Diagnosis of Schizophrenia using CBF Measures as a Classification Feature – A FBIRN Phase 3 Multisite ASL Study at 3T

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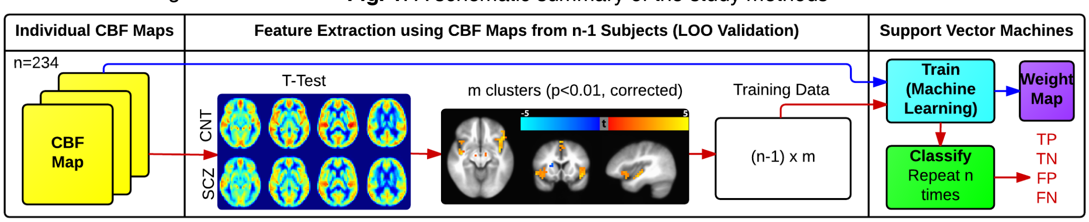
Introduction: Schizophrenia (SCZ) is a severe chronic mental disorder that affects more than 1.2% of the US population. Diagnosis of SCZ is often difficult, and is currently based on a combination of self-assessments, reported abnormalities in behavior, and rigorous psychological evaluations. The availability of more objective measures can help psychiatrists in maximizing diagnostic accuracy while minimizing false negatives. Several voxel-based morphometric (VBM) studies have shown structural differences between SCZ patients and healthy controls [1, 2] and these differences have been used as detectable patterns in machine learning techniques to distinguish between individual patients and healthy controls. Support Vector Machines (SVM) is one such technique, and in a recent study involving a large study population (n=239), SVM achieved a classification accuracy of 71.4% using VBM features [3]. Using resting state ASL data collected from the multisite Functional Bioinformatics Research Network (FBIRN) Phase 3 Project, a recent study identified several brain regions where the baseline cerebral blood flow (CBF) was significantly lower in SCZ patients [4]. Given this initial finding, the motivation of this study was to use SVM to assess its potential as an objective diagnostic tool, based on the CBF maps and unique brain regions associated with hypoperfusion in the patient population. To our knowledge, this is the first study of its kind, i.e. a large-scale ASL study using SVM to assess its diagnostic potential.

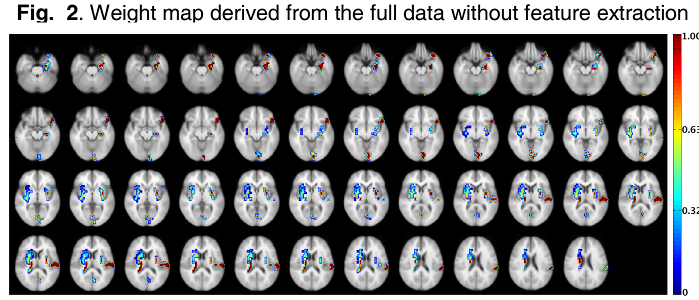
Methods: The study included 234 subjects (173 men vs. 61 women, 112 normal vs. 122 schizophrenic, 38.2 age ± 11.4) recruited from seven different research sites in the U.S: Duke University, University of California San Diego, University of California Irvine, University of California San Francisco, University of Iowa, University of Minnesota, and the Mind Research Network. The CBF maps warped to standard Talairach space and derived from FAIR ASL data (TI1/TI2=600ms/1600ms, 10cm tag width, 1cm tag-slice gap) were downloaded from the CBFBIRN Database [5]. We used SVM^{Light}, a C-based SVM package [6] in combination with MATLAB scripts to carry out the classification. The study consisted of two parts and the processes associated with each part are represented with red and blue arrows in Figure 1.

Fig. 1. A schematic summary of the study methods



Part 1: The classification performance was evaluated using Leave-one-out (LOO) cross validation, which is the standard method to assess how well the model will generalize to a new data set. In order to minimize processing time and the influence of noise to classification, relevant features were first extracted from the individual CBF maps by identifying clusters of voxels with group differences (t-test, $p<0.01$, corrected). The mean CBF values across these clusters were then used as the training data. The training was carried out on all subjects while excluding one, which was then used in the classification. The training and classification cycles were repeated 234 times until all subjects were left out only once. The classification performance was measured using three parameters, i.e. sensitivity = TP/(TP+FN), specificity = TN/(TN+FN), and accuracy = (sensitivity + specificity)/2, where TP, TN, FP, FN were the number of true positives, true negatives, false positives, and false negatives, respectively. *Part 2:* As a separate study for validation of the methodology, the SVM algorithm used in Part 1 was trained once using the full data consisting of 234 CBF maps (without feature extraction), from which a weight map was generated.

Fig. 2. Weight map derived from the full data without feature extraction



Results & Discussion: The sensitivity, specificity, and accuracy for the LOO validation were 75.9%, 75.5%, and 75.7%, respectively. Figure 2 shows the weight-vector values from the classification mapped onto the brain, identifying the brain regions that contributed most in differentiating between the patients and healthy controls. Notably, the left superior temporal gyrus, and left/right insular regions can be seen. The insula is a key region responsible for discriminating between self-generated and external information [7]. The left superior temporal gyrus consists of a primary and secondary auditory cortex, which has long been implicated with auditory hallucination [8]. In summary, we have demonstrated that 1) resting state ASL data may be used with SVM to distinguish between normal controls and SCZ patients with high accuracy (75.7% vs 71.4% from a previous VBM study [3]); 2) the SVM-derived weight map showed brain regions that have been previously implicated in SCZ. In practice, the results presented suggest that the CBF map acquired from a 5-minute FAIR ASL scan, combined with SVM classification may be useful as a complimentary tool for diagnosis of SCZ.

References: [1] Olabi, et al. Biol. Imaging 21:300, 2011. [2] Wright et al. J. Psychiatry 157:16, 2000. [3] Nieuwenhuis et al. NeuroImage 61:606, 2012. [4] Shin et al. Abstract #1456, ISMRM, 2013. [5] Shin et al. Front. Neuroinform. 7:21, 2013. [6] Joachims. SVMLight, http://svmlight.joachims.org. [7] Wylie et al. Schizophr Res.123:93, 2010. [8] Ford et al. Schizophrenia Bulletin. 58:66, 2009.