Comparison of Structural Connectivity Metrics
for Multimodal Brain Image Analysis

Mohammad Bajammal, Burak Yoldemir, Rafeef Abugharbieh

Biomedical Signal and Image Computing Lab, The University of British Columbia, Canada

ABSTRACT

Multimodal brain image analysis is gaining popularity as exemplified in the recent surge of techniques dedicated to fusing structural and functional connectivity information. The performance of such endeavors relies on the metrics used to quantify connection strength. Compared to functional connectivity (FC) metrics, structural connectivity (SC) metrics received less scrutiny by the neuroimaging community despite being widely utilized in the literature. In this paper, we analyze the performance of commonly used SC metrics. Specifically, we analyze the relationship between SC and FC during resting-state and different tasks with the assumption of an inherent dependence between brain structure and function. Among the tested metrics, we show that parcel volume-normalized fiber count correlates best with FC, and that total fiber length has the least bias in favor of shorter distances between brain regions. We also show relatively consistent SC-FC correlation across tasks, supporting the notion that SC constitutes the backbone of brain connectivity facilitating a diverse repertoire of functional connectivity patterns.

Index Terms— brain connectivity, diffusion MRI, fiber count, fiber length, fractional anisotropy, functional MRI, multimodal

1. INTRODUCTION

Diffusion magnetic resonance imaging (dMRI) and functional MRI (fMRI) are becoming increasingly popular for assessing structural and functional connectivity of the brain. The integration of structural connectivity (SC) and functional connectivity (FC) information is an active field of research having emerging applications such as fMRI guided fiber tracking [1], multimodal connectivity estimation [2] and the use of SC priors for regularizing functional activation detection [3]. A recent review of these fusion techniques and applications can be found in [1].

Multimodal analyses require the quantification of connectivity, and inaccurate connectivity metrics may lead to flawed inferences. Even though the neuroimaging community has largely settled on functional connectivity metrics, with Pearson's correlation between observed fMRI time courses being the most popular by far [4], investigations of structural connectivity metrics have received less attention. In this paper, we present a comparison of structural connectivity metrics assessed from the perspective of the largely accepted inherent relationship between brain structure and function.

Quantifying structural connectivity in the brain is most commonly based on quantifying one or more aspects of the streamlines reconstructed using deterministic tractography, though computationally expensive approaches based on probabilistic tractography techniques were also explored [5]. The choice of which streamline property to measure and of how to map it into a structural connectivity metric are key aspects affecting the structural connectivity estimates. Arguably the most common SC metric is the number of reconstructed streamlines between pairs of brain regions, commonly referred to as fiber count. A variant of this approach involves a normalization of the fiber count by the total volume of the region pairs they connect to account for the variable size of the brain regions [6]. Besides metrics based on fiber count, use of the total length of reconstructed streamlines has also been suggested as a measure of structural connectivity [7] aiming to correct for the fact that longer tracts have larger accumulated error, leading to lower fiber counts. Another metric, the average fractional anisotropy (FA) along streamlines connecting regions, has also been proposed as a proxy for structural connectivity strength [8].

It is important to acknowledge that all of the aforementioned SC metrics are confounded by several factors, limiting their interpretability. First, tractography can only delineate bundles of fibers in the brain, and not individual fibers. The term *fiber count* can thus be misleading. Indeed, using the term *streamline count* has been recently proposed as an alternative [9]. Nonetheless, we use the term fiber count for easier interpretation and to conform to the jargon used in existing literature, with the understanding that it is the streamlines that are actually being counted. Moreover, we note that the number of fibers is dependent on the number of seeds used for tracking the fibers, the tractography method used, and several features of the pathway such as curvature, length and width [9]. Additionally, we highlight that FA not only depends on the reliability of local diffusion information, but also on a large

number of modulating factors such as axonal ordering, axonal density, amount of myelination, and increase in extracellular or intracellular water [9]. Such confounding factors did not impede the adoption of a variety of SC metrics, driven by a practical need for quantifying the degree of connection between brain regions. We propose that reconciling the presence of confounding factors with the practical need for connectivity estimation calls for a detailed analysis, in a quantitative comparison, to determine which SC metric has the highest potential of being of practical use in multimodal brain image analysis efforts. To this end, we compare four commonly used SC metrics in terms of their impact on the relationship between estimates of SC and FC. On 38 subjects from the Human Connectome Project (HCP) database [10], we show that region volume-normalized fiber count best correlates with FC. We also show that total fiber length has the least bias towards distance between brain regions. We further demonstrate that these results hold across seven different tasks and resting-state data.

2. METHODS

We start by obtaining an FC matrix from the fMRI time courses of each subject (Section 2.1). We then proceed to estimate SC for each subject using four SC metrics (Section 2.2). Finally, we compare the SC metrics based on their statistical relationship with FC.

2.1. Functional Connectivity Estimation

Let $\mathbf{Z}$ be a $t \times d$ matrix of demeaned fMRI time courses, where t is the number of time points and d is the number of brain regions. We estimate FC using Pearson's correlation:

$$\mathbf{FC} = \mathbf{Z}^{\mathrm{T}} \, \mathbf{Z} \, / \, (t\text{-}1). \qquad (1)$$

Even though partial correlation, which controls for indirect effects, can also be used, we opt to use Pearson's correlation since it is the most common FC metric by far.

2.2. Structural Connectivity Estimation

Let $r_{i,j}^{\;k}$ be the kth reconstructed fiber between a pair of structurally connected regions P_i and P_j. We consider four widely used structural connectivity measures in this work: fiber count ($f_{i,j}$), fiber count normalized by the total volume of the connected regions ($N_{i,j}$), total length of fibers connecting region pairs ($L_{i,j}$), and average FA along the fibers. For each subject, we compute the Pearson's correlation between the FC and SC estimates to quantify the SC-FC relationship for each SC metric. More formally, the metrics can be expressed as follows:

$$N_{i,j} = \frac{f_{i,j}}{V(P_i) + V(P_j)} \qquad (2)$$

$$L_{i,j} = \sum_k \ell(r_{i,j}^{\;k}) \qquad (3)$$

where $V(\cdot)$ is the volume of the corresponding region, and $\ell(r_{i,j}^{\;k})$ is the length of $r_{i,j}^{\;k}$.

Prior to the computation of SC metrics, we reconstruct the fibers via global tractography on constant solid angle orientation distribution function (ODF) using MITK [11]. Global tractography was chosen over the more common streamline tractography since it was recently shown to facilitate higher SC-FC consistency [12]. In global tractography, short fiber segments are connected together to generate the set of fiber tracts that best explains the measured dMRI data. As such, at regions with unreliable local diffusion information, the geometry of the surrounding fibers drives the tracking process to prevent premature termination of fibers as is commonly observed in streamline tractography.

3. MATERIALS

In our comparison we used resting-state fMRI, task-fMRI and dMRI data from 38 subjects (17 males and 21 females, ages ranging from 22 to 35 years) from the Human Connectome Project (HCP) Q2/2013 dataset [10]. This release of the dataset has 40 subjects for which all of the modalities were made available. We excluded two subjects from the dataset (#209733 and #528446) as per HCP's recommendation, due to reported structural brain abnormalities. Each of the 38 subjects had four 15-minute RS-fMRI scans, with a TR of 0.72 s and 2 mm voxels (isotropic). Each subject also had 7 task-fMRI datasets (two 2-5 minute scans each for working memory, gambling, motor, language, social cognition, relational processing, and emotional processing) obtained using the same acquisition parameters as the RS-fMRI. The dMRI data had a voxel size of 1.25 mm (isotropic), 3 shells (b=1000, 2000 and 3000 s/mm^2) and 288 gradient directions. Further acquisition details can be found in [10].

Beyond the minimal preprocessing already applied by HCP [13], we regressed out motion artifacts, mean white matter and cerebrospinal fluid signals from both RS-fMRI and task-fMRI data. We further regressed out the principal components of high variance voxels found using CompCor [14] from RS-fMRI data. This step was not applied for task-fMRI data to avoid discarding task-evoked signals. The dMRI data, which have already been corrected by HCP for EPI distortion, eddy current, gradient nonlinearity and motion artifacts [13], were downsampled to 2 mm isotropic resolution in order to reduce the computational cost during tractography. On average, we reconstructed 65,000 fibers per subject.

We parcellated the brain into 200 regions by applying Ward clustering [15] on the voxel time courses temporally concatenated across subjects. The number of regions was set
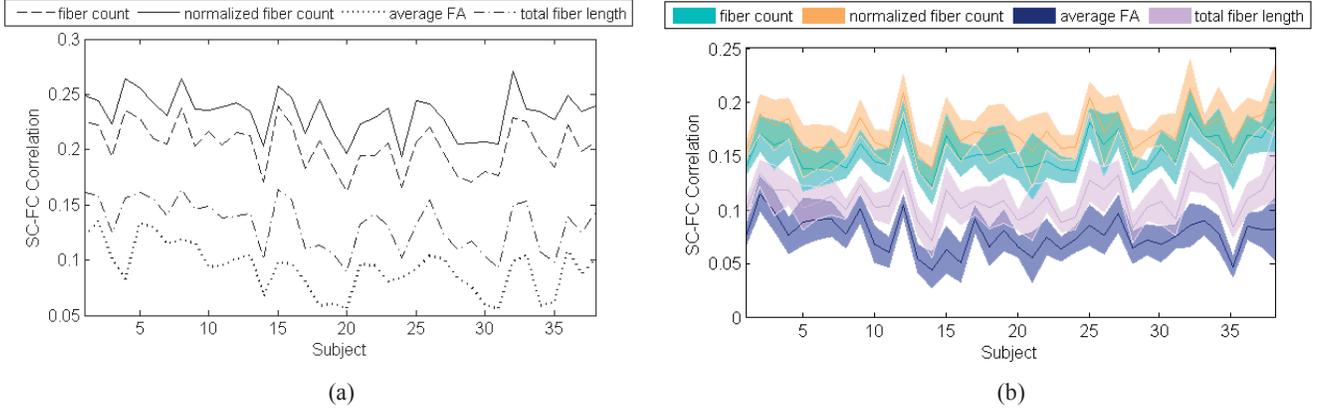
Fig. 1. Correlation between SC and FC using four SC metrics: fiber count, normalized fiber count, average FA, and total fiber length. Correlation was performed for 38 subjects from the Human Connectome Project data using: (a) resting-state fMRI, and (b) task-fMRI. The narrow shaded bands in (b) represent the standard deviation of SC-FC correlation across 7 different tasks.

based on the results of a previous study [16] which recommended the use of 200 or more parcels to attain lower intra-subject variance compared to inter-subject variance. We finally warped the resulting group parcellation map onto the native dMRI space of each subject for the computation of SC metrics.

4. RESULTS AND DISCUSSION

The results of the SC-FC correlation for resting-state and task fMRI are shown in Fig. 1(a) and (b), respectively. As observed from these figures, average FA has lower correlation with FC compared to the rest of the examined SC metrics (fiber count, volume-normalized fiber count, and total fiber length). This is true for both resting-state and task fMRI. We speculate that the reason for the observed low average FA correlation can be attributed to the large number of factors affecting local diffusion anisotropy [9]. Fig. 1 also shows that the volume-normalized fiber count has the highest correlation with FC compared to the rest of the examined SC metrics for both resting-state and task fMRI. The pairwise differences between SC-FC correlation assessed using normalized fiber count and other SC metrics were found to be statistically significant at $p < 0.001$ based on the Wilcoxon signed rank test. Our results thus imply that the compensation (due to normalized fiber count) for the differences in number of fibers due to the variable size of brain regions yields better depiction of structural networks.

We also note that the relatively consistent SC-FC correlation levels across a variety of tasks and resting-state data support the notion that SC forms the backbone of the brain connectivity around which functional reorganization occurs to respond to different tasks. A diverse repertoire of functional brain connectivity patterns can thus arise constrained by the same structural substrate.

Fig. 2 shows a qualitative comparison between functional and structural connectivity patterns. We averaged the subject-specific connectivity matrices to compute group

results. Specifically, the top 10 parcels having strongest connectivity to posterior cingulate cortex (PCC) are projected onto the brain using these group-level connectivity matrices. PCC was selected as the seed as it is known to be a structural and functional hub facilitating efficient communication in the brain [6]. Due to space limitations, only the results obtained using SC metrics having the highest and lowest correlation with FC are shown. This figure shows that the SC patterns estimated using normalized fiber count resemble the FC patterns more than those estimated using average FA.
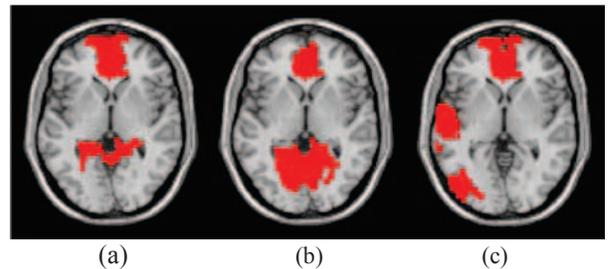

Fig. 2. Parcels with highest connectivity to posterior cingulate cortex as obtained from: (a) FC, (b) normalized fiber count, and (c) average FA. Note how the arrangement of connected parcels obtained by normalized fiber count has a better resemblance to the parcels obtained by FC, compared to average FA.

Since shorter fibers are easier to be reconstructed, SC metrics have an inherent bias in favor of shorter fibers. This in turn induces a dependency of the SC-FC relationship on distance. To quantify the extent of this phenomenon, we computed the difference between group-averaged SC-FC correlation values of the longest and shortest 20% of all fibers, which we refer to as fiber length bias. As shown in Table 1, total fiber length metric has the smallest fiber length bias. This finding confirms that total fiber length indeed partially corrects for length bias fiber count metrics suffer from.

Table 1. Comparison of fiber length bias for SC metrics.

SC metric	Fiber length bias
fiber count	0.14
normalized fiber count	0.17
average FA	0.15
total fiber length	**0.10**

5. CONCLUSIONS

We presented a comparison of four SC metrics computed from tractography results with respect to their relationship to FC. Among the metrics considered, we showed that volume-normalized fiber count has the highest correlation with FC for both resting-state and task data. On the other hand, our results showed that average FA has the lowest correlation with FC. We speculate that the reason of this low correlation is the non-specificity of FA, with several inadvertent factors (such as axonal density, axonal ordering, and amount of myelination) modulating it along with the reliability of local diffusion information. In addition, we also demonstrated that total fiber length metric reduces the fiber length bias associated with shorter fibers. Our results therefore suggest that average FA may not be the best metric to quantify SC, and that the choice among other SC metrics warrants special attention depending on the question being addressed and the scale of the problem (e.g. whole-brain or local regional analysis).

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