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PREVAIL: Predicting Recovery through Estimation and Visualization of Active and Incident Lesions

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ABSTRACT

Objective: The goal of this study was to develop a model that integrates imaging and clinical information observed at lesion incidence for predicting the recovery of white matter lesions in multiple sclerosis (MS) patients.
Methods: Demographic, clinical, and magnetic resonance imaging (MRI) data were obtained from 60 subjects with MS as part of a natural history study at the National Institute of Neurological Disorders and Stroke. A total of 401 lesions met the inclusion criteria and were used in the study. Imaging features were extracted from the intensity-normalized T_1-weighted (T_1w) and T_2-weighted sequences as well as magnetization transfer ratio (MTR) sequence acquired at lesion incidence. T_1w and MTR signatures were also extracted from images acquired one-year post-incidence. Imaging features were integrated with clinical and demographic data observed at lesion incidence to create statistical prediction models for long-term damage within the lesion.
Validation: The performance of the T_1w and MTR predictions was assessed in two ways: first, the predictive accuracy was measured quantitatively using leave-one-lesion-out cross-validated (CV) mean-squared predictive error. Then, to assess the prediction performance from the perspective of expert clinicians, three board-certified MS clinicians were asked to individually score how similar the CV model-predicted one-year appearance was to the true one-year appearance for a random sample of 100 lesions.
Results: The cross-validated root-mean-square predictive error was 0.95 for normalized T_1w and 0.064 for MTR, compared to the estimated measurement errors of 0.48 and 0.078 respectively. The three expert raters agreed that T_1w and MTR predictions closely resembled the true one-year follow-up appearance of the lesions in both degree and pattern of recovery within lesions.
Conclusion: This study demonstrates that by using only information from a single visit at incidence, we can predict how a new lesion will recover using relatively simple statistical techniques. The potential to visualize the likely course of recovery has implications for clinical decision-making, as well as trial enrichment.
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1. Introduction

Multiple sclerosis (MS) is an inflammatory disease of the central nervous system, which is typically characterized by demyelinating lesions that occur in the brain and spinal cord. These lesions evolve dynamically from actively inflamed tissue over a period of months to more stable demyelinated regions of acute long-term axonal injury (Lassmann, 2013; Lassmann et al., 2007). A competing process of remyelination is also known to occur to varying degrees in patients, and has been documented in both relapsing-remitting and progressive cases (Patrikios et al., 2006; Bramow et al., 2010). Both the destructive and remyelinating processes are known to progress through the disease course (Frischer et al., 2015), and are associated with disability and morbidity. As therapeutics designed to promote tissue repair and remyelination are being developed, sensitive markers for in vivo assessment of these processes are increasingly important for studying therapeutic efficacy and patient management.

Magnetic resonance imaging (MRI) is a commonly used technique for identifying lesions, particularly in the white matter of the brain (Radü & Sahraian, 2008). The presence of new and active lesions is a key factor in the diagnosis and monitoring of MS, and several MRI sequences have been demonstrated to be effective in measuring the severity of these lesions (Polman et al., 2011; Sweeney et al., 2016; Sweeney et al., 2013; Pike et al., 2000). In recent years, successful attempts have been made to utilize quantitative methods in concert

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with MRI for the study of tissue damage in lesions. These techniques have included the use of advanced quantitative MRI sequences including T_1 mapping (Larsson et al., 1989; Vrenken et al., 2006), magnetization transfer imaging (van Waesberghe et al., 1998; van Waesberghe et al., 1999), and diffusion tensor imaging (Narayanan et al., 1997; Werring et al., 1999; Filippi et al., 2001), as well as statistical techniques for modeling tissue damage using conventional MRI (Shinohara et al., 2011; Mejia et al., 2015; Reich et al., 2015) and the development of time-series models to examine lesion activity (Sweeney et al., 2016; Meier et al., 2007; Meier & Guttmann, 2003; Meier & Guttmann, 2006).

Specifically, much research has engaged with the apparent paradox related to the lack of coherence between the presence of lesions and clinical disease measures (Barkhof, 2002). One recent study retrospectively related the longitudinal behavior of lesions, as opposed to simply their presence, to clinical covariates and treatment status (Sweeney et al., 2016). Significant relationships between treatment and longitudinal behavior indicated that receiving disease-modifying therapy or steroids was associated with a better healing trajectory within lesion tissue. These findings signify the presence of potentially important relationships between the repair processes in the brain, therapeutics, and disability.

Unfortunately, today there is still relatively little that can be determined in advance about the way specific lesions will recover, or the degree to which they may be responsive to treatment. The ability to visually examine the likely course of recovery for a given incident lesion would have the potential to be useful in several settings. Specifically, such visualizations could be a beneficial tool for physicians, providing them important supplemental information when making treatment decisions. Additionally, knowledge of how patients' brains are likely to recover from lesion damage could be beneficial in clinical trials, for which advanced knowledge of lesion characteristics could inform recruitment enrichment and trial design.

To build on the previous work, and to address the needs outlined above, the current study attempted to develop a statistical model that would be capable of prospectively predicting how lesions would heal over the course of a year. In this paper, we discuss the development of such prediction models for two outcome MRI modalities, we present statistical and clinical measures of validity and prediction accuracy, and we discuss the implications and potential next steps of this line of research.

2. Methods

2.1. Image acquisition and preprocessing

Details of the image acquisition and preprocessing have been previously published (Sweeney et al., 2016) and are summarized in this section. Whole-brain two-dimensional T2-weighted FLAIR, PD, T2, and three-dimensional T1-weighted 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 T_1 volume was acquired using a gradient-echo sequence. All scanning parameters were clinically optimized for each acquired image.

For image preprocessing, we used 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). All images for each subject at each visit were interpolated to a voxel size of 1 mm^3 and rigidly co-registered longitudinally and across sequences to a template space (Fonov et al., 2011). To coregister the T_1 images across study visits, a two-step procedure was applied: first, subject-specific templates were generated by averaging after rigid alignment of the T_1 images to the MNI template. Second, all T_1 images were then realigned to the subject-specific templates. Finally, the additional MRI sequences were aligned to the T_1 images within each study visit and this transformation was composed with the T_1-based transformation to the subject-specific template.

Extracerebral voxels were removed using a skull-stripping procedure (Carass et al., 2007) and the brain was automatically segmented using the T_1 and FLAIR images (Shiee et al., 2010) to produce a mask of normal-appearing white matter (NAWM), or white matter excluding lesions. Intensity normalization was then conducted using z-scoring based on the mean and variance of the variability in the NAWM (Shinohara et al., 2011; Shinohara et al., 2014). After preprocessing, studies were manually quality controlled by a researcher with over five years' experience with structural MRI (EMS) and studies with motion or other artifacts were removed.

2.2. Patient demographics

For this study, 60 subjects diagnosed with MS were scanned between 2000 and 2008 on a monthly basis over a period of up to 5.5 years ($mean = 2.2$ years, $sd = 1.2$) as part of a natural history study at the National Institute of Neurological Disorders and Stroke in Bethesda, Maryland. To be included in the analysis, subjects were required to meet certain pre-specified inclusion criteria. Specifically, only subjects with at least one new lesion during the observation period were included, and these subjects were required to have been rescanned at least twice 360 days after lesion incidence. 32 subjects met these criteria and were included in the analyses. The 32 subjects ranged from 18 to 60 years of age, with a mean age of 37 years ($sd = 9$). Of the 32 subjects, 11 were male and 21 were female. The majority of the subjects ($n = 27$) were diagnosed with relapsing-remitting MS, and the remaining five were characterized as secondary-progressive. Subjects were either untreated or treated with a variety of disease-modifying therapies during the observation period, including both FDA-approved therapies (Avonex, Betaseron, Daclizumab, and Rebif) and experimental therapies.

2.3. Prediction model

2.3.1. Outcomes

The outcomes of interest in this study were 1) normalized T_1-weighted voxel intensity (nT_1w) (Shinohara et al., 2014) and 2) MTR voxel intensity approximately one-year post-incidence, and is denoted by $Y_{post,i}(v)$ for subject i in voxel v. Due to the noise inherent in both sequences, outcome variables were created by averaging the intensity of each voxel at the visit immediately following the 360-day cutoff (referred to as the one-year visit), the visit prior to the one-year visit ($mean = 10.6$ months from incidence, $sd = 1.3$ months), and the visit following the one-year visit. Because no change is expected in the lesion after that length of time, this average only reduced variability due to measurement error (Meier et al., 2007). Thus, the average score represents a more precise estimate of true voxel intensity than the one-year visit intensity alone.

2.3.2. Predictors

A dataset made up of scan data and relevant demographic variables was created to predict the one-year post-incidence voxel intensities. For each voxel, this included the MTR as well as the nFLAIR, nPD, nT_2w, and pre- and post-contrast nT_1w intensities at incidence, denoted by $\boldsymbol{Y_{inc,i}}(v)$. After applying a 3D Gaussian smoother with variance parameter 3 mm and width 5 mm, each voxel's blurred intensities on the five scan modalities, $G\boldsymbol{Y_{inc,i}}(v)$, were also included, as well as the distance, in number of voxels, from the voxel to the nearest boundary of the lesion, $d_i(v)$, and the size, in number of voxels, of the lesion, $s_i(v)$. Additional predictors $\boldsymbol{X_i}$ included were the patient's age, sex, disease subtype, expanded disability status score (EDSS; (Kurtzke, 1983)), disease-modifying treatment status (treated versus untreated, with use of one or more therapies counting as treated), and steroid status (receiving steroids versus not on steroids) at the time of lesion incidence.

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