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DISCRIMINATIVE ANALYSIS OF FUNCTIONAL NEAR-INFRARED SPECTROSCOPY SIGNALS FOR DEVELOPMENT OF NEUROIMAGING BIOMARKERS OF ELDERLY DEPRESSION

YE ZHU[*,‡], TIANZI JIANG[*,§], YUAN ZHOU[*] and LISHA ZHAO[†]
[*]*National Laboratory of Pattern Recognition*
Institute of Automation, Chinese Academy of Sciences
Beijing 100080, P.R. China
[†]*Beijing Anding Hospital*
Affiliate of Capital University of Medical Science
Beijing 100088, Beijing, China
[‡]*yzhu@nlpr.ia.ac.cn*
[§]*jiangtz@nlpr.ia.ac.cn*

Functional near-infrared spectroscopy (fNIRS) is a neuroimaging technology which is suitable for psychiatric patients. Several fNIRS studies have found abnormal brain activations during cognitive tasks in elderly depression. In this paper, we proposed a discriminative model of multivariate pattern classification based on fNIRS signals to distinguish elderly depressed patients from healthy controls. This model used the brain activation patterns during a verbal fluency task as features of classification. Then Pseudo-Fisher Linear Discriminant Analysis was performed on the feature space to generate discriminative model. Using leave-one-out (LOO) cross-validation, our results showed a correct classification rate of 88%. The discriminative model showed its ability to identify people with elderly depression and suggested that fNIRS may be an efficient clinical tool for diagnosis of depression. This study may provide the first step for the development of neuroimaging biomarkers based on fNIRS in psychiatric disorders.

Keywords: Functional near-infrared spectroscopy (fNIRS); Fisher linear discriminant analysis (FLDA); depression.

1. Introduction

As the number of older psychiatric patients increases all over the world, elderly depression has become a major public health problem. According to related reports, 7%–10% of elderly population are affected by depression.[1] Current available diagnosis of depression is mainly based on clinical signs and symptoms and medical history. Therefore, more objective approaches are desired to help diagnose elderly depression in clinical practice.

Functional near-infrared spectroscopy (fNIRS) is a recently developed functional neuroimaging technology that allows noninvasive in vivo measurements of changes in the concentration of oxygenated ([OxyHb]) and deoxygenated ([DeoxyHb]) hemoglobin in brain issue.[2] Compared to other functional neuroimaging techniques, such as PET, SPECT and fMRI, fNIRS is especially suitable for psychiatric patients, due to the following reasons: low insensitive to movement artifacts, less

[‡,§]Corresponding authors.

restrictive, and low cost. Accordingly, fNIRS has been applied to the examination of brain functions in various kinds of psychiatric disorders, including schizophrenia, major depression, bipolar disorder, and post traumatic stress disorder.[3–6] These researches have examined task-related hemodynamic changes and found abnormal brain functional activities in psychiatric patients. However, these studies were focusing on finding the most significant differences of brain activation between psychiatric patients and healthy subjects. Such a group-level statistical difference is less helpful to diagnosis.

Currently, increasing attention has been devoted to the applications of multivariate statistical methods in neuroimaging data analysis.[7–9] Such methods can distinguish patients from normal controls and may provide the first step toward development neuroimaging biomarkers in psychiatry. Unfortunately few were concerned on fNIRS information. In this work, we assessed brain activation of patients with elderly depression during a verbal fluency task (VFT) measured by fNIRS. We took the activation patterns as the classification features and proposed a discriminative approach based on Fisher Linear Discriminant Analysis (FLDA) to distinguish depression patients from healthy individuals. The performance of the classifier was evaluated by using a leave-one-out (LOO) cross-validation approach. As fNIRS is perfectly suitable to measure functional brain activity in psychiatric patients, a discriminative approach based on the fNIRS may have potential in clinical applications.

2. Materials

2.1. *Subjects*

Thirteen elderly patients with major depressive disorder (8 males and 5 females, age 67.8 ± 5.92 years) and 12 healthy controls (5 males and 7 females, age 68.67 ± 6.32 years) participated in the present study. The two groups were matched in age, sex, and education. The patients were recruited from the inpatients of Beijing Anding Hospital and were diagnosed according to the criteria in the DSM-χ.[10] All patients were receiving selective serotonin reuptake inhibitors at the time of NIRS examination (six, 20 mg paroxetine daily; two, 30 mg paroxetine daily; four, 30 mg citalopram daily; one, 50 mg sertraline daily). All control subjects were medication free and without preexisting neurological or psychiatric disorders. All subjects were right-handed and were given written informed consent before the start of the investigation, which was approved by the Medical Research Ethics Committee of Beijing Anding Hospital.

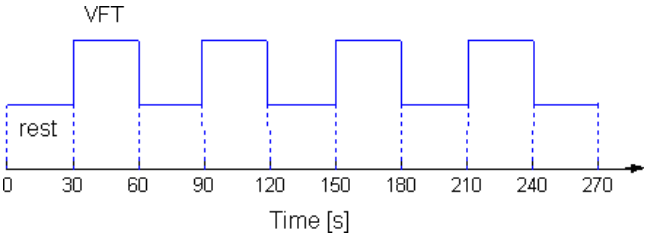

Fig. 1. Verbal fluency task (VFT) protocol.

2.2. *Activation task*

We used a block design with four 60-s blocks consisting of 30 s task and 30 s resting period (See Fig. 1). The task was the VFT in a category version. The subjects were instructed to produce nouns belonging to the categories animals, vegetables, fruits, and cities in the task condition. The order of the category was counterbalanced among the subjects. In the resting condition, subjects were instructed to watch a white background and avoid movements.

2.3. *NIRS measurements*

NIRS measurements were conducted with a multichannel continuous wave optical instrument (CW 5, TechEn Inc, American). The CW5 uses near infrared light at two wavelengths 690 and 830 nm, whose difference in the absorption spectrum enables the measurement of [OxyHb] and [DeoxyHb].[11] In this study, we used two 14-channel arrays of probes for bilateral frontal lobes. Each array was consisted of four optical laser-sources and eight detector-receivers. A measurement point (channel) was defined as the region between one source and its neighbor detector (distance between the probes was 3 cm). So one array allows to measure the relative changes in [OxyHb] and [DeoxyHb] at 14 channels and covered an area of 5.7 cm × 5.8 cm on the scalp. The probes were mounted on two plastic helmets that were held by adjustable straps over the subject's bilateral frontal lobes, with the most inferior and former probe positioned Fp1 (left) or Fp2 (right), according to the international 10/20 system used in electroencephalography. The measurement points were superimposed on a magnetic resonance image of a three-dimensionally reconstructed cerebral cortex. Measurement points were labeled as

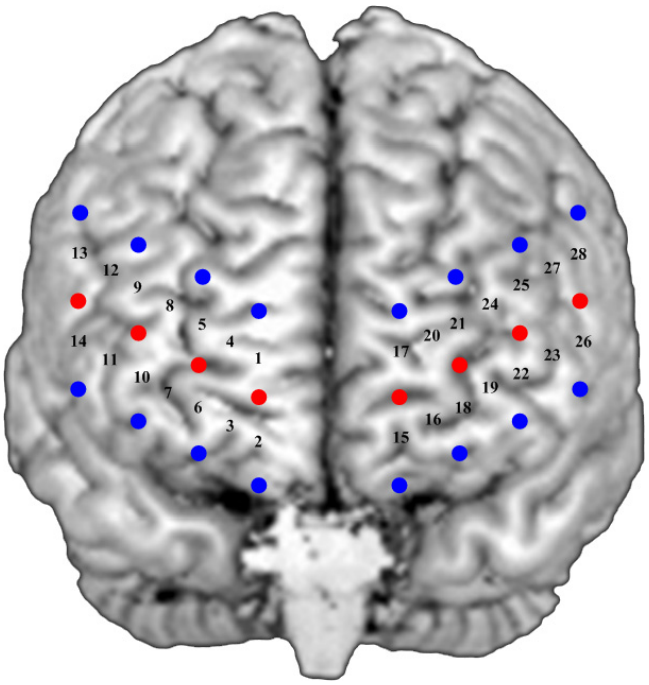

Fig. 2. The sources and detectors are superimposed on a magnetic resonance image of a three-dimensionally reconstructed cerebral cortex. The red circles indicate light sources and the blue circles indicate light detectors. The numbers between the optodes indicate the measurement channels.

Ch1-14 for right frontal channels and Ch15-28 for left frontal channels (See Fig. 2).

3. Methods

3.1. *Data Preprocessing and feature extraction*

The optical raw data were first demodulated against the laser carrier frequencies to separate individual source contributions and then low-pass filtered and downsampled to 10 Hz. The data was further analyzed with Homer software (available at http://www.nmr.mgh.harvard.edu/PMI/). First, the data were band-pass filtered within the range 0.01–0.5 Hz to eliminate slow drifts and the blood pressure variations. Then the optical signals for the two wavelengths were translated to hemoglobin concentrations using the modified Beer–Lambert equation.[12]

For applying pattern classification algorithms, activation level of each channel was estimated by the general linear model (GLM) approach.[13] The fNIRS time series was predicted by convolution of a boxcar function of the stimulus design with a hemodynamic response function (HRF) and the corresponding regression coefficient (beta) was taken to represent the activation level. We calculated the beta weights for both [OxyHb] and [DeoxyHb] data at each channel in the task condition. Cortical activation usually causes an increase in [OxyHb] and a corresponding decrease in [DeoxyHb].[14] Thus positive beta weights in the [OxyHb] data and negative beta weights in the [DeoxyHb] data indicated cortical activation.[15] In the next section, we used the beta weights as the classification feature to discriminate depression patients from healthy controls.

3.2. *Pseudo-Fisher linear discriminant analysis*

FLDA is a widely used classification method that projects high-dimensional data onto a line and performs classification in this one-dimensional space.[8,9,16] Theoretically, this line can be found by maximizing the ratio of between-class separability to within-class variability. To this purpose FLD considers maximizing the following objective function:

$$J(\omega) = \frac{\omega^T S_B \omega}{\omega^T S_W \omega}, \tag{1}$$

where S_B is the between class scatter matrix and S_W is the within classes scatter matrix. The definitions of the scatter matrices are:

$$S_B = (m_1 - m_2)(m_1 - m_2)^T, \tag{2}$$

$$S_W = \sum_{i=1}^{N_1} (x_1^i - m_1)(x_1^i - m_1)^T + \sum_{i=1}^{N_2} (x_2^i - m_2)(x_2^i - m_2)^T, \tag{3}$$

where $x_i^1 (i = 1, 2, \ldots, N_1)$ and $x_i^2 (i = 1, 2, \ldots, N_2)$ are n-dimensional feature vector of each sample, m_1 and m_2 are mean feature vectors, and N_1 and N_2 are sample sizes of two classes, respectively. In this study, the feature vectors are the beta weights representing the activation level during the task condition obtained in Sec. 3.1. Theoretically, the optical projective direction can be determined by:

$$\omega^* = S_W^{-1}(m_1 - m_2). \tag{4}$$

However, the number of features is higher than the number of total training samples in this research. Computing inverse matrix of S_W will lead to an ill-posed problem and therefore FLD would yield an unreliable result. To solve this problem, we used a Pseudo-Fisher Linear Discriminant analysis

(pFLDA) which first applied a Principal Component Analysis (PCA) on the sample feature $x \in \Re^n$ to get a low-dimensional feature $x' \in \Re^{n'}(n' \leq N_1+N_2-1)$. Then the classical FLD procedure can be performed in the low-dimensional feature space to find $\omega^* \in \Re^{n'}$.

Projecting each sample $x' \in \Re^{n'}$ on to the direction $\omega^* \in \Re^{n'}$ to get a discriminative score z by:

$$z = \omega^{*T} x'. \tag{5}$$

Finally, the classification threshold z_0 is determined by:

$$z_0 = (N_1 m_1^z + N_2 m_2^z)/(N_1 + N_2), \tag{6}$$

where m_1^z and m_2^z are the mean values of the discriminative scores of the two classes.

3.3. *Leave-one-out (LOO) cross-validation*

The LOO approach has been widely used as a reliable estimator of the true generalization performance, especially when the sample size is very limited.[8] When using the LOO method, the learning algorithm is trained multiple times, using all but one of the training set. In this study, one subject was first selected as a testing sample, and the remaining subjects were trained for discriminative model.

4. Experimental Results

There were totally 25 samples in this work, including 13 depression patients and 12 healthy controls and the grand average fNIRS time courses were shown in Fig. s1 and s2 (see Supplementary material for details). pFLDA was applied to the feature vectors extracted from the [OxyHb] and [DeoxyHb] data, respectively.

We evaluated the performance of the classifier using a full LOO cross-validation. In each LOO validation case, one subject was first selected as a testing sample, and the remaining subjects were trained for discriminative model. Classification results were listed in Table 1. The pattern of brain activity revealed by the [OxyHb] data correctly classified up to 88% (92% for patients and 83% for control subjects), while the classification accuracy based on the [DeoxyHb] data was 80% (77% for patients and 83% for controls). The distribution of discriminative scores of both the training and testing samples in a 25-round LOO test were shown in Figs. 3 and 4.

Table 1. Classification results.

Discriminative model	Training set correct rate (%)	LOO test correct rate		
		Depression (%)	Controls (%)	Total (%)
[OxyHb]	100	92	83	88
[DeoxyHb]	100	77	83	80

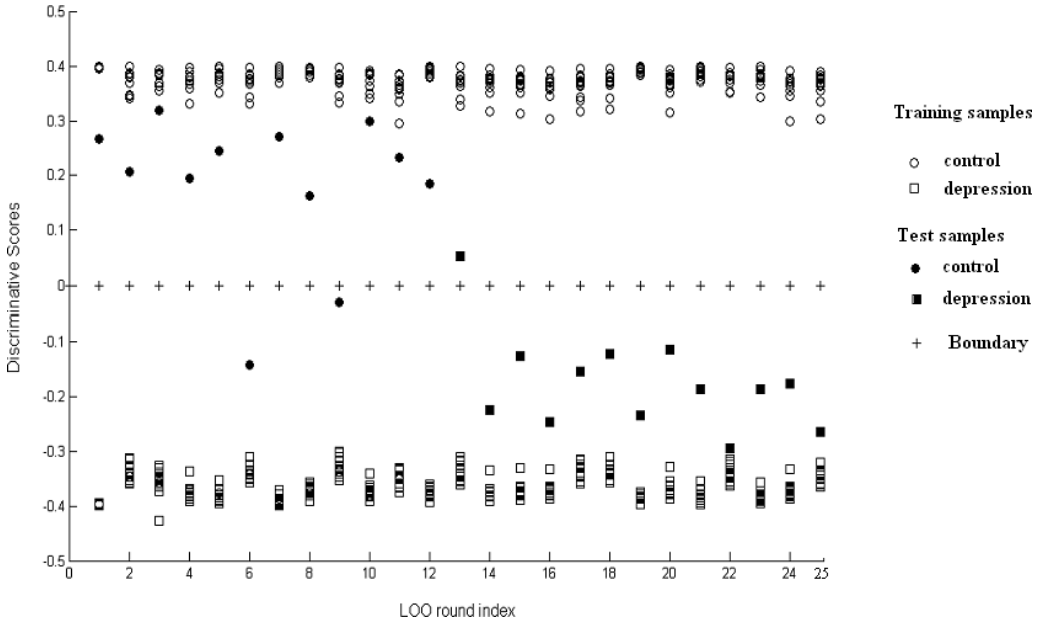

Fig. 3. Distribution of discriminative scores in 25-round LOO test based on the [OxyHb] data.

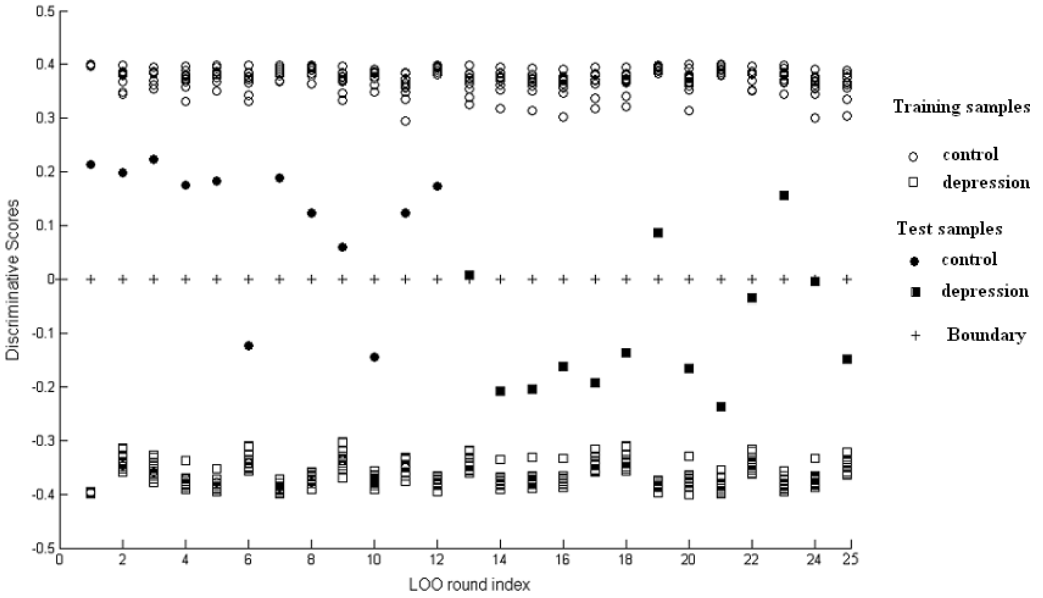

Fig. 4. Distribution of discriminative scores in 25-round LOO test based on the [DexyHb] data.

As in Fig. 2, there are only two testing controls (rounds 6 and 9) and one testing patients (round 13) located on the wrong sides of the classification boundary by the classifier based on the [OxyHb] data. And in Fig. 3, there are two testing controls (rounds 6 and 10) and three testing patients (rounds 13, 19, and 23) located on the wrong sides of the classification boundary by the classifier based on the [DeoxyHb] data.

5. Discussion and Conclusion

The present study proposed a multivariate classification approach for distinguishing patients with elderly depression from normal controls based on the pattern of brain activity during a VFT measured by fNIRS. The experimental results indicated that the proposed method achieved satisfactory classification accuracy in this study.

As noted in the Introduction part, fNIRS is a noninvasive neuroimaging technique, with low cost and the possibility for examinations in a natural setting, it is perfectly suitable for psychiatric patients. Previous researches have found abnormal brain activation of psychiatric patients using fNIRS in cognitive tasks.[3–6] Accordingly, the brain activation pattern is a promising feature for the classification of psychiatric disorders and we used it in this study as the classification feature for depressed patients.

Besides the classification feature, learning algorithm is another important aspect of pattern recognition. In the present study, we adopted FLDA, one of linear learning algorithms, because they are more insensitive to overfitting problems than nonlinear ones, especially in the case of high feature dimension and small sample size.[9] We also compared with other two classifiers, Batch Perceptron and SVM.[17] The classification rates were 56% for Batch Perceptron and 80% for SVM. Both of them were lower than the proposed classifier (88%).

Our results also showed that the discriminative model based on the [OxyHb] data had higher classification accuracy than the [DeoxyHb] data. This can be explained by the findings of Ehlis *et al.*[18] that an increase in [OxyHb] is the best indictor in cognitive fNIRS studies.

Future work will involve the evaluation of the proposed method with a new and larger sample and combining with other types of features to improve the efficiency of the discriminative model. Our results suggested that fNIRS may be a promising clinical tool for helping diagnose depression. Such analysis of neuroimaging data with multivariate pattern analysis methods may provide the first step toward developing neuroimaging biomarkers in psychiatry.

References

1. K. N. Fountoulakis, R. O'Hara, A. Iacovides, C. P. Camilleri, S. Kaprinis, G. Kaprinis, J. Yesavage, "Unipolar late-onset depression: A comprehensive review," *Ann. Gen. Hosp. Psychiatry* **2**, 11 (2003).

2. F. F. Jobsis, "Noninvasive, infrared monitoring of cerebral and myocardial oxygen sufficiency and circulatory parameters," *Science* **198**, 1264–1267 (1977).
3. K. Matsuo, T. Kato, M. Fukuda, N. Kato, "Alteration of hemoglobin oxygenation in the frontal region in elderly depressed patients as measured by near-infrared spectroscopy," *J. Neuropsychiatry Clin. Neurosci.* **12**, 465–471 (2000).
4. K. Matsuo, Y. Onodera, T. Hamamoto, K. Muraki, N. Kato, T. Kato, "Hypofrontality and microvascular dysregulation in remitted late-onset depression assessed by functional near-infrared spectroscopy," *Neuroimage* **26**, 234–242 (2005).
5. T. Suto, M. Fukuda, M. Ito, T. Uehara, M. Mikuni, "Multichannel near-infrared spectroscopy in depression and schizophrenia: cognitive brain activation study," *Biol. Psychiatry* **55**, 501–511 (2004).
6. K. Matsuo, K. Taneichi, A. Matsumoto, T. Ohtani, H. Yamasue, Y. Sakano, T. Sasaki, M. Sadamatsu, K. Kasai, A. Iwanami, N. Asukai, N. Kato, T. Kato, "Hypoactivation of the prefrontal cortex during verbal fluency test in PTSD: A near-infrared spectroscopy study," *Psychiatry Res.* **124**, 1–10 (2003).
7. C. H. Fu, J. Mourao-Miranda, S. G. Costafreda, A. Khanna, A. F. Marquand, S. C. Williams, M. J. Brammer, "Pattern classification of sad facial processing: Toward the development of neurobiological markers in depression," *Biol. Psychiatry* **63**, 656–662 (2008).
8. K. Wang, T. Jiang, M. Liang, L. Wang, L. Tian, X. Zhang, K. Li, Z. Liu, "Discriminative analysis of early Alzheimer's disease based on two intrinsically anti-correlated networks with resting-state fMRI," *Med. Image Comput. Comput. Assist. Interv. Int. Conf. Med. Image Comput. Comput. Assist. Interv.* **9**, 340–347 (2006).
9. C. Z. Zhu, Y. F. Zang, Q. J. Cao, C. G. Yan, Y. He, T. Z. Jiang, M. Q. Sui, Y. F. Wang, "Fisher discriminative analysis of resting-state brain function for attention-deficit/hyperactivity disorder," *Neuroimage* **40**, 110–120 (2008).
10. "American Psychiatric Association, Diagnostic and Statistical Manual of Mental Disorders," 4th edition, American Psychiatric Association, Washington, DC (1994).
11. M. A. Franceschini, D. K. Joseph, T. J. Huppert, S. G. Diamond, D. A. Boas, "Diffuse optical imaging of the whole head," *J. Biomed. Opt.* **11**, 054007 (2006).
12. M. Cope, D. T. Delpy, E. O. Reynolds, S. Wray, J. Wyatt, P. van der Zee, "Methods of quantitating cerebral near infrared spectroscopy data," *Adv. Exp. Med. Biol.* **222**, 183–189 (1988).
13. J. C. Ye, S. Tak, K. E. Jang, J. Jung, J. Jang, "NIRS-SPM: Statistical parametric mapping for near-infrared spectroscopy," *Neuroimage* **44**, 428–447 (2009).
14. H. Obrig, R. Wenzel, M. Kohl, S. Horst, P. Wobst, J. Steinbrink, F. Thomas, A. Villringer, "Near-infrared spectroscopy: Does it function in functional activation studies of the adult brain?" *Int. J. Psychophysiol.* **35**, 125–142 (2000).
15. M. M. Plichta, S. Heinzel, A. C. Ehlis, P. Pauli, A. J. Fallgatter, "Model-based analysis of rapid event-related functional near-infrared spectroscopy (NIRS) data: A parametric validation study," *Neuroimage* **35**, 625–634 (2007).
16. R. O. Duda, P. E. Hart, D. G. Stork, *Pattern Classification*, Wiley, New York (2001).
17. V. N. Vapnik, *Statistical Learning Theory*, J. Wiley, New York (1998).
18. A. C. Ehlis, M. J. Herrmann, A. Wagener, A. J. Fallgatter, "Multi-channel near-infrared spectroscopy detects specific inferior-frontal activation during incongruent Stroop trials," *Biol. Psychol.* **69**, 315–331 (2005).