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Relating multi-sequence longitudinal intensity profiles and clinical covariates in incident multiple sclerosis lesions

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ABSTRACT

The formation of multiple sclerosis (MS) lesions is a complex process involving inflammation, tissue damage, and tissue repair — all of which are visible on structural magnetic resonance imaging (MRI) and potentially modifiable by pharmacological therapy. In this paper, we introduce two statistical models for relating voxel-level, longitudinal, multi-sequence structural MRI intensities within MS lesions to clinical information and therapeutic interventions: (1) a principal component analysis (PCA) and regression model and (2) function-on-scalar regression models. To do so, we first characterize the post-lesion incidence repair process on longitudinal, multi-sequence structural MRI from 34 MS patients as voxel-level intensity profiles. For the PCA regression model, we perform PCA on the intensity profiles to develop a voxel-level biomarker for identifying slow and persistent, long-term intensity changes within lesion tissue voxels. The proposed biomarker's ability to identify such effects is validated by two experienced clinicians (a neuroradiologist and a neurologist). On a scale of 1 to 4, with 4 being the highest quality, the neuroradiologist gave the score on the first PC a median quality rating of 4 (95% CI: [4,4]), and the neurologist gave the score a median rating of 3 (95% CI: [3,3]). We then relate the biomarker to the clinical information in a mixed model framework. Treatment with disease-modifying therapies ($p < 0.01$), steroids ($p < 0.01$), and being closer to the boundary of abnormal signal intensity ($p < 0.01$) are all associated with return of a voxel to an intensity value closer to that of normal-appearing tissue. The function-on-scalar regression model allows for assessment of the post-incidence time points at which the covariates are associated with the profiles. In the function-on-scalar regression, both age and distance to the boundary were found to have a statistically significant association with the lesion intensities at some time point. The two models presented in this article show promise for understanding the mechanisms of tissue damage in MS and for evaluating the impact of treatments for the disease in clinical trials.

1. Introduction

Structural magnetic resonance imaging (MRI) can be used to detect lesions in the brains of multiple sclerosis (MS) patients. The formation of these lesions is a complex process involving inflammation, tissue damage, and repair — all of which MRI has been shown to be sensitive. The McDonald criteria for diagnosis of MS emphasize the key role of dissemination of lesions in the central nervous system on MRI not only in space, but also in time (Polman et al., 2011). Characterizing the longitudinal behavior of lesions on structural MRI is therefore likely to be important for monitoring disease progression and response to therapy and for understanding the etiology of the disease. Surprisingly, there is poor association between clinical findings and the radiological extent of involvement on MRI using traditional volumetric measures, a phenomenon referred to as the clinico-radiological paradox (Barkhof, 2002). Here we address this paradox by modeling the association between the longitudinal behavior of lesions after incidence on MRI and clinical covariates and disease-modifying treatment.

Previous work to characterize the longitudinal behavior of lesions on structural MRI and to further relate these changes to clinical information has only involved single structural MRI sequences. In the

Abbreviations: CI, confidence interval; FLAIR, fluid-attenuated inversion recovery; NINDS, National Institute of Neurological Disease and Stroke; NAWM, normal-appearing white matter; MRI, magnetic resonance imaging; MS, multiple sclerosis; PC, principal component; PCA, principal component analysis; PD, proton density-weighted; RRMS, relapsing remitting MS; SPMS, secondary progressive MS; sd, standard deviation; T1, T1-weighted; T2, T2-weighted; T, Tesla.

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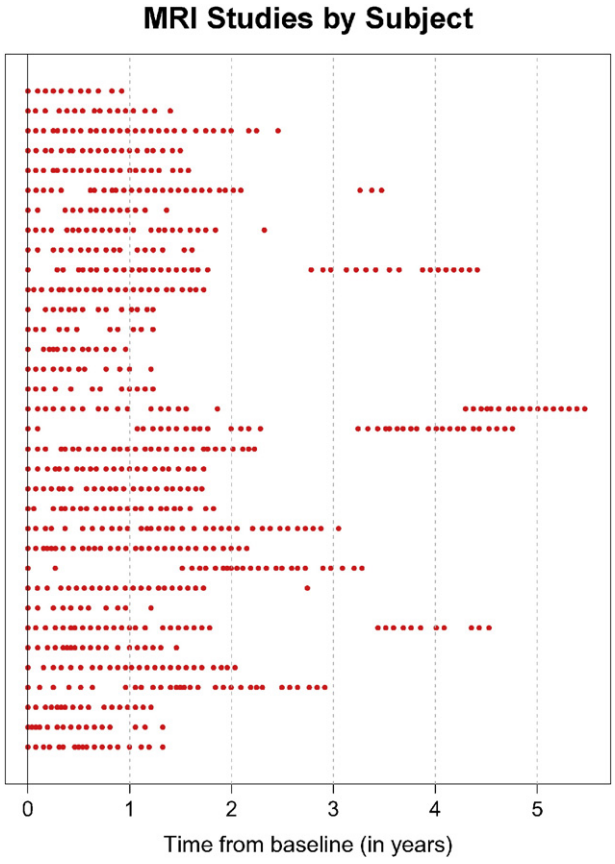

Fig. 1. The time points at which each of the 34 subjects included in the analysis was scanned. Each row of the plot is a subject, and each point in the plot represents an MRI study. The horizontal axis represents the time from the subject's baseline visit in years.

work of Meier and Guttmann (2003), Meier and Guttmann (2006) and Meier et al. (2007), longitudinal lesion behavior is characterized only on the intensity normalized proton density (PD) volume, using bi-weekly MRI studies. Although they did not relate these changes to clinical covariates, it was found that the maximal insult within a lesion occurred at the center of the lesion, that lower initial intensity within a lesion was predictive of repair, and that most lesion activity did not last beyond 10 weeks. More recently, Ghassemi et al. (2014) examined the change over a 2-year period in normalized T1-weighted (T1) intensity within new lesions, and compared these changes in pediatric and adult-onset MS patients. A generalized linear mixed-effects model was used to relate clinical covariates, such as disease duration and treatments, to changes in intensity in the MRI. The only statistically significant relationship was that the T1 intensity in lesions increased between incidence and 1-year follow-up, and this recovery was more pronounced in children. Work has also been done to relate longitudinal changes in lesion intensity to sample size calculations for clinical trials. Reich et al. (2015) used the change in the 25th percentile of intensity-normalized PD signal within a lesion over time to estimate necessary sample sizes for clinical trials of differing lengths. The 25th, 50th, and 75th percentiles of multiple MRI sequences were assessed, and it was found that the 25th percentile of the normalized PD yielded the smallest sample size requirements. A limitation of these studies is that each uses only one MRI sequence to characterize the behavior of the lesions, which ignores information known to be available in the other sequences (McFarland et al., 2002).

Here, we describe two models to understand the relationship between clinical covariates and the longitudinal intensity profiles in lesion tissue from the T1, T2, T2-weighted fluid-attenuated inversion recovery (FLAIR), and PD sequences. The first is a principal component analysis (PCA) and regression model and the second consists of function-on-scalar regression models (Fan and Zhang, 2000). We use multi-sequence MRI studies acquired at the National Institute of Neurological Disease and Stroke (NINDS), with subjects being scanned on average once every 37 days (sd 52.3, range [13, 889]) yielding an average of 21 scans per subject (sd 8.0, range [10, 37]). In the PCA and regression model, we first reduce the data to a scalar, voxel-level biomarker for identifying slow and persistent, long-term intensity changes (which we will refer to from this point on as intensity changes for simplicity) within lesion tissue. The ability of the biomarker to identify these changes is then validated in an expert rater trial with two raters, a neuroradiologist and a neurologist. After this validation, we relate the biomarker to clinical information in a voxel-level mixed-effects regression framework. In the function-on-scalar regression, we directly relate the entire longitudinal trajectories from each sequence to the clinical covariates. This allows for assessment of how the clinical information relates to the intensity points at the post-lesion incidence time periods at which these associations occur, unlike in the PCA regression model.

2. Material and methods

In this section, we first describe the image acquisition and preprocessing, followed by the patient demographics. Next, we briefly describe the longitudinal lesion intensity profiles in the subsection *Lesion Profiles*, with a more complete description of the pipeline for extracting these profiles provided in Appendix A. We then introduce two models for studying the relationship between the lesion profiles and the clinical information in the subsections *Principal Component Analysis and Regression* and *Function-on-Scalar Regressions*. The subsection *Principal Component Analysis and Regression* also includes the expert rater trial of the voxel-level biomarker for identifying intensity changes within lesion tissue. All analysis, except for image preprocessing, was performed in the R environment (R Development Core Team, 2008) using the R package oro.nifti (Whitcher et al., 2011).

2.1. Image acquisition and preprocessing

Whole-brain 2D FLAIR, PD, T2, and 3D T1 volumes were acquired in a 1.5 Tesla (T) MRI scanner (Signa Excite HDxt; GE Healthcare, Milwaukee, Wisconsin) using the body coil for transmission. The 2D FLAIR, PD, and T2 volumes were acquired using fast-spin-echo sequences, and the 3D T1 volume was acquired using a gradient-echo sequence. The PD and T2 volumes were acquired as short and long echoes from the same sequence. The scanning parameters were clinically optimized for each acquired image.

For image preprocessing, we use Medical Image Processing Analysis and Visualization (http://mipav.cit.nih.gov) and the Java Image Science Toolkit (http://www.nitrc.org/projects/jist) (Lucas et al., 2010). We interpolate all images for each subject at each visit to a voxel size of 1 mm^3 and rigidly co-register all volumes longitudinally and across sequences to the Montreal Neurological Institute standard space (Fonov et al., 2009). We remove extracerebral voxels using a skull-stripping procedure (Carass et al., 2007). We automatically segment the entire brain using the T1 and FLAIR images (Shiee et al., 2010) to produce a mask of normal-appearing white matter (NAWM), or white matter excluding lesions. After preprocessing, studies were manually quality controlled by a researcher with over four years experience with structural MRI (EMS). Studies with motion or other artifacts were removed.

2.2. Patient demographics

For this analysis, we use 60 subjects scanned at the NINDS, with the earliest scan performed in 2000 and the most recent scan performed in