SPANDIDOS PUBLICATIONS

Visible and near-infrared spectral changes in plasma of psychiatric patients

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Abstract. In the present study, the possible difference in visible and near-infrared (Vis-NIR) spectra of plasma in psychiatric patients compared to healthy control subjects was investigated. Mean Vis-NIR spectra of 60 psychiatric patients showed several specific peaks in the 630- to 930-nm region. Principal component analysis (PCA) and soft independent modeling of class analogy (SIMCA) were applied to manifest the spectral characteristics of each group. The PCA and SIMCA models demonstrated successful discrimination of the two groups using a score plot of the third versus fourth principal component and a Coomans plot, respectively. The PCA loadings were generally consistent with the discriminating power of the SIMCA model, indicating a specific pattern of Vis-NIR spectra in the plasma of psychiatric patients. The specific pattern possibly indicates altered superoxide, amine, and primary and secondary amides in plasma and may provide a possible indicator for the diagnosis of heterogeneous psychiatric disorders. This is the first step toward a clinical tool which has the potential to be applied in the diagnosis of psychiatric disease. Yet, there remain obstacles to its practical usage.

Introduction

Since Engel's theory of a bio-psycho-social model emerged in 1977 (1), descriptions of the clinical state of psychiatric disorders have accumulated. Currently, psychiatric diagnoses have a descriptive nosology, that is, they are based on description rather than cause. This is because we do not yet know the mechanisms by which brain disorders lead to psychiatric illness. In this descriptive classification system, psychiatric disorders are defined by empirical data [Diagnostic and Statistical Manual of Mental Disorders, 4th edition, Text Revision (DSM-IV-TR) (2) and/or 10th revision of the International Classification of Diseases and Related Health Problems (ICD-10) (3)]. Therefore, this system has shaped current psychiatric research. However, recent reports have shown that there are many problems in clarity, logical coherence, factual content, redundancy, and ambiguity with DSM-IV-TR (4) and ICD-10 (5,6). These problems have questioned the diagnostic validity and reliability of these methods and have severely influenced psychiatric research. Therefore, an objective diagnostic method for psychiatric disorders is warranted.

In this study, to test the hypothesis that the plasma of psychiatric patients has specific components, differences in visible and near-infrared (Vis-NIR) spectra of plasma between psychiatric patients and healthy donors were compared. A possible diagnostic method using Vis-NIR spectroscopy was explored by examining the differences in Vis-NIR spectra.

Materials and methods

Sample collection. Plasma samples from 60 psychiatric patients and 60 healthy donors were collected at the Osaka General Medical Center and the Medical Hospital of Osaka City University, respectively. All of the subjects were free of colds at the time of the collection. A venous-blood sample (10 ml) from each subject was obtained from an antecubital vein. All samples were diluted 10-fold with phosphate-buffered saline and adjusted to a constant volume (1 ml) in a polystyrene cuvette (Sarstedt, Aktiengesellschaft, Germany) prior to Vis-NIR spectroscopy. This research project was approved by the Ethics Committee of Osaka General Medical Center and Osaka City University, and written informed consent was obtained from all psychiatric patients and healthy donors.

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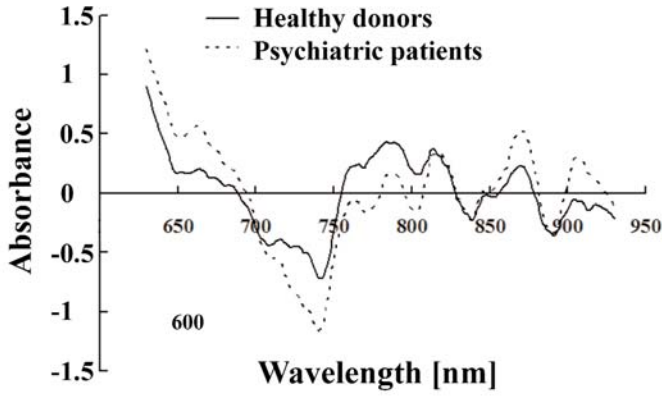


Figure 1. Visible and near-infrared (Vis-NIR) spectra of plasma from psychiatric patients and healthy donors. Transmittance Vis-NIR spectra of plasma from psychiatric patients and healthy donors were collected at wavelengths of 630-930 nm and subjected to smoothing and standard normal variates (SNV) to minimize noise and baseline shifts. The mean spectra of each group (healthy donors, solid line; psychiatric patients, dashed line) are shown.

Instruments, data collection, and data analysis. Vis-NIR spectra were measured at a resolution of 1 nm with an MCPD-7700 (Otsuka Electronics Co., Ltd., Japan). The temperature of the sample box was controlled with a water bath at 25˚C during the Vis-NIR measurements. The spectral data were collected as absorbance values [log (1/T)], where T is the transmittance in the range of wavelengths from 630 to 930 nm. Pirouette software (ver. 3.11; Infometrix, Woodinville, WA) was employed for data processing. To minimize differences between spectra caused by baseline shifts and noise, preprocessing of Vis-NIR spectra, including mean-centering, smoothing (7) and/or standard normal variates (SNV) (8), was applied. The mean spectra of smoothing- and SNV-treated spectra were compared between psychiatric patients and healthy donors. To further identify the predominant absorbance peaks in the spectra, a principal component analysis (PCA) (9) and soft independent modeling of class analogy (SIMCA) (10) were also applied to develop models for the diagnosis of psychiatric disorders. For visualization of the PCA results, PCA score plots, which plot score values of two principal components (PCs), were used. The SIMCA results were visualized with a Coomans plot (11), which plots class distances against each other, to assess the classification performance of the SIMCA model by predicting class membership in terms of distance from the model. The critical distance from the model used corresponded to the 0.05 level and defined a 95% tolerance interval. Through calculations of the PCA and SIMCA, loadings and discriminating power were obtained. The mathematical formulas of PCA, SIMCA, and preprocessing are available in the Pirouette manual. Statistical analyses of correlation and differences were performed by Spearman rank correlation analysis and Kruskal-Wallis test, where p-values <0.05 were considered significant.

Sample information. In PCA and SIMCA analysis, plasma samples from 45 psychiatric patients (50.3±15.3 years of age; male/female, 16/29), diagnosed on the basis of DSM IV-TR, and 45 healthy donors (37.1±10.4 years of age; male/female, 22/23) were used as test samples to develop a calibration model, whereas samples from the other 15 psychiatric patients (45.3±13.8 years of age; male/female, 5/10) and 15 healthy donors (36.3±12.2 years of age; male/female, 5/10) were masked and used for predictions. Psychiatric patients were divided into 13 groups: schizophrenia (33.3%), major depressive disorders (25%), bipolar I disorders (20%), generalized anxiety disorders (3.3%), undifferentiated somatoform disorders (3.3%), dysthymic disorders (3.3%), pain disorder (1.7%), hypochondriasis (1.7%), somatization disorder (1.7%), hypochondriasis with pain disorder (1.7%), posttraumatic stress disorder (1.7%), bipolar I disorder with psychotic features (1.7%) and limbic encephalitis (1.7%).

Results

A total of 120 subjects were examined: 60 subjects with psychiatric disorders (49.1±15.0 years of age; male/female, 21/39) (Table I) and 60 healthy donors (36.9±10.8 years of age; male/female, 27/33). Among the subjects with psychiatric disorders, one patient requested counseling from a clinical psychologist but was not medicated at the time of blood collection. The medications of the other subjects with psychiatric disorders were : major and minor tranquilizers (n=29), minor tranquilizer only (n=5), minor tranquilizer + antidepressant (n=5), major tranquilizer only (n=3), major and minor tranquilizers + antidepressant (n=3), minor tranquilizer + lithium carbonate (n=3), major tranquilizer + antidepressant (n=1), minor tranquilizer + antidepressant + lithium carbonate (n=1), major and minor tranquilizers + antidepressant + lithium carbonate (n=1), major and minor tranquilizers + lithium carbonate (n=1), minor tranquilizer + hormonal agent + vitamins + others (n=1), major and minor tranquiliter + antiphlogistic analgetic (n=1), major and minor tranquilizers + antidepressant + antiphlogistic analgetic + others (n=1), major and minor tranquilizers + antiphlogistic analgetic + muscle relaxtant + others (n=1), major and minor tranquilizers + antiphologistic analgetic + anticoagulant + others (n=1), major and minor tranquilizers + antihypertensive + others (n=1), and hormonal agent (n=1).

As raw Vis-NIR spectra showed noise and a baseline shift, it was difficult to find any significant difference between psychiatric patients and healthy donors. Thus, to minimize noise and baseline shift, Vis-NIR spectra of plasma from psychiatric patients and healthy donors were subjected to smoothing and SNV. Then, mean spectra of the smoothed and SNV-treated spectra were compared between the two groups. Several peaks were found in both groups in the region 630-930 nm, while slight differences were observed between the groups in this region. In particular, there were spectral differences between the groups in the regions 650-675, 720-740, 770-790, 850-875 and 900-925 nm (Fig. 1).

Next, spectra were further subjected to PCA and SIMCA. Clear discrimination of the plasma samples of psychiatric patients from those of healthy donors was noted in PCA scores using the third principal component (PC3) and fourth principal component (PC4) (Fig. 2A). The SIMCA model using test samples also allowed correct separation of Vis-NIR spectra of 43 of 45 (95.6%) healthy donor plasma and

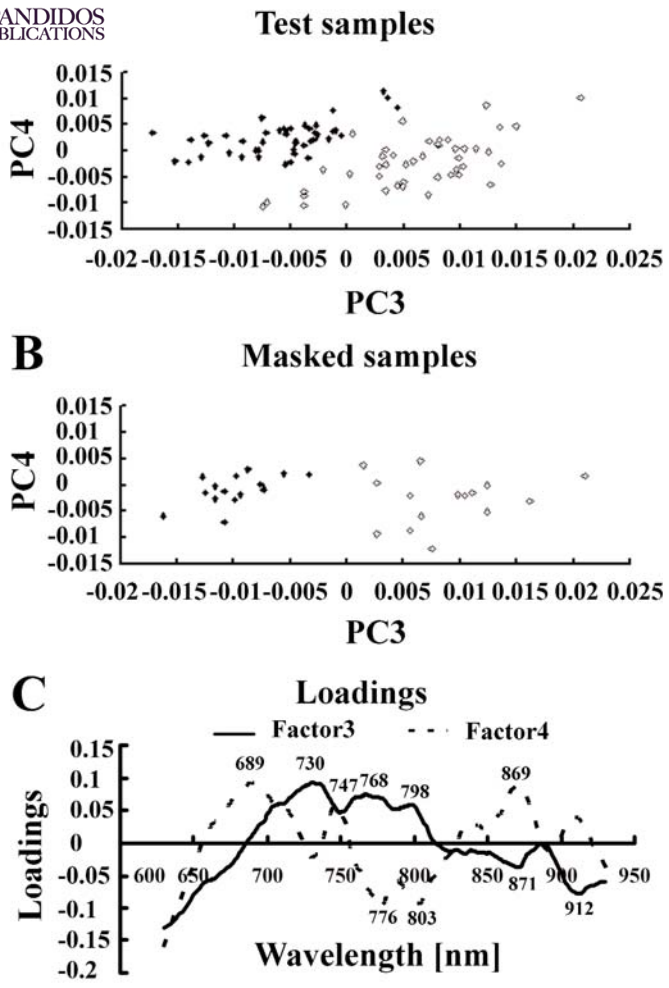


Figure 2. Principal component analysis (PCA) of the Vis-NIR calibration model for test samples and the predictions for masked samples using plasma of psychiatric and healthy donors. Plasma samples from healthy donors and psychiatric patients were subjected to Vis-NIR spectroscopy. After the collection of Vis-NIR spectra of plasma samples, the spectral data were pre-processed by mean centering and smoothing and subjected to PCA calibration modeling to develop a multivariate model to distinguish between healthy donors and psychiatric patients. The PCA score plot of the third principal component (PC3) versus the fourth principal component (PC4) for Vis-NIR spectra of test samples (A) and masked samples (B) from healthy donors and psychiatric patients by the PCA model showed a clear distinction between healthy donors (closed diamonds) and psychiatric patients (open diamonds). (C) PC3 (solid line) and PC4 (dashed line) loadings of the PCA.

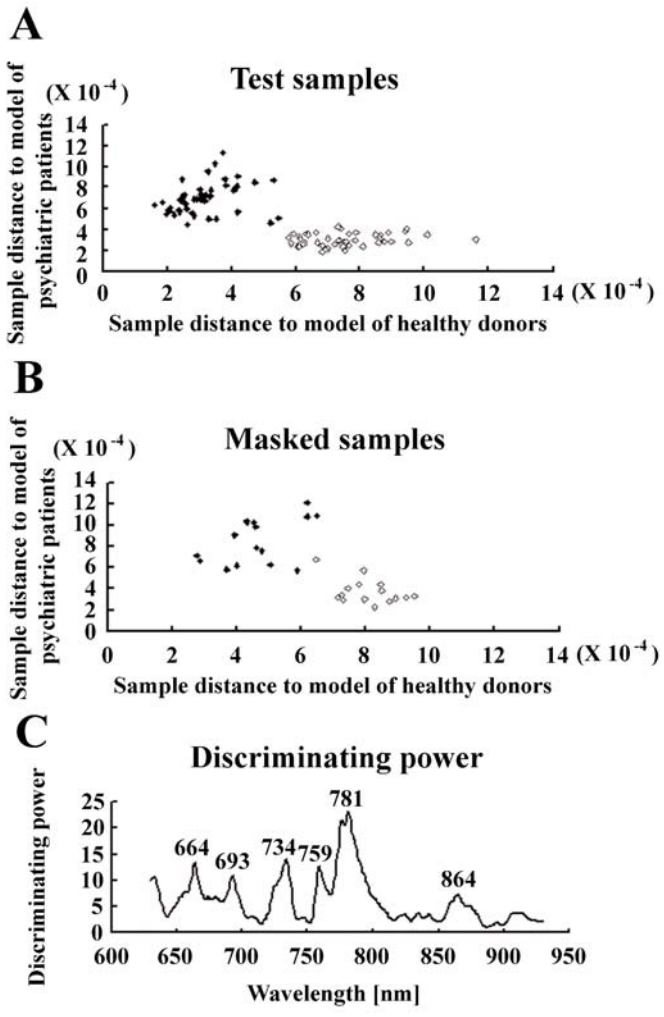


Figure 3. Soft modeling of class analogy (SIMCA) of the Vis-NIR calibration model for test samples and the predictions for masked samples using plasma of psychiatric and healthy donors. Vis-NIR spectral data of plasma samples from healthy donors and psychiatric patients were pre-processed by mean centering and smoothing and subjected to SIMCA calibration modeling to develop a multivariate model to manifest the characteristics of psychiatric patient plasma. A Coomans plot of SIMCA demonstrating that the healthy donor class (closed diamonds) and psychiatric patient class (open diamonds) of test samples (A) and masked samples (B) did not share multivariate space. (C) Discriminating power from the SIMCA calibration model shows several important peaks separating the plasma of psychiatric patients from that of healthy donors.

45 of 45 (100%) psychiatric patient plasma samples (Fig. 3A). SIMCA using the Coomans plot demonstrated that plasma classes from healthy donors and psychiatric patients did not share multivariate space, providing validation for the separation (Fig. 3A). Furthermore, the masked samples were subjected to Vis-NIR spectroscopy and further predictions with the PCA and SIMCA models. Complete discrimination of the masked plasma samples between psychiatric patients and healthy donors was attained using the PCA and SIMCA models of Vis-NIR spectra (Figs. 2B and 3B). PCA showed a clear distinction of the masked samples between healthy donors and psychiatric patients. SIMCA predicted 14 of 15 (93.3%) healthy donors and 14 of 15 (93.3%) psychiatric patients based on Vis-NIR spectra from masked plasma samples. In this model, the effect of medication could be ruled out, because subjects with psychiatric disorders included unmedicated patient but could be clearly separated from healthy donors. Furthermore, the affected period and medication of psychiatric patients did not have any significant correlation with PC3 and PC4 scores or distances of each sample to the model of healthy donors in the Coomans plot (data not shown). These results indicate that drugs and affected periods did not influence the discrimination. On the other hand, it should be mentioned that complications with mental disorders, such as hypertension, diabetes mellitus, cancer, and so on, were not considered.

Using these reliable models, the spectral information modelled by PCA and SIMCA was extracted by the corresponding loadings and discriminating power, respectively. Concerning PC3, the loadings positively peaked at ~730 and 770 nm, negatively peaked at ~870 nm and 910 nm, were slightly high at ~690-810 nm and were slightly low at ~810-

Table I. Clinical characteristics of psyciatric patients (n=60).

Patient no.	Gender	Age (years)	Affected period[b]	Diagnosis	Stage and/or symptoms	Medication[a]									
						Major tranquilizer	Minor tranquilizer	Anti-depressant	Lithium carbonate	Hormonal agent	Vitamins	Antiphlogistic analgetic	Muscle relaxant	Anti-coagulant	Anti-hypertensive
1	F	49	6	Hypochondriasis, Pain disorder	Chronic	-	+	-	-	+	+	-	-	-	-
2	F	30	5	Hypochondriasis	Chronic	+	+	+	-	-	-	+	-	-	-
3	F	41	4yr, 5m	Major depressive disorder	Just after suicide attempt, under tracheotomy	+	+	+	-	-	-	-	-	-	-
4	F	73	7	Bipolar I Disorder	Depressive, insomnia, photophobia	+	+	+	+	-	-	-	-	-	-
5	M	57	36	Major depressive disorder	Remission	+	+	-	-	-	-	-	-	-	-
6	F	29	8	Schizophrenia	Chronic	+	+	-	-	-	-	-	-	-	-
7	M	71	17	Schizophrenia	Chronic	+	+	-	-	-	-	-	-	-	-
8	F	59	35	Schizophrenia	Chronic	+	+	-	-	-	-	-	-	-	-
9	F	43	13	Bipolar I disorder	Remission	+	+	-	-	-	-	-	-	-	-
10	F	29	3yr, 9m	Pain disorder	Chronic	+	+	-	-	-	-	+	+	-	-
11	F	44	8	Schizophrenia	Chronic	+	+	-	-	-	-	+	-	+	-
12	F	46	14	Bipolar I disorder	Flights of fancy	+	+	-	-	-	-	-	-	-	-
13	F	62	9	Undifferentiated somatoform disorder	Chronic	-	-	-	-	+	-	-	-	-	-
14	M	47	18	Bipolar I disorder	Mildly depressed, fatigue, insomnia, loss of concentration	+	+	-	-	-	-	-	-	-	-
15	F	49	8	Bipolar I disorder	Remission	+	+	-	-	-	-	-	-	-	-
16	M	65	21	Bipolar I disorder	Remission	-	+	-	+	-	-	-	-	-	-
17	F	33	2yr, 5m	Generalized anxiety disorder	Chronic, fatigue, myalgia, arthralgia	-	-	-	-	-	-	-	-	-	-
18	F	68	8m	Major depressive disorder	Severely depressed	-	+	+	-	-	-	-	-	-	-
19	F	43	20	Schizophrenia	Chronic	+	+	-	-	-	-	-	-	-	-
20	F	65	22	Bipolar I disorder	Remission	-	+	-	+	-	-	-	-	-	-
21	M	35	2yr, 5m	Schizophrenia	Chronic	+	+	-	-	-	-	-	-	-	-
22	F	35	10	Schizophrenia	Chronic	+	+	-	-	-	-	-	-	-	-
23	M	60	23	Schizophrenia	Remission	+	-	-	-	-	-	-	-	-	-
24	M	65	7	Major depressive disorder	Acute, severely depressed, communication difficulty	+	-	+	-	-	-	-	-	-	-
25	F	72	16	Major depressive disorder	Remission	-	+	+	+	-	-	-	-	-	-
26	M	39	15	Schizophrenia	Chronic	+	+	-	-	-	-	-	-	-	-
27	M	32	13	Schizophrenia	Chronic	+	+	-	-	-	-	-	-	-	-
28	F	30	9	Schizophrenia	Chronic	+	+	-	-	-	-	-	-	-	-
29	M	65	11	Bipolar I disorder	Remission with communication difficulty	+	+	-	-	-	-	-	-	-	-
30	F	72	2m	Generalized anxiety disorder	Remission	-	+	-	-	-	-	-	-	-	-

Table I. Continued.

Patient no.	Gender	Age (years)	Affected period[b]	Diagnosis	Stage and/or symptoms	Medication[a]									
						Major tranquilizer	Minor tranquilizer	Anti-depressant	Lithium carbonate	Hormonal agent	Vitamins	Antiphlogistic analgetic	Muscle relaxant	Anti-coagulant	Anti-hypertensive
31	F	40	5yr, 5m	Schizophrenia	Chronic	+	+	-	-	-	-	-	-	-	-
32	F	70	30	Major depressive disorder	Remission with lightheaded	+	+	-	-	-	-	-	-	-	+
33	M	40	4m	Major depressive disorder	Chronic	+	+	-	-	-	-	-	-	-	-
34	M	48	>25	Schizophrenia	Chronic	+	+	-	-	-	-	-	-	-	-
35	F	72	9	Somatization disorder	Chronic phase with mouth pain during night	-	+	+	-	-	-	-	-	-	-
36	F	55	5yr,10m	Schizophrenia	Remission	+	-	-	-	-	-	-	-	-	-
37	F	37	20	Schizophrenia	Chronic phase with osteomyelitis of left lower extremity	+	+	-	-	-	-	-	-	-	-
38	M	54	23	Schizophrenia	Remission	+	+	-	-	-	-	-	-	-	-
39	F	16	1	Schizophrenia	Almost in remission with difficulty going to school	+	-	-	-	-	-	-	-	-	-
40	M	59	>14	Schizophrenia	Remission	+	+	-	-	-	-	-	-	-	-
41	F	62	4yr, 2m	Dysthymic disorder	Remission with staying indoors	-	+	-	-	-	-	-	-	-	-
42	F	65	33	Major depressive disorder	Remission with anxiety and irritable mood	-	+	+	-	-	-	-	-	-	-
43	M	67	21	Major depressive disorder	Remission with irritable mood	-	+	+	-	-	-	-	-	-	-
44	M	32	10	Schizophrenia	Remission	+	+	-	-	-	-	-	-	-	-
45	F	40	14yr, 4m	Schizophrenia	Chronic	+	+	-	-	-	-	-	-	-	-
46	F	47	13	Bipolar I disorder	Manic	+	+	-	-	-	-	-	-	-	-
47	F	38	11	Bipolar I disorder	Remission	+	+	-	-	-	-	-	-	-	-
48	F	30	23	Major depressive disorder	General malaise	+	+	-	-	-	-	-	-	-	-
49	M	57	18	Major depressive disorder	Remission	-	+	+	-	-	-	-	-	-	-
50	M	58	6	Bipolar I disorder	Mildly manic	+	+	-	-	-	-	-	-	-	-
51	F	19	1yr, 8m	Posttraumatic stress disorder	Chronic	+	+	-	-	-	-	-	-	-	-
52	M	45	1m	Limbic encephalitis	Drowsy	-	+	-	-	-	-	-	-	-	-
53	F	70	8	Major depressive disorder	Mildly depressive	+	+	+	-	-	-	-	-	-	-
54	F	28	2yr, 2m	Undifferentiated somatoform disorder	Chronic	+	+	-	-	-	-	-	-	-	-
55	F	34	>10	Major depressive disorder	Remission	+	+	+	-	-	-	-	-	-	-
56	F	43	35	Major depressive disorder	Remission	+	+	-	-	-	-	+	-	-	-
57	M	43	5	Dysthymic disorder	Remission	-	+	-	-	-	-	-	-	-	-
58	F	43	5	Bipolar I disorder	Remission	+	+	-	+	-	-	-	-	-	-
59	M	40	4	Major depressive disorder	Depressive	-	+	-	-	-	-	-	-	-	-
60	F	69	22	Bipolar I disorder, with psychotic features	Chronic	-	+	-	+	-	-	-	-	-	-

[a]In addition to the prescribed medication, certain patients were medicated with gastrointestinal agents or herbal medicines, while patient no. 17 was never medicated. [b]Year, month.

Table II. Possible assignment of peaks in discriminating power of the SIMCA model.

Wavelength (nm)	Assignment	References
664	Unknown	-
693	4th overtone of superoxide tetrahydrate O_2-.(H_2O)2 (696.8 nm)	(17)
734	OH stretch, 3rd overtone of ROH (738 nm)	(18)
759	N-H stretch, 3rd overtone of amides (secondary, bonded; one band) (750-800 nm)	(19)
	O-H stretch, 3rd overtone of H_2O (760 nm)	(18)
781	N-H stretch, 3rd overtone of RNH_2 (779 nm)	(18)
	N-H stretch, 3rd overtone of amides (primary, ponded; two bonds) (~788 nm)	(19)
864	C-H stretch, 3rd overtone of ArCH. (Aromatics) (857-890 nm)	(19)

890 nm (Fig. 2C). PC4 loadings positively peaked at ~690, 750, 870, and 910 nm, negatively peaked at ~770 and 800 nm, were slightly high at ~ 650-720 and 830-890 nm, and were slightly low at ~760-830 nm (Fig. 2C). The most prominent discriminating power, which represents independent variables (wavelengths) important in discriminating two classes (psychiatric and healthy), were peaks at ~660, 690, 735, 760, 785 and 865 nm (Fig. 3C). The PCA loadings were generally consistent with the discriminating power of the SIMCA model, except for loadings of ~950-nm peaks (Figs. 2C and 3C).

Discussion

Although the knowledge of psychiatric disorders has expanded and the need for research has become increasingly more important after Engel proposed his bio-psycho-social model in 1977 (1), progress in diagnostic procedures in the field of psychiatry has been slower than was hoped. The main reason for this is the biological, environmental and genetic complexity of psychiatric disorders, whose etiologies remain unknown. Recent study has shown the association between a specific allele of the 5' promoter of the serotonin transporter gene and a high risk for developing depression in response to stress, but this represents only the tip of a gigantic iceberg in terms of our understanding of how biological, environmental and genetic factors interact to produce both healthy and psychiatric differences (12). Therefore, presently, a descriptive classification is used for diagnosis, which takes a long time period in which to reach a final decision, resulting in a delay in early treatment intervention.

Recently, the possibility of diagnosing viral infections (13), chronic fatigue syndrome (CFS) (14), and anti-phospholipid antibodies (15) by Vis-NIR spectroscopy combined with multivariate analysis has been reported. Vis-NIR radiation is absorbed due to the combination and overtone of vibrations such as the stretching and bending of hydrogen-bearing functional groups including C-H, N-H and O-H (16), which are included in most biomolecules. Therefore, the spectral change in the Vis-NIR region reflects the change of biomolecules in samples.

The current descriptive method for the diagnosis of psychiatric disorders has not been performed objectively. The findings of this study indicate the possibility of a new objective diagnostic approach using Vis-NIR spectroscopy, since a specific spectral pattern was found in plasma samples of psychiatric patients. The possible band assignment of discriminating power in the SIMCA model suggests that the spectral change is due to altered superoxide (17), amine (18), and primary and secondary amides (19) in plasma (Table II). Recent study has shown that dysfunction of the endocrine system in the hypothalamic-pituitary-adrenal axis is common in psychiatric patients (20). It would be of interest to analyze whether the spectral change observed in this study is related to neuroendocrine mechanisms. Further information obtained from the detailed analysis of Vis-NIR spectra may make significant contributions not only to the diagnosis but also to the understanding of the pathogenesis of psychiatric disorder.

In our previous study, we showed that sera of CFS patients could be distinguished from sera of healthy donors (14). Notably, the peaks distinguishing the CFS patients from healthy donors (14) were different from those discriminating psychiatric patients from healthy donors in the present study. These observations suggest that psychiatric disorders share some factors different from CFS and may provide some additional information on the controversial issue of whether psychiatric disorders are comorbidities of CFS (21,22). Finally, it should be mentioned that instability and low between-run reproducibility of Vis-NIR spectra of liquid samples were sometimes noted. Temperature, water vapor, instrumental noise, and sampling errors would be considered the source of these problems. Therefore, great attention to minimize these factors should be paid during Vis-NIR measurements. Significant improvement to overcome these obstacles is necessary before the practical use of this method in diagnosis.

In conclusion, our findings suggest that plasma of psychiatric patients can be distinguished from that of healthy donors by Vis-NIR spectroscopy. The spectral change observed in psychiatric patients may provide a novel index of psychiatric disorders, suggesting Vis-NIR spectroscopy to be a promising tool with which to objectively diagnose psychiatric disorders. This may contribute to the early medical intervention of psychiatrics disorders; however, there remain obstacles such as the instability of Vis-NIR spectra which need to be addressed before its practical use.

SPANDIDOS PUBLICATIONS **edgements**

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