Published in final edited form as:

IEEE J Biomed Health Inform. 2015 July ; 19(4): 1375–1383. doi:10.1109/JBHI.2015.2444917.

Anatomically Informed Metrics for Connectivity-based Cortical Parcellation from Diffusion MRI

Rosalia L. Tungaraza,

Department of Radiology, University of Washington, Seattle, WA 98195. She is now with ARAZOO, New York, NY 10022.

Sonya H. Mehta,

Department of Psychology, University of Washington, Seattle, WA 98195.

David R. Haynor, and

Department of Radiology, University of Washington, Seattle, WA 98195.

Thomas J. Grabowski

Departments of Radiology and Neurology, University of Washington, Seattle WA 98195.

Abstract

Connectivity information derived from diffusion MRI can be used to parcellate the cerebral cortex into anatomically and functionally meaningful subdivisions. Acquisition and processing parameters can significantly affect parcellation results, and there is no consensus on best practice protocols. We propose a novel approach for evaluating parcellation based on measuring the degree to which parcellation conforms to known principles of brain organization, specifically cortical field homogeneity and inter-hemispheric homology. The proposed metrics are well behaved on morphologically-generated whole-brain parcels, where they correctly identify contralateral homologies, and give higher scores to anatomically versus arbitrarily generated parcellations. The measures show that individual cortical fields have characteristic connectivity profiles that are compact and separable, and that the topological arrangement of such fields is strongly conserved between hemispheres and individuals. The proposed metrics can be used to evaluate the quality of parcellations at the subject and group levels, and to improve acquisition and data processing for connectivity-based cortical parcellation.

Keywords

Cerebral Cortex; Davies-Bouldin; Diffusion Weighted Imaging; Earth Mover's Distance; Cortical Parcellation; Topological Distance; Tractography

I. INTRODUCTION

The primate cerebral cortex is comprised of a mosaic of anatomic fields occupying contiguous regions of cortex [1]. Each cortical field is believed to have a distinct cytoarchitecture, myeloarchitecture, neurotransmitter receptor architecture, and pattern of connectivity that differentiate it from neighboring fields. Cortical fields may function as neurophysiologic units [2]. The ability to accurately and reliably delineate cortical fields in vivo would be fundamentally useful for studying neuroanatomical variation and the

organization of brain function in humans. Recent work has demonstrated the feasibility of using diffusion MRI (dMRI) to segment the human cortex into units based on patterns of estimated anatomical connectivity to other brain regions[3]-[16].

Cortical field structure and its relationship to connectivity has been worked out most clearly in experimental animals, and particularly in the primate visual cortex [17],[18]. Studies of higher order association regions in the human brain have appeared in recent years but the extent to which these regions may also be differentiated and defined by connectivity is incompletely known.

One human association region that has been parcellated with more than one modality is the inferior parietal lobule (IPL). It has been divided based on receptor distribution [19], cytoarchitectonics [20], anatomical connectivity (dMRI) [14]–[16],[21], and functional connectivity (rsfMRI) [22]. The histologic approach sub-divides the IPL into seven regions, while a receptor-based approach suggests dividing the IPL into three sub-regions [19]. Parcellations using diffusion MRI and rsfMRI result in 3 to 7 sub-regions [3],[11],[14]–[16] depending on the processing pipeline used and/or level of granularity assumed.

Connectivity-based parcellation is influenced by diffusion image acquisition and post-processing methods [23]. There is as yet no consensus on a “best practice” workflow and no gold standard for evaluating the truth of dMRI parcellation per subject, *in vivo* (See [24] or more discussion on this issue). Aside from comparing parcellation across modalities, approaches used to evaluate the quality of dMRI parcellation have included evaluating reproducibility across independent acquisition sessions, and consistency in number and location of parcels across different subjects [12].

Here we propose a complementary approach to parcellation evaluation that is based on known principles of brain organization, specifically inter-hemispheric anatomic homology and cortical field anatomic homogeneity. Cortical homology states that the two hemispheres of the normal human brain possess the same inventory of cortical regions, in similar positions, and that the same is true for distinct human subjects. Cortical homology is a well-established principle that is observable in many contexts. Examples include the Brodmann cytoarchitectonic parcellation [25], parcellations based on genetic information [26] and rsfMRI [27], and the receptor-architectonic and cytoarchitectonic parcellations of the human IPL and other regions [19],[20]. Note that inter-hemispheric homology does not imply an expectation that the hemispheres are mirror images of each other, because there are variations in cortical folding and in the size and shape of individual fields. Despite these first-order differences, the topological arrangement of each pair of homologs across the two hemispheres is generally preserved (e.g. as in [20], Figure 14). Thus, a valid parcellation process, conducted independently in two hemispheres, should result in homologous parcellations.

In addition to connectivity-defined parcels having counterparts in the other hemisphere, parcellations across hemispheres should produce the same topological arrangement of homologous regions. In the work reported here, we develop and evaluate a metric which tests whether segmentation of cortex by connectivity profiles fulfills this expectation.

Finally, we expect that the anatomic connectivity of homologous regions will be more similar than the connectivity patterns of regions that are not homologs. Some prior evidence from dMRI is available. A study by [28] used the Jülich probabilistic cytoarchitectonic parcellation of the human IPL to investigate the anatomic connectivity pattern of five IPL sub-regions (PFt, PF, PFm, PGa, and PGp). The study computed probabilistic fiber tracks using these sub-regions mapped onto the brains of 40 healthy humans. They found that the connectivity profiles (also called “fingerprints”) of homologous regions were qualitatively more similar compared to non-homologous regions [28], and though not evaluated specifically, the relative locations of homologs with respect to their physical neighbors also appeared similar in the results.

We employ three quantitative measures that collectively capture the degree of homology across dMRI-parcellations: Earth Mover's Distance (EMD), Topological Distance (TpD) and the Davies-Bouldin Index (DB). EMD [29]–[31] has been used in computer vision for image similarity and retrieval and is adapted here to match homologous regions on the basis of connectivity. We devised the TpD metric specifically to measure the similarity of the topological arrangement of putative homologous brain areas between hemispheres and across subjects. DB [32] is commonly used in studies of clustering as a measure of cluster homogeneity. These three measures can be used in conjunction, in addition to other metrics outlined above for validating dMRI parcellations in vivo, and have the advantage of allowing within subject/acquisition assessment.

We used three approaches to evaluate the proposed metrics. (1) First, we explored their behavior in coarse whole brain parcellations in which boundaries were defined by subject-specific macroscopic anatomical landmarks. We assigned between-hemisphere homologs by minimizing EMD on the parcel-wise tractograms and then tested whether the topological arrangement of the regions so assigned was preserved, measured by TpD. Performance was compared to arbitrary parcellations. (2) Second, we evaluated a five-region dMRI parcellation of the human inferior parietal lobule. We chose the IPL because it is relatively artifact free in dMRI, has an available cytoarchitectonic gold standard, and is part of association cortex where folding pattern specifics are variable, making it impossible to parcellate on the basis of morphology alone. Again, the fundamental test was whether homologous parcels, as assigned by EMD, had a similar topological arrangement, assessed by TpD, compared to arbitrary parcellations. Finally, (3) we evaluated the performance of the metrics after dMRI-based parcellation of IPL across different human individuals.

The organization of this paper is as follows: in Section 2, we describe our methodology for computing the connectivity-driven EMD, TpD, and DB measures, and evaluating the utility of these measures both within and across subjects. Section 3 presents our results. Section 4 contains the discussion and our conclusions are presented in Section 5. A preliminary version of this work was reported in [33].

II. Methodology

A. Data Acquisition

Diffusion MRI data were acquired on a Siemens TIM Trio 3T scanner, and consisted of high angular resolution dMRI with 64 unique diffusion directions, with a b-value of 1000mm/s^2 , 2 mm isotropic voxels, and whole brain coverage. Each acquisition had one baseline image with no gradients applied. We also obtained high resolution T1-weighted images with an MP-RAGE pulse sequence with 1 mm isotropic resolution. There were 19 healthy participants (10 males and 9 females, age range 21 - 53 years). Subjects gave informed consent and participated in accordance with University of Iowa institutional review board guidelines.

B. Data Processing

1) Structural Image Processing—We processed each subject's high-resolution T1-weighted MP-RAGE image with FreeSurfer's "recon-all" pipeline [34],[35], yielding tissue-segmented images, cortical surface reconstructions, and cortical anatomic segmentation according to the Desikan-Killiany [36] and Destrieux atlases [37]. For each subject we identified a subcortical mask, consisting of voxels 2mm subjacent to the cortical gray-white matter interface as defined by FreeSurfer; and a tractography mask containing all subcortical voxels, the brain stem, and the cerebellum. We identified the IPL seed region mask for probabilistic tractography as all voxels in the subcortical mask subjacent to cortex in the following Destrieux atlas regions: the angular gyrus, supramarginal gyrus, and intermedius primus (Jensen) sulcus. All three mask images were mapped to the diffusion weighted image space on a subject-specific basis using a non-linear registration algorithm (FNIRT) implemented in the FMRIB Software Library (FSL) [38].

2) Diffusion Data Processing—All diffusion-weighted images were corrected for bulk head motion and eddy current distortions using tools from FSL [38]. The fiber orientation distribution was then estimated for each subject using the constrained spherical deconvolution method implemented in the MRtrix software package [39]–[41]. The maximum spherical harmonics degree (l_{max}) was 8. We inferred connectivity between our seed voxels and all other white matter voxels using the probabilistic streamline algorithm implemented in MRtrix. For each seed voxel, we generated 5000 streamlines and set all the other tracking parameters to their default values. For each set of tracks computed from a seed voxel we created a streamline density map based on the fraction of tracks entering each target voxel (see step 7 below).

3) Parcellation of the IPL Seed Region—We created two types of parcellations for each IPL: The parcellation of interest, based on the probabilistic tractograms described above, and a set of arbitrary ("random") parcellations created by random seeding and region growing, ignoring connectivity information. There is as yet no consensus on how many sub-regions the human IPL should be divided into when using dMRI. We chose to divide each IPL seed region into five clusters because this level of parcel granularity has been successfully used by others to segment the IPL and perform further analysis on it using dMRI ([11],[28]).

a) Generation of random parcellations: We generated 100 random parcellations of each IPL using Zalesky's MATLAB function for random node generation (<http://andrewzalesky.com/software.html/>) to produce random clusters that were approximately equal in size to those obtained from the dMRI-based parcellations. Beginning from 5 randomly generated seeds, the algorithm grew the region of each cluster voxel-by-voxel, subject to the following rules: (1) a voxel is assigned to an existing cluster that maximizes the contact area between the voxel and the chosen cluster, (2) a voxel cannot be assigned to a cluster with which it shares no contact area, (3) if two or more clusters are equally strong candidates based on contact, the cluster whose center of mass is closest to the voxel is chosen, (5) any further ties between clusters are broken randomly. This process was repeated until all IPL voxels had been assigned to exactly one cluster [42].

b) Generation of connectivity-defined parcellations: We used the affinity propagation (AP) clustering algorithm described in [43] to divide the IPL seed region. AP has been successfully used for connectivity-based cortex parcellation of the inferior frontal gyrus together with the precentral gyrus in [8]. While AP outperforms other clustering algorithms in many applications, there are many alternative algorithms, and we did not perform an exhaustive comparison. We used AP to cluster the tractograms of each IPL seed region into five clusters as follows: (1) we constructed an $N \times N$ matrix M of correlations between the tractograms of all N voxels in the IPL seed region; (2) using M as a similarity matrix, the AP method identified five voxels from the set of all voxels in the IPL seed region as cluster exemplars. Each of the remaining voxels was then assigned to the most similar exemplar.

4) Cluster Quality Evaluation Using the Davies-Bouldin Index (DB)—We assessed the quality of the resulting segmentation for each type of parcellation and for each IPL independently. We used the DB index [32] to assess the extent to which the resulting clusters are compact (i.e. voxel-level tractograms within the same cluster have high intra-cluster similarity) and separable (i.e. voxel-level tractograms from different clusters have low similarity). There are other similar cluster validation measures that could also be used (refer to [32] for an overview). DB is given by the formula:

$$DB = \frac{1}{n} \sum_{i=1}^n \max_{i \neq j} \left(\frac{\alpha_i + \alpha_j}{d(c_i, c_j)} \right) \quad (1)$$

where n is the number of clusters, c_i and c_j are the centroids of clusters i and j respectively, α_i and α_j are the average distances between all elements in clusters i and j respectively, and $d(c_i, c_j)$ is the distance between cluster c_i and c_j , defined as the average distance between tractograms in the two clusters. We computed the DB for each hemisphere independently and then averaged the score from both hemispheres to obtain the DB score for a given parcellation.

5) Calculating connectivity profiles for whole brain anatomic parcellation—We created a connectivity profile from each Desikan-Killiany atlas region to the 34 ipsilateral regions using probabilistic fiber tracking. All MRtrix parameters were kept at default values except the number of tracks to be generated, where we used 10,000 tracks. We normalized each tractogram by the total number of tracks that reached any of the 35 target regions. The

result was a 35×35 matrix for each hemisphere, in which each row represented the connectivity profile (“fingerprint”) of a given Desikan-Killany atlas region.

6) Quantifying Homology in Whole-Brain Parcellation—We identified pairs of homologous parcels from the whole-brain parcellations between hemispheres by minimizing the average pairwise EMD of their connectivity profiles.

EMD is a metric used to quantify the dissimilarity between two histograms [29]. Compared to a simple sum-of-squares difference between two histograms, the EMD allows for the possibility that some pairs of bins (regions in this case) are more similar than others (as measured by a between-bins “ground distance”, d). It measures the minimum total cost of redistributing the probability mass within one histogram so as to match the other, where the cost per unit of mass moved from one bin to another is given by the ground distance between the two bins. In our application of the metric we seek to quantify the dissimilarity between the connectivity fingerprints of two brain regions. For the ground distance matrix D , we used the Jeffrey-divergence distance between two regions l and r , defined as:

$$d_{lr} = \sum_k \left(l_k \times \log \frac{l_k}{a_k} \right) + \left(r_k \times \log \frac{r_k}{a_k} \right) \text{ where } a_k = \frac{l_k + r_k}{2}, \text{ and } k \text{ indexes the connectivity fingerprint bins, i.e. the other regions.}$$
 If l and r have identical tractograms, d will be 0. Once the ground distance between bins has been defined, the EMD is based on solving a linear programming problem [29]; this is done for each pair of regions. A low value of EMD implies that the connectivity pattern of two brain regions is similar. After the EMD has been computed between every pair of regions, the assignment algorithm was used to compute the optimal pairing of sub-regions across the hemispheres [44].

7) Calculating connectivity profiles for IPL connectivity-based parcellation—

We created connectivity profiles for the 5 regions of each IPL as follows. For each subject, we performed probabilistic fiber tracking from each IPL region to the 75 cortical regions of FreeSurfer's Destrieux atlas ipsilateral to the seed. We used the Destrieux atlas, rather than the Desikan-Killiany atlas, because of its finer anatomic resolution and because it tends to separate sulcal from gyral regions, a distinction often accompanied by differences in cytoarchitecture. We rejected fiber tracks that started and ended in the same region. We randomly seeded 10,000 tracks from each region, keeping all other MRtrix parameters at their default values. Clustering was performed using the AP algorithm, and the connectivity profile was computed for each cluster by normalizing the cluster's tractogram by the total number of tracks that reached any of the 75 target regions. The product was a 5×75 matrix, one per IPL, in which each row is the normalized connectivity profile (“fingerprint”) of a given cluster. Optimal connection-based homology between contralateral IPLs was then established using the EMD as described above for whole brain parcellation.

8) Measuring conservation of subregion topology using the TpD—Once a correspondence between left and right brain homologs was defined, we projected the parcel labels from the subcortical seed voxels to the cortex using Freesurfer. We relabeled all clusters in the two contralateral parcellations such that each left region had the same cluster label as its homologous (computed as described above) right hemisphere region. We computed an $N \times N$ topology matrix for each IPL/hemisphere, where N is the total number

of subregions. The (i, j) entry of this matrix was the number of voxels from region i that are spatially in contact (26-nearest neighbor) with voxels from region j . We then normalize each row to sum to 1. The TpD between the left and right IPL/hemisphere is defined as the cosine distance of the two normalized matrices after vectorizing them. The TpD score ranges from 0 to 1. A score close to 0 suggests that two IPLs or hemispheres have similar topology, while a score closer to 1 indicates they have maximally dissimilar topology.

9) Cross-subject Homology Assignment—We also evaluated the utility of the connectivity-driven EMD for identification of homologous IPL regions across subjects. We did this for each hemisphere independently in three steps: (1) pooling together the parcel-level connectivity fingerprints of all subjects across that hemisphere; (2) identifying five exemplar connectivity fingerprints from the pooled connectivity fingerprints using AP clustering, which we term the group exemplars; and (3) using the EMD-based approach described above in step 6 to assign each subject's set of parcel-level connectivity fingerprints to the group exemplar that was most similar to it.

10) Visualization of Homologous Parcellations—For display purposes, after EMD was used to identify homologs across hemispheres, we labeled each pair of homologous regions with a unique index and an associated RGB color. For cross-subject analysis of the IPL we used the AP algorithm to jointly cluster all 38 IPLs into 5 clusters, each with a groupwise exemplar, as explained in step 8. Then we labeled each cluster in an individual subject with the index and color of the group exemplar to which its connectivity profile was most closely matched.

III. Results

A. The metrics correctly demonstrate that connections in the two hemispheres are very similar, at a coarse scale

The connectivity among 35 cortical regions in the Desikan-Killiany atlas was analyzed using the proposed measures. We compared results to those generated by EMD-based assignment of “homology” in random parcellations (Figure 1). Both EMD and TpD scores were much lower for true parcellations and both metrics cleanly separate the Desikan-Killiany parcellations from the random parcellations. Just as importantly, homology assignments based on connectivity similarity reflected the true anatomic labels, (Figure 2). Further, TpD clearly shows similar topological relations between homologously connected portions of the brain, reinforcing the idea that EMD is tapping into the brain's biological structure. In other words, both EMD and TpD demonstrate that connections in the two hemispheres are very similar, and that connectivity information is sufficient to identify anatomically homologous regions at the scale of conventional regional brain atlases. The sole and specific exception was that the connectivity profiles of the medial orbitofrontal (MOF) cortex and the frontal pole (FP) exchanged labels across hemispheres in three subjects (S3, S6, and S11, see bottom panel). We believe this error is due to the well-known magnetic field inhomogeneity-related artifacts affecting diffusion imaging in the orbitofrontal cortex, which lies immediately above the frontal sinus.

Though EMD was also generally matched the random parcels (Figure 2) to contralateral parcels in similar locations, these parcellations generated higher EMD values than the true parcellations, presumably because random parcellations violate field boundaries, and much higher TpD values.

Finally, the 3 subjects with a (single) reversed pair of anatomic labels were separated from those with entirely correct labels by their TpD scores (Figure 1, circled data points), demonstrating that the TpD metric is a potentially sensitive measure of individual parcellation quality.

B. The metrics find consistent structure in the connectivity of IPL regions, within and across normal individuals

We parcellated the IPL regions of the 19 subjects based on dMRI, assigned homologies on the basis of EMD, and assessed the EMD, TpD, and average DB measures. We found that the variables EMD and TpD were highly correlated. We therefore summed EMD and TpD scores to produce a score that estimated the degree to which an IPL parcellation resulted in homologous clusters, and plotted this score and DB for the 19 connectivity-based parcellations and the 1900 random parcellations. The results (Figure 3) clearly distinguish connectivity-based and random parcellations. The 1900 random parcellations of the 19 subjects generated mean and standard deviations of the EMD, TpD, and average DB scores of 0.24 ± 0.05 , 0.22 ± 0.13 , and 2.00 ± 0.15 , respectively (crosshairs in Fig 3). The instances of connectivity-based parcellations concentrate in the favorable corner of the plot, and a cluster of 10 of the 19 subjects outperforms virtually all random parcellations, with scores in the lower 10% of scores for each measure. Visual inspection of the parcellations in these subjects show that homologous parcellations assigned by EMD had similar topological arrangements (Figure 4). Finally, in the remaining 9 subjects whose metric scores did not cluster toward the origin in Figure 3 (blue dots not circled) inspection of the parcellations (Figure 4, middle column) confirms departures in topology across hemispheres. For example: (1) the blue cluster in the left hemisphere of S3 is divided by the yellow cluster; (2) the green and yellow clusters of S5 are in contact in the left hemisphere but not the right; (3) the red and green clusters of S13 have inverted positions across hemispheres.

C. Cross-subject Homolog Identification Using EMD

Homology assigned by EMD and parcel-level connectivity fingerprints (step 8, above) also successfully matched the same-side hemispheres of different subjects. Figure 5 depicts results for the left hemispheres. It shows a consensus anterior to posterior topological arrangement of parcels, corresponding to the colors: green, blue, red, brown, and yellow. All but 3 subjects (S7, S19, and S11) adhered to this pattern. For S19 and S11 the yellow and brown clustered were exchanged, while S7 exchanged the red and blue clusters. There was also a consensus topological arrangement of homologous parcels for the right hemisphere (not shown), but fewer (11 of 19) subjects fully adhered to the pattern. Studies in more subjects will be required in order to know if this variability is real or reflects limitations of dMRI-based parcellation.

IV. Discussion

Absent a “ground truth” for evaluating subject-specific dMRI parcellation *in vivo*, we pursued an alternative strategy of joint consideration of measures that operationalize known principles of brain organization, namely interhemispheric anatomic homology, topological similarity across individuals, and homogeneity and spatial contiguity of cortical fields. We suggest that the degree of consistency with these principles is a valuable assessment of parcellation quality.

We present three complementary measures. EMD expresses how well the parcel-level connectivity profiles of regions in one hemisphere can be made to map onto those of an independently segmented (contralateral or different subject) hemisphere. TpD evaluates the degree to which the EMD-driven solution produces topologically similar parcellations across hemispheres and subjects. Finally, DB expresses how homogeneous and separable the connectivity profiles are in the parcellation.

A. EMD, TpD, and DB metrics find consistent biological structure in dMRI cortical connectivity

The proposed metrics were face valid and well-behaved on an anatomically-driven whole brain parcellation, perfectly distinguishing them from random parcellations. The EMD-driven solution correctly recovered anatomic homologies, except for a few failures in a specific region (orbitofrontal cortex) known to be artifact-prone in our dataset, which did not use phase-reversed acquisition techniques. The same local failures were also reflected in higher TpD scores, underscoring the utility of the metrics in identifying good-quality parcellations.

We then evaluated performance on these metrics for fine-grained parcellation of an association region (IPL) with variable surface anatomy, based entirely on the diffusion MRI data. The dMRI-based parcellations generated parcels that were more similar across hemispheres than random parcellations. The parcels matched in this way had the same topological arrangement, as measured by TpD, even though the matching approach imposed no such constraint.

The IPL parcellations that emerged were notable for two other reasons. First, the clusters that emerged were spatially contiguous, though no spatial constraints were incorporated in the processing and clustering algorithm we used for dMRI connectivity-based parcellation. (As noted in Methodology, only the random parcels are spatially contiguous by design.) Second, there was a high correlation of the EMD and TpD scores for individual subjects. This need not necessarily have been the case, since EMD depends only on connectivity and TpD only on topology. In other words, when two opposite hemisphere IPL parcellations are matched so as to minimize EMD, the homologous regions will be arranged spatially in the same way. These emergent relationships are evidence that consistent biological structure is present in cortical connectivity, and, specifically, that specific profiles of connectivity identify individual contiguous patches of cortex, within which the profiles are relatively homogenous.

Analogously, we produced homologous parcellations across different subjects. Homology was assigned purely on the basis of the diffusion information, and did not explicitly incorporate morphological or stereotactic coordinate information. A canonical parcellation was obtained for the IPL in almost all subjects, strongly suggesting that different individuals have a similarly arranged set of IPL subregions with similar connectivity profiles, further supporting the fundamental biological validity of our approach.

B. Using the proposed metrics to evaluate individual parcellation and parcellation workflow

Our workflow performed well on most subjects, but better on some data sets than others. The proposed metrics appeared to be sensitive to these cases. In the coarse anatomic parcellations the three (incorrect) anatomic label exchanges resulted in increased TpD values. In the IPL segmentations, the diffusion-segmented parcellations that had higher EMD and TpD values also displayed violations of anatomic homology. We suggest the metric variability indicates shortcomings of the workflow or data quality, as opposed to the metrics themselves.

Our purpose was to demonstrate the utility of our measures in identifying better parcellations, and we used one of a number of conceivable image processing pipelines to segment the IPL. dMRI segmentation results are likely influenced by the technical details of acquisition and processing, such as: (1) the number of unique diffusion gradient directions, (2) the b-value(s), (3) voxel size, (4) methods for removing data artifacts, correcting for eddy current distortions and subject motion, (5) model for diffusivity in each voxel (e.g. tensor, fiber orientation distribution function, etc.), (6) definition of seed and target regions, (7) tractography approach and implementation (deterministic or probabilistic), (8) the values of free parameters for tractography such as minimum fiber length, number of fibers to initiate tractography with and, the criteria for terminating tracks, (9) the tractogram clustering approach, and (10) the granularity of parcellation. Each variation can potentially affect the resulting parcellation [23], and there is as yet no consensus on a “best practice” workflow.

The measures presented here, in combination, can be used to evaluate and guide the development of best practices for connectivity-based cortical parcellation. We expect that improved quality of diffusion data and/or processing will improve the separation between diffusion-segmented and randomly-segmented data sets and reduce the topological variation among resultant IPL parcellations. In this formulation, a parcellation is applied independently to each subject, and a good parcellation approach is one that optimizes these metrics across the group.

Whether diffusion-based and other *in vivo*-defined cortical fields (e.g. by resting state fMRI [27],[45]-[47], fMRI meta-analysis [48], or myelin content [49]) coincide with those defined *ex vivo* by histologic structure [19],[20],[25], is an ongoing focus of work. Preliminary comparisons of the parcellations obtained using these different modalities have shown both similarities and mismatches in terms of the location, boundaries, and level of granularity of the segmented regions. These measures presented here are complementary to these and other approaches to appraising parcellation, such as reproducibility across sessions/subjects, or

convergence with task or resting fMRI, and have the virtue of being independent of other imaging modalities or MRI acquisition sequences.

C. Limitations of the Proposed Metrics

The measures have several limitations..

First, the optimization of metric values is only approximate with respect to accurate identification of cortical fields. Our decision to confine analysis to the IPL may have resulted in variable inclusion of cortical fields at the temporo-parieto-occipital junction, which is not anchored by an invariant landmark, and where the FreeSurfer morphologic parcellation consequently probably varied with respect to cortical field boundaries, potentially introducing seed voxels belong to adjacent fields. This would not be a problem for whole-brain parcellation, which was beyond the scope of the current work. Similarly, an inherent contributor of variability in DB is the fact that we defined cortical targets via morphologically defined areas, and there is known to be variability of cortical field boundaries with respect to cortical folding features. Finally, the fact that DB, a measure of cluster homogeneity, was not uniformly lower for “true” parcellations than in random parcellations probably reflects residual connectional heterogeneity at the level of the anatomical atlases we used, which consist of large regions that, in reality, comprise multiple more homogeneous subregions, as we see in the IPL.

Second, a perfect parcellation would not be expected to have perfect EMD and TpD scores because anatomic morphology and connectivity probably have, inherently, some degree of hemispheric asymmetry. For instance, the human cerebral hemispheres are known to have significant functional asymmetry. While this is best known in the case of language-related regions, it is also known to be the case in other domains such as attentional processing, object recognition., and others [50],[51]. Yet despite a well-established degree of *functional* lateralization in the human brain, there exists remarkable structural symmetry, at the macroscopic level [52]–[54]. It is likely that these functional differences are reflected in quantitative differences in the relative strength of fiber connections among cortical fields, which nonetheless remain homologous across the two hemispheres. For example, there are between-hemisphere differences in the size of the arcuate fasciculus [55]–[57] in fiber-tracked connections in the temporoparietal junction [58]. These differences may be a matter of degree rather than tract destination, and it is likely, and experimentally testable, that homologous regions have a more similar connectivity profile than non-homologous regions, even for components of functionally lateralized systems. Consistent with this idea, our metrics were well behaved on whole cortex coarse morphologic parcellations.

Finally, the metrics will not detect systematic bias that preserves and/or promotes consistency across hemispheres e.g. signal dropout along similar regions of both hemispheres. This might result in parcellations that do not reflect cortical fields, while still exhibiting strong correspondences across the two hemispheres. Both limitations can be overcome through the concurrent use of other evaluation criteria and/or use of data that attenuates systematic biases in homology (e.g. right-left phase encoding of dMRI during acquisition).

V. Conclusion

We demonstrate the use of three complementary metrics rooted in experimentally-based knowledge about cortical structure and homology, for assessing the quality of cortical parcellation. Analysis of these measures strongly supports the notion that individual cortical fields have characteristic connectivity profiles that are compact and separable, and that the topological arrangement of such fields is strongly conserved between hemispheres and individuals.

These metrics can be used for quality control of individual parcellations and to guide improvements in acquisition, reconstruction, and/or clustering approaches for diffusion MRI data. They are complementary to, rather than exclusive of, other approaches.

We believe that this work contributes to the development MRI-based approaches capable of detecting, and rendering scientifically accessible the structure of brain systems supporting cognition and behavior. Connectivity-based cortical parcellation makes possible the segmentation of the mesoscale cortical units (“cortical fields”) on anatomic grounds in individual subjects, and can be a powerful adjunct to multimodal cognitive neuroscience studies of brain-behavior relations and interindividual differences.

Acknowledgments

This work was supported by the U.S. National Institutes of Health under grant RC4 NS073008

References

1. Roland PE, Zilles K. Structural divisions and functional fields in the human cerebral cortex. *Brain Research Rev.* May; 1998 26(2-3):87–105. [PubMed: 9651489]
2. Passingham RE, et al. The anatomical basis of functional localization in the cortex. *Nat. Rev. Neurosci.* 2002; 3(8):606–616. [PubMed: 12154362]
3. Wang, E., et al. Multi-subject connectivity-based parcellation of the human IPL using gaussian mixture models and hidden markov random fields. *Int. Symp. Biomedical Imaging*; San Francisco, CA. 2013. p. 520-523.
4. Roca, P., et al. Tractography-based parcellation of the cortex using a spatially-informed dimension reduction of the connectivity matrix. *Int. Conf. Medical Image Computing and Computer-Assisted Intervention*; London, UK. 2009. p. 935-42.
5. Crippa A, et al. Heuristics for connectivity-based brain parcellation of SMA/pre-SMA through force-directed graph layout. *NeuroImage.* Feb.2011 54(3):2176–84. [PubMed: 20933092]
6. Perrin M, et al. Connectivity-based parcellation of the cortical mantle using q-ball diffusion imaging. *Int. J. of Biomedical Imaging.* 2008; 2008:368–406.
7. Tomassini V, et al. Diffusion-weighted imaging tractography-based parcellation of the human lateral premotor cortex identifies dorsal and ventral subregions with anatomical and functional specializations. *J. of Neuroscience.* Sep.2007 27(38):10259–69. [PubMed: 17881532]
8. Gorbach NS, et al. Hierarchical information-based clustering for connectivity-based cortex parcellation. *Frontiers in Neuroinformatics.* 2011; 5:18. [PubMed: 21977015]
9. Anwender A, et al. Connectivity-Based Parcellation of Broca's Area. *Cerebral Cortex.* Apr.2007 17(4):816–25. [PubMed: 16707738]
10. Klein JC, et al. Connectivity-based parcellation of human cortex using diffusion MRI: Establishing reproducibility, validity and observer independence in BA 44/45 and SMA/pre-SMA. *NeuroImage.* Jan.2007 34(1):204–11. [PubMed: 17023184]

11. Mars RB, et al. Diffusion-weighted imaging tractography-based parcellation of the human parietal cortex and comparison with human and macaque resting-state functional connectivity. *J. of Neuroscience*. Mar.2011 31(11):4087–100. [PubMed: 21411650]
12. Jbabdi S, et al. Multiple-subjects connectivity-based parcellation using hierarchical Dirichlet process mixture models. *NeuroImage*. Jan.2009 44(2):373–84. [PubMed: 18845262]
13. Behrens, T., et al. Connectivity-based Parcellation of Gray Matter. In: Jones, DK., editor. *Diffusion MRI: theory, methods, and applications*. Oxford Univ. Press; 2011. p. 409-424.
14. Soran B, et al. Parcellation of human inferior parietal lobule based on diffusion MRI. *Annu. Int. Conf. of the IEEE Engineering in Medicine and Biology Society*. 2012:3219–22.
15. Wang J, et al. Tractography-based parcellation of the human left inferior parietal lobule. *NeuroImage*. Nov.2012 63(2):641–52. [PubMed: 22846658]
16. Tungaraza, RF., et al. Identifying the structural architecture of the human inferior parietal lobule using diffusion MRI. *IEEE Symp. Biomedical Imaging; Barcelona*. 2012. p. 506-509.
17. Felleman DJ, Van Essen DC. Distributed hierarchical processing in the primate cerebral cortex. *Cerebral Cortex*. 1991; 1(1):1–47. [PubMed: 1822724]
18. Van Essen DC, et al. Mapping visual cortex in monkeys and humans using surface-based atlases. *Vision Research*. 2001; 41(10–11):1359–1378. [PubMed: 11322980]
19. Caspers S, et al. Organization of the Human Inferior Parietal Lobule Based on Receptor Architectonics. *Cerebral Cortex*. Mar.2012 23(3):1–14. [PubMed: 22275480]
20. Caspers S, et al. The human inferior parietal cortex: cytoarchitectonic parcellation and interindividual variability. *NeuroImage*. Nov.2006 33(2):430–48. [PubMed: 16949304]
21. Caspers S, et al. Connectivity of human inferior parietal lobule assessed by diffusion tensor imaging reveals similarities to connectivity patterns in macaques. *Society for Neuroscience Abstracts*. 2009
22. Nelson SM, et al. A parcellation scheme for human left lateral parietal cortex. *Neuron*. Jul.2010 67(1):156–70. [PubMed: 20624599]
23. Blumensath T, et al. Spatially constrained hierarchical parcellation of the brain with resting-state fMRI. *NeuroImage*. Aug.2013 76:313–24. [PubMed: 23523803]
24. Van Essen DC, Glasser MF. In vivo architectonics: A cortico-centric perspective. *NeuroImage*. Jun.2013 93:157–164. [PubMed: 23648963]
25. Brodmann, K. *Localisation in the cerebral cortex*. Garey, LJ., editor. Springer; 2006.
26. Chen CH, et al. Hierarchical genetic organization of human cortical surface area. *Sci*. Mar.2012 335:1634–6.
27. Yeo BTT, et al. The organization of the human cerebral cortex estimated by intrinsic functional connectivity. *J. of Neurophysiology*. Sep.2011 106(3):1125–65. [PubMed: 21653723]
28. Caspers S, et al. Probabilistic fibre tract analysis of cytoarchitectonically defined human inferior parietal lobule areas reveals similarities to macaques. *NeuroImage*. Sep.2011 58(2):362–380. [PubMed: 21718787]
29. Rubner Y, et al. The earth movers distance as a metric for image retrieval. *Int. J. of Comp. Vision*. 2000; 40:99–121.
30. Rubner, Y., et al. A Metric for Distributions with Applications to Image Databases. *IEEE Int. Conf. Computer Vision; Bombay, India*. 1998. p. 59-66.
31. Pele, O.; Werman, M. Fast and robust earth mover's distances. *Int. Conf. Computer Vision; Kyoto, Japan*. 2009. p. 460-467.
32. Cluster Analysis. Wikipedia. Nov.. 2014 [online]http://en.wikipedia.org/wiki/Cluster_analysis
33. Tungaraza, R., et al. Homology and topology based metrics for evaluating cortical parcellations generated using diffusion MRI. *IEE Engineering in Medicine and Biology Society Annual Conference. Proceedings*; 2014.
34. Dale AM, et al. Cortical surface-based analysis I. Segmentation and surface reconstruction. *NeuroImage*. Feb.1999 9(2):179–194. [PubMed: 9931268]
35. Fischl B, et al. Cortical surface-based analysis. II: Inflation, flattening, and a surface-based coordinate system. *NeuroImage*. Feb.1999 9(2):195–207. [PubMed: 9931269]

36. Desikan RS, et al. An automated labeling system for subdividing the human cerebral cortex on MRI scans into gyral based regions of interest. *NeuroImage*. Jul.2006 31(3):968–80. [PubMed: 16530430]
37. Destrieux C. Automatic parcellation of human cortical gyri and sulci using standard anatomical nomenclature. *NeuroImage*. Oct.2010 53(1):1–15. [PubMed: 20547229]
38. Smith SM, et al. Advances in functional and structural MR image analysis and implementation as FSL. *Neuroimage*. 2004; 23:208–219.
39. Tournier JD, et al. Robust determination of the fibre orientation distribution in diffusion MRI: Non-negativity constrained super-resolved spherical deconvolution. *Brain Research*. May; 2007 35(4):1459–1472.
40. Tournier JD, et al. Direct estimation of the fiber orientation density function from diffusion-weighted MRI data using spherical deconvolution. *NeuroImage*. Nov.2004 23(3):1176–85. [PubMed: 15528117]
41. Tournier JD, et al. MRtrix: Diffusion tractography in crossing fiber regions. *Int. J. of Imaging Syst. and Technology*. 2012; 22:53–66.
42. Zalesky A, et al. Whole-brain anatomical networks: does the choice of nodes matter? *NeuroImage*. Apr.2010 50(3):970–83. [PubMed: 20035887]
43. Frey BJ, Dueck D. Clustering by passing messages between data points. *Sci*. Feb.2007 315:972–6.
44. Munkres J. Algorithms for the Assignment and Transportation Problems. *Journal of the Society for Industrial and Applied Mathematics*. Mar.1957 5(1):32–38.
45. Saxe, R.; Brett, M.; Kanwisher, N. Divide and Conquer: A Defense of Functional Localizers. In: Hanson, SJ.; Bunzl, M., editors. *Foundational Issues in Human Brain Mapping*. MIT Press; Cambridge: 2010. p. 25-42.
46. Saxe R, et al. Divide and conquer: a defense of functional localizers. *NeuroImage*. 2006; 30:1088–96. discussion 1097–9. [PubMed: 16635578]
47. Cohen AL, et al. Defining functional areas in individual human brains using resting functional connectivity MRI. *NeuroImage*. May; 2008 41(1):45–57. [PubMed: 18367410]
48. Eickhoff SB, et al. Co-activation patterns distinguish cortical modules, their connectivity and functional differentiation. *NeuroImage*. Aug.2011 57(3):938–49. [PubMed: 21609770]
49. Glasser MF, Van Essen DC. Mapping human cortical areas in vivo based on myelin content as revealed by T1- and T2-weighted MRI. *J. of Neuroscience*. Aug.2011 31:11597–11616. [PubMed: 21832190]
50. Mesulam, M-M. *Principles of Behavioral and Cognitive Neurology*. 2nd Ed. Oxford University Press; 2000.
51. Damasio, H.; Damasio, AR. *Lesion Analysis in Neuropsychology*. Oxford University Press; 1989.
52. Jo HJ, et al. Quantifying Agreement between Anatomical and Functional Interhemispheric Correspondences in the Resting Brain. *PloS ONE*. 2012; 7:e48847. [PubMed: 23144995]
53. Zuo XN, et al. Growing together and growing apart: regional and sex differences in the lifespan developmental trajectories of functional homotopy. *The J. of Neuroscience*. Nov.2010 30:15034–43.
54. Joliot M, et al. Establishing homotopic inter-hemispheric regional correspondences via rest functional connectivity. *Organization for Human Brain Mapping Abstracts*. 2012; 795
55. Qiu D, et al. Lateralization of the arcuate fasciculus and its differential correlation with reading ability between young learners and experienced readers: a diffusion tensor tractography study in a Chinese cohort. *Human Brain Mapping*. Dec.2011 32(12):2054–63. [PubMed: 21259386]
56. Catani M, Mesulam M. The arcuate fasciculus and the disconnection theme in language and aphasia: history and current state. *Cortex*. Sep.2008 44(8):953–961. [PubMed: 18614162]
57. Glasser MF, Rilling JK. DTI tractography of the human brain's language pathways. *Cerebral cortex*. Nov.2008 18(11):2471–82. [PubMed: 18281301]
58. Kucyi A, et al. Hemispheric asymmetry in white matter connectivity of the temporoparietal junction with the insula and prefrontal cortex. *PloS ONE*. 2012; 7:e35589. [PubMed: 22536413]

Figure 1.

The pairwise EMD and TpD scores for all 19 subjects (blue circles: Desikan-Killiany parcellation, green diamonds: random parcellation). The 3 circled subjects with higher TpD scores are discussed in text and Figure 3.

Figure 2.

Top panel: whole brain parcellations of two subjects (S15 and S17) whose homologous Desikan-Killiany regions are matched perfectly across hemispheres based on diffusion data. Middle panel: random parcellations for the same subjects showing ROIs matched to similar anatomic locations across the two hemispheres, but did not respect major morphological boundaries, e.g superior temporal sulcus. Bottom panel: Erroneous homology assignment of Desikan-Killiany parcels for the three subjects (S11, S3, and S6) circled in Figure 2 for whom the combined EMD and TpD scores were unfavorable relative to the other 15 subjects. In all three cases the mismatched ROIs were the Frontal Pole (white arrows on S3) and Medial Orbital Frontal regions (white arrows on S6 and S11).

Figure 3.

Average DB versus Average TpD+EMD for the IPL parcellations (blue circles: dMRI-based; green diamonds: random). Encircled: 10 subjects in the extreme favorable corner of the metric space.

Figure 4.

Homology assignments of 5 IPL parcels between hemispheres. Left column: 6 of the 10 subjects encircled in Figure 4 whose TpD+EMD and average DB scores were highly favorable. Middle column: 6 of the remaining 9 subjects whose TpD+EMD and average DB scores less favorable (see text for discussion). Right column: Representative random parcellations, (corresponding to same subjects as left column). Homologs are color coded, with different coding schemes across subjects.

Figure 5. Within-hemisphere, between-subject homology assignment of the IPL based on dMRI-based parcellation of the left hemisphere. Subjects are arranged row-wise ranked by EMD score with respect to the group prototype (top row most similar to prototype). Homologous regions have the same color.