Multivariate classification of placebo versus drug in fibromyalgia patients

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TARGET AUDIENCE Investigators interested in pain, identifying drug effects, or multivariate analysis.

INTRODUCTION

The pathophysiological brain mechanism operative in chronic widespread pain conditions such as fibromyalgia and its responses to pharmacological treatment remain an open challenge. Previous work in fibromyalgia has examined effects of the drug pregabalin on brain connectivity and functional response [1].

In functional neuroimaging, multivariate pattern classification and prediction can offer an alternative to standard univariate analysis techniques, and has been applied in MR imaging using support vector machines (SVM) [2]. This study applies SVM classification to a group of chronic widespread pain patients before and after pregabalin and placebo.

METHODS

Subjects: A subset of patients in a previous drug study [1] were used in this study. Seventeen female subjects with fibromyalgia were randomized in a reported double-blind, two-period, crossover study of pregabalin versus placebo. In brief, patients randomized to pregabalin for Period 1 underwent dose escalation of pregabalin to 450 mg/day over the course of 14 days, and maintained at that fixed dose for the last 3 days. Those randomized to placebo for Period 1 took matching placebo pills over the course of 14 days. After Period 1, all patients underwent a 7-day taper and 8 days of placebo treatment for washout. Following washout, patients crossed over to the other treatment for Period 2. Patients were presented with an fMRI visual stimulation paradigm (flashing checkerboard) before and after the pregabalin and placebo periods (pre-treatment and post-treatment timepoints).

Data acquisition: T2*-weighted data was acquired on a 3.0 T GE scanner using a spiral-in sequence (TR/TE/FA/FOV=2.5s/30ms/90/22cm, 64x64 matrix, 3mm slice thickness, 48 slices). Anatomical T1 overlays matching the prescription of the functional data and whole-brain T1 SPGRs were also collected for normalization. The visual stimulus consisted of a flashing checkerboard alternating with a fixation cross (200s duration, 80 timeframes, 20s checkerboard/20s fixation per cycle, 5 cycles).

Preprocessing: Data were preprocessed and analyzed using FSL (www.fmrib.ox.ac.uk/fsl) and SPM (Functional Imaging Laboratories, London, UK). Preprocessing steps included physiological noise correction using RETOICOR [3], motion correction, normalization and spatial smoothing (8 mm FWHM). GLM contrast images were then calculated by applying a linear contrast of the parameter estimates of the checkerboard versus the static fixation condition for each participant. Difference contrast images were created for every subject for each scanning condition (post-pre drug, post-pre placebo), which were then used in the SVM analysis.

Multivariate analysis: Support vector machine learning was performed using the libsvm toolbox version 3.18 [4] in MATLAB, using the difference contrast images for each subject, labeled by treatment (drug or placebo). SVM classification was performed using a linear kernel, with five-fold cross validation for C parameter optimization in the training data, and leave-one-subject-out cross-validation in the testing data to calculate classification accuracies and predicted values. SVM model weights were averaged across all subjects to investigate spatial distribution of the weights.

RESULTS

SVM classification results in 82% overall accuracy in classifying Pregabalin vs. Placebo, with 76% sensitivity within Pregabalin, and 88% within Placebo (see Figure 1).

The average support vector weight map has larger weights in the insula, visual cortex, medial frontal areas, and cerebellum (see Figure 2).

DISCUSSION

In subjects with chronic pain, functional activation differences in response to visual stimulation, post-pre treatment, were found to discriminate between pregabalin and placebo with high accuracy. Top model weights included the insula, which is implicated in pain and higher order sensory processing. Future work will examine if these methods may be extrapolated to other pharmacologic treatments in different chronic pain conditions.

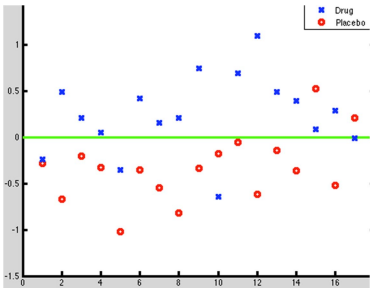

Figure 1. Predicted class (drug: blue x, placebo: red o) for each subject. Decision plane is indicated at 0 with a green line, with ideal results being Drug >0, Placebo <0.

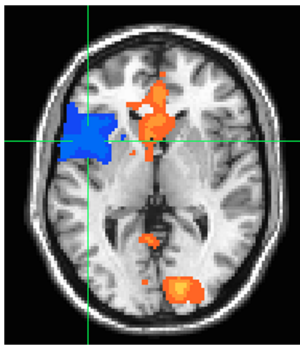

Figure 2. Average SVM weight map for drug vs. placebo classification, thresholded for visualization purposes. Larger weights are located in insula (blue), and medial frontal and visual areas (orange).

References: [1] Harris, Anesthesiology, 119:1453 (2013). [2] LaConte, NeuroImage, 26:317 (2005). [3] Glover, Magn Reson Med, 44:162 (2000). [4] Chang, ACM Trans Int Sys Tech 2:27 (2011).