Multi-modal Surface-Based Alignment of Cortical Areas Using Intra-cortical T1 Contrast

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Abstract. The position of cortical areas in the brain is related to cortical folding patterns; however, intersubject variability remains, particularly for higher cortical areas. Current cortical surface registration techniques align cortical folding patterns using sulcal landmarks or cortical curvature, for instance. The alignment of cortical areas by these techniques is thus inherently limited by the sole use of geometric similarity metrics. Magnetic resonance imaging T1 maps show intra-cortical contrast that reflects myelin content, and thus can be used, in addition to cortical geometry, to improve the alignment of cortical areas. In this article, we present a new symmetric diffeomorphic multi-modal surface-based registration technique that works in the level-set framework. We demonstrate that the alignment of cortical areas is improved by using T1 maps. Finally, we present a unique group-average ultra-high resolution T1 map at multiple cortical depths, highlighting the registration accuracy achieved. The method can easily be extended to include other MR contrasts, such as functional data and anatomical connectivity, as well as other neuroimaging modalities.

Keywords: neuroimaging analysis, multi-modal, multi-contrast, surface registration, cortical areas, cortical folding, cortical curvature, cortical morphometry, myelin, quantitative T1, brain mapping, group analysis.

1 Introduction

In magnetic resonance imaging (MRI) studies of the cerebral cortex, surface-based registration, based on aligning the geometry of 2D manifolds, is often preferred over volume-based registration to align cortical areas between subjects or with an atlas. Cortical areas that are close in volume space may be very distant from each other along the cortical surface. The pioneering work of Brodmann [1] and recent neuroimaging studies [2, 3] have analyzed the relationship between cortical folding patterns and the functional/architectonic boundaries of cortical areas, which is particularly strong for primary cortical areas. Surface-based registration driven by cortical folding patterns has been shown to improve

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the statistical power and spatial specificity of group functional MRI analysis [4]. Current surface-based registration techniques use a variety of similarity metrics to describe cortical geometry: manually or automatically defined landmarks such as sulcal curves [5,6], automatic shape features such as curvature and sulcal depth [7–10], or a combination of both [11]. Pantazis et al. present a comparison of different methods [12]. Unfortunately, the relationship between cortical folding patterns and architectonic areal boundaries is complex and variable, particularly in higher cortical areas and regions of high inter-subject folding variability. Thus the alignment of cortical areas is inherently limited by the sole use of geometric similarity metrics.

Recent studies have shown intra-cortical contrast in group average T1 maps [13, 14], T2* maps [15] and T1-weighted/T2-weighted images [16]. Primary areas as well as extrastriate visual areas, which are more densely myelinated, are clearly discernible in these images mapped onto the inflated cortical surface. More discrete contrast is also visible in other regions, including the frontal lobe. We propose to use T1 maps, a quantitative index of myelin density [13], to improve the surface-based alignment of cortical areas. High-resolution T1 maps show exquisite intra-cortical contrast that varies as a function of cortical depth.

We present a novel automated surface-based registration technique for accurate surface registration, with key improvements over current methods. Our method provides a direct symmetric diffeomorphic transformation between the original surfaces. Similarly to Tosun et al. [8], we developped a multi-scale approach that is applied to partially inflated surfaces. Our multi-modal technique applies SyN [17], one of the leading non-linear volume-based registration algorithms [18], to surface information represented in volume space. We include two geometrical contrasts, the level-set representation of the cortical surface and cortical curvature, and intra-cortical T1 contrast. The method can be extended to include other MR contrasts and neuroimaging modalities instead of or in addition to T1, such as functional data.

Our surface-based registration technique can be applied to standard clinical data sets (typically 1 mm isotropic T1-weighted images) using the geometrical contrasts only, similarly to currently available methods. We chose to include ultra-high resolution T1 maps of five subjects to demonstrate the full potential of our technique. We evaluate the addition of T1 contrast to surface-based registration by comparison to our purely geometric implementation. Finally, we show the resulting group-average high-resolution T1 map at different cortical depths.

2 Methods

2.1 Data Acquisition and Pre-processing

Five subjects were scanned on a 7 Tesla (T) MR scanner with a 24-channel receive-only head coil. T1 maps were acquired using the MP2RAGE sequence ($TI_1/TI_2 = 900/2750$ ms, TR = 5 s, TE = 2.45 ms, $\alpha_1/\alpha_2 = 5°/3°$, bandwidth = 250 Hz/px, echo spacing = 6.8 ms, partial Fourier = 6/8) [19]. A whole brain scan was performed at 0.7 mm isotropic resolution with a GRAPPA acceleration

factor of 2 (11 minutes), followed by a 0.5 mm isotropic scan (28 minutes) of each hemisphere for a total scan time of 67 minutes. In the inferior temporal lobes, the image quality was impaired due to insufficient radiofrequency transmit field provided by the coil. We do not discuss the results in this area. The B1 transmission field homogeneity could be improved by using dielectric pads in future studies [20]. A major concern at high resolutions and long scan times is subject motion. We selected subjects with previous scanning experience and detected no gross motion artifacts, such as ringing or blurring, in the images. An example of a 0.5 mm^3 T1 map is shown in Fig. 1.

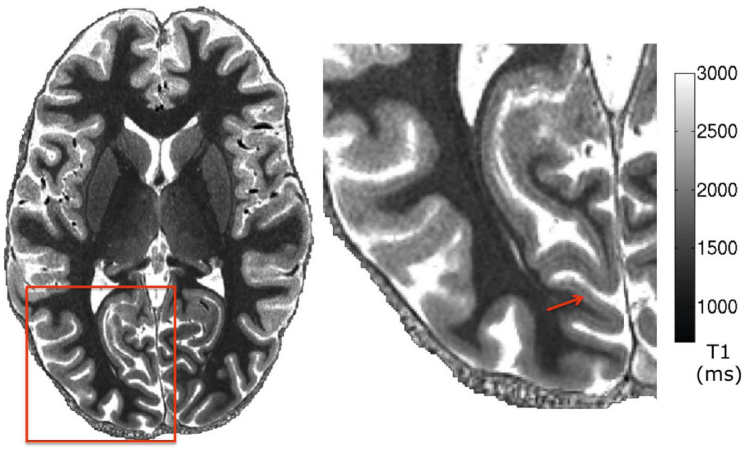

Fig. 1. Axial view of a co-registered and fused T1 map at 0.4 mm isotropic resolution displaying intra-cortical contrast, including layer structure such as the Stria of Gennari (red arrow)

The three T1 maps were co-registered into MNI space at 0.4 mm isotropic to minimize blurring caused by resampling, and the 0.5 mm images were fused to generate a whole brain T1 map. The resulting T1 maps were segmented [21] and the cortical surfaces of the left hemispheres reconstructed [22]. Realistic cortical layers (20 in number) were defined using a novel volume-preserving layering model [23], which follows the cortical laminae in areas of curvature. Cortical profiles were reconstructed perpendicularly to these layers. The level-set corresponding to the middle of the cortex (layer 10) was used for registration. The T1 times corresponding to the central 10 layers of the cortical profiles were averaged for registration. We excluded the first and last pairs of layers to minimize partial volume effects with white matter and cerebral spinal fluid, and divided the remaining 16 layers into 4 groups: Layer 1 (outer - near pial surface), Layer 2 (outer middle), Layer 3 (inner middle), and Layer 4 (deep - near white matter surface). Once the 0.4 mm isotropic T1 maps were sampled at the appropriate cortical depths, the images were downsampled to an isotropic resolution of 0.8 mm for the registration process. This will only affect the resolution in the tangential plane of the cortical surface.

2.2 Surface Registration

The surface registration algorithm we present here applies SyN, a symmetric image normalization algorithm that maximizes the cross-correlation within the space of diffeomorphic maps [17], to level-set representations of cortical surfaces and cortical features mapped onto these surfaces, curvature and T1.

We used a multi-scale approach by partially inflating the level-set surface φ using Eq. 1, where G is a Gaussian kernel and κ is the surface curvature. Eq. 1 is applied iteratively until the desired level of inflation is reached. The four scales used in our experiments are illustrated in Fig. 2. The SyN algorithm was applied at each scale using a specific set of coarse, medium and fine iterations.

$$\frac{\partial \varphi}{\partial t} = [(\varphi - G * \varphi_0) - \kappa] \cdot |\Delta \varphi| \tag{1}$$

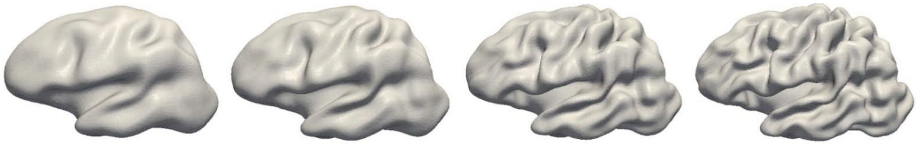

Fig. 2. The four cortical inflation scales at which the SyN algorithm is applied, from left to right, to gradually refine the mapping between two surfaces

The width of the level-set narrow band at each scale was equal to the maximum distance d between the source and target level-sets. The level-set φ was modulated using the sigmoid function in Eq. 2, where the slope is steepest at the intersection with the surface.

$$\tilde{\varphi} = \frac{1}{1 + e^{4\varphi/d}} \tag{2}$$

In addition to this contrast, which is radial to the cortical surface, we used curvature and T1 as tangential image contrasts. The curvature was calculated at each inflation scale as the product of the shape index and the curvedness [24]. The T1 times were smoothed tangential to the cortical surface using a Gaussian kernel of 3 mm FWHM for the purpose of registration only. The resulting T1 times were mapped to each scale during the inflation process by coordinate tracking [25]. For both tangential contrasts, curvature and T1, the values were dilated radially from the surface to the full width of the narrow band. The tangential contrasts were linearly rescaled to the range [-0.5, 0.5]. An example of the three contrasts is shown in Fig. 3.

The radial and tangential contrasts had an equal weighting of one. We performed three surface registration experiments with different tangential contrast combinations: 1) curvature only, 2) half curvature half T1, and 3) T1 only. The three contrasts were used to measure convergence. The cortical surface of a single subject was chosen as the target. After registration, the unmodulated level-sets,

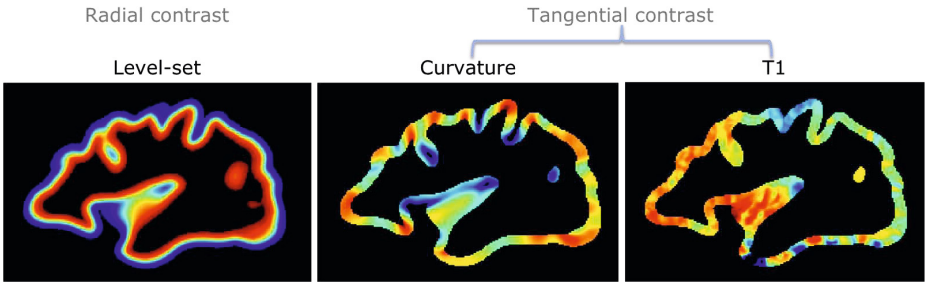

Fig. 3. Sagittal view of the three image contrasts used to align the partially inflated cortical surfaces: the level-set that varies radially to the surface, the curvature and T1 that vary tangentially to the surface

curvature maps and unsmoothed T1 maps at the final inflation scale were transformed using the direct mapping and averaged across the five subjects.

3 Results

The group-average T1 maps, corresponding to the mean of the middle 10 layers of the cortex, shown in Fig. 4. Primary areas, which are more densely myelinated, exhibit a shorter T1. The results from the three experiments using different contrast combinations are very similar. This observation agrees with previous reports that cortical areas are correlated with cortical folding. However, there are some small, yet important, differences between the averaged T1 maps which are highlighted in Fig. 4. For instance, in the average registered by T1 alone, the boundaries of the primary motor (M1) and somatosensory (S1) cortices are sharpest, mainly in the direction parallel to the central sulcus. We can also see a clearer cluster of decreased T1 times on the lateral occipital cortex corresponding to the motion-sensitive visual area V5/MT+. The frontal cortex contains more structure in the average T1 maps by using T1, including two clusters of decreased T1 in the inferior frontal gyrus corresponding to Broca's area (Brodmann areas 44 and 45, related to speech and language). The cingulate cortex, a very fine structure that is more difficult to register using smoothed data or inflated surfaces, is also better aligned using T1 contrast.

The level-set standard deviation shown in the first row of Fig. 5 represents the standard deviation of the remaining distance between the registered surfaces. These values are very low for all three experiments, and lowest for experiment 2 that combines all three contrasts for registration. This may be because the level-set has the strongest relative weighting of the three contrasts in experiment 2. There is an area of high standard deviation in the temporal lobe and near V5/MT+ where there is known to be intersubject variability in cortical

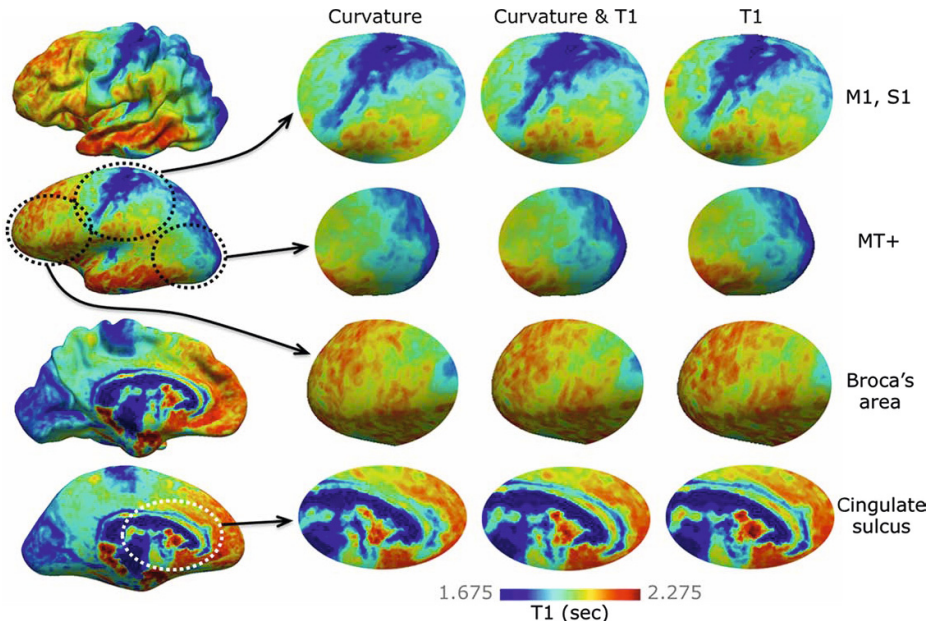

Fig. 4. Group-average of the aligned 0.8 mm isotropic unsmoothed T1 maps for the three tangential contrast combinations used for registration: 1) curvature, 2) curvature and T1, 3) T1. Regions of interest (ROIs) are outlined on the surfaces on the left, and zoomed-in on the right. ROIs are centred around (in vertical order): M1 and S1, MT+, Broca's area, cingulate sulcus.

folding patterns. There is also a higher standard deviation in the frontal lobe near higher cognitive areas that have a weaker relationship with cortical folding. It may therefore be more difficult to optimize both T1 and level-set alignment in these areas.

The curvature standard deviation in the second row of Fig. 5 is lowest for experiment 1, as expected. The penalty of using only T1 contrast in experiment 3 is very small. This may be because the level-sets themselves include information about the geometry of the cortex. There is a small increase in standard deviation at the sulcal fundi, where the curvature gradients are strongest, and a decrease at the gyral crowns. The increase in standard deviation in experiments 2 and 3 is indicative that the relationship between cortical areas and cortical folding is variable, as highlighted in previous studies [2].

The curvature standard deviation only highlights alignment errors perpendicular to the cortical folds. In contrast, the T1 standard deviation is a representation of the error in alignment of cortical areas, based on tissue microstructure, in all directions within the cortical surface. The T1-driven surface-based registration results from experiment 3 are characterized by a reduction in intersubject

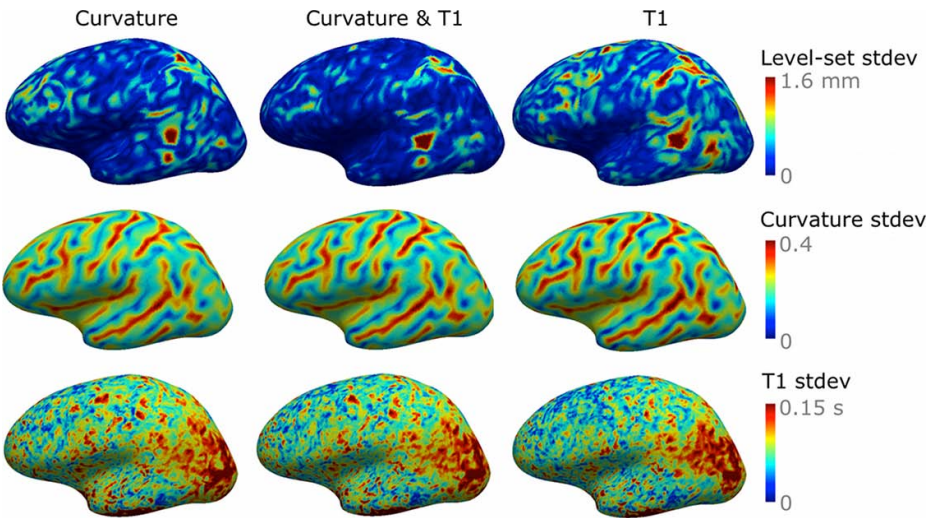

Fig. 5. Group-standard deviations of the aligned 0.8 mm isotropic image contrasts (rows: level-set, curvature, T1) for the three registration experiments (columns): 1) curvature, 2) curvature and T1, 3) T1. All experiments include the level-set contrast.

variability in T1 times, as shown in Fig. 5, even near the boundaries of primary areas. There is a strong decrease in T1 standard deviation in proximity to the cingulate cortex, at the eccentricity boundary of the primary visual cortex (V1) and in the frontal lobe. There is a cluster of high T1 variability on the lateral occipital and inferior parietal cortex for all three experiments, although it is most widespread for curvature-based and most focused for T1-based registration. The curvature-based registration is penalized by high intersubject variability in cortical folding patterns in this area, whereas the T1-based registration benefits from the T1 contrast arising from the highly myelinated extrastriate visual areas.

In Fig. 6, the T1 times from T1-based registration are shown for four different cortical depths, defined in Section 2.1. The T1 contrast varies significantly with cortical depth. The most striking examples are the greater contrast between M1 and S1 in Layer 3 in comparison to Layer 1, and the contrast between V5/MT+ and neighbouring cortex for deeper Layers 3 and 4 in comparison to superficial Layers 1 and 2. Brodmann areas 44 and 45 in the frontal lobe also show a distinct laminar structure, with highest contrast in Layer 2. Although these observations of the group-averaged T1 laminar structure of cortical areas are preliminary, they are in agreement with myeloarchitectonic descriptions of the cortex and indicate that careful alignment of T1 along the cortical surface can outline many cortical boundaries based on MR imaging of tissue microstructure.

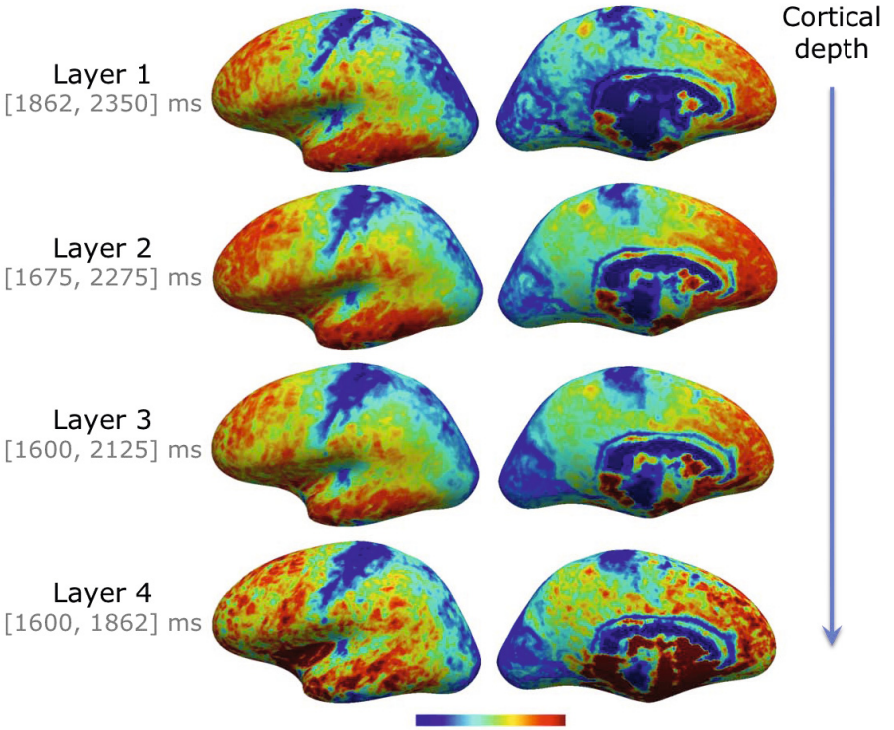

Fig. 6. Group-average of the aligned 0.4 mm isotropic unsmoothed T1 maps for the four cortical layers defined in Section 2.1. T1 generally becomes longer towards the pial surface, thus the T1 scales are different for each layer to highlight the inter-layer differences in T1 contrast.

4 Conclusion

We developed a novel surface-based registration technique that provides highly accurate symmetric diffeomorphic mappings between the original surfaces. The multi-scale approach based on partial levelset inflation improves the registration of the cortex over the SyN algorithm applied directly. This approach avoids reparametrization to a sphere and minimizes distortions. We work with the natural shape of the anatomy, making it a more general framework that is not limited to cortical surfaces.The low standard deviation of the level-sets across subjects clearly shows the high precision that was achieved. Errors in the target cortical surface could mislead the registration process, therefore future group registration experiments could alternatively be performed as an evolving group average template. Additional inflation scales can be included until complete registration or the original level-sets is achieved at the cost of processing time. This may be more suitable for morphometry as opposed to functional studies.

We demonstrated that the inclusion of T1 maps improves the alignment of cortical areas without deteriorating the geometric alignment (or at minor costs in geometric alignment). The alignment is improved for primary cortical areas, which are known to have a close relationship to cortical folding patterns, mainly in the direction parallel to the cortical folds. There are also improvements in the alignment of cortical areas that are more variable with respect to cortical folding patterns, and in the alignment of fine cortical structures. The alignment of cortical areas which exhibit strong T1 contrast may also improve the alignment of neighbouring areas with weaker differences in T1, assuming that the topology of cortical areas is consistent across subjects.

The exceptional image quality of the ultra-high resolution T1 maps allowed us to show unprecedented structural detail at the group level, including differences in T1 times between cortical layers. This represents a big step for in vivo brain mapping based on microstructure, a new and exciting direction of research [26]. High-resolution and quantitative data sets are becoming more widely available with developments in image acquisition at 3 T and higher field strengths [14,27], and bring new challenges and opportunities to image processing.

Our novel surface-based registration technique can be applied to a very wide range of datasets, both in terms of image resolution and contrasts. Our technique can be applied to standard datasets, typically $1\,\mathrm{mm}^3$ T1-weighted images, as other cortical surface alignment tools. In addition, surfaces created using other software packages, such as FreeSurfer, can be imported into our framework for registration. The $0.4\,\mathrm{mm}^3$ images were downsampled to $0.8\,\mathrm{mm}^3$ to reduce computation time. However, the algorithm has also been tested on the original $0.4\,\mathrm{mm}^3$ data as well as images at $1\,\mathrm{mm}^3$ resolution. The multi-modal approach can be extended to include other modalities, in addition to or instead of T1, that feature intra-cortical contrast of interest for brain parcellation. Future work will include the use of other MR contrasts that reflect cortical microstructure (eg. T2* and quantitative susceptibility mapping), as well as multi-layer contrast in high-resolution images. Another interesting application would be the inclusion of functional and anatomical connectivity data.

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