MRI time series modeling of MS lesion development

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A mathematical model was applied to new lesion formation in multiple sclerosis, as apparent on frequent T2-weighted MRI. The pathophysiological motivated two-process model comprises two opposing nonlinear self-limiting processes, intended to represent degenerative and reparatory processes, respectively, investigating T2 activity from a dynamic/temporal rather than a spatial/static perspective. Parametric maps were obtained from the model to characterize the MRI dynamics of lesion development, answering the questions of how long new T2 lesion activity persists, how much residual damage/hyperintensity remains and how the T2 dynamics compare to those of contrast-enhancing MRI indicating active inflammation.

997 MRI examinations were analyzed, acquired weekly to monthly from 45 patients over a 1-year period. The model was applied to all pixels within 332 new lesions, capturing the time profiles with excellent fidelity (r = 0.89 ± 0.03 average correlation between model and image data). From this modeling perspective, the observed dynamics in new T2 lesions are in agreement with two opposing processes of longitudinal intensity change, such as inflammation and degeneration versus resorption and repair. On average, about one third of a new lesion consisted of transient signal change with little or no residual hyperintensity and activity of 10 weeks or less. Global lesion burden as MRI consisted of transient signal change with little or no residual hyperintensity change, such as inflammation and degeneration versus resorption and repair. Concentric patterns of dynamic properties within a lesion were observed, consistent with concentric histological appearance of resulting MS plaques.

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Introduction

We present a model-based approach to the pixel-wise assessment of the short-term dynamics of new lesion formation in multiple sclerosis (MS), as apparent from serial T2-weighted magnetic resonance imaging (MRI). Serial MRI provides effective and valuable data for understanding both natural history and treatment effects of neurodegenerative diseases. In MS, the current state of knowledge supposes a dynamic sequence of inflammatory/autoimmune, degenerative, and restorative processes that result in the pathological findings of focal demyelination and remyelination, inflammatory infiltrates, axonal loss and fibrillary astrocytosis. Little is known about the timing, sequence and interplay of these processes leading to both white and gray matter damage. From the MRI perspective, lesion pathogenesis comprises an acute phase with blood–brain barrier leakage lasting a few weeks followed by a chronic phase of T2 hyperintensity (T2 lesions) and occasional T1 hypointensity (black holes). Morphometric assessment of MRI lesion burden is a commonly used surrogate in large-scale clinical trials (Filippi et al., 1995; Jacobs et al., 1996; Li and Paty, 1999; Miller et al., 1999), and long-term trends thereof serve as indicators of disease activity and therapeutic effect (Molyneux et al., 1998).

T2 hyperintensity is considered pathologically non-specific, but it remains unclear to what extent different pathological processes could be distinguished based on the sequence and dynamics of the T2 signal. That such dissociative potential exists in serial MRI is illustrated, for example, by a recent study on the evolution of enhancing inflammatory lesions into permanent T1-hypointense lesions (black holes), which showed that less than a quarter of all enhancing lesions became “black holes” and that those were preceded by longer duration of enhancement (Bagnato et al., 2003).

We have previously presented a time series analysis strategy to study longitudinal changes in tissue quality (composition) (Meier and Guttmann, 2003). Based on this work, we here examine the dynamics of new T2 lesions in the context of a pathologically motivated mathematical model. Specifically, we aim to answer the following:

• How well is the short-term variation of new T2 lesions explained by a model of two opposing processes (e.g. representative of inflammation/degeneration and resorption/repair)?
• How long is new T2 lesion activity sustained on average? Does this differ from the duration of contrast enhancement?
• Does the spatio-temporal distribution of new T2 hyperintense lesions exhibit a characteristic pattern?
Methods

Image acquisition and preprocessing

Weekly to monthly MRI was obtained from 45 MS patients (64% female) over 1 year. Mean subject age was 39 ± 8 years (25–55 years), with 26 patients classified as relapsing–remitting MS (RRMS), 14 as secondary progressive (SPMS) and 5 as “stable MS” (Weiner et al., 2000). The MRI was obtained at 1.5 T with a conventional spin echo sequence with 3 mm contiguous axial slices (axial spin echo, variable echo multi-planar, PDw/T2w, TE = 30/80 ms, TR = 3000 ms, with 0.93 × 0.93 × 3 mm³ nominal voxel size). The 5 stable patients received monthly examinations; the remaining 40 patients received 8 weekly scans, followed by 8 scans every other week, followed by 6 monthly examinations.

Preprocessing included integration and normalization of all serial scans into a contiguous 4-dimensional dataset using the method outlined and validated in Meier and Guttmann (2003). This method applies a bias-field correction to account for field inhomogeneities, an automated spatial co-registration and tissue class segmentation. The last step is a tissue-class-specific intensity normalization, applied to each examination timepoint, to correct for inter-scan intensity variations from scanner drift or other technical sources. Validation of this processing pipeline, for the same MRI series with 3 mm axial slices, demonstrated an average spatial precision of 0.4 ± 0.2 mm and sensitivity to local intensity changes of 3% (Meier and Guttmann, 2003).

MRI follow-up was done weekly or every other week for the first 6 months followed by six monthly examinations. For consistent fitting quality, only lesions that newly appeared during the first 6 months of the 1-year follow-up were included in this study. The region of interest (ROI) for subsequent model fitting was defined manually as a rectangular three-dimensional bounding box placed around the area of change.

Because the obtained dynamic metrics were not calculated from pairwise comparison of subsequent timepoints, but instead obtained from a least-square fit model, the irregular follow-up spacing had no significant effect on the quality of the derived rates or durations.

Time series modeling

The co-registered serial MRI datasets yield an intensity time series profile for each voxel. The following model, consisting of two opposing, self-limiting processes (modeled as sigmoid-functions), was applied to the time series of each lesion voxel (Fig. 1a): $I(t) = x_0 + \frac{a_1}{1 + e^{-\frac{b_1}{c_1}t}} - \frac{a_2}{1 + e^{-\frac{b_2}{c_2}t}}$. The first process represents processes that shift the MRI signal toward hyperintensity (e.g. inflammation and degeneration); and the second process produces a shift toward isointensity (e.g. denoting resorption and repair). The two processes occur simultaneously, but with individual delay, rate and amplitude, yielding in superposition the characteristic temporal intensity profiles shown in Fig. 1b. The fitting parameters are baseline offset ($x_0$), amplitude ($a_1$, $a_2$), rate of change ($b_1$, $b_2$) and delay ($c_1$, $c_2$). Time is denoted by $t$ and signal intensity is $I(t)$.

The following three profile characteristics were extracted from the model parameters: $F_1 = x_1/x_0$ represents hyperintensity above baseline, $F_2 = (x_1 - x_2)/x_1$ denotes residual hyperintensity, and the duration of the transient portion $F_3$ was defined as the width at a given intensity level $\kappa$: $F_3 = \gamma_2 - \gamma_1 + \frac{\ln(\kappa - 1)}{\ln(\kappa - 1)}$. The intensity threshold $\kappa$ is the intensity level where the width is measured, we choose $\kappa = 0.15$ (width where the two opposing processes reach 15% and 85% of their maximum amplitude,
respectively). For example, a lesion pixel profile rising to 70% hyperintensity above baseline and returning to within 20% of isointensity after 8 weeks would have $F_1 = 0.7$, $F_2 = 20\%$, $F_3 = 8$ weeks.

The empirically chosen model provided a good balance between fitting precision, the ability for pathophysiological interpretation (one “degenerative” versus one “reparatory” process) while keeping the number of parameters small relative to the number of temporal sampling points.

A nonlinear least square fitting algorithm (trust-region reflective Newton method, Matlab, Mathworks Inc., Natick MA), with upper and lower bounds on each parameter, was used to fit each profile. Preliminary testing showed a more robust model fit to the short-echo T2 (proton-density weighted) MR image, likely due to its higher signal-to-noise. The short-echo image was therefore used for all the results shown herein.

Lesion delineation and feature map creation

Feature maps for $F_1$, $F_2$ and $F_3$ were calculated from the fitting parameters and masked based on fit quality. A mask of $R^2 > 0.5$ provided an empirical sensitivity threshold for reliably identifying active lesion pixels within the ROI box. A selective median filter, applied to parameter values more than a factor $k$ away from their 8-neighbors, was applied as speckle noise filter. Two iterative passes with $k = 6$ and $k = 3$ were applied. An example of ROI definition, time series data and extracted feature maps is shown in Fig. 2.

In summary, the processing steps were (1) bias-field correction, co-registration and inter-scan intensity normalization (Meier and Guttmann, 2003), (2) interactive identification of all new lesions and manual ROI box placement (Fig. 2), (3) time profile model fit through each pixel of the ROI, (4) extracting principal features ($F_1 = \text{hyperintensity}$, $F_2 = \text{residual}$, $F_3 = \text{duration}$) from the fitting parameters, (5) masking and speckle noise filtering of feature maps.

Results

Results are reported in three sections: (1) how well the model fitted each time profile, (2) the spatial patterns of lesion dynamics

![Image](image_url)
represented as feature maps and (3) the statistical distribution of duration and residuals over the examined cohort.

Profile fit and model validation

A total of 332 new lesions were observed in 32 patients, 13 patients had no new lesions during the 1-year follow-up. The number of new lesions per patient ranged from 1 to 44 (median ± SD, 4 ± 9.4). Thirty eight lesions were excluded as they appeared less than 6 months before the last follow-up and did not provide sufficient data for accurate modeling.

How well is the short-term variation of new T2 lesions explained by a two-component model of two opposing processes that drive the T2 signal toward hyper- and isointensity, respectively? An example profile fit is shown in Fig. 3 (same lesion as shown in Fig. 2). Very high fitting quality was obtained throughout with the chosen two-process model. Fitting quality for the main body of this lesion was $R^2 = 0.72 \pm 0.14$ (range 0.5 to 0.996).

A direct validation of the fitting fidelity was obtained by rebuilding the MRI intensity image series from the model and comparing it to the original data (Fig. 4). Average image correlation (Pearson, averaged over the ROI box) between the model and the original data across the entire cohort was $0.89 \pm 0.03$.

It is interesting to note that the lesion’s texture at any single timepoint appears better defined and crisper in the image reconstructed according to the model fit (Fig. 4) than in the original images, suggesting that the proposed temporal model successfully removes noise in the spatial domain. This is similar to the observed gains in signal to noise and contrast to noise when averaging or linear fitting with detrending of multiple images of a same session in the absence of change, with the limitation that any signal changes of biological origin that do not fit the model are also removed.

Feature maps

Does the spatial distribution of new T2 lesion dynamics exhibit a characteristic pattern? Feature maps of the three lesion characteristics ($F_1$: hyperintensity, $F_2$: residual and $F_3$: duration) are shown in Fig. 5. A distinct local pattern of lesion evolution is apparent, with strong concentric characteristics, present for all three features,
that is, the highest ($F_1$) and longest ($F_3$) activity with greatest residual hyperintensity ($F_2$) is found in the lesion center. A positive relation between the level of peak intensity and amount of residual hyperintensity is also qualitatively apparent, that is, a lower level of peak intensity appears to be predictive of the chance of recovery. The comparison of the hyperintensity and the residual map also shows the spatial extent to which a lesion recovers and where. A concentric pattern is also apparent, albeit weaker, for the duration of activity ($F_3$), relating longer activity to higher residual (Fig. 5). This is in agreement with findings of contrast-enhancing lesion duration correlating with the likelihood of developing into a permanent T1 hypointensity (black hole) (Bagnato et al., 2003).

Residual hyperintensity and duration of transient lesion activity

Static measures of global lesion burden are obviously confounded by the portion of hyperintensity that is transient. Two questions arise: (1) how much of an average lesion retains a given level of hyperintensity, how much returns to a mostly isointense state? (2) What is the average duration of the transient hyperintensities? This is answered by cumulative distribution estimates (Kaplan–Meier) for the residual and duration variables ($F_2$, $F_3$), calculated for each lesion and averaged over the entire cohort. On average, about a third of the volume of a new lesion retained 20% or less residual hyperintensity and 90% of a lesion retained 60% or less (Fig. 6).

The duration of the 20% residual hyperintensity proportions is shown in Fig. 7, that is, a lesion pixel at 20% residual hyperintensity ($F_2$) or less is considered as transient. On average, 81% ± 18% of the resolving lesion volume does so within 10 weeks or less.

Discussion

The presented model-based analysis of lesion formation presents an attempt to approach structural MRI change as a process rather
than in terms of the end result. T2 hyperintensity alone is considered non-specific with respect to the outcome of processes such as inflammation, neurodegeneration and repair. The return to T2 isointensity also is not necessarily equivalent with complete lesion repair (Barkhof et al., 2003) nor is T2 “activity” necessary for diffuse WM changes to occur (Goodkin et al., 1998). However, the observed subacute phase of T2 activity indicates that there are two levels to this MRI specificity: (1) the specificity of the MR signal toward microscopic tissue composition, (2) the duration and timing of individual processes producing MRI signal change. In other words, the pathological specificity of MRI morphometry is not entirely a limitation of the MRI signal but also depends critically on how the signal is sampled in both space and time.

Remyelinated lesions, for example, have been reported as hyperintense on T2 (Barkhof et al., 2003; Hart et al., 1998; Schmierer et al., 2004), reasonably attributed to wider extracellular spaces due to the new myelin being thinner and more sparsely structured (Barkhof et al., 2003). This hyperintensity also is in a static/spatial context, i.e. relative to the surrounding NAWM, whereas in the presented paradigm, hyperintensity indicates a temporal variable relative to baseline before the lesion occurred. In this dynamic/sequential context, a remyelinated lesion is hypo-intense relative to its preceding demyelinated state, hence to include remyelination as part of the modeled reparatory/resorptive process appears plausible.

The applied two-process model was capable of describing the dominant signal changes with excellent fidelity. The dominant short-term fluctuations in new MS lesions would therefore be consistent with two opposing processes that drive the T2 signal toward hyper- and isointensity, respectively. This result does not assign unequivocally two opposing processes of inflammation/degeneration versus resorption and repair as the sole origins of such MRI signal changes, but it supports a view of T2 signal change as a superposition of different underlying pathogenic mechanisms. Other MRI sequences may effectively complement the generic T2 signal: magnetization transfer (MT), for example, appears to correlate with demyelination (Schmierer et al., 2004), and a certain predictive potential of MT has been reported (Chen et al., 2005).

The parametric maps of residual hyperintensity showed concentric patterns of lesion dynamics (with the most permanent hyperintensity in the lesion center (Fig. 5), alike to spatial patterns reported from visual MRI analysis (Guttmann et al., 1995). Similar concentric patterns were also described in histopathological studies, such as active plaque edges with accumulating macrophages (Lucchinetti et al., 2000). The use of single-timepoint global lesion burden appears significantly confounded by transient signal change that does not represent permanent damage (Fig. 6). The widely observed lack of clinical correlation and specificity of T2-weighted MRI is likely to stem in part from this effect. While we found the duration of new T2 lesion activity to be 10 weeks on average, the spectrum reaches out to approximately 5–6 months (Fig. 7), and additional changes beyond that cannot be excluded since they may be below the sensitivity of the model or the MRI signal.

Does the observed T2 activity differ from the duration of contrast enhancement? Analysis of the evolution of contrast-enhancing lesions on weekly T1-weighted MRI, performed on the same cohort as presented here with half-dose Gd-DTPA (T1-weighted spin echo sequence, approximately 3–5 min after injection of a 10 ml intravenous bolus of 0.5 M Gd-DTPA), yielded an average duration of enhancement of 3 weeks, with 97% of lesions enhancing less than 2 months (Cotton et al., 2003). A comparison with present findings (Fig. 7) indicates a subacute phase of T2 activity that lasts significantly beyond the enhancing period, supporting a model that marks active inflammation and water/edema resorption (and possibly some level of repair/ remyelination/glialosis) as the chief contributors to the visible T2 activity in the first 10 weeks of new lesion evolution. A monthly study of T1 hypointense lesions showed 44% of initially hypointense T1 lesions returning to isointensity (van Waesbergh et al., 1998), which roughly matches our observations on T2. So while short-term T1 hypointensity changes are also readily attributed to inflammatory/edematous water resorption, chronic T1 hypointensity has nevertheless been proposed as marker for more serious matrix destruction (chronic T1 black holes).

While weekly MRI follow-up is currently not feasible in clinical practice, the observed short-term dynamics nevertheless cast important light on the limitations of infrequent MRI. Annual MRI is common in clinical trials and routine practice. The lesion dynamics observed in this study suggest that morphometric variables related to new, enlarging and resolving lesions require frequent follow-up to more accurately represent disease activity.

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