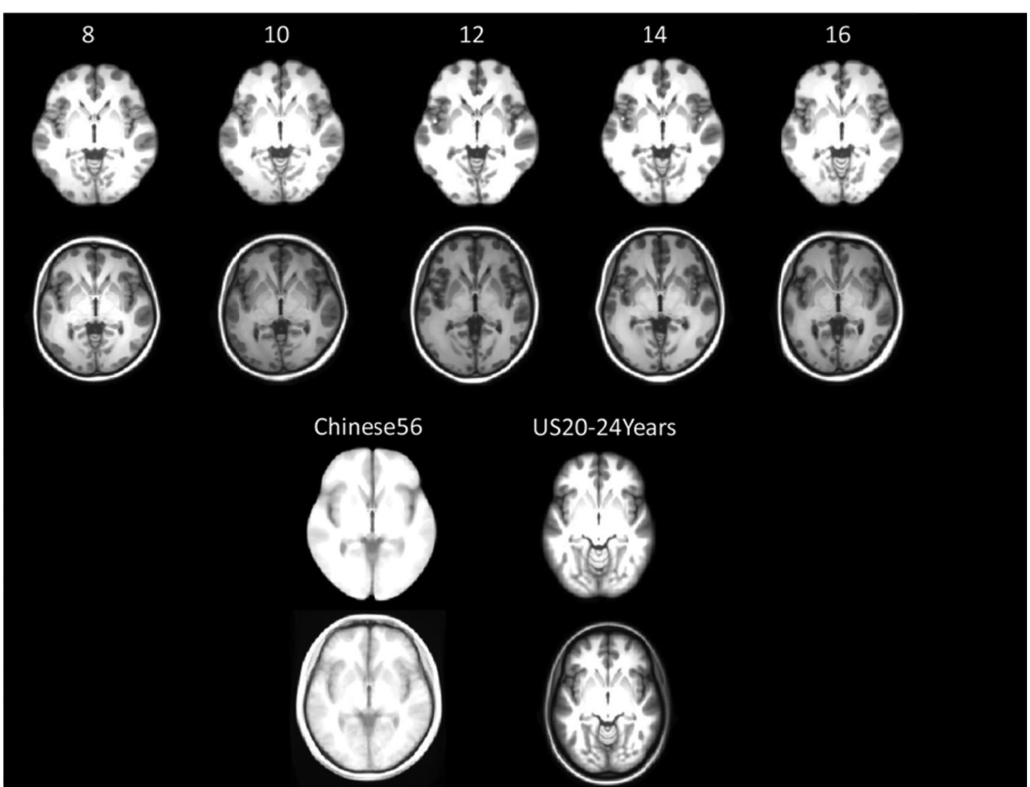

Fig. 3. Axial slices for the Chinese children brain and head templates.

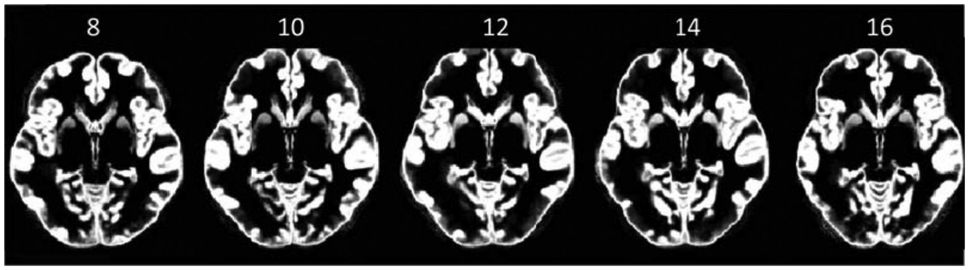

Fig. 4. Gray matter tissue classification for the age-specific Chinese templates.

Table 3
Internal test: comparison of brain morphological characteristics (length, width, and height) between registering the images of the internal subjects separately into the nationality-appropriate child templates, the nationality-inappropriate child templates, the Chinese56 adult template, and the US20–24 adult template using a 12-parameter transformation.

Nationality of participants	Measurements and age	Original images (OIs) (M ± S.D.)	Registered to nationality appropriate children templates (CN to CN, US to US)	Registered to nationality inappropriate children templates (CN to US, US to CN)	Registered to the Chinese56	Registered to the US20–24
	Length					
	8	164.3 ± 4.62	164.40	**178.25*****	**184.00*****	**176.75*****
	10	167.82 ± 7.01	169.41	**177.22*****	**185.05*****	**177.22*****
Chinese	12	171.27 ± 5.82	170.92	**179.35*****	**183.62*****	**176.43*****
	14	171.15 ± 5.89	171.90	**178.97*****	**183.38*****	**176.00*****
	16	168.9 ± 6.29	169.50	**177.45*****	**184.10*****	**176.70*****
	8	177.9 ± 6.01	178.00	**164.60*****	**184.00***	176.30
	10	175.70 ± 9.03	175.00	168.10	**182.30***	175.60
U.S.	12	173.90 ± 7.99	175.70	169.40	**182.20****	173.90
	14	174.50 ± 11.74	178.00	171.30	**182.50****	175.20
	16	176.50 ± 5.30	175.00	**167.40***	**182.10***	174.30
	Width					
	8	146.45 ± 4.98	147.05	144.10	**155.10*****	**135.00*****
	10	147.45 ± 4.38	149.14	**132.09*****	**155.14*****	**134.91*****
Chinese	12	145.57 ± 5.18	145.65	**136.22*****	**155.35*****	**134.76*****
	14	145.08 ± 5.40	145.21	**134.92*****	**155.36*****	**134.97*****
	16	143.35 ± 6.52	143.45	**133.65*****	**155.70*****	**135.15*****
	8	139.6 ± 4.51	148.00	**152.00****	**162.40*****	139.30
	10	143.1 ± 7.65	133.70	**151.00*****	**158.00*****	137.10
U.S.	12	137.4 ± 4.19	138.20	**149.50*****	**159.60*****	137.70
	14	139 ± 8.76	138.20	**149.60****	**160.60*****	138.30
	16	140.9 ± 3.74	135.70	**148.40*****	**160.60*****	137.60
	Height					
	8	139.90 ± 4.76	140.15	139.55	142.65	**131.45*****
	10	140.95 ± 3.20	141.27	**131.87*****	142.95	**132.87*****
Chinese	12	141.22 ± 5.18	141.84	139.00	142.81	**133.05*****
	14	142.41 ± 5.92	144.00	**137.56*****	144.31	**134.26*****
	16	141.55 ± 5.37	141.80	**137.15****	**146.65*****	**136.20*****
	8	139.3 ± 3.27	141.10	141.40	142.60	**132.80***
	10	135.50 ± 7.79	130.90	140.70	**142.30***	131.30
U.S.	12	137.10 ± 4.28	138.00	142.30	143.30	132.80
	14	139.40 ± 2.41	139.50	**145.60***	**146.20***	134.70
	16	139.10 ± 8.39	136.00	141.60	**146.00***	134.90

Significant differences are bolded. $^{*}p < 0.05$, $^{**}p < 0.01$, $^{***}p < 0.001$.

Table 4
External test: comparison of brain morphological differences between registering the 20 external subjects separately into the Chinese children templates, the U.S. children templates, the Chinese56 adult template, and the US20–24 adult template using a 12-parameter transformation.

Measurements	Original images (OIs) $N = 20$ (M ± S.D.)	Registered to Chinese children templates (Diff to OIs, *p* value)	Registered to U.S. children templates (Diff to OIs, *F* value)	Registered to the Chinese56 (Diff to OIs, *F* value)	Registered to the US20–24 (Diff to OIs)
Length	166.35 ± 5.97	**3.15***	**12.00*****	**17.75*****	**10.30*****
Width	144.25 ± 5.23	1.95	**−8.40*****	**11.25*****	**−9.15*****
Height	140.75 ± 4.94	1.10	**−4.10****	2.40	**−7.70*****
W/L	0.87 ± 0.04	−0.01	**−0.11*****	**−0.03***	**−0.11*****
H/L	0.85 ± 0.03	−0.01	**−0.08*****	**−0.07*****	**−0.10*****
H/W	0.98 ± 0.04	−0.01	**0.03*****	**-0.06*****	0.01

The values in the last four columns show the differences/changes between the registered brain images and original brain images. Significant differences are bolded. $^{*}p < 0.05$, $^{**}p < 0.01$, $^{***}p < 0.001$.

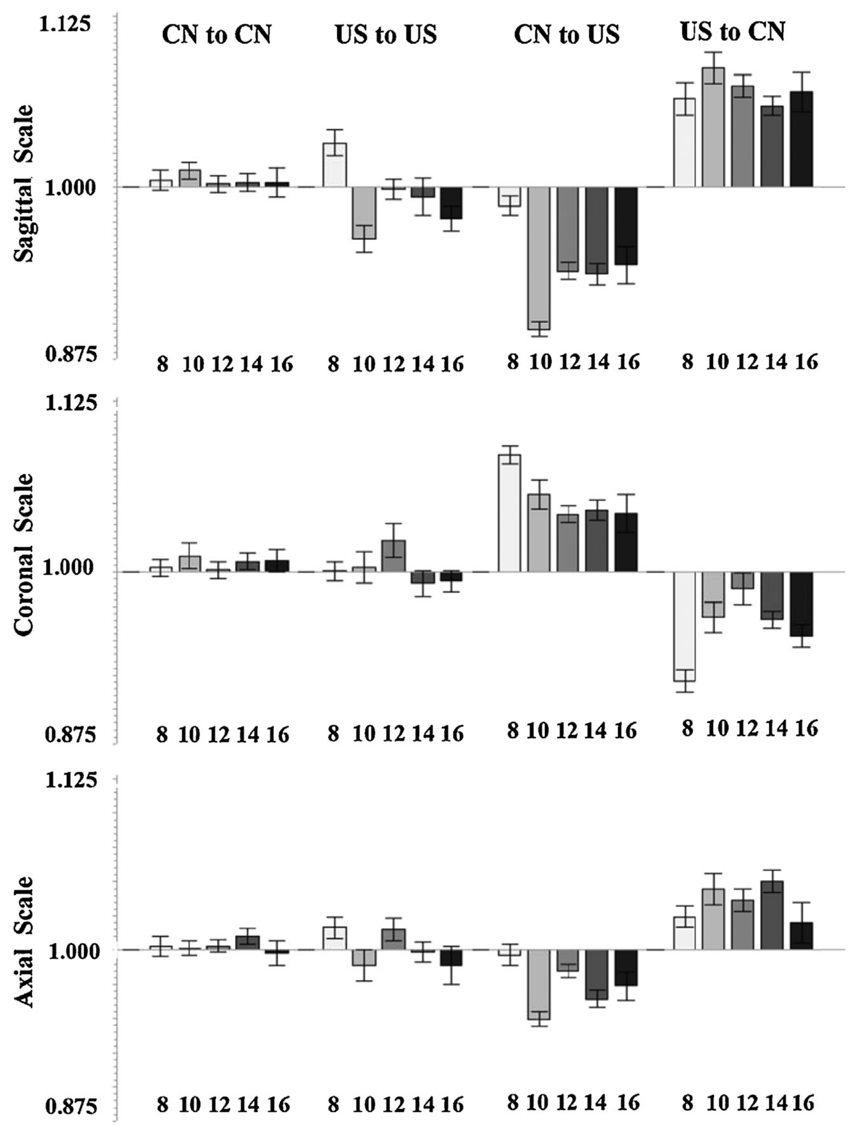

Fig. 5. Sagittal, coronal, and axial scale parameters for linear registrations for age-appropriate and within-nationality (CN to CN: Chinese participants to Chinese template; US to US: US participants to US templates) or cross-nationality (Chinese participants to US templates; US participants to Chinese template) registrations.

fit the U.S. child templates, whereas the opposite pattern of change was necessary for the U.S. participants to fit the Chinese child templates (Fig. 5). This indicates that the Chinese participants' brains were wider than the U.S. templates, whereas the U.S. participants' brains were narrower than the Chinese templates. The change of coronal scale was in the opposite direction, suggesting that Chinese children's brains were shorter than the U.S. child templates, and U.S. children's brains were longer than the Chinese child templates.

The comparisons for linear and non-linear registration were done with the external test sample. The external test samples were Chinese and US children registered to MRI templates for which they were not included in the construction (external validation). The values were examined using ANOVA's that included age (5: 8, 10, 12, 14, 16), match (2: participant-nationality-match, participant-nationality-mismatch), and nationality (2: U.S., Chinese) as factors. There was a main effect of nationality for all three directions. There was a significant interaction between nationality and match for the sagittal direction (F (1, 30) = 93.63, p < .0001), coronal direction (F (1, 30) = 99.94, p < .0001), and the axial direction (F (1, 30) = 117.99, p = .0075). Fig. 6 shows the values from registration of the Chinese and U.S. children's brain images into nationality matched and mismatched brain templates and depicts the findings of the interaction by showing greater accuracy during registration to nationality-matched templates for both Chinese and U.S. children and the opposite pattern for registration between the two nationalities.

2.4. Comparison of the non-linear registration parameters

We assessed the deformation/warp value obtained from the non-linear (ANTS) registration. Chinese and U.S. children's average deformation values for the non-linear registration in the internal tests are shown in Fig. 7. It shows the comparison of the average amount of deformation required in the registration of their brain images into the nationality appropriate (i.e. matched) and inappropriate (i.e. mismatched) templates. The value for the nationality-matched template was significantly smaller than the mismatched template for Chinese and U.S. participants across the five ages, which indicates that more volumetric deformations were required during registration into a nationality-mismatched template.

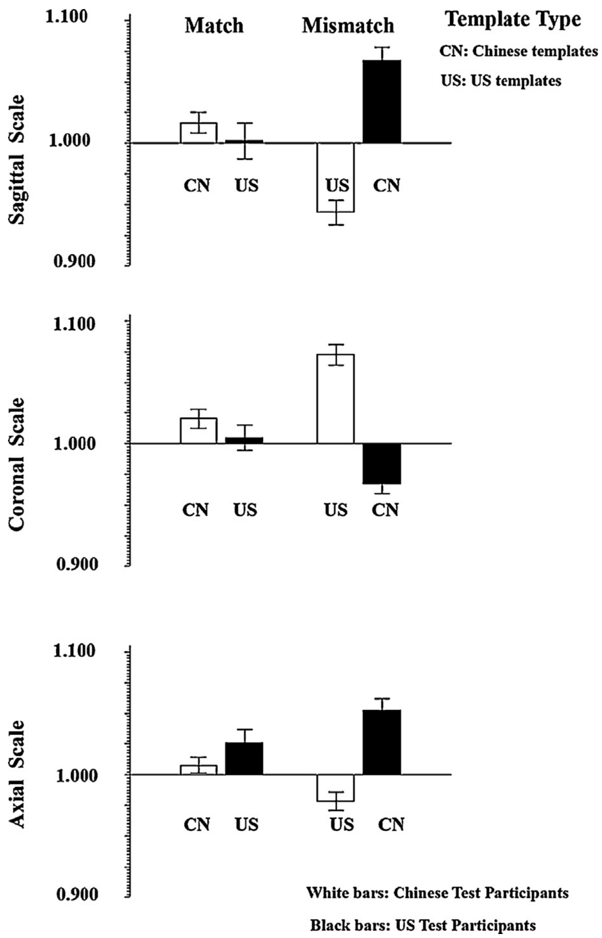

Fig. 6. External test results for sagittal, coronal, and axial scales from the registration process using within-nationality and cross-nationality brain templates. Match refers to that Chinese test participants were registered to Chinese template or US test participants to US template; mismatch means that Chinese test participants were registered to US template, or US test participants to Chinese template.

Similarly, the deformation value from the non-linear registration was examined with the external participants by an Age by Match by Nationality mixed-design ANOVA. There was a significant main effect of match, F (1, 30) = 424.12, p < .0001. Fig. 8

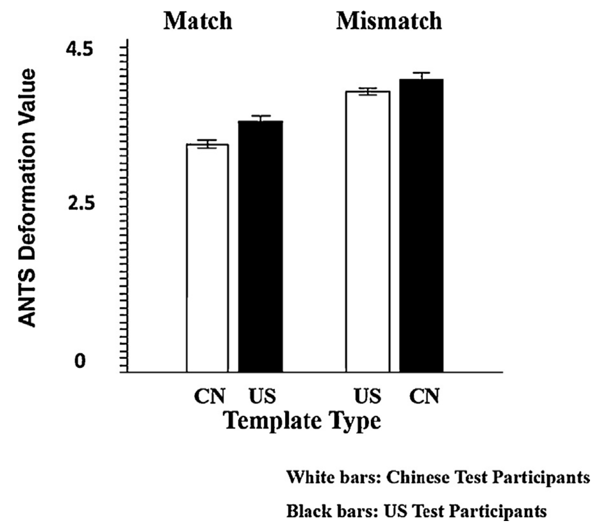

Fig. 8. Results for the deformation values from ANTS non-linear registration using nationality-match and nationality-mismatch brain templates for the external participants. Match refers to that Chinese test participants were registered to Chinese template or US test participants to US template; Mismatch refers to that Chinese test participants were registered to US template, or US test participants to Chinese template.

shows the deformation values from the non-linear registration for the Chinese and U.S. external participants to nationality-matched and -mismatched templates. These values were smaller when nationality-matched templates were used as the reference, indicating that less deformation in the voxel level occurred during the non-linear registration.

2.5. Comparison of tissue segmentation results

We assessed the effect of using nationality appropriate and inappropriate templates for tissue segmentation on the volumetric changes of GM and WM for Chinese participants. Two mixed-design ANOVAs were performed to analyze the volumetric changes (Chinese-GM, Chinese-WM) as a function of Age (5: 8, 10, 12, 14, 16), Match (2: participant-nationality-match, participant-nationality-mismatch), and Program (2: FSL, SPM). For the GM segmentation, there were significant main effects

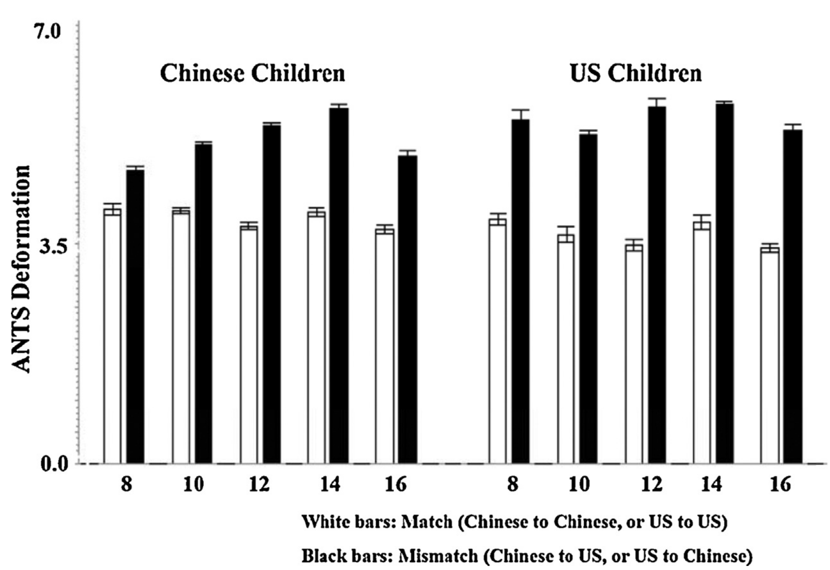

Fig. 7. Deformation value from ANTS non-linear registration for within-nationality and cross-nationality registrations for internal participants.

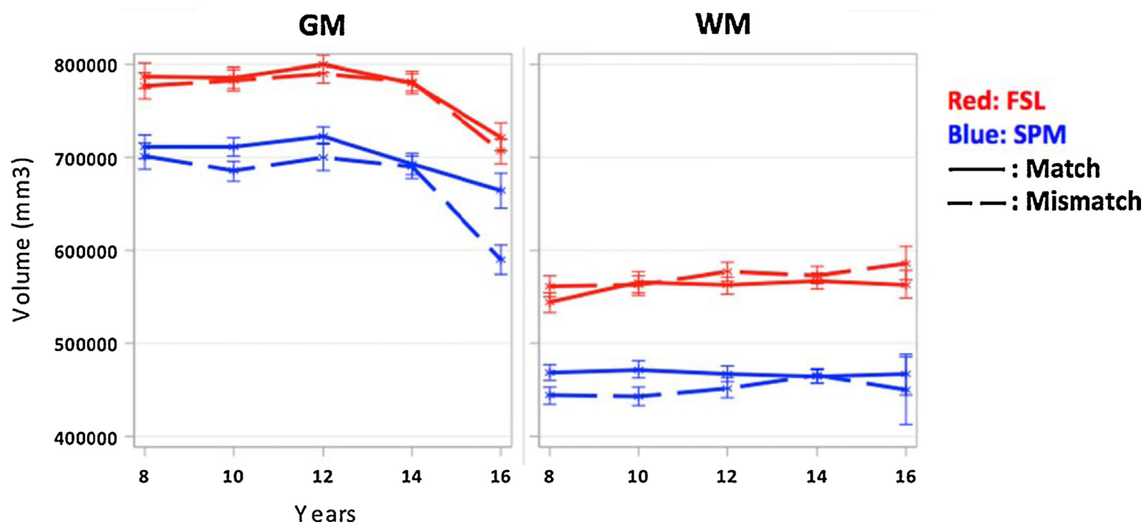

Fig. 9. GM and WM development for Chinese participants as a function of age, separately for the nationality-matched or mismatched template and the computer program. Left panel shows the changes of the GM and right panel shows the changes of the WM. The color of red is used for results from the FSL and blue is for SPM. Solid lines represent results from using nationality-appropriate (or match) templates and dash lines are for nationality-inappropriate templates.

of the participant-template nationality match, F (1, 132) = 50.96, p < .0001, and computer program, F (1, 132) = 451.18, p < .0001; interactions between participant-template national match and age, F (4, 132) = 8.98, p < .0001, and match by program, F (1, 132) = 21.22, p < .0001, and a three-way interaction between participant-template nationality match, program, and age, F (4, 132) = 5.18, p = .0007. Fig. 9 (left panel) shows the GM volume as a function of age, separately for the nationality-matched or mismatched template and the computer program. Of the significant effects, the one most relevant for our concern was the three-way interaction. A simple effects comparing the pattern of volume changes over age for the FSL program when the participant either matched or did not match the nationality of the template had a significant interaction between match and age (p < .05); the same was true for the SPM program. This analysis showed different developmental patterns of the GM volume changes across age when the nationality of the participant either matched or did not match the participants making up the average MRI template. There were similar effects for the WM analysis. Fig. 9 (right panel) shows the WM volume as a function of age, separately for the nationality-matched or mismatched template and the computer program. There were main effects of program, an interaction of the program and participant-nationality match, and a three-way interaction between participant-template nationality match, program, and age. A follow-up simple effects analysis like the one done with the GM showed that the developmental pattern for the WM volume changes across ages was different for the match/mismatch factor for the FSL program, but not for the SPM program. Note: we also did similar analysis for the U.S. participants (e.g., using age-appropriate Chinese or U.S. template), and found analogous findings.

3. Discussion

We created age-specific average T1W brain and head templates for Chinese children from 7 through 16 years of age. The head and brain templates were constructed using averaging techniques based on iterative methods that have become the norm for MRI template construction (Fonov et al., 2011; Sanchez et al., 2012a,b). The resulting templates show fine details of brain structure and should be useful in a wide range of neuroimaging studies with Chinese or Asian pediatric populations. These Chinese child templates appear to be different in global features, such as length, width, height, and shape, than the U.S. age-related templates. The internal and external validation tests showed that these Chinese age-specific templates fit Chinese children's MR images significantly better than age-specific templates based on U.S. children, and adult templates based on either Chinese or U.S. adults. These analyses of the change of brain images required during the linear and non-linear registration process across nationality-appropriate and -inappropriate child templates supported the findings from our examination of internal and external consistency. Registration of original brain images with nationality-appropriate child templates required significantly less deformation than with nationality-inappropriate child templates in both linear and non-linear transformations.

Our findings indicate that U.S. child (Fonov et al., 2011; Sanchez et al., 2012a), Chinese adult (Tang et al., 2010), and North American adult (Mazziotta et al., 2001; Sanchez et al., 2012a; also see Richards and Xie, 2015; Richards et al., 2015) templates may not provide an optimal reference for neuroimaging research with Chinese or Asian pediatric populations. The internal and external consistency tests showed that the global shape and size of the Chinese children's brain images changed significantly after registration into the nationality- or age-inappropriate templates. However, using Chinese child brain templates for registration retained these morphological features from their original images. These findings show that the Chinese age-specific templates require less deformation of the Chinese children's brain for registration of their MR images into a common stereotaxic space. Tang et al. (2010) found that there was significantly more consistency between the original brain images of Chinese adults and the images registered into the Chinese56 template compared with the ICBM-152 template. Our results not only replicated that result, but also extended it to Chinese children and national-appropriate and inappropriate MRI templates.

There are both morphological and volumetric differences between these Chinese child templates and U.S. age-related templates. The Chinese age-specific brain templates are likely shorter, wider, and taller than age-related U.S. templates. The internal and external consistency tests showed that brain images of Chinese children became longer, narrower, and shorter in height after registration with the age-related U.S. templates. The opposite pattern of morphological changes was found for brain images of U.S. children after registration into brain templates created from their Chinese peers. The morphology of the brain images of Chinese and U.S. children was also significantly changed after registration with Chinese and U.S. adult templates. It should be noted that the Chinese56 template seems to be smoothed during its construction process (Figs. 2 and 3). However, it should not affect the results from the consistency tests that utilized linear (12-dof Affine) transformations. The assessment of deformation parameters from the non-linear registration process suggests that differences between Chinese and U.S. child templates exist at the voxel level as well as gross morphological size and shape.

The anatomical differences found between the Chinese and U.S. child templates parallel the findings of brain differences between these two developmental populations from previous research. For example, Guo et al. (2007) found different trajectory of GM development between Chinese and U.S. children and adolescents. In specific, Chinese children showed a linear decrease of cerebral GM from 7 to 23 years of age, while an inverted U-shape was found with North American children within this age range (e.g., Giedd et al., 1999). A more recent study, Xie et al. (2014), directly compared brain anatomical and developmental trajectories between Chinese and U.S. children and adolescents and found morphological and volumetric differences. Chinese children's brains were found to be shorter, wider, and taller compared with brains of their U.S. peers. Moreover, greater cortical GM but less WM volume was shown in Chinese children brain, and differences in GM volume were found in some key brain structures, such as the fusiform gyrus, lingual gyrus, middle and superior temporal gyri, orbitofrontal gyrus, superior frontal gyrus, between the two populations. These findings supported the anatomical differences between the Chinese and U.S. child templates shown in the current study.

The differences between Chinese and U.S. child templates in brain shape and size were also consistent with previously reported differences between North American and Asian adult templates (Lee et al., 2005; Tang et al., 2010). This suggests that the differences in these brain features are already present in children at least 8 years old. We are uncertain about the cause of these anatomical differences, but suspect that genetic and environmental dissimilarities may both contribute to the dissociations of brain development. Since this was not a goal of the current research, no comprehensive discussion will be included.

Using an age- and nationality-appropriate child templates should affect analyses that depend on registration of individual participants to average templates. For example, in VBM ("voxel-based morphometry"), fMRI, and volumetric analyses, the individual participants need to be transformed to a common stereotaxic space (VBM, fMRI) and possibly segmenting priors or atlases based on the average template are used (e.g., VBM). Our analysis used an example of a volumetric analysis of GM and WM changes for Chinese participants across age (e.g., Fig. 9). The GM and WM changes over age were dissimilar to each other when using the templates based on the Chinese participants than templates based on the U.S. templates, for both the FSL (GM, WM) and SPM (GM) computer programs. The GM development for the Chinese children obtained using nationality-appropriate templates were more consistent with those found in Xie et al. (2014). For example, the global GM development for Chinese children showed an inverted U-shape peaking at 12 years of age (Xie et al., 2014) similar to what was found in the current analysis (Fig. 9, left panel). It is likely that these findings were due to registration differences and to different GM/WM tissue volumes in the Chinese and U.S. participants making up the segmenting priors. We believe these differences would be exacerbated in VBM analyses, which depends both on the transformation of voxels from the participants to the normative template and the segmenting priors from the template.

Gender is an important factor in the delineation of brain structures for children and adolescents (Giedd et al., 1999; Lenroot et al., 2007). However, two popular sets of MRI templates for North American children and adolescents (Fonov et al., 2011; Sanchez et al., 2012a; also see Richards and Xie, 2015; Richards et al., 2015) did not create templates specific to males and females. Tang et al. (2010) created the Chinese56 adult template for neuroimaging research with Chinese male participants only. We did not create separate templates for Chinese males and females in the current study due to the potential limitation of the number of subjects at some ages. Because gender also has effects on human brain development, future studies should further examine its effect on Chinese children's brain development and create separate brain templates for males and females.

Population-specific templates are necessary for modern structural and functional neuroimaging research. This work, along with studies conducted by Lee et al. (2005) and Tang et al. (2010) imply that brain templates created with North American populations do not provide optimal references for processing MR brain images of Chinese or Asian populations. Similarly, our study and several other neuroimaging studies examining North American developmental populations (Altaye et al., 2008; Muzik et al., 2000; Wilke et al., 2002), suggest that using average adult MRI templates for research with infants and children may result in excessive deformation, inaccurate measurements, and the misinterpretation of results (Richards and Xie, 2015). Therefore, population-specific (e.g., age, nationality) should be recommended to promote the quality and accuracy of measurements and interpretations. This current study should lay the foundation for creating more comprehensive population-specific templates, such as younger Asian child templates and gender-specific Asian child templates, in the future.

In conclusion, Chinese age-specific average MRI templates are recommended for neuroimaging research with Chinese or Asian children and adolescents. We have created the first brain and head average MRI templates constructed specifically for Asian pediatric populations. Given the similarity between the Korean (Lee et al., 2005) and Chinese (Tang et al., 2010) adult MRI templates, it is likely that these templates will be useful for research with other Asian pediatric populations as well. Our Chinese age-specific pediatric templates may be used to replace or complement the default templates included in popular neuroimaging processing programs (e.g., FSL, SPM).

4. Template availability

The Chinese average head and brain MRI templates are publicly available for research including clinical and experimental studies of brain development. Data access is limited to scientific professionals for research purposes. The template volumes are available in compressed NIFTI format (http://nifti.nimh.nih.gov). The data are on a file server that may be accessed with the Secure Shell (SSH) file transfer protocols (SCP or SFTP). Instructions for access are given online on our website: (http://jerlab.psych.sc.edu/NeurodevelopmentalMRIDatabase/ChineseChildren).

Conflicts of interest

All authors, Wanze Xie, John E. Richards, Du Lei, Hongan Zhu, Kang Lee, and Qiyong Gong, have approved the manuscript and agree with its submission. These authors declare no conflict of interest.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.dcn.2015.08.008.

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