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A pipeline for automated diffusion MRI analysis: overview and application to the study of Alzheimer's Disease

Introduction

Background: Diffusion MRI (D-MRI) has proved invaluable for the study of Alzheimer's Disease, probing tissue structural properties at scales beyond the reach of more rudimentary MR sequences and allowing for advanced 3D modelling of nerve bundle trajectories. Here, we introduce a pipeline for the analysis of D-MRI brain scan data, incorporating steps for the minimisation of common artefacts (subject motion, EPI distortion, eddy currents), calculation of diffusion tensor and *NODDI*[1] metrics for 200+ gray and white matter regions, and exploration of structural connectivity properties via the combination of streamline tractography and graph analytics. In addition to being automated and configurable, the pipeline is fully-integrated into IXICO's regulatory-compliant trial management software, *TrialTracker*™: a web-based tool for data upload, storage, analysis and quality assessment of processed data.

Objectives: to demonstrate pipeline validity via i) comparison with *ExploreDTI*[2]: a software package widely used in academic research (but which requires significant manual intervention), and ii) by application to a cohort of older adults with and without Alzheimer's Disease.

Methodology

D-MRI and T1-weighted MRI for 45 cognitively-normal older adults (CN, average age=73, no. males=19) and 41 adults with Alzheimer's Disease (AD, average age=76.4, no. males=30) was downloaded from the *Alzheimer's Disease Neuroimaging Initiative* (ADNI) database[3]. T1-weighted images were segmented into anatomical subregions, using IXICO's LEAP pipeline[4]. Processed T1 images and raw D-MRI images were then processed according to the steps outlined in **Figure 1.** Image analysis was repeated using ExploreDTI, and Spearman's correlation was used to assess the similarity of several endpoints common to both pipelines: measures of tissue structural organisation - fractional anisotropy (FA) and mean diffusivity (MD) - averaged over anatomical regions-of-interest, as well two measures of brain structural network configuration: node degree and local efficiency. To identify AD-related changes in brain structural properties, plugin endpoints (FA, MD and 5 network measures) were collated and contrasted across disease groups using the permutation test. *p*-values were corrected for multiple comparisons using the Benjamini-Hochberg procedure.

Results

In comparing our pipeline with ExploreDTI, strong correlations were found for regionally-averaged FA (Spearman's r=.94, p<.001) and MD (Spearman's r=.92, p<.001) endpoints. Concerning network measures, node degree was similar between pipelines (Spearman's r=.72, p<.001), but network local efficiency yielded a weaker (but still significant) relationship (Spearman's r=.28, p<.001). This discrepancy may stem from the use of the *Anatomically-constrained tractography*[5] modifier within our pipeline, which employs biologically-realistic tissue priors in order to reduce false positive connections between regions (leading to sparser, but more accurate networks). Visual inspection of structural connectomes (**Figure 2.**) corroborates this interpretation.

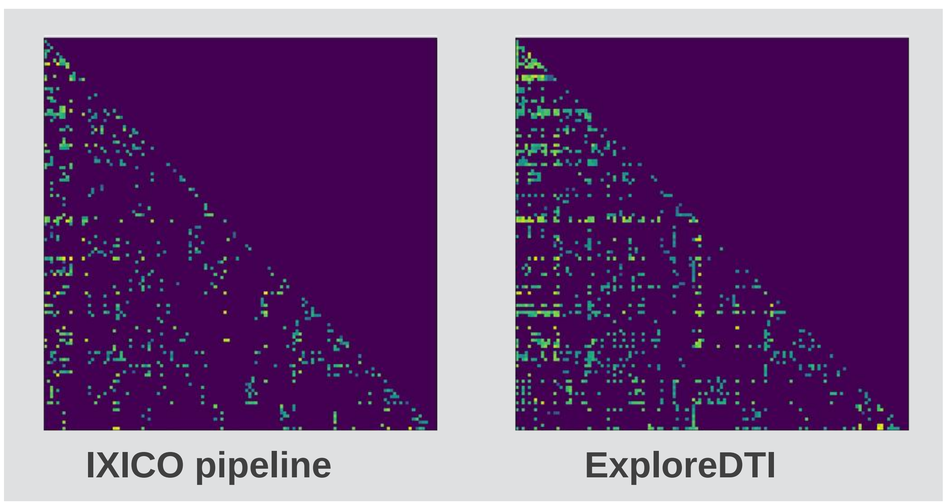

Figure 2. Structural connectivity matrices generated by our pipeline (left) and by the ExploreDTI software suite (right) for the same subject. Cells contain the average fractional anisotropy values for white matter pathways connecting 125 distinct gray matter regions (matrix columns/rows).

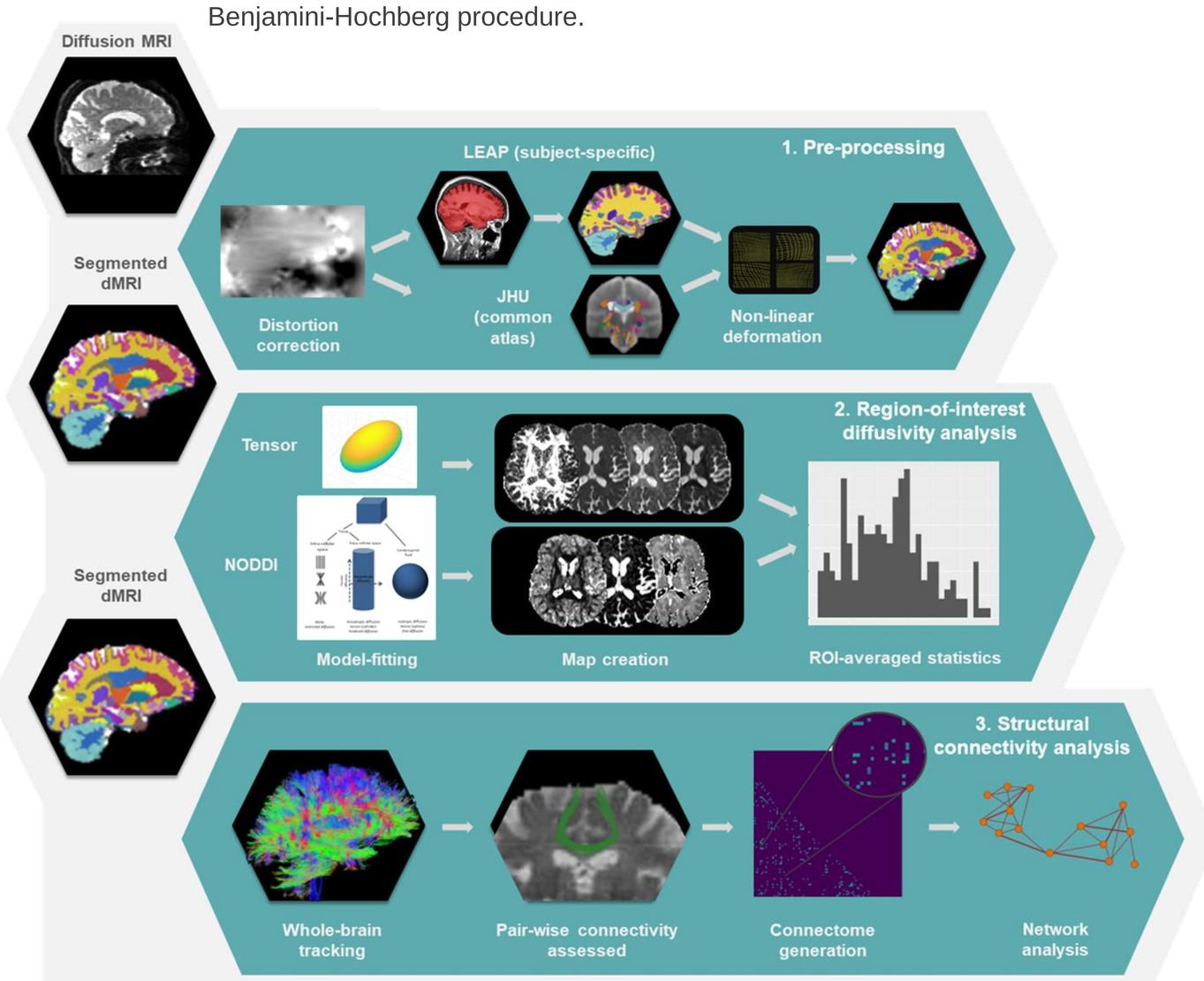

Figure 1. Overview of the diffusion MRI analysis pipeline

Differences between AD and CN groups in FA and MD were found in regions including the hippocampus, fornix and splenium of the corpus callosum, but not in the corticospinal tract, brainstem (medulla) or the cerebellar white matter, consistent with previous reports. Whole-brain structural network analysis revealed AD-related alterations predominantly in nodes associated with the *Default Mode Network*, a collection of regions repeatedly implicated in the pathogenesis of the disease. Specific examples include: reduced clustering in the right posterior cingulate gyrus, increased node degree in the left anterior cingulate gyrus, and reduced node degree in the right hippocampus (**Figure 3.**)

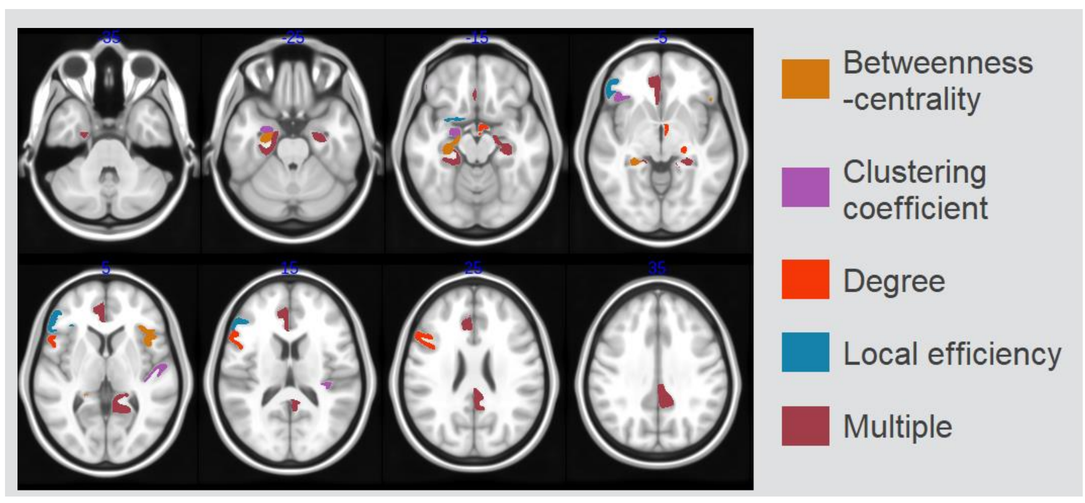

Figure 3. Gray matter regions with significantly altered structural network properties (defined using streamline counts between regions) across CN and AD subjects.

References

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Conclusions

We present a pipeline for diffusion MRI analysis and demonstrate its potential for analysis in Alzheimer's Disease. The fully-automated nature of our pipeline, coupled with its integration into the TrialTracker platform, allows for high-throughput application in phase 2 and 3 clinical trials in a regulatory-compliant manner.