NeuroImage: Clinical 19 (2018) 417–424

Contents lists available at ScienceDirect

NeuroImage: Clinical

journal homepage: www.elsevier.com/locate/ynicl

Baseline biomarkers of connectome disruption and atrophy predict future processing speed in early multiple sclerosis

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ARTICLE INFO

Keywords:
Multiple sclerosis
Connectome
White matter
Follow-up studies
Atrophy
Cognition
Prognosis

ABSTRACT

The development of accurate prognoses in multiple sclerosis is difficult, as the disease is characterized by heterogeneous patterns of brain abnormalities that relate in an unclear way to future impairments. Here, we use a statistical modeling approach to determine if the baseline pattern of connectome disruption due to T2-FLAIR lesions could predict a patient's future processing speed, as measured using the Symbol Digits Modality Test scores. Imaging data, demographics and Symbol Digits Modality Test scores were collected from 61 early relapsing remitting multiple sclerosis patients. The Network Modification Tool was used to estimate damage to the connectome by quantifying white matter abnormalities' effects on 1) global network properties, 2) regional connectivity and 3) connectivity between pairs of regions. MS subjects showed significant improvement of processing speed between baseline and follow-up ($t = -2.6$, $p = 0.0096$); however, both baseline ($t = -4.01$, $p = 0.00012$) and follow-up ($t = -2.10$, $p = 0.038$) processing speed were significantly lower than age-matched healthy controls. Partial Least Squares Regression was used to create models that predict future processing speed from between baseline imaging metrics and demographics. The model based on region-pair disconnection and gray matter atrophy had the lowest AIC and highest prediction accuracy ($R^2 = 0.79$) compared to models based on global ($R^2 = 0.41$) or regional ($R^2 = 0.66$) disconnection and gray matter atrophy, overlap with an ROI-based atlas and gray matter atrophy ($R^2 = 0.73$) or gray matter atrophy alone ($R^2 = 0.71$). We found that baseline measures of connectivity disruption in various parietal, temporal, occipital and subcortical regions and atrophy in the putamen were important predictors of future processing speed. We conclude that information about disruptions to pairwise brain connections is more informative of future processing speed than regional or global metrics or gray matter atrophy alone. The combination of quantitative disconnectome metrics, gray matter atrophy and statistical modeling approaches could enable clinicians in developing more accurate, individualized prognoses of future cognitive status in multiple sclerosis patients.

1. Introduction

The increased availability of neuroimaging data sets from clinical populations provides many opportunities for gaining a deeper understanding of brain anatomy and physiology. One important, clinically-relevant goal is to better understand how pathological brain abnormalities map to impairments and how the brain compensates for these abnormalities in recovery. The former information would help in developing more accurate prognoses and the latter would help in developing effective treatments. One disease that could provide a unique opportunity for understanding such brain-behavior relationships is multiple sclerosis (MS). MS is a disease associated with focal lesions mostly in the white matter (WM) and some in gray matter (GM) and cortical/subcortical atrophy that result in impairments of sensory-motor function, vision and cognition. The spatial and temporal pattern of MS lesions is heterogeneous across both patients and over time, and the impact of said lesions on current and future impairment is not well-known. Quantifying brain-behavior relationships and how they evolve over time is crucial in developing accurate prognoses and provides insight as to how the brain recovers from disease-related damage.

WM pathology and structural networks have been studied extensively in MS (Rocca et al., 2012; Shu et al., 2011), with many studies using tractography methods (Hu et al., 2011; Mesaros et al., 2012). However, tractography is not always clinically feasible as it is onerous, requires a high level of expertise and can be particularly challenging in pathology (Jones and Cercignani, 2010) due to decreased signal-to-

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https://doi.org/10.1016/j.nicl.2018.05.003
Received 7 March 2018; Received in revised form 4 May 2018; Accepted 6 May 2018
Available online 08 May 2018

noise ratio in the diffusion MRI (Kuceyeski et al., 2011; Pagani et al., 2007; Pierpaoli et al., 2001; Wheeler-Kingshott and Cercignani, 2009). In place of using tractography in the patient, we propose using The Network Modification (NeMo) Tool (Kuceyeski et al., 2013). The NeMo Tool can be used to estimate global, regional and network-level structural connectivity losses from a WM abnormality mask only; it does not require performing tractography or even diffusion MRI in patient populations. We previously applied the NeMo Tool to a similar dataset of MS patients and found that a moderate amount of baseline processing speed impairment ($R^2 = 0.42$) could be explained by baseline regional GM atrophy and regional disconnection scores (Kuceyeski et al., 2015a).

Here, in the spirit of clinical relevancy, our goal is to predict future processing speed from baseline imaging of GM atrophy as well as global, regional and region-pair disconnection measures derived from the NeMo Tool. We hypothesize that considering an MS patient's specific pattern of pathology and quantifying how that pattern disrupts structural connections can be used to predict future neurological outcomes and disease progression. We use Partial Least Squares Regression (PLSR) to relate baseline imaging biomarkers of disconnection and GM atrophy to future processing speed. Our goals are to 1) identify which of our five models (based on GM atrophy, global, regional and region-pair disconnectivity and atlas overlap) has the best accuracy in predicting follow-up processing speed and to 2) identify which of the global/regional/pairwise disconnectivity, atrophy and atlas overlap metrics in these models are significant predictors of future processing speed. To the author's knowledge, this is the first study that uses baseline structural disconnectivity metrics and GM atrophy biomarkers to predict future cognitive changes in early MS.

2. Materials and methods

2.1. Subjects

Data was collected from 61 early relapsing-remitting MS patients (Table 1). Study procedures were explained to and consent was obtained from subjects in this IRB-approved study. All but three patients were on disease modifying therapies for MS at the time of MRI, with average treatment duration of 0.5 ± 0.9 years. All patients' baseline MRIs were acquired within 5 years of their first neurologic symptom. Three sets of images were acquired on a 3 T GE scanner (HDxt 16.0) using 8-channel phased-array coil: T1-weighted sagittal 3D-BRAVO ($1.2 \times 1.2 \times 1.2$ mm), T2 ($0.5 \times 0.5 \times 3$ mm) and T2-FLAIR ($1.2 \times 0.6 \times 0.6$ mm). The written version of the Symbol Digits Modality Test (SDMT), which measures processing speed, was performed on this cohort at baseline and on average 28.6 ± 10.3 months follow-up. Processing speed is one of the earliest cognitive domains affected in MS and the SDMT is particularly sensitive to this type of impairment (Bergendal et al., 2007).

Table 1
Subject demographics.

	MS subjects ($N = 60$)	Normal Controls ($N = 14$)
Age	36.8 ± 9.3 years	37.3 ± 13.3
Sex M/F	16/44	5/9
Disease Duration	1.5 ± 1.3 years	N/A
Treatment Duration	0.5 ± 0.9 years	N/A
Baseline EDSS	1.1 ± 1.1	N/A
Baseline SDMT	48.1 ± 11.5	N/A
Follow-up SDMT	53.3 ± 9.9	N/A
Time between baseline and follow-up SDMT	28.6 ± 10.3 months	N/A

2.2. T2-FLAIR hyperintensity lesion masks

Lesion masks were created as in our previous work (Kuceyeski et al., 2015a). As in that work, FreeSurfer (Dale et al., 1999; Fischl et al., 1999) was used on the T1 images to create tissue segmentations and subcortical and cortical parcellations, which were manually edited for misclassification due to hyperintensities in WM and temporal region errors. The T2 FLAIR images were linearly coregistered to the T1, masked with the WM and subcortical masks and thresholded to create a preliminary WM abnormality mask. The preliminary WM abnormality mask was then manually edited using the T2 and T2 FLAIR overlay and final approval given by a trained neurologist. T1 images were also acquired on 14 age-matched healthy volunteers and processed with the same pipeline to produce cortical thicknesses for calculating GM atrophy (see Table 1).

2.3. The NeMo tool

The NeMo Tool can be used to estimate changes to the structural connectivity network that result from a particular pattern of WM pathologies by referencing a database of 73 normal control tractograms in a common space (Montreal Neurological Institute). MS subjects' WM abnormality masks were normalized to MNI space using first a linear coregistration followed by non-linear normalization in SPM8. The atlas used within the NeMo Tool was derived from FreeSurfer, with 68 cortical regions, 16 subcortical and 2 cerebellar structures. Pairwise disconnection measures are identified by removing those streamlines passing through the WM abnormality mask and recalculating the strength of connections between pairs of regions, resulting in the "modified connectome". Global metric changes are estimated by calculating graph-theoretic metrics, i.e. efficiency, characteristic path length, clustering coefficient and betweenness centrality, on this modified connectome. Regional disconnectivity changes are estimated via the Change in Connectivity (ChaCo) score that is the percent of tracts that pass through the WM abnormality mask for a given GM region. The NeMo Tool calculates one "modified connectome", associated global connectome measures and set of ChaCo scores for each of the 73 controls and reports the average over these values. We use the average value as input to our predictive models. We also calculate the z-scores of the pairwise connections in each subject's "modified connectome" compared against the 73 control connectomes in the NeMo Tool to identify which region-pairs had the most disconnection. The number of lesions a tract passes through is not considered; tracts removal was a binary process. To compare an imaging metric not related to connectivity, we also calculated the overlap of the WM abnormality masks with the JHU-MNI "Eve" atlas of 176 gray and white matter regions. For each region in the atlas, the percent of voxels in the region within the lesion mask was calculated. Finally, atrophy was measured by calculating standard z-scores of average thickness for 68 cortical regions, volume for 16 subcortical regions and 2 cerebellar regions from the FreeSurfer atlas, using a group of 14 age- and sex-matched normal controls (see Table 1) that had the same scans and pre-processing. The 86-region atlas used in the NeMo Tool (global network metrics, ChaCo scores and pairwise disconnection measures) and for GM atrophy measures was identical.

2.4. Partial least squares regression

The modeling approach used here is similar to the work done in our previous paper that predicted baseline SDMT from baseline imaging metrics (Kuceyeski et al., 2015a). PLSR models were constructed to predict follow-up SDMT based on a subject's age, sex, disease duration, treatment duration, baseline SDMT, baseline EDSS, number of months between time points, regional GM atrophy and one of four imaging metrics: three levels of connectivity disruption metrics from the NeMo Tool (global, regional and pairwise disconnection measures) and the