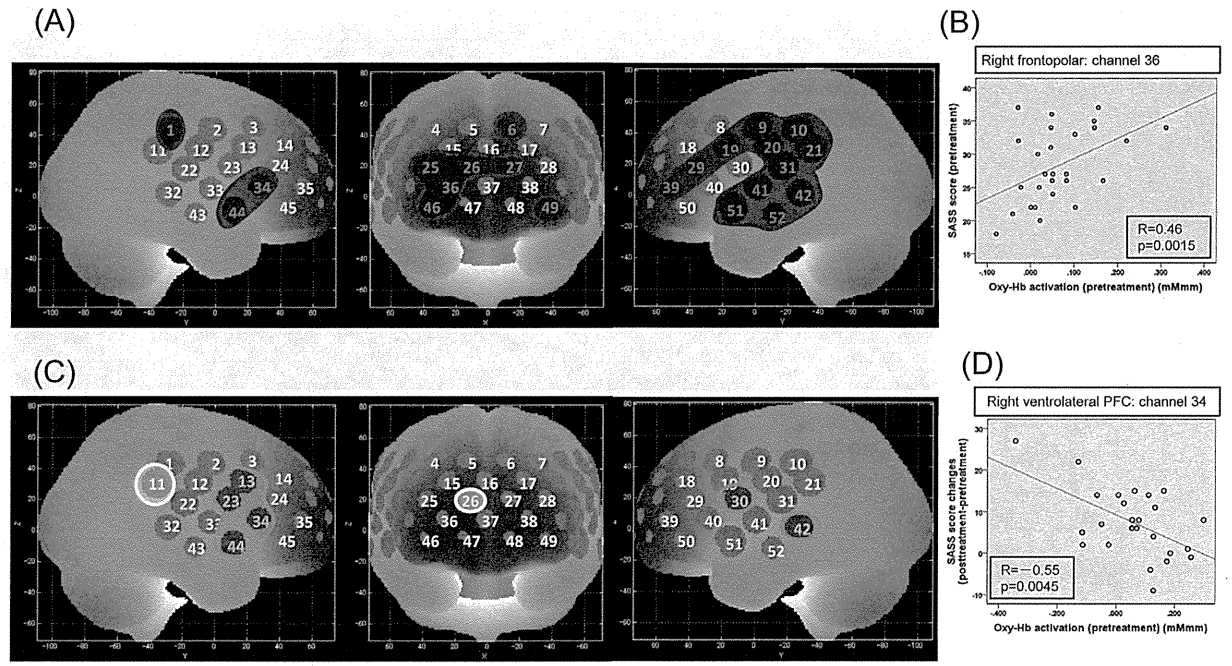

Fig. 5. Relationship between pretreatment NIRS activation and pretreatment SASS score, degree of improvement in the SASS score (posttreatment-pretreatment) in patients with LOD. (A) The brain areas indicated in blue correspond to the NIRS channels that exhibited a significant correlation (Pearson's product moment correlation; $p < 0.05$) between pretreatment NIRS activation and pretreatment SASS score. (B) Scatter diagram at channel 36 (right frontopolar; Pearson's product moment correlation; $R = 0.46$ and $p = 0.0015$). (C) The brain areas indicated in yellow and green correspond to the NIRS channels that exhibited a significant correlation (Pearson's product moment correlation; $p < 0.05$) between pretreatment NIRS activation and degree of improvement in the SASS score (posttreatment-pretreatment). Of these 8 (yellow and green) nominally significant correlations, 6 (green) were still (nominally) significant after correction for baseline SASS values. (D) Scatter diagram at channel 34 (right ventrolateral PFC; Pearson's product moment correlation; $r = -0.55$ and $p = 0.0045$). The locations of NIRS channels were estimated probabilistically and labeled anatomically in the standard brain space in accordance with Tsuzuki et al. (2007).

correlated with social functioning in untreated patients with LOD, but also predicted the treatment response. However, the relationship was somewhat reverse; increased NIRS activation in the PFC was related to higher social functioning but predicted decreased improvement in social functioning after 8 weeks of treatment.

In agreement with our previous study (Pu et al., 2008), we found a cross-sectional relationship between brain activity in the frontopolar, dorsolateral PFC and social functioning. Social functioning requires complex operations of executive function that include monitoring, reasoning, organizing, selecting, and planning. Burgess et al. (2000) noted that the frontopolar region is involved in high-level executive control and, thus, is likely to be a vital component of social functioning. Moreover, the dorsolateral PFC has primarily been associated with cognitive or executive functions, such as the maintenance and manipulation of items, working memory, intention formation, goal-directed action, abstract reasoning, and attentional control (Miller and Cohen, 2001). Considering these observations, it may be reasonable to postulate that the hemodynamic response observed in these areas during the VFT in the present study was associated with social functioning level.

The area where the pretreatment NIRS activation showed negative correlation with the improvement in social functioning was mainly the right ventrolateral PFC, which did not overlap so much with the area that showed cross-sectional positive relationship with the SASS score. It has been suggested that the cerebral blood flow and metabolism in the ventrolateral PFC at rest are abnormally increased in unmedicated patients with depression (Baxter et al., 1987; Biver et al., 1994; Cohen et al., 1992; Drevets et al., 1992). However, a complex relationship exists between depression severity and physiologic activity in the ventrolateral PFC. Although physiologic activity in the area is elevated in the depressed phase, the activity correlates inversely with depression severity (Drevets et al., 1992). Also, physiologic activity in the area is increased in outpatient, treatment-responsive patients but not in more severely ill or treatment-refractory patients with depression. The patients that gained better response by the treatment in the present study showed lower pretreatment NIRS activation in the ventrolateral PFC, which may have been due to the relatively higher pre-task baseline activation causing the "ceiling effect" than those who showed poor treatment response.

There have been only few studies that investigated whether NIRS methodology may be useful for predicting the treatment response in patients with depression. Eschweiler et al. (2000) have reported that pretreatment NIRS is useful for predicting the effects of depression treatment (improvement in depression status), although they did not predict the degree of social functioning improvement. They found a negative correlation between the improvements in depression symptoms by magnetic stimulation and pretreatment NIRS activation in the left PFC region during a mirror-drawing task, which is similar to the results of our study, indicating that the chance of improvement is better in those with initially lower pretreatment NIRS activation in the PFC region. On the contrary, in a study by Mimura et al. (2005), a negative correlation was seen between pretreatment NIRS activation in the right PFC and post-treatment HAM-D scores, suggesting that the chance of an improvement in the depression symptoms was better in those with higher NIRS activation in the right temporal area (ch43). In the study by Mimura et al. (2005), better post-treatment depression severity, but not improvement, was seen in individuals with higher NIRS activation during the VFT, which was contradictory to our results. However, the sample size was extremely small ($n = 7$) and the brain area of the NIRS activation that predicted better post-treatment depression severity in the study was different from the area indicated in the present study, and also they did not use the

degree of improvement as the treatment outcome. Another possible reason may be the difference in the treatment subjects between their study (young-and middle-age-onset depression) and ours (LOD); it is possible that the implications of the pretreatment NIRS findings differ in different age groups. When analyzing the NIRS data of depression, it may be important to consider differences in the age groups, including those with young- and middle-age-onset depression and those with LOD because the pathophysiology of the illness may differ depending on the age groups. According to Alexopoulos (1989), there are differences in various aspects, such as genetic causes, organic abnormalities in the brain, treatment resistance, and persistence, depending on the initial onset age of the patients, even if they all suffer from LOD. Because differences in etiology, pathology, symptoms, and prognosis have been reported to be caused by differences in the initial onset age, it is also important to conduct analyses by carefully taking the age of initial onset into consideration.

The above two studies focused on severity of depression symptoms as the treatment outcome. In the present study, we adopted the social functioning level as one of the outcomes and found that the pretreatment NIRS activation was related to improvement in social functioning but not in depression severity. In real-world clinical settings, treatment of patients with depression not only focuses on improving depression symptoms but also considers improving and recovering social functioning. Social functioning is defined as the ability to fulfill a role in a relationship with a partner and family and to engage in work and social activities among mutual interactions of the environment and the individual. It has been suggested that depression severity and levels of social functioning are not always closely associated. According to Bosc (2000) and Keller et al. (2000), depression symptoms do not necessarily coincide with social functioning when one is recovering from depression, and, according to Hirschfeld et al. (2002), the social functioning disorder remains despite the improvements in the depression symptoms, suggesting that the recovery periods for the depression symptoms and social functioning are different. Kennedy et al. (2007) suggests that residual symptomatology of depression after remission, as well as sustained neurocognitive deficits, may lead to enduring social functioning disorder. According to our previous study, we assumed that pretreatment activity in the PFC associated with verbal fluency task is related to both pretreatment and degree of improvement in social functioning but not depression severity in patients with LOD. We should await further studies using multivariate analysis including independent variables such as depression severity, cognitive function and social functioning to reach a conclusion about the relationship between these factors and NIRS activation. In any way, taking into consideration the capital importance of social functioning improvements in depression treatment, not only the improvement of depression status but also the improvement and recovery of social functioning should be considered more in evaluating the responsiveness of depression treatment.

Finally, there were a number of limitations in the present study. First, the second evaluation was conducted 8 weeks after the initiation of treatment; this was probably too short a period for evaluating the response to treatment, especially in terms of social functioning. In the future, it is important to analyze the long-term treatment response at 3 months, 6 months, and 1 year after the initiation of treatment. Second, NIRS data was measured only at the initial examination of the untreated patients and not at the post-treatment time point. In the future, we plan on conducting long-term longitudinal analyses of NIRS data at 3 months, 6 months, and 1 year after the start of treatment and analyzing whether the depression-related hypoactivation that is observed at the initial examination is improved in a state-dependent manner. Third, the effects of multiple tests were not taken into account in the correlation analyses, and thus, the findings are at best explorative. Future studies with a larger sample size should be undertaken taking into consideration this matter.

The present study indicated a correlation between the degree of improvement in social functioning due to 8 weeks of treatment and pretreatment NIRS activation in the right ventrolateral PFC region. The pretreatment NIRS activation not only correlated with social functioning in untreated patients with LOD, but also predicted the treatment response in social functioning. Although NIRS is not without several disadvantages, it is an active brain function imaging technique that can be performed quickly and noninvasively in the outpatient ward. Thus, it is considered to have a high clinical utility, especially for elderly patients.

5. Conclusion

We investigated whether the response to medical treatment of untreated patients with LOD, particularly social functioning improvements, could be predicted by NIRS findings in the initial examination. We found that pretreatment NIRS activation in the right ventrolateral PFC was associated with the improvements in social functioning. NIRS is a relatively simple method that may be used before treatment to evaluate the social functioning levels of patients with LOD, and may predict social functioning improvement after treatment.

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Contributors

1. Conception and design, or acquisition of data, analysis and interpretation of data (Shenghong Pu, Kazuyuki Nakagome, Takeshi Yamada, Katsutoshi Yokoyama, Hiroshi Matsumura, Izumi Nagata, Koichi Kaneko).
2. Drafting the article or revising it critically for important intellectual content (Shenghong Pu, Kazuyuki Nakagome, Takeshi Yamada, Katsutoshi Yokoyama, Hiroshi Matsumura, Izumi Nagata, Koichi Kaneko).
3. Final approval of the version to be published (Shenghong Pu, Kazuyuki Nakagome, Takeshi Yamada, Katsutoshi Yokoyama, Hiroshi Matsumura, Izumi Nagata, Koichi Kaneko).

Conflict of interest

All the authors declare that they have no conflicts of interest with respect to this study or its publication.

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Research report

Association between social functioning and prefrontal hemodynamic responses in elderly adults

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HIGHLIGHTS

- Prefrontal hemodynamic responses and social functioning in elderly adults was studied.
- Hemodynamic responses measured by near-infrared spectroscopy during verbal fluency task.
- Social functioning assessed using social adaptation self-evaluation scale (SASS).
- Prefrontal cortical activation is associated with the SASS total score.
- NIRS might prove to be a useful biological marker for social functioning in elderly adults.

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ABSTRACT

Social functioning has received widespread attention as one of the most important outcomes in psychiatric disorders and has been related to cognitive functioning and the underlying brain activity. Cognitive decline, however, appears not only in the psychiatric population but also in aged individuals. In our previous study, we demonstrated a significant relationship between social functioning and prefrontal cortex (PFC) activity in patients with depression. However, it has not been shown whether the above relationship could be extended to healthy populations. The purpose of the present study was to investigate a possible association between social functioning and prefrontal hemodynamic responses in healthy elderly adults by using a non-invasive and low-constraint functional neuroimaging technique, near-infrared spectroscopy (NIRS). Study subjects included 55 healthy, elderly volunteers. We measured hemodynamic responses over prefrontal cortical (PFC) areas during the verbal fluency task by using multi-channel NIRS and analyzed the relationship between task-associated hemodynamic responses and social functioning as measured by the social adaptation self-evaluation scale (SASS). A significant positive relationship was observed between the SASS total score and PFC activation. Our findings suggest that PFC activation is associated with social functioning in healthy elderly adults. Furthermore, hemodynamic responses assessed using non-invasive NIRS could be a useful biological marker of these characteristics.

1. Introduction

Cognitive function in elderly adults is an important area of study not only in Japan but also world-wide as the average lifespan continues to increase because of improvements in technology and modern medicine. While early work primarily focused on the pathological changes in cognitive function associated with systemic medical disease (e.g., cardiovascular disease) or neurological disease (e.g., Alzheimer's disease), recent studies have begun to focus on the cognitive changes that occur as a part of healthy aging.

It is well established that cognitive functions, such as selective attention, memory, and executive function, decline with age [1,2]. Today, larger numbers of individuals are reaching ages where functional decline is more common [3]. As the proportion of individuals over the age of 60 grows, it is of utmost socioeconomic importance to promote their functional independence and increase their quality of life. Seniors consistently cite cognitive health as important for quality of life [4], and cognition is widely recognized by researchers

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as an important contributor to late life functioning [5–7]. Without sufficient cognitive skills, it becomes difficult to meet social and financial duties that are part of daily life. Major individual differences in rate and onset of decline are observed [8,9], but even minor cognitive deficits can severely impact the ability of elderly adults to cope with the demands of daily living. One major aspect of cognition relevant to social functioning is executive function, which has been defined as the ability to deviate from a stereotyped behavior locked to environmental stimuli. Executive function is typically associated with the prefrontal cortex (PFC), a region involved in other high-level cognitive functions, such as working memory and language processing. Considering the significance of social functioning in healthy elderly adults, it may be worthwhile to elucidate the relationship between PFC neural activity and social functioning in this group.

Here, we examined hemodynamic responses in frontotemporal regions during engagement in an executive task in healthy elderly adults by using the non-invasive neuroimaging method of multi-channel near-infrared spectroscopy (NIRS). Near-infrared light penetrates into tissues and is absorbed by hemoglobin, and the degree of absorption is dependent on the oxygenation state of the tissue [10]. It is well established that oxygen consumption, regional cerebral blood response, and oxygenated hemoglobin supply are increased in highly activated neural regions [11,12]. NIRS allows the measurement of oxygenated ([oxy-Hb]) and deoxygenated hemoglobin ([deoxy-Hb]) concentrations in micro-blood vessels, which are correlated with changes in regional cerebral blood volume (rCBV) [13–15]. Recent research supports the utility of NIRS as an early detection method for dementia [16,17]. In contrast to other neuroimaging methodologies, such as functional magnetic resonance imaging (fMRI) and positron emission tomography (PET), NIRS can be easily, rapidly, and non-invasively performed in a restraint-free environment, making it especially suitable for psychiatric patients. NIRS has been used to assess brain functions in elderly adults [18–21] and in patients with various psychiatric disorders, including schizophrenia, depression, and bipolar disorder [22–24].

One of the most useful tools for assessing social functioning is the social adaptation self-evaluation scale (SASS). This 21-item scale was developed by Bosc et al. [25] to evaluate patients' social motivation and behavior in depression; the reliability and validity of the Japanese version of the SASS were subsequently confirmed [26]. Each item is scored from 0 to 3, corresponding to minimal and maximal social adjustment, with a total score range of 0 to 60. The subjects are asked to instantly provide their opinion about the question. Previous studies used principal component analysis to demonstrate that 21 SASS items could be summarized into three factors: interpersonal relations, interest and motivation, and self-perception (Table 1) [26]. Many mood disorder patients with symptoms in remission fail to successfully reintegrate into society, presumably because of their residual social functioning deficit, which is relevant to their cognitive capacity. Extending the view to nonclinical populations, cognitive dysfunction in healthy elderly adults may also affect social functioning capacity and social adaptation. We have demonstrated the association of reduced prefrontal [oxy-Hb] activation induced by a verbal fluency task (VFT) with functional impairment assessed by SASS in patients with geriatric depression by using 52-channel NIRS [20]; however, medication is a possible mediator of this association. If similar findings are obtained for generally healthy, unmedicated elderly adults, those would support the universal relevance of the prefrontal hemodynamic responses to social functioning.

The purpose of the present study was to investigate an association between social functioning and PFC hemodynamic responses in healthy elderly adults by using NIRS. We hypothesized that PFC hemodynamic responses associated with executive function should correlate with social functioning in healthy elderly adults, as we previously demonstrated in patients with geriatric depression [20].

Table 1
The items included in each factor obtained by principal component analysis of the Japanese version of the social adaptation self-evaluation scale (SASS).

First factor: interpersonal relations
10. External relationship quality
9. Relationship seeking behavior
8. Gregariousness
12. Social attractiveness
7. Family relationship quality
11. External relationship appreciation
6. Family seeking behavior
13. Social compliance
Second factor: interest and motivation
16. Intellectual interest
3. Work enjoyment
1. Job interest or 2. Home work interest
4. Interest in hobbies
15. Social inquisitiveness
14. Community involvement
21. Control of surroundings
5. Quality of spare time
Third factor: self-perception
18. Rejection sensitivity
17. Comminication difficulties
19. Vainess
20. Difficulties in coping with resources

2. Material and methods

2.1. Subjects (Table 2)

A total of 55 healthy elderly volunteers (26 males and 29 females) aged between 60 and 81 years (mean ± SD, 70.1 ± 5.4) participated in this study. All the participants were recruited between April 2007 and March 2009 on the basis of consecutive referrals. All participants were right-handed with the criterion of more than 80% by the Edinburgh Inventory Index [27] and were native Japanese speakers.

Two experienced psychiatrists screened participants and excluded those with psychiatric symptoms above the threshold level. Our exclusion criteria were as follows: history of neurological or psychiatric disease; use of psychoactive medications; substance misuse; and serious medical conditions, including history of heart disease, diabetes, or untreated hypertension. Participants whose hypertension was controlled by prescription medication were admitted into the study. All participants were screened for dementia by using the Mini Mental State Examination (MMSE) [28,29], and any individual scoring below 24 was excluded.

All subjects provided written consent after receiving comprehensive information about the protocol. The study was approved by the ethics committee of Tottori University Faculty of Medicine.

2.2. Self-report measures

Prior to scanning, all the participants completed two self-assessments: the Beck Depression Inventory (BDI) for depression severity and the SASS for social functioning.

2.3. Activation task

The task procedure in the present study was similar to that described by Takizawa et al. [30]. The cognitive activation task included a 30-s pre-task baseline, a 60-s VFT, and a 70-s post-task baseline. For the pre- and post-task baseline periods, the subjects were instructed to consecutively repeat the five Japanese vowels

("a," "i," "u," "e," and "o") aloud. The subtraction method (task minus the average of the pre- and post-task baseline) was used to minimize the vocalization effects during VFT. During the task 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 during the VFT was adopted as a measure of task performance.

2.4. NIRS machine

Hb changes were measured with a 52-channel NIRS machine (ETG-4000; Hitachi Medical Co., Tokyo, Japan). Each patient sat in a comfortable chair and was instructed to minimize head movement, jaw clenching, and eye blinking during the NIRS measurement to reduce artifacts. The NIRS machine measures relative changes in [oxy-Hb] and [deoxy-Hb] by using two wavelengths of infrared light (695 and 830 nm) based on the modified Beer–Lambert law [31]. In this system, these Hb values include a differential pathlength factor (DPF). Zhao et al. [32] used a Monte Carlo simulation and reported that the estimated DPF variation in the forehead region of adult humans was homogeneous. Therefore, the distance between pairs of source-detector probes was set at 3 cm, and each measurement area between pairs of source-detector probes was defined as a "channel" (ch). The machine measures points at a depth of 2 to 3 cm below the scalp, which corresponds to the cortical surface [33,34]. The probes of the NIRS machine were placed on the frontotemporal region of each participant, with the midcolumn of the probe located over Fpz, and the lowest probes placed along the T3-Fp1-Fpz-Fp2-T4 line in accordance with the international 10/20 system for electroencephalography. This arrangement enabled the measurement of Hb values from both prefrontal and superior temporal cortical surface regions. The correspondence between the NIRS channels and the measurement points on the cerebral cortex was confirmed by a multi-subject study of anatomical craniocerebral correlation [35] and was presented according to the results of the virtual registration method [36].

The rate of data sampling was 0.1 s, and the obtained data were analyzed using the integral mode: the pre-task baseline was determined as the mean over the 10-s period immediately before the task period, and the post-task baseline was the mean over the last 5 s of the post-task period. Linear fitting was applied to the data recorded between both baselines. A moving average method, using a 5-s window width, was applied to remove short-term motion artifacts. Because we could not remove all artifacts in this way, we applied automatic rejection of data with artifacts separately for each channel [22,37].

For the analysis of the hemodynamic response data, Hb variables for each channel were averaged for the both time segments (pre-task baseline and task period). We focused on [oxy-Hb] concentrations during the 60-s task period, since the oxy-Hb change (task period – pre-task baseline period) was assumed to more directly reflect cognitive activation than the deoxy-Hb change, as previously shown by animal studies and correlations with fMRI blood oxygenation level-dependent signals [12,38]. However, the [deoxy-Hb] analyses are also presented.

2.5. Data analyses

All statistical analyses were performed using SPSS Statistics 19.0 (Tokyo, Japan).

The mean [Hb] changes for the pre-task baseline period and that for the task period were compared in each channel by using Student's paired *t*-tests to confirm the statistically significant increase associated with the VFT. Because we performed 52 paired two-tailed t-tests, we applied a correction for multiple comparisons using a false discovery rate (FDR); we set the value of *q* specifying the maximum FDR to 0.05, so that there were no more than 5% false positives on average [39].

Pearson's product moment correlation coefficients were calculated to determine if there were relationships between the mean [Hb] changes during the task period and SASS scores for each NIRS channel. We again adopted an FDR-based procedure for the multiple testing correction in correlational analyses for 52 channels and focused on those channels where r values reached a significance level of $P < 0.05$ (FDR-corrected). For primary analysis, we examined the relationship between task-related [Hb] changes and SASS total scores. As secondary analyses, we also examined the relationship between task-related [Hb] changes and three SASS factor scores: interpersonal relations, interest and motivation, and self-perception (Table 1) [26]. Moreover, to detect any confounding factors, we also investigated the relationships between [Hb] changes and task performances of VFT, BDI, MMSE; age; and education level.

Table 2
Participant characteristics.

Demographics	healthy older adults ($n = 55$) mean (SD)
Age (years)	70.1 (5.4)
Gender (females/males)	29/26
Right-handedness (%)	96.8 (7.4)
Education (years)	11.4 (1.9)
MMSE	27.4 (2.4)
BDI	5.7 (4.7)
SASS total	39.4 (7.2)
Interpersonal relationships	16.6 (4.0)
Interest and motivation	15.9 (3.2)
Self-perception	6.9 (1.3)
Number of words generated	12.0 (4.3)

3. Results

Table 2 shows the participants' demographic data and task performance.

3.1. Test for significance in [Hb] change during activation period relative to baseline

The grand-averaged waveforms of [oxy-Hb], [deoxy-Hb], and [total-Hb] during VFT in healthy elderly adults are shown in Fig. 1.

We found a significant [oxy-Hb] increase during VFT performance in 47 channels (ch2 to 5, 8, 10, 12 to 52; FDR-corrected *P* vales: 0.001 to 0.045) and a significant [deoxy-Hb] decrease during the VFT in 42 channels (ch2, 8 to 11, 13, 14, and 18 to 52; FDR-corrected *P*: 0.001 to 0.040), which confirmed cognitive activation during the VFT.

3.2. Correlation analyses

The mean [oxy-Hb] changes showed a significant positive correlation with total SASS score in 22 channels (ch3, 6, 7, 14, 15, 17 to 19, 25 to 29, 35 to 37, 39, and 46 to 50; *R*: 0.33 to 0.48; FDR-corrected *P*: 0.001 to 0.021), with the highest correlations located approximately in the frontopolar, left ventrolateral, and bilateral dorsolateral PFC regions (Figs. 2a and 3).

Moreover, the mean [oxy-Hb] change positively correlated with the following two SASS factor scores: interpersonal relationship (19 channels: ch17, 18, 25, 26, 28, 29, 35 to 37, 39, 40, and 44 to

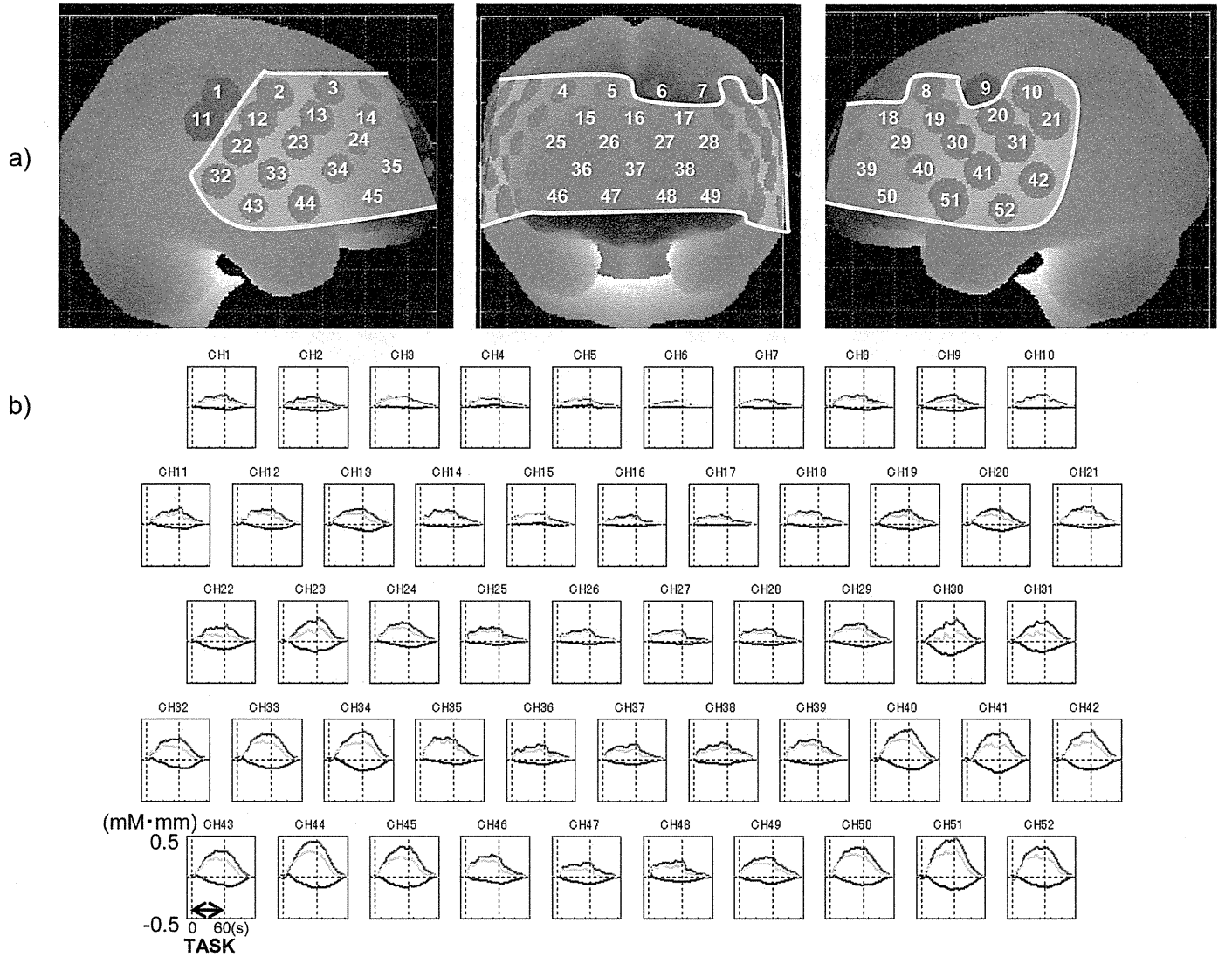

Fig. 1. (a) The yellow regions correspond to the NIRS channels, which showed significant increases in mean [oxy-Hb] during the task period compared with the pre-task baseline (FDR-corrected $P < 0.05$). (b) Grand average waveforms in healthy elderly adults ($n = 55$). [Oxy-Hb], [deoxy-Hb], and [total-Hb] concentration changes during the 60-s verbal fluency task (between two dotted vertical lines in each graph) are presented as grand average waveforms for all 52 channels as red, blue, and green lines, respectively. NIRS channel locations were probabilistically estimated and anatomically labeled in the standard brain space in accordance with Tsuzuki et al. [36].

51; *R*: 0.33 to 0.51; FDR-corrected *P*: 0.001 to 0.018), located predominantly in the frontopolar and ventrolateral PFC (Figs. 2b and 3); and interest and motivation (13 channels: ch6, 14, 17, 25 to 28, 37, 39, and 46 to 49; *R*: 0.35 to 0.49; FDR-corrected *P*: 0.001 to 0.011), located predominantly in the frontopolar and dorsolateral PFC (Figs. 2c and 3); however, the hemodynamic response did not show any significant relationship with self-perception factor scores.

There was no significant correlation between mean [oxy-Hb] change (in any channel) and task performance during VFT (*R*: −0.29 to 0.06, ns), BDI (*R*: −0.40 to −0.01, ns), MMSE (*R*: −0.11 to 0.22, ns), age (*R*: −0.29 to 0.26, ns), or education level (*R*: −0.15 to 0.20, ns).

The mean [deoxy-Hb] changes in any channel were not significantly correlated with the SASS total scores (*R*: −0.32 to 0.29, ns), interpersonal relationship (*R*: −0.29 to 0.21, ns), interest and motivation (*R*: −0.31 to 0.31, ns), self-perception (R: −0.38 to 0.18, ns) factor scores, task performance during VFT (*R*: −0.21 to 0.33; ns), BDI (*R*: −0.20 to 0.30, ns), MMSE (*R*: −0.32 to 0.15, ns), age (*R*: −0.26 to 0.31, ns), or education level (*R*: −0.10 to 0.29, ns).

4. Discussion

Using 52-channel NIRS, we observed considerable hemodynamic responses over prefrontal and superior temporal areas during the VFT in healthy elderly adults. Furthermore, the task-associated [oxy-Hb] increase showed a significant positive correlation with the average total SASS score, and this relationship was strongest with regard to PFC activation. More specifically, a significant positive relationship was observed between SASS interpersonal relationship factor scores and frontopolar and ventrolateral PFC activation, and between SASS interest and motivation factor scores and frontopolar and dorsolateral PFC activation. Our findings suggest that PFC activation is associated with social functioning in healthy elderly adults. The frontal hypothesis of cognitive aging assumes that the cerebral cortex deteriorates disproportionately and that aging affects the frontal lobe first [40]. Neurobiological data [41] tend to support this hypothesis; age-related deterioration of the brain have been shown to occur earliest in the PFC [42], which is involved in memory, attention, executive function and emotion, as well as other complex cognitive

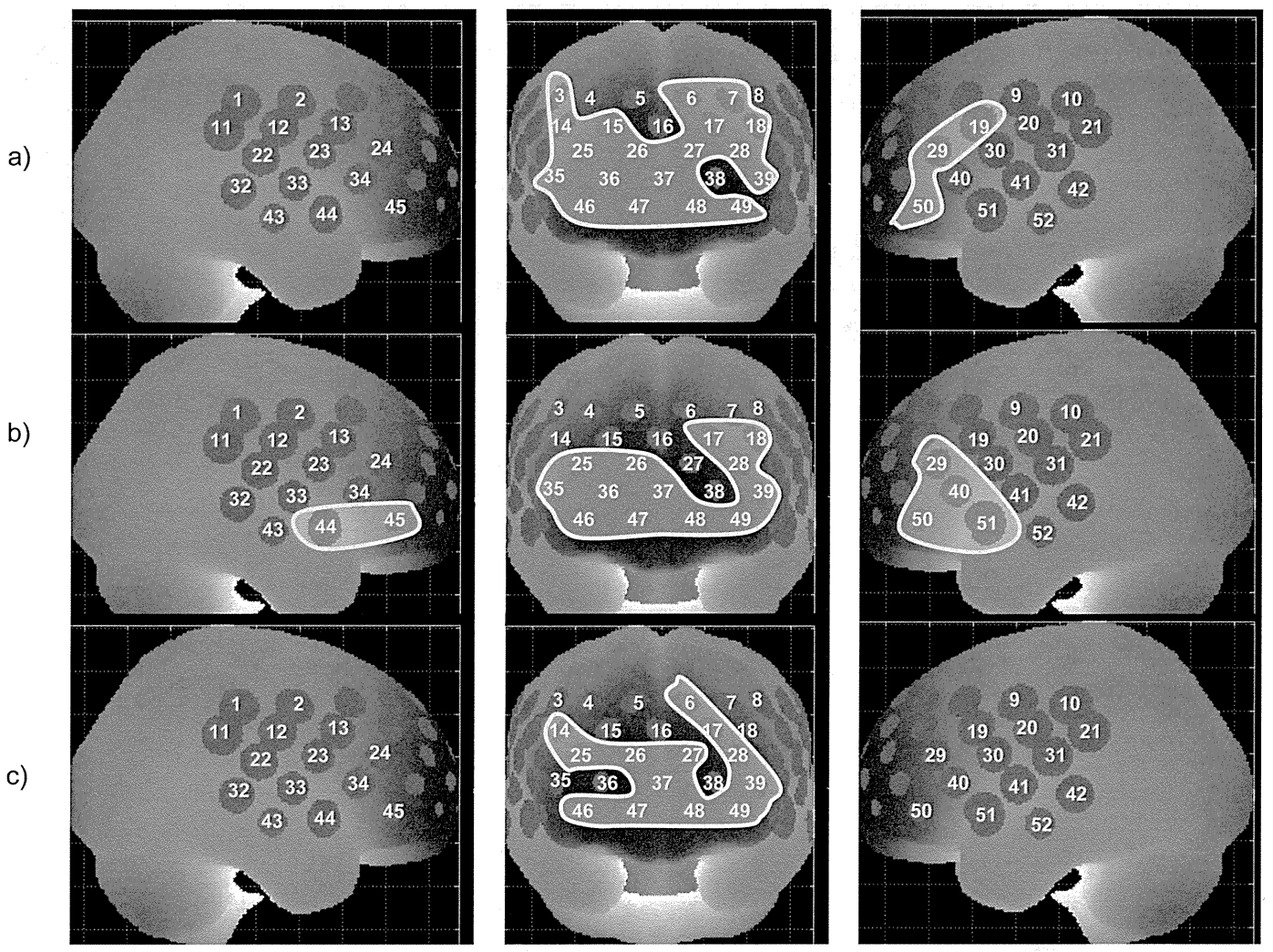

Fig. 2. The relationship between [oxy-Hb] and SASS scores in healthy elderly adults. Yellow brain areas correspond to NIRS channels that showed a significant positive correlation (Pearson's product moment correlation, FDR-corrected $P < 0.05$) between [oxy-Hb] and total SASS (a), interpersonal relationship (b), and interest and motivation (c) scores.

functions [40,43,44]. In addition, older age has been associated with lower blood flow and metabolism at rest, particularly in frontal cortex [45]. In the present study, we identified specific PFC regions associated with functional level in healthy elderly adults.

The PFC is cytoarchitectonically subdivided into several regions: dorsolateral (BA 9/46), ventrolateral (BA 44/45/47), and frontopolar (BA 10) [46,47]. However, these regions have not been successfully mapped to specific cognitive functions. The frontopolar cortex is the most anterior part of the frontal lobe, which is one of the least well-understood regions of the human brain. It has been suggested to have enlarged and become specialized during hominid evolution [48], and is assumed to provide a higher level of control to coordinate ventro- and dorsolateral functions to maximize task performance [47,49]. One important feature of the frontopolar cortex is that the number of dendritic spines per cell and the total spine density are higher than in other PFC regions [50]. This indicates that the functional properties of the frontopolar cortex are more likely to be involved in integration.

A close association between NIRS response and social functioning has been shown for some psychiatric diseases. Takizawa et al. [30] showed reduced PFC [oxy-Hb] activation during VFT in schizophrenia patients by using NIRS and the inverse relationship between hemodynamic responses and social functioning using global assessment of functioning scores. We similarly demonstrated an association of reduced [oxy-Hb] activation in the PFC regions during VFT with functional impairment assessed by SASS total scores in late-onset major depressive disorder patients [20]. Social functioning requires complex operations of executive function that include monitoring, reasoning, organizing, selecting, and planning. Burgess et al. [51] noted that the frontopolar region is involved in high-level executive control and, thus, is likely to be a vital component of social functioning. Considering these observations together, it may be reasonable to postulate that the hemodynamic response observed in the frontopolar regions during the VFT in the present study was associated with social functioning level. The functional properties of the frontopolar cortex are particularly important from a clinical point of view in that they may provide some hint as to how social functioning can be improved in elderly adults.

Furthermore, a significant positive relationship was observed between SASS interpersonal relationship factor scores and frontopolar and ventrolateral PFC activation, and between SASS interest and motivation factor scores and frontopolar and dorsolateral PFC activation. The dorsolateral PFC appears to manipulate information, whereas the ventrolateral PFC appears to store and retrieve information from short-term stores [42,52–54]. Moreover, the dorsolateral PFC and lateral frontopolar cortex are involved in integrating emotion and cognition [43] and motivation and cognition

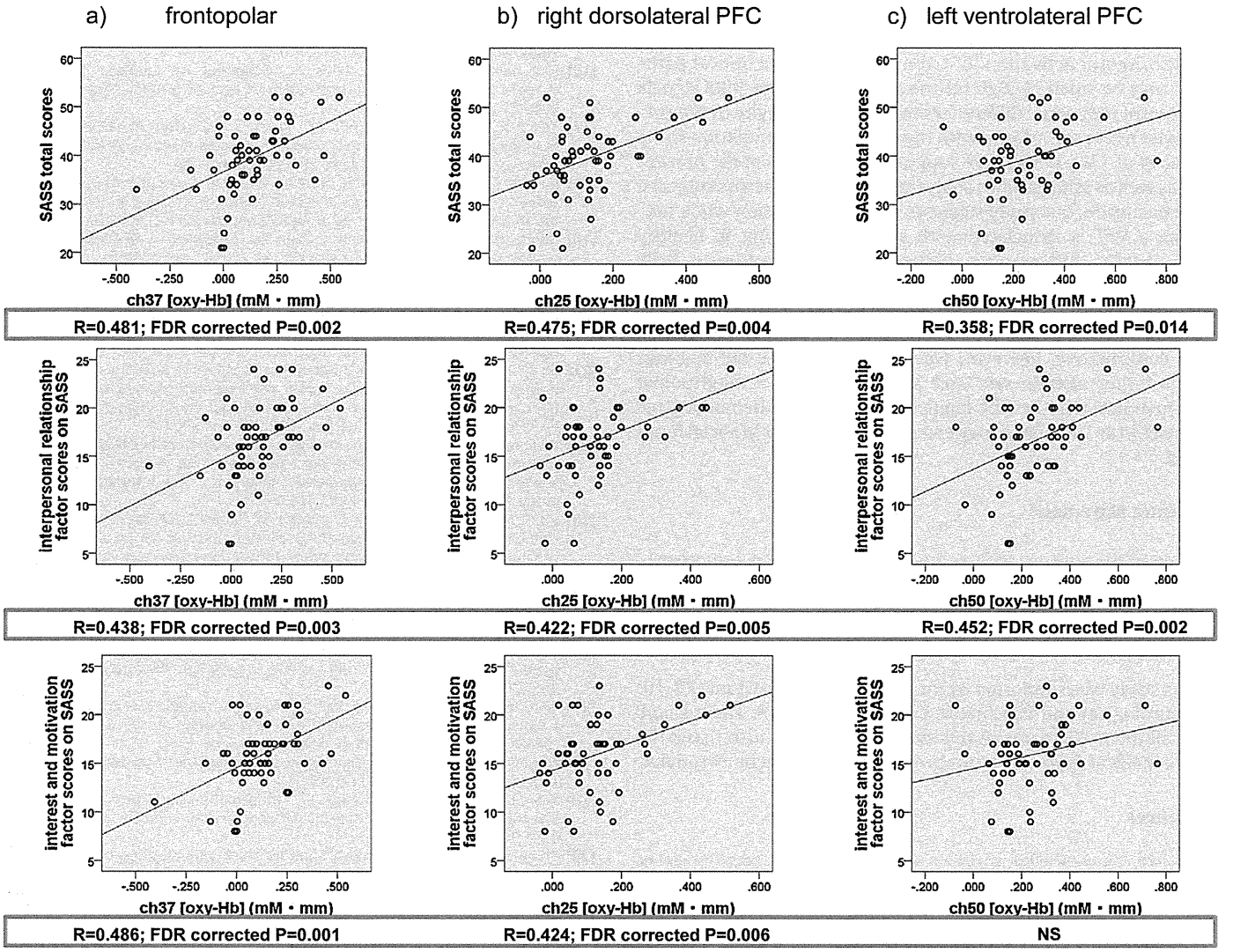

Fig. 3. Scatter diagrams showing the relationship between SASS scores and mean [oxy-Hb] changes in channels 37 (frontopolar) (a), 25 (right dorsolateral PFC) (b), and 50 (left ventrolateral PFC) (c).

[55,56]. Accordingly, it seems reasonable to consider that [oxy-Hb] activation in the dorsolateral PFC is relevant to the interest and motivation factor, and in the ventrolateral PFC, it is relevant to the interpersonal relationship factor in social functioning.

In the present study, instead of using fMRI, we used NIRS to measure neuronal activation at the surface of the prefrontal and temporal cortices. One of the primary advantages of using NIRS is that the technique can be performed under less body constraint than other imaging modalities such as fMRI, which requires the subject to maintain an unusual body posture with restricted head movement; thus, NIRS is useful for studying brain activity under more "natural" conditions, especially suitable for elderly adults [20,21,57–60]. Furthermore, NIRS can measure brain activity in the frontpolar region with high signal-to-noise ratio, whereas fMRI has potential problems for data quality of areas located under the frontal sinus [61].

Although NIRS has advantages compared to fMRI as above, it is also associated with a limitation in measurement depth and poor spatial resolution. In the present study, we could not investigate other areas than PFC, such as hippocampus and/or posterior regions of the brain, which are known to be related to memory and visuo-spatial processing. Moreover, intermingling effect of extracranial hemodynamic changes such as skin blood flow in the measurement data has raised a question as to what extent NIRS signals reflect hemodynamic changes in the brain. For example, Takahashi et al. [62] suggested that the majority of the hemodynamic changes measured by NIRS in the forehead reflected the skin blood flow during a verbal fluency task. This finding indicated that extracranial hemodynamic changes such as skin blood flow are a considerable source of the task-related signals in the forehead and may be present in a wide range of cognitive tasks. However, the impact of the extracranial artifacts, including their significance and generality, has not been clarified. On the other hand, recent studies using simultaneous NIRS-fMRI measurements investigating PFC showed a significant correlation between NIRS and BOLD signals, although with a wide regional and inter-individual variability [38,63]. More recently, Sato et al. [64] demonstrated that temporal changes in the NIRS signals in the activated area were significantly correlated with the BOLD signals in the gray matter rather than the extracranial BOLD signals or skin blood flow measured with a laser Doppler flowmeter. Moreover, the amplitudes of the task-related responses of the NIRS signals were significantly correlated with the BOLD signals in the gray matter *across participants*. The finding is important. As the amplitude of the NIRS signals includes the differential pathlength factor (DPF), which is assumed to be variable among different individuals, some researchers consider that direct comparison of the

amplitude between individuals is somewhat problematic. However, according to their finding as well as a similar finding obtained for sensorimotor activation [65], the variation in the optical pathlength may be small enough for the amplitude of the NIRS signals to represent individual differences in functional activity of the cortices, which is in accordance with the Monte Carlo simulation study by Zhao et al. [32]. It may give support to the results of the present study as well as other studies analyzing NIRS signals across subjects.

In conclusion, our study suggests that PFC activation while performing a VFT is associated with social functioning in healthy elderly adults; furthermore, hemodynamic responses to WFT assessed using non-invasive NIRS could be a useful biological marker of social functioning in aged populations, more specifically in terms of interpersonal relationship, and interest and motivation. To be confirmative, however, we need to replicate our findings using a larger sample size and also implement a longitudinal study to assure whether the longitudinal change of hemodynamic responses in an individual may correspond to change in social functioning.

Disclosure statement

None of the authors reports any financial interests or potential conflicts of interest.

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Serotonin$_{1A}$ Receptors in the Action of Aripiprazole

To the Editors:

I have read with interest the article by Lerond et al[1] about serotonin$_{1A}$ receptor binding in patients with schizophrenia receiving antipsychotic drugs. Using [^{18}F]4-(2-methoxyphenyl)-1-[2-(N-2-pirydynyl)-p-luorobenzamido]-ethyl-piperazine ([^{18}F]MPPF) as a positron emission tomography (PET) radiotracer, the authors observed decreased [^{18}F]MPPF binding in patients treated with aripiprazole (with high affinity for serotonin$_{1A}$ receptors) compared with healthy control subjects and patients given risperidone or olanzapine. Because the latter 2 antipsychotic drugs lack a noticeable affinity for serotonin$_{1A}$ receptors, the decreased [^{18}F]MPPF binding by aripiprazole was considered to represent occupancy of serotonin$_{1A}$ receptors by the drug.[1] These findings add to the growing interest in the role for serotonin$_{1A}$ receptors in the action of antipsychotic drugs.[2–6] Here, I would like to provide additional discussions on the results of the work of Lerond et al,[1] which would provide further insights.

Lerond et al[1] argued that the existence of high- and low-affinity states of serotonin$_{1A}$ receptors could explain the discrepancy between their observations with PET, that is, decreased serotonin$_{1A}$ binding potentials in schizophrenia, and postmortem findings in the literature, that is, increased binding density; the antagonist PET tracer [^{18}F]MPPF binds to both high-affinity (G protein coupled) and low-affinity (uncoupled) serotonin$_{1A}$ receptors, whereas agonist radioligands for postmortem studies, such as [^{3}H]8-OH-DPAT, preferentially bind to high-affinity receptors. To support these assumptions, the authors[1] only quoted the study of Mongeau et al[7] that used [^{3}H]8-OH-DPAT to label serotonin$_{1A}$ receptors in the rat brain. Further evidence comes from our own investigation[8] that indicated, for the first time, the presence of high-affinity and low-affinity serotonin$_{1A}$ receptors in the postmortem human brain. Specifically, I found an increase in the high-affinity serotonin$_{1A}$ receptors in the prefrontal cortex from patients with schizophrenia compared with normal controls.[8] Subjects in that study was relatively young (younger than 40 y), and none had been treated with neuroleptics with a noticeable affinity for serotonin$_{1A}$ receptors,[8] excluding the influence of age and drug exposure, a possibility Lerond et al[1] (2013) suggested. Rather, the change of the serotonin$_{1A}$ receptor density in postmortem samples (eg, Sumiyoshi et al[8] and Hashimoto et al[9]) may be related to the pathophysiology of schizophrenia, the other possibility Lerond et al[1] raised.

Lerond et al[1] deliberately concluded that the greater reduction of [^{18}F]MPPF binding in patients given aripiprazole compared with those given risperidone or olanzapine may represent serotonin$_{1A}$ partial agonist actions of aripiprazole. The clinical implications for this hypothesis would deserve discussions. Decreased [^{18}F]MPPF binding in subjects treated with aripiprazole was evident in cortical areas, for example, prefrontal cortex,[1] which is associated with negative symptoms and cognitive deficits of schizophrenia. The data from an animal model study[10] report the ability of aripiprazole to restore phencyclidine-induced memory impairment in mice, which was blocked by pretreatment with a serotonin$_{1A}$ antagonist. This may provide support to the role of serotonin$_{1A}$ agonism in the distinct cognition-enhancing property of aripiprazole in clinical subjects.[11] Accordingly, the addition of serotonin$_{1A}$ partial agonists, for example, buspirone and tandospirone, to ongoing treatment with risperidone, olanzapine, or haloperidol was found to improve several cognitive domains governed by frontal regions in patients with schizophrenia.[12–14] These behavioral observations are consistent with the ability of augmentation therapy with tandospirone to ameliorate diminished mismatch negativity, an electrophysiologic measure of cognitive function, in patients receiving olanzapine.[15] These considerations are expected to help refine the rational choice of antipsychotic/neurotrophic drugs to improve functional outcome of individuals with schizophrenia or related disorders.

AUTHOR DISCLOSURE INFORMATION

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Effect of Aripiprazole Augmentation for Treatment-Resistant Somatoform Disorder
A Case Series

To the Editors:

Although there is opposition, hypochondriasis is supposed to be included as an obsessive-compulsive spectrum disorder,[1–3] and the effectiveness of treatment with selective serotonin reuptake inhibitors (SSRIs) has been demonstrated.[4,5] Because somatoform disorder has features common with hypochondriasis, the effectiveness of SSRIs for this disorder is significant.[6,7] Besides, augmentation with antipsychotics is effective in case of SSRI-resistant obsessive-compulsive disorder (OCD).[8,9] Therefore, augmentation with antipsychotics may be effective in the treatment of SSRI-resistant somatoform disorder. However, except for body dysmorphic disorder,[10–13] few reports have evaluated the combined use of SSRIs and antipsychotics in patients with somatoform disorder.[14] Accordingly, we present 2 patients with somatoform disorder who had insufficient therapeutic effect with SSRI but showed marked improvement with concomitant use of aripiprazole (APZ).

CASE 1

The patient was a 65-year-old woman living with her husband. She and her family had no history of psychiatric disorders. Over the past 20 years, she developed laryngopharynx discomfort, persistent abdominal pain, back pain, lumbago, and fatigue, and thus, she quit her job and was confined to bed most of the time. Although she consulted physicians in otorhinolaryngology, orthopedics, and internal medicine, no abnormality was found. After psychiatric consultations, she was prescribed 1.2 mg/d alprazolam, but her symptoms did not improve. She subsequently underwent psychiatric examination at another hospital, and 100 mg/d milnacipran was prescribed for possible masked depression; however, it was ineffective. She continued undergoing clinical examinations at the gastroenterology department of our hospital because of her uneasiness, and after no abnormality was found, she was eventually referred to our psychiatry department.

She exhibited hypochondriacal fear of having pancreatic cancer and obsessive concern with her physical condition, without apparent signs of depression. According to the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision* (DSM-IV-TR), we diagnosed her with undifferentiated somatoform disorder. The treatment of 100 mg/d milnacipran was switched to 40 mg/d paroxetine. Although slight improvement was observed, her treatment was discontinued because of an adverse effect of sleepiness. She then revisited our department because of aggravated symptoms. We restarted her therapy with fluvoxamine, and improvement was observed after increasing the dosage to 300 mg/d. However, about half of the symptoms still persisted. Aripiprazole was added to the treatment 12 weeks later. Aripiprazole was initiated at 6 mg/d and was increased to 18 mg/d. Signs of improvement were observed within 4 weeks, and her symptoms disappeared without any adverse effects 8 weeks later. The patient was able to do household chores. Because the remission lasted for 2 years, we decreased and discontinued her medications successfully with no aggravation of symptoms.

CASE 2

The patient was a 69-year-old woman living with her husband. She and her family had no history of psychiatric disorders. She experienced numbness on the right side of her face and dizziness lasting for 5 years. She underwent multiple otorhinolaryngological, cardiological, and neurological examinations based on her self-diagnosis through medical books; however, no abnormality was observed. She visited our department because she was annoyed with the disturbing thought of having a serious brain disease.

She exhibited hypochondriacal anxiety and obsessive concern with her physical state, without any apparent signs of depression. Her condition was diagnosed with undifferentiated somatoform disorder according to DSM-IV-TR and treated with 50 mg/d paroxetine. Although some improvement was observed, about half of the symptom still persisted. Then, 6 mg/d of APZ was added 12 weeks later. Signs of improvement were observed within 2 weeks, and her symptoms disappeared 4 weeks later without any adverse drug reaction. She was able to do household chores. After 6 months remission, her medication was decreased and then discontinued. We terminated the therapy with no aggravation of symptoms.

DISCUSSION

As reported previously for OCD, our study suggested that antipsychotics are effective augmentation therapy for SSRI-resistant somatoform disorder.

Based on evidence of augmentation with APZ in SSRI-resistant OCD,[15–19] we consider APZ to be effective for patients who are closer to hypochondriasis (ie, similar to OCD). Olanzapine or quetiapine could be more effective for patients who are emotionally unstable with severe anxiety, restlessness, or anger and are closer to somatization disorder.

Because patients with somatoform disorder are usually sensitive to adverse drug reactions, they often cannot tolerate drugs and discontinue medications or hospital visits. Therefore, it is necessary to note any adverse drug reactions when treating somatoform disorder. Aripiprazole is well tolerated and, in particular, has less of a sedative effect, which could be a common problem for patients except those with schizophrenia or a manic episode. Therefore, we selected APZ among antipsychotic agents for our cases, and no adverse drug reaction was observed.

Although antipsychotic augmentation for OCD could show efficacy at a low dose, a comparatively high dose of APZ was required in case 1; this may have been the case because APZ is a partial dopamine agonist.

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Serotonin and dopamine receptors in motivational and cognitive disturbances of schizophrenia

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Negative symptoms (e.g., decreased spontaneity, social withdrawal, blunt affect) and disturbances of cognitive function (e.g., several types of memory, attention, processing speed, executive function, fluency) provide a major determinant of long-term outcome in patients with schizophrenia. Specifically, motivation deficits, a type of negative symptoms, have been attracting interest as (1) a moderator of cognitive performance in schizophrenia and related disorders, and (2) a modulating factor of cognitive enhancers/remediation. These considerations suggest the need to clarify neurobiological substrates regulating motivation. Genetic studies indicate a role for the monoamine systems in motivation and key cognitive domains. For example, polymorphism of genes encoding catecholamine-O-methyltransferase, an enzyme catabolizing dopamine (DA), affects performance on tests of working memory and executive function in a phenotype (schizophrenia vs. healthy controls)-dependent fashion. On the other hand, motivation to maximize rewards has been shown to be influenced by other genes encoding DA-related substrates, such as DARPP-32 and DA-D_2 receptors. Serotonin (5-HT) receptors may also play a significant role in cognitive and motivational disabilities in psychoses and mood disorders. For example, mutant mice over-expressing D_2 receptors in the striatum, an animal model of schizophrenia, exhibit both decreased willingness to work for reward and up-regulation of 5-HT_{2C} receptors. Taken together, genetic predisposition related to 5-HT receptors may mediate the diversity of incentive motivation that is impaired in patients receiving biological and/or psychosocial treatments. Thus, research into genetic and neurobiological measures of motivation, in association with 5-HT receptors, is likely to facilitate intervention into patients seeking better social consequences.

Keywords: serotonin, 5-HT receptors, motivation, cognition, schizophrenia, dopamine, negative symptoms, psychosis

INTRODUCTION

Disturbances of mental processes, including cognitive function (e.g., several types of memory, attention, processing speed, and executive function, fluency) and motivation characterize many of the psychiatric illnesses, such as schizophrenia, mood disorders, and substance abuse (Simpson et al., 2011; Choi et al., 2014; Sumiyoshi, in press). Recently, the development of biological (e.g., pharmacotherapy and brain stimulation) and psychosocial (e.g., cognitive rehabilitation) interventions is targeting social function/adaptation as an important outcome measure (Harvey et al., 2011; Leifker et al., 2011). In this context, negative symptoms (decreased spontaneity, social withdrawal, and blunt affect) and cognitive impairment provide a major determinant of long-term outcome. Specifically, motivation deficits have been attracting interest as a moderator of (1) cognitive performance in patients with schizophrenia and related disorders, and (2) beneficial influence of cognitive enhancers/remediation (Fervaha et al., 2014; Strauss et al., 2014). These considerations suggest the need to clarify neurobiological substrates regulating motivation for improving quality of life in a rational and effective manner.

We herein present a theory/hypothesis that the research into genetic and neurobiological measures of motivation, linked to serotonin (5-HT) receptors, would facilitate treatment of patients with schizophrenia or other psychiatric illnesses.

MOTIVATIONAL DISTURBANCES IN SCHIZOPHRENIA

Schizophrenia is characterized by a range of symptoms, e.g., positive symptoms (delusions, hallucinations, thought disorders), negative symptoms, mood symptoms, and cognitive impairment. Specifically, there is a suggestion that negative symptoms can be separated into two domains; (1) a motivational dimension, consisting of avolition, anhedonia, and asociality, and (2) a diminished expressivity dimension, consisting of restricted affect and alogia (Strauss et al., 2014). There is a general consensus that motivational disturbances may overlap some (e.g., anhedonia), but not all (e.g., blunt affect, alogia) aspects of negative symptoms. The former dimension has been considered to be of greater importance in terms of functional outcome, quality of life, and recovery from the disease (Strauss et al., 2014). Whether other aspects of symptomatology of schizophrenia (e.g., mood

symptoms) may substantially affect motivation in patients or vulnerable people remains to be determined (Schlosser et al., 2014).

DOPAMINE (DA) SYSTEMS GOVERNING MOTIVATION AND COGNITION

The neural basis for intrinsic motivation has been an issue of extensive research. For example, activity of the anterior striatum and prefrontal cortex (PFC), measured by the functional MRI, has been shown to be associated with intrinsic motivation (Murayama et al., 2010). This line of anatomical evidence is consistent with genetic studies indicating a role for the monoamine systems in cognition and motivation, as discussed below.

The Val158Met polymorphism of the genes encoding catecholamine-O-methyltransferase (COMT), an enzyme catabolizing DA, affects performance on tests of working memory and executive function in a phenotype (schizophrenia vs. healthy controls)-dependent fashion (Egan et al., 2001). Thus, individuals with the val/val carriers in *COMT* show greater efficacy of the enzyme, leading to decreased DA levels in the PFC. The enzyme has also been suggested to mediate uncertainty-based exploration that is linked to DA levels in the PFC. For example, individuals with at least one met-allele show enhanced exploration compared to those with val/val genotype (Frank et al., 2007).

On the other hand, motivation to maximize rewards has been shown to be influenced by other DA-related genes expressed in the striatum/nucleus accumbens (NAc). Specifically, reward learning and negative reward avoidance are affected by genotypes of a polymorphism (rs907094. A/G) of the gene encoding DARPP-32 (a protein required for synaptic plasticity and reward learning mediated by DA-D_1 receptors) and the D_2 receptor (related to avoidance of negative outcomes), respectively (Frank et al., 2007; Klein et al., 2007). Thus, individuals with T/T genotype show greater expression of mRNA for the DARPP-32 gene, leading to greater performance to maximize rewards compared to C-allele carriers (reviewed in Frank et al., 2009). Similarly, T/T carriers of genes encoding D_2 receptors are associated with greater density of these receptors in the striatum and greater likelihood to maximize rewards (Hirvonen et al., 2004; Frank et al., 2007). A recent study (Simpson et al., 2013) reported that overexpression of D_3 receptors, a member of the D_2 receptor family, in the striatum selectively impaired incentive motivation, as measured by an operant task.

The mechanisms by which DA receptors govern motivation and cognitive functions may involve timing perception. For example, genetically-engineered mice overexpressing D2 receptors in the striatum have been shown to elicit impaired working memory, behavioral flexibility and sensorimotor gating, i.e., behavioral abnormalities reminiscent of schizophrenia (Kellendonk et al., 2006). These model animals also demonstrate reduced motivation, as well as alteration of interval timing organization, as measured by the operant timing task (Drew et al., 2007). Further studies indicate that the impaired timing in these mutant mice mediates the ability of decreased motivation to worsen cognitive functions, including working memory and attention (Ward et al., 2009). These lines of evidence suggest a strategy for the intervention into motivational disturbances, in terms of biological and/or tailor-made treatments.

Figure 1 summarizes a concept about how genes encoding these DA-related substrates contribute to cognitive and motivational behaviors.

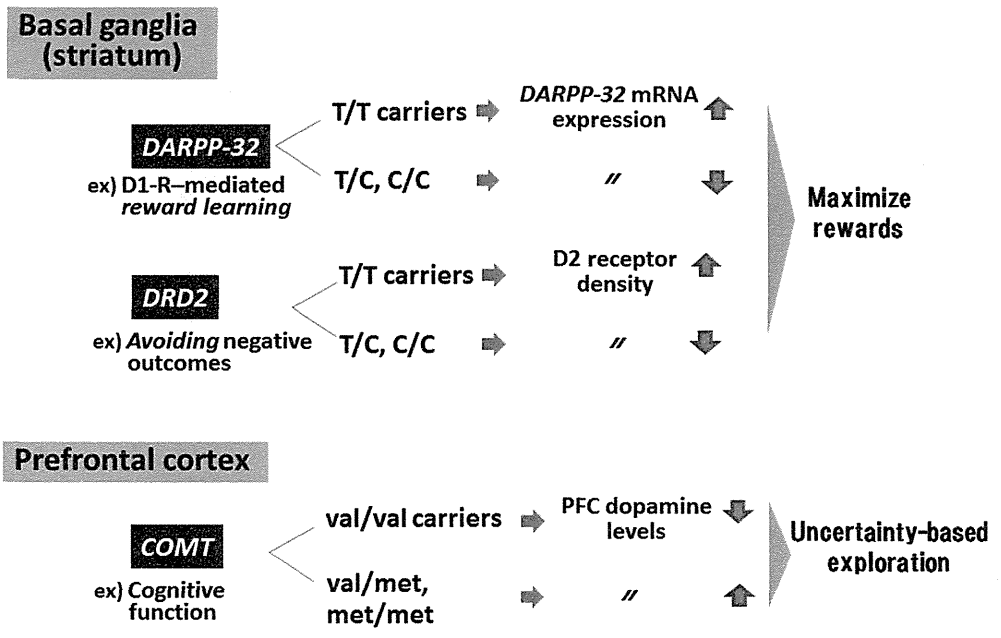

FIGURE 1 | Genes in the dopaminergic motivational system. Polymorphisms of genes encoding *DARPP-32* and dopamine (DA)-D_2 receptors *(DRD2)* affect behaviors to maximize rewards, while the polymorphism in *COMT* are associated with uncertainty-based exploration. Information in the Figure was extracted from Frank et al. (2009).

5-HT RECEPTOR SUBTYPES IN MOTIVATION-RELATED BEHAVIORS

5-HT receptors, e.g., 5-HT_{1A}, 5-HT_{2A}, and 5-HT_{2C} subtypes, may also play a role in cognitive and motivational disabilities in psychoses and mood disorders (Meltzer and Massey, 2011; Newman-Tancredi and Albert, 2012; Ohno et al., 2012). For example, several antipsychotic and antidepressant drugs have been suggested to ameliorate negative symptoms and mood disturbances, partly through actions on 5-HT_{1A} and 5-HT_{2A} receptors (Newman-Tancredi and Albert, 2012; Ohno et al., 2012; Sumiyoshi et al., 2013; Sumiyoshi, 2014). Clozapine, the prototype of atypical antipsychotic drugs, which is most effective in treating negative symptoms, may act as an inverse agonist on 5-HT_{2C} receptors (Meltzer and Massey, 2011).

Data from recent investigations support the contribution of 5-HT receptors to motivational behaviors. For example, mutant mice over-expressing D_2 receptors in the striatum, exhibit both decreased willingness to work for reward and up-regulation of 5-HT_{2C} receptors (Simpson et al., 2011). Furthermore, increased D_1, D_2 and 5-HT_{2C} receptors co-exist in mice mis-expressing ADAR2, an RNA-editing enzyme, and these animals elicit altered expression of reward-related mRNAs in the brain (Akubuiro et al., 2013). Collectively, these observations indicate the importance of some 5-HT receptor subtypes, e.g., 5-HT_{2C} receptors, in the pathophysiology and treatment of motivational disturbances associated with psychoses (**Figure 2**).

The role for 5-HT_{2C} receptors in psychiatric symptoms relevant to functional outcome is also supported by observations in mice whose 5-HT-synthesizing enzyme (tryptophan hydroxyxlase-2) was genetically engineered (Del'Guidice et al., 2014). Thus, treatment with the 5-HT_{2C} agonist CP809,101 ameliorated impairments in cognitive flexibility and reversal learning in these mutant animals (Del'Guidice et al., 2014).

As noted above, up-regulation of 5-HT_{2c} receptors in the striatum may be associated with a decrease in incentive motivation (Simpson et al., 2011). Further, 5-HT_{2c} receptors localized in DA and GABA neurons in the ventral tegmental area (VTA) also have been suggested to regulate motivation by modulating transmissions to NAc (Bubar et al., 2011) (**Figure 2**). It should be noted that a proportion of NAc-projecting VTA neurons may release both DA and GABA (Bubar et al., 2011). Altered balance in this complicated 5-HT_{2c} receptor-associated network is postulated to cause reward-related disorders, such as schizophrenia, depression, and addiction (Bubar et al., 2011).

Other 5-HT receptor subtypes, such as 5-HT_{1A} and 5-HT_{2A}receptors, may directly or indirectly influence this neural system for motivational behaviors as well. For example, 5-HT_{1A} receptor gene promotor polymorphism (rs6295, C-1019G) has been associated with treatment effects on negative symptoms of schizophrenia (Reynolds et al., 2006). **Figure 2** illustrates a putative neural network mediating motivational behaviors in relation to 5-HT receptors, which, together with

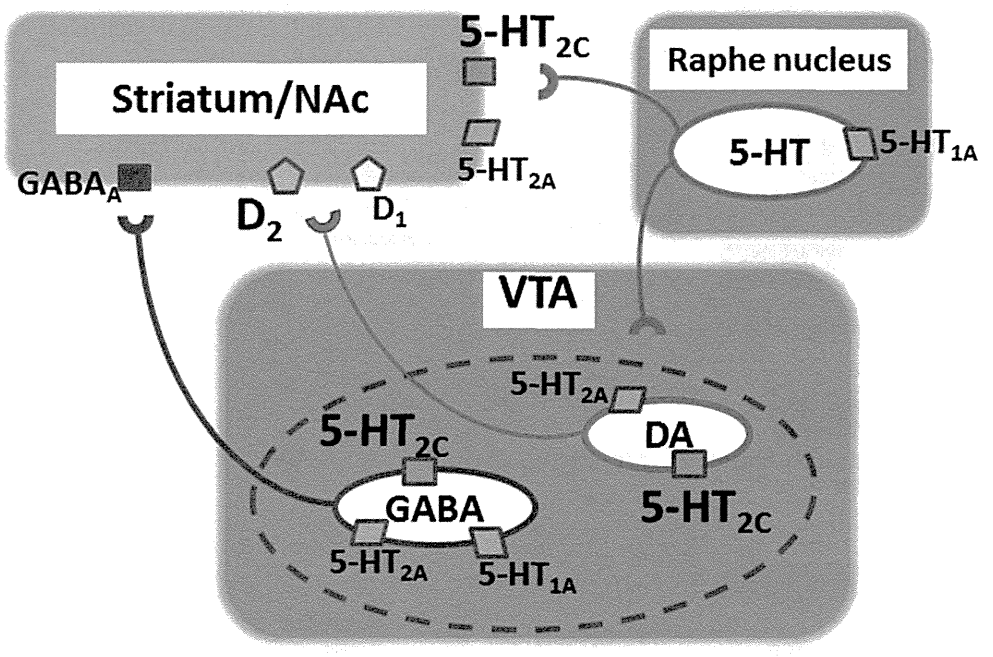

FIGURE 2 | A putative neural network mediating motivational behaviors in relation to serotonin (5-HT) receptors. (1) Up-regulation of 5-HT_{2c} receptors in the nucleus accumbens (NAc)/striatum may be associated with a decrease in incentive motivation in mutant mice over-expressing dopamine (DA)-D_2 receptors in the striatum, an animal model of schizophrenia (Simpson et al., 2011). SB242084, a selective *ant*agonist at these receptors, increases incentive motivation in these model mice. (2) 5-HT_{2c} receptors localized in DA and GABA neurons in the ventral tegmental area (VTA) also affect motivation by modulating transmissions to NAc, including actions on D_1 and D_2 receptors (Bubar et al., 2011). The dotted line indicates that a proportion of NAc-projecting VTA neurons releases both DA and GABA (Bubar et al., 2011). (3) Other 5-HT receptor subtypes, such as 5-HT_{1A} and 5-HT_{2A}, may also directly or indirectly regulate this neural system of motivational behaviors.

Figure 1 (upper part), may suggest the contribution of DA-5-HT interactions.

CLINICAL PERSPECTIVES AND FUTURE DIRECTIONS

Based on the discussions so far, drugs acting on some 5-HT receptor subtypes, particularly, 5-HT_{2C} receptors, are likely to improve motivational deficits in individuals with schizophrenia. For example, SB242084, a selective *ant*agonist at 5-HT_{2C} receptors, has been shown to increase incentive motivation in mice over-expressing D_2 receptors in the striatum, an animal model of schizophrenia (Simpson et al., 2011). By contrast, the 5-HT_{2C} receptor *ago*nist CP809,101 has been demonstrated to enhance performance on some cognitive tasks in mice with decreased 5-HT synthesis (Del'Guidice et al., 2014). These preclinical observations warrant clinical studies of the effect of agents for specific 5-HT receptor subtypes, e.g., 5-HT_{2C} receptors, on motivational and cognitive disturbances. Specifically, it is important to see if such putative pro-motivation drugs will lead to improvement of functional outcome affected by cognitive function on which such compounds might act in variable directions.

In view of a possible influence of motivation on cognitive training, it may be interesting to determine if augmentation with pro-motivation compounds, e.g., 5-HT_{2C} agents, would provide additional merits for cognitive and functional outcome in patients with schizophrenia. Also, whether genetic variations regarding 5-HT and/or DA receptors affect motivational response to treatment with existing pharmacological or psychosocial interventions deserves further study.

In summary, genetic predisposition related to 5-HT and DA receptors may mediate the diversity of incentive motivation that is impaired in patients with schizophrenia. This concept is expected to facilitate rational treatment with biological and/or psychosocial tools to improve social consequences for people with psychiatric illnesses.

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Reliability and Validity of the New Tanaka B Intelligence Scale Scores: A Group Intelligence Test

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Abstract

Objective: The present study evaluated the reliability and concurrent validity of the new Tanaka B Intelligence Scale, which is an intelligence test that can be administered on groups within a short period of time.

Methods: The new Tanaka B Intelligence Scale and Wechsler Intelligence Scale for Children-Third Edition were administered to 81 subjects (mean age ± SD 15.2±0.7 years) residing in a juvenile detention home; reliability was assessed using Cronbach's alpha coefficient, and concurrent validity was assessed using the one-way analysis of variance intraclass correlation coefficient. Moreover, receiver operating characteristic analysis for screening for individuals who have a deficit in intellectual function (an FIQ<70) was performed. In addition, stratum-specific likelihood ratios for detection of intellectual disability were calculated.

Results: The Cronbach's alpha for the new Tanaka B Intelligence Scale IQ (BIQ) was 0.86, and the intraclass correlation coefficient with FIQ was 0.83. Receiver operating characteristic analysis demonstrated an area under the curve of 0.89 (95% CI: 0.85–0.96). In addition, the stratum-specific likelihood ratio for the BIQ≤65 stratum was 13.8 (95% CI: 3.9–48.9), and the stratum-specific likelihood ratio for the BIQ≥76 stratum was 0.1 (95% CI: 0.03–0.4). Thus, intellectual disability could be ruled out or determined.

Conclusion: The present results demonstrated that the new Tanaka B Intelligence Scale score had high reliability and concurrent validity with the Wechsler Intelligence Scale for Children-Third Edition score. Moreover, the post-test probability for the BIQ could be calculated when screening for individuals who have a deficit in intellectual function. The new Tanaka B Intelligence Test is convenient and can be administered within a variety of settings. This enables evaluation of intellectual development even in settings where performing intelligence tests have previously been difficult.

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Introduction

If delayed intellectual development in a child remains unnoticed and proper care is not received in a timely manner, maladjustment in society, loss of self-esteem, and behavioral problems may occur [1–7]. In fact, many published reports have suggested a high prevalence of deficit in intellectual function in offenders [8–10]. Therefore, in child-rearing and educational settings, providing services adjusted to the cognitive characteristics of a child, including intellectual development, is important. In addition, from a point of social safety, it is also desirable to provide specific approaches to offenders with intellectual disability (ID) that reflect their intellectual development in order to reduce recidivism [11–13]. Therefore, individually assessing intellectual development adequately and with flexibility in many settings is desired.

The Wechsler Intelligence Scale for Children (WISC) [14] is commonly used for intelligence testing. The WISC uses special test equipment, is administered on individuals, and in addition to overall intelligence, it can assess abilities in several domains, including verbal and performance IQ. Testing requires approximately 1–2 hours, with a trained examiner administering all testing materials. A shorter version of the WISC [15], which uses certain subtest items to estimate overall intellectual development, is available. However, the short form is similar to the full test in that it can only be performed on individuals, and requires special test equipment as well as experience in administering the test. Therefore, in settings where there are many individuals suspected of having ID, but a relative lack of specialists in ID or mental health, such as in justice facilities, it is impractical to perform individual intelligence tests on individuals within an entire group. Consequently, convenient intelligence tests or simple screening scales become more attractive.

On the other hand, intelligence tests administered on groups of individuals are available. To our knowledge, there are several group tests which have been standardized in English-speaking countries [16–21], but only a few tests exist outside English-