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OASIS is Automated Statistical Inference for Segmentation, with applications to multiple sclerosis lesion segmentation in MRI

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ABSTRACT

Magnetic resonance imaging (MRI) can be used to detect lesions in the brains of multiple sclerosis (MS) patients and is essential for diagnosing the disease and monitoring its progression. In practice, lesion load is often quantified by either manual or semi-automated segmentation of MRI, which is time-consuming, costly, and associated with large inter- and intra-observer variability. We propose OASIS is Automated Statistical Inference for Segmentation (OASIS), an automated statistical method for segmenting MS lesions in MRI studies. We use logistic regression models incorporating multiple MRI modalities to estimate voxel-level probabilities of lesion presence. Intensity-normalized T1-weighted, T2-weighted, fluid-attenuated inversion recovery and proton density volumes from 131 MRI studies (98 MS subjects, 33 healthy subjects) with manual lesion segmentations were used to train and validate our model. Within this set, OASIS detected lesions with a partial area under the receiver operating characteristic curve for clinically relevant false positive rates of 1% and below of 0.59% (95% CI; [0.50%, 0.67%]) at the voxel level. An experienced MS neuroradiologist compared these segmentations to those produced by LesionTOADS, an image segmentation software that provides segmentation of both lesions and normal brain structures. For lesions, OASIS out-performed LesionTOADS in 74% (95% CI: [65%, 82%]) of cases for the 98 MS subjects.

To further validate the method, we applied OASIS to 169 MRI studies acquired at a separate center. The neuroradiologist again compared the OASIS segmentations to those from LesionTOADS. For lesions, OASIS ranked higher than LesionTOADS in 77% (95% CI: [71%, 83%]) of cases. For a randomly selected subset of 50 of these studies, one additional radiologist and one neurologist also scored the images. Within this set, the neuroradiologist ranked OASIS higher than LesionTOADS in 76% (95% CI: [64%, 88%]) of cases, the neurologist 66% (95% CI: [52%, 78%]) and the radiologist 52% (95% CI: [38%, 66%]).

OASIS obtains the estimated probability for each voxel to be part of a lesion by weighting each imaging modality with coefficient weights. These coefficients are explicit, obtained using standard model fitting techniques, and can be reused in other imaging studies. This fully automated method allows sensitive and specific detection of lesion presence and may be rapidly applied to large collections of images.

1. Introduction

Multiple sclerosis (MS) is an inflammatory disease of the brain and spinal cord characterized by demyelinating lesions that are most easily identified, at least on magnetic resonance imaging (MRI) studies, in the white matter of the brain (Sahraian and Radue, 2007). Quantitative analyses of MRI, such as the number and volume of lesions, are essential for diagnosing the disease and monitoring its progression (Rovira and León, 2008; Rovira et al., 2009). MRI measures are also a common

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primary endpoint in phase II immunomodulatory drug therapy trials (Sormani et al., 2009). In these trials, either manual or semi-automated segmentations are used to compute the total number of lesions and the total lesion volume (Lladó et al., 2011). Manual delineation is challenging as three-dimensional information from several MRI modalities must be integrated (Lladó et al., 2011). Manual assessment of MRI is also prone to large inter- and intra-observer variability (Simon et al., 2006). While semi-automated methods have been found to decrease inter- and intra-rater variability, they still require manual reader input and are time consuming (García-Lorenzo et al., 2013). Therefore a sensitive and specific automated method to detect lesions in the brain is essential for the analysis of studies with a high numbers of MS patients.

Lladó et al. (2011) provides a comprehensive review of currently available automated cross-sectional MS lesion segmentation methods, or methods used to identify lesions from a single MRI study. We divide these methods into four categories: supervised classifier with an atlas, supervised classifier with no atlas, unsupervised classifier with an atlas, and unsupervised classifier with no atlas. We focus on supervised methods without atlases, as the method we propose is in this category. Supervised methods without atlases train on manually segmented images annotated by experts and use image intensities of MRI to classify lesions (Lladó et al., 2011). Supervised classification algorithms are applied to the volumes: artificial neural networks (Goldberg-Zimring et al., 1998), spatial clustering (Alfano et al., 2000), k-nearest neighbors (Anbeek et al., 2004, 2005, 2008), Parzen window (Sajja et al., 2006), Parzen window and morphological grayscale reconstruction (Datta et al., 2006), Bayes (Scully et al., 2008), AdaBoost (Morra et al., 2008), simulated annealing and Markov random fields (Subbanna et al., 2009), and graph cuts (Lecoeur et al., 2009). All of the aforementioned methods except Anbeek et al. (2008) use multi-modality MRI information to classify lesions. The most widely-used feature across all segmentation methods is voxel intensity, which derives strength from a multi-modality approach (Lladó et al., 2011).

The method we propose uses a logistic regression model to assign voxel-level probabilities of lesion presence in structural MRI of patients with MS. Logistic regression models have been used for segmentation of brain tissues and pathology in MRI (Bullmore et al., 1999; Dinh et al., 2012; Lee et al., 2005). For applications to MS, logistic regression has been used for detection of gadolinium enhancing lesions (Karimaghaloo et al., 2012), prediction of gadolinium enhancing lesions without administering contrast agents (Shinohara et al., 2012), and for segmentation of new and enlarging MS lesions (Sweeney et al., 2013). To our knowledge logistic regression has not been used in cross-sectional segmentation of MS lesions in structural MRI.

One difficulty in automated segmentation of MRI is due to variable imaging acquisition parameters (Lladó et al., 2011). All of the segmentation methods reviewed in Lladó et al. (2011) have tuning parameters that are adjusted to a particular data set and may not generalize to a new data set with different acquisition parameters. These parameters are not informed by the data and therefore must be tuned empirically, often with little to no interpretability of the parameter. Application to a new data set may require several iterations of segmentations to adjust the tuning parameters to values that produce acceptable segmentations. A method in which the tuning parameters are informed by the data and for which adjustments are intuitive and simple would therefore be valuable.

A second difficulty in intensity-based segmentation is that MRI data are acquired in arbitrary units; units can vary widely between and within imaging centers. These variations are attributed to scanner hardware, interactions between hardware and patients, and variations in acquisition parameters (Simmons et al., 1994). Therefore, proper intensity normalization is essential in developing a generalizable segmentation method. Many of the segmentation methods use intensity-normalized volumes (Lladó et al., 2011), but these methods do not demonstrate the generalizability of the normalization procedure to changes in imaging acquisition parameters and imaging centers. In García-Lorenzo et al. (2013) the authors performed a PubMed and Google Scholar search for MS lesion segmentation papers. Of the 47 papers that met their search criteria, only 13 of these papers used multicenter data for validation, and the largest database used for validation consisted of 41 subjects. To show generalizability, methods must be validated on multicenter data with many subjects.

A third difficulty is intensity inhomogeneity, the slow spatial intensity variations of the same tissue within an MRI volume. Inhomogeneity can significantly reduce the accuracy of image segmentation (Hou, 2006), and therefore some form of spatial normalization is necessary for accurate lesion segmentation. Most lesion segmentation methods assume that these inhomogeneities have been corrected during image preprocessing, but we have found strong spatial patterns within tissue type even after the N3 inhomogeneity correction algorithm (Sled et al., 1998) is applied.

To address these and related problems, we propose OASIS is Automated Statistical Inference for Segmentation (OASIS), a fully automated, generalizable, and novel statistical method for cross-sectional MS lesion segmentation. Using intensity information from multiple modalities of MRI, a logistic regression model assigns voxel-level probabilities of lesion presence. After training on manual segmentations, the OASIS model produces interpretable results in the form of regression coefficients that can be applied to imaging studies quickly and easily. OASIS uses intensity-normalized brain MRI volumes, enabling the model to generalize to changes in scanner and acquisition sequence. OASIS also adjusts for intensity inhomogeneities that preprocessing bias field correction procedures do not remove, using smoothed volumes. This allows for more accurate segmentation of brain areas that are highly distorted by inhomogeneities, such as the cerebellum. One of the most practical properties of OASIS is that the method is fully transparent, easy to explain and implement, and simple to modify for new data sets.

To illustrate the generalizability of OASIS to changes in imaging acquisition parameters, we evaluated the performance of the algorithm on a total of 300 MRI studies from two separate imaging centers with varying acquisition parameters. This is a crucial criterion for assessing the generalizability and utility of the method.

2. Materials and methods

In this section we introduce OASIS, a method inspired by Subtraction Based Inference for Modeling and Estimation (SuBLIME), an automated method for the longitudinal segmentation of incident and enlarging MS lesions (Sweeney et al., 2013). Before the OASIS logistic regression model is fit, a brain tissue mask is created, all MRI volumes are intensity normalized, and smoothed volumes are created to capture local spatial information and adjust for remaining field inhomogeneities. The OASIS method involves two iterations of model fitting: the first to perform an initial lesion segmentation and the second to use this initial lesion segmentation to remove lesions, which can distort the smoothed volumes. After the final model is fit, the regression coefficients are applied to produce three dimensional maps of voxel-level probabilities of lesion presence.

We evaluate the performance of OASIS on MRI volumes of the brain acquired with various acquisition protocols. We use data sets from two different imaging centers for validation, which we refer to as Validation Set 1 and Validation Set 2. Validation Set 1 has manual lesion segmentations. We trained the OASIS method on a subset of the studies in this dataset, and tested on the remaining studies. An expert evaluated the segmentations from Validation Set 1. Validation Set 2 is used to demonstrate generalizability to changes in image acquisition parameters. We applied the coefficients from the model trained on Validation Set 1 to the studies in Validation Set 2, and experts evaluated the OASIS lesion segmentations.