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

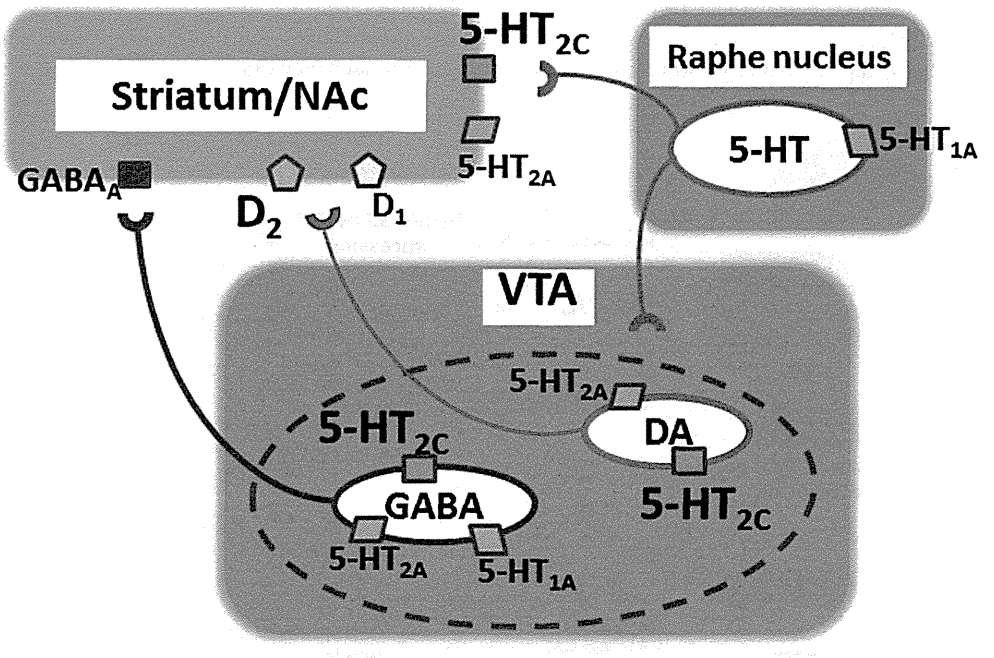

FIGURE 2 | A putative neural network mediating motivational behaviors in relation to serotonin (5-HT) receptors. (1) Up-regulation of 5-HT_{2c} receptors in the nucleus accumbens (NAc)/striatum may be associated with a decrease in incentive motivation in mutant mice over-expressing dopamine (DA)-D_2 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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PLOS ONE

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-

speaking countries. One of which is the new Tanaka B Intelligence Scale [22]. Testing may be conducted simultaneously on groups, with no special equipment required, and only writing materials, test paper, and a short time (only 40–45 minutes) frame are required. This is convenient for assessing overall intellectual development. This test seems to be suitable for individuals with varied educational backgrounds, in varied linguistic environments, and over a wide range of linguistic levels, because it does not need complex instructions and is easily understood. This test was originally developed by Kanichi Tanaka in 1936 and has repeatedly been revised and restandardized since the 1930s. The test was most recently restandardized in 2001–2002 and has very high split-half correlations ($r = 0.89$ to 0.96) and high test-retest reliability ($r = 0.73$ to 0.79). There is high validity ($r = 0.69$ to 0.78) with overall scholastic ability, including Japanese language, mathematics, science, social studies, and English [22].

However, academic performance is influenced not only by intellectual development, but also by various environmental factors, including educational background. To the best of our knowledge, the correlation between the new Tanaka B Intelligence Scale and other intelligence tests has not yet been investigated. Therefore, more information about the reliability and validity of this test is needed along with a standardized test to assess individual intellectual development.

Thus, the present study examined the reliability of the new Tanaka B Intelligence Scale and its concurrent validity with the Wechsler Intelligence Scale for Children-Third Edition (WISC-III), which is one of the most-used tests to assess the intelligence quotient of individuals. Moreover, the clinical utility of the new Tanaka B Intelligence Scale as a screening scale for individuals who have a deficit in intellectual function [WISC-III full intelligence quotient (FIQ) less than 70] was evaluated. If the new Tanaka B Intelligence Scale is standardized, intellectual assessment becomes possible even in settings where the number of cases who can receive individual assessment has previously been limited, such as schools and correctional facilities. This will contribute to setting goals for those individuals and planning strategies to achieve those goals.

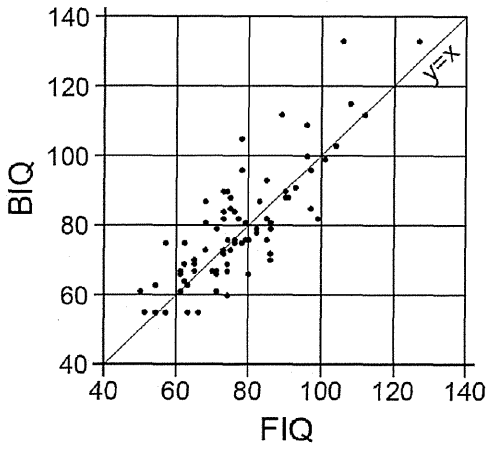

Figure 1. Distribution of BIQ and FIQ scores. Notes: The straight line represents the diagonal line y = x.
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Materials and Methods

New Tanaka B Intelligence Scale

The new Tanaka B Intelligence Scale [22,23] uses diagrams, pictures, and symbols (such as numbers), and has no tasks or problems presented in story form. Diagrams and symbols are used for responses, so testing is not readily affected by learning differences, such as reading or writing, or by linguistic or cultural influences. There are seven subtest items, including mazes, calculating cubes, replacing figures and numbers, difference discrimination of character strings, completing a number series, erasing figures, and completing figures. Testing is divided into five parts depending on the subject's age, including testing for ages 6–8 years old (early elementary school), ages 8–10 years old (middle elementary school), ages 10–12 years old (late elementary school), ages 12–14 years (junior high school years 1 and 2), and age 14-adult (junior high school year 3 and high school and up). Testing was performed for subjects aged ≥14 years in the present study.

Procedures and Subjects

Of the 81 children/adolescents in a juvenile detention home between January 1, 2009 and December 31, 2010, all took both the new Tanaka B Intelligence Scale and the WISC-III. One juvenile detention home is generally located in each prefecture. These are public facilities where children/adolescents from age 12 to less than 20 years who have committed a criminal act in a prefecture are detained for a maximum of eight weeks until a court hearing and for the purpose of evaluating the individual and deciding a future educational plan. The homes are administered by the Correction Bureau of the Ministry of Justice in Japan.

Individuals who are detained at any juvenile detention home in Japan take a test battery which is prescribed by the Correction Bureau to assess their abilities and needs within three days when they enter a home. If it is determined that additional tests need to be performed, each home can perform them at its discretion. The new Tanaka B Intelligence Scale, some personality tests and so on are contained in the battery. It is conducted in a party of three to fifteen people. The home in question performs the Wechsler Intelligence Scale in addition to the battery at its own discretion, because most tests in the battery have not been standardized, yet. The WISC-III was performed individually by a psychologist who was not same tester who examined the new Tanaka B Intelligence Scale between the day after the group test and a judgment. Motivations of the cases for all the tests (group tests and individual tests) were high, because their attitude during the tests is reflected in their court.

Although some subjects had multiple admissions to the juvenile detention home, testing was not performed on the second admission or thereafter. In other words, no subject was enrolled in the study more than once.

The mean age of the subjects was 15.2 (SD 0.7) years, with a range of 14.0 years to 16.8 years; 77 (95.1%) subjects were male, and four (4.9%) were female. Regarding intellectual development, the mean WISC-III FIQ was 76.5 (SD 15.0), with a range from 51 to 127. There were 58 individuals who had an FIQ<85 (71.6%), of which 26 individuals had an FIQ<70 (32.1%). However, no subject had been detected having a deficit in intellectual function prior to testing. There were absolutely no subjects who received special services to aid intellectual development. Moreover, as well as 26 out of 81 cases having ID (FIQ less than 70), 5 cases had *Attention Deficit/Hyperactivity Disorder*, and 1 each respectively exhibited *Pervasive Developmental Disorder - Not Otherwise Specified*, *Conduct Disorder*, and *Somatoform Disorder*. There were no individuals who had more than two diagnoses. These diagnoses were

Table 1. Mean IQs and Intraclass correlation coefficients between BIQ and each of the WISC-III IQs.

	Mean (S.D.)	ICC between BIQ and each IQ
FIQ	76.5 (15.0)	0.83
VIQ	79.0 (14.2)	0.72
PIQ	78.8 (15.7)	0.81
BIQ	78.5 (16.9)	-

Notes. ICC, intraclass correlation coefficient; BIQ = The new Tanaka B Intelligence Scale IQ; FIQ = Full IQ; VIQ = Verbal IQ; PIQ = Performance IQ.
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determined based on the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, by experienced child psychiatrists.

Statistical Analysis

Power calculation. Power analysis was performed to establish the power needed to interpret the results for the present study. A SD of 15 was estimated for both the new Tanaka B Intelligence Scale IQ (BIQ) and the FIQ. Power was calculated using a 95% confidence interval (±5) of the difference between the two intelligence tests.

Internal consistency. To assess the internal consistency of the new Tanaka B Intelligence Scale, Cronbach's alpha coefficient was calculated for the seven subtest items, including mazes, calculating cubes, replacing figures and numbers, difference discrimination, completing a number series, erasing figures, and completing figures.

Accuracy of the BIQ score for the FIQ score. The BIQ and FIQ scores were plotted, and the differences between them were determined. To assess deviation and accuracy of the BIQ for the FIQ, mean percentage error (MPE) and root mean squared error (RMSE) were calculated [24].

Validity and clinical utility. To assess concurrent validity of the new Tanaka B Intelligence Scale with the WISC-III, the IQ scores on both tests were examined using a one-way analysis of variance intraclass correlation coefficient (ANOVA ICC).

Next, the performance of the new Tanaka B Intelligence Scale as a screening scale was evaluated using receiver operating characteristic (ROC) curve analysis. Areas under the ROC curve (AUC) and their 95% confidence intervals (95% CIs) were calculated using the parametric method. In addition, the likelihood and post-test probability for detection of FIQ<70 for each BIQ stratum were calculated using the stratum-specific likelihood ratio (SSLR) [25].

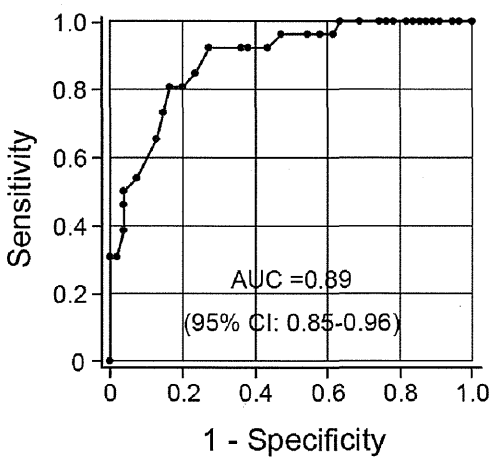

Figure 2. Receiver operating characteristic curves for BIQ for intellectual disability according to the WISC-III. Notes: AUC, area under the curve; 95% CI, 95% confidence interval.
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The SSLR indicates the odds ratio and is calculated as the "proportion of persons with a positive test among those with a disorder" divided by the "proportion of persons with a negative test among those without the disorder." The SSLR for each stratum is calculated as follows: $SSLR = (n_{1\,g}/N_1)/(n_{0\,g}/N_0)$, where $n_{1\,g}$ is the weighted number of subjects with the disorder in the g^{th} stratum, N_1 is the weighted total number of subjects with the disorder, $n_{0\,g}$ is the weighted number of subjects without the disorder in the g^{th} stratum, and N_0 is the weighted total number of subjects without the disorder. The post-test probability is a function of the SSLR, pretest odds, and post-test odds and is calculated as follows: pretest odds × SSLR = post-test odds, and post-test probability = (post-test odds)/(1+ post-test odds) [26]. Therefore, if the SSLR = 1, then the discrimination accuracy of the test is equal to chance probability. The closer the SSLR is to greater than one, the higher the likelihood of having a disorder. The closer the SSLR is to less than one, the lower the likelihood of having a disorder.

The validity of a test has traditionally been assessed using a single cut-off point approach in terms of sensitivity and specificity. A drawback in this case is that values not meeting the cut-off point, even values of results obtained as continuous variables, are treated uniformly regardless of magnitude. When using the SSLR for values of results obtained as continuous variables, the values of the results are stratified, and the probability of a disorder within each stratum can be calculated.

Ethical Considerations

The protocol of this study was approved by the Ethics Committees of the Japanese Association of Correctional Medicine and the Nagoya University Graduate School of Medicine, and the study itself was conducted in conformity with the established ethical standards of all institutions. All cases involved in this study had come out of the home. Furthermore, all of the data which was used in this study was clinical data obtained conventionally during the course of considering diagnosis and treatment, and we used it secondarily and retrospectively. Therefore, the requirement for informed consent was waived. Cooperation in the study placed no burden on individual cases. Personal information regarding subjects in this study and the resulting data were rendered anonymous, and analyses were performed using only quantitative data that could not be linked to any particular subject.

Table 2. Stratum-specific likelihood ratios and posttest probabilities of the BIQ for FIQ<70.

BIQ Stratum	Subjects		SSLR (95% CI)	Posttest probability
	FIQ≥70	FIQ<70		
51–60	1	8	16.9 (3.2–90.2)	0.89
61–65	1	5	10.6 (1.9–60.6)	0.83
66–70	7	8	2.4 (1.0–5.8)	0.53
71–75	6	3	1.1 (0.3–3.6)	0.33
76–85	19	1	0.1 (0.02–0.6)	0.05
≥86	21	1	0.02 (0.02–0.5)	0.05

Notes. SSLR, Stratum-specific likelihood rations; 95% CI, 95% confidence interval; BIQ = The new Tanaka B Intelligence Scale IQ; FIQ = Full IQ.
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Results

Power Calculation and Internal Consistency

The power for the present study including the 81 subjects was 0.85. Cronbach's alpha coefficient for the seven BIQ subtest items was $\alpha = 0.86$, indicating high internal consistency.

Accuracy of the BIQ Score for the FIQ Score

Figure 1 shows the distributions of the FIQ and BIQ scores. The mean FIQ was 76.5 (SD 15.0), while the mean BIQ was 78.5 (SD 16.9). The mean difference was 2.0 (SE 1.0, 95% CI −4.1–0.1). The MPE ± SE was 0.03±0.01, and the RMSE was 0.13. There was little deviation of the BIQ from the FIQ.

Validity and Clinical Utility

ANOVA ICC. The ANOVA ICC between the BIQ and FIQ was very high (0.83). Additionally, the ICC between BIQ with both the WISC-III verbal IQ (VIQ) and the performance IQ (PIQ) were also high (correlation coefficients: ICC = 0.72 and 0.81, respectively). Neither the VIQ alone nor the PIQ alone was predominantly reflected (see Table 1).

ROC analysis and the SSLRs. ROC analysis showed that the BIQ enabled screening of FIQ<70 with a high discrimination ability for FIQ<70 (area under the curve (AUC) = 0.89, 95% CI: 0.85–0.96) (see Fig. 2).

Next, the SSLRs were calculated. For the BIQ 51–60 stratum and the BIQ 61–65 stratum, the SSLRs were ≥10 (post-test probability for each stratum: 89%, 83%, respectively). Thus, individuals who have a deficit in intellectual function could be identified as possible. In addition, for the BIQ 76–85 stratum and the BIQ≥86 stratum, the SSLRs were approximately 0.1 (post-test probability of both strata: 5%). Thus, individuals who have a deficit in intellectual function could also be ruled out. For the BIQ 66–70 and 71–75 strata, the SSLRs were 2.4 and 1.1, respectively; the post-test probabilities were 33% and 53%, respectively (see Table 2). In the BIQ≤65 group overall, the SSLR was 13.8 (95% CI: 3.9–48.9, post-test probability: 87%); in the BIQ≥76 group overall, the SSLR was 0.11 (95% CI: 0.03–0.4, post-test probability: 5%).

Discussion

The new Tanaka B Intelligence Scale, an intelligence test that can be administered on groups, has been shown to have high split-half correlations, test-retest reliability, and concurrent validity with academic performance. However, there has not been enough information about this test for use as a standardized intelligence test. To standardize the new Tanaka B Intelligence Scale, the present study examined the reliability of the test and its concurrent validity with the WISC-III, an already established and standardized test for individual testing. Additionally, the clinical utility of the new Tanaka B Intelligence Scale was considered. Using the new Tanaka B Intelligence Scale in subjects aged ≥14 years old, there was high internal consistency and concurrent validity with the WISC-III. This demonstrated that, even in settings where performing individual intelligence tests (e.g. the WISC-III) is difficult, the new Tanaka B Intelligence Scale, a group intelligence test can be easily performed, can assess overall intellectual development and become one of the alternative to an individual test such as the WISC-III.

With an IQ score of the new Tanaka B Intelligence Scale≤65, the SSLR was ≥10 (post-test probability: 87%), and in the BIQ≥76 strata, the SSLRs were approximately 0.1 (post-test probability: 5%). Therefore, individuals who have FIQ<70 could be ruled in or out. In other words, ID can be efficiently diagnosed using detailed intelligence tests in individuals with a BIQ range of 66–75. Thus, this may be a useful test to easily screen for ID in the future.

The new Tanaka B Intelligence Scale can be administered on groups within a short period of time, with no special equipment or training required. Therefore, it can be performed in a variety of settings, enabling expanded assessment of intellectual development, even in locations where administering the WISC-III has previously been difficult. Furthermore, the verbal exchanges are simple instructions, and no complex interaction is required. Additionally, testing can be conducted on individuals with various linguistic backgrounds and verbal levels. In the present study, aside from a single cut-off point, by calculating SSLRs, predicted post-test probability for the results obtained could be determined. This point is important and significant in terms of clinical usefulness.

The SD of the FIQ for subjects in the present study was 15.0, so that the overall variation was normal. The range in intelligence was an FIQ of 51–127, thus covering the approximate strata for the general intelligence category and the category requiring an estimate of deficit in intellectual function. Furthermore, there was little work-up bias or spectrum bias in the juvenile detention home. However, the mean IQ was low, at 76.5±15.0, and 32.1% of the sample had an FIQ<70. The mean IQ of residents in juvenile correctional systems is lower than the IQ in the general public [27–33], which probably had an effect. However, none of the subjects had moderate to severe deficit in intellectual function, such as an FIQ≤50. Therefore, although there was some sample bias, many subjects had an IQ near the borderline for deficit in intellectual function, which was also an advantage in this study. Future studies should include a broader range of subjects. In

addition, 95.1% of the subjects were male, therefore future studies may also want to investigate the influence of sex. However, previous studies have reported that sex differences in VIQ, PIQ, and FIQ were negligible in Japanese and American samples [34].

In this study, the ratios of individuals who were diagnosed as having psychiatric disorders other than ID; such as Attention Deficit/Hyperactivity Disorder, were not significantly high compared with prevalence of these disorders in the general population. Therefore, sample bias on this point might be negligible. On the other hand, in terms of delinquent behavior, there might be sample bias, because most cases in this study conducted, or were entangled in, a delinquent act.

In conclusion, this study demonstrated sufficient reliability and concurrent validity of the new Tanaka B Intelligence Scale, a group intelligence test. In addition, the clinical utility of the scale in screening for individuals who have a deficit in intellectual function was also demonstrated. The validity of this test should be further evaluated within a broader setting including a wider range of subjects, for example, using a randomized sample of the general population. Additionally, the new Tanaka B Intelligence Scale may be performed on many different cultures, since it is easy to conduct, has simple instructions, and is not influenced by strong barriers to language. It is hoped that the present study's results contribute to the proper assessment of intellectual development as well as specialized and effective care and services based on the current findings.

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Author Contributions

Conceived and designed the experiments: YU HM YI. Performed the experiments: YU HM YI. Analyzed the data: YU RY MA NO. Contributed reagents/materials/analysis tools: YU HM YI. Wrote the paper: YU HM RY YI MA NO.

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A pilot study on the effects of cognitive remediation on hemodynamic responses in the prefrontal cortices of patients with schizophrenia: A multi-channel near-infrared spectroscopy study

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ABSTRACT

The regional neuronal changes taking place between before and after cognitive rehabilitation are still not characterized in schizophrenia patients. In addition, it is not known whether these regional changes are predictive or correlated with treatment response. We conducted a preliminary quasi-experimental study to investigate the effects of a Neuropsychological Educational Approach to Cognitive Remediation (NEAR), one of the cognitive remediation therapies, on neurocognitive functioning assessed by the Japanese version of the Brief Assessment of Cognition in Schizophrenia (BACS-J), and on prefrontal and temporal hemodynamic responses during working memory (WM) task (2-back, letter version) using 52-channel near-infrared spectroscopy (NIRS). We assessed 19 patients with schizophrenia or schizoaffective disorder twice with an interval of 6 months. Moreover, taking into consideration the possible practice effect, we assessed 12 control patients twice with an interval of 6 months. The NEAR group, in comparison with the control group, showed significant improvement in two subcomponents of BACS-J, that is, motor speed and executive function along with the composite scores. The NEAR group also showed a significant increase in brain activation in the bilateral cortical regions associated with WM, and in comparison with the control group the between-group differences were restricted to the right frontopolar area. In addition, the amount of enhancement in some cognitive subcomponents was positively correlated with the magnitude of an increase in hemodynamic response during WM task predominantly in the right hemispheres. These findings suggest that neurocognitive deficits in schizophrenia and their neural dysfunction may be improved by NEAR, and NIRS may be a useful tool to assess the changes of the neural activity underlying the improvement of neurocognitive functioning elicited by neurocognitive rehabilitation.

1. Introduction

Cognitive impairment in schizophrenia is now considered to be a core symptom along with the positive, negative and mood symptoms. Of these 4 core symptom categories, cognitive impairment has been demonstrated to result in the greatest difficulties in daily functioning, such as those related to working capacity and daily living. Cognitive regions that show marked impairment in schizophrenia include attention (vigilance), executive function, long-term and learning memory, working memory, and verbal fluency (Green, 1996; Rund and Borg, 1999; Green et al., 2000; Pantelis and Maruff, 2002; Sharma and Antonova, 2003). In a meta-analytic review by Green et al. (2000), the authors subdivided the functional outcome into three general categories; a) psychosocial skill acquisition, b) social problem solving/instrumental skills, and c) community/daily activities. They found that secondary verbal memory was reliably related to every outcome domain, and immediate memory was related to psychosocial skill acquisition. Card sorting and verbal fluency were both associated with community outcomes, and vigilance was linked to skill performance. Moreover, they suggested that the total amount of variance in functional outcome that can be explained by neurocognition in general was approximately 20–60% (Green et al., 2000), however, in a more recent study the amount was downsized to 20–40% (Couture et al., 2006). Green et al. (2004) also suggested that longitudinal studies revealed considerable support for longitudinal associations between cognition and community outcome in schizophrenia.

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Cognitive impairment is already present in the prodromal phase of schizophrenia and is exacerbated when the first episode occurs; moreover, there is often little subsequent change. Meier et al. (2013) demonstrated that there is substantial neuropsychological decline in schizophrenia from the premorbid to the post-onset period, particularly in the field of processing speed, learning, executive function, and motor function, but the extent and developmental progression of decline varied across mental functions. For instance, processing speed deficits increased gradually from childhood to beyond the early teen years, whereas verbal deficits emerged early but remained static thereafter. Cognitive impairment did not change even when positive symptoms or other psychiatric symptoms are improved after drug therapy (Bratti and Bilder, 2006); in fact, a longer duration of untreated psychosis (DUP) typically results in more marked cognitive impairment (Perkins et al., 2005). However, the degree of cognitive impairment greatly varies among different individuals. Whereas approximately 15% of patients remain within the normal range on almost all aspects of cognitive function, most patients score 1–1.5 standard deviations (SD) lower on cognitive function assessments than healthy individuals (Bilder et al., 2000; Heinrichs, 2004). Although a wide range of cognitive properties are impaired, and much research has been conducted to understand how the cognitive impairments in schizophrenia impact daily functioning, an overall picture has not yet emerged. It is more or less an established fact that cognitive impairment has a crucial effect on social turning points; for example, levels of impairment in verbal memory, attention, and executive functioning are predictors of goal achievement in society (Green et al., 2004). Furthermore, attentional impairments continue to hinder the acquisition of life skills even after the effects of social skills training or other forms of rehabilitation have been manifested (Medalia and Choi, 2009); therefore, therapies targeting cognitive impairment are crucial. Currently, the typical effect size of atypical antipsychotic agents for cognitive impairment is small (0.2–0.5) (Woodward et al., 2005; Keefe et al., 2007), and their effects are limited when used alone. On the other hand, there are great expectations for the non-pharmacological treatment of cognitive rehabilitation. Cognitive remediation has been indicated to improve neuropsychological functioning (Krabbendam and Aleman, 2003; Twamley et al., 2003; McGurk et al., 2007; Wykes et al., 2011; Ikezawa et al., 2012), although not all (Ueland and Rund, 2004; Dickinson et al., 2010). However, little research has been conducted on the effects of cognitive rehabilitation on brain function (Wykes et al., 2002; Haut et al., 2010; Bor et al., 2011; Subramaniam et al., 2012).

We have become interested in one of the cognitive remediation therapies "Neuropsychological Educational Approach to Cognitive Remediation (NEAR)" (Medalia and Freilich, 2008; Medalia and Choi, 2009), which was theoretically based on neuropsychology, educational psychology, learning theory and cognitive psychology. NEAR is an evidence-based approach to cognitive remediation specifically developed for use with psychiatric patients. NEAR is a group-based treatment that provides a positive learning experience to each and every client, to promote independent learning, and to promote optimal cognitive function in everyday life.

Near-infrared spectroscopy (NIRS) is a neuroimaging tool that offers several advantages: it is noninvasive, easy to set up, requires minimal constraints, does not occupy a large space, and works silently. NIRS is therefore suitable for assessing prefrontal activation in patients with severe mental illnesses, including schizophrenia. Indeed, NIRS has been used to assess brain functions in many psychiatric disorders (Kameyama et al., 2006; Pu et al., 2012, 2013; Takizawa et al., 2013).

In the present pilot study, we investigated the feasibility of NIRS during performance of a working memory (WM) task as an assessment tool for detecting changes in brain function associated with the pre–post intervention effects of 6 months of NEAR on neuropsychological improvement. We also explored the feasibility of NIRS data as a predictor of the effects of NEAR when neurocognitive functioning and psychiatric symptoms were treated as outcome measures.

2. Methods

2.1. Patients (Table 1)

After a complete explanation of the study, informed consent was obtained from the participants. The protocol of this study was approved by the Ethics Committee of Tottori University. Inclusion criteria were outpatients or inpatients (a) with a diagnosis of schizophrenia or schizoaffective disorder according to DSM-IV-TR criteria, (b) between 13 and 65 years old, (c) able to sit for a one-hour session, (d) willing to participate in the study, and (e) the treatment being recommended by their doctors. Exclusion criteria were patients (a) with active substance or alcohol abuse or post detox within 1 month, or (b) with traumatic head injury within the past 3 years. The diagnoses were made by two expert psychiatrists.

Nineteen patients with schizophrenia or schizoaffective disorder participated in the study. Twelve were paranoid schizophrenia, 2 disorganized schizophrenia, 1 undifferentiated schizophrenia, 1 residual schizophrenia, and 3 were schizoaffective disorder. As can be seen by the mean PANSS scores at baseline (Table 2), the symptom severity of the patients was mild to moderate level (Leucht et al., 2005; Levine et al., 2008).

Although the medications were changed throughout the whole period as little as possible, there were 7 patients whose medications needed to be changed because of clinical decisions. The change in the medication status of these 7 patients was only related to daily dosage levels.

Moreover, we assessed 12 control patients, meeting the inclusion criteria (a), (b) and exclusion criteria (a), (b), twice with an interval of 6 months, taking into consideration a possible practice effect, which may have affected the scores of neuropsychological tests. They did not receive any cognitive training program including NEAR. Although the age was not significantly different from the NEAR group, the onset age was significantly younger and the duration of illness was longer than those of the NEAR group suggesting more chronicity in the control group. Moreover, the daily dosage level of antipsychotic drugs was significantly lower than the NEAR group. Besides these between-group differences, the level of cognitive function assessed using BACS-J was not significantly different between the two groups.

The NEAR group and the control group were nonrandomized, and thus, the study design was quasi-experimental.

2.2. NEAR program

The NEAR program consisted of two one-hour computer sessions per week and an additional group meeting session lasting 30 to 60 min once a week. The subjects completed approximately six months of NEAR sessions before being assessed for the efficacy.

In each computer session, patients engaged in some educational computer software that involved various domains of cognitive function including attention, memory, and executive function (see Supplementary Table 1), taking into account the profiles of the patients' cognitive impairments. The computer software also involves various levels of complexities and is adapted to personal level of cognitive abilities and the subject's interest.

The main aim of the group meeting sessions is to contextualize the computer training into their everyday activities. More specifically, the patients would talk about the difficulties they meet in their everyday activities and try to relate them to certain cognitive regions and finally to the computer software they are engaged in. The process should lead to enhancing motivation and generalization of cognitive skills to daily life. The fidelity of both computer sessions and group meeting sessions were checked by a supervisor, who had already undergone training to become a trainer.

Table 1
Baseline demographic variables.

		NEAR group N = 19 (mean ± SD)	Control group N = 12 (mean ± SD)
Number of patients		Sch:16 SchAf: 3	Sch:12 SchAf: 0
Age, years		28.5 ± 7.60	31.4 ± 9.60
Gender, women/men		11/8	9/3
Handedness (%)		77.3 ± 48.74	68.5 ± 73.67
Education, years		13.7 ± 1.88	14.7 ± 2.46
Estimated premorbid IQ		98.5 ± 10.41	102.8 ± 11.50
Age at onset, years *		22.2 ± 5.91	18.3 ± 3.77
Duration of illness, years *		6.3 ± 5.74	13.1 ± 9.47
NEAR attendance rate (%)		92.7 ± 9.84	
BACS-J	Verbal memory	−1.321 ± 0.882	−1.326 ± 1.231
	Working memory	−1.186 ± 0.822	−0.975 ± 1.087
	Motor speed	−1.953 ± 1.159	−0.833 ± 1.703
	Verbal fluency	−0.916 ± 0.765	−0.270 ± 0.980
	Attention and speed of information processing	−1.366 ± 0.640	−1.335 ± 0.920
	Executive function	−0.868 ± 1.580	−0.435 ± 1.223
	Composite score	−1.269 ± 0.706	−0.862 ± 1.025
Mean dosage of antipsychotics * (Chlorpromazine equivalent dose) (mg/day)		663.3 ± 448.87 (baseline) 621.0 ± 379.94 (post-treatment)	368.3 ± 204.52 (baseline) 369.4 ± 269.75 (post-treatment)

Abbreviations: Sch, Schizophrenia; SchAf, Schizoaffective disorder; IQ, Intelligence Quotient; NEAR, Neuropsychological Educational Approach to Cognitive Remediation.
* $p < 0.05$ Student's *t*-test.

2.3. Assessments

The following tests were administered twice, once before beginning NEAR (pre-treatment) and once after completing NEAR (post-treatment at 6 months period):

a) Brief Assessment of Cognition in Schizophrenia, Japanese version (BACS-J) (Keefe et al., 2004; Kaneda et al., 2007);

b) Positive and Negative Syndrome Scale (PANSS) (Kay et al., 1987).

Finally, NIRS was used to measure changes in the cerebral blood volume in the frontotemporal cerebral cortices during performance of a 2-back task (WM task).

2.3.1. Cognitive function

We assessed cognitive function by using BACS-J. Z scores were calculated for each subcomponent scores using means and standard deviations based on the dataset of 340 healthy control Japanese populations; however, it must be noted that age, sex, and socio-economic status of the healthy controls were not necessarily controlled with the patients in the present study. Composite scores were calculated by averaging all z scores of the six subcomponents (verbal memory, WM, motor speed, verbal fluency, attention and speed of information processing, and executive functions), and then re-normed based upon the standard deviations (SD) of the average of those scores in the normative sample (SD = 0.6).

2.3.2. NIRS measurements

2.3.2.1. Activation task. We used a 2-back task with a blocked periodic baseline–activation–baseline (Fig. 1) design to activate brain regions specialized for maintenance components of verbal WM, as originally described by Cohen et al. (1994). Two contrasting conditions were visually presented in 60-s periods to subjects on a computer screen placed approximately 1 m away from the subjects' eyes. During the period of the baseline (B) condition, subjects viewed a series of figures (0–9), which appeared one at a time, and were required to press a button with their right index finger whenever the figure "9" appeared (0-back). During the period of the activation (A) condition, subjects again viewed a series of figures (0–9) and were required to press a button with their right index finger if the currently presented figure was the same as that presented 2 trials previously (2-back, e.g., 5–1–5 but not 2–6–3–2 or 2–7–7). The WM task consisted of a 60-s pre-task period

Table 2
Before-and-after test and time * group interaction effect in ANOVA on BACS-J data, PANSS, and behavioral indicators of the 2-back task in comparison with control group.

		NEAR group N = 19 (mean ± SD)		Before-and-after test		Control group N = 12 (mean ± SD)		Time * group interaction	
		Baseline	Post-treatment	*t*	p	Baseline	Post-treatment	F	p
BACS-J	Verbal memory	−1.321 ± 0.882	−0.365 ± 1.165	−4.69	<0.0005	−1.326 ± 1.231	−1.093 ± 1.491	6.05	<0.05
	Working memory	−1.186 ± 0.822	−0.922 ± 0.970	−1.56	n.s.	−0.975 ± 1.087	−0.746 ± 0.974	0.02	n.s.
	Motor speed	−1.953 ± 1.159	−0.805 ± 1.347	−4.09	<0.001	−0.833 ± 1.703	−0.934 ± 1.625	11.03	<0.005
	Verbal fluency	−0.916 ± 0.765	−0.689 ± 0.944	−1.21	n.s.	−0.270 ± 0.980	−0.355 ± 0.967	1.45	n.s.
	Attention and speed of information processing	−1.366 ± 0.640	−0.994 ± 0.674	−3.02	<0.01	−1.335 ± 0.920	−1.311 ± 0.942	4.33	<0.05
	Executive function	−0.868 ± 1.580	0.071 ± 1.046	−3.40	<0.005	−0.435 ± 1.223	−0.435 ± 0.981	6.58	<0.05
	Composite score	−1.269 ± 0.706	−0.619 ± 0.648	−6.18	<0.0001	−0.862 ± 1.025	−0.812 ± 0.964	18.70	<0.001
PANSS	Total	65.1 ± 11.05	61.2 ± 12.26	1.49	n.s.	62.8 ± 13.63	60.0 ± 14.38	0.19	n.s.
	Positive	13.5 ± 3.83	11.9 ± 3.91	2.43	<0.05	13.3 ± 3.52	12.8 ± 3.39	1.94	n.s.
	Negative	18.7 ± 5.06	17.8 ± 4.83	0.71	n.s.	18.2 ± 4.91	16.8 ± 5.52	0.02	n.s.
	General psychopathology	32.9 ± 5.83	31.5 ± 7.33	0.79	n.s.	31.3 ± 7.77	30.3 ± 7.88	0.05	n.s.
Task performance (2-back)	Reaction time (ms)	715.3 ± 209.97	701.5 ± 221.57	0.40	n.s.	818.6 ± 251.60	719.2 ± 138.68	2.11	n.s.
	Sensitivity A′	0.93 ± 0.120	0.97 ± 0.097	−1.90	<0.1	0.94 ± 0.078	0.96 ± 0.054	0.36	n.s.

NEAR, Neuropsychological Educational Approach to Cognitive Remediation; BACS-J, Brief Assessment of Cognition in Schizophrenia, Japanese version; PANSS, Positive and Negative Symptom Scale.

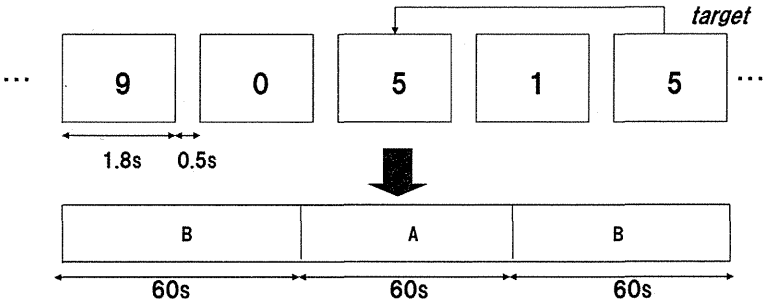

Fig. 1. The task design of 2-back task. A: Activation condition: 2-back. B: Baseline condition: 0-back, "9" as target.

(baseline (B) condition), a 60-s 2-back task period (activation (A) condition), and a 60-s post-task period (baseline (B) condition). Each period comprised 25 stimuli (5 targets, stimulus duration 1.8 s, stimulus onset asynchrony (SOA) = 2.3 s). Behavioral performance for the 2-back task was monitored and measured in terms of reaction time (RT) to target figures and sensitivity A′ (Grier, 1971). Sensitivity A′ is an index of information processing ability using both "hit rate (HR)" and "false alarm rate (FAR)" for calculation, which is expressed as below:

$$A' = 0.5 + (HR - FAR)(1 + HR - FAR)/4HR(1 - FAR)$$

High A′ implies high information processing ability. All subjects received a brief period of identical training to ensure that they understood the rule of the task prior to measurement.

2.3.2.2. NIRS machine. The 52-channel NIRS (ETG-4000, Hitachi Medical Co.) machine measures relative changes in oxy-Hb and deoxy-Hb using 2 wavelengths (695 and 830 nm) of infrared light based on the modified Beer–Lambert law (Yamashita et al., 1996). In this system, these Hb values include a differential pathlength factor (DPF). In addition, Zhao et al. (2002), using a Monte Carlo simulation, reported that the estimated DPF variation in the forehead region of adult humans was regarded as roughly homogeneous. The distance between pairs of source-detector probes was set at 3 cm, and each measuring 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. This corresponds to the surface of the cerebral cortex (Toronov et al., 2001; Okada and Delpy, 2003). The probes of the NIRS machine were placed on the frontotemporal region of the participant, with the midcolumn of the probe located over Fpz, and the lowest probes were located along the T3–Fp1–Fpz–Fp2–T4 line in accordance with the international 10/20 system for electroencephalography. The arrangement of the probes enabled the measurement of Hb values from both prefrontal and temporal cortical surface regions (Fig. 2). The correspondence between the NIRS channels and the measurement points on the cerebral

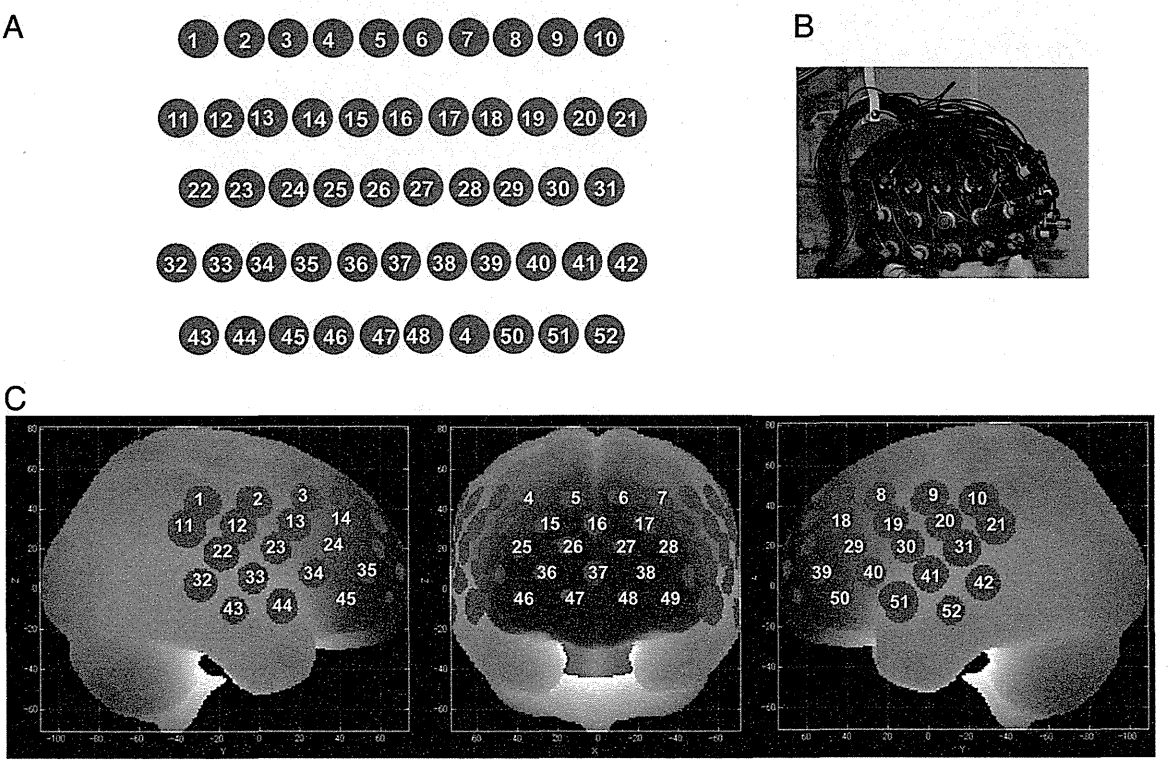

Fig. 2. Probe setting and measurement points for 52-channel near-infrared spectroscopy (NIRS). (A) The 52 measuring areas are labeled ch1 to ch52 from the right posterior to the left anterior. (B–C) The probes with 3 × 11 thermoplastic shells were placed over a subject's bilateral prefrontal and superior temporal cortical surface regions. The channel numbers are indicated above the estimated cortical regions.

cortex was confirmed by a multi-subject study of anatomical cranio-cerebral correlation (Okamoto et al., 2004), and was presented according to the results of the virtual registration method (Tsuzuki et al., 2007).

The rate of data sampling 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 immediately before the task period; and the post-task baseline was determined as the mean over the last 5 s of the post-task period. Linear fitting was applied to the data between these 2 baselines. A moving average method using a window width of 5 s was applied to remove any short-term motion artifacts. Because we could not remove all artifacts in this way, we applied semi-automatic rejection of data with artifacts separately for each channel (Takizawa et al., 2008; Pu et al., 2012).

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 (Hoshi et al., 2001; Strangman et al., 2002).

2.4. Statistical analysis

Statistical analyses were performed using SPSS Statistics 19.0 software (Tokyo, Japan).

Cognitive function (BACS-J data) and psychiatric symptoms (PANSS) pre- and post-6 months of NEAR were compared with paired *t*-tests. Behavioral indicators of the 2-back task (reaction time, sensitivity A′) assessed before and after NEAR treatment were compared with a Wilcoxon signed-rank test. The mean [oxy-Hb] changes were compared between the two measurements (pre- and post-NEAR sessions) for each channel using a paired *t*-test. Moreover, repeated measures analyses of variance were performed on BACS-J data and the mean [oxy-Hb] changes using 'group' (NEAR group, control group) as an inter-individual factor, while 'time' (baseline, post-treatment) was used as an intra-individual factor. With the aim of controlling for the between-group differences in age of onset, duration of illness and daily dosage levels, additional analyses were performed using these variables as covariates. A p value <0.05 was considered to be statistically significant.

The correlations between change in [oxy-Hb] pre- and post-NEAR (or pre-NEAR) with WM performance and BACS-J, PANSS data, behavioral indicators, and NEAR attendance rate were examined with Spearman's Rho.

3. Results

Table 1 shows the participants' demographic data.

3.1. The NEAR treatment change of BACS-J data, PANSS, behavioral indicators of the 2-back task (Table 2), and [oxy-Hb] activation during WM task (Fig. 3)

There were significant improvements in the scores of verbal memory, motor speed, attention and speed of information processing, executive functioning and the composite score of BACS-J (Table 2).

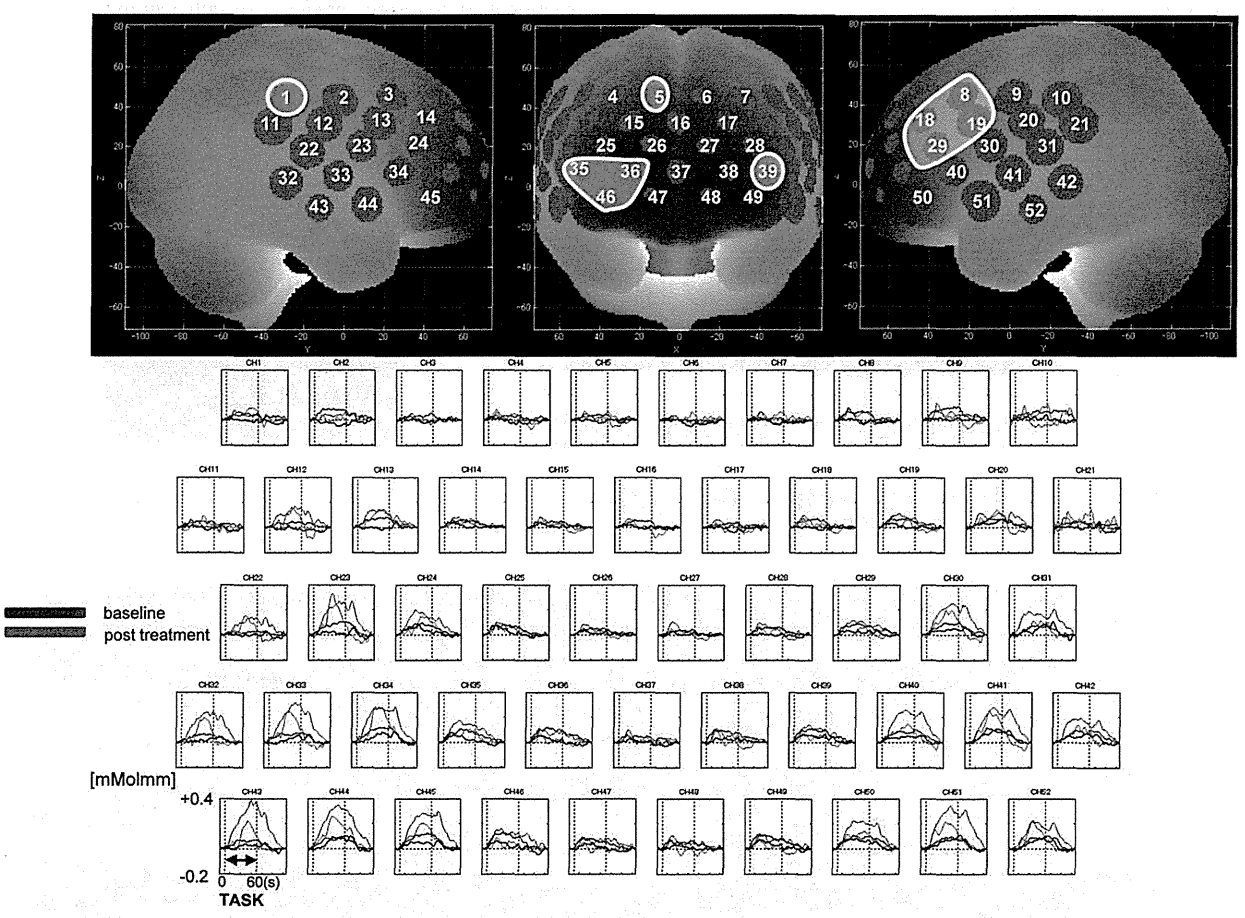

Fig. 3. Above: Brain area in yellow corresponds to the NIRS channels with significantly increased [oxy-Hb] in the after completing NEAR than in the before beginning NEAR. The locations of NIRS channels were probabilistically estimated and anatomically labeled in the standard brain space in accordance with Tsuzuki et al. (2007). Below: Grand averaged waveforms of [oxy-Hb] during WM task (between two dotted vertical lines in each graph) in 52 channels over the frontal and temporal regions measured by NIRS. Red and blue lines represent baseline and post-treatment, respectively. Thin and thick lines represent NEAR and control groups.

After NEAR, the PANSS positive scale significantly improved (paired t-test: $p < 0.05$), but the overall score, negative scale, or general psychopathology scale did not change (paired t-test: n.s.) (Table 2).

There were no significant differences between the two measurement points (pre- and post-NEAR sessions) in task performance (reaction time, sensitivity A′) (Table 2).

Post-treatment was associated with significantly increased [oxy-Hb] changes compared to pre-treatment at 10 channels (ch1, ch5, ch8, ch18, ch19, ch29, ch35, ch36, ch39, and ch46; paired t-tests p: 0.005 to 0.05). The cortical areas in question were primarily the bilateral dorsolateral prefrontal cortices (PFC) (BA9, 46), left ventrolateral PFC (BA45, Broca's area), and right frontopolar (BA10) (Fig. 3).

3.2. In comparison with control patients

There were significant interactions between 'group' and 'time' in verbal memory, motor speed, attention and speed of information processing, executive function, and composite scores (Table 2). The improvement of these areas was significantly greater in the NEAR group than in the control group. The significant interactions observed for motor speed, executive function and composite scores survived after controlling for the age of onset, duration of illness and daily dosage levels. There were no difference between groups in terms of the change in working memory and verbal fluency.

There were significant interactions between 'group' and 'time' in 12 channels (ch12, ch13, ch28–30, ch33, ch35, ch36, ch39, ch40, ch45, and ch46; F: 4.395 to 7.131; p: 0.014 to 0.048). The increase of [Hb] changes in these areas was significantly greater in the NEAR group than in the control group. The cortical areas in question overlapped the areas where significant increase was observed in the before-and-after test. The significant interactions were observed after controlling for the age of onset, duration of illness and daily dosage levels in the four channels (ch33, ch36, ch44, and ch46; F: 4.380 to 7.100; p: 0.012 to 0.046) located mainly in the right frontopolar (BA10) area.

3.3. Correlation analyses

Regarding the relationship between change in cognitive function and the cerebral blood volume, significant positive correlations were observed in 5 channels (ch22, ch23, ch32, ch33, and ch44; rho: 0.49 to 0.57; p: 0.01 to 0.05) in the right hemisphere between changes in verbal memory in the BACS-J and changes in [oxy-Hb] elicited by the WM task pre- and post-NEAR. The cortical areas in which correlations were observed were the superior and medial temporal cortices (BA21, 22), and the temporopolar area (BA38) (Fig. 4A, B). Significant positive correlations between changes in verbal fluency in the BACS-J and changes in [oxy-Hb] were also observed in 7 channels (ch2, ch6, ch14, ch25, ch26, ch36, and ch37; rho: 0.47 to 0.61; p: 0.01 to 0.05), primarily in the right hemisphere. The cortical areas in which these correlations were observed were the dorsolateral PFC (BA9, 46), and frontopolar (BA10) (Fig. 4A, C). No significant correlations were observed between changes in the other 4 subcomponents of the BACS-J (WM, motor speed, attention and speed of information processing, executive functioning) and changes in [oxy-Hb] elicited by the WM task pre- and post-NEAR.

Regarding the relationship between changes in the cerebral blood volume and psychiatric symptoms and behavioral indicators of the 2-back task, no significant correlations were observed between changes in the PANSS positive (rho: −0.43 to 0.32, n.s.), negative (rho: −0.59 to 0.39, n.s.), general psychopathology (rho: −0.51 to 0.45, n.s.), and total

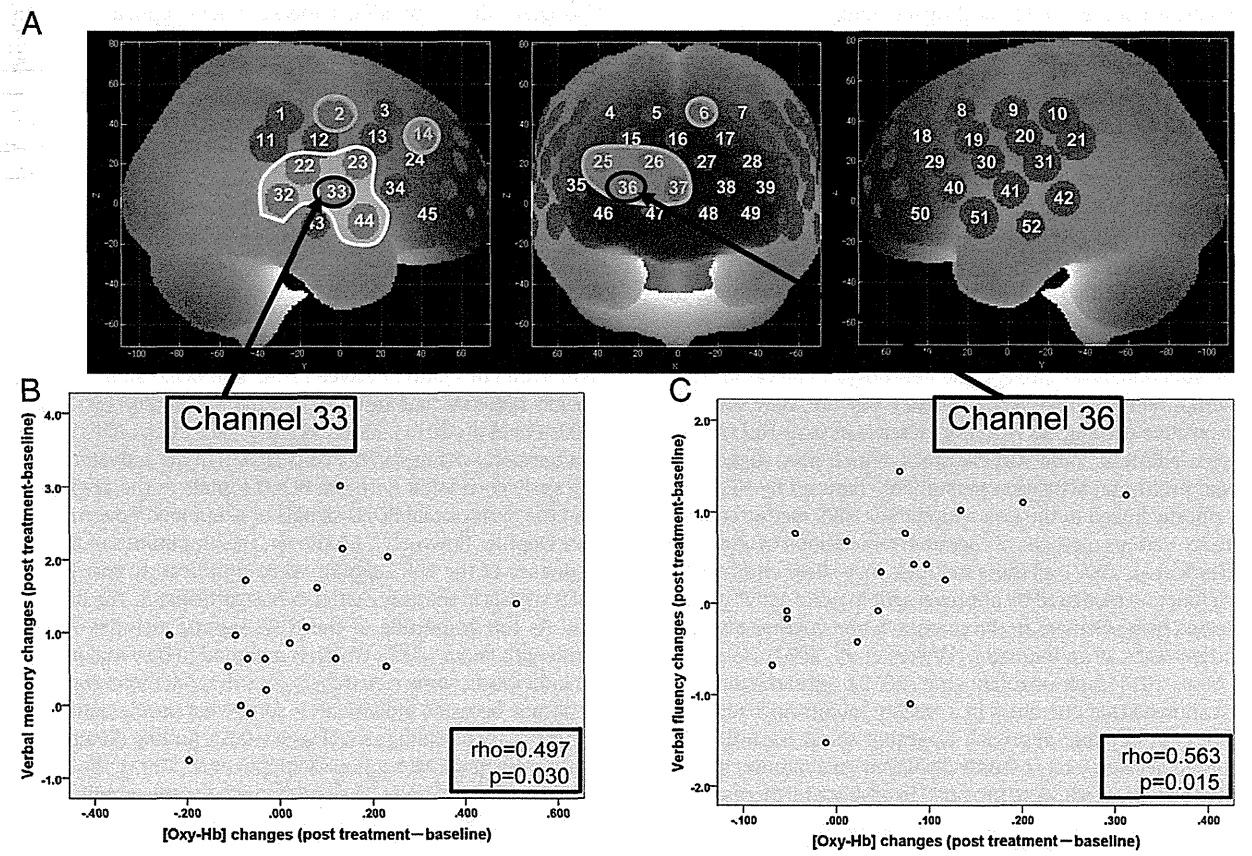

Fig. 4. (A) The relationship between cognitive function and changes in [oxy-Hb] associated with working memory tasks before and after NEAR. Green and yellow represent verbal memory and verbal fluency changes in the BACS-J, respectively. (B) Scatter diagrams showing the relationship between verbal memory and [oxy-Hb] changes in channel 33 (Spearman's Rho; rho = 0.497, p = 0.030). (C) Scatter diagrams showing the relationship between verbal fluency and [oxy-Hb] change in channel 36 (Spearman's Rho; rho = 0.563, p = 0.015). The locations of NIRS channels were probabilistically estimated and anatomically labeled in the standard brain space in accordance with Tsuzuki et al. (2007).

(rho: −0.53 to 0.46, n.s.) scale, reaction time (rho: −0.39 to 0.43, n.s.), and sensitivity A′ (rho: −0.26 to 0.41, n.s.) and changes in [oxy-Hb] pre- and post-NEAR.

Significant positive correlations were observed in only 2 channels (ch21, rho = 0.54, p = 0.03; ch29, rho = 0.58, p = 0.009) in the left ventrolateral PFC (BA45) between the improvement in the composite score of BACS-J and [oxy-Hb] elicited by the WM task at pre-NEAR.

4. Discussion

In the present study, we performed a preliminary examination about the feasibility of NIRS as an assessment tool to assess the effects of NEAR, a form of cognitive task remediation, on brain function. In certain cortical areas, 6 months of NEAR was shown to induce the plastic change of increased [oxy-Hb] elicited by the 2-back WM task. The cortical areas in which activation due to NEAR was inferred were the bilateral dorsolateral PFC (BA9, 46), left ventrolateral PFC (BA45, Broca's area), and right frontopolar (BA10). The finding in the before-and-after test was supported by the significant interaction effect in the repeated measures ANOVA including the control group. Although the number of channels that showed significant interactions was reduced, the effect was still significant in four channels after controlling for the between-group differences in age of onset, duration of illness and daily dosage levels. In contrast, the sensitivity A′, which represents the task performance only showed a tendency for significant improvement. Considering the high level of sensitivity A′ at pre-NEAR (0.93) the lack of significant improvement may be due to the ceiling effect. These cortical areas roughly coincide with the n-back activation areas observed in healthy volunteers (Cohen et al., 1997; Owen et al., 2005). Although preliminary as it is, the finding suggests that the activation of the brain due to NEAR represents a change towards "normalization," but not the compensatory changes occurring in areas not activated in healthy individuals.

Hypofrontality (Callicott et al., 1999) shown in WM tasks was once considered to be a trait marker of schizophrenia. However, results from recent functional neuroimaging studies have demonstrated that intensive cognitive rehabilitation increases activity in brain areas associated with WM (Wexler et al., 2000; Wykes et al., 2002; Bor et al., 2011). Although NEAR does not include training using 2-back tasks, the results of the present study indicated that 6 months of NEAR has the potential to give rise to functional plasticity in cortical areas associated with this task. Although WM in BACS-J did not improve in our target group, significant improvement had been observed in a larger sample study using NEAR (Ikezawa et al., 2012); thus, it is possible that improvement in brain function, as indicated by [oxy-Hb] increase, may lead to improved WM function. Alternatively, the neuropsychological improvement in verbal memory and verbal fluency but not WM showed a significant positive correlation with the increase in [oxy-Hb] between pre- and post-NEAR in some cortical areas, which may suggest that the observed prefrontal activation presumably induced by NEAR may not be specifically linked to the task adopted for NIRS measurement.

As there are various methods of cognitive remediation in addition to NEAR (McGurk et al., 2007), all these methods may show improvement in cognitive function mediated by improvement in brain activity, which can be assessed using changes in the cerebral blood volume associated with cognitive tasks as an indicator (Wykes et al., 2002; Haut et al., 2010; Bor et al., 2011; Subramaniam et al., 2012). Subramaniam et al. (2012) first showed that outcomes in a "reality monitoring" task were improved by a systematic approach targeting social cognition. The task requires subjects to look at words displayed on a monitor and distinguish whether the words were provided in advance by themselves or someone else; importantly, patients with schizophrenia are considered to be poor at distinguishing words that they provided themselves from those provided by others. The larger the change in medial PFC activation correlating with behavioral indicators in this task, the more favorable social functioning appeared when assessed 6 months following the completion of rehabilitation. Therefore, it was shown that the level of activation in medial PFC during this task might predict the effects of rehabilitation on social functioning (Subramaniam et al., 2012). We also found a positive correlation between the [oxy-Hb] elicited by the 2-back task in left PFC (ch29, rho = 0.58, p = 0.009) before NEAR and changes in the composite score of BACS-J after 6 months of NEAR. The outcome in the present study was cognitive functioning instead of social functioning, nevertheless, the baseline activation (before NEAR) of the cerebral blood volume elicited by the WM task before NEAR may also predict the effects of cognitive remediation on cognitive functioning.

Eack et al. (2010) found that a two-year trial of cognitive enhancement therapy targeting impairments in both neurocognition and social cognition suppressed disease-related volume reductions in the left hippocampus, parahippocampal gyrus, fusiform gyrus, and amygdala, thereby demonstrating an apparent neuroprotective effect of this mode of cognitive therapy (Eack et al., 2010). Although very little research has been conducted on the mechanisms of improvement in brain function due to cognitive remediation (Vinogradov et al., 2009), the mechanisms may be related to both the neuroprotective effect and the plasticity of relevant neural circuits.

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. Furthermore, NIRS can measure brain activity in the frontpopolar with high signal-to-noise ratio, whereas fMRI has potential problems for data quality of areas located under the frontal sinus (Koike et al., 2013).

Although NIRS has advantages compared to fMRI as above, it is also associated with a limitation in measurement depth and poor spatial resolution. 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. (2011) 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 (Strangman et al., 2002; Cui et al., 2011). More recently, Sato et al. (2013) 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 (Mehagnoul-Schipper et al., 2002), 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. (2002). It may give support to the results of the present study as well as other studies analyzing NIRS signals across subjects.

This pilot feasibility study has the following limitations and certainly not conclusive: 1) the sample size is small; 2) changes in brain function

in certain areas (the medial PFC, parietal lobe and other areas in the posterior part of the cortex, and the subcortical core) could not be detected due to the limitation of NIRS; and 3) the effects of multiple tests were not taken into account. In future studies, these points should be addressed in a randomized control trial with a larger sample size.

Our study suggests that neurocognitive deficits in schizophrenia and its related disorder, and their underlying neural dysfunction may be improved by NEAR, and NEAR may improve neurocognitive functioning through biological effects involving changes in the cerebral blood volume.

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.schres.2014.01.031.

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Contributors

Shenghong Pu, Kazuyuki Nakagome, Tamiko Mogami and Koichi Kaneko designed the study and wrote the protocol. Shenghong Pu, Kazuyuki Nakagome and Koichi Kaneko undertook the statistical analysis. Shenghong Pu, Takeshi Yamada, Satoru Ikezawa, Masashi Itakura, Takahiro Satake, Hisahito Ishida, Izumi Nagata, Tamiko Mogami and Koichi Kaneko conducted data acquisition. Shenghong Pu, Kazuyuki Nakagome and Koichi Kaneko analyzed the data. Shenghong Pu, Kazuyuki Nakagome and Koichi Kaneko wrote the first draft of the manuscript, and the other authors revised it critically for important intellectual content. All authors have approved the final version of the manuscript.

Conflict of interest statement

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

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Regular Article

New instrument for measuring multiple domains of social cognition: Construct validity of the Social Cognition Screening Questionnaire (Japanese version)

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Aim: The present study aimed to test the construct validity and internal consistency of the Social Cognition Screening Questionnaire (SCSQ) (Japanese version).

Methods: We first tested whether the subscale scores and the total score of the SCSQ could discriminate patients with schizophrenia from normal controls. Next, we tested the internal consistency. Finally, we investigated the relation between the subscale scores and other measures of social cognition and social functioning that were presumed to correspond to the subscale's scores, including the Hinting Task, the Ambiguous Intentions Hostility Questionnaire (AIHQ), the Beck Cognitive Insight Scale and the Social Functioning Scale.

Results: The subscale scores and the total score appeared to show more robust between-group differences than other measures of social cognition, such as the AIHQ and the Hinting Task. The total score distinguished the patients from normal controls with an area under the receiver–operator curve of 0.84, which indicated a high level of discrimination. The Cronbach's alpha for the four subscales was 0.72, which was considered acceptable. In terms of criterion-related validity, theory of mind, metacognition and hostility bias subscale scores showed significant correlations with the Hinting Task, Beck Cognitive Insight Scale and AIHQ, respectively. Moreover, the theory of mind subscale score showed a significant correlation with four domain scores of the Social Functioning Scale. The present results indicated good construct validity and internal consistency of the SCSQ.

Conclusions: Although this is an interim report with a small sample size, the SCSQ holds promise as an efficient measure for social cognition.

Key words: attributional bias, metacognition, schizophrenia, social cognition, theory of mind.

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SCHIZOPHRENIA IS A chronic, severe, and disabling illness that affects approximately 1% of individuals in the population.[1] It is characterized by a combination of positive, negative, and affective symptoms. There is growing evidence that social cognition may serve as a mediator between neurocognition and functional outcome.[2–6]

Social cognition refers to the cognitive and emotional functions required to understand and predict other people's mental state and behavior.[7,8] Schizophrenia patients experience substantial social cognition deficits across multiple domains. The most commonly studied domains involve emotion perception, social perception, attributional bias, metacognition, and theory of mind (ToM).[9] There are a number of assessment tools to measure social cognition that were developed outside Japan; however, there are very few that have been verified in Japan. Furthermore, as far as we know, there are no social cognition instruments that can measure multiple domains within one test. Taking into consideration the complex and multiple domains of social cognition, it can be a heavy burden on the patient to be administered many tests to achieve an estimate of his or her social cognitive functioning.

Roberts *et al.* developed the Social Cognition Screening Questionnaire (SCSQ)[10] to measure multiple domains of social cognition and differentiate performance in these domains from non-social cognition. The SCSQ includes subscales measuring the non-social domains of verbal memory and schematic inference, as well as the social cognitive domains of ToM, metacognition, and hostile attributional bias. It takes 15–20 min to complete the test, it is objectively scored, and is feasible to be used in clinical settings. Roberts *et al.*[10] verified the validity of the scale by testing the convergent, discriminant and ecological validity using established measures of ToM, attributional bias, metacognition, verbal memory and social functioning. They found fairly strong convergent and discriminant validity in all domains. The results also showed good ecological validity in the domains of ToM and hostility bias but not in the metacognition. They also found that all four domains of SCSQ significantly discriminated between schizophrenia patients and normal controls. They concluded that the SCSQ has promise as a broad and efficient measure of social cognition in schizophrenia. The present study aimed to test the validity of the Japanese version of SCSQ.

ToM is the ability to characterize the mental states of other people and to consider them in explaining or predicting people's behavior,[11] and is widely measured using the Hinting Task.[12] Schematic inference refers to the ability to infer what is occurring in a specific situation from uncertain and ambiguous context information. This is somewhat similar to ToM; however, it is not associated with interpersonal mentalizing, and therefore the SCSQ's schematic inference subscale is not expected to correlate with ToM measures.

Metacognition refers to cognition about one's own cognition, such as, 'How well do I understand what is happening in my own mind?' Metacognitive deficits in schizophrenia include decreased ability to evaluate the accuracy of one's own judgments, often due to overconfidence in their accuracy. This domain may share similar underlying causes with 'jumping to conclusions'[13] and 'bias against disconfirmatory evidence',[14] which have also been observed in schizophrenia. It then follows that cognitive insight, which is a capacity to reflect upon the self's thought processes from the imagined perspective of another, will be impaired in schizophrenia patients with poor metacognition. Poor cognitive insight in schizophrenia patients can be assessed with the Beck Cognitive Insight Scale (BCIS),[15] the Japanese version of which has been validated already.[16]

Attributional bias refers to individuals' tendencies in explaining the causes of events. There are three main types that have been studied: the first is situational, in which people infer that the event is due to situational factors; the second is external-personal, in which people attribute the event to others; and the third is internal-personal, in which people attribute the event to oneself. Schizophrenia subjects tend to show a stronger bias towards external-personal style when explaining negative events, and towards internal-personal style when explaining positive events.[17] There is a correlation between persecutory ideation and external-personal attributional bias.[17] The Ambiguous Intentions Hostility Questionnaire (AIHQ) is one of the most widely used measures for assessing attributional bias in schizophrenia.[18]

Although we have very few validated tests for assessing social cognition in Japan, we examined the validity of the SCSQ subscales of ToM, metacognition and hostility bias by investigating their correlation with translated versions of the Hinting Task,[12] BCIS,[16] AIHQ[17] and Social Functioning Scale (SFS),[19] respectively. We expect the findings of the present study to

help establish validated assessment tools to evaluate social cognition of schizophrenia patients in Japan and facilitate the development of a social cognition training program in Japan, such as Social Cognition and Interaction Training (SCIT),[20] originally developed in the USA.

METHODS

Subjects

The sample consisted of 105 participants: 52 individuals with schizophrenia and 53 normal control participants who were native Japanese and had no history of psychiatric disorders. Schizophrenia patients were diagnosed by clinicians according to DSM-IV diagnostic criteria. The patients were recruited from the National Center of Neurology and Psychiatry, Teikyo University School of Medicine, Tottori University, Fukushima Medical University, and Osaka Psychiatric Medical Center. Normal controls were recruited from the local community. They were matched with schizophrenia patients of the same age and sex (Table 1). There were between-group differences in years of education and estimated IQ using the Japanese Adult Reading Test.[21] The severity of symptoms in the patients was relatively mild, as can be seen by the mean scores of the Positive and Negative Syndrome Scale.[22] All patients except one were taking antipsychotic medication.

Written consent was obtained from all participants and the protocol was approved by the Ethics Committee of each participating site.

Back-translation of social cognition measures

To develop a Japanese version of the SCSQ, professionals specializing in mental health translated the original SCSQ from English to Japanese. Afterward, a person isolated from the first group of translators performed a back-translation. Modifications of some terms were made to fit local culture. We performed the same procedure for the Hinting Task and the AIHQ. All back-translations were supervised and approved by one of the persons who developed the tests.

Measures

Social cognition measures

SCSQ

The SCSQ contains five subscales: verbal memory, schematic inference, ToM, metacognition, and hostil-

Table 1. Demographic and clinical variables of patients with schizophrenia and normal controls

	Schizophrenia patients ($n = 52$)	Normal controls ($n = 53$)	Between-group comparison
Sex, male : female	28 : 24	25 : 28	NS
Age	38.1 (10.8)†	37.8 (10.2)	NS
Years of education	13.7 (2.2)	16.5 (2.3)	$Z = -5.46$, $P < 0.0001$
JART	99.3 (17.5)	110 (7.5)	$Z = -4.37$, $P < 0.0001$
Settings, admission : outpatients	31 : 21		
Duration of illness (months)	158.5 (120.6)		
PANSS			
Total	63.4 (14.7)		
Positive	14.9 (5.1)		
Negative	17.1 (4.8)		
General	31.3 (7.7)		
SFS (total scores)	104.4 (31.8)		
GAF	52.9 (11.0)		
Daily dosage level (chlorpromazine equivalent)	707.0 (590.4)		

†Mean (SD).
GAF, Global Assessment of Functioning; NS, not significant; JART, Japanese Adult Reading Test; PANSS, Positive and Negative Syndrome Scale; SFS, Social Functioning Scale.