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Tests of cortical parcellation based on white matter connectivity using Diffusion Tensor Imaging

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Abstract

The cerebral cortex is conventionally divided into a number of domains based on cytoarchitectural features. Diffusion tensor imaging (DTI) enables non-invasive parcellation of the cortex based on white matter connectivity patterns. However, the correspondence between DTI-connectivity-based and cytoarchitectural parcellation has not been systematically established. In this study, we compared histological parcellation of New World monkey neocortex to DTI connectivity-based classification and clustering in the same brains. First, we used supervised classification to parcellate parieto-frontal cortex based on DTI tractograms and the cytoarchitectural prior (obtained using Nissl staining). We performed both within and across sample classification, showing reasonable classification performance in both conditions. Second, we used unsupervised clustering to parcellate the cortex and compared the clusters to the cytoarchitectonic standard. We then explored the similarities and differences with several post-hoc analyses, highlighting underlying principles that drive the DTI-connectivity-based parcellation. The differences in parcellation between DTI-connectivity and Nissl histology probably represent both DTI's bias toward easily-tracked bundles and true differences between cytoarchitectural and connectivity defined domains. DTI tractograms appear to cluster more according to functional networks, rather than mapping directly onto cytoarchitectonic domains. Our results show that caution should be used when DTI-tractography classification, based on data from another brain, is used as a surrogate for cytoarchitectural parcellation.

Keywords

Cortical parcellation; DTI tractography; white matter connectivity; classification; cross-validation

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1. Introduction

Parcellation of cerebral cortex is a prerequisite for understanding the structure and function of the brain. Traditional parcellation methods rely on distinguishing microstructural features or electrically stimulated movement, e.g., cytoarchitecture [1–3], myeloarchitecture [2, 4], electrophysiological observation [5], immunohistochemistry [6] and receptor autoradiography [7]. Although these methods allow us to identify microstructural borders, they are extremely time- and labor-intensive, and are exclusively applicable to postmortem tissue or invasive studies. By contrast, modern neuroimaging methods, especially magnetic resonance imaging (MRI) techniques, are capable of parcellating the living cerebral cortex noninvasively. In an individual's MRI images, each cortical voxel can be assigned to a certain domain based on template-derived warping [8–10], surface-based or volume-based geometrical features [11–13], and contrast associated with myelin content [14], which are all local cortical features.

Diffusion tensor imaging (DTI) [15] and DTI-derived tractography [16–19] are unique in their ability to estimate white matter pathways throughout the brain, *in vivo*. The hypothesis that the cortical surface can be parcellated reliably using DTI is the foundation for potentially important new tools for systems and clinical neuroscience. The underlying assumption is that intra-domain voxels should have greater similarity of connectivity than would inter-domain voxels. For example, Johansen-Berg et al. found the border between the supplementary motor area (SMA) and pre-SMA by locating an abrupt change in connectivity patterns [20]. Anwander et al. subdivided Broca's area by automatic clustering of the correlations among connectivity signatures [21].

Although the accuracy of diffusion models and tractography has been evaluated [22–29], there are few studies that investigate the correspondence between DTI-connectivity based and cytoarchitectural parcellation. Some previous parcellation studies have tested the agreement of DTI with information from other modalities, e.g., Johansen-Berg [20] compared centers-of-gravity of connectivity-derived SMA/pre-SMA volumes to the task fMRI-based parcellation from the same individual. Similarly, Anwander [21] compared probability maps of Brodmann's area 44/45 derived from DTI connectivity with previously published cytoarchitectonic domains in atlas space. However, these tests focused on relatively small and specific regions, which limit their applicability to larger cortical areas. In addition, comparisons made between two different groups of subjects introduce a potential confounding factor due to uncontrolled variations between individuals.

Therefore, in this study, we performed DTI-WM-connectivity-based parcellation over a large cortical area, including the frontal and parietal lobes, in squirrel monkey brains. We focused attention on the following specific questions. First, to what extent does DTI-connectivity-based parcellation reflect cytoarchitectonic parcellation within the same brain? Second, to what extent does DTI-connectivity-based parcellation reflect cytoarchitecture across brains? Third, what does blind DTI-connectivity-based parcellation look like and why? To address these questions, we 1) trained classifiers with DTI-WM-connectivity features using the cytoarchitectonic labels on cortical training points, then classified the cortical test points in

the same monkey, and evaluated the true positive rate; 2) trained the classifiers on one monkey's cortical points, then classified another monkey's cortical points and evaluated the true positive rate; and 3) clustered the cortical points with DTI-WM-connectivity features, and then assessed the correspondence of the resulting clusters to the cytoarchitectural labels. True positive rates were calculated relative to the cytoarchitectural parcellation derived from traditional Nissl stains. Finally, we investigated why the unsupervised clustering results are different from histological domains using several post-hoc analyses.

2. Methods

2.1 Overview

Three squirrel monkeys were included in this study. The analysis pipeline is graphically shown in Fig. 1 and briefly summarized as follows. First, the monkey brains were scanned *ex vivo* using MRI and the cerebral cortical points were classified or clustered with DTI-WM-connectivity-based features. In addition, the cerebral cortices were parcellated based on Nissl-revealed cytoarchitecture. Next, the correspondence between DTI-connectivity parcellation and cytoarchitectonic parcellation was evaluated.

2.2 DTI-Connectivity-based Parcellation and Evaluation

2.2.1 Diffusion Weighted Imaging, Tractography and Feature Vector

Calculation—The animals were perfusion fixed as described previously [23, 30]. Each fixed brain was scanned on a 9.4T Agilent scanner. First, T2-weighted structural images were acquired by running a standard gradient echo multi-slice (GEMS) sequence with full brain coverage (TR=963ms, TE=4ms, flip angle=20°, voxel size=300µm isotropic, data matrix=192×128×115, SNR≈50). Then diffusion weighted imaging was performed using a pulsed gradient spin echo (PGSE) sequence [31] with the same FOV as the structural images (TR=5.2s, TE=26ms, number of diffusion gradient directions=31, b=0 and 1000s/mm², voxel size=300µm isotropic, data matrix=192×128×115, number of acquisitions=10, SNR≈30, scanning time≈50hr). The b value used in this experiment was lower than is optimal for diffusion studies in fixed tissue, due to hardware limitations. A low b value decreases the available diffusion contrast-to-noise ratio (CNR) in the image data, which has the same effect as higher image noise. To compensate for this shortcoming, we extended the scan time to 50 hours, which yielded a CNR comparable to *in vivo* human studies (equivalent to an *in vivo* study with mean diffusivity $\approx 0.7 \times 10^{-3}$ mm²/s and SNR≈20).

The FSL diffusion tool (FDT, <http://fsl.fmrib.ox.ac.uk/fsl/fslwiki/FDT/>) was used to correct eddy current effects, fit a multi-compartment diffusion model and perform probabilistic tractography [32]. The seed voxels were those located at the white-gray matter (WGM) interface underneath the 16 cortical domains (see Table 1); the number of seed voxels was on the order of ten thousand. The WGM interface was the boundary of the white matter mask which was segmented using a variational level set approach [33] on the aligned T2 images. Probabilistic tractography was initiated from each individual seed voxel (sample number per seed = 5000, curvature threshold = 0.2, modified Euler streamlining = on, step length = 0.1 mm and distance correction = on), yielding a 3D density map of tracts, the so-called tractogram, corresponding to that seed voxel. The (approximately) ten thousand runs

of tractography were submitted to the Advanced Computing Center for Research and Education (ACCRE) for distributed computation.

For convenience of computation, each tractogram was downsampled at rate of 2.5 [20] in each dimension and the downsampled tractogram was then squeezed into a 1D vector representing features of the corresponding seed voxel. In machine learning terms, each seed voxel is an observation and the 1D vector is the feature vector.

2.2.2 Classification Similarity: Intra-Monkey—To quantify the similarity between DTI-based and histological classification within each animal, 10% of the seed voxels were randomly selected to be training seeds and the other 90% in the same monkey were the test seeds. Given the training feature vectors along with their cytoarchitectonic class labels (obtained as described in section 2.3), three classifiers were trained, including K-nearest neighbors (KNN), support vector machine (SVM), and decision tree (DT). In KNN method, the number of nearest neighbors used was one and distance was Euclidean distance. In SVM method, we chose one-against-one or pairwise strategy, with linear kernel function. All the other parameters were default settings in MATLAB built-in functions. Each classifier was then applied to the test feature vectors, assigning a domain to each test seed. Two feature vectors were investigated: the tractogram and the binary mask of the tractogram. The threshold for binarization was 250, which was 5% of the number of samples per seed.

We calculated two rates of agreement, RI and rI for each scheme. RI is a ratio of the number of test seeds that agree with the histological classes to the total number of test seeds. This rate indicates how many out of the total number of seeds received the same classification by DTI and histology. rI is the ratio of the number of seeds in the intersection of a histological domain and its corresponding DTI-connectivity-derived class to the union of this domain and class.

2.2.3 Classification Similarity: Inter-Monkey—To determine how well the classifiers generalize to other brains, the inter-monkey similarity of DTI and histological classification was assessed. Given two squirrel monkey brains, B1 and B2, the seeds from monkey B1 were used as training seeds and those from B2 as test seeds. Probabilistic tractography originating from each individual seed point was performed in the brain's native space. The training tractograms in B1 were transformed into B2's native space by applying the 3D deformation field derived from registering B1's b=0 volume to B2's. The transformed training tractograms and native test tractograms were downsampled at a rate of 2.5 (in each dimension) and then squeezed into 1D feature vectors. The classifiers (i.e., SVM, KNN, and DT) were trained with the training feature vectors and cytoarchitectonic labels in B2's native space and then were applied to the test seeds. Two feature vectors were investigated: the tractogram and the binary mask of the tractogram. To measure the similarity of histology and DTI using each classification scheme, we calculated the agreement rates with the same definition as RI and rI , in this case denoted by $R2$ and $r2$.

2.2.4 Unsupervised Parcellation and Evaluation—Two classic clustering algorithms were implemented to partition the feature vectors of each monkey: (1) naïve k -means and (2) hierarchical clustering (agglomerative algorithm). Each hemisphere was clustered separately

and the number of clusters for each hemisphere was set up to be 8. The distance metric used was cosine distance. To evaluate the agreement between histology and unsupervised parcellation of DTI data, we calculated the average (over clusters) maximum of the Jaccard similarity coefficients between one cluster and each of the 16 histological domains, denoted by J . To visually judge how well the unsupervised clusters or histological domains were separated from the point of view of machine learning, we calculated a similarity matrix for each case and then re-ordered the similarity matrix based on labels of clusters or domains. Each row or column corresponds to a seed point. The similarity measure is cosine similarity, i.e., cosine of the included angle between the feature vectors of two seed points. Besides reordering between groups, the rows and columns within each cluster or domain were sorted by the point-to-centroid similarities. The point-to-centroid similarity is the similarity between the feature vector of one seed point in a cluster and the average feature vector of all the seed points within the same cluster.

To quantitatively compare unsupervised clustering and histological parcellation, we calculated the within-cluster ‘energy,’ the sum of point-to-centroid distances for each k -means clustering case, denoted by E_{kmeans} , and for each histological parcellation, denoted by E_{histo} . The distance metric used was the cosine distance.

2.3 Cytoarchitectonic Parcellation

The same procedure for acquiring histological labels was repeated on all three monkey brains and will be described for one brain for convenience.

2.3.1 Electrophysiological Mapping and Tracer Injection—We used the bidirectional neurotracer, biotinylated dextran amine (BDA), to label the forelimb projection areas in M1. All animal procedures were approved by the Vanderbilt University Animal Care and Use Committee, and followed guidelines of the National Institutes of Health for the care and use of laboratory animals. Intracortical electrical stimulation was performed to identify functional zones in M1. Those zones included trunk, forelimb and face representation areas, which evoked movement of the corresponding body part under stimulation. Then, BDA was injected into 8–10 sites within the forelimb representation area at 1mm intervals. More details of the procedure are given in our previous publications [23, 34, 35].

2.3.2 Sectioning, Staining and Image Digitization—After the *ex vivo* MRI scan (described in the above section), the brain was immediately placed in 30% sucrose for cryoprotection. Two days later, the brain was cut serially on a frozen microtome in the coronal plane in 50 μ m thick slices. Prior to cutting off every third slice (i.e., at 150 μ m intervals), the remaining frozen tissue block was photographed using a Cannon digital camera (image resolution=50 μ m/pixel, image size=3330 $\times$ 4000pixels) rigidly mounted above the microtome to facilitate registration from micrograph space to MRI space [36].

The serial slices were divided into 5 or 6 interleaved series. One series was processed for Nissl substance [37]. The Nissl stained slices were photographed digitally under 0.5 $\times$ magnification using a Nikon DXM1200F digital camera mounted on a Nikon E-800 microscope (image resolution=7 μ m/pixel, image size=6660 $\times$ 6660pixels). Each image was

defined as a “standard micrograph”. Another series was processed for BDA and photographed.

2.3.3 Identification and Extraction of Domains—An expert neuroanatomist identified the borders of each cortical domain based on cytoarchitectonic features (e.g., cell topology, lamination, etc.) [34, 35], revealed by Nissl stain observed under microscopy or on a tablet computer displaying high resolution micrographs; and then drew the borders on the standard micrographs. Eight pairs of cortical domains were identified, which together covered most of the frontal and parietal lobes—these are listed in Table 1. A stack of 2D enclosed contours of each cortical domain was manually drawn on the micrographs. The voxels corresponding to each domain were extracted as a stack of 2D binary masks in the space of standard micrographs.

2.3.4 Transformation to DTI space—Standard micrographs were registered to the DTI space in a multiple-step procedure. First, every standard micrograph was down-sampled (to 256×256 pixels) and registered to the down-sampled photograph (256×256 pixels) of the corresponding tissue block through a 2D affine transformation followed by a 2D non-rigid transformation, automatically calculated using the adaptive bases algorithm (ABA) [38]. Next, all the down-sampled block photographs were assembled into a block volume, then registered to the DTI volume using a 3D affine transformation followed by a 3D non-rigid transformation via ABA. The registration procedure was very similar to the one validated in Choe’s work [30], which showed that the accuracy of the overall registration was approximately one MRI voxel (0.3mm).

For each cytoarchitectonic domain, the deformation fields were applied to the stack of 2D masks of the domain in standard micrograph space, yielding a 3D binary mask of the domain in DTI space. All the voxels inside the domain were assigned a cytoarchitectonic class label number.

2.4 White Matter Tract Identification

To interpret the results of DTI-connectivity-based parcellation from an anatomical perspective, we identified several white matter (WM) bundles in the monkey brains (see [39] for more details). Tensor estimation, seed region selection, deterministic fiber tractography, and trimming fiber tracts were all performed in DSI Studio (<http://dsi-studio.labsolver.org>) [40]. Since WM anatomy of the squirrel monkey brain is similar to that of macaque, we used delineated WM regions revealed by histological tracer pathways of the macaque brain [41] as a reference for seed definition and to refine the tracts (i.e., select, delete and cut) by editing ROIs. The tracking parameters, primarily including termination FA threshold, termination angle threshold, step size and smoothing size, were adjusted slightly according to the characteristics of each WM bundle. Each WM bundle was tracked, edited and stored as a single 3D fiber density map through DSI Studio. Then the density map was thresholded to remove the voxels with less than 3%–5% average density, yielding a binary mask. The binary mask could be used as a new seed region to repeat the above process iteratively until the quality was good. The criteria of “good” include correctness of 1) the coarse shape and

orientation of the WM bundle; 2) the gray matter structures or ventricles next to the WM bundle along the entire pathway and 3) the cortical regions connected by the WM bundle.

3. Results

3.1 Classification Similarity: Intra-Monkey

Rows 1–3 in Fig. 2 display the classified test points (column 1–6) and histological domains (column 7) in each monkey's native DWI space. The overall agreement rate, $R1$, for each case is in the range 0.70–0.87. The variation of $R1$ between the tractogram feature vector (column ①) and binary feature vector (column ②) is not significant for any of the classification methods. Row 4 in Fig. 2 shows the average agreement rate, $r1$, for each domain across three monkeys.

3.2 Classification Similarity: Inter-Monkey

Rows 1–3 in Fig. 3 display classified points (column 1–6) and histological domains (column 7) in each test monkey's native DWI space. The overall agreement rate, $R2$, for each case is in the range of 0.38–0.86. The variation of $R2$ between the tractogram feature vector (column ①) and binary feature vector (column ②) is not significant for any of the classification methods. Row 4 in Fig. 3 shows the average agreement rate, $r2$, for each domain across three monkeys. Figure 4 displays more detail with three views on the best case from Fig. 3 – monkey B3's parcellation using KNN method and histological domains.

3.3 Unsupervised Parcellation and Evaluation

Figure 5 displays clustered points (columns 1–4) and histological domains (column 5) in each monkey's native DWI space. The overall Jaccard index, J , for each case is in the range 0.18–0.44. The variation of J between the tractogram feature vector (column ①) and binary feature vector (column ②) is not significant for any of the classification methods.

To explore the reasons the data-driven clusters differ from the histological domains, we studied the connectivity profiles in greater detail. Figure 6 illustrates one possible source of bias. Four seed voxels were selected, located at dorsal M1 (point 1), lateral M1 (point 2), dorsal PM (point 3) and lateral PM (point 4) in the left hemisphere, displayed on histological domains and unsupervised clusters for reference, shown in Fig. 6AB. Four fiber pathways (tracts 1–4) originating from those seed points were overlaid on FA maps in Fig. 6C. Tract 1 traveled immediately beneath cortex, within SLFII, and terminated in superior PM and PA. Tract 2 traveled via SLFIII to CR and EC, via FCCb then the body of CC to the opposite hemisphere, and via IC downwards. Tract 3 traveled within SLFII. Tract 4 traveled via SLFIII to CR, via FCCb then CC to the opposite hemisphere, and via IC down to the peduncle. Figure 6D quantifies the projection of pathways on the major fiber bundles identified previously. Both visible tracts (6C) and the fiber density matrix (6D) indicate that tracts 2 and 4 have more similar distributions than tracts 1 and 2 do. Hence, points 2 and 4 were grouped into the same cluster, which is located laterally through PM, M1 and PA, as shown in Fig. 6B. This is shown in greater detail in Fig. 7, which demonstrates that the connectivities of the forelimb areas are similar in PM and M1 (points 1 and 3) and the connectivities of the face areas are similar in PM and M1 (points 2 and 4). These similarities

are greater than between the forelimb and face areas within either PM or M1. This reflects the existence of parallel but similar connection patterns across cortical regions.

Figure 8 illustrates similarity matrices along with energies for k-means clustering (below the diagonal, where color indicates cosine similarity values) and histological parcellation (above the diagonal, where color indicates cosine similarity values) of each monkey. The hot line segments outline diagonal blocks representing the k-means clusters and histological domains. The energy results indicate that E_{kmeans} is significantly lower than E_{histo} for every monkey, that is unsupervised clustering provides better separated clusters of tractography data than do the histological domains.

The correspondence between cortical domains and major white matter bundles is illustrated in Fig. 9. Figure 9A shows the “cortical domain-to-major bundle” connectivity matrix generated using the data from monkey B2. Each matrix element is the sum of FSL-derived fiber tracts originating from all seed points in the corresponding anatomical domain and located in the corresponding white matter bundle, normalized by number of seed points and then normalized by number of occupied voxels. Hence, every row in Fig. 9 can be viewed as a low-dimensional feature vector for parcellation, with relatively low sensitivity because each feature variable corresponds to an entire major white matter bundle. We surveyed the literature to summarize the established connections between cortex and white matter fiber bundles. We based the summary on previous anatomical tracer studies in new world monkeys [35, 42–45] and the old world macaque [41, 46, 47]. Figure 9B shows our summary of the literature. White matrix elements indicate that histological connectivity has been reported either in New World or Old World monkeys (overall, the connectivity patterns are very similar, and therefore are not shown separately).

4. Discussion

The effectiveness of DTI-connectivity as a feature for cortical parcellation depends on two essential conditions: 1) that true anatomical connectivity is a reliable feature for parcellation and 2) that DTI tractography accurately reflects anatomical connectivity. In this study, ‘anatomical connectivity’ refers to the spatial distribution of connected white matter pathways.

To test the first condition, we assessed true anatomical connectivity using the results of tracer injection experiments. We surveyed the literature to summarize the established connections between cytoarchitectonic cortex and white matter fiber bundles (Fig. 9B). The DTI-tractography results in this study were used to generate a “cytoarchitectonic domain-to-major bundle” connectivity matrix, shown in Fig. 9A. Figure 9A indicates that each cytoarchitectonic cortical domain investigated in this study gives rise to a unique combination of major fiber bundles, and these are in good general agreement with the tracer literature (Fig 9B). It is conceivable that the white matter connectivity of cortical regions is intrinsically associated with their cytoarchitecture, because axon and cell body are parts of the same neuron. For example, M1 is characterized by a prominent layer V. The giant pyramidal neurons in layer V, Betz Cells, emit long axons down to the basal ganglia, brain stem and spinal cord. If the assumption is valid, then white matter connectivity would reflect

cytoarchitecture to some extent. In addition, Passingham et al. demonstrated that no two cortical domains share identical cortico-cortical connections [48], which also supports the view that each cortical domain has a unique white matter connection pattern. However, other factors could complicate this relationship. For example, previous studies have demonstrated that white matter connectivity is related to function [49, 50] and the specificity of cortical function might be finer than the detectable cytoarchitectural specificity [51]. Therefore, white matter connectivity likely carries information from both cytoarchitectural and functional domains. Passingham et al. also suggest that connectional fingerprints underlie the observed cell-firing differences between areas during different tasks.

The validity of the second condition has been discussed since DTI tractography was proposed: to what extent does DTI tractography represent white matter anatomical connectivity? To answer the question, several studies [23, 24, 26, 29, 52] have compared DTI-tractography connectivity with tracer-revealed connectivity, and found that they are largely in agreement but accuracy is limited by voxels in which axons are not parallel (i.e., fibers cross, diverge, or bend sharply). In practice, the accuracy of DTI tractography estimates of fiber structure depends on multiple factors: diffusion modeling method, tractography algorithm, data quality and so on [53]. In our study, the ball-and-stick diffusion model, 30 diffusion gradient directions and SNR together determine that two white matter bundles with 45 degrees or smaller angular difference in the same voxel would not be fully resolved [32]. Even if multiple fiber orientations could be resolved completely, tractography would be challenging since there is no unifying rule to specify how fibers should be tracked through all types of complex fiber geometries [27], especially given that complex voxels occupy at least one third of white matter voxels [32, 54]. However, the accuracy requirement might be loosened for the purpose of parcellation, as long as DTI-tractography captures the intra-domain similarity and inter-domain dissimilarity reliably. It has been shown that the variation of major white matter structures across individuals is small in most cases [55] and the reproducibility of DTI tractography is high [56]. Thus the uniqueness of connectivity features representing a domain may still hold, given the same tractography strategy and parameter settings. Although false positive (e.g., IAC-ISLFI) and false negative elements (e.g., IPF-PC) exist, if we compare DTI tractography results (Fig. 9A) with the assumed true anatomy (Fig. 9B), the unique distribution of fiber density originating from each cortical domain is preserved. Hence, on the coarse scale of entire cortical domains, connectivity appears to distinguish one domain from the others. This does not imply, however, that domains have homogeneous connectivity patterns on a finer spatial scale.

To balance sensitivity and computation cost, we chose to downsample data to an effective voxel size of 0.75mm isotropic for feature variable calculation in our tests, comparable (as a fraction of brain size) to previous human parcellation studies [20]. Principal component analysis is also a promising way to reduce feature variable dimensionality, but the agreement rate was not significantly better (data not shown). Figure 2 indicates the performance of the feature vectors by showing agreement rates of classifications using 10% of these feature vectors as training and the rest as the test dataset in the same monkey. The cytoarchitectonic labels of the training feature vectors are essentially the prior to derive the classification models. The agreement of the trained classifiers with histology is generally reasonable, based on the overall agreement rate, R . Using fiber density or the binary mask as feature

vectors did not show significant differences. Among all the domains, left and right SMA have the lowest agreement rates, $r1$. On one hand, approximately 20%–60% of histological SMA test seeds were assigned to the DTI-based AC, PM, M1 or PA class. On the other hand, about 20%–30% of assigned SMA points actually belong to other histological regions.

In most parcellation studies, the true labels (i.e., the prior) from the same individual may not be available, but the true labels from another individual or common reference template may be known. Interpreting cytoarchitectonic domains as the ‘true’ labels, Figure 3 indicates the agreement, $R2$, of inter-subject DTI parcellation is lower than the accuracy of intra-subject parcellation. Among all domains, SMA again has lower agreement rates, $r2$, for all the three classifiers. The lower agreement of inter-subject parcellation is probably due to the variation of white matter morphology across individuals and volume-to-volume misregistration. Based on our previous study, the dice indices for all the WM bundles in the common space across squirrel monkeys are between 5%–81%, depending on the bundle [39]. We also transferred histological domains from training to test monkey space using the same transformation field obtained in inter-monkey analyses and compared the transferred training-monkey domains with the test-monkey histological domains. We found that the average correspondence of histological domains across the three monkeys is around 0.76. Moreover, with respect to reproducibility of our results, we switched training and test monkey in each pair and repeated the procedure of inter-monkey comparisons for all the three pairs. The average $R2$ of the repeated pairs is very close to average of the original pairs (data not shown).

Unsupervised or ‘blind’ parcellation is purely data driven, meaning without any prior labels. As revealed by Fig. 5, the clusters located in the PM, M1 and sometimes PA domains are more extended in the anterior-posterior direction, rather than the medial-lateral direction of the cytoarchitectural domains. Especially the most lateral areas of M1 and PM tend to merge together in all the three monkeys. A previous tracer study of owl monkeys [35] reveals that dorsal PM is organized somatotopically, and is continuous with M1’s somatotopic segments, (in order from medial to lateral) hindlimb, trunk, forelimb and face representations. The most anterior part of PA, Brodmann area 3a, has a similar somatotopic pattern. Furthermore, somatotopic segments in PM, M1, and PA, representing the same part of the body are more strongly connected than are segments within M1 representing different parts of the body. For example, the forelimb area of M1 has much stronger connections to forelimb areas in PM and PA than to non-forelimb M1 areas (hindlimb, trunk, or face). The results of the tracer study imply that domains defined by connectivity should be different from those defined by cytoarchitecture, at least in sensorimotor cortex. Evidently, our unsupervised parcellation results reflect the connectional structure better than cytoarchitectural structure in the lateral motor cortex.

As shown in Fig. 6 and Fig. 7, the DTI pathways originating from lateral M1 and PM show greater similarity with each other than with pathways originating more medially within the same domain (M1 and PM, respectively). The most lateral area is likely the face representation area, shown in Figure 7C and 7F. On the one hand, the DTI callosal pathways from the medial part of M1 or PM were severely blocked by the SLFII bundle immediately beneath the cortex due to the well-known limitation of DTI tracking in regions of crossing fibers [32]. On the other hand, tracer studies in macaques [41] found that two separate white

matter cords from the face motor representation area entered the corpus callosum and internal capsule without apparent difference in quantity, but a massive contingent of fibers from the hand, trunk or foot motor representation areas entered the ipsilateral internal capsule and the remaining fibers went through the corpus callosum. Another tracer study in owl monkeys [57] found that the face motor representation has dense callosal connections; forelimb and hindlimb motor representations appeared to be less callosally-connected; especially the caudal motor forelimb and hindlimb have very slight callosal connections. Results in both species support the view that the relative strengths of connections can vary significantly between subareas within a given cortical domain. If these variations are repeated in somatotopically organized domains such as M1 and PM, it is not surprising that DTI tractography would cluster homologous subareas across domain boundaries. According to Fig. 8, unsupervised DTI tractography-based clustering generates clusters with higher within-cluster similarity, lower cross-cluster similarity, and lower overall energy than do histological domains. The results shown in Figs 5–8 suggest that DTI tractography-based parcellation carries different information from Nissl cytoarchitecture. Hence, the difference between DTI-clusters and Nissl-defined domains probably represents a combination of DTI tracking errors and true differences in the spatial variation of connectivity and cytoarchitecture features. In any case, our results show that caution should be used when DTI-tractography classification, based on data from another brain, is used as a surrogate for cytoarchitectural parcellation. However, improvements in tracking algorithms may make tractography a reliable measure of true anatomical connectivity across individuals, providing new information on human brain connectivity and structure.

5. CONCLUSION

In summary, our study found that 1) intra-monkey supervised DTI-WM based parcellation had up to 87% agreement with cytoarchitectonic parcellation 2) inter-monkey supervised parcellation had up to 71% agreement and 3) unsupervised parcellation had 39% agreement. The differences between DTI-WM-based parcellation and Nissl histology probably represent both DTI tracking errors and true differences between cytoarchitectural and WM connectivity defined domains. DTI-WM connectivity seems to cluster more according to functional properties, rather than simply mapping onto cytoarchitecture. Finally, caution should be used when DTI-tractography classification, based on data from another brain, is used as a surrogate for cytoarchitectural parcellation.

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References

1. Brodmann, K. *Vergleichende Lokalisationslehre der Grosshirnrinde*. Leipzig: Johann Ambrosius Barth Verlag; 1909.
2. Campbell, AW. *Histological Studies on the Localisation of Cerebral Function*. Nature Publishing Group; 1905.

3. von Economo, C., Koskinas, GN. Die Cytoarchitektur der Hirnrinde des erwachsenen Menschen. Nature Publishing Group; 1925.
4. Vogt C, Vogt O. Allgemeinere Ergebnisse unserer Hirnforschung. J Psychol Neurol. 1919; 25:292–398.
5. Penfield W, Boldrey E. Somatic motor and sensory representation in the cerebral cortex of man as studied by electrical stimulation. Brain. 1937; 60:389–443.
6. Baleydier C, Achache P, Froment JC. Neurofilament architecture of superior and mesial premotor cortex in the human brain. NeuroReport. 1997; 8
7. Zilles K. Architectonics of the human cerebral cortex and transmitter receptor fingerprints: reconciling functional neuroanatomy and neurochemistry. Eur Neuropsychopharmacol. 2002; 12:587–599. [PubMed: 12468022]
8. Hammers A, Allom R, Koepp MJ, Free SL, Myers R, Lemieux L, Mitchell TN, Brooks DJ, Duncan JS. Three-dimensional maximum probability atlas of the human brain, with particular reference to the temporal lobe. Human Brain Mapping. 2003; 19:224–247. [PubMed: 12874777]
9. Sandor S, Leahy R. Surface-based labeling of cortical anatomy using a deformable atlas. Medical Imaging, IEEE Transactions on. 1997; 16:41–54.
10. Thompson PM, Schwartz C, Toga AW. High-Resolution Random Mesh Algorithms for Creating a Probabilistic 3D Surface Atlas of the Human Brain. NeuroImage. 1996; 3:19–34. [PubMed: 9345472]
11. Desikan RS, Segonne F, Fischl B, Quinn BT, Dickerson BC, Blacker D, Buckner RL, Dale AM, Maguire RP, Hyman BT, et al. An automated labeling system for subdividing the human cerebral cortex on MRI scans into gyral based regions of interest. Neuroimage. 2006; 31:968–980. [PubMed: 16530430]
12. Van Essen DC. A Population-Average, Landmark-and Surface-based (PALS) atlas of human cerebral cortex. NeuroImage. 2005; 28:635–662. [PubMed: 16172003]
13. Fischl B, van der Kouwe A, Destrieux C, Halgren E, Segonne F, Salat DH, Busa E, Seidman LJ, Goldstein J, Kennedy D, et al. Automatically parcellating the human cerebral cortex. Cerebral Cortex. 2004; 14:11–22. [PubMed: 14654453]
14. Glasser MF, Van Essen DC. Mapping Human Cortical Areas In Vivo Based on Myelin Content as Revealed by T1-and T2-Weighted MRI. The Journal of Neuroscience. 2011; 31:11597–11616. [PubMed: 21832190]
15. Basser PJ, Mattiello J, Leblond D. Estimation of the effective self-diffusion tensor from the NMR spin-echo. Journal of Magnetic Resonance Series B. 1994; 103
16. Basser PJ, Pajevic S, Pierpaoli C, Duda J, Aldroubi A. In vivo fiber tractography using DT-MRI data. Magnetic Resonance in Medicine. 2000; 44:625–632. [PubMed: 11025519]
17. Mori S, Crain BJ, Chacko VP, van Zijl PCM. Three-dimensional tracking of axonal projections in the brain by magnetic resonance imaging. Annals of Neurology. 1999; 45:265–269. [PubMed: 9989633]
18. Conturo TE, Lori NF, Cull TS, Akbudak E, Snyder AZ, Shimony JS, McKinstry RC, Burton H, Raichle ME. Tracking neuronal fiber pathways in the living human brain. Proceedings of the National Academy of Sciences. 1999; 96:10422–10427.
19. Catani M, Howard RJ, Pajevic S, Jones DK. Virtual in vivo interactive dissection of white matter fasciculi in the human brain. Neuroimage. 2002; 17:77–94. [PubMed: 12482069]
20. Johansen-Berg H, Behrens TEJ, Robson MD, Drobnyak I, Rushworth MFS, Brady JM, Smith SM, Higham DJ, Matthews PM. Changes in connectivity profiles define functionally distinct regions in human medial frontal cortex. Proceedings of the National Academy of Sciences of the United States of America. 2004; 101:13335–13340. [PubMed: 15340158]
21. Anwender A, Tittgemeyer M, von Cramon DY, Friederici AD, Knösche TR. Connectivity-Based Parcellation of Broca's Area. Cerebral Cortex. 2007; 17:816–825. [PubMed: 16707738]
22. Schilling K, Janev V, Gao Y, Stepniewska I, Landman B, Anderson A. Comparison of 3D orientation distribution functions measured with confocal microscopy and diffusion MRI. Neuroimage. 2016

23. Gao Y, Choe AS, Stepniewska I, Li X, Avison MJ, Anderson AW. Validation of DTI Tractography-Based Measures of Primary Motor Area Connectivity in the Squirrel Monkey Brain. *PloS one*. 2013; 8:e75065. [PubMed: 24098365]
24. Dyrby TB, Sogaard LV, Parker GJ, Alexander DC, Lind NM, Baare WFC, Hay-Schmidt A, Eriksen N, Pakkenberg B, Paulson OB, Jelsing J. Validation of in vitro probabilistic tractography. *Neuroimage*. 2007; 37:1267–1277. [PubMed: 17706434]
25. Choe AS, Stepniewska I, Colvin DC, Ding Z, Anderson AW. Validation of diffusion tensor MRI in the central nervous system using light microscopy: quantitative comparison of fiber properties. *Nmr in Biomedicine*. 2012; 25:900–908. [PubMed: 22246940]
26. Seehaus AK, Roebroek A, Chirý O, Kim D-S, Ronen I, Bratzke H, Goebel R, Galuske RAW. Histological Validation of DW-MRI Tractography in Human Postmortem Tissue. *Cerebral Cortex*. 2013; 23:442–450. [PubMed: 22345356]
27. Reveley C, Seth AK, Pierpaoli C, Silva AC, Yu D, Saunders RC, Leopold DA, Ye FQ. Superficial white matter fiber systems impede detection of long-range cortical connections in diffusion MR tractography. *Proceedings of the National Academy of Sciences*. 2015; 112:E2820–E2828.
28. Calabrese E, Badea A, Cofer G, Qi Y, Johnson GA. A Diffusion MRI Tractography Connectome of the Mouse Brain and Comparison with Neuronal Tracer Data. *Cerebral Cortex*. 2015; 25:4628–4637. [PubMed: 26048951]
29. Dauguet J, Peled S, Berezovskii V, Delzescaux T, Warfield SK, Born R, Westin CF. Comparison of fiber tracts derived from in-vivo DTI tractography with 3D histological neural tract tracer reconstruction on a macaque brain. *Neuroimage*. 2007; 37:530–538. [PubMed: 17604650]
30. Choe A, Gao Y, Li X, Compton K, Stepniewska I, Anderson A. Accuracy of image registration between MRI and light microscopy in the ex vivo brain. *Magnetic Resonance Imaging*. 2011; 29:683–692. [PubMed: 21546191]
31. Stejskal EO, Tanner JE. Spin diffusion measurements: Spin echoes in the presence of a time-dependent field gradient. *Journal of Chemical Physics*. 1965; 42:288–292.
32. Behrens TEJ, Berg HJ, Jbabdi S, Rushworth MFS, Woolrich MW. Probabilistic diffusion tractography with multiple fibre orientations: What can we gain? *Neuroimage*. 2007; 34:144–155. [PubMed: 17070705]
33. Li C, Huang R, Ding Z, Gatenby C, Metaxas D, Gore J. A variational level set approach to segmentation and bias correction of images with intensity inhomogeneity. *MICCAI*. 2008:1083–1091. 1083–1091.
34. Preuss TM, Stepniewska I, Kaas JH. Movement representation in the dorsal and ventral premotor areas of owl monkeys: A microstimulation study. *Journal of Comparative Neurology*. 1996; 371:649–675. [PubMed: 8841916]
35. Stepniewska I, Preuss TM, Kaas JH. Architectonics, somatotopic organizations, and ipsilateral cortical connections of the primary motor area (M1) of owl monkeys. *Journal of Comparative Neurology*. 1993; 330:238–271. [PubMed: 7684050]
36. Toga AW, Ambach KL, Schluender S. High-resolution anatomy from in-situ human brain. *Neuroimage*. 1994; 1:334–344. [PubMed: 9343583]
37. Reiner A, Veenman CL, Medina L, Jiao Y, Del Mar N, Honig MG. Pathway tracing using biotinylated dextran amines. *Journal of Neuroscience Methods*. 2000; 103:23–37. [PubMed: 11074093]
38. Rohde GK, Aldroubi A, Dawant BM. The adaptive bases algorithm for intensity-based nonrigid image registration. *IEEE Transactions on Medical Imaging*. 2003; 22:1470–1479. [PubMed: 14606680]
39. Gao, Y., Parvathaneni, P., Schilling, K., Wang, F., Stepniewska, I., Xu, Z., Choe, A., Ding, Z., Gore, J., Chen, L., et al. SPIE Medical Imaging. San Diego, California US: 2016. A 3D high resolution ex vivo white matter atlas of the common squirrel monkey (*Saimiri sciureus*) based on diffusion tensor imaging.
40. Yeh F-C, Verstynen TD, Wang Y, Fernández-Miranda JC, Tseng W-YI. Deterministic Diffusion Fiber Tracking Improved by Quantitative Anisotropy. *PLoS ONE*. 2013; 8:e80713. [PubMed: 24348913]
41. Schmahmann, J., Pandya, D. *Fiber Pathways of the Brain*. Oxford University Press; 2009.

42. Stepniewska I, Preuss TM, Kaas JH. Ipsilateral cortical connections of dorsal and ventral premotor areas in New World owl monkeys. *The Journal of Comparative Neurology*. 2006; 495:691–708. [PubMed: 16506197]
43. Gharbawie OA, Stepniewska I, Kaas JH. Cortical Connections of Functional Zones in Posterior Parietal Cortex and Frontal Cortex Motor Regions in New World Monkeys. *Cerebral Cortex*. 2011; 21:1981–2002. [PubMed: 21263034]
44. Krubitzer LA, Kaas JH. The organization and connections of somatosensory cortex in marmosets. *The Journal of Neuroscience*. 1990; 10:952–974. [PubMed: 2108231]
45. Stepniewska I, Cerkevich CM, Kaas JH. Cortical Connections of the Caudal Portion of Posterior Parietal Cortex in Prosimian Galagos. *Cerebral Cortex*. 2015
46. Lu M-T, Preston JB, Strick PL. Interconnections between the prefrontal cortex and the premotor areas in the frontal lobe. *The Journal of Comparative Neurology*. 1994; 341:375–392. [PubMed: 7515081]
47. Kaas JH, Stepniewska I. Evolution of posterior parietal cortex and parietal-frontal networks for specific actions in primates. *Journal of Comparative Neurology*. 2016; 524:595–608. [PubMed: 26101180]
48. Passingham RE, Stephan KE, Kotter R. The anatomical basis of functional localization in the cortex. *Nat Rev Neurosci*. 2002; 3:606–616. [PubMed: 12154362]
49. Honey CJ, Sporns O, Cammoun L, Gigandet X, Thiran JP, Meuli R, Hagmann P. Predicting human resting-state functional connectivity from structural connectivity. *Proceedings of the National Academy of Sciences*. 2009; 106:2035–2040.
50. Rushworth MFS, Behrens TEJ, Johansen-Berg H. Connection Patterns Distinguish 3 Regions of Human Parietal Cortex. *Cerebral Cortex*. 2006; 16:1418–1430. [PubMed: 16306320]
51. de Reus MA, van den Heuvel MP. The parcellation-based connectome: Limitations and extensions. *NeuroImage*. 2013; 80:397–404. [PubMed: 23558097]
52. Thomas C, Ye FQ, Irfanoglu MO, Modi P, Saleem KS, Leopold DA, Pierpaoli C. Anatomical accuracy of brain connections derived from diffusion MRI tractography is inherently limited. *Proceedings of the National Academy of Sciences*. 2014; 111:16574–16579.
53. Jones DK, Knösche TR, Turner R. White matter integrity, fiber count, and other fallacies: The do's and don'ts of diffusion MRI. *NeuroImage*. 2013; 73:239–254. [PubMed: 22846632]
54. Cohen Y, Assaf Y. High b-value q-space analyzed diffusion-weighted MRS and MRI in neuronal tissues -a technical review. *NMR in Biomedicine*. 2002; 15:516–542. [PubMed: 12489099]
55. Oishi K, Zilles K, Amunts K, Faria A, Jiang H, Li X, Akhter K, Hua K, Woods R, Toga AW, et al. Human brain white matter atlas: Identification and assignment of common anatomical structures in superficial white matter. *NeuroImage*. 2008; 43:447–457. [PubMed: 18692144]
56. Heiervang E, Behrens TEJ, Mackay CE, Robson MD, Johansen-Berg H. Between session reproducibility and between subject variability of diffusion MR and tractography measures. *NeuroImage*. 2006; 33:867–877. [PubMed: 17000119]
57. Gould HJ, Cusick CG, Pons TP, Kaas JH. The relationship of corpus callosum connections to electrical stimulation maps of motor, supplementary motor, and the frontal eye fields in owl monkeys. *The Journal of Comparative Neurology*. 1986; 247:297–325. [PubMed: 3722441]

Highlights

- DTI-connectivity-based parcellation and Nissl histology are compared.
- Intra-subject supervised DTI parcellation has up to 87% agreement with Nissl histology.
- Inter-subject supervised DTI parcellation has up to 71% agreement with Nissl histology.
- Unsupervised DTI parcellation has 39% agreement with Nissl histology.
- Differences are from DTI errors and true differences between connectivity-defined and cytoarchitectural domains.

Figure 1. Graphic representation of analysis pipeline

(Top) Each brain was scanned using DTI and cortical voxels were used as seed points for tracking. The density of tracks in each white matter voxel comprised the feature vector for classification. (Bottom) Each brain was then sectioned, Nissl stained, and cortical domains were labeled by an expert (see text for region abbreviations). Finally, the Nissl-derived labels were registered to the MR data and compared to the DTI-derived classes.

Figure 2.

Intra-subject DTI parcellation of three monkey brain cortices and their agreement with histology. For rows 1–3, each row displays one monkey's data in its native space. The gray surfaces are the white-gray matter interfaces. The points in color in the left six columns indicate the test cortical voxels (90% of all voxels) classified with two DTI-connectivity-derived feature vectors (column ① and column ②) via three classification methods: support vector machine (SVM), K nearest neighbors (KNN) and decision tree (DT). The number at the right bottom corner of each case is the overall agreement rate, $R1$, with histology. For visual comparison, the points in color in the 7th column illustrate the cytoarchitectonic domains. The legend at the top right side lists the color assignment of the domains. Row 4 shows the average agreement rates of each domain across three monkeys. Dark gray bars indicate fiber density as feature vectors and light gray bars indicate binary mask of fiber density as feature vectors. The bars on the left and right side of 0 correspond to the $r1$ in the left and right hemispheres, respectively.

Figure 3.

Inter-subject classification of three monkey brain cortices and their agreement with histology. For rows 1–3, each row displays one test monkey's data in its native space. The gray surfaces are the white-gray matter interfaces. The points in color in columns 1–6 indicate the test cortical voxels classified with two DTI-connectivity-derived feature vectors (column ① and column ②) via three classification methods: support vector machine (SVM), K nearest neighbors (KNN) and decision tree (DT). The number at the right bottom corner of each case is the overall agreement rate, R^2 , with histology. For visual comparison, the points in color in column 7 illustrate the cytoarchitectonic domains. The legend at the top right side lists the color assignment of the domains. Row 4 shows the average agreement rates of each domain across three monkeys, r^2 . Dark gray bars indicate r^2 using fiber density as the feature vectors and light gray bars indicate r^2 using the binary mask of fiber density as feature vectors. The bars on the left and right side of 0 correspond to the r^2 in the left and right hemispheres, respectively.

Figure 4.

Three views of monkey B3 with KNN inter-subject classification. The gray surfaces are the white-gray matter interface. For better visualization in ventral and medial views, the white matter structures inferior to internal and external capsules and lateral sulcus are removed (AC-anterior commissure, LS-lateral sulcus, CF-commissure of fornix and CC-corpus callosum).

Figure 5.

Unsupervised parcellation of three monkey brain cortices and its agreement with histological domains. Each row displays one monkey's data in its native space. The gray surfaces are the white-gray matter interfaces. The points in color in columns 1–4 indicate the cortical voxels clustered with two DTI-connectivity-derived feature vectors (column ① and column ②) via two clustering methods: K-means and Hierarchy. The colors for the hierarchy clusters are randomly assigned. The number at the right bottom corner of each case is the overall Jaccard index, J . For visual comparison, the points in color in column 5 illustrate the cytoarchitectonic domains.

Figure 6. An example of differences between histology and DTI parcellation in monkey B3. (A) shows the histological domains with points 1–4 indicating the seed points at left dorsal M1, lateral M1, dorsal PM and lateral PM, respectively. (B) shows the unsupervised parcellation result with the same seed points labeled. (C) displays the DTI-derived fiber tracts 1–4 originating from seed points 1–4, overlaid on (orthogonal) fractional anisotropy slices. The orange color indicates fiber pathways and the green asterisk indicates the seed point. (D) plots the projections of tracts 1–4 on major fiber bundles listed on the right.

Figure 7.

Coronal view of pathways shown in Figure 6. (A,B,D,E) show the DTI pathways originating from seed points 1–4 in yellow-red colormap on grayscale fractional anisotropy maps. The seed points are indicated by yellow arrows. (C) is the tissue slice corresponding to (A,B). Brown arrows point to the forelimb (F.L.) motor representation area which was detected by electrical micro-stimulation and then injected with the neuro tracer BDA. (F) is the micrograph of the slice corresponding to (D,E). Brown arrows point to the F.L. premotor representation. The face (F.) representation areas lie laterally to the F.L. areas. Seed points that project to the same part of the body (forelimb or face), but are in different histological domains (M1 or PM) have more similar tractograms than points that project to different parts of the body but are located in the same histological domain.

Figure 8.

Similarity matrix and energy of unsupervised clustering and histological parcellation. The lower triangle is reordered based on labels of unsupervised clusters and the higher triangle is reordered based on labels of histological domains. The distance measure for similarity or energy calculation is cosine distance between tractograms of two seed points. Data are shown for both Left and Right hemispheres.

Connectivity matrices of large cortical domains in the frontal and parietal lobes of the squirrel monkey. Each row is a cortical domain and each column is a major white matter fiber bundle. Each matrix element represents the connectivity between the corresponding domain and white matter fiber bundle. (A) shows DTI-tractography-derived connectivity using the normalized sum of white matter fiber density as the matrix element values. (B) shows the histological connectivity with binary values as matrix elements: 0 (black) - no observed histological connectivity in either new world or old world monkey and 1 (white) - observed connectivity in new world and/or old world monkey. Connectivity in the left and right hemispheres in (B) is assumed to be equal.

Table 1

List of cortical domains identified by Nissl-stained tissues in squirrel monkey brain.

Abbr.	Domain	Abbr.	Domain
PF	prefrontal cortex	PP	posterior parietal lobe
PM	premotor cortex	PVR	ventral and rostral parietal lobe
M1	primary motor cortex	AC	anterior cingulate cortex
S1	primary sensory cortex	SMA	supplemental motor area