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Predicting outcome in clinically isolated syndrome using machine learning

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ABSTRACT

We aim to determine if machine learning techniques, such as support vector machines (SVMs), can predict the occurrence of a second clinical attack, which leads to the diagnosis of clinically-definite Multiple Sclerosis (CDMS) in patients with a clinically isolated syndrome (CIS), on the basis of single patient's lesion features and clinical/demographic characteristics.

Seventy-four patients at onset of CIS were scanned and clinically reviewed after one and three years. CDMS was used as the gold standard against which SVM classification accuracy was tested. Radiological features related to lesional characteristics on conventional MRI were defined a priori and used in combination with clinical/demographic features in an SVM. Forward recursive feature elimination with 100 bootstraps and a leave-one-out cross-validation was used to find the most predictive feature combinations.

30 % and 44 % of patients developed CDMS within one and three years, respectively. The SVMs correctly predicted the presence (or the absence) of CDMS in 71.4 % of patients (sensitivity/specificity: 77 %/66 %) at 1 year, and in 68 % (60 %/76 %) at 3 years on average over all bootstraps. Combinations of features consistently gave a higher accuracy in predicting outcome than any single feature.

Machine-learning-based classifications can be used to provide an "individualised" prediction of conversion to MS from subjects' baseline scans and clinical characteristics, with potential to be incorporated into routine clinical practice.

1. Introduction

Machine learning is an emerging area of computer science and artificial intelligence that provides an increasing variety of algorithms capable of learning patterns from input data to solve classification and prediction problems (Bishop, 2006). Support vector machines (SVMs) are well-established classification algorithms (Vapnik, 1995) and a popular choice due to their simplicity and high performance in a range of applications. In the context of medical imaging, SVMs have shown promise for binary classifications (e.g. disease vs. healthy status), on the basis of imaging characteristics (Ashburner and Klöppel, 2011). In this context, SVMs first learn the characteristics of, say, MRI scans in each of two groups; then, they use that knowledge to assign new brain scans, which have not been used in the training procedure, to one of the two groups. SVMs have been applied in this way to imaging data from a variety of neurological and psychiatric diseases to assist in the diagnostic process, including pre-symptomatic Huntington's disease (Klöppel et al., 2009), Alzheimer's disease (Klöppel et al., 2008a), autism spectrum disorder (Anderson et al., 2011), and major depressive disorder (Mwangi et al., 2012). A few studies have applied SVMs to data from patients with MS, suggesting that SVMs may become a useful tool for automatic classification of MS patients vs. healthy controls (Weygandt et al., 2011) and MS patients with different characteristics (such as patients with early MS vs. those with late MS) (Bendfeldt et al., 2012). A key question that is of direct clinical relevance, and is addressed in this study, is whether SVMs can be applied to MRI scans and clinical characteristics of patients with early features of Multiple Sclerosis (MS) to predict their prognosis.

For most patients with MS, the onset of their condition is with an episode of neurological disturbance, known as a clinically isolated syndrome (CIS) (Miller et al., 2012). About 30 % of patients with CIS present with a second clinical attack within 1 year from onset, leading to the

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diagnosis of clinically-definite MS (CDMS) (Miller et al., 2012). However, about 20 % of CIS patients do not convert to MS after two decades, even if they have an abnormal brain scan at onset (Fisniku et al., 2008). Therefore, individual patients presenting with CIS face the uncertainty of if and when a second relapse will occur.

Research into the predictors of clinical outcome in CIS has demonstrated that the number, location and distribution of asymptomatic white matter lesions on a brain scan at first presentation are associated with the risk of having a second clinical attack (Brex et al., 2002; Giorgio et al., 2013; Swanton et al., 2007; Tintore et al., 2006). For example, patients with CIS whose baseline scans fulfil 3 or 4 Barkhof criteria (i.e., the occurrence of gadolinium enhancing lesion, juxtacortical lesion, infratentorial lesion and periventricular lesion) (Barkhof et al., 1997) have an adjusted hazard ratio of 17 (95 % confidence interval (CI) 6.7–43.5) for clinical conversion to MS during a 7-year follow-up (Tintore et al., 2006). When dissemination in space criteria are considered (i.e., at least one lesion in at least two typical locations: periventricular, juxtacortical, posterior fossa, and spinal cord) (Polman et al., 2011), the likelihood ratio for CDMS in patients with CIS is 2.1 (95 % CI 1.7–2.7) during a 3-year follow-up, with a sensitivity of 85.9 % and specificity of 59.4 % (Swanton et al., 2007). Additionally, demographic and clinical characteristics at the onset of a CIS, such as younger age, female gender and multifocal neurological involvement, are also associated with a higher risk of developing MS in short-term (Miller et al., 2012).

These MRI and clinical factors are commonly used in clinical practice to counsel individual patients about their risk of developing CDMS, but they are not combined to provide an overall estimate of risk of conversion. Ideally, a person-specific "individualised" risk of a second clinical relapse would be estimated, instead, based on an individual scan and clinical characteristics; this represents a crucial step in the improvement of patient management.

Therefore, the primary aim of this study was to determine whether SVMs can predict clinical conversion to MS (or the absence of clinical conversion) from CIS during one- and 3-year follow-ups. A secondary aim was to highlight lesional and clinical/demographic features that appear important to the prediction of CDMS.

2. Methods

2.1. Subjects

This is a retrospective study. None of the patients studied was on disease modifying treatments. Seventy-four patients were scanned after a mean of 6.15 weeks (SD 3.4) from the onset of a CIS, and clinically reviewed after 1 year; 70 patients attended a follow-up visit after 3 years. This represents a subgroup of a larger cohort recruited between 1995 and 2004; to be included in the present study, at least one demyelinating lesion must have been visible on baseline scans, and those scans, together with their corresponding lesion masks, had to be available for inclusion in this project. Additionally, clinical data at one and three year follow-ups must have been available.

In all patients, clinical and demographic information at onset, including type of CIS presentation (i.e., spinal cord, optic nerve, brainstem, multifocal), age, gender, and Expanded Disability Status Scale (EDSS) at baseline, was recorded. Clinical conversion to MS due to the occurrence of a second clinical attack attributable to demyelination of more than 24 hours in duration and at least 4 weeks from the initial attack was noted at each follow-up review. Informed consent from each patient and ethical approval by the local ethics committee was obtained prior to the study. The patients' characteristics are summarised in Table 1.

2.2. MRI acquisition and pre-processing

Baseline MRI protocol was undertaken using a 1.5 T GE Signa MRI scanner. A brain FSE dual echo sequence, yielding proton density (PD) and T2 weighted images (TR = 3200 ms, TE = 15/90 ms, contiguous 3 mm axial slices, in-plane resolution 0.9375×0.9375 mm^2) was obtained. Binary lesion masks were created by one experienced neurologist marking the lesions in the PD images of all patients, using the corresponding T2 images as reference (Fig. 1), with an in-house semi-automated software.

All the PD and T2 images were spatially normalised to the MNI152 standard space T1 image using a diffeomorphic registration with NiftyReg (Modat et al., 2010) (http://cmic.cs.ucl.ac.uk/home/software/). The resulting transformation parameters were applied to the lesion masks allowing us to define a spatial reference point that can be used to calculate distance-based features for all patients.

2.3. Classification analysis

In this study, Support Vector Machines (Vapnik, 1995; Vapnik, 2008) were used for binary classification. SVMs are supervised learners that work in two phases. In the training phase, a subset of the available data points as well as their associated classes is used to iteratively find a linear boundary or hyperplane that separates the two classes optimally. In the testing phase, new, previously unseen data points in the same space as the training points are classified depending on their position relative to the boundary as shown in Fig. 2. In this study, each data point is a multidimensional vector consisting of a relatively small number of a priori defined features but, generally, data points can contain any information associated with the respective subject including much larger feature sets, such as all MRI voxel intensities, as in e.g. Klöppel et al. (2008a) or Bendfeldt et al. (2012).

2.3.1. Feature definition

Each feature represents one dimension of the data points used for training and testing. We selected a priori demographic/clinical features and lesion features, which were chosen to capture information on white matter lesion load, distribution, size, and signal intensity. The mean and SDs of all features are shown in Supplementary Table 1.

The four demographic/clinical features are age, gender, type of CIS, and EDSS at baseline. The gender was coded with 1 referring to male and 0 to female. The CIS type was coded according to 1=optic neuritis, 2=spinal cord, 3=brainstem, and 4=other. This coding was arbitrarily chosen. A permutation of this numbering, however, has little effect and reduces the accuracies of the best feature combinations by a maximum of 1.7 % (detailed results not shown). The following 8 lesion features were extracted from the PD/T2 images and lesion masks of each patient:

(1) Lesion count: this feature reflects the total number of lesions in the brain, extracted from the native lesion masks; it was computed using the original binary lesion masks and an 18-neighbourhood for voxel connectivity.
(2) Lesion load: this feature reflects the total lesion volume, in voxels, extracted from the native lesion masks
(3) Average lesion PD intensity: this feature reflects the average PD intensity of the lesional voxels marked in the native lesion masks.
(4) Average lesion T2 intensity: this feature reflects the average T2 intensity of the lesional voxels included in the native lesion masks.
(5) Average distance of lesions from the centre of the brain: this feature gives the average distances between all lesional voxels and the centre of the brain (defined as the central voxel of the MNI152 registration template), providing information on how spread out the lesions were on the registered images [Supplementary Fig. 1].
(6) Presence of lesions in proximity of the centre of the brain: this binary feature is 1 if there are lesions within a cube of 1 cm^3 centred around the central voxel of the SPM template, or 0 if no lesions were in the central box. This feature was selected because of the evidence that lesions located in the corpus callosum, which is a midline brain structure, are useful in predicting conversion to