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Individual classification of children with epilepsy using support vector machine with multiple indices of diffusion tensor imaging

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ABSTRACT

Introduction: Support vector machines (SVM) have recently been demonstrated to be useful for voxel-based MR image classification. In the present study we sought to evaluate whether this method is feasible in the classification of childhood epilepsy intractability based on diffusion tensor imaging (DTI), with adequate accuracy. We applied SVM in conjunction DTI indices of fractional anisotropy (FA), mean diffusivity (MD), radial diffusivity (RD) and axial diffusivity (AD). DTI studies have reported white matter abnormalities in childhood-onset epilepsy, but the mechanisms underlying these abnormalities are not well understood. The aim of this study was to examine the relationship between epileptic seizures and cerebral white matter abnormalities identified by DTI in children with active compared to remitted epilepsy utilizing an automated and unsupervised classification method.

Methods: The DTI data were tensor-derived indices including FA, MD, AD and RD in 49 participants including 20 children with epilepsy 5–6 years after seizure onset as compared to healthy controls. To determine whether there was normalization of white matter diffusion behavior following cessation of seizures and treatment, the epilepsy subjects were grouped into those with active versus remitted epilepsy. Group comparisons were previously made examining FA, MD and RD via whole-brain tract-based spatial statistics (TBSS). The SVM analysis was undertaken with the WEKA software package with 10-fold cross validation. Weighted sensitivity, specificity and accuracy were measured for all the DTI indices for two classifications: (1) controls vs. all children with epilepsy and (2) controls vs. children with remitted epilepsy vs. children with active epilepsy.

Results: Using TBSS, significant differences were identified between controls and all children with epilepsy, between controls and children with active epilepsy, and also between the active and remitted epilepsy groups. There were no significant differences between the remitted epilepsy and controls on any DTI measure. In the SVM analysis, the best predictor between controls and all children with epilepsy was MD, with a sensitivity of 90–100% and a specificity between 96.6 and 100%. For the three-way classification, the best results were for FA with 100% sensitivity and specificity.

Conclusion: DTI-based SVM classification appears promising for distinguishing children with active epilepsy from either those with remitted epilepsy or controls, and the question that arises is whether it will prove useful as a prognostic index of seizure remission. While SVM can correctly identify children with active epilepsy from other groups' diagnosis, further research is needed to determine the efficacy of SVM as a prognostic tool in longitudinal clinical studies.

1. Introduction

Diffusion tensor imaging in childhood epilepsy has improved our understanding of the impact of epilepsy on brain structure. Children with mixed new-onset epilepsy syndromes have been shown to exhibit reduced fractional anisotropy (FA) and increased radial diffusivity (RD) in the posterior corpus callosum and cingulum (Hutchinson et al., 2010), as well as significantly higher FA and lower MD, AD and RD in the internal capsule, cingulum, body of the corpus callosum, superior corona radiata and superior fronto-occipital fasciculus (Amarreh et al., 2013). Reduced FA in the anterior limbs of the internal capsule (AIC), the posterior limbs of the internal capsule (PIC), and the splenium of the corpus callosum (SCC) and higher MD, RD and axial diffusivity (AD) were reported in the AIC, PIC and SCC in adolescents and children with epilepsy (Meng et al., 2010). Additionally, DTI results from

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pediatric temporal lobe epilepsy studies include significantly reduced FA in the hippocampus contralateral as well as ipsilateral to the side of seizure onset (Kimiwada et al., 2006) and decreased anisotropy in white matter tracts (uncinate, arcuate, and inferior longitudinal fasciculus as well as corticospinal tract) both contralateral as well as ipsilateral to the side of seizure onset (Govindan et al., 2008). These white matter abnormalities have been reported in regions both near to as well as distant from the primary epileptic zone (Arfanakis et al., 2002; Concha et al., 2009; Diehl et al., 2008; Knake et al., 2009; Rodrigo et al., 2007; Thivard et al., 2005).

In addition to DTI, maps of functional activation and connectivity, measured by neuroimaging modalities such as task-based fMRI and resting state functional MRI (rsfMRI) respectively, have shown that epilepsy is associated not only with structural but also with functional brain changes, further improving our understanding of the neurobiology of epilepsy (Arfanakis et al., 2002; Duncan, 2002, 2008; Hermann et al., 2006; Obenaus and Jacobs, 2007). To date, differences in structural and functional images have been used mainly to characterize disparities between groups, i.e., controls vs. epilepsy groups. Unfortunately, group-based methods are not helpful in inferring specific clinical outcomes for an individual patient. Therefore, and for the purpose of individual discrimination, a desirable method would be one that can compare a single subject's scans to a group of healthy controls. Machine learning (ML) algorithms, such as support vector machine (SVM) pattern recognition algorithm, fulfills this requirement.

In epilepsy, the use of machine learning algorithms has been primarily for seizure detection. SVM classifiers have been applied to discriminate between seizure and non-seizure EEG epochs in newborns with seizures secondary to hypoxic ischemic encephalopathy (Temko et al., 2011). Also, SVM classifiers have been used to identify the onset of seizures in non-invasive EEG from pediatric subjects suffering from a variety of seizure types (Shoeb et al., 2004). Recently in a study of temporal lobe epilepsy using SVM, DTI indices were reported to have diagnostic advantage over other T-1 based classification (Focke et al., 2012). To the best of our knowledge, the present study is among the first to examine SVM as a tool for classifying seizure outcomes in children with epilepsy (remitted versus persisting seizures).

2. Methods and materials

We previously conducted a cross-sectional analysis of DTI measures in children with epilepsy vs. healthy controls 5–6 years after seizure onset (Amarreh et al., 2013), examining differences between the control and epilepsy groups overall as well as by epilepsy status (active versus remitted epilepsy), using tract based spatial statistics (TBSS) pipeline within FSL (Smith et al., 2006). Of special interest were comparisons within the epilepsy group categorized into groups based on their seizure outcomes (active, remitted) and compared to controls. Here we utilize DTI measures from the TBSS pipeline with SVM, our goal being to evaluate the feasibility of individual classification of children with epilepsy.

2.1. Subject groups

Participants were 49 children and adolescents (aged 8–18 years at the recent onset of epilepsy) including 20 participants with epilepsy (9 females, 11 males) and 29 normally developing participants (median age = 18 years; 13 females, 16 males). The epilepsy participants were selected based on a diagnosis of idiopathic epilepsy with no other developmental disabilities or neurological disorders and normal brain MRI scans. The epilepsy group contained 9 with active epilepsy (median age = 19 years; 5 females, 4 males) and 11 with remitted epilepsy (median age = 16 years; 4 females, 7 males). Epilepsy remission was defined as remaining seizure free for 12 months and no longer taking anti-epileptic drugs (AEDs). Children with localization-related (n = 6) and generalized epilepsy (n = 5) were equally represented in the remitted group. The 29 control participants were first-degree cousins of the children with epilepsy who were comparable in age, gender and handedness to the epilepsy group (Table 1). The control group had no history of seizures and no other developmental or neurological diseases. The full details on the selection criteria are available elsewhere (Hermann et al., 2006). The results presented here involve DTI scans taken at the third visit—5-6 years after their baseline evaluation. A total of 84 DTI scans were collected, but due to a scanner malfunction, 32 scans contained image artifacts and were not included in this analysis, leaving a final sample size of 23 epilepsy participants and 29 controls. Three epilepsy subjects could not be confidently classified as active or remitted and thus were not included in the analysis. This study was reviewed and approved by the Institutional Review Boards of both institutions. On the day of study participation families and children gave informed consent and assent and all procedures were consistent with the Declaration of World Medical Organization (1996).

2.2. Image acquisition

T1, T2, and diffusion weighted (DWI) MRIs' were acquired for each participant. All MRI scans were collected on a clinical 1.5 T GE Signa LX MRI scanner (General Electric Corporation, Milwaukee, WI). T1-weighted, Axial Bravo stealth scans are collected with TR/TE = 10.6/4.36 ms, flip angle = 13°, axial acquisition with a reconstructed matrix size of 512 × 512, field of view (FOV) = 162 mm, slice thickness 1.5 mm and contiguous spacing. DTI scan parameters are as follows: one reference scan with b = 0 s/mm^2 and 25 diffusion weighted scans with b = 1000 s/mm^2 each with a unique set of gradient directions optimized for DTI axial acquisition with a reconstructed matrix size of 256 × 256, FOV = 120 mm, and slice thickness = 3 mm.

2.3. DTI analysis

Images were transferred to an offline workstation for processing. After initial conversion of the imaging data to the NIFTI format, preprocessing was performed with the FMRIB Software Tools (FSL) software

Table 1
Demographic characteristics of the epilepsy and control groups.

	Epilepsy (n = 20)	Control (n = 29)	Median
	Remit (n = 11)	Active (n = 9)	
	Median	Median	
Age (years)	16	19	18
Gender	7 M/4 F	4 M/5 F	16 M/13 F
IQ full score*	120.27 (9.50)*	107.00 (8.12)*^	117.14 (10.63)^
Seizure duration (years)	6.81 (0.72)*	5.90 (0.70)*	–
Age of onset (years)	11.53 (3.20)	11.95 (3.52)	
Syndrome	6 ILRE/5 IGE	7 ILRE/2 IGE	
Antiepileptic drugs (polytherapy, monotherapy, none)	0/0/11*	4/4/1*	–

Superscript symbol pairs ("*", "^") denote significant differences; $p < 0.05$. ILRE = idiopathic localization-related epilepsy; IGE = Idiopathic generalized epilepsy.