SVM-based Markers Yield Outcome Measures for Neuroimaging Clinical Trials of Alzheimers Disease

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Our Aims

- Propose a new class of outcome measures for **clinical trials**
- Demonstrate through simulated trials that our **SVM-based** outcome measures are more sensitive than standard methods

Introduction

Neuroimaging is the only way to examine and compare the degree of relative atrophy in living subjects. This is especially important in clinical trials of treatments being developed for Alzheimer's Disease (AD); see [4]. However, high dimensionality can raise multiple comparisons issues in some settings, while leading to unnecessary model complexity in others. We propose a novel neuroimaging-based clinical trial methodology which uses Support Vector Machines (SVMs) to produce an outcome measure having superior sensitivity to treatment effects. Existing methods instead use the mean voxel intensity in a Region of Interest (ROI) as an outcome measure. Our method trains an SVM to discriminate between treatment and placebo participants. The SVM's output on unseen subjects is used as the outcome measure, and a t-test is used to establish significant group-level differences. Drawing on canonical results from the machine learning literature (see refs in [1,5]), we observe that linear functions (i.e., any linear combination of observed variables,) vary widely in their discriminative ability, measured in terms of low overlap of distribution functions. By harnessing the power of SVMs to choose a discriminative linear function, we can derive a highly sensitive outcome measure for use in neuroimaging-based clinical trials. Cross-validation ensures that there are no multiple-comparisons issues to contend with, and model complexity is controlled by SVM regularization. Moreover, by interpreting the weights of the SVM we can verify that the accuracy with which the SVM discriminates treatment from placebo subjects is genuinely due to sensitivity to reduction of disease-related atrophy. We also note that other neuroimaging studies can use such a measure as the "contrast" between populations as well.

Methods

We compared our proposed methodology with a standard baseline method, using imaging data provided by the Alzheimer's Disease Neuroimaging Initiative (ADNI) to simulate a clinical trial of a hypothetical treatment which reduces AD-related atrophy by 25%; see [3]. We used longitudinal Tensor-Based Morphometry (TBM) analysis of MR images [2] to quantify atrophy, and simulate the effect of both disease and treatment. Recognizing that AD affects not only the mean atrophy in each voxel, but their covariances as well, we simulated the effect of AD-related atrophy by choosing an affine warp of the stable Mild Cognitive Impairment (MCI) population to match the converting population, (i.e., those MCI subjects who converted to AD within 2 years, of which there were 38). We then simulated the treatment effect as a 25% reduction in the displacement of each stable MCI subject due to the affine warp. 50% of stable MCI subjects were randomly assigned to the treatment, and the rest to the placebo. Note that this model only measures reduction in disease-related atrophy, rather than disease plus age-related atrophy. Further, our methodology uses only MCI subjects, which is much more challenging than using AD subjects, but is also more relevant to clinical trials [3]. Using leave-one-out cross validation, an SVM was trained to recognize treatment vs. placebo groups, and a *p*-value was derived from the *t*-statistic of the SVM's output on the two groups. For the baseline method, we performed a *t*-test on the mean voxel intensity within the training set, and averaged over each fold. Both *p*-values are plotted in Fig. 1 in -log scale as a function of the number of trial participants. Fig. 2 shows the classifier weights chosen by the SVM.

Relevant brain regions

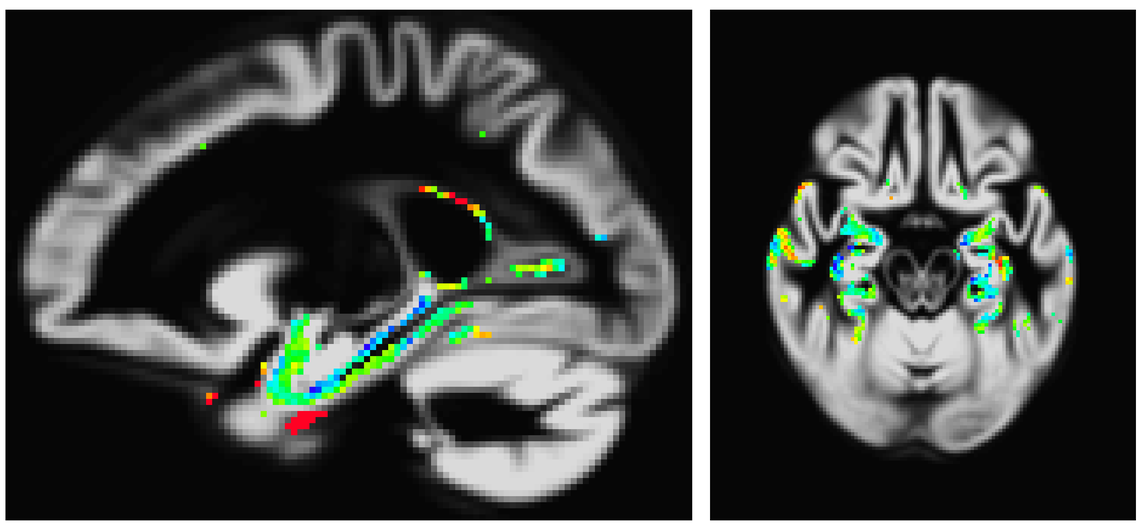

Figure: Relative weights chosen by the SVM to distinguish between simulated treatment and placebo participants. Weights are relative, and hence have no scale. Cooler colors indicate regions in which treatment subjects showed more expansion, while warmer colors indicate regions in which placebo subjects showed more expansion.

Results

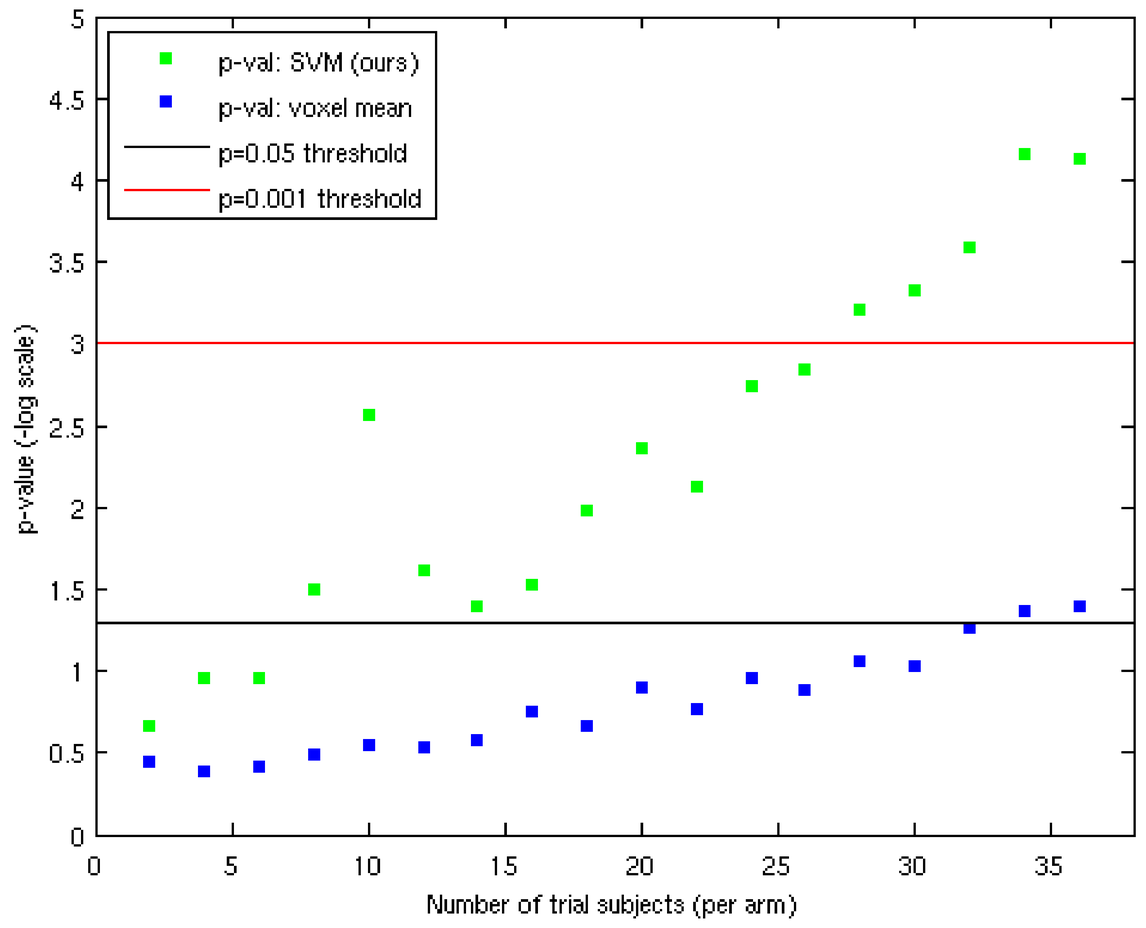

Figure: *p*-values for our method (shown in green), and for the baseline method (shown in blue). Note that the *p*-values for the baseline method barely surpass the 0.05 significance level, while our proposed methodology gives *p*-values below 10^{-3} with only 28 subjects per arm, and below 10^{-4} with only 34 subjects per arm.

Comparison of tissue types

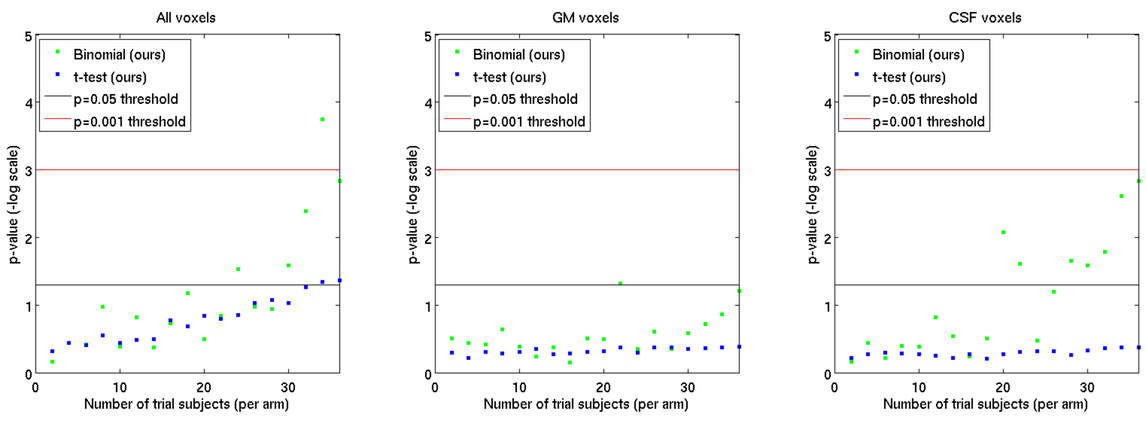

Figure: We can further break voxels into GM and CSF compartments. Left: All voxels used in cross-validated simulated trials; Middle: Results when only GM voxels were used; Right: Results when only CSF voxels were used.

Conclusions

- There is a great potential for increasing the sensitivity of clinical trials by using **SVM-based custom outcome measures**.
- Our simulated trials showed **over 3 orders of magnitude** difference in *p*-values.

References

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