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Population differences in brain morphology: Need for population specific brain template

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ABSTRACT

Brain templates provide a standard anatomical platform for population based morphometric assessments. Typically, standard brain templates for such assessments are created using Caucasian brains, which may not be ideal to analyze brains from other ethnicities. To effectively demonstrate this, we compared brain morphometric differences between T1 weighted structural MRI images of 27 healthy Indian and Caucasian subjects of similar age and same sex ratio. Furthermore, a population specific brain template was created from MRI images of healthy Indian subjects and compared with standard Montreal Neurological Institute (MNI-152) template. We also examined the accuracy of registration of by acquiring a different T1 weighted MRI data set and registering them to newly created Indian template and MNI-152 template. The statistical analysis indicates significant difference in global brain measures and regional brain structures of Indian and Caucasian subjects. Specifically, the global brain measurements of the Indian brain template were smaller than that of the MNI template. Also, Indian brain images were better realigned to the newly created template than to the MNI-152 template. The notable variations in Indian and Caucasian brains convey the need to build a population specific Indian brain template and atlas.

1. Introduction

The shape and size of human brains vary significantly across different races. This poses a major challenge for comparing brain structure and function in neuroscience research (Tang et al., 2010). A critical pre-processing step involved in analysis of structural and functional brain images using automated image analysis techniques like voxel based morphometry (VBM) is spatial normalization. This involves matching each subject's image to a standard template enabling a one to one correspondence between brains of different individuals (Ashburner and Friston, 2000). Brain templates and atlases provide a standard anatomical platform for population based assessments (Ashburner and Friston, 1999; Collins et al., 1994; Evans et al., 1993; Lancaster et al., 1999; Mazziotta et al., 2001a; Toga and Thompson, 2001). The conventional Talairach and Tournoux template (Talairach and Tournoux 1988) is the most commonly used brain template for neurosurgical procedures though it has many limitations. It was developed from the post-mortem brain sections of a single elderly female and has uneven slice thickness between 3 and 4 mm (Chau and McIntosh, 2005; Lancaster et al., 2007; Mazoyer, 2008). These limitations necessitated the development of a digital brain atlas for spatial normalization purposes. With advances in magnetic resonance imaging (MRI), digital brain templates and atlases created using multiple subjects have replaced the conventional brain templates (Toga et al., 2006). The higher signal to noise ratio and better contrast between gray and white matter (Bohland et al., 2009) are advantages of digital brain templates over conventional brain templates. Moreover, digital atlases are made from multiple subjects and thus can generalize well to other subjects. The Montreal Neurological Institute (MNI) and International consortium for brain mapping (ICBM) digital templates are used in popular software packages for image analysis like statistical parametric mapping (SPM) and FMRIB software library (Mazziotta et al., 2001a,

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2001b, 1995a; Evans et al., 1993; Toga and Thompson, 2001).

However, these templates were created using Caucasian young adult brains, making their applicability to non-western populations is questionable. Previous studies have reported regional and global differences in shape, size, and volume between Caucasian and eastern populations (Lee et al., 2005; Tang et al., 2010; Uchiyama et al., 2013) as well as between Caucasians and African-Americans (Isamah et al., 2010; Xie et al., 2015). Normalization of non-Caucasian brain images to standard Caucasian template may result in misregistration and inaccurate measurements, which can be avoided with the creation of population specific brain atlases. Furthermore, population specific templates for Chinese, Korean, and Japanese populations have also shown significant differences in brain shape and size between western and eastern templates (Lee et al., 2005; Tang et al., 2010; Uchiyama et al., 2013). A recent study comparing Chinese, Malay, and Indian neonate brain images reported global and regional anatomical variations in spinal-cerebellar and cortical-striatal-thalamic circuits emphasising the need for a population specific brain template for Indian subjects (Bai et al., 2012). To the best of our knowledge, there is no specific template created for Indian population. The aim of this study was to examine the differences in brain structures between Indian and Caucasian populations and to determine whether there is a need for a population specific brain template. In addition, we aimed to develop a pilot, population specific brain template using MR brain images from healthy young Indian subjects and evaluate differences between the newly created one with standard brain template (example being MNI-152) by statistical analysis and accuracy of image registration.

2. Materials and methods

2.1. Subjects

Twenty-seven healthy volunteers (seventeen males and ten females with mean age 24.77 years) were scanned at Government Medical College, Aurangabad, India. All subjects belonged to the district of Aurangabad, Maharastra located in Western India. All subjects were examined by a certified psychiatrist using Mini International Neuropsychiatric interview to rule out psychiatric illness. Additionally, comprehensive clinical history and neurological examination were conducted to exclude volunteers with medical or neurological illness. All images were examined by a certified radiologist and reported to have no structural abnormalities. Similarly, brain images of twenty-seven (seventeen males and ten females; mean age 26.33 years) Caucasian healthy volunteers were selected from the IXI dataset (http://biomedic.doc.ic.ac.uk/brain-development/index.php?n=Main.Datasets). These caucasian subjects were scanned at the Guy's Hospital, London. The sex distribution between the Indian and Caucasian subjects was examined using Chi-square test and age difference was examined using independent *t*-test.

2.2. Data acquisition

The T1 structural scans of Indian subjects were acquired using a 1.5 T machine with the following scanning parameters using spin-echo sequence: TR = 7 ms, TE = 2.45 ms, flip angle = 8°, acquisition matrix of 256*256*176, and voxel size of 1*1*1 mm^3. Similarly, MRI images of Caucasian subjects were acquired using 1.5 T machine with the following scanning parameters: TR = 9.813 ms, TE = 4.603 ms, flip angle = 8°; acquisition matrix of 256*256*150, and voxel size of 0.938*0.938*1.2 mm^3. The dataset can be accessed using the link (http://brain-development.org/ixi-dataset/). The IXI dataset contains people from different ethnicities (Caucasian, Asian, Chinese, African, and other) along with their details such as sex and age at the time of the scan. We used the information provided in the IXI dataset and selected twenty-seven Caucasian subjects such that they had similar age and same sex ratio as Indian subjects.

2.3. Measurement of global brain features and regional brain structures

The global brain features of individual subjects provide a preliminary idea about variations between the two populations. Four global brain features namely length, width, height, and the distance between anterior commissure (AC) to posterior commissure (PC) were measured using a valid method described in a previous study (Tang et al., 2010). To clarify, we used SPM toolbox (www.fil.ion.ucl.ac.uk/spm) at the level of axial plane passing through anterior-posterior commissure and measured: (1) length of the brain as the distance of the line running from the anterior pole to the posterior pole and passing through the midpoint of AC-PC in the axial plane (2) width as the distance from left to right in the same slice as above (3) brain height as the distance from the superior pole to the inferior pole in the coronal plane (4) AC-PC distance in the sagittal plane as the distance from the center of AC to the center of PC.

To examine the differences in volumes of individual brain structures of two datasets, we utilized Freesurfer software v5.3 (http://surfer.nmr.mgh.harvard.edu) to derive quantitative conclusions. The automatic reconstruction process of Freesurfer involves surface and volume processing streams. In the surface based stream, first, the volumes are affine registered with the ICBM template followed by estimation of B1 bias field by measuring the variation in white matter intensity. The white matter points were selected based on their intensity, local neighborhood intensities, and their locations in the Talairach space. The skull was stripped (Ségonne et al., 2004) using deformable template model. The cutting planes divide the brain into two hemispheres and remove cerebellum and brain stem. The cutting planes operate on several rule-based algorithms that encode the expected shape of these structures. This yielded an initial surface for each hemisphere and tracing the intensity gradients on this surface brings out the gray matter and CSF. The final brain surfaces were examined by overlaying the surfaces on the original brain volume. The volume based stream involved affine registration with MNI305 space followed by initial volumetric labeling (Fischl et al., 2004, 2002). The variation in intensity due to the B1 bias field was corrected using an algorithm different from the one used in the surface extraction sequence. The brain masks were created using skull stripped images - obtained from the surface extraction sequence - on which the labeling was performed. Next, the volumetric labels were assigned to each voxel using Destrieux-2009 atlas and later converted to MNI305 space for quantifying regional volumes. The global brain volumes and regional brain differences between Indian and Caucasian brain subjects were examined using independent *t*-test (2 – tailed). For global brain regions, a p value of < 0.0125 was considered significant after applying Bonferroni correction for multiple comparisons. Monte Carlo simulations (at a threshold of 4.0) were performed using QDEC tool available in the Freesurfer software to correct for multiple comparisons while examining differences in regional brain volume.

2.4. Construction of Indian template

The T1 images of all Indian subjects were reoriented using statistical parametric mapping followed by skull-stripping using the brain extraction toolbox (BET) of FMRIB software library (FSL) (Jenkinson et al., 2005). The extracted images were visually examined for the accuracy of extraction. Using the skull stripped images, the template was created using *buildtemplateparallel (BTP)* script of ANTs (Avants et al., 2011) (Fig. 1). The goal of the *BTP* script was to derive a "most representative" single image from a set of images,, where $\mathscr{E}$ is the objective function that will optimize with respect to all images based on cross-correlation similarity criterion. The shape of was also decided by its diffeomorphism, after considering possible template shapes. Symmetric Normalization (Avants et al., 2008). The goal of *BTP* script is to derive a "most representative" single image T from a set of N images, $T = \mathcal{E}(\{N_i\})$, where $\mathscr{E}$ will optimize T with respect to cross correlation similarity

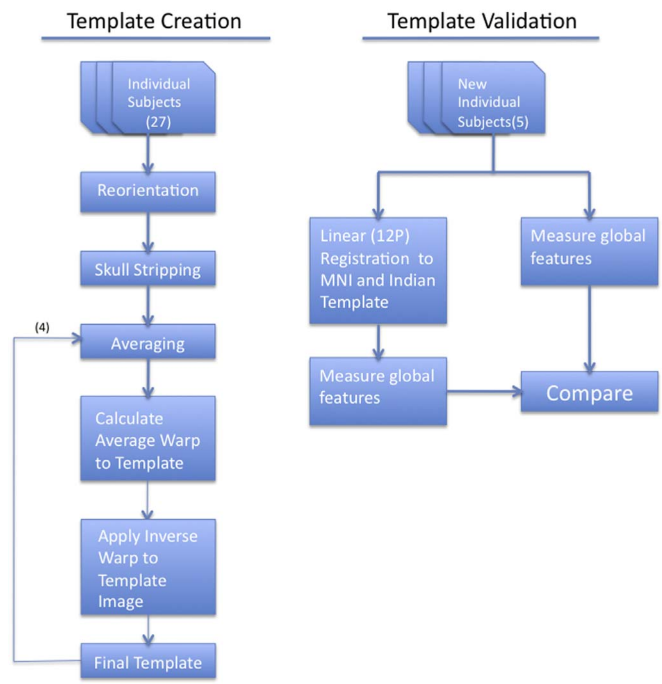

Fig. 1. Schematic representation of workflow for the construction of Indian brain template. Individual images were initially reoriented, skull stripped and then processed using buildtemplateparallel script. Later the template accuracy was examined using an independent set of 5 images which were linearly registered to Indian and MNI templates. The global features of registered images were measured and compared.

criterion. The shape of T is also decided by its diffeomorphism, Ψ, after exploring possible template shapes, $T(\Psi(x))$. Symmetric Normalization (Avants et al., 2008) (SyN) finds a set of diffeomorphisms $\{\varphi_i\}$ and a template shape such that an optimal shape is found by optimizing a similarity criterion with respect to a given template and a set of initial conditions.

$$\mathcal{E}_{T'} = \sum_{i=1}^{N} \mathcal{E}_s(T', N_i, \varphi_i) where \quad \forall \ i, \quad \varphi_i(x,0) = \Psi(x), \quad N = 27 \tag{1}$$

here, Ψ represents the initial conditions of φ_i and each *pairwise problem (*Avants et al., 2010*)* is solved with *SyN*.$\mathcal{E}_T$,is iteratively minimized with respect to the initial conditions set by Ψ and T is defined by the optimal template appearance making the process as symmetric group wise normalization (*SyGN*). The template in case of first iteration is computed as the Euclidean average (Avants et al., 2006) appearance image obtained after affine alignment; this creates an unbiased initial shape, later used by gradient descent algorithm for updating the appearance. The steps below give an overview of optimal template construction.

1. Calculate φ_i for each image N_i by minimizing $\mathcal{E}_s$ in equation-1. $T'$is fixed in this case.
2. Update T' by using gradient descent algorithm:

a. Normalize the intensities of all deformed images in the range 0–1 and compute the gradient similarity term given by cross correlation with respect to T'.
b. Obtain the average similarity measure, set the gradient step size as 0.1 and update $T'$by incorporating the average similarity measure and the step size.
c. Repeat (a) and (b) until convergence is reached.

3. Perform minimization in the diffeomorphism space on $\sum_i D^2(\varphi_1^i(x,0), \varphi_1^i(x,1))$ with respect to Ψ at time t=0, where $\varphi_1^i(x,0)$ is the start and $\varphi_1^i(x,1)$, the end point of the path of split diffeomorphisms. Initially, Ψ will identity diffeomorphism. This calculation yields an average velocity field which in turn results in a new $\Psi(x, t')$ by integrating average velocity over small time t'.
4. $T'$is updated with $\Psi(x, t')$which further participates in defining the identity with respect to T'. Then, $\varphi_i(x,0)$ is set to $\Psi(x, t')$ and the process repeats from step1. In our case the default iteration limit – 4 was used.

In summary, the algorithm optimizes the mappings with fixed template appearance first, then optimizes the template appearance with fixed shape and mapping, and finally optimizes the template shape.

2.5. Validation registration accuracy

To examine the registration accuracy, we separately scanned five new healthy young male volunteers (average age: 22.85 years) at the National Institute of Mental Health and Neurosciences, Bangalore, India, using a 3 T MRI machine with the following parameters: TR =7 ms, TE =2.5 ms, flip angle =8°, matrix size: 256*256*232 and voxel size: 1*1*1 mm^3. It is important to note that these images were not used in template creation. After the acquisition, these five new Indian brain images were separately registered to the Indian template and the MNI template using linear 12-parameter affine model. The linear alignment was achieved using FMRIB's Linear Image Registration Tool (FLIRT) (Greve and Fischl, 2009; Jenkinson et al., 2002; Jenkinson and Smith, 2001). The global measure ratios were compared using non-parametric Mann-Whitney *U* test and to check the registration accuracy paired *t*-test was utilized.

3. Results

3.1. Comparison of Indian brain images and Caucasian brain images

The Indian and Caucasian subjects were matched on age (t=1.02; p > 0.3) and sex (p=1.0). There was a significant difference between Indian brain images and Caucasian brain images on both global (Table 1 and Fig. 2A) and regional brain measures (Fig. 2B). The two groups significantly differed in length, width, and AC-PC distance, but not in brain height; the Caucasian brains had increased length and breadth. There was also a significant difference between groups in

Table 1
Global brain measurements between Indian and Caucasian brains.

a	**Indian brains (n=27)** Mean ± SDin mm	**Caucasian brains (n=27)** Mean ± SDin mm	**t**[a]	**p**
Length	154.12 ± 7.41	173.98 ± 7.37	9.87	< 0.001
Width	127.82 ± 8.34	133.3 ± 4.69	2.97	0.005
Height	106.71 ± 6.61	107.17 ± 5.64	0.27	0.787
AC-PC	25.23 ± 1.27	27.15 ± 1.35	5.35	< 0.001

b	**Indian brains (n=27)** Mean ± SDin mm	**Caucasian brains** **(n=27)** Mean ± SDin mm	**z**[b]	**p**
Width/ Length	0.83 ± 0.06	0.76 ± 0.03	− 4.835	< 0.001
Height/ Length	0.69 ± 0.02	0.61 ± 0.02	− 6.116	< 0.001
Height/ Width	0.83 ± 0.07	0.80 ± 0.04	− 2.102	0.036

[a] Independent *t*-test – two tailed.
[b] Mann-Whitney *U* test.

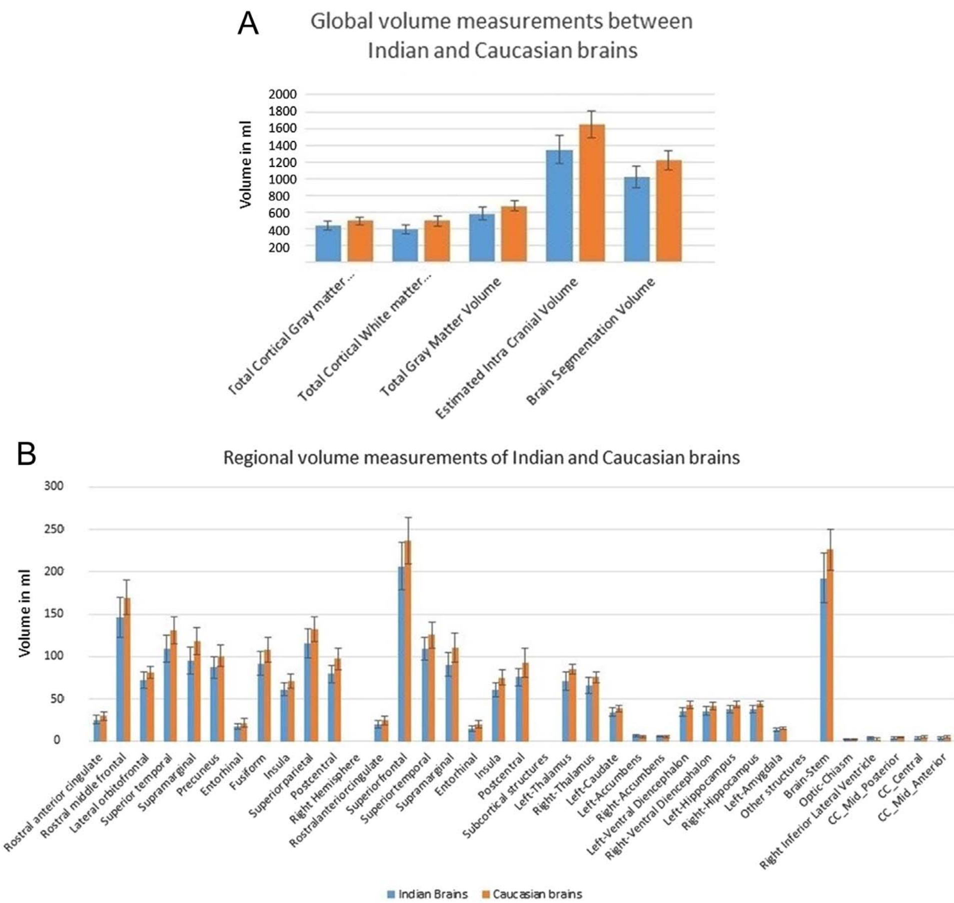

Fig. 2. Bar chart representing the differences between Indian brain images and Caucasian brain images in global brain measures (2A) and regional brain measures (2B).

width/length, height/length, and height/width, with lower ratios in the Caucasian brains. The Caucasian brains had a higher total cortical gray matter volume, total cortical white matter volume, total gray matter volume, and estimated intra cranial volume. Given the differences in global brain measures, there were significant differences in regional brain measures as well. Significant differences were noted in bilateral supramarginal gyri, bilateral lateral orbitofrontal cortex, left transverse temporal gyrus, inferior temporal gyrus, postcentral gyrus, postcentral gyrus, fusiform gyrus, Precuneus, postcentral gyrus, superiortemporal gyrus, rostralmiddlefrontal gyrus and right insula, fusiform gyrus, superior temporal gyrus and superior parietal gyrus ($p < 0.05$; monte carlo corrected) (Fig. 2B).

3.2. Comparison on global measures between Indian, MNI and Chinese templates

We compared the global measures i.e. length, width, height, and AC-PC distance among the Indian template, the MNI-152 template and the Chinese-56 template (Table 2 and Figs. 3 and 4). The Chinese template measures were taken from a previous report (Tang et al., 2010). The Indian brain template was smaller than the MNI-152 template and Chinese template in length, height, and width. The Chinese-56 template was smaller than the MNI-152 template in length & height, and was broader than MNI-152.

Table 2
Comparison between Indian, MNI and Chinese brain templates.

	Indian template	MNI template	Chinese template
Length	155.60	180.80	176.20
Width	127.60	144.20	148.50
Height	105.80	124.80	110.80
AC-PC	24.90	28.10	26.50
W/L	0.82	0.80	0.84
H/L	0.68	0.69	0.63
H/W	0.83	0.87	0.75

3.3. Registration accuracy of other Indian images

The new images were better realigned to the Indian template than to the MNI-152 template. As shown in Table 3, there was a significant difference in length, width, height, and AC-PC distance between original brain images and brain images registered to MNI template indicating significant deformations. On the contrary, there was no significant difference in length, width, height, and AC-PC distance between original brains and brains registered to Indian template (Fig. 5) thus reaffirming that population specific template can play a significant role in VBM type studies.

4. Discussion

Results of this investigation indicate noteworthy differences in global and regional volumes of Indian and Caucasian brains. As this was a proof of concept (pilot) study, the number of subjects used for creation of Indian template was only 27, which was fewer compared to the MNI-152 template, ICBM template and Chinese template. While the optimal number of subjects required to create a population specific template is not well defined, the significant differences between the populations, even with the small number of subjects, indicates the need for population specific template with larger number of subjects.

The MNI-ICBM 152 template was created as a representative brain of the caucasian population based on the probabilistic framework. This

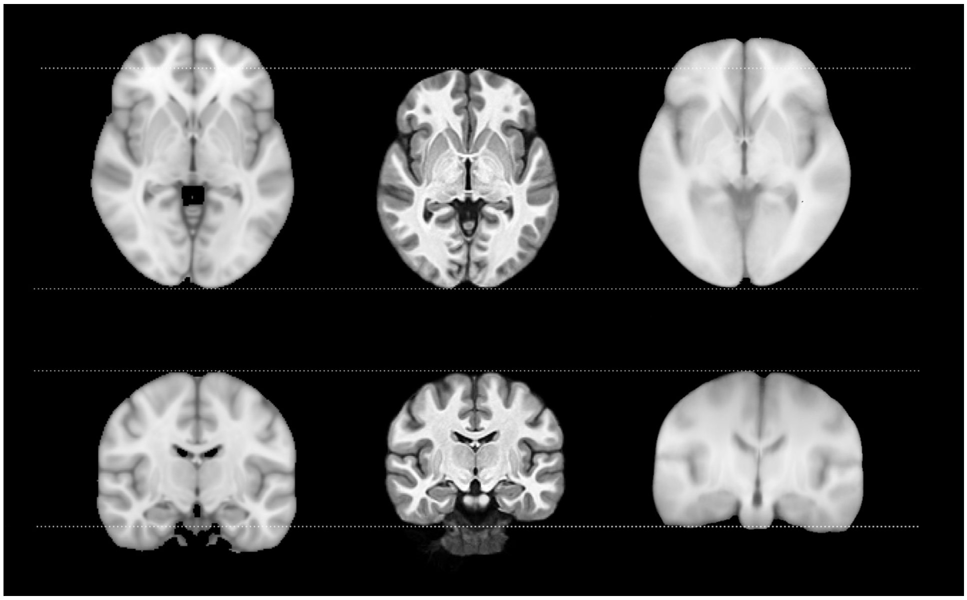

Fig. 3. Comparison of global measures, such as length and height between the Indian template (middle), the MNI-152 template (left) and the Chinese-56 template (right). The Indian brain template was smaller than the MNI-152 template and Chinese template in length and height.

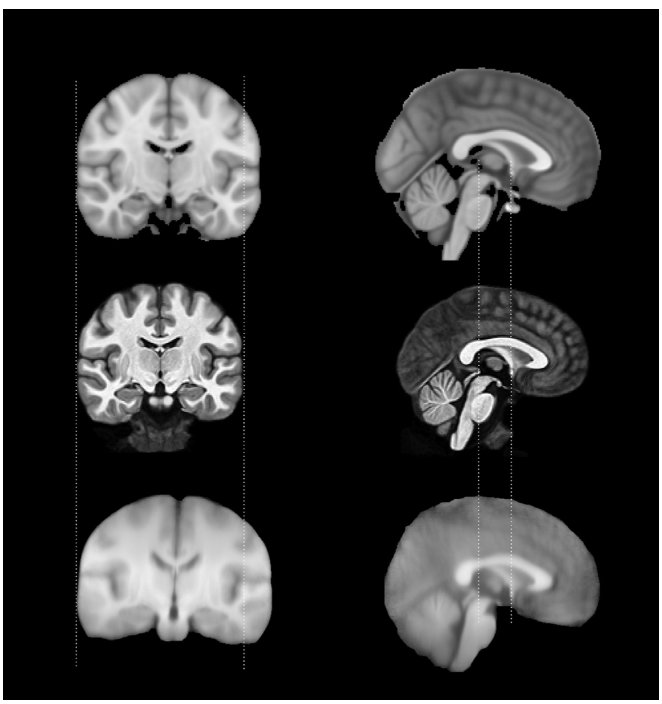

Fig. 4. Comparison of global measures width and AC-PC distance between the Indian template (middle), the MNI-152 template (left) and the Chinese-56 template (right). The Indian brain template was smaller than the MNI-152 template and Chinese template in width and AC-PC distance.

template was the average of 152 normal MRI scans that had been matched to the initial template of MNI-305 using a nine parameter affine transform. The MNI-305 was matched to the Talairach brain in a two-stage procedure. Initially, 241 normal MRI brain images were manually labelled for various landmarks including a line similar to the AC-PC line and edges of the brain. Subsequently, MRI data from 305 normal subjects was used in an automated 9 parameter linear registration algorithm to match to the average brain created using 241 normal brains that were matched to the Talariach atlas. In summary, MNI-305 was created first that was used later to make current ICBM152 template (Evans et al., 1993; Mazziotta et al., 1995a, 1995b).

Table 3
Global brain size changes after registering to the MNI-152 template and Indian template.

	Original brain Mean ± SD in mm	**Registered to Indian template** Mean ± SD in mm	**p**[a]
Length	159.36 ± 9.46	153.48 ± 2.1	0.25
Width	134.42 ± 7.37	129.2 ± 1.35	0.2
Height	109.48 ± 1.3	108.66 ± 3.54	0.618
AC-PC	25.8 ± 1.87	25.24 ± 0.45	0.5
H/L	0.84 ± 0.07	0.84 ± 0.01	0.5
W/L	0.68 ± 0.04	0.7 ± 0.02	0.9
H/W	0.81 ± 0.04	0.84 ± 0.02	0.29
	Original brain Mean ± SD in mm	**Registered to MNI template** Mean ± SD in mm	**p**
Length	159.36 ± 9.46	176.5 ± 2.59	0.01
Width	134.42 ± 7.37	142.96 ± 1.55	0.05
Height	109.48 ± 1.3	127.3 ± 4.11	< 0.001
AC-PC	25.8 ± 1.87	28.1 ± 0.54	0.03
H/L	0.84 ± 0.07	0.81 ± 0.01	0.23
W/L	0.68 ± 0.04	0.72 ± 0.02	0.35
H/W	0.81 ± 0.04	0.89 ± 0.02	0.02

[a] - Paired *t*-test – two tailed.

This study findings show significant differences in global and regional anatomical brain measures between Indian and Caucasian subjects. Hence the commonly used digital brain atlases created using Caucasian brains may not be optimal for analysis of Indian brain images. In our study, Indian brain images had decreased length and width compared to the Caucasian brain images. These findings were similar to the findings from earlier studies (Tang et al., 2010; Evans et al., 2012). Interestingly, a Chinese brain template (Tang et al., 2010) created using 56 healthy Chinese individuals, significantly differed from MNI-152 template. Notable differences among individual Chinese and Caucasian populations were also found in global and regional anatomical brain measurements. Furthermore, Caucasian brains were generally longer and Chinese brains were generally rounder in shape as they were shorter and wider than the Caucasian brains. Another study compared Korean brain template (Lee et al., 2005) for MRI and Positron emission tomography (PET) with Caucasian brains. The Korean brains had lower length and height, but similar width compared to Caucasian brains. While previous two studies examined the adult patients, one

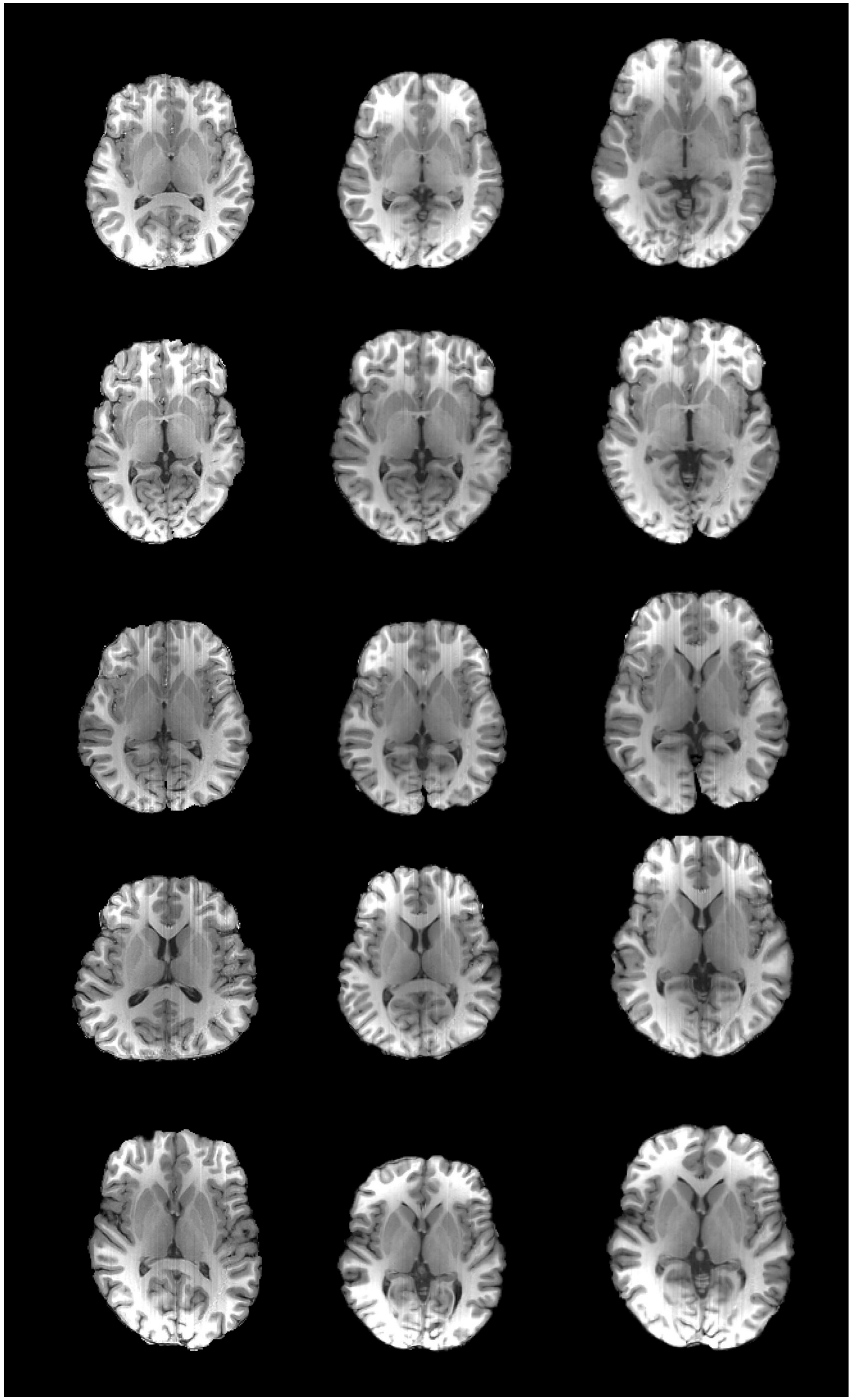

Fig. 5. Five individual Indian brain images (left) separately aligned to Indian brain template (middle) and MNI 152 template (right).

study examined differences between western adult brains and Japanese paediatric brains and reported significant differences in size, particularly along the antero-posterior diameter and in height (Uchiyama et al., 2013). There is a close match of this study results with the ones reported in the literature, demonstrating significant differences between the Caucasian and non-Caucasian brain templates. Hence a population specific template had been recommended for better interpretation (Mandal et al., 2012).

Study findings also indicate possible differences in global brain measurements between Indian and Chinese populations. While the Chinese brain template was shorter but wider than the Caucasian brain template, the Indian brain template was smaller than both templates in length and width. Though both Chinese and Indian populations were Asian, differences in brain morphology and microstructure between these populations had been reported (Bai et al., 2012). An earlier study compared the brain morphology and white matter microstructure using structural MRI and DTI of 75 Chinese, 73 Malay, and 29 Indian healthy neonates (Bai et al., 2012). The brain length of Indian neonates was significantly higher compared to Malay neonates. On VBM brain analysis, differences were noted in left putamen, right thalamus, right globus pallidus, right lingual gyrus, left and right posterior corona radiate among Chinese, Malay, and Indian neonates even after controlling for post-gestational age and the body weight on the day of the MRI scan (Bai et al., 2012). Study findings also indicated significant differences in volumes of several regions between Indian brains and Caucasian brains. These findings were similar to earlier studies which identified regional brain differences between Chinese and Caucasian brains. While differences in global volumes and global gray matter may account for these regional brain differences, one cannot rule out other factors as regional differences were seen only in a few, but not in all brain regions.

The scan parameters for the Indian images and IXI dataset images were different. Even though it is desirable to have the same scan parameters, the atlas creation process normalizes the scan parameters and ideally individual registrations with respective templates will remove the bias as well. As registration process was manually verified in our work, the impact of data comparison was insignificant. Moreover, earlier studies have reported that scan parameters have limited impact on data comparison (Liang, P. et al. 2015).

While 3 T brain images would have offered higher resolution, we chose to use 1.5 T images so that they will be comparable with the widely used western templates like MNI-152, ICBM 452 (Evans et al., 2012). Moreover, India being a developing country, very few centres are equipped with 3 T scanners. A recent Chinese template with more than 2000 subjects also used 1.5 T scanner (Liang et al., 2015). As differences in the strength of the magnetic fields may introduce variations between the imaging characteristics, future studies with a larger sample is required to examine the utility of the template for images from 3 T scanners. Future studies can include a subgroup of images acquired in higher resolution 3 T scanners for comparison. The small sample used in our study may not be a representative of the multi-ethnic Indian population. As the aim of our study was to compare Indian subjects with Caucasian subjects, we did not collect ancestral details from these subjects.

Study findings need to be considered in the background of following limitations. Considering the diverse multi-ethnic nature of population in India, a large representative sample need to be included in the future studies to improve the generalizability of the template. We did not manually edit and quantify the accuracy of registration which could have added to the methodological rigor. Future studies need to consider these measures to avoid potential errors in skull stripping.

Findings of our study have important implications. Image analysis, in particular, VBM involving Indian subjects would benefit from the template as spatial normalization in these analyses was achieved by transforming the individual subject's data into common stereotactic space. The population specific template provides a better framework for accurate registration and decreases the inter-subject variability. Similarly, in functional MRI analysis, this would reduce the mislocalization of activated brain regions measured with functional MRI as spatial mismatches had been reported while interpolating original fMRI data to the MNI template (Jao et al., 2009). Our findings also raise important methodological questions about interpretation of global studies involving subjects of Indian ethnicity as careful consideration must be given when comparing the brains of Indian ethnic subjects with brains of Caucasian subjects. Lastly, our findings have implications for research examining neurobiological ethnic differences in the clinical presentation and course of psychiatric illness.

5. Conclusion

Our pilot study showed significant differences in global brain volumes and regional brain volumes between Indian and Caucasian healthy individuals. Significant differences in accuracy of registrations was noted between newly created Indian brain template and MNI brain template. Population specific Indian brain template and atlas is required for better interpretation of data from Indian subjects. Future studies with larger sample size is prescribed for the creation and validation of population specific brain template and atlas.

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