Investigating the consequences for connectomic metrics of methods to correct fibre tracking biases

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Target Audience: This study is intended for those interested in robust quantifications of structural connectome metrics based on diffusion MRI tractography.

Purpose: Diffusion MRI and streamlines tractography have become major techniques for inferring structural cortical networks through reconstruction of the brain connectome [1-2], where connectivity weightings are typically characterised by the number of streamlines interconnecting cortical brain regions. However, quantification of the structural connectome based on streamline count is known to be problematic in two aspects. Firstly, streamline terminations determined by the criteria chosen for the tractography algorithm may fail to end within cortical grey matter (GM); secondly, the number of streamlines connecting regions is known to be an unreliable quantitative marker of fibre connectivity [3]. For the latter, a pioneer study on structural network analysis [2] suggested scaling the contribution of each streamline to the connectome by its inverse length, to compensate for the bias introduced by homogeneous seeding throughout white matter (WM), though the efficacy of this approach remains unproven. The issues described above can potentially be solved through application of the ACT (anatomically-constrained tractography) [4] and SIFT (spherical-deconvolution informed filtering of tractograms) [5-6] methods, which have been proposed to improve the robustness of determining streamline terminations, and provide a tractography reconstruction with quantitative properties, respectively. It is reasonable to infer, therefore, that the derived network metrics will also be more biologically accurate following ACT and SIFT; however, the practical consequences of these methods on such network measures have not been determined. Hence, the purpose of this study is to investigate the effects of length scaling, ACT, and SIFT on brain network metrics.

Methods:

A) MRI acquisition: Ten healthy volunteers were scanned in a Siemens 3T Tim Trio system (Erlangen, Germany). T1-weighted images (T1WIs) were acquired using the MPRAGE sequence with TE/TI/TR=2.6/900/1900 ms, flip angle=9°, 0.9 mm isotropic resolution. Diffusion-weighted images (DWIs) were acquired using a twice-refocused spin-echo EPI sequence with TE/TR=110/8400 ms, 2.5 mm isotropic resolution, 60 diffusion sensitization directions at b=3000 s/mm^2.

B) Tractogram reconstruction: (i) Following pre-processing of DWI volumes (i.e. correction for inter-volume motion, susceptibility-induced distortion, and B_1 bias field), fibre orientation distributions (FODs) were then computed using constrained spherical deconvolution (CSD) [7]. (ii) T1WI-based brain tissue segmentation was performed using FSL [8] and followed by cortical parcellation using FreeSurfer [9] with 84 structural connectome nodes defined by the Desikan-Killiany atlas [10]. (iii) For all streamline reconstructions, the iFOD2 algorithm [11] was employed with step size=1.25 mm, maximum curvature=45°, length=5-250 mm, and FOD threshold=0.1. For each scan, tractograms of 10^7 and 10^8 streamlines were generated through seeding from WM mask, tracking either with or without ACT. For those reconstructions consisting of 10^8 streamlines, SIFT was applied to filter the reconstruction from 10^8 to 10^7 streamlines. Thus, we created four tractograms with the same streamline count (10^7) for each subject.

C) Network construction and metrics: Connectomes were generated from the tractograms and subject GM parcellation using one of the following three edge weightings: (i) Streamline count ('N'); (ii) Sum of inverse streamline lengths ('L^{-1}') [2]; (iii) Streamline count following SIFT ('N_{SIFT}'). This was repeated for tractograms generated either with or without ACT. Where ACT was used, streamlines were assigned to the closest node within 2 mm of the streamline endpoint; where ACT was not used, a search was performed from each endpoint of a streamline toward the midpoint to find the last traversed node. Finally, for each connectome matrix, we used a weighted mean coefficient of variation (*wmCoV*) [6] to provide a global measure of network variance (contributed by all edges), and used Brain Connectivity Toolbox [12] to calculate a range of key weighted network metrics for network analysis (superscript 'W' in network measures denotes weighted network metric variants).

Results & Discussion: Table 1 provides the results of the mean network metrics across 10 subjects. Note that K^W and L^W of those matrices using the L^{-1} connectivity weighting are omitted from Table 1 as their magnitudes are drastically different so as to preclude meaningful comparison.

All network metrics vary considerably in magnitude as a function of the connectivity weighting used (streamline count, length scaling, or SIFT) and application of the ACT framework during streamlines tractography. The greatest difference occurs for the K^W metric (mean strength; essentially the mean number of streamlines exiting each node, excluding self-connections) depending on whether ACT is used, despite these reconstructions involving generations of an identical number of streamlines: this reflects how without the use of ACT, many streamlines terminate prematurely in the WM [4] and are therefore not attributed to a parcellation node. Although changing the connectivity weighting from streamline count to the sum of inverse streamline lengths tends to move the values of network metrics toward those provided by SIFT, this may be an under- or over-correction depending on the particular metric being investigated, suggesting that this popular heuristic is inadequate for correcting all biases inherent in whole-brain streamlines tractography reconstructions.

Table 1. Weighted network metrics for different connectome weighting schemes (mean±std)

	Without ACT			With ACT		
	N	L^{-1}	N_{SIFT}	N	L^{-1}	N_{SIFT}
wmCoV	0.450	0.358	0.356	0.436	0.396	0.342
K^W	48335±6338	-	31390±2457	144315±4580	-	84103±5027
L^W	6.63±0.83	-	8.13±0.53	2.77±0.09	-	4.06±0.43
C^W	7.01±1.01	2.96±0.64	3.76±0.38	8.15±1.22	7.23±0.74	6.61±0.95
B^W	3.20±0.18	4.34±0.15	4.87±0.19	2.73±0.11	3.24±0.14	4.19±0.23
V^W	7.63±0.33	5.90±0.95	6.58±0.97	7.41±0.13	7.61±0.20	8.46±0.22
$E_g{}^W$	7.52±1.28	6.61±1.21	6.99±0.62	7.51±1.19	9.73±1.18	8.03±1.21
$E_l{}^W$	1.39±0.21	0.69±0.15	0.87±0.08	1.52±0.23	1.46±0.15	1.31±0.19
Q^W	0.373±0.025	0.530±0.017	0.561±0.017	0.307±0.017	0.467±0.011	0.552±0.013

Abbreviations: N: streamline count; L^{-1}: streamline length correction; N_{SIFT}: streamline count after SIFT; ***wmCoV***: weighted mean coefficient of variation; K^W: mean strength; L^W: characteristic path length ($\times 10^{-4}$); C^W: mean clustering coefficient ($\times 10^{-3}$); B^W: mean betweenness centrality ($\times 10^{-2}$); V^W: mean eigenvector centrality ($\times 10^{-2}$); $E_g{}^W$: global efficiency ($\times 10^{-2}$); $E_l{}^W$: mean local efficiency ($\times 10^{-2}$); Q^W: modularity

Conclusion: Our data demonstrate how common global metrics of structural brain networks vary considerably when novel reconstruction techniques such as ACT and SIFT are applied, and that a popular heuristic correction for streamline connection density based on streamline length is not an adequate substitute for these methods, highlighting the necessity for the use of such advanced reconstruction techniques in connectome construction.

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