Synopsis
A method for systematic analysis of time domain information, derived from serial MRI, is presented and validated. Goal is the characterization of inflammatory, degenerative and reparatory tissue changes. Normalized temporal intensity profiles of multiple sclerosis lesions are presented as examples of achievable sensitivity from standard clinical protocols. No external phantoms or a priori calibration is required. Data from large longitudinal studies served as basis for a tissue-specific intensity normalization model. We compared and validated different approaches to image registration, partial volume correction and intensity normalization. Results suggest that MRI intensity dynamics contain information of interest for studies of MS pathophysiology.

Introduction
In progressive neurological disorders, such as multiple sclerosis (MS), MRI follow-up is used to monitor disease activity and progression, and to understand the underlying pathogenic mechanisms. While MRI appears to be collectively sensitive to these changes, MRI-derived metrics thus far lack specificity in differentiating between different lesion processes and phenotypes. In this work we evaluate methods of time series analysis (TSA) to leverage the information present in the dynamic sequence of serial MRI. Recent efforts in TSA include pilot experiments on the discriminatory value of the time domain for purposes of lesion segmentation [1, 2] and application of statistical fMRI tools for purposes of segmenting and characterizing evolving MS lesions [3, 4]. The work presented here focuses on establishing a rigorous framework for spatial- and intensity normalization and its validation on large sets of longitudinal studies.

Methods

The integration of serial 3D MRI scans into a 4D volume comprises four main steps: (1) spatial normalization, (2) intensity normalization, (3) artifact filtering, (4) baseline normalization and fusion into a 4D volume. Standard tools of intensity-based rigid and non-rigid registration were compared in terms of spatial registration error (reproducibility) and residual intensity variation (sensitivity). The serial registration tools available in SPM99 [5] were used as example of an intensity-driven registration. Affine and non-rigid registration methods [6] were also evaluated (results not shown). Extraparenchymal and pathological tissue was automatically excluded from the registration cost function. A large set of weekly to monthly dual echo studies (PD/T2) was evaluated for the tissue-specific variability of intensities. Results provided the basis for a two-parameter intensity correction model assuming Gaussian intensity distributions. The intensities of each tissue class in a follow-up scan are stretched by $\kappa_1 = \sigma_1/\sigma_2$ and shifted by $\kappa_2 = \mu_2 - \mu_1$, so that distribution mean $\mu$ and standard deviation $\sigma$ match. This correction is applied in a hierarchical fashion, based on automated template-driven segmentation [7, 8] of tissue classes into the intra-cranial cavity (ICC), gray- and white matter (GM/WM), cerebrospinal fluid (CSF) and white matter lesions (WMSA). The latter were again considered a separate compartment to be excluded from actively driving the normalization, yet grouped with the WM class for passive adjustment. Residual partial volume artifacts after registration were addressed by a deliberate additional “coloring” of the spatial autocorrelation (i.e. a 1D Gaussian filter step in slice direction only) in each scan.

Results
A total of N=733 image sets (each containing a dual echo PD/T2 and T1 scan) of 46 MS patients, acquired over a 5-year period, were segmented into tissue compartments of ICC, WM, GM, CSF and WMSA. Their relative intensities as a function of overall brightness were compared by linear regression. All tissue compartments showed predominantly linear dependencies ($R^2>0.9$, $p<10^{-5}$), but slopes significantly different from eachother ($p<10^{-5}$), except GM/CSF ($p=0.32$) in the PDw brightness (WM, GM, CSF, WMSA). The latter were again grouped with the WM class for passive adjustment. Residual partial volume artifacts after registration were addressed by a deliberate additional “coloring” of the spatial autocorrelation.

Discussion & Conclusion
Subvoxel precision and high levels of sensitivity to signal change (3%) are achievable with TSA registration and intensity normalization. Regression results also indicate that individual tissue classes respond linearly but differentially to changes in image brightness (such as caused by long-term scanner drift). Hence a single-compartment model for intensity normalization is inadequate. How does this TSA concept differ from current longitudinal studies applying quantitative MRI? Current longitudinal studies in neurodegenerative diseases report discrete changes of morphometric variables extracted from each MRI scan. The segmentation step involved in this form of morphometric analysis introduces an inevitable data reduction, which may ultimately result in a loss of sensitivity and specificity. We consider the presented TSA technique well suited for studying tissue quality dynamics of neurodegenerative diseases.

References