A Parametric Approach to Evaluating the Statistical Significance of Pathway Dependent Diffusion Measures

Mark J Lowe[1], Ken E Sakaie[1], Jian Lin[1], Lael Stone[2], and Micheal D Phillips[1]
[1]*Imaging Institute, Cleveland Clinic, Cleveland, OH, United States,* [2]*Neurologic Institute, Cleveland Clinic, Cleveland, OH, United States*

Introduction:

We have previously introduced pathway dependent diffusion measures as a way of determining functionally relevant disease burden in multiple sclerosis(MS)[1]. This method determines the mean diffusion properties (i.e. FA, radial diffusivity (RD), longitudinal diffusivity (LD)) along a pathway determined with probabilistic tractography. Although we feel that this approach is attractive in order to better correlate diffusivity measures of disease burden with clinical measures of impairment, there is a significant drawback to the method in that the sensitivity can be quite low due to the fact that tissue diffusion parameters will vary substantially along some pathways (e.g. transcallosal motor pathway). Producing an average across brain regions with different tissue characteristics is clearly a flawed approach. In this study, we utilize a parametric approach to determine local pathway diffusion properties and derive a statistical approach to determining if a given fiber path indicates significant disease burden in MS.

Methods:

Eight multiple sclerosis patients and 8 age and sex-matched controls were examined in a protocol approved by the local institutional review board. Anatomical images, fMRI response to bilateral finger-tapping and high angular resolution diffusion imaging [2] were acquired on a Siemens TIM Trio with a standard 12-channel head coil (Siemens Medical Systems, Erlangen). Probabilistic tractography [1] between bilateral hand motor cortices mapped the transcallosal motor pathway.

The transcallosal motor pathway was parameterized using a method described by us in a separate abstract at this meeting. The result of the parameterization is a point-by-point characterization of the mean diffusion properties (i.e. FA, RD, AD) along a line connecting the two motor cortices. In order to compare across subjects, it is necessary to account for scale differences between subjects' brains. To do this, 6 points were defined in each subjects brain using the high resolution anatomic scan: right hemisphere(RH) starting point, RH corona radiata, RH corpus callosum, left hemisphere(LH) corpus callosum, LH corona radiata, LH end point. With the exception of the endpoints, each point was defined as where the line intersected the indicated structure. The track was then piecewise interpolated to the same length for all subjects. At this point, in principle, each point along the parametric line is in similar tissue for all patients and control subjects. We then produce mean, standard deviation and normalized residual for each point along the track for all control subjects.

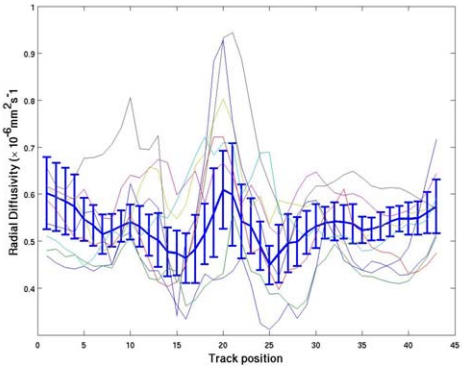

Figure 1: Solid dark blue is mean+standard deviation for control subjects. Superposed are the parametric RD's for the 8 MS patients.

Results and Discussion:

Figure 1 shows the mean, sd for each point calculated for the 8 control subjects. Superposed on the mean control track is the parameterized RD for each of the eight MS patients. Significant deviations are apparent for many of the patients. Figure 2 shows the histogram of the residual, for control subjects, of all points to their respective mean value along the track. The histogram has the appearance of a standard normal distribution. From this, we can expect that less than 1 in 1000 track points can be expected to have a residual greater than 2.95 due to random fluctuations. We see from Fig 2 that none of the control tracks has a residual greater than 2.95. However, 27 points on the patients tracks have a residual greater than 2.95. These were distributed among 5 of the eight patients. In these patients, we can conclude that there is evidence of significant diffusion abnormalities along the transcallosal pathway.

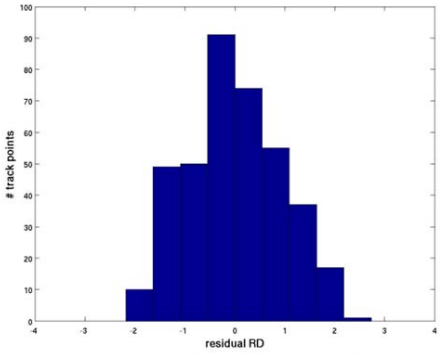

Figure 2: Normalized point-by-point residual for all control subject track points.

Conclusion:

We present a parametric approach to establishing significant diffusion abnormalities along diffusion tractography-defined pathways in the brain. We demonstrate that, by establishing pathway norms in control subjects, we are sensitive to local deviations in diffusivity in MS patients.

References:

[1] Lowe, M.J., et al. 2008. Hum Brain Mapp 29, 818-827 [2]Tuch, D.S., et al. 2002. Magn Reson Med 48, 577-582.