Reproducibility of the structural connectome and other open challenges

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TARGET AUDIENCE: researchers in Diffusion Weighted Imaging (DWI), researchers working with structural connectomics, neurologists

PURPOSE: Brain networks are becoming forefront research in neuroscience. Network-based analysis on the functional and structural connectomes can lead to powerful imaging markers for brain diseases. However, constructing the structural connectome can be based upon different acquisition and reconstruction techniques whose information content and mutual differences has not yet been properly studied and addressed. The variations of the structural connectome if not properly understood can lead to dangerous conclusions when performing these types of studies. In this work we address the reproducibility of the structural connectome if acquired under different q-space sampling conditions, and in the same and different scanning session. We furthermore split the connectivity matrix in 3 different sub-matrices depending on the area of the brain and we evaluate the connectivity results w.r.t. reproducibility. Finally, we address several caveats that should be taken with care when performing this type of analysis approaches with DWI data.

METHODS: **Data –** MRI acquisitions were performed on a 5 healthy volunteers (4 male and 1 female, age: 31.2±2.9 years) using 3T Siemens Trio MRI scanner. The MRI protocol included a 3D structural T1-weighted MPRAGE sequence (TR/TE=1900/4.44ms, TI=1050ms, Flip angle: $8°$, FOV: 220×220mm^2, isometric 1mm^3), DWI sequences were performed using a twice refocused spin-echo echo-planar imaging sequence (see table 1 top). We have acquired in total 21 datasets from which 7 DTI, 6 HARDI and 8 DSI. For some of the subjects the scans were repeated in the same scanning session or after one month. In table 1 (bottom) we report the subset of data we used for each of the performed analysis and the number of subjects involved.

Modality	DTI	HARDI	DSI
$b-val$ (s/mm^2)	1000	1500	b_{max}=8000
num. grad.	30	82	515
num. b_0	1	6	N/A
spatial res. (mm^3)	2.5×2.5×2.5*	1.25×1.25×2.5	2.2×2.2×3**
TR/TE	6900/89	7600/98	8200/164
acq.time(min)	3.56	11.33	35.42
Evaluation	DTI	HARDI	DSI	#subjects
reproducibility	5	4	6	3
% missing fibers	6	5	8	5

Table 1. **Top**: Scanning parameters used in our DWI acquisitions. *Due to technical problems 2 DTI datasets were obtained using spatial resolution of $1.25°x1.25°x2.5mm^3$. **Due to technical problems 1 DSI dataset was obtained using spatial resolution of $3mm^3$ isometric. **Bottom**: Data overview per performed test.

Analysis – We calculated the connectomes using the connectome mapper (cmp) software[1]. For all imaging modalities we used the default settings. For DTI fiber tracking, the cmp uses the standard FACT method and for Qball and DSI FACT-alike algorithm implemented in the Diffusion Toolkit[2]. We employed Lausanne parcellation[3] at lowest scale (33). Depending on the imaging acquisition, DTI, HARDI (Qball) or DSI reconstruction was performed. For the network creation, we first apply an absolute threshold in order to discard edges with less than 10 fibers and the connectivity matrices are created by either binarizing edge weights, or by normalizing the edge weights with maximum number of found fibers.
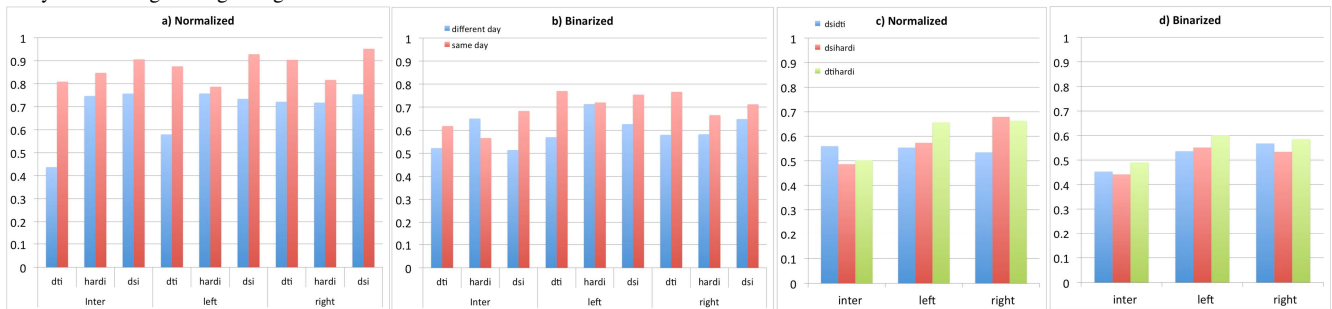

Figure 1. Results from the data reproducibility (a,b), similarities between modalities (c,d) in normalized (a,c) and binarized (b,d) connectomes.

RESULTS: In figure 1(a,b) we present the results of the correlation of the connectivity matrices from the scans done in the same and different imaging session. When the matrices are normalized, we observe highest correlation of the DSI connectome. There is a 20% drop, on average, of the correlation when the scans are performed in a different imaging session. DTI has worse reproducibility when performed in different imaging session with about 0.45 correlation. Binarizing the data (figure 1b) changes the trends significantly, mainly in drop of correlation. Here DTI even outperforms DSI in both left and right hemispheres. In figure 1c and 1d we examine the average correlation of the connectivity matrices constructed by the different acquisition and modeling techniques per subject. We observe similar trends where the correlation drops when the matrices are binarized. The connectivity matrices constructed from all modalities give similar inter-hemispheric connectivity in both normalized and binarized matrices. We observe highest correlation in both right and left hemisphere (both binarized and normalized) between DSI and HARDI, suggesting that the fibertracks and connectivity matrices generated from this data are the most similar.

DISCUSSION: Overall, binarization introduces a decrease in correlation, and decreases the differences among the connectomes acquired under different q-space sampling. Therefore, binarizing and analyzing the data with network metrics will introduce fewer differences in the data. Furthermore, when reconstructing the connectome we discard about 50% of the fibers, regardless the acquisition or tractography technique (DTI 47%±2, HARDI 58%±3, DSI 51%±3). These fibers are either unable to reach the gray matter or unable to pass across the hemispheres. Therefore it has been recently reported[4] very low correlation between the resting state fMRI and the structural connectome. This work addresses important limitation of the structural connectome that should be taken into account before analyzing clinical data with this technique or making a choice for the acquisition technique.

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