A multivariate approach to a MR based biomarker for amyotrophic lateral sclerosis

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Introduction

Amyotrophic lateral sclerosis (ALS) is a progressive degenerative motor neuron disease involving the motor cortex, corpus callosum, cortical spinal tract and spinal anterior horn neurons[1]. The disease has a uniformly fatal outcome, although the clinical presentation and course is quite heterogeneous, with median survival times between 2 – 4 years[2]. **There is no definitive diagnostic test for ALS**, and confident diagnosis is mainly based on clinical assessments and relies on the detection of upper motor neuron and lower motor neuron signs in multiple body segments[3] together with a history of progression of symptoms. In addition, evaluation of lower motor neuron pathology in ALS is commonly supplemented by electromyography whereas upper motor neuron pathology is solely assessed on clinical grounds, hindering diagnosis[4]. Unfortunately, there is on average a one-year delay between onset of symptoms and diagnosis for this rapidly progressive disease[5], which prevents early treatment with emerging disease-modifying drugs. **Thus, reliable biomarkers for the early diagnosis, disease prognostication, and the evaluation of emerging treatments are needed[6].** In this work we examine the efficacy of using machine learning (Support Vector Machine) and MR data to classify between participants with amyotrophic lateral sclerosis (ALS) and healthy individuals.

Methods

Thirty-two ALS patients (21M, 11F, mean-age=58.2±6.6 years) and thirty-one age-matched controls (16M, 15F, mean-age=57.1±5.1 years) underwent MR imaging after consent as per our local IRB protocol. All scanning took place on a GE 3T Excite 2 (GE, Milwaukee, Wisconsin). All participants had high-resolution anatomic T_1 imaging (SPGR high-resolution images were collected with a 256^2 matrix, 220mm FOV, and 1.0mm slice thickness) and resting-state fMRI. T_2*time-series data were acquired parallel to AC-PC axis using a reverse-spiral k-space readout. A total of 240 T_2*-weighted volumes were collected during each scanning session (TR=2s, 40-slice volumes, 3mm slice thickness, no skip, TE=30ms, 64x64 matrix, field-of-view FOV=220mm). Additionally, a subset of the participants (nALS=25, 16M, 9F, mean-age=59.1±6.5; nHC=24, 12M, 12F, mean-age=57.1±4.5) also underwent diffusion tensor imaging (DTI) (EPI, 15 directions, b=1000 s/mm^2, one b=0 volume, 39 slices, 3mm skip 0.1mm, 240mm FOV, 96^2 matrix). Time-series corrected for physiological confounds (cardiac and respiratory cycles), slice-time and movement corrected using FSL. To facilitate the use of a common cerebrum mask all time-series data were normalized to MNI coordinates using SPM8/VBM8. DTI images were processed in the TBSS framework, including field-map correction. To investigate efficacy of resting-state networks to classify between ALS and HC we used the 10 networks identified by Smith [7] as major features within the resting-state analysis. Additionally we used implicated white matter regions (corpus callosum, cortical spinal tracts, peduncle, internal capsule, and superior corona radiate) to extract FA values after normalization of FA maps to MNI space via TBSS. These regional FA extractions were used as features in an SVM. We examined all possible combinations of the 10 resting state network, and all possibly combination of DTI regions.

Results/Discussion

The SVM was able to achieve up to ~80% proper classification using just DTI FA measures in regions implicated in ALS[8]. Classification by use of resting state networks alone was able to achieve upwards of 70% accuracy for disease state prediction.

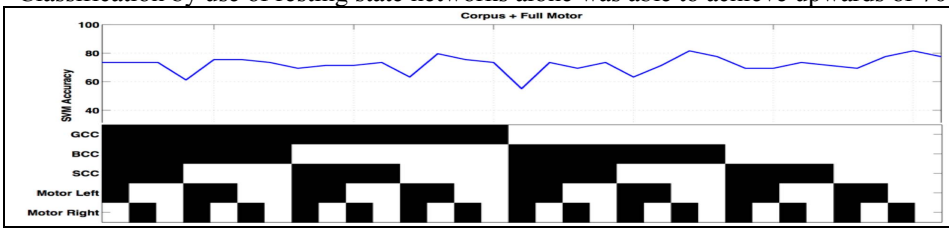

Figure 1. Support vector machine accuracy (top plot) to properly classify individual as ALS or HC based on inclusion of white matter region (bottom figure with white indicating inclusion). Analysis was performed within a leave-one-out-cross-validation.

Conclusion

We demonstrate that machine learning (namely SVM) has utility in the classification between states of the diseased brain (amyotrophic lateral sclerosis) and the healthy brain. Inclusion of additional modalities that have been shown to be sensitive to the ALS disease process, such as structural changes[9] and GABA/spectroscopic[10] changes are warranted for further investigation and inclusion in a multi-modal, multivariate disease state classifier based on machine learning methodology.

References

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