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Abstract. Abnormal prefrontal function plays a central role in the cognition deficits of schizophrenic patients; however, the character of the relationship between discriminant analysis and prefrontal activation remains undetermined. Recently, evidence of low prefrontal cortex (PFC) activation in individuals with schizophrenia has also been found during verbal fluency tests (VFT) and other cognitive tests with several neuroimaging methods. The purpose of this study is to assess the hemodynamic changes of the PFC and discriminant analysis between schizophrenia patients and healthy controls during VFT task by utilizing functional optical topography. A total of 99 subjects including 53 schizophrenic patients and 46 age- and gender-matched healthy controls were studied. The results showed that the healthy group had larger activation in the right and left PFC than in the middle PFC. Besides, the schizophrenic group showed weaker task performance and lower activation in the whole PFC than the healthy group. The result of the discriminant analysis showed a significant difference with P value <0.001 in six channels (CH 23, 29, 31, 40, 42, 52) between the schizophrenic and healthy groups. Finally, 68.69% and 71.72% of subjects are correctly classified as being schizophrenic or healthy with all 52 channels and six significantly different channels, respectively. Our findings suggest that the left PFC can be a feature region for discriminant analysis of schizophrenic diagnosis. [DOI: 10.1117/1.JBO.19.1.011006]

Keywords: schizophrenia; prefrontal cortex dysfunction; functional optical topography; discriminant analysis; near-infrared spectroscopy.

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1 Introduction

Schizophrenia is an irreversible neurodevelopmental disorder with severe individual, family, and societal burdens.[1] Several studies have indicated that schizophrenic patients showed impaired performance in various aspects of social cognition, including theory of mind, emotion processing, and agency judgments.[2–5] The neuroimaging techniques such as functional magnetic resonance imaging (fMRI) and positron emission tomography (PET) have been widely used to image brain functions for many neurodegenerative diseases.[6–12] These techniques have greatly increased our knowledge about the neuropathological process of schizophrenia based on cognitive and emotional processes. Although these methods offer noninvasive imaging with excellent spatial resolution, the limitation of huge size of instruments and confinement of the participants to restricted positions inside the magnet cannot be applied for patient-oriented diagnosis. Also, PET requires the injection of radioactive materials. These drawbacks make the imaging modalities difficult or impossible to apply in clinical diagnosis for neonates, children, old people, and claustrophobic patients.

Functional optical topography (fOT), imaging based on functional near-infrared spectroscopy measurement, is an another noninvasive neuroimaging technique that provides continuous recording of brain hemodynamic activity with detection of oxy- and deoxy-hemoglobin concentration changes. There are several benefits such as lower cost, nonionizing radiation imaging, real-time measurement, long time monitoring, and easy operation.[13] Although spatial resolution is limited, fOT offers more comprehensive information of brain activity than blood-oxygenation-level-dependent signal of fMRI.[14] Furthermore, the optical method can provide completely patient-oriented measurement. The fOT is also applicable for psychological test, because its temporal resolution is high enough to detect the changes of short duration such as the brain activation during cognitive task. In previous studies, fOT method has been shown to be sensitive enough for monitoring of physiological blood oxygenation changes during cognitive activation in schizophrenia.[15–17] Recently, fOT is being increasingly applied for investigation of prefrontal cortex (PFC) dysfunction in schizophrenia, because the social cognition of schizophrenic patients was associated with PFC activation. PFC dysfunction in individuals with schizophrenia has been detected and evidenced during verbal fluency test (VFT) and other cognitive tests by utilizing fOT.[18–22] However, the previous studies only show the group

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averaged data and correlational analysis between fOT and clinical symptoms. There are few studies reporting significantly different regions of PFC and discriminant analysis between schizophrenic and healthy subjects based on fOT measurement. The significantly different regions of PFC could be an indicator to evaluate the PFC function of schizophrenia in patient-oriented diagnosis. Thus, the goal of this study is to characterize/analyze fOT image between schizophrenia patients and healthy controls during VFT.

In this paper, we perform statistical analyses of PFC fOT image with VFT. The imaging results between schizophrenia and healthy controls are significantly different. Furthermore, the left PFC shows significant difference between schizophrenic and healthy subjects under the 0.1% significance level. In discriminant analysis, the 68.69% and 71.72% are correctly classified as being schizophrenic or healthy subjects with all 52 channels and six significantly different channels over the left PFC, respectively. Our results imply that the left PFC fOT imaging could be a feature region for schizophrenia-aided diagnosis.

2 Material and Methods

2.1 *Participants*

The study includes 53 schizophrenic patients [female/male: 27/26; mean age: 34.4; standard deviation (SD): 11] and 46 age- and sex-matched healthy controls (female/male: 25/21; mean age 35.1; SD 11.2), who were recruited from the Tottori University Hospital in Yonago, Japan. The diagnosis for schizophrenia was based on the Structured Clinical Interview for Diagnostic and Statistical Manual of Mental Disorders (DSM)-IV.[23] Healthy controls had no history of psychiatric or neurologic disorders. All subjects were native Japanese speakers. There was no difference between schizophrenic and control groups with respect to age, gender, and body mass index (BMI). However, the education, estimated premorbid IQ, and number of words generated show significant differences. Schizophrenic symptoms were evaluated with the Positive and Negative Syndrome Scale (PANSS) and Global Assessment of Functioning.[24–27] Table 1 shows the clinical characteristics of the schizophrenic and healthy groups. All participants gave written informed consent. The study was in accordance with the latest version of the Declaration of Helsinki, and approved by the Ethics Committee of Tottori University Faculty of Medicine.

2.2 *Functional Optical Topography*

The fOT measurements were conducted with a 52-channel ETG-4000 Optical Topography System (Hitachi Medical Co., Tokyo, Japan). The near-infrared sources at dual-wavelength 695 and 830 nm were used, and the temporal resolution of detection

Table 1 Clinical characteristics of the schizophrenic patients and healthy controls.

Clinical variables	Schizophrenia group ($n = 53$)		Healthy group ($n = 46$)		Group difference P value
	Mean	SD	Mean	SD	
Age (years)	34.4	11	35.1	11.2	0.756
Gender (female/male)	27/26	—	25/21	—	0.735[a]
Handedness (right/left)	48/5	—	46/0	—	—
Education (years)	13.2	2.28	15.24	2.35	<0.001
Estimated premorbid IQ	97.69	12.36	104	10.25	<0.01
Age at onset (years)	23.59	6.97	—	—	—
Number of words generated	12.3	4.11	14.61	5	<0.001
Duration of illness (years)	10.24	9.03	—	—	—
Positive and Negative Syndrome Scale (PANSS) (positive)	16.49	7.4	—	—	—
PANSS (negative)	17.46	5.43	—	—	—
PANSS (general psychopathology)	33.74	7.31	—	—	—
Global Assessment of Functioning	58.67	12.71	—	—	—
Chlorpromazine equivalent dose (mg/day)	653.65	387.17	—	—	—
Diazepam equivalent dose (mg/day)	5.68	6.68	—	—	—
Biperiden equivalent dose (mg/day)	0.47	0.99	—	—	—
Body mass index (BMI)	23.25	4.88	22.67	4.34	0.55

[a]Chi-square test was used for testing group difference. Otherwise, *t*-test was used.

is 0.1 s. According to the modified Beer–Lambert law,[28,29] the concentration changes in oxygenated hemoglobin (oxy-Hb) and deoxygenated hemoglobin (deoxy-Hb) could be obtained. Previous studies indicate that [oxy-Hb] is the most sensitive indicator of changes in regional cerebral blood flow in fOT measurement.[30,31] In fOT system, 17 emitters and 16 detectors are plugged into a probing holder and arranged as 3×11 array for 52-channel detection with 30-mm source–detector separation. In order to cover the whole PFC, the array was positioned according to the international 10-20 system.[32] Specifically, the detector 13 was placed in F_z; the midline of channels nos. 46 and 49 were placed in the F_{p2} and F_{p1}, and the source 23 and 28 were fitted around T_4 and T_3, respectively (as shown in Fig. 1).

2.3 *Data Acquisition: VFT Tasks*

The subjects were seated in a comfortable chair in a silent room and kept eyes open during the fOT monitoring. The VFT consists of a 60-s long VFT (letter version), a 30-s long pretask baseline, and a 70-s long posttask baseline. The three syllables (I: /to/, /se/ or /o/; II: /na/, /i/ or /ta/; III: /a/, /ki/ or /ha/) were announced in the order which was counterbalanced across participants. The fOT data were obtained by subtracting the baseline [oxy-Hb] while the subjects were simply repeating "a," "i," "u," "e," and "o" loudly. The VFT requires subject to say the words beginning with a specific syllable as many as possible. The schematic diagram of the task is shown in Fig. 2.

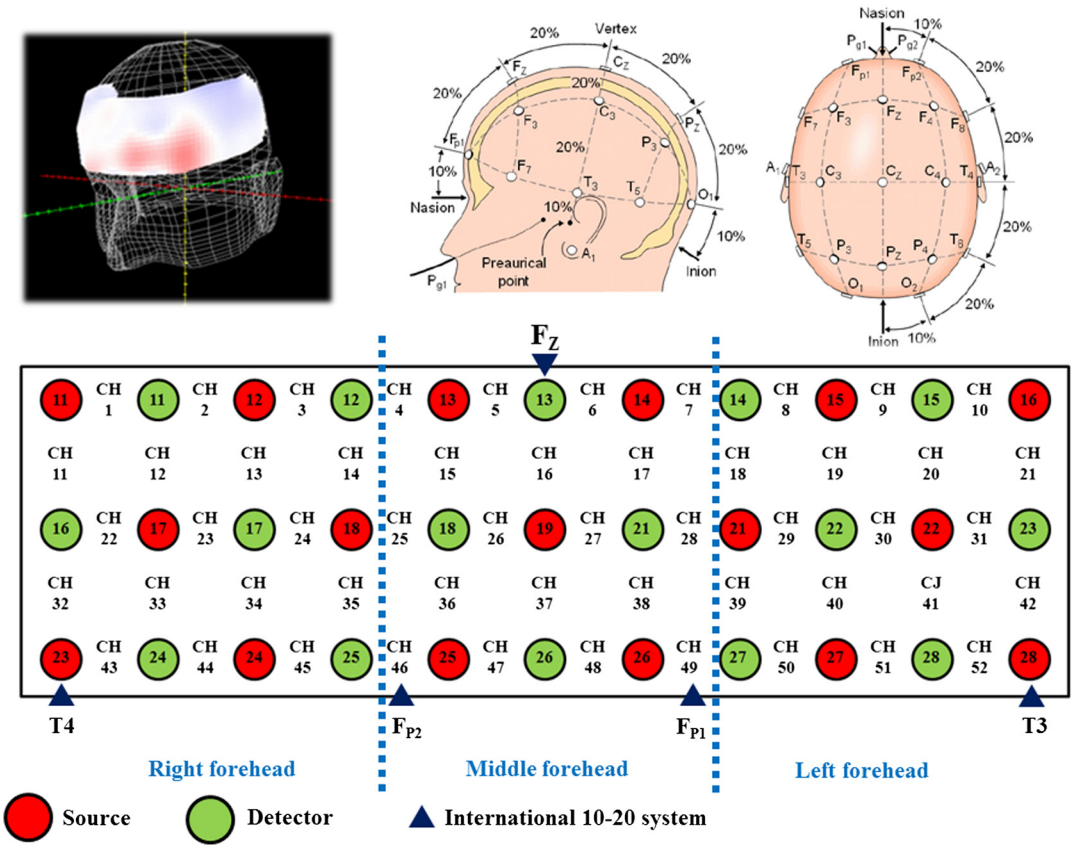

Fig. 1 The functional optical topography (fOT) channels localization. The localizations of all 52 channels were positioned according to the international 10-20 system. Red and green circles indicate near-infrared light emitter and detector positions, respectively. By using the international 10-20 system, the detector 13 was positioned on the F_z marker point, while the bottom row of channels was placed on a line between T_3 and T_4.

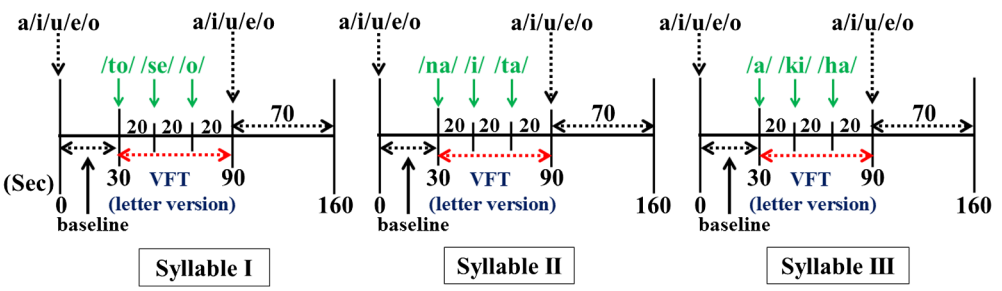

Fig. 2 The sequence consists of 60-s long verbal fluency test (VFT). Pretask baseline consists of 30-s long VFT and posttask baseline consists 70-s long VFT. The three syllables (I: /to/, /se/ or /o/; II: /na/, /i/ or /ta/; III: /a/, /ki/ or /ha/) are announced in the order which was counterbalanced across participants.

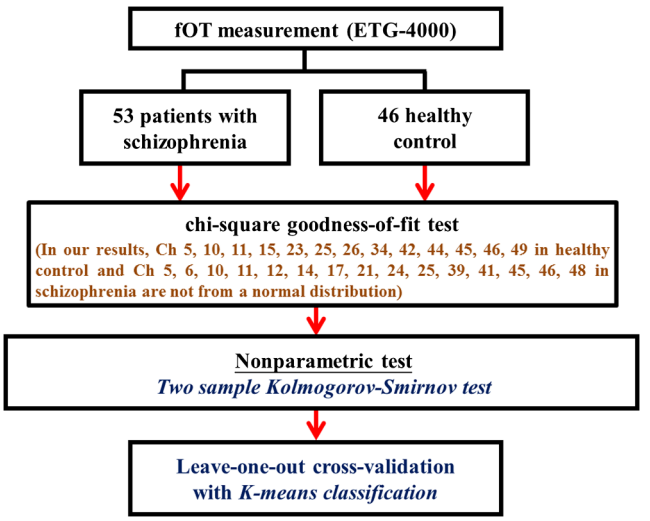

Fig. 3 The flowchart of data analyses with fOT. The two-sample K-S test of nonparametric methods was used to find the significantly different channels because some channels in healthy group and schizophrenic group are not normally distributed by using the chi-square goodness-of-fit test. Finally, the leave-one-out cross-validation with *k*-means clustering was used for discriminant analysis from healthy to schizophrenia group.

2.4 *Data Analyses*

Figure 3 shows the flowchart of fOT data analyses. In each subject, the mean levels in [oxy-Hb] of all 52 channels are calculated from both baseline and activation task of VFT. In order to find the significantly different regions of PFC, the fOT data are analyzed based on statistical tests. We adopt a chi-square goodness-of-fit test for statistical hypothesis testing. The chi-square test-statistic can be expressed as[33,34]

$$\chi^2 = \sum_{i=1}^{n} \frac{(O_i - E_i)^2}{E_i}, \tag{1}$$

where O_i is an observed count and E_i is an expected count; χ^2 is Pearson's cumulative test statistic; and n is the number of cells in the table. The statistic has an approximate chi-square distribution when the counts are sufficiently large. In our results, CH 5, 10, 11, 15, 23, 25, 26, 34, 42, 44, 45, 46, and 49 in healthy group and CH 5, 6, 10, 11, 12, 14, 17, 21, 24, 25, 39, 41, 45, 46, and 48 in schizophrenic group are not normally distributed. Due to physiological noise, the majority of the channels were found to be nonnormally distributed, and therefore, we used the nonparametric test on all the data. The two-sample Kolmogorov–Smirnov test (K-S test) is one of the most powerful nonparametric methods with highly sensitive comparison in both location and shape of the empirical cumulative distribution functions of the two samples.[35,36]

The two-sample K-S test is expressed as

$$D_{n,n'} = \underset{x}{\mathrm{SUP}} |G_n(x) - F_{n'}(x)|, \tag{2}$$

where SUP is the supremum of the set of distances; and $G_n(x)$ and $F_{n'}(x)$ are the empirical distribution functions of the first and the second variables, respectively. The null hypothesis is rejected at significance level α if

$$\sqrt{\frac{nn'}{n+n'}} D_{n,n'} > K_\alpha. \tag{3}$$

Equation (3) implies $G_n(x)$ and $F_{n'}(x)$ are significantly different. The test statistic K_α is the maximum difference between the curves. After K-S testing, the significantly different regions of PFC are defined between healthy and schizophrenic groups. Then, the discriminant analysis is applied by leave-one-out cross-validation with *k*-means clustering.[37] In statistics and data mining, the *k*-means method is one of the most widely used clustering algorithms with nearest mean, drawing its popularity from its speed in practice.[37,38] Leave-one-out cross-validation involves single observation from the original sample as the validation data, and the remaining observations as the training data. The validation step is looped until all observations are used once as the validation data. In this study, one subject is selected from all 99 subjects in sequence. Thus, the other 98 subjects are treated as training data with *k*-means clustering. The 99 times clustering of test data is then used for accuracy estimation of discriminant analysis.

3 Results

Figure 4 shows the [oxy-Hb] mapping of group-level statistics on averaging of healthy controls and schizophrenic patients. The [oxy-Hb] concentration of schizophrenic patients is significantly smaller than healthy controls during VFT.

In case of healthy controls, the [oxy-Hb] response is stronger on both sides than in middle PFC. For quantitative analysis, the mean of [oxy-Hb] on right, middle, and left PFC during VFT are demonstrated in Fig. 5. There exists the significant difference between healthy and schizophrenic groups (paired *t*-test, $^*P < 0.005$, $^{**}P < 0.001$).

Figure 6 shows the [oxy-Hb] mapping via 52 channels comparisons based on two-sample K-S test. The CH 23, 29, 31, 40, 42, and 52 are significantly different with $P < 0.001$. We can observe that the channel on the left regions of PFC is significantly different. This result implies that the left PFC may provide significant feature region to distinguish schizophrenia from healthy subjects in clinical diagnosis. The discriminant analysis reveals the significant difference with K-S test by utilizing leave-one-out cross-validation with *k*-means clustering. The four possible outcomes from a binary classifier of 52 and six

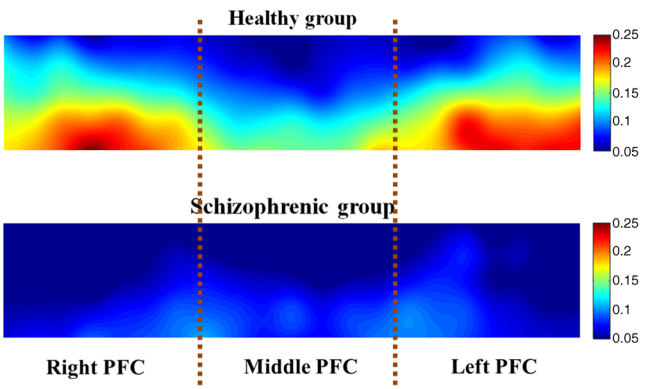

Fig. 4 Group-level [oxy-Hb] mapping with statistics on average during the VFT task. The prefrontal cortex (PFC) was divided into three regions (right, middle, and left PFC) to analyze. The [oxy-Hb] concentration of healthy group is significantly higher in right and left PFC. The PFC activation of schizophrenic patients is significantly smaller than healthy group (healthy group: $N = 46$; schizophrenic group: $N = 53$).

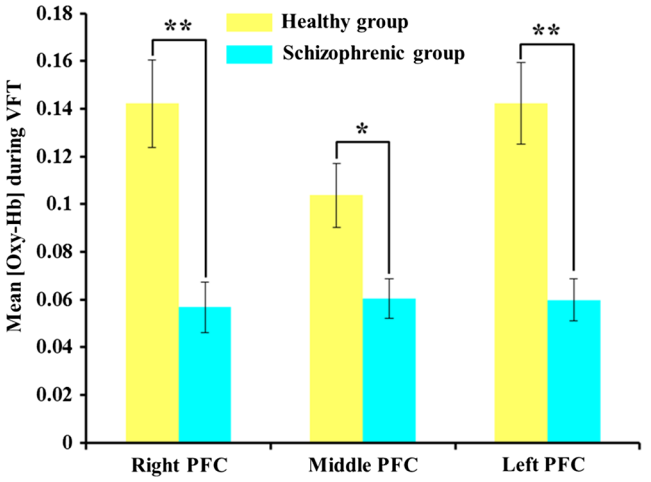

Fig. 5 The results of group-level statistics on averaging. The activation of right and left PFC between healthy and schizophrenia groups are significantly different with $P < 0.001$ and with $P < 0.005$ on middle PFC (paired t-test, $^*P < 0.005$, $^{**}P < 0.001$).

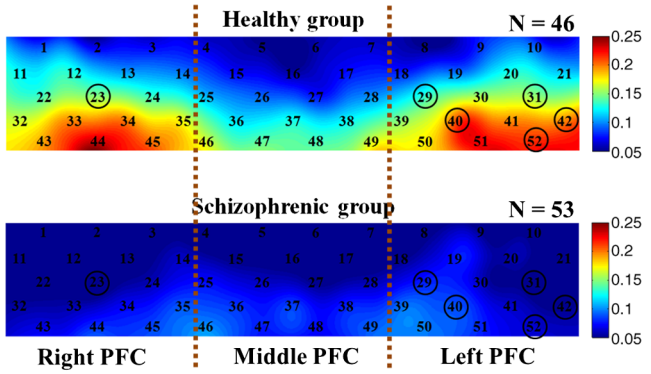

Fig. 6 The result of two-sample K-S test. The CH 23, 29, 31, 40, 42, and 52 are significantly different with $P < 0.001$ between healthy and schizophrenia groups. This result further indicates that the activation of left PFC during VFT is significantly different between healthy and schizophrenia group.

dimensions are shown in Table 2. The accuracy of correctly classified with 52 dimensions was 68.69% with a sensitivity of 85% and a specificity of 50% (i.e., true positive = 45 of the 53 schizophrenic patients and true negative = 23 of the 46 healthy controls). In the case of six significant difference dimensions, the accuracy of correctly classified was 71.72% with a sensitivity of 77% and a specificity of 65% (i.e., true positive = 41 of the 53 schizophrenic patients and true negative = 30 of the 46 healthy controls).

4 Discussion and Conclusions

The [oxy-Hb] responses on both sides of PFC are stronger than middle PFC from healthy controls, which implies deeper light penetration in the interhemispheric fissure that causes the fewer backscattered photons to be received. Furthermore, the [oxy-Hb] mapping of schizophrenic case is significantly weaker than normal on PFC and no significant difference is found among right, left, and middle forehead areas. It indicates the task-dependent profile of functional abnormalities can be observed from the brain metabolism on schizophrenic PFC. Also, the fOT measurement may offer a good potential to detect the structural change of brain. To our knowledge, we are the first to report the significant difference regions of PFC by utilizing discriminant analysis between schizophrenic and healthy subjects based on fOT monitoring. Although Azechi et al. used prefrontal activation with frontal lobe tasks for discriminant analyzing between schizophrenic and healthy subjects,[39] they did not provide the significant difference regions of PFC for discriminating schizophrenia. In this study, we pointed out the significant difference regions of PFC between schizophrenia and healthy controls. Figure 2 shows the group-level of [oxy-Hb] in right, left, and middle PFC that is significantly different between schizophrenia and healthy controls. According to two-sample K-S test, the channels of significant difference are analyzed on left PFC. Abnormal structural and/or functional hemisphere asymmetries in schizophrenia disorders have been assessed based on fOT.[18,40] In an fMRI study, reduced activation of the left frontal regions during word production was found in schizophrenia patients compared with normal.[41] The other study shows that schizophrenia produces a failure of attentional modulation that leads to a breakdown in the selective enhancement or inhibition of semantic/lexical representations, whose biological substrata are widely distributed across left (dominant) temporal and frontal lobes.[42] These findings can be interpreted as a sign of reduced specific lateralized PFC reactivity, possibly based on a left hemisphere functional deficit between schizophrenia and normal. Our result of the significant difference regions on left PFC is in agreement with previous studies. Therefore, the left PFC shows a great potential of feature region for discriminant analysis of schizophrenia. Table 2 demonstrates the accuracy of classification by applying six significant channels, which is better than 52 channels. Therefore, the significant channels in fOT can be used for schizophrenia diagnosis with discriminant analysis. However, the limitation of this study must be taken into account. Discriminant analysis with fOT can reveal significant differences between the probability distributions of signals in healthy and diseased groups, but cannot provide an individual diagnosis. Nevertheless, optical imaging with fOT can still be used as an auxiliary tool in schizophrenia diagnosis.

Table 2 The four possible outcomes from a binary classifier of 52 and 6 dimensions.

		k-means classification (all 52 dimensions)		*k*-means classification (6 significant dimensions by Kolmogorov–Smirnov test)	
Accuracy of classification		Schizophrenic	Healthy	Schizophrenic	Healthy
Original truth	Schizophrenic ($N = 53$)	45	8	41	12
	Healthy ($N = 46$)	23	23	16	30

Note: 52 dimensions: accuracy = $(23 + 45)/(46 + 53) * 100 = 68.69\%$; 6 dimensions: accuracy = $(30 + 41)/(46 + 53) * 100 = 71.72\%$.

In conclusion, the [oxy-Hb] PFC mapping of schizophrenia cases is weaker than healthy ones during VFT. The low [oxy-Hb] change of cognitive activation is concomitant with PFC dysfunction of schizophrenia. The significantly different channels of left PFC provide high-accuracy discrimination for schizophrenia. fOT offers both structural and functional information simultaneously with patient-oriented diagnosis. Furthermore, it could be used for the neural circuitry abnormality detection and estimation of pharmacological treatment and/or cognitive rehabilitation.

Acknowledgments

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References

1. T. Walsh et al., "Rare structural variants disrupt multiple genes in neurodevelopmental pathways in schizophrenia," *Science* **320**(25), 539–543 (2008).
2. R. I. M. Dunbar, "The social brain hypothesis," *Evol. Anthropol.* **6**(5), 178–190 (1998).
3. G. Bush, P. Luu, and M. I. Posner, "Cognitive and emotional influences in anterior cingulate cortex," *Trends Cogn. Sci.* **4**(6), 215–222 (2000).
4. T. Jellema et al., "Neural representation for the perception of the intentionality of actions," *Brain Cognition* **44**(2), 280–302 (2000).
5. J. K. Burns, "An evolutionary theory of schizophrenia: cortical connectivity, metarepresentation, and the social brain," *Behav. Brain Sci.* **27**(6), 831–885 (2004).
6. D. S. Manoach et al., "Schizophrenic subjects activate dorsolateral prefrontal cortex during a working memory task, as measured by fMRI," *Biol. Psychiat.* **45**(9), 1128–1137 (1999).
7. R. E. Gur et al., "An fMRI study of facial emotion processing in patients with schizophrenia," *Am. J. Psychiat.* **159**(12), 1992–1999 (2002).
8. Y. Zhou et al., "Functional disintegration in paranoid schizophrenia using resting-state fMRI," *Schizophr. Res.* **97**(1–3), 194–205 (2007).
9. Y. Zhoua et al., "Functional dysconnectivity of the dorsolateral prefrontal cortex in first-episode schizophrenia using resting-state fMRI," *Neurosci. Lett.* **417**(3), 297–302 (2007).
10. D. Mamo et al., "Differential effects of aripiprazole on D2, 5-HT2, and 5-HT1A receptor occupancy in patients with schizophrenia: a triple tracer PET study," *Am. J. Psychiat.* **164**(9), 1411–1417 (2007).
11. R. Mizrahi et al., "Adverse subjective experience with antipsychotics and its relationship to striatal and extrastriatal D2 receptors: a PET study in schizophrenia," *Am. J. Psychiat.* **164**(4), 630–637 (2007).
12. O. D. Howes et al., "Elevated striatal dopamine function linked to prodromal signs of schizophrenia," *Arch. Gen. Psychiat.* **66**(1), 13–20 (2009).
13. G. Boas, "Noninvasive imaging of the brain," *Opt. Photon. News* **15**(1), 52–55 (2004).
14. S. C. Bunce et al., "Functional near-infrared spectroscopy," *IEEE Eng. Med. Biol.* **25**(4), 54–62 (2006).
15. Y. Fukuji et al., "Changes of cerebral blood volume in frontal region during mirror drawing task measured by two channel NIRS in schizophrenics," *Int. Congr. Ser.* **1232**, 667–671 (2002).
16. B. S. Folley and S. Park, "Verbal creativity and schizotypal personality in relation to prefrontal hemispheric laterality: a behavioral and near-infrared optical imaging study," *Schizophr. Res.* **80**(2), 271–282 (2005).
17. S. Sumitani et al., "Activation of the prefrontal cortex during the wisconsin card sorting test as measured by multichannel near-infrared spectroscopy," *Neuropsychobiology* **53**(2), 70–76 (2006).
18. Y. Kubotaa et al., "Prefrontal activation during verbal fluency tests in schizophrenia-a near-infrared spectroscopy (NIRS) study," *Schizophr. Res.* **77**(1), 65–73 (2005).
19. A.-C. Ehlis et al., "Cortical activation during two verbal fluency tasks in schizophrenic patients and healthy controls as assessed by multi-channel near-infrared spectroscopy," *Psychiat Res Neuroimag.* **156**(1), 1–13 (2007).
20. R. Takizawa et al., "Reduced frontopolar activation during verbal fluency task in schizophrenia: a multi-channel near-infrared spectroscopy study," *Schizophr. Res.* **99**(1–3), 250–262 (2008).
21. H. Hori et al., "Schizotypal traits in healthy women predict prefrontal activation patterns during a verbal fluency task: a near-infrared spectroscopy study," *Neuropsychobiology* **57**(1–2), 61–69 (2008).
22. K. Ikezawa et al., "Impaired regional hemodynamic response in schizophrenia during multiple prefrontal activation tasks: a two-channel near-infrared spectroscopy study," *Schizophr. Res.* **108**(1–3), 93–103 (2009).
23. M. First et al., "Structured Clinical Interview for DSM-IV-TR Axis I Disorders, Research Version, Patient Edition (SCID-I/P)," *Biometrics Research*, NYSPI, New York (2002).
24. S. R. Kay, A. Fiszbein, and L. A. Opler, "The positive and negative syndrome scale (PANSS) for schizophrenia," *Schizophr. Bull.* **13**(2), 261–275 (1987).
25. S. Leuchta et al., "What does the PANSS mean?," *Schizophr. Res.* **79**(2–3), 231–238 (2005).
26. S. H. Jones et al., "A brief mental health outcome scale reliability and validity of the Global Assessment of Functioning (GAF)," *Br. J. Psychiat.* **166**(5), 654–659 (1995).
27. M. Startup, M. C. Jackson, and S. Bendix, "The concurrent validity of the Global Assessment of Functioning (GAF)," *Br. J. Clin.* **41**(4), 417–422 (2002).
28. Y. Yamashita et al., "Noninvasive near-infrared topography of human brain activity using intensity modulation spectroscopy," *Opt. Eng.* **35**(4), 1046–1049 (1996).
29. L. Kocsis, P. Herman, and A. Eke, "The modified Beer–Lambert law revisited," *Phys. Med. Biol.* **51**(5), N91–N98 (2006).
30. Y. Hoshi, "Functional near-infrared spectroscopy: current status and future prospects," *J. Biomed. Opt.* **12**(6), 062106 (2007).
31. C.-M. Lu et al., "Use of fNIRS to assess resting state functional connectivity," *J. Neurosci. Methods* **186**(2), 242–249 (2010).
32. M. Okamoto et al., "Three-dimensional probabilistic anatomical cranio-cerebral correlation via the international 10–20 system oriented for transcranial functional brain mapping," *NeuroImage* **21**(1), 99–111 (2004).
33. R. L. Plackett, "Karl Pearson and the chi-squared test," *Int. Stat. Rev.* **51**(1), 59–72 (1983).
34. D. M. Glover, W. J. Jenkins, and S. C. Doney, *Lecture 3: Least Squares and Regression Techniques, Goodness of Fit and Tests, Non-linear Least Squares Techniques*, Woods Hole Oceanographic Institute, Massachusetts (2008).
35. R. H. C. Lopes, I. Reid, and P. R. Hobson, "The two-dimensional Kolmogorov-Smirnov test," in *Proc. Sci., XI International Workshop on Advanced Computing and Analysis Techniques in Physics Research*, Amsterdam, The Netherlands, pp. 1–12 (2007).
36. G. W. Corder and D. I. Foreman, *Nonparametric Statistics for Non-Statisticians: A Step-by-Step Approach*, Wiley, Hoboken, New Jersey (2009).
37. D. Arthur, B. Manthey, and H. Roeglin, "K-means has polynomial smoothed complexity," in *Proceedings of the 50th Annual IEEE Symposium on Foundations of Computer Science (FOCS)*, pp. 405–414 (2009).
38. H. Zha et al., "Spectral relaxation for K-means clustering," *Adv. Neural Inform. Process. Syst.* **14**(NIPS'01), 1057–1064 (2001).
39. M. Azechi et al., "Discriminant analysis in schizophrenia and healthy subjects using prefrontal activation during frontal lobe tasks: a near-infrared spectroscopy," *Schizophr. Res.* **117**(1), 52–60 (2010).
40. M. J. Herrmann et al., "Cerebral oxygenation changes in the prefrontal cortex: effects of age and gender," *Neurobiol. Aging* **27**(6), 888–894 (2006).
41. D. A. Yurgelun-Todd et al., "Functional magnetic resonance imaging of schizophrenic patients and comparison subjects during word production," *Am. J. Psychiat.* **153**(2), 200–205 (1996).
42. P. G. Nestor et al., "Semantic disturbance in schizophrenia and its relationship to the cognitive neuroscience of attention," *Biol. Psychol.* **57**(1–3), 23–46 (2001).