Anatomical Connectivity Mapping – Measuring connectivity changes in Multiple Sclerosis

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Introduction

Anatomical Connectivity Mapping (ACM) based on diffusion MRI generates a scalar map that reflects the connectivity of each voxel with the rest of the brain [1, 2]. The value of an ACM voxel reflects white mater integrity both locally and globally and the ACM is therefore able to reveal effects not seen with traditional diffusion maps such as Mean Diffusivity (MD) or Fractional Anisotropy (FA), specifically with a disease that results in a varying degree of local and global pathology changes along white matter axons. Multiple Sclerosis (MS) is a disease that fits this profile with its heterogeneous disease pattern where lesions along a given tract may have varying impact on the global conductivity/connectivity of the underlying axons. The ACM map is estimated using probabilistic tractography performed within a brain mask which is usually made by manual delineation by a clinician or obtained from automatic brain segmentation tools. We suggest a variation of ACM particularly suited for group studies that avoid brain masks defined in individual subject space as done in previously [2] and demonstrate it on a group of patients with MS. It is known that MS patients with higher Expanded Disability Status Scale (EDSS) have an increased motor handicap and our aim is to show that this effect is measurable using ACM by testing the hypothesis that a group of patients with high motor impairment (High EDSS) has a significant decreased connectivity profile along the corticospinal tract (CST) compared to a group of patients with low motor impairment (Low EDSS). The results demonstrate that ACM is able to reveal group wise differences not seen in FA.

Method

Patients: 24 patients with secondary progressive MS were included. Clinical disability was rated using the EDSS score. The patients were divided in two groups based on the EDSS. One group had a disease score of EDSS≤3.5 (n=10) and the second group had EDSS≥5 (n=14).

Diffusion MRI and preprocessing: Whole brain diffusion MRI was acquired on a Siemens TRIO 3T MR scanner using TR=8200ms, TE =100 ms, 96x96x61 image matrix with an isotropic voxel size of 2.3 mm^3, consisting of 10 b0 and 61diffusion weighted images acquired at a b-value of 1200 mm/s^2. Data was corrected for subject motion, Eddy current and EPI distortion using SPM8 and re-sliced to an isotropic 2mm resolution.

Anatomical Connectivity Mapping: In previous ACM studies [2, 3] a brain mask is formed in individual subject space. This is problematic since differences in head size and inconsistencies with brain masks across the subjects will result in bias effects of the ACM estimates. For instance making the brain mask erroneously large will cause the nearby ACM voxels to increase in value. We remove this source of bias by deforming the multi-tensor models to a common standard space with a fixed predefined brain mask. The procedure was:

A multi-tensor method with a maximal of three fiber directions was fitted to the preprocessed diffusion measurements [4]. Tensors were spatially deformed to the standard space of FMRIB58_FA atlas space of FSL [5]. The deformation field was based on a B-Spline parameterization and estimated using a multilevel image registration. The deformation field was estimated from the FA in subject space towards the FA Atlas space. To deform multi-tensors using a non-rigid warp while retaining correct tensor orientation we use the idea of [3] for single tensors but extend it for multi-tensors. After deforming the tensors, ACM's are generated by performing probabilistic tractography in each voxel of the brain and counting the number of times each voxel is hit by a streamline. The whole brain seed mask from which we seed the tractography was based on the FA Atlas. This means our seed region consist of gray matter, white matter and CSF voxels. Using a standard space brain mask removes any need for hit count normalization with regards to brain size as needed in [2]. Therefore we can feed raw hit counts into subsequent statistical analysis. Prior analysis on the stability of the ACM led to a choice of using 500 streamlines per voxel.

Group statistics: A voxelwise two sample t-test was estimated, comparing the groups with low and high EDSS scores for both ACM and FA. The t-test statistics and adjustments for age and gender were made using spm8 [5]. To determine significantly different voxels, three criteria were combined: (1) A t-test significance level of 0.005, (2) FA of > 0.25, and (3) more than 8 contiguous voxels per cluster. This combination limits the number of false positive voxels by assuming that the effects should be in white matter tracts and supported by neighbouring voxels.

Results

ACM yield significant clusters of voxels in the CST at the posterior limb of internal capsule, in cerebellar white matter and subcortical white matter in the visual cortex as verified in the top row of Figure 1 showing significant voxels overlaid on the mean ACM of both groups. In the bottom row of Figure 1, the same comparison were done with FA maps only showing spurious significant voxels being part of considerably smaller clusters than the ACM. Importantly, there were no consistent/significant FA decreases in the CST.

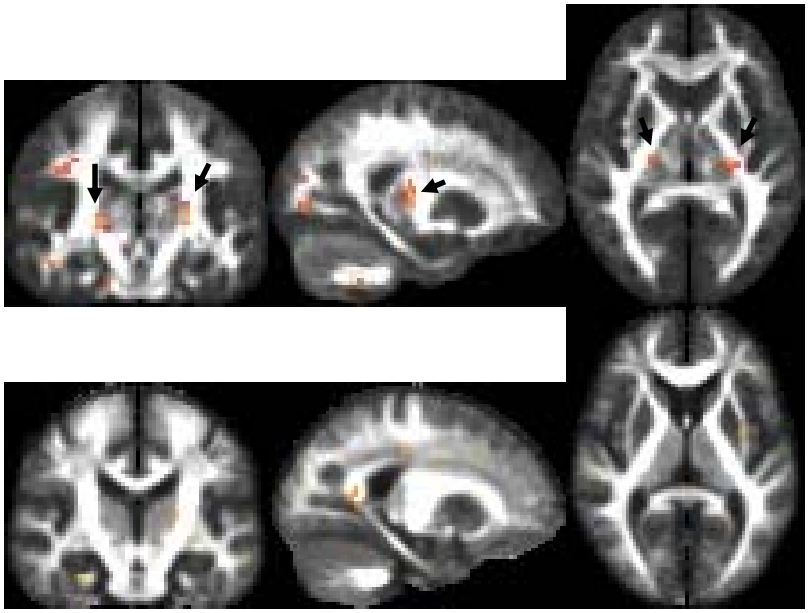

Figure 1: Shows cluster of significant group effects with hypothesis μ_1-μ_2>0, where μ_1 is hit count for patients with low and μ_2 with high disease score. Top row shows the areas of significant ACM difference in the corticospinal tracts, in coronal, sagittal and transversal planes as indicated by the black arrows, bottom row shows FA effects for same slices.

Discussion

What we have demonstrated is that ACM and FA are complementary measuring global and local properties. The group study clearly reveals the strength of ACM, and how it can be used to encompass a disease effect occurring along given tracts. In contrast FA only probes tissue locally. A critical step of performing this group study is the spatial deformation towards the Atlas. However, the clustering and positions of the significant voxels along the CST suggest that our analysis is fairly robust towards spatial deformation errors. Besides significant voxels in the CST we saw several other significant regions. This correlate well with the complexity of the disease and the fact that EDSS scores reflects symptoms related to the disintegration of pathways to several different systems of the brain. A more comprehensive analysis is left for future works. In conclusion, our ACM group analysis approach is sensitive to localized connectivity differences between patients with MS.

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