Background  Mapping whole-brain structural connectivity using diffusion-weighted imaging has recently become a popular research topic in neuroscience. Here, the brain is considered as a network of grey matter regions linked by white matter tracts. Connectivity between all regions is quantified using tractography techniques and network properties, describing the local and global topology of anatomical connections, can be derived using graph theoretical analysis [1]. Previous studies have shown that network properties such as global clustering coefficient and pathlength, which describe the segregation and integration properties of the network, are altered in cases of neurological disease, providing hope that such network metrics may be useful biomarkers [2]. However, a variety of different methods may be used to reconstruct the structural network and there is currently no consensus on which method gives metrics of the highest anatomical relevance or is most sensitive to disease [3,4]. To address this issue, the intra- and inter-subject reproducibility of network metrics obtained from two different reconstruction pipelines was investigated. Identifying and reducing sources of intra-subject network variation may allow greater reliability and robustness to network analyses, facilitating the delineation of group effects on network measures in clinical studies.

Objectives  This work aims compare the intra and inter-subject reproducibility of whole-brain network metrics derived using two different reconstruction pipelines.

Methods  2 T1-weighted images (3D FLASH) and 3 repeats of a 63-direction echo-planar diffusion weighted sequences were acquired at 1.5T from a group of 28 young healthy subjects. Two pipelines (P1 and P2 are delineated using '/') were applied to reconstruct whole-brain connectivity. The structural images were skull-stripped, registered to improve signal:noise, and parcellated into 68/44 cortical regions, as defined in the Desikan/Hammers Atlas, using Freesurfer/NiftySeg software. Structural images were non-linearly registered to the subjects b=0 image using FSL/NiftyReg registration tools. The voxel orientations of white matter fibers in diffusion-weighted images of (2.5mm)³ resolution were obtained using FSL-BEDPOSTX/Constrained Spherical Deconvolution (CSD). 100 probabilistic streamlines were seeded from each diffusion space ROI voxel, and connectivity was quantified between all ROI pairs as the sum of connecting streamlines divided by the mean ROI volume. In a preliminary analysis we investigated the reproducibility of the raw connection matrices (CM) using the intra- and inter-subject coefficient of variation (CV) and intra-class correlation coefficient (ICC).

Results  Accuracy of cortical parcellations, registrations, fiber modelling and streamline tracking were reasonable as assessed by visual inspection. P2 reconstructed CMs had higher connection densities (60±11% vs 96±3%), subject grand mean connection strengths (0.05±0.16 vs 0.15±0.34, Fig. 1), and intra- and inter-subject reproducibility (CV, intra-: 0.73±0.4 vs 0.30±0.14, inter- 1.87±0.89 vs 0.75±0.35, Fig. 1). The majority of connections had a high ICC for P2 (mean 0.79±0.11), whereas P1 connections had lower reproducibility (mean 0.595±0.227).

Conclusions  The results show that measurement variation in network connection strengths is strongly dependent on the reconstruction method used to generate connection strengths. Networks from P2 were more strongly connected and had higher connection densities, which may reflect the greater ability of tractography streamlines to track through areas of complex fiber architectures using CSD, or the fewer and therefore larger volumes of grey matter nodes in the parcellation. Connections in P2 networks had lower intra and inter-subject CVs and high ICCs, suggesting that this pipeline is less sensitive to noise and other image artefacts in repeat scanning and is therefore better able to describe true subject anatomy. However, for both pipelines the intra and inter-subject CV of connection strengths was inversely proportional to the connection strength itself, indicating a possible distance bias in the connection quantification. It is to be expected that network metrics derived from P2 connectivity matrices will have superior reproducibility than those from P1. Future work will investigate sources of bias in connection quantification, as well as quantifying reproducibility of graph theoretical values derived from these connection matrices. Identifying and reducing sources of variation in network measures will allow greater discriminatory power for clinical studies of network architecture.
