Published in final edited form as:

Neuroimage. 2014 November 1; 101: 256–267. doi:10.1016/j.neuroimage.2014.07.001.

A Bayesian approach to the creation of a study-customized neonatal brain atlas

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Abstract

Atlas-based image analysis (ABA), in which an anatomical “parcellation map” is used for parcel-by-parcel image quantification, is widely used to analyze anatomical and functional changes related to brain development, aging, and various diseases. The parcellation maps are often created based on common MRI templates, which allow users to transform the template to target images, or vice versa, to perform parcel-by-parcel statistics, and report the scientific findings based on common anatomical parcels. The use of a study-specific template, which represents the anatomical features of the study population better than common templates, is preferable for accurate anatomical labeling; however, the creation of a parcellation map for a study-specific template is extremely labor intensive, and the definitions of anatomical boundaries are not necessarily compatible with those of the common template. In this study, we employed a Volume-based Template Estimation (VTE) method to create a neonatal brain template customized to a study population, while keeping the anatomical parcellation identical to that of a common MRI atlas. The VTE was used to morph the standardized parcellation map of the JHU-neonate-SS atlas to capture the anatomical features of a study population. The resultant “study-customized” T1-weighted and diffusion tensor imaging (DTI) template, with three-dimensional anatomical parcellation that defined 122 brain regions, was compared with the JHU-neonate-SS atlas, in terms of the registration accuracy. A pronounced increase in the accuracy of cortical parcellation and superior tensor alignment were observed when the customized template was used. With the customized atlas-based analysis, the fractional anisotropy (FA) detected closely approximated the

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manual measurements. This tool provides a solution for achieving normalization-based measurements with increased accuracy, while reporting scientific findings in a consistent framework.

Keywords

Neonatal brain atlas; customized atlas; Volume-based Template Estimation (VTE); MRI; registration accuracy

Introduction

Advances in magnetic resonance imaging (MRI) have enabled significant progress in the characterization of neonatal brain development (Chan et al., 2012; Courchesne et al., 2000; Hasan et al., 2010; Huppi et al., 1998; Knickmeyer et al., 2008; Knickmeyer et al., 2011; Lodygensky et al., 2010; Oishi et al., 2011; Qiu et al., 2013), and in the early detection of neurological abnormalities (Bartzokis, 2002; Bava et al., 2007; Brown et al., 2002; Courchesne et al., 2001; Hazlett et al., 2012; Hermann et al., 2010; Kalpakidou et al., 2012; Murakami et al., 1999; Worley et al., 1996). These studies commonly applied whole-brain analysis as a hypothesis-free method to quantify neuroanatomical development, or to explore the effects of various brain injuries. Whole-brain analysis could be performed on a template space or on original image space. For example, voxel-based analysis uses a template space to which all raw images are mathematically transformed. This template space provides a basis for common anatomical locations on multiple images to allow voxel-by-voxel statistical analysis. On the other hand, atlas-based analysis (ABA) can be performed on an original image space. Namely, a pre-segmented set of anatomical structures for the entire brain (parcellation map) in a template space can be transformed to the original image to quantify the volume of each anatomical structure, as well as to measure the intensities of the images (Aljabar et al., 2009; Collins et al., 1995; Heckemann et al., 2006; Heckemann et al., 2010; Jia et al., 2012; Joshi et al., 2004; Klein and Hirsch, 2005; Maldjian et al., 2003; Mori et al., 2008; Oishi et al., 2009; Oishi et al., 2008; Tzourio-Mazoyer et al., 2002; Warfield et al., 2004). This ABA is suitable for creating a “growth percentile chart” of each anatomical structure, which is necessary to interpret individual images based on population statistics (Oishi et al., 2013).

To perform the whole-brain analysis of the neonatal brain, a common atlas has become a pressing demand for both VBA and ABA. The brain tissue composition of the neonatal brain is substantially different from that of the adult brain; for instance, the gray/white matter contrast is reversed compared to the adult brain. Furthermore, rapidly increasing myelination during early brain development alters the gray/white matter contrast, but at different rates depending on the brain regions (Barkovich et al., 1988; Huppi et al., 1998; van der Knaap and Valk, 1990). These unique features of the neonatal brain have motivated the development of dedicated neonatal brain MRI templates (Kazemi et al., 2007; Oishi et al., 2011; Prastawa et al., 2005; Sanchez et al., 2012; Shi et al., 2010; Shi et al., 2011; Song et al., 2007; Weisenfeld et al., 2006; Weisenfeld and Warfield, 2009; Xue et al., 2007). Among these, the Johns Hopkins University (JHU)-neonate atlas (Oishi et al., 2011) was specifically

developed for multimodal (T1- and T2-weighted structural MRI and DTI) analysis and ABA. The JHU-neonate atlas consists of group-averaged templates based on linear and non-linear image transformations, as well as a single-subject template (JHU-neonate-SS). A single-subject template, with an image contrast similar to that of an original subject image, is suitable for high-order nonlinear registration (Wu et al., 2011; Zhang et al., 2014), in which the image intensity provides a cost-function for optimizing mapping. The sharp image contrast also enables the definition of clear boundaries of various anatomical structures, which results in a detailed parcellation map (PM) of 122 anatomical structures. The main advantage of using this parcellation map is that it provides a common reference for consistent anatomical labeling. Indeed, the definition of the anatomical boundary of each brain structure is often ambiguous; for example, the reported normal hippocampal volumes differ by up to 2.5-fold, depending on the definition of the boundary that is manually drawn to measure the volume (Boccardi et al., 2011). The use of a standardized PM is important to avoid inter-institutional, inter-reader, and intra-reader variability of anatomical boundary definitions, and thus, enables researchers to report their findings in a consistent manner (Bai et al., 2012; Qiu et al., 2013; Ratnarajah et al., 2013).

It is well recognized that a study-specific template that is created based on the average anatomical features of a study group, rather than on a generic template, is important for achieving higher registration accuracy (Fonov et al., 2011; Hamm et al., 2009; Jia et al., 2011; Klein et al., 2010; Tang et al., 2009). However, little attempt has been made to create a study-specific neonate template for ABA due to several challenges. The creation of a parcellation map is extremely labor-intensive because it must cover the entire brain three-dimensionally, and manual drawing requires professional anatomical knowledge. More importantly, even if such a study-specific template with a parcellation map could be created, the anatomical boundary of the study-specific parcellation map would not exactly match that of the standardized parcellation map; therefore, results may not be directly comparable to those obtained with a standardized parcellation map.

The purpose of this study was to create a neonatal brain template with a parcellation map (PM) specifically customized for a study group, while keeping the PM boundary definitions consistent with that of the JHU-neonate-SS atlas. The volume-based template estimation (VTE) technique (Ma et al., 2008; Zhang et al., 2014; Zhang et al., 2011) was employed to customize the JHU-neonate-SS atlas to represent the average anatomical features of the study group. In a deformable template model of computational anatomy, the images are regarded as the orbit under the diffeomorphic transformations acting on templates. The VTE technique is based on this model; namely, the brain anatomical shapes are treated as a random orbit under the action of the group of diffeomorphisms (Grenander and Miller, 1998), and the variability of anatomical shapes is balanced based on a geodesic metric measure. That means that, when the created atlas remains in the orbit of the initial JHU-neonate-SS template in shape space, the topology of the atlas image remains unchanged. The group ‘center’ is obtained by a metric-based averaging, which is different from relying on cross-subject intensity averaging (Joshi et al., 2004). In addition, a Bayesian framework is combined with the metric averaging for atlas estimation by iteratively deforming an initial atlas (chosen as the JHU-neonate-SS atlas) to the ‘center’ of the group (Allasonniere et al., 2007; Ma et al., 2008; Ma et al., 2010; Zhang et al., 2014; Zhang et al., 2011). The neonatal

atlas thus created is expected to remain in the orbit of the initial JHU-neonate-SS in shape space. We further examined the registration performance of our customized neonatal atlas with respect to the original JHU-neonate-SS atlas, and applied our new atlas to the atlas-based analysis of FA measurements.

Materials and Methods

Neonatal brain MRI data

Subjects—The subject scans used for this study were obtained from neonates who were recruited and scanned at the MR Research Center at the University of Hawai'i and the Queen's Medical Center in Honolulu, HI. The research was reviewed and approved by the institutional review boards from both institutions, and each parent provided a written consent for the neonates to be studied and for data sharing. The brain MRI data for these infants were de-identified to create our database. The database contains nine full-term, healthy neonates from two to 13-days old (38.4 to 41.1 weeks post-menstrual age (PMA) at birth; 39 to 42.8 weeks PMA at scan), and includes two boys and seven girls.

Data acquisition—The MR scans were performed without sedation while the infants were asleep. The infants were fed by their mothers and allowed to fall asleep naturally. Each baby was wrapped in a vacuum immobilization mat (Noras MRI Products, Hoechberg, Germany) and the ears were covered with earmuffs. The subjects were then placed on cushions that occupied the space between the subject and the RF coil.

T1- and diffusion- weighted images were acquired using a 3 Tesla Siemens scanner (TIM Trio, Siemens Medical Systems, Erlangen, Germany). MPRAGE images were acquired using an echo time of 4.15 ms and a repetition time of 3.2 s, a flip angle of 7°, with an imaging matrix of $176 \times 256 \times 160$, and a 1 mm isotropic in-plane resolution. The slice orientation was sagittal and the slice thickness was 1 mm. For DTI data, diffusion-weighted images were acquired with an imaging matrix of 80×80 and a field of view of 160×160 mm, which gave a nominal 2 mm isotropic in-plane resolution. The matrix was zero-filled to 256×256 mm. The slice orientation was axial with a 2.5 mm thickness parallel to the anterior–posterior commissure (AC–PC) line. Forty to fifty slices covered the entire hemisphere and the brainstem. The echo time was 90 ms and the repetition time was 9.5 s. Diffusion weighting was applied along 12 independent axes (Jones et al., 1999), with $b = 1000 \text{ s/mm}^2$. The scanning time for one complete DTI dataset was approximately three minutes.

Data processing—The quality of the raw images was reviewed to remove scans without whole-brain coverage. The T1-w images were manually skull-stripped and rigidly aligned to the JHU-neonate-SS atlas (Oishi et al., 2011) according to the AC-PC line, and re-sampled to match the dimension of the JHU-neonate-SS (matrix: $180 \times 220 \times 180$, with 0.6 mm isotropic resolution). Pre-processing of the diffusion-weighted images was performed using the DTIstudio software (Jiang et al., 2006). The fractional anisotropy (FA) and TRACE contrasts were calculated, and these images were skull-stripped with manual touch-up, and rigidly aligned to the JHU-neonate-SS atlas according to the AC-PC line.

Creation of study-customized neonatal atlases

The study-customized T1-weighted atlas and DTI atlas were created independently in this study, because co-registration of DTI to T1-weighted images is not straightforward. Several methods have been postulated, such as using distortion field or co-registration via T2-weighted images. However, the methodology is still developing and has been under active debate. We would like to leave this issue to a future study to keep our focus on the VTE application to neonatal images, although an important future direction is to establish a method for creating a customized multimodality atlas, in which a T1-weighted image and a DTI of each subject are spatially co-registered and used to create a T1-weighted and a DTI atlas in exactly the same space.

T1-weighted atlas—We applied the VTE technique (Zhang et al., 2014; Zhang et al., 2011) to create the atlas. The main approach was to evolve the initial atlas to the representative ‘center’ of the study population, based on the morphological information from this population. The integration of shape information is reflected as a metric-based average on a Riemannian manifold, rather than spatial averaging of the images across the population. In addition, a generative model was used under a Bayesian framework. Namely, the initial atlas serves as *a priori* information to constrain the solution in the orbit of the group of the diffeomorphisms, and the MAP estimation is obtained through an Expectation–Maximization (EM) algorithm. Details of the algorithm and the validation on whole-brain images have been reported (Ma et al., 2008; Zhang et al., 2013; Zhang et al., 2011).

The procedure (shown in Fig.1) followed three major steps. First, the JHU-neonate-SS atlas was chosen as the initial atlas I_{atlas} , because of its high spatial resolution and the rich whole-brain anatomical definitions. Although the JHU-neonate-linear and JHU-neonate-nonlinear were also available, they were generated by linearly or nonlinearly averaging the normalized subject images, and therefore, the sharpness was worse than the JHU-neonate-SS.

Second, the customized atlas $I_{customized}$ was estimated through an iterative process. In the k -th iteration, the deformation, $\varphi_1^k, \varphi_2^k \dots \varphi_N^k$ between the initial atlas and each target image, $I_1, I_2 \dots I_N$, was calculated by intensity-based LDDMM (large deformation diffeomorphic metric mapping (Beg et al., 2005)), and the deformation-weighted mean image $\bar{I}^k$ of the population was estimated by:

$$\bar{I}^k = \frac{\sum_{n=1}^N |Jac_n^k| \cdot I_n \circ \varphi_n^k}{\sum_{n=1}^N |Jac_n^k|}$$

where Jac_n^k represents the Jacobian determinant of the deformation φ_n^k . A weighted LDDMM image-matching was then performed between the initial atlas and the mean image to estimate the optimal deformation $(\phi_k)^*$, under the cost function that minimizes the deformation energy and image mismatch error with appropriate Jacobian weighting:

$$\operatorname{argmin}_{\nu: \dot{\varphi}_t = \nu_t(\varphi_t)} \left\{ \int_0^1 \|\nu_t^k\|_v^2 dt + \frac{1}{\sigma^2} \left\| (\bar{I}^k - I_{atlas} \circ (\varphi^k)^{-1}) \sqrt{Jac^k} \right\|_2^2 \right\}$$

where v is the velocity field of the diffeomorphic mapping (Beg et al., 2005). The shape information of the study group was then integrated in the deformed initial atlas, and the atlas was updated:

$$I_{atlas}^{k+1} = I_{atlas}^k \circ ((\varphi^k)^*)^{-1}$$

After a few iterations, the difference between the updated atlas and the mean image converged to a small tolerance, ε , and the iteration terminated. Third, the customized atlas was created by applying the diffeomorphic mapping on the initial atlas:

$$I_{customized} = I_{atlas} \circ (\varphi^*)^{-1}$$

Since it was generated based on the group-averaged (GA) shape features, we refer to it as the Cus-neo-GA atlas hereafter.

DTI atlases—To accommodate multiple contrasts from DTI data and create a set of co-registered DTI atlases, we extended the VTE method to a multi-channel version, in which the diffeomorphic mapping takes all contrasts into account. The FA and TRACE contrasts from the JHU-neonate-SS atlas were chosen as the initial atlas set $\{I_{(FA)}, I_{(TR)}\}$. The deformation, $\varphi_1^k, \varphi_2^k \dots \varphi_N^k$ between the initial atlas set and each target image set, $\{I_{(FA),1}, I_{(TR),1}\}, \{I_{(FA),2}, I_{(TR),2}\}, \dots, \{I_{(FA),N}, I_{(TR),N}\}$, was calculated using dual-channel LDDMM. The FA and TRACE were used to transform DTI, based on our previous observation that this contrast combination could well align the tensor-derived information with reasonable computational load (Ceritoglu et al., 2009). The mean image set, $\{\bar{I}_{(FA)}^k, \bar{I}_{(TR)}^k\}$, was calculated:

$$\bar{I}_{(FA)}^k = \frac{\sum_{n=1}^N |Jac_n^k| \cdot I_{FA,n} \circ \varphi_n^k}{\sum_{n=1}^N |Jac_n^k|} \quad \bar{I}_{(TR)}^k = \frac{\sum_{n=1}^N |Jac_n^k| \cdot I_{TR,n} \circ \varphi_n^k}{\sum_{n=1}^N |Jac_n^k|}$$

Finally, we obtained the optimal mapping by the cost function below, considering both channels of image contrasts:

$$\operatorname{argmin}_{\nu: \dot{\varphi}_t = \nu_t(\varphi_t)} \left\{ \int_0^1 \|\nu_t^k\|_v^2 dt + \frac{1}{\sigma_{FA}^2} \left\| \left(\bar{I}_{FA}^k - I_{FA,atlas} \circ (\varphi_{atlas}^k)^{-1} \right) \sqrt{Jac^k} \right\|_2^2 + \frac{1}{\sigma_{TR}^2} \left\| \left(\bar{I}_{TR}^k - I_{TR,atlas} \circ (\varphi_{atlas}^k)^{-1} \right) \sqrt{Jac^k} \right\|_2^2 \right\}$$

The Cus-neo-GA atlases for DTI were obtained by:

$$I_{(FA),customized} = I_{(FA),atlas} \circ \varphi_{atlas}^{-1} \quad I_{(TR),customized} = I_{(TR),atlas} \circ \varphi_{atlas}^{-1}$$

which were co-registered images.

Parcellation map of the customized MRI atlases

The published JHU-neonate-SS atlas contains 122 manually parcellated brain structures. The DTI-derived contrasts were used to define the deep white matter structures, while the cortical and subcortical gray matter structures were defined with the guidance of MPRAGE and T2-weighted images. This parcellation map (PM) was transformed to our Cus-neo-GA atlas space by applying the deformation: $PM_{customized} = PM_{atlas} \circ \varphi_{atlas}^{-1}$. Therefore, the parcellation map for our customized atlases was obtained automatically, and closely corresponds to the anatomical definition in the JHU-neonate-SS atlas.

Evaluation of the brain volume and the deformation needed for group normalization

Based on T1-weighted neonate images, we measured the total brain volume (TBV) of all subjects in the group, as well as that of the JHU-neo-SS atlas and the Cus-neo-GA atlas. Further, we employed a geodesic metric, $d(I_i, T)$ (Miller and Younes, 2001), to quantify the amount of nonlinear deformation for normalizing each subject, I_i , to the template, T . The diffeomorphic mapping (LDDMM) generated a flow between the two images (I_i and T) on a shape space. The metric was calculated by:

$$(I_i, T) = \inf \{ d(Id, \varphi), T = I_i \circ \varphi^{-1} \} = \inf \left\{ \int_0^1 \|\nu_t\|_V dt \right\},$$

where Id was the identity map, ν_t was the associated velocity field, and $\|\nu_t\|_V$ was an appropriate Sobolev norm on the velocity field (Zhang et al., 2013; Zhang et al., 2011).

Evaluation of the registration accuracy

Registration accuracy was evaluated on each individual's image (native space) using the manual segmentation of each image as the "gold standard." We inversely transformed the atlas parcellation map to each image for the automated image segmentation, and compared the result with that of the gold standard manual segmentation. The registration accuracy was measured using the Dice overlap coefficient. The automated segmentations based on the Cusneo- GA atlas and the JHU-neo-SS atlas were compared to determine whether there was an improvement in the Dice overlap coefficient using the Cus-neo-GA atlas.

Manual delineations—For the T1 atlas, regions-of-interest (ROIs) covering five deep gray matter structures, one white matter structure, and six cortical structures were manually delineated on pre-selected 2D slices, both in the published JHU-neo-SS atlas and in our Cus-neo-GA atlas. Two raters (K.O. and Y.Z.) performed the manual delineation (*manualseg*) for each subject image in the native space. For the DTI atlas set, nine brain structures were delineated following the same manual delineation procedure. Although the structural delineation closely followed the parcellation in the JHU-neo-SS atlas, we modified the boundary of the ROIs to make them suitable to evaluate registration accuracy. In our previous study using the JHU-neonate-SS atlas, the accuracy of the automated registration in deep white matter areas was already very similar to the inter-rater reproducibility. This means that there is little room to improve the accuracy by improving the template. On the other hand, the registration accuracy of the areas close to the brain surface was lower than that of the inter-rater reproducibility, which means that there is room to improve the

accuracy by modifying the template (Oishi et al., 2011). However, evaluation of the registration accuracy in the cortical areas is not straightforward because of the huge amount of normal variation seen in the gyrification pattern and the related difficulty with reproducible manual delineation. Fortunately, there are several fissures and sulci, which could be seen in most of the human brain with less variations, including the Sylvian fissure, the central sulcus, and the parieto-occipital sulcus (Ono et al., 1990). We used these highly preserved grooves seen in the brain surface and adjacent gyri to evaluate the registration accuracy and avoid other areas for the evaluation. A list of these structures and their location coordinates are shown in Table 1. The protocol used to draw the manual ROIs is listed in Appendix A.

Automated delineations—An image transformation-based anatomical parcellation method, which is commonly used in the research community, was applied, as described below. The rigidly aligned neonatal images were linearly registered to our Cus-neo-GA atlas using the AIR linear tool (<http://www.loni.ucla.edu/Software/AIR>), followed by an LDDMM. The overall transformation was applied to each subject image and normalized the images to the atlas space. After obtaining the transformation matrices from the subjects' native space to the atlas space, a set of ROIs for accuracy evaluation on the Cus-neo-GA atlas space was back-transformed to each subject's native space for automated segmentation (*autoseg1*). The same procedure was performed using the JHU-neo-SS atlas and the automated segmentation was obtained (*autoseg2*). Note that the set of ROIs used for this automated ROI delineation was manually created on the JHU-neo-SS atlas, mostly following the protocol in Appendix A. The only difference was that the ROI delineation was performed on four consecutive slices above and below (in the axial slice) or medially and laterally (in the sagittal slice) on the selected slice, which resulted in a total of nine slices for each ROI and in a three-dimensional ROI to account for the variation in brain shape. The set of ROIs on the JHU-neo-SS atlas was then transformed to the Cus-neo-GA atlas space by applying the deformation: $PM_{customized} = PM_{atlas} \circ \varphi_{atlas}^{-1}$

Measurement of accuracy—The spatial overlap between the automated and manual segmentations was quantified by Dice overlap indices. Each ROI was saved as a binary map. The pixels were categorized into three types: (1) pixels that were outside the structures ("0") in either method (nn); (2) pixels that were defined as the structure of interest ("1") in only one of the two methods (pn, np); and (3) pixels that contained the structure in both methods

(pp). Dice overlap was defined as $\frac{2*pp}{pn+np+2*pp}$. The Dice indices for the two atlases were calculated. Wilcoxon signed rank tests were further applied to compare the registration performance of the two atlases, and results were corrected for multiple comparisons with an FDR approach (Benjamini and Hochberg, 1995).

Evaluation of the DTI tensor alignment

A similarity metric of diffusion tensors, *CohPE* (Coherence of Primary Eigenvectors, (Basser and Pajevic, 2000; Jones et al., 2002)), was used to assess the accuracy of tensor matching achieved with the Cus-neo-GA atlas-based image registration for the neonatal brain dataset. Because the traditional arithmetic averaging might be a poor estimate of the

mean eigenvector, since the sign of the eigenvector can be positive or negative, we instead calculated the mean dyadic tensor, which is a positive, semi-definite symmetric matrix:

$$\langle \varepsilon_1 \varepsilon_1^T \rangle = \left\langle \begin{pmatrix} \varepsilon_{1x}^2 & \varepsilon_{1x}\varepsilon_{1y} & \varepsilon_{1x}\varepsilon_{1z} \\ \varepsilon_{1y}\varepsilon_{1x} & \varepsilon_{1y}^2 & \varepsilon_{1y}\varepsilon_{1z} \\ \varepsilon_{1z}\varepsilon_{1x} & \varepsilon_{1z}\varepsilon_{1y} & \varepsilon_{1z}^2 \end{pmatrix} \right\rangle = \frac{\sum_{i=1}^N \varepsilon_1^i \varepsilon_1^{iT}}{N}$$

where ε_1^i was the primary eigenvector of the i -th subject, ε_{1x}^i , ε_{1y}^i , and ε_{1z}^i were the three components of the primary eigenvector, and N was the total number of subjects. The coherence of primary eigenvectors from multiple co-registered tensors was estimated using:

$$CohPE = 1 - \sqrt{\frac{\beta_2 + \beta_3}{2\beta_1}}$$

where β_1 , β_2 , and β_3 are the primary, secondary, and tertiary eigenvalues of the mean dyadic tensor. The quantity *CohPE* attains a maximum of “1” when there is no scatter of the aligned principal eigenvectors of the study population, suggesting a perfect normalization of the diffusion tensors. Higher *CohPE* values indicate better tensor alignment of the group by using the corresponding atlas for DTI registration. Spatial maps of the coherence of primary eigenvectors were produced for normalization by the Cus-neo-GA atlas, as well as by the JHU-neo-SS atlas.

The histograms of *CohPE* for the white matter areas were produced and appropriately normalized by the total number of voxels for each atlas. The threshold of the white matter area for our neonatal brain population was defined as $FA > 0.18$; this ensured the exclusion of cortical areas while retaining commonly identified white matter regions. Since we intended to evaluate the tensor alignment of the common white matter bundles, which are seen in most normal neonates with less anatomical variability, we chose this FA value, which is higher than that of the boundary of the white/gray matters at this age.

We also calculated the mean *CohPE* value for each subject and for each of the 56 pre-defined white matter structures (listed in Table 2) by using each of the two atlases for normalization. A Wilcoxon rank-sum test was performed on each ROI structure to assess the significance of differences between the two atlases (corrected for multiple comparisons with a Bonferroni approach).

Application: customized-atlas-based diffusion property measurement

We measured the FA values of five manually defined white matter structures on the DTI data: the left and right pre-central white matter (PrCWM_L, PrCWM_R); the left and right superior temporal white matter (STWM_L, STWM_R); and the corpus callosum (CC). The subject images were normalized to the Cus-neo-GA atlas by affine and LDDMM transformations. The parcellation map of the atlas was then back-transformed to the subject space using inverse-transformation, and overlaid on the subject FA maps to calculate the mean FA for each structure. To compare the performance of detecting diffusion properties

(e.g., fractional anisotropy, FA), the automated FA measurements were also performed by the JHU-neo-SS atlas-based analysis. In addition, the FA measurements from the manual parcellation served as the “gold standard” for evaluating the performance of the two atlases.

Results

Study-customized neonatal brain atlas

Figure 2 shows T1-weighted, FA, and TRACE images and their structural parcellation maps generated with the Cus-neo-GA atlas (Fig.2 – top row) and with the JHU-neo-SS atlas (Fig.2 – bottom row). The parcellation maps based on T1 and DTI were very similar, but slight differences were seen. The discrepancies are mainly seen in the deep gray and white matter areas, where DTI shows a clear contrast, but T1 does not.

Our customized atlas adopted the contrast from the JHU-neo-SS atlas, and preserved the sharp tissue contrast as well as the initial template (i.e., the JHU-neo-SS). From the axial view of the images, the brain shape of the frontal lobe of the Cus-neo-GA atlas was closer to that of the study population, while the JHU-neo-SS atlas had a narrower frontal lobe (see the red arrows in Fig.2). The average of the total brain volume (TBV) of our study group, measured on T1-weighted images, was 465 ± 55 mL. The TBV from our customized atlas (458 mL) was closer to the average of this study group than that of the JHU-neo-SS atlas (441 mL), although the brain volume could be normalized by simple affine registration, and therefore, was not necessarily a good marker for the template. The diffeomorphic deformation to normalize each neonatal brain to the atlas was quantified as a metric distance and is shown in Figure 3. The total amount of deformation required to normalize the study group to the JHU-neo-SS atlas was 11.0 (unit), while this amount was only 9.4 (unit) for the Cus-neo-GA atlas. The mean of the metric distance decreased significantly using our customized atlas for group normalization (p-value for t-test: 0.0057, T-statistics: 3.7427).

Improved registration on T1 and DTI images by the study-customized neonatal atlas

The overlap indices of automated versus manual segmentations are shown in Figure 4. Our customized atlas achieved superior registration accuracy (Dice overlap) in all twelve structures, including the deep gray matter, white matter, and cortex. The structures with significant improvement using the Cus-neo-GA atlas (marked with an asterisk (*)) included the left central sulcus, the left and right Sylvian fissure, the left striatum, the corpus callosum, and the parieto-occipital sulcus.

The registration performance for diffusion tensor images is shown in Figure 5. Using the customized neonatal atlas, significantly improved registration was observed in seven of the nine brain structures. These brain structures included the right pre-central white matter, the right thalamus, the left and right lenticular nuclei, the left and right superior temporal white matter, and the corpus callosum.

Figure 6 showcases the automated segmentation results from the JHU-neonate atlas and our customized atlas on a representative subject. In Figure 6A, T1w image-based segmentations from the JHU-neo-SS atlas (top row, in green) severely deviated from the actual anatomical location (indicated by the manual segmentation as the gold standard (yellow)), while the

automated delineation by the Cus-neo-GA atlas (bottom row, in green) captured the gyri and sulci areas accurately (with overlaps of the green and gold regions of interest). Consequently, the Cus-neo-GA atlas achieved a higher Dice value than the JHU-neo-SS atlas. In Figure 6B, automated segmentation by the JHU-neo-SS atlas yielded a larger lenticular nucleus and a smaller thalamus region than the manual delineation, while these regions from the Cus-neo-GA yielded segmentations similar to those on the manual delineation.

Superior tensor alignment by the customized DTI atlas

The whole-brain *CohPE* maps using the JHU-neo-SS and the Cus-neo-GA as templates for normalization were color-coded, and are shown in Figure 7A. The group of voxels in the region of the posterior thalamic radiation (PTR) (indicated by black arrows in Fig.7A) achieved higher *CohPE* values in the Cus-neo-GA atlas-based alignment than that in the JHU-neo-SS. Figure 7B compares the normalized histograms of *CohPE*. The peak of the histogram from the Cus-neo-GA (red curve) lies to the right of the histogram from the JHU-neo-SS (green curve). At the range of *CohPE* > 0.7, there was an increased proportion (area under the histogram curve) for the Cus-neo-GA than for the JHU-neo-SS, indicating a better tensor alignment by our customized atlas.

The *CohPE* values for the 56 pre-defined white matter structures are shown in the Supplementary Figure, and statistical test results are listed in Table 2. Of these structures, 46 showed higher *CohPE* values using our customized atlas for normalization, and 40 of these were significantly better (* $p < 8.9 \times 10^{-4}$).

Diffusion property measurement of the normal-term neonatal brains

Figure 8 shows the FA values obtained with our customized atlas (bar plots in red), the JHU-neo-SS atlas-based analysis (in blue), and manual measurements (in gray) for four superficial white matter structures and one core white matter structure. For the healthy term infants, all mean FA values obtained with the Cus-neo-GA atlas closely approximated the manual-based results, with a difference below 1%. Conversely, the mean FA value using the JHU-SS atlas differed from the manual result by 3–9%.

Discussion

Important features of the customized atlas creation routine

In this study, we extended the VTE algorithm (Zhang et al., 2013) to accommodate multimodal images, including T1-weighted images and DTI. The JHU-neonate-SS atlas, which is the only multimodal neonatal atlas currently available online, was chosen as the initial template. By integrating the random orbit Bayesian model framework and generating the maximum-likelihood estimator of the template representing the population, as described originally in (Ma et al, 2008), the VTE algorithm for estimating the template is robust. This is in contrast to methods such as those proposed previously (Joshi et al., 2004), in which the expectation-maximization algorithm is not used and the generalized likelihood estimator of the template, as well as the individual deformations onto the population, is generated. The latter procedure would not benefit from a consistency theory, since, as the population sample

size becomes large, the number of estimated diffeomorphic re-parameterizations would grow with the sample size. The neonatal-customized atlas adopts the advantage of the VTE algorithm, and gains three important features that help achieve a more accurate ABA. First, the atlas preserves the image contrast (as shown in Fig.2), no matter how many images are used to create the atlas, because the VTE procedure employs the metric average in shape space, rather than using a spatial averaging scheme (Zhang et al., 2013; Zhang et al., 2011). Second, the anatomical variability of a study population was considered in the atlas generation, and the resultant atlas localizes at the averaged shape features, in a much less biased way than a single-subject atlas. The centered atlas reduced the total amount of deformation needed to transform the template to all the subjects (as shown in Fig.3), and lowered the possibility of mapping failures due to large shape differences. This effect is emphasized when the anatomical features of the study population are different from those of the common template. Many of the past neonatal studies have targeted a specific demographic population (e.g., sex and race), medical status (e.g., prematurity and exposure to stimulants), or small group (a number of participants less than 50). The VTE atlas could provide a basis for common anatomical locations for each of these studies to allow voxel-by-voxel statistical analysis. However, if the anatomical features of the study population are similar to those of the common space, the advantage of using the VTE atlas over a common template might be reduced. In such a situation, a template created simply by averaging a large group, such as ICBM atlases with corresponding probabilistic parcellation maps, might work well. Third, since the new atlas is a derived version of the initial atlas (i.e., the JHU-neonate-SS), the precise anatomical parcellation of the customized atlas is obtained automatically. The deformation from the atlas image of the previous iteration to the current iteration is stored and accumulated, and the final atlas is obtained by applying the accumulated transformation to the initial atlas. Therefore, the pre-stored labeling information on the JHU-neonate-SS atlas is naturally carried to the new atlas space in a diffeomorphic manner, and the topological structure of each three-dimensional ROI is preserved by diffeomorphism. This automatic generation of the parcellation map not only avoids the labor-intensive manual drawings of 3D ROIs and reduces the requirement for a professional with extensive anatomical knowledge, but also ensures a standardized definition of tissue boundaries for the new parcellation map, which is valuable for reporting and comparing scientific findings consistently among the research community.

There are several alternatives to the automated anatomical parcellation. Among them, a group of methods using a multi-atlas-based framework is postulated to reduce the impact of erroneous mapping related to a single-template approach. The basic procedure is to label anatomical structure(s) in multiple (N) atlases, warp each atlas to a to-be-parcellated image, and then the N labels are casted onto the subject image and fused, based on various algorithms, such as those proposed by (Artachevarria et al., 2009; Kittler and Alkoot, 2003; Kittler et al., 1998; Langerak et al., 2010; Lötjönen et al., 2010; Rohlfing et al., 2004; Warfield et al., 2004). If the mis-registration of each atlas causes random errors, integrating N labels could reduce the errors. The multi-atlas framework has been applied to study neonatal images (Gousias et al., 2013), in which the gray matter of T1-weighted images could be parcellated into 50 areas with the mean Dice overlap coefficients ranging from 0.64 to 0.93. Although the impact of using a multi-atlas framework over other approaches needs

to be elucidated, it has the potential to accommodate the large anatomical variability encountered in clinical images and to deliver a high level of parcellation accuracy. However, the strength of our single-atlas approach is the capability to observe the brain from very different granularity levels using the same analytical framework. Namely, once images are transformed to the atlas space, an analysis could be performed on the atlas space at a high granularity level, such as voxel-by-voxel statistics, which could potentially provide information about changes in confined anatomical areas or about a small portion of a structure. One could also perform ABA in the native image space, which is suitable to detect small but widespread changes in the anatomical structures. In this way, VBA and ABA are complementary to each other for a whole-brain analysis, and the single-atlas approach has the capability to perform both analyses simultaneously.

Accuracy of image registration and tensor alignment

We evaluated the performance of both image registration and tensor alignment using our customized neonatal atlas. To evaluate T1-weighted image registration, we selected twelve 2D ROIs, including deep gray matter, white matter, and cortical structures, which are highly preserved structures that can be identified reliably for all brains. For DTI, we identified nine structures covering the deep gray matter, the core white matter, and the superficial white matter regions, which are typical targeted areas pertinent to many clinical studies. For these ROIs, our study-customized neonatal atlas provided superior image normalization than did the generic JHU-neonate-SS atlas. To evaluate DTI tensor alignment, we quantified the tensor alignment of the study group on a voxel level (Fig.7A, *CohPE* map), an ROI level (Table 2 and Supplementary Figure), and a whole-brain level (Fig.7B, *CohPE* histogram). In all granularities, the tensor alignment was improved using our customized neonatal atlas for group registration.

The improved registration performance likely resulted from our customized atlas providing a closer representation of the shape features of the study population. Generally, it is easier to register two nearby subjects with similar structures than to register two subjects distant from each other (Wu et al., 2011) for iteration-based nonlinear registration algorithms, such as LDDMM. Problematic local optimal solutions could be avoided to achieve the global optimal solution when the two images have “closer” shapes.

It is beneficial to achieve superior registration in the application of ABA and group comparisons. The neonatal cortex is a critical region for exploring normal brain development, to correlate with various brain functions, and for early detection of developmental abnormalities. In infant brains, while the major cortical gyri and sulci are formed (Dubois et al., 2008; Hill et al., 2010), the cortical patterns may vary greatly across the healthy population and even more in abnormal populations (Dubois et al., 2008; Inder et al., 2005). Therefore, achieving accurate cortical registration to characterize cortical development is important. With improved registration, the atlas-based automated segmentation on each subject becomes more accurate.

Rather than using the JHU-neonate atlas, one could also use an image from a study group to create a study-customized template based on the VTE procedure. Since the scanner and scan parameters of the template image would be identical to that of the study group, and

anatomical variation among normal neonates is less than that seen in adult brains, we would expect a higher accuracy in image registration than that based on the customized JHU-neonate atlas, or that reported previously based on an elderly population (Zhang et al., 2013). This might be an option when the study does not require a standard parcellation map of the JHU-neonate atlas for reporting. A tradeoff between registration accuracy and computational cost is a general issue. As we have reported in the past, computation time for the VTE atlas is comparable to that of other iterative atlas generation methods. For accurate registration, a customized template based on all images of the study group is preferable, but that based on a portion of the study group might be acceptable when the anatomical variability within selected images is similar to that of the images from the entire study images. The latter approach is suitable for the analysis of ongoing clinical studies, in which the number of images continually increases.

Applications for atlas-based analysis of diffusion properties

For automated DTI parameter measurement, we characterized FA values in term infants within one week after birth. The FA values detected by the JHU-neo-SS atlas produced as much as a 9% mismatch from the actual value in the right pre-central white matter (PrCWM_R), a superficial white matter region close to the cortex, and surrounded by gray matter structures with very low FA values. Therefore, the mis-registration of the superficial WM regions is expected to produce noticeably large errors on the mean FA read-out by the ABA. Our customized atlas achieved higher registration accuracy; hence, the ABA based on this customized atlas detected the FA more accurately (error within 1%), as expected. Future studies using the customized neonatal atlas have the potential to detect more subtle FA changes compared to those detected by the general JHU-neonate-SS atlas. In addition, it should be emphasized that the VTE method is applicable to any type of parcellation map. For example, one of the effective ways to evaluate developmental change in the diffusion property of fiber tracts is to create tracts-of-interest (TOI) in a template space, and transform the TOI to each individual image for further analysis (Goodlett et al., 2009). The VTE method could be used to customize the common TOI to a study group to improve the registration accuracy, while preserving the anatomical definition used in the common TOI.

Limitations

The current level of registration accuracy for our customized neonatal atlas was achieved in a population with normal brain development; images from infant brains with pathological development (e.g., pre-term births) or lesions may be more challenging and lead to less accurate registrations. As the shape and intensity variability enlarges or topological changes occur in diseased brains, the large structural difference from the standard neonatal atlas may cause inaccurate registration from each subject to the initial atlas; therefore, the VTE features may match the newly generated atlas poorly. Possible solutions include the use of a multi-atlas label fusion approach (Gousias et al., 2008; Tang et al., 2013), which is an important future direction.

Conclusion

In conclusion, we developed an extended VTE method to create a multimodal neonatal brain atlas customized to a study population, while maintaining an anatomical parcellation identical to that of the common MRI neonatal atlas. A pronounced increase in the accuracy of cortical parcellation and superior tensor alignment were observed when the customized template was used. This study demonstrates the important role for a customized neonatal atlas in providing accurate neuroanatomical parcellation, and in reporting the findings using a common definition of anatomical labeling. We expect that the VTE atlas is suitable for studying a group with a specific demographic feature or a specific disease group, and for small study groups, in which the anatomical features are biased compared with a larger study group. The applicability of the VTE to such groups needs further evaluation in the future.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

This publication was made possible by grants R21AG033774, R01HD065955, 2K24DA16170, U54NS056883, G12MD007601-26, and P41EB015909 from the National Institutes of Health, the Yousem Family Research Fund, and grant 46039500 from the Central Norway Regional Health Authority. The contents of this paper are solely the responsibility of the authors and do not necessarily represent the official view of NIH, the Yousem Family Research Fund, or the Central Norway Regional Health Authority. The terms of this arrangement are being managed by Johns Hopkins University in accordance with its conflict of interest policies. The authors are grateful to the families of our research participants, and our research staff (Heather Johansen, Antonette Hernandez, and Robyn Yamakawa, Caroline Jiang, Dr. Daniel Alicata, and Dr. Steven Buchthal) who assisted with the data collection and data transfer. We also thank Ms. Mary McAllister for help with manuscript editing.

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Figure 1.

Schematic diagram of the study-customized atlas creation process. The process can accommodate more than one image contrast for each subject and generate a co-registered multi-contrast atlas image set. The mappings from the atlas to each subject were generated by a nonlinear image-matching technique (LDDMM). The tissue parcellation map of the final atlas was automatically transferred from the initial atlas without manual intervention.

Figure 2.

The study-customized neonatal atlas with parcellation map (top row) and comparison to the previous atlas (bottom row). The T1-w, FA, and TRACE contrasts and the tissue parcellation maps were included in the atlas set. The Cus-neo-GA atlas was divided into 122 brain structures by the parcellation map, and there was a noticeable shape difference in the frontal lobe of the two atlases.

—◆— Metric to JHU-neo-SS atlas

—■— Metric to Cus-neo-GA atlas

Figure 3.

The amount of diffeomorphic deformation needed for group normalization. The metric distance, which is a quantity of diffeomorphic deformation measurement, is shown individually for each subject. Markers in blue represent the metric distance from the JHU-neonate-SS atlas to each subject, and markers in red show the distance from the customized template. The mean of the metric distance is significantly smaller for the customized atlas than for the JHU-neonate-SS atlas.

Figure 4.

The registration performance comparison between the JHU-neonate-SS atlas and our customized atlas. The manual delineations of the twelve structures on both atlases were used to automatically segment the subject images separately, and the automated results were compared with each individual's manual delineation quantitatively by a Dice coefficient. Most cortical structures showed significant improvement in segmentation with the customized atlas-based automated segmentation than with the JHU-neonate-SS.

Figure 5.

The DTI image registrations are compared between the two atlases. Nine manually delineated ROIs were used to automatically segment the subject images separately, and the automated results were compared with each individual's manual delineation quantitatively by a Dice coefficient. All examined structures showed improvement of segmentation with the customized atlas-based automated segmentation over those derived from the JHU-neonate-SS, and the improvement in seven of the nine structures was significant.

Figure 6.

Comparison of manual delineation and automated segmentations by the two atlases for the neonatal cortical structures in T1-w images (Fig.6A) and subcortical structures in DTI (Fig. 6B). Fig 6A: automated parcellations (green) of six cortical regions using the JHU-neo-SS (top row) and Cus-neo-GA (bottom row) atlases for one representative neonate brain. Manual delineations (yellow) overlaid. Dice values for each structure by both atlases are shown. The red arrows point to the locations where the spatial mismatching between automated and manual results was greatly improved by using the VTE atlas. Fig 6B: Representative results of automated parcellations by the JHU-neonate-SS and the Cus-neo-GA atlas. The thalamus, the putamen, and the superior temporal white matter area from automated segmentations and manual segmentation are shown.

Figure 7.

The coherences of primary eigenvectors (*CohPEs*) using the two atlases for DTI data normalization are shown. Fig.7A: whole-brain *CohPE* maps for the two atlases. In each voxel, the *CohPE* was calculated and a value between 0 and 1 was obtained. Higher *CohPE* values indicate better diffusion tensor alignment of the study group using the corresponding atlas for DTI registration. Fig.7B: Histograms of the *CohPE* maps. The green curve represents the *CohPE* distribution using the JHU-neonate-SS atlas, and the red curve represents the *CohPE* of the customized atlas. The histograms were appropriately

normalized for the white matter areas, which were defined as the areas with an $FA > 0.18$. The peak of the red curve is at the right of that of the green curve, indicating an improvement in tensor alignment by the customized neonatal atlas.

Figure 8.

Comparison of the mean FA values measured through manual parcellation and atlas-based analysis. The FA values measured by the customized neonatal atlas closely approximated the values from the manual segmentation-based measurements. The FA values measured by the JHU-SS atlas were underestimated for the superficial white matter structures (such as the pre-central WM and the superior temporal WM in both hemispheres), and were overestimated for the corpus callosum.

Table 1

List of manually-segmented brain structures and their anatomical locations

Manually segmented structures for T1 and DTI	
Axial #	
z=91	Thalamus, Striatum, Lenticular nucleus
z=65	Midbrain
z=131	Sylvian, Pre-Cuneus White Matter
Sag #	
x=40,140	Superior Temporal White Matter
x=90	Corpus Callosum
x=32,148	Central Sulcus
x=84,98	Parieto-Occipital Gyrus

Table 2

Appendix Significance of the comparison of mean CohPE for the two atlases on each of the 56 pre-defined white matter structures in neonatal brain population.

label	Structures abbreviation	Left/right	CohPE of JHU-neo-SS		CohPE of Cus-neo-GA		p-value
			Mean	Std	Mean	Std	
1	CC	left	0.7205	0.0641	0.7304	0.0609	<10 ⁻¹⁵ *
2	CC	right	0.7125	0.0681	0.7194	0.0613	<10 ⁻¹⁵ *
3	ALIC	left	0.7283	0.0768	0.7422	0.0645	<10 ⁻¹⁵ *
4	ALIC	right	0.7260	0.0767	0.7373	0.0610	<10 ⁻¹⁵ *
5	PLIC	left	0.7655	0.0451	0.7615	0.0454	<10 ⁻¹⁵ *
6	PLIC	right	0.7161	0.0364	0.7174	0.0369	<10 ⁻¹⁵ *
7	RLIC	left	0.6934	0.0521	0.7009	0.0605	2.5 × 10 ⁻¹
8	RLIC	right	0.6948	0.0543	0.7041	0.0437	<10 ⁻¹⁵ *
9	ACR	left	0.6156	0.1329	0.6594	0.1164	<10 ⁻¹⁵ *
10	ACR	right	0.6318	0.1534	0.6774	0.1305	<10 ⁻¹⁵ *
11	SCR	left	0.6136	0.0973	0.6290	0.0911	<10 ⁻¹⁵ *
12	SCR	right	0.5522	0.1357	0.5929	0.1173	<10 ⁻¹⁵ *
13	PCR	left	0.5814	0.0910	0.594	0.0877	<10 ⁻¹⁵ *
14	PCR	right	0.6081	0.0750	0.6243	0.0670	<10 ⁻¹⁵ *
15	CGC	left	0.6065	0.1347	0.6099	0.1370	<10 ⁻¹⁵ *
16	CGC	right	0.6161	0.1166	0.6089	0.1240	1.3 × 10 ⁻¹
17	CGH	left	0.5352	0.1148	0.5653	0.1079	2.1 × 10 ⁻²
18	CGH	right	0.5128	0.1203	0.5486	0.1074	<10 ⁻¹⁵ *
19	Fx	left	0.6804	0.0779	0.6785	0.0720	<10 ⁻¹⁵ *
20	Fx	right	0.6734	0.0906	0.6753	0.0831	8.9 × 10 ⁻²
21	ST	left	0.6616	0.0695	0.6674	0.0717	6.9 × 10 ⁻¹

label	Structures abbreviation	Left/right	CohPE of JHU-neo- SS		CohPE of Cus-neo- GA		p-value
			Mean	Std	Mean	Std	
22	ST	right	0.6713	0.0776	0.6962	0.0568	1.3×10^{-3}
23	TAP	left	0.6578	0.0765	0.6483	0.0694	$<10^{-15} *$
24	TAP	right	0.6080	0.0769	0.6518	0.0540	$<10^{-15} *$
25	SLF	left	0.5402	0.1126	0.5291	0.1119	$<10^{-15} *$
26	SLF	right	0.4924	0.1153	0.5200	0.1241	$6.0 \times 10^{-4} *$
27	EC	left	0.6681	0.0956	0.6793	0.0854	$<10^{-15} *$
28	EC	right	0.6515	0.0949	0.6731	0.0675	$<10^{-15} *$
29	PTR	left	0.6445	0.1057	0.6835	0.0957	$<10^{-15} *$
30	PTR	right	0.6261	0.1024	0.6579	0.0937	$<10^{-15} *$
31	SS	left	0.7172	0.0706	0.7276	0.0667	$<10^{-15} *$
32	SS	right	0.7305	0.0905	0.7491	0.0728	$<10^{-15} *$
41	CP	left	0.7048	0.044	0.7067	0.0437	$2.0 \times 10^{-4} *$
42	CP	right	0.6631	0.051	0.6707	0.0513	9.2×10^{-3}
43	SFO	left	0.7067	0.0738	0.7447	0.0572	$<10^{-15} *$
44	SFO	right	0.6457	0.0996	0.6691	0.0868	$<10^{-15} *$
45	IFO	left	0.7551	0.0565	0.7590	0.0520	$<10^{-15} *$
46	IFO	right	0.7606	0.0560	0.7651	0.0572	6.6×10^{-2}
47	CST	left	0.5533	0.1604	0.5549	0.1548	$<10^{-15} *$
48	CST	right	0.5193	0.1430	0.5263	0.1464	9.9×10^{-1}
49	SCP	left	0.6757	0.1055	0.6835	0.0907	2.8×10^{-1}
50	SCP	right	0.6805	0.1058	0.6835	0.1049	7.5×10^{-1}
51	MCP	left	0.7168	0.0851	0.6964	0.0942	4.7×10^{-1}
52	MCP	right	0.7205	0.0820	0.6974	0.0860	$<10^{-15} *$
53	ICP	left	0.5699	0.1005	0.6306	0.0939	$<10^{-15} *$

label	Structures abbreviation	Left/right	CohPE of JHU-neo- SS		CohPE of Cus-neo- GA		p-value
			Mean	Std	Mean	Std	
54	ICP	right	0.5752	0.1177	0.6248	0.1090	$<10^{-15} *$
55	PCT	left	0.5928	0.1385	0.5905	0.1300	$<10^{-15} *$
56	PCT	right	0.6026	0.1244	0.5876	0.1353	6.3×10^{-1}
57	UNC	left	0.6871	0.0276	0.6853	0.0282	5.4×10^{-2}
58	UNC	right	0.7031	0.0414	0.7008	0.0422	4.3×10^{-1}
61	Pons	left	0.6205	0.1222	0.6475	0.1153	2.2×10^{-1}
62	Pons	right	0.6372	0.1313	0.6798	0.1010	$<10^{-15} *$
63	ML	left	0.6313	0.1236	0.6694	0.0990	$<10^{-15} *$
64	ML	right	0.5637	0.1532	0.6019	0.1537	$1.0 \times 10^{-4} *$
65	Medulla	left	0.4740	0.1307	0.5574	0.1194	$<10^{-15} *$
66	Medulla	right	0.5005	0.1137	0.5942	0.1034	$<10^{-15} *$

* $p < 8.9 \times 10^{-4}$