Assessment of the Reproducibility of HARDI Tractography based Cortical Connectivity Measures suitable for Clinical Populations using a Bootstrap Approach

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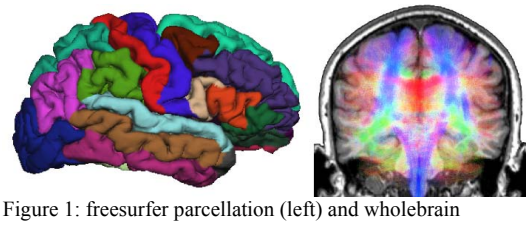

Figure 1: freesurfer parcellation (left) and wholebrain tractogram (right)

Introduction: The assessment of structural connectivity in the human brain *in vivo* using MR diffusion tractography has gained significant interest over recent years. A connectivity matrix [1] of cortical connectivity can be obtained in a fully automated fashion using a combination of high-resolution structural images and MR diffusion tractography. The information contained in these matrices may provide unique insight into brain development and importantly mechanisms of injury and plasticity of key neural networks. In order to study the human connectome in clinical populations, it is important to assess the reliability and reproducibility of connectivity measures, of which tractography seeding methods play a critcal role. In this study we probe two imporant questions: how many streamlines per voxel must be seeded to obtain stable and reproducible connectivity measures and how reproducible is strucutral connectivity over time?

Methods: High-resolution structural images and HARDI data (64 diffusion encoding directions, b-value 3000 s mm^{-1}, 2.5 mm isotropic resolution) were acquired using a 3T Siemens Tim Trio, (Erlangen, Germany) on healthy volunteers. The cerebral cortex was parcellated from the structural image (MPRAGE, 1 mm isotropic resolution) using Freesurfer (http://surfer.nmr.mgh.harvard.edu/fswiki; figure 1). The fibre orientation distribution was calculated using constrained spherical harmonics deconvolution [2]. Probabilistic diffusion tractography was performed using MRtrix (http://www.nitrc.org/projects/mrtrix). One streamline was seeded for every voxel of the entire brain volume. The tractography experiment was repeated 400 times. A termination mask was subsequently applied to prevent streamlines from crossing cortical folds and the cortico-cortical connectivity matrix was calculated for each of the 400 tractography experiments by hit-testing each streamline's terminal endings with every cortical region. Multiple-seed connectivity matrices were generated from the set using a bootstrap approach. For each desired number of seeds per voxel n (up to 200 in steps of 10), 100 multiple-seed matrices were generated. The stability of the connectivity measures was assessed by calculating the standard deviation σ across these 100 multiple-seed matrices. The number of seeds, n_{stable}, that is required to obtain a predefined stability (here 1% deviation from the mean), can be calculated through

$$\sigma(n) \propto (\sqrt{n})^{-1} \qquad \text{(eq 1)}$$

The reproducibility of the connectivity measures was assessed by randomly selecting pairs of multiple-seed matrices generated from data obtained in different scan sessions, and calculating the bias (average difference) and variation (standard deviation of the difference) of the connectivity values for the varying numbers of seeds described above. The reproducibility Δ was determined using the limit of agreement [3]:

$$\Delta(n) = |\ \text{bias}(n)\ | + 1.96 * \text{variation}(n) \qquad \text{(eq 2)}$$

The course of $\Delta(n)$ can be described by an equation similar to (eq 1), and the required number of seeds n_{rep} to obtain a desired reproducibility over time (here 10%) can be estimated, as well as the best achievable reproducibility $\Delta(n \rightarrow \infty)$.

Results: Figure 2a shows a 3D bar plot of the connectivity matrix obtained using 200 seeds per voxel using the initial dataset. The colour of the bars indicates the number of seeds (n_{stable}) that are required to obtain a deviation in the connectivity measure using one dataset of less than 1% (σ). Figure 2b shows an equivalent plot, with the colour encoding the number of seeds (n_{rep}) that are required for a reproducibility in the connectivity measure over time Δ of 10%. Bars in grey indicate that a reproducibility over time of 10% is not achievable given the data. The reproducibility $\Delta(n \rightarrow \infty)$ that can be achieved given the quality of the data is depicted in figure 2c.

Discussion and Conclusion: Our analysis demonstrates that every connection of interest requires a different number of seeds to obtain stable and/or reproducible connectivity measures, and that while connectivity measures of some regions are highly reproducible over time, other connections show poor reproducibility. Research currently undertaken in our laboratory on a larger number of participants includes the study of the effect of different seed point selection methods, different registration methods to align diffusion image space with structural image space, and use of gyral white matter targets rather than grey matter targets on the stability and reproducibility of connectivity measures, as well as the assessment of inter-subject variability and power analysis.

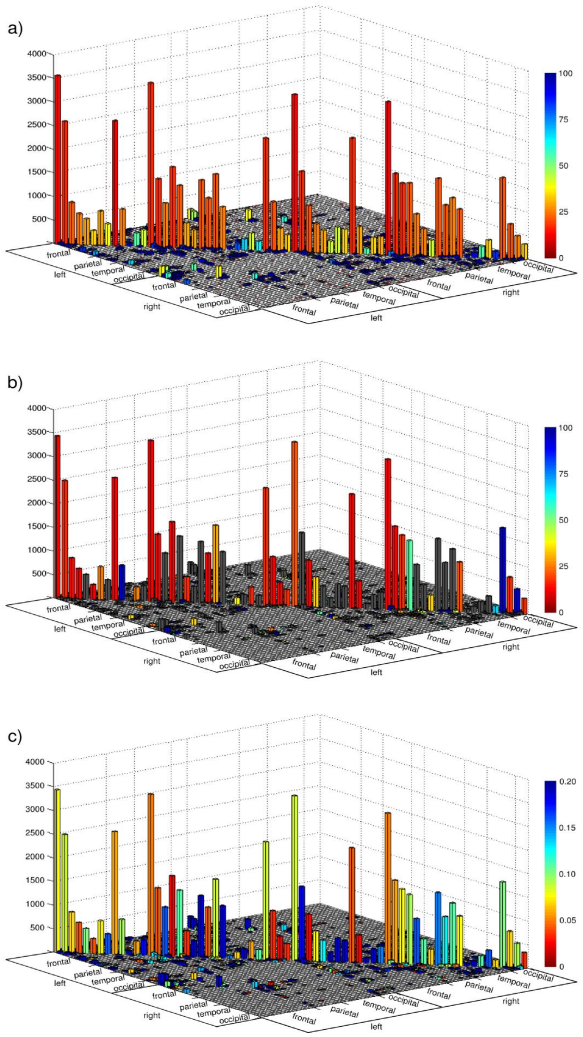

Figure 2: Representative connectivity matrix displayed as 3D bar plot. The colours of the bars encode a) n_{stable}, b) n_{rep} and c) $\Delta(n \rightarrow \infty)$

References: [1] Perrin et al, Int J Biomed Imaging 2008:368406; [2] Tournier et al., NeuroImage 2007, 35:1459; [3] Bland and Altman, Lancet 1986, 1:307-10