Residual Symptoms Were Differentially Associated with Brain Function in Remitted Patients with Major Depressive Disorders

Mieko Masai, Shenghong Pu, Katsutoshi Yokoyama, Hiroshi Matsumura, Takehiko Yamanashi, Masashi Itakura, Takuya Sugie, Akihiko Miura, Izumi Nagata, Masaaki Iwata and Koichi Kaneko

Division of Neuropsychiatry, Department of Brain and Neuroscience, School of Medicine, Tottori University Faculty of Medicine, Yonago 683-8503, Japan

ABSTRACT

Background The desirable goals of the treatment of major depressive disorder (MDD) are considered both to achieve symptom remission and to help the patients be restored to their premorbid levels of functioning. Remission has often been defined clinically as a threshold using standardized scales. Such a definition, however, allows several residual symptoms to be present in the remitted state. The aim of this study was to examine the relationship between the levels of residual symptoms and social functioning and also the relationship between residual symptoms and brain function.

Methods The subjects were 21 patients with MDD in remission, defined operationally using clinician-rated 17-item Hamilton Depression Scale. Depressive symptoms and social functioning were self-assessed with the Japanese versions of the Center for Epidemiologic Studies Depression Scale (CES-D) and the Social Adaptation Self-evaluation Scale (SASS), respectively. Brain function was measured by the changes in concentration of oxy-hemoglobin ([oxy-Hb]) in the prefrontal and temporal cortices during verbal fluency task using near-infrared spectroscopy (NIRS).

Results The mean CES-D total score was 18.0, s = 13.2, indicating that they have on average mild depression. Scores of CES-D total and those of its four factors showed a significantly negative correlation with the SASS total score. Among the four factors, "Interpersonal problems" factor showed the strongest correlation with it. CES-D total score and those of its three factors, "Depressed affect", "Somatic and retarded activity" and "Positive affect", showed significantly negative correlations with the mean [oxy-Hb] changes mainly in the left hemisphere, whereas "Interpersonal problems" factor showed a significantly positive correlation with the size of NIRS activation predominantly in right prefrontal regions.

Conclusion Our results indicate that remitted patients with MDD possibly have residual symptoms which are most likely to impair their social functioning and that these symptoms are differentially associated with brain function measured with NIRS.

Key words major depressive disorder; near-infrared spectroscopy; prefrontal cortex; remission; residual symptoms

Major depressive disorder (MDD) is one of the serious health problems worldwide. From a currently prevailing view, MDD is assumed to be of a chronic or recurrent nature with many patients encountering enormous difficulty in achieving full remission.[1] These properties may prevent them from returning to premorbid functioning levels.[2] The desirable goals of its treatment thus are both to achieve symptom remission and to fully recover social functioning. To date, remission has been operationalized, however, in clinical trials as a cut-off score using standardized rating scale. Specifically, a score of 7 or less on the 17-item Hamilton Depression Rating Scale (HAM-D17) typically designates remission.[3] In large prospective study, 28% of the participants achieved remission after initial treatment[4] with lower rates for those requiring subsequent treatment.[5] As regards long-term outcome, patients in remission at follow-up entry were shown to be less likely to relapse than those not in remission.[5]

Although achieving remission is thus a highly recommended goal of the treatment of MDD in order for the patients to return to normal functioning, the serious problem is that patients who are in remission defined operationally do not necessarily achieve full recovery.[6] As such definitions do not require that patients be completely asymptomatic, they may have a varying degree

Corresponding author: Koichi Kaneko, MD, PhD
kaneko@med.tottori-u.ac.jp
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Abbreviations: CES-D, Center for Epidemiologic Studies Depression Scale; "D", group with depression; DLPFC, dorsolateral prefrontal cortex; DMN, default mode network; GAF, Global Assessment of Functioning; HAM-D17, 17-item Hamilton Depression Rating Scale; MDD, major depressive disorder; MINI, the Mini-International Neuropsychiatric Interview; "ND", group without depression; NIRS, near-infrared spectroscopy; PFC, prefrontal cortex; [oxy-Hb], concentration of oxy-hemoglobin; SASS, Social Adaptation Self-evaluation Scale; VFT, verbal fluency task

of residual symptoms. Many clinical studies have shown that the presence of residual symptoms is a strong predictor of relapse.[7–9] Moreover, their presence may prevent even remitted patients from functioning normally. In addition to common symptoms such as low mood and loss of interest, patients with MDD often have as residual symptoms interpersonal difficulties as well, which are usually not used for the diagnosis[10] but may nevertheless seriously hinder social functioning as well. The interpersonal problems have a pivotal role in the perpetuation of depressive symptoms[11] with the efficacy of interpersonal therapy for MDD providing indirect evidence for its role in the maintenance of depression.[12]

In addition to adversely affected mood, MDD is also characterized by impaired cognition.[13] Neuropsychological dysfunction contributes to poor functional outcome[14]: e.g., verbal fluency deficits were found to predict poor functioning. In previous study, we found a positive relationship between the verbal fluency task (VFT)-related hemodynamic responses in the prefrontal regions of MDD patients measured with near-infrared spectroscopy (NIRS) and levels of social functioning.[15] In addition, impaired cognition has been demonstrated irrespective of their current mood even in first-episode patients.[16] These cognitive deficits are thus most likely to persist into the remitted state, and might compromise their social functioning possibly in association with residual symptoms.

We should then address the critical issues of characterizing the clinical and pathophysiological nature of the residual symptoms, which are likely involved in the impaired functioning in a certain portion of remitted MDD patients. Little is known, however, about the relationship in remitted state of MDD between brain dysfunction and residual symptoms. In this pilot cross-sectional study, as the first approach to characterizing the possible relationship of residual symptoms with brain function and social functioning, we performed NIRS measurements during VFT period in MDD patients in operationally defined remission using clinician-assessed HAM-D17.[7] Self-report depressive symptoms were also examined with the Japanese version of the Center for Epidemiologic Studies Depression Scale (CES-D),[17] which is assumed to be the only instrument that assesses interpersonal aspects besides common symptoms. When using VFT as a task, NIRS is approved for application in clinical practice for assisting differential diagnosis of depression in Japan because attenuated VFT-related prefrontal activation in depressed MDD patients is a consistent finding.[15, 18] It is therefore well established that VFT-related NIRS signals are a useful tool for evaluating the pathophysiological aspects of MDD. We hypothesized that, even in remitted MDD patients, certain residual symptoms are associated with impaired psychosocial functioning, and that impaired brain activity in the prefrontal or temporal cortical regions underlies these residual symptoms.

SUBJECTS AND METHODS

Subjects (Table 1)

Twenty-one euthymic patients with MDD (7 males, 14 females) were enrolled in the study after they provided a written informed consent. All the patients were recruited from among the outpatients at Tottori University Hospital. They had been diagnosed with MDD during their clinical course based on the Diagnostic and Statistical Manual of Mental Disorders, fourth edition[19] using the Mini-International Neuropsychiatric Interview (MINI).[20] They were also demonstrated at study initiation to have been in the state of remission for at least one month, defined as a score of seven or less on the HAM-D17[3] evaluated by two trained psychiatrists. None of the subjects had clinical evidence of other central nervous system disorders based on history and medical examination. Patients with previous head trauma, stroke, electroconvulsive therapy, and current or previous history of substance abuse were excluded from the study. All the participants were right-handed by the criterion on the Edinburgh Inventory Index[21] and were native speakers of Japanese. The study was approved by the Ethics Committee of Tottori University Faculty of Medicine and the investigation was carried out in accordance with the latest version of the Declaration of Helsinki.

Clinical Assessment

Prior to NIRS measurement, all the participants self-assessed depression symptom with the Japanese version of the CES-D scale.[17] This scale consists of twenty questions which measure depressive symptomatology during the past week. Respondents rate the frequency of occurrence of each symptom on a 4-point Likert scale (0: less than 1 day; 1: last for 1–2 days; 2: last for 3–4 days; and 3: last for 5–7 days). The scores for each item can be summed to give a total score ranging from 0 to 60 with higher scores indicating more severe depression. Based on the total score, patients can be categorized as having mild depression (score 16 to 26) or major depression (score 27 to 60). The CES-D has been shown to consist of four factors, namely "Depressed affect", "Positive affect", "Somatic and retarded activity" and "Interpersonal problems".[22]

All the subjects also self-assessed the Japanese version of social functioning with the Social Adaptation Self-Evaluation Scale (SASS), which is a 21-item scale developed for the evaluation of patients' social functioning by Bosc

et al.[23]; the reliability and validity of the Japanese version have been confirmed.[24] Levels of social functioning were also objectively evaluated with Global Assessment of Functioning (GAF) scale by a trained psychiatrist.

Activation task

The task procedure in this study was similar to that of Takizawa et al.[25] The changes in concentration of oxyhemoglobin ([oxy-Hb]) were measured during VFT (letter version). Each subject sat on a comfortable chair and was instructed to minimize movement during the NIRS measurements so as to avoid artifacts. The activation task included a 30-s pre-task baseline, a 60-s VFT and a 70-s post-task baseline. For the two baseline periods, the subjects repeat the five Japanese vowels ("a", "i", "u", "e", "o") aloud. The subtraction method (task minus pre- and post-task baseline) minimized the vocalization effects during VFT. During VFT period, they were instructed to generate as many Japanese words beginning with a designated syllable as possible. The three sets of initial syllables (A; /to/, /se/, /o/, B; /a/, /ki/, /ha/, C; /na/, /i/, /ta/) were presented in counterbalanced order among the subjects and each syllable changed every 20 s during the 60-s task. The total number of correct words generated was adopted as a measure of performance.

NIRS measurements

The 52-channel NIRS machine (ETG-4000; Hitachi Medical, Tokyo, Japan) measures relative changes in [oxy-Hb] and concentration of deoxy-hemoglobin using two wavelengths (695 and 830 nm) of infrared light based on the modified Lambert-Beer law. In this continuous-wave NIRS system, these [Hb] values include a differential pathlength factor; therefore, the unit of NIRS measurement is mM·mm. The distance between pairs of source detector probes was set at 3.0 cm and each measuring area between them was defined as 'channel'. It is considered that the machine measures the surface regions of the cerebral cortex.[26] The probes of the NIRS machine were placed on a subject's fronto-temporal region with the mid column of the probe located over Fpz, and the lowest probes are located along the T3–Fp1–Fpz–Fp2–T4 line in accordance with the international 10/20 system used in electroencephalography. Their arrangement enabled the measurement of concentration of hemoglobin values from bilateral prefrontal and superior temporal cortical surface regions. The correspondence between the NIRS channels and the measurement points on the cerebral cortex was confirmed by the previous study that performed simultaneous recording of NIRS and functional magnetic resonance imaging.[27] The sampling rate was 0.1 s. The obtained data were analyzed using the "integral mode"; the pre-task baseline was determined as the mean over a 10-s period prior to the VFT period, and the post-task baseline as the mean over the last 5 s of the post-task period.

Statistical analysis

When making a comparison of SASS total score between the two groups of differing CES-D total score (0–15, the group without depression, termed as "ND" vs. 16–60, the group with depression, termed as "D"), Student's *t*-test was performed. Additionally, we investigated the relationships between these clinical or psychosocial variables using Spearman's ρ because the scores of CES-D total and individual factors did not show normal distribution.

We then tested the relationships between the clinical variables and the mean [oxy-Hb] change during the VFT period for each channel. The clinical and psychosocial variables assessed were as follows: HAM-D17, CES-D, SASS and GAF. As regards CES-D, each score of its four factors were tested for its correlation with the mean task-related [oxy-Hb] change as well as the total score. We investigated these relationships using Spearman's ρ as well.

All the statistical analyses were performed using SPSS 21.0 software. A P value of < 0.05 was considered statistically significant. The multiplicity of the correlation analyses including NIRS data from 52 channels was not corrected, and the results should therefore be taken as exploratory.

RESULTS

Demographic and clinical data of patients in remission

Table 1 summarizes demographic characteristics and clinician-rated severity (HAM-D17) of depressive symptom in the remitted MDD patients. Only patients with HAM-D17 score of 7 or less for more than one month were eligible for the present study.

Residual depressive symptoms and social functioning

Table 2 summarizes self-report severity of depression symptom (CES-D), self- and clinician-rated social functioning, SASS and GAF, respectively and task performance on the VFT. In MDD patients who were operationally classified as being in the state of remission, the mean CES-D total score was 18.0, s = 13.2, indicating that the self-report severity of residual symptoms in this sample were yet in the range of mild depression on average. The numbers of the participants classified into each

Table 1. Clinical and demographic characteristics of the remitted patients with MDD

	Remitted MDD patients (n = 21)
Age (years old)	59.4 ± 12.0 (32–81)
Gender (male/female)	7/14
Education (years)	12.3 ± 2.1 (9–16)
Estimated premorbid IQ	101.9 ± 15.0 (73–120)
HAM-D17 total score	2.8 ± 2.5 (0–7)
Medication	
Imipramine equivalent dose (mg/day)	85.7 ± 71.5 (0–300)

Values are expressed as mean ± s (range).
HAM-D17, 17-item Hamilton Depression Rating Scale; IQ, intelligence quotient; MDD, major depressive disorder.

Table 2. Self-assessed residual symptoms, social functioning and task performance

	Remitted MDD patients (n = 21)
CES-D total	18.0 ± 13.2 (0–47)
Depressed affect	4.4 ± 5.2 (0–17)
Somatic and retarded activity	4.8 ± 4.6 (0–14)
Interpersonal problems	1.0 ± 1.6 (0–6)
Positive affect	7.8 ± 3.7 (0–12)
SASS	34.1 ± 10.1 (18–56)
GAF	80.3 ± 9.8 (61–100)
VFT performance (words generated)	12.3 ± 4.0 (5–18)

Values are expressed as mean ± s (range).
CES-D, The Center for Epidemiologic Studies Depression Scale; GAF, Global Assessment of Functioning; MDD, major depressive disorder; SASS, Social Adaptation Self-Evaluation Scale; VFT, verbal fluency task.

of the two categories of mood state were as follows: i) twelve in "ND" (range of CES-D total score, 0–15) and ii) nine in "D" (16–60). Any combination of two factors within CES-D scale showed a significant, positive correlation between one another (ρ = 0.45 to 0.88, P = 0.00001 to 0.02).

Relationships between severity of residual symptoms and degrees of psychosocial impairment (Table 3)

When subdividing the participants into the two subgroups based on the CES-D total score, that is, "ND" (0–15) and "D" (16–60), SASS total score was significantly higher in "ND" than in "D" ("ND", mean 40.5, s = 7.7 vs. "D", mean 30.4, s = 8.6, $P < 0.05$). In contrast, GAF scores of the two groups were of similar levels ("ND", mean 83.3, s = 7.5 vs. "D", mean 76.2, s = 11.5, P = 0.13).

Table 3. Correlational analyses between severity of depression and social functioning

Severity of depressive symptoms	Social functioning	
	SASS	GAF
CES-D total	–0.57*	–0.42
Depressed affect	–0.54**	–0.45*
Somatic and retarded activity	–0.63***	–0.25
Interpersonal problems	–0.65***	–0.70****
Positive affect	–0.51*	–0.50*
HAM-D17 total	–0.45*	–0.54*

Values are expressed as Spearman's ρ.
*$P < 0.05$, **$P < 0.01$, ***$P < 0.005$, ****$P < 0.001$.
CES-D, Center for Epidemiologic Studies Depression Scale; GAF, Global Assessment of Functioning; HAM-D17, 17-item Hamilton Depression Rating Scale; SASS, Social Adaptation Self-Evaluation Scale.

Levels of self-assessed residual symptoms were correlated with those of SASS (Table 3): Scores of the CES-D total and of any of its individual factors showed a significant negative correlation with the SASS total score. Among these factors, "Interpersonal problems" factor showed the strongest correlation with the SASS total score. In contrast, CES-D total score merely indicated a trend towards a correlation with clinician-rated GAF score (ρ = –0.42, P = 0.06). Of its four factors, levels of three factors were significantly negatively correlated with the GAF score with "Interpersonal problems" factor again showing the strongest association (Table 3). HAM-D17 total score was also significantly correlated with either scale for social functioning, although with much smaller significance compared with most individual factors of CES-D (Table 3).

Cognitive task-related changes in [oxy-Hb] changes

The mean VFT-related [oxy-Hb] changes averaged across 11 channels in the prefrontal region was 0.03, s = 0.06 (in mM·mm) in the remitted MDD patients group (n = 21). Those values averaged across 10 channels each in the left and right temporal regions were 0.07, s = 0.10 and 0.08, s = 0.10, respectively.

The mean VFT-related [oxy-Hb] changes in the prefrontal region were roughly comparable when classifying the subjects into two subgroups, "ND" and "D", whereas those in the bilateral temporal regions showed

a trend to be larger in "ND" than in "D" : i) prefrontal region; "ND", mean 0.03, s = 0.05 vs. "D", mean 0.02, s = 0.06, P = 0.92, ii) right temporal region; "ND", mean 0.11, s = 0.10 vs. "D", mean 0.05, s = 0.09, P = 0.14, iii) left temporal region, "ND", mean 0.11, s = 0.09 vs. "D", mean 0.03, s = 0.08, P = 0.06.

Relationship between VFT-related [oxy-Hb] changes and demographic and clinical variables.

In remitted patients, the mean task-related [oxy-Hb] changes were not significantly correlated with any of demographic variables except for a negative correlation with imipramine-equivalent doses in four channels: ch15, ch25, ch36 and ch48. The hemodynamic responses were not correlated with clinician-rated HAM-D total scores either except for single channel 33 (ch33). On the other hand, scores of CES-D total and its two factors showed significantly negative correlations with the responses at multiple channels mainly in the left hemisphere: CES-D total in two channels (ch41 and ch52; ρ = –0.50 and –0.45, respectively; P = 0.03 to 0.04); "Depressed affect" in three channels (Fig. 1A and 1C; ch31, ch41 and ch52; ρ = –0.53 to –0.48; P = 0.01 to 0.03); "Somatic and retarded activity" in five channels (ch31, ch34, ch41, ch44 and ch52; ρ = –0.60 to –0.44; P = 0.01 to 0.05). In contrast, "Interpersonal problems" showed a positive correlation with the NIRS activation in five channels located in the bilateral prefrontal regions (Figs. 1A and 1B; ch14, ch17, ch35, ch36 and ch47; ρ = 0.49 to 0.55; P = 0.01 to 0.02). Among the channels whose hemodynamic responses were likely affected by medication, only ch36 was related to the severity of residual symptoms with the responses there being positively associated exclusively with "Interpersonal problems" factor. Medication dose, however, did not show any correlation with the levels of this factor at all (ρ = 0.10, P = 0.66), excluding the possibility that medication mediated the close association between the brain activation and the symptom severity.

The distribution pattern of the NIRS channels correlated with the symptom severity indicated differential associations of distinct self-assessed residual symptoms

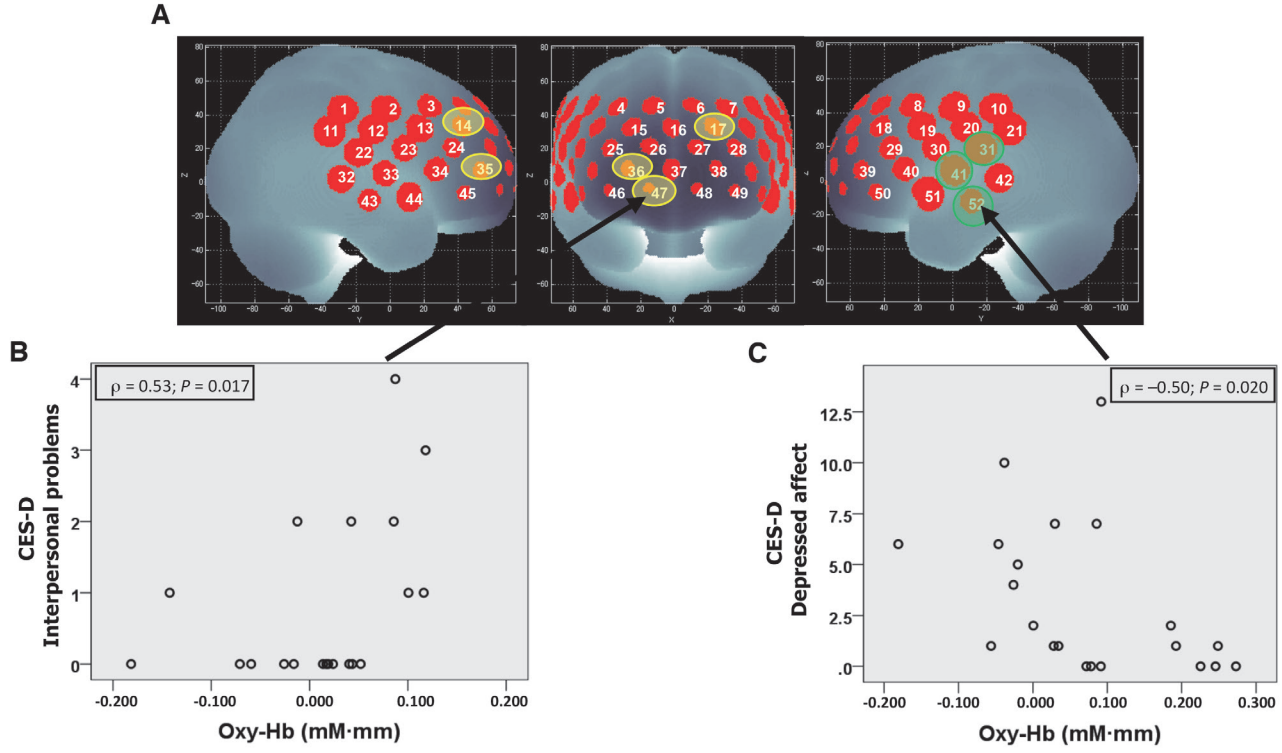

Fig. 1. Relationship between the amount of VFT-related [oxy-Hb] changes and severity of self-report residual symptoms in remitted patients with MDD. **A**: The brain regions depicted in yellow and green correspond to the NIRS channels that exhibited a significant positive correlation (Spearman's rank-order correlation; P < 0.05) between the degrees of NIRS activation and scores of "Interpersonal problems" (yellow) and "Depressed affect", respectively, factors of CES-D. **B**: Representative scatter diagram at channel 47 (right orbitofrontal and frontopolar cortical regions; Spearman's rank correlation; ρ = 0.53 and P = 0.017). **C**: Representative scatter diagram at channel 52 (left superior and middle temporal cortical regions; Spearman's rank correlation; ρ = –0.50 and P = 0.020). The location of NIRS channels were estimated and labeled anatomically in the standard brain space in accordance with Sato et al.[27]
CES-D, Center for Epidemiologic Studies Depression Scale; MDD, major depressive disorder; NIRS, near-infrared spectroscopy; [oxy-Hb], concentration of oxy-hemoglobin; VFT, verbal fluency task.

of MDD with task-related brain activation in the cortical regions: i) CES-D total, "Depressed affect" and "Somatic and retarded activity" factors predominantly in left temporal and ventrolateral prefrontal regions and ii) "Interpersonal problems" factor mainly in right dorsolateral, orbitofrontal and frontopolar prefrontal regions. There was no overlap in the distribution of the correlated NIRS channels between these two symptom groups.

DISCUSSION

The present study showed that MDD patients presumed to be in the state of symptom remission defined as a score of seven or less on the clinician-rated HAM-D17 nevertheless self-reported a mild level of residual symptoms on the CES-D scale on average, and that the severity of the residual symptoms was negatively correlated with levels of social functioning self-rated with SASS. Moreover, VFT-related hemodynamic responses measured with NIRS revealed differential associations between the distinct residual symptoms and the hemodynamic responses in different brain regions. Specifically, scores of CES-D total and of its two factors, "Depressed affect" and "Somatic and retarded activity", were negatively correlated with the activation chiefly in the left temporal regions, whereas the relationship was somewhat reverse for "Interpersonal problems", that is, positive correlations in the multiple prefrontal subregions. These findings indicate that residual symptoms may compromise levels of social functioning even in a certain subpopulation of patients in operationally defined remission, and that the residual symptoms were possibly linked with dysfunctional task-related neuronal activation in the prefrontal and temporal cortical regions.

Although remission is commonly defined using cut-off score on a rating scale for depressive symptoms,[3],defining it this way has been shown to not identify a relatively homogeneous group of patients as for morbidity and functioning. Judd et al.[8] have found that remitted MDD patients with residual symptoms were at greater risk for relapse and had more severe psychosocial impairment than those without them. Participants of the present study were also found to be rightly subdivided into two subgroups based on the CES-D total score, which may be justified on the grounds of clear negative correlation between residual symptoms and of self-rated social functioning. Such associations were also observed for any of the four factors of CES-D with "Interpersonal problems" factor exhibiting much stronger association than the other factors representing common depressive symptoms. "Interpersonal problems" factor is made up of the two items, "people were unfriendly" and "I felt that people dislike me", both of which may be rightly interpreted to examine the aspect of interpersonal sensitivity[28] or rejection sensitivity[29] in depression. Importantly, interpersonal life events have been shown to predict persistence of depressive symptoms in MDD patients.[30] The present finding thus indicated the importance of evaluating this crucial aspect even in remitted patients when considering the likely impairment in psychosocial functioning due to relationship problems, although the items that tap into this aspect have not been included in the common rating scale, and thus not been routinely examined in the clinical practices. However, it should also be borne in mind that rejection sensitivity may be trait-dependent rather than state-dependent.

As regards the cross-sectional relationship between the self-report residual symptoms (CES-D) and the [oxy-Hb] activation in the remitted MDD patients, NIRS measurements during VFT task period revealed differential associations between the distinct residual symptoms of depression and brain activations in the fronto-temporal cortical regions: scores of CES-D "Interpersonal problems" factor were *positively* correlated with the extent of the activation predominantly in the *right* prefrontal cortex (PFC), whereas those of "Somatic and retarded activity" and "Depressed affect" factors were *negatively* correlated with it mainly in the *left* temporal cortex. These distinct cortical distributions of the associated channels were such that there was not a partial overlap in these channels between the two groups of residual symptoms. This apparent lack of overlap in the distribution of the correlated channels suggests the possible involvements of distinct neural networks in the persistence of different class of residual symptoms into the remitted state. As the amount of mean task-related [oxy-Hb] changes in the remitted MDD patients in this study was of a comparable level to that of patients in current depression, which we previously examined in similar research settings,[15, 31, 32] the patients in this study may well be considered to be associated with more attenuated activation than healthy population. These results, taken together, suggest that, even in remitted patients, residual symptoms are related to dysfunction of frontal and/or temporal cortices, although causal relationship cannot be determined due to the cross-sectional nature of this study. As the physiological dysfunction in the PFC in MDD patients with ongoing symptoms has been increasingly clarified by functional neuroimaging studies,[33–35] our results suggest that such dysfunction persist into the remitted state. As for currently depressed patients, many cross-sectional studies, however, failed to find their association when generally assessing symptom severity with total score of HAM-D17.[15, 36, 37] By contrast, using self-assessed CES-D scale and its four factors,[22] the

present study indicated possible associations between symptom severity and pathophysiological responses in a remitted MDD sample, although the distribution of correlated regions exhibited a rather complex pattern. The temporal and ventrolateral cortical regions in the left hemisphere associated negatively with the two factors, "Somatic and retarded activity" and "Depressed affect", topographically overlapped to some extent. This finding suggests the possibility of shared pathophysiology of these two classes of residual symptoms. Similar associations were previously shown in these brain regions of MDD patients with ongoing depression as for "Psychomotor retardation" item on the HAM-D scale.[35] In this context, it is noteworthy that a meta-analytic study by Fitzgerald et al.[38] demonstrated dysfunctional activity at rest of superior and middle temporal gyri and ventrolateral cortex in MDD patients. This might support the aforementioned idea of the persistence of pathophysiology underlying current depression into remitted state. On the other hand, "Interpersonal problems" factor were positively associated with the activation in wide regions of the PFC including dorsolateral prefrontal cortex (DLPFC), frontopolar PFC and orbitofrontal PFC. Two possible mechanisms are suggested to be involved in this observation. First, impaired DLPFC function may have a role for its inefficient activation. Recent studies suggest that DLPFC-mediated cognitive control may pertain to the regulation of negative emotion through reappraisal.[39] Considering the coexistence of "Interpersonal problems" and "Depressed affect" in certain remitted patients as suggested by a strong association between these symptoms, regulation of negative emotion, such as rejection sensitivity, by the DLPFC was likely to just partially work despite its greater activation. Second, reduced deactivation of the prefrontal network functionally related to social relationships may be associated with rejection sensitivity. As rejection sensitivity is known to predict increased depressive rumination,[29] which is defined as repetitive self-focused brooding, elevated scores of "Interpersonal problems" factor might reflect ongoing ruminative thinking in certain MDD patients. Recently it has been shown that the brain's default mode network (DMN), whose normal activity is mostly correlated in the resting state and suppressed by external task requirements,[40] is closely involved in the pathophysiology of depressive rumination.[41, 42] DMN consists mainly of medial frontal structures, which appears to make it difficult for NIRS to directly measure its activity. Sasai et al.[43] have demonstrated, however, that [oxy-Hb] changes measured with NIRS in the ventral prefrontal region partly reflect correlated activity of DMN. Attenuated suppression of DMN by VFT might thus partly contribute to the observed association. As the attenuation is a possible predictor of relapse,[44] symptoms resulting from dysfunctional DMN might be of a clinical importance. Longitudinal studies are required to investigate the predictability of outcome by symptoms representing impaired social relationships in remitted MDD patients.

Finally, the current study has a number of limitations. First, the sample size of the present study was relatively small, which implies that our findings may not be generalizable to the broader population. Second, we did not make a direct comparison of the size of brain activation between our remitted MDD sample and those with current depression. However, our previous findings on currently depressed patients indicate the comparable size of the activation for the two groups.[15, 31, 32] Third, the effects of multiple comparison tests were not considered in the correlation analyses, indicating that the findings are at best explorative. Finally, the cross-sectional design of this study was not intended to resolve the causal relationship between residual symptoms of depression and hemodynamic responses assessed with NIRS. This design also prevented us from determining whether residual symptoms, "Interpersonal problems" factor in particular, are best recognized as trait or state dependent. Future longitudinal studies of the relationships between changes in NIRS data and those in residual symptoms should be undertaken to address these problems.

In conclusion, a subpopulation of MDD patients in remission operationally defined with a threshold using HAM-D17 self-reported several residual symptoms of depression, the degrees of which were found to be positively correlated with the levels of self-assessed social functioning. In addition these symptoms were suggested to be differentially associated with dysfunction of cortical regions.

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