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分担研究報告書

メタ認知トレーニングの効果に関する予備的研究

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研究要旨：
統合失調症では、結論への性急な飛躍、外的帰属バイアス、反証に対するバイアス、エラーに対する過剰確信、そして心の理論など、認知的バイアスと陽性症状の関連を示す研究が相当量存在している。こうした認知的バイアスの存在とそれが非機能的であることについての認識（メタ認知）を高めるために開発されたのがメタ認知トレーニング（Metacognitive Training:MCT）であり、日本版（MCT-J）も存在する。直感的な有用性と実施の簡便さから、本邦においても、MCT-Jの実践が、多様な職種によって、統合失調症のリハビリテーション現場に急速に普及しつつあるが、実際の効果について対照群を用いて検証した研究が不足しているのが現状である。そこで、本研究では、MCT-Jのパイロット無作為化比較試験を行い、統合失調症患者に対するMCT-Jの効果検証を行うことを目的とした。本年度は、MCT-Jの修正、研究計画、評価法等を確定し、第１クールを実施した。

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A. 研究目的

統合失調症の症状転帰、職業的転帰にはさらなる改善の余地が相当あるとして様々な試みが続けられている。薬物療法が進展したとはいえ、抗精神病薬の効果量はプラセボに比して中程度であるし、コンプライアンスも高いとはいえない。そこで社会復帰に向けては、心理療法も補完的アプローチとして活用されており、中でも効果検討が比較的多くされているのが認知行動療法である。精神病性障害に対する認知行動療法は、通常治療と比べて低～中等度の効果量を示し、英国、米国、カナダ等の統合失調症治療ガイドラインにて推奨されている。一方、統合失調症では、結論への性急な飛躍、外的帰属バイアス、反証に対するバイアス、エラーに対する過剰確信、そして心の理論など、認知的バイアスと陽性症状の関連を示す研究が相当量ある（Moritz, 2007）。

上記をふまえ、Moritzら（2007）が開発したのが「認知の歪みと、それがいかに非機能的かについての認識（メタ認知）を高める」ことを目的とした「メタ認知トレーニング（Metacognitive Training: MCT）」である。内容としては、認知行動療法 Cognitive behavioural therapy（精神病症状をターゲット）と認知矯正療法 Cognitive remediation

therapy（神経認知課題に取り組む）のハイブリッドである。MCTはこれまでのところ、妄想苦痛度、結論への飛躍バイアスに対する改善が繰り返し確認されており、PANSS測定による陽性症状や記憶に対する効果を示した研究も存在する（Moritz, 2011）。

MCTの特徴は、実施の簡便性にある。内容はPublic domainに属し、ウェブサイト上に公開されており、日本版（石垣,2012）も存在している。全8回の内容は、マニュアルに従い、パワーポイントスライドを使用することで、精神保健領域の専門家であれば、認知行動療法や認知矯正療法に熟練していなくとも実施することが可能である。直感的な有用性と実施の簡便さから、本邦においても、MCT-Jの実践が、多様な職種によって、統合失調症のリハビリテーション現場に急速に普及しつつあるが、実際の効果について対照群を用いて検証した研究が不足しているのが現状である。そこで、本研究では、MCT-Jのパイロット無作為化比較試験を行い、統合失調症患者に対するMCT-Jの効果検証を行うことを目的とした。

B. 研究方法

1. 対象

DSMIV-TRにより、統合失調症または統合失調感情障害と診断された患者のうち、以下の適格基準、除外基準を満たす者とした。

適格基準：

a) スクリーニング時の年齢が20歳以上65歳以下である者

b) 本研究の目的、内容を理解し、自由意思による研究参加の同意を文書で得られた者

c) 国立精神・神経医療研究センター病院に通院中の者

除外基準：

a) スクリーニング時の3カ月以内にアルコール・物質乱用の既往を認める者

b) MCT実施期間（週1回、8週間）の50%以上の参加が困難であると予想される者

c) スクリーニング時にMCT-J遂行が困難な認知機能障害（病前推定IQ70以下）を認める者

d) 精神症状が不安定なために、研究期間に薬物の変更が必要となると予想される者

e) その他、主治医あるいは研究者が本研究の対象として不適当と判断した者

2. 研究デザイン

MCT-J実施群と待機対照群（通常治療群；TAU群）とのパイロット無作為化比較試験。

割付は介入に関わらない独立した研究者が実施し、評価者に対しては、割付をマスクする。（シングルブラインド）。

3. 介入方法・介入期間

3-1. 介入方法

MCT-Jはマニュアルに準拠して実施する。全8回の内訳は表1示す。

表1. MCT-J各回の構成

	モジュール名	介入ターゲット
第1回	原因帰属	外的帰属バイアス
第2回	結論への飛躍Ⅰ	情報収集バイアス
第3回	思い込みを変える	確信度
第4回	共感することⅠ	心の理論
第5回	記憶	記憶の過信
第6回	共感することⅡ	心の理論
第7回	結論への飛躍Ⅱ	情報収集バイアス
第8回	自尊心	抑うつ思考スタイル

MCT-J実施者はMCT-Jの基礎訓練を修了した者で構成される。患者は約8-10名で構成されたグループを対象に実施し、治療者は原則としてリーダーとコ・リーダーの2名からなる。

MCT-J群およびTAU群のいずれにおいて

も、介入期間中、薬物療法およびリハビリテーション治療について、可能な限り変更なく続けるものとする。

なお、使用するスライドについては、MCT-J作成者である石垣らの許可を得て、原著者Moritz が認める範囲で一部修正を行った。具体的には、ドイツ語原版 MCT を参考に、MCT-J の文言を一部修正した。また、文化の違いから分かりにくいとされる図版の代替（Moritz が配布し、これを石垣らが日本語に翻訳した物）を入手し、差し替えを行った。

3-2. 介入期間

8 週間（原則として週 1 回約 90 分の MCT-J セッションを計 8 回）

4. 評価項目

評価は、ベースライン評価(0 週)、MCT-J および TAU 実施期間終了点（8 週）、の 2 時点で実施される。

①スクリーニング評価項目：年齢、性別、精神医学診断(DSM-IV-TR)、病前推定 IQ（Japanese Adult Reading Test：JART）

②ベースライン(0 週)及び介入後（8 週）における評価項目（*は主要アウトカム）

・メタ認知：BCIS*（Beck Cognitive Insight Scale）
・結論への性急な飛躍バイアス：ビーズ課題（Beads Task）*
・心の理論：WAIS-Ⅲ絵画完成テスト*
・陽性症状の質的評価：PSYRATS*Psychotic Symptoms Rating Scales）
・抑うつ：BDI-2*(Beck Depression Inventory)*
・精神症状：PANSS（Positive and Negative Syndrome Scale）
・神経認知機能：BACS（Brief Assessment of Cognition in Schizophrenia）
・知覚統合：WAIS-Ⅲ行列推理検査

③介入後（8 週後）のみ評価する項目

・内発的動機付け：IMI（Intrinsic Motivation Inventory）尺度

5. 倫理的配慮

本研究計画は、独立行政法人国立精神・神経医療研究センターの倫理審査委員会、及び、国立精神・神経医療研究センター病院臨床研究推進委員会より、承認を得た（平成 25 年 8 月承認）。研究に参加する患者に対しては、研究内容や倫理的配慮についての十分な説明を行い、書面にて同意を得た上で研究を実施している。データの取り扱いに際しては、匿名化の管理と徹底を行っている。

C. 研究結果

第 1 クールには、12 名がリクルートされ、その内、包含基準を満たし、書面による同意の得られた 8 名が MCT-J 群（4 名）と待機群（4 名）に無作為に割付けられた。8 週間後に、MCT-J 群で 1 名が検査を辞退した（図 1）。

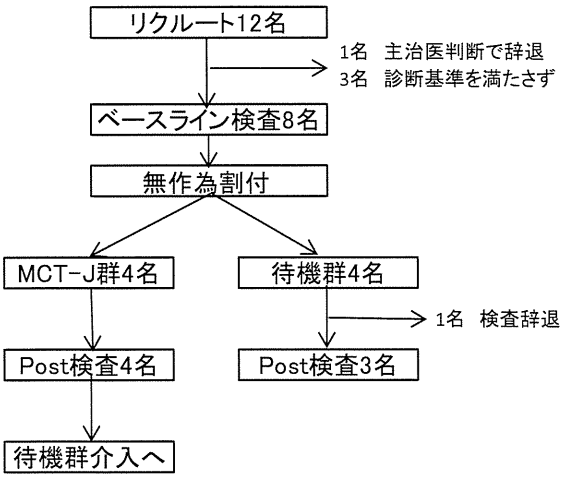

図 1. 第 1 クール試験プロフィール

参加者の基本属性は、表 2 の通りであった。

表 2. 第 1 クール対象者 8 名の基本属性

	MCT-J群	待機群
性別(男:女)	1:3	2:2
平均年齢(SD)	34.0(9.3)	37.5(2.1)
診断	統合失調症4	統合失調症4
推定病前IQ	106.3(7.3)	99.8(15.1)

第 1 クール参加者 8 名の主要アウトカムであるメタ認知（BCIS 合成点)、結論への飛躍バイアス（ビーズ課題の決断までの回数)、心の理論（WAIS 絵画配列)、抑うつ（BDI-2）の中央値は表 3 の通りであった。PSYRATS は当初、主要アウトカムに想定していたが、評価時点で幻覚症状が無い者が 8 名中 6 名にのぼり、本研究の評価法として不適切であることがわかった。

表 3. 第 1 クール参加者の中央値

	MCT-J群		待機群	
	pre	post*1	pre	post
BCIS	9.00	10.00	5.00	6.00
JTC	6.00	10.33	10.00	6.50
WAIS絵画配列	14.50	14.00	7.00	10.00
BDI-2	18.00	15.00	7.50	7.00

*1: MCT-J群postデータのみn=3。他は各群4名。

D. 考察

今年度は、介入に使用する①MCT-J のスライドを修正の上、確定し、②研究計画について倫理審査委員会からの承認を得て、③介入の第 1 クールを実施した。

リクルートの結果、介入時点で幻聴が無いために PSYRATS の評定が不可能な参加者がいた（8 名中 6 名)。活発な陽性症状の存在は、本研究の適格基準に含まれていないため、介入クールを重ねても相当数の欠損値が生じると考えられ、次クールからの評価項目として残すかどうかの検討が必要である。また、MCT-J がターゲットにしている認知的バイアスの変化を評価する方法についてもさらなる検討を要する。

E. 結論

メタ認知トレーニングの日本版を使用し、統合失調症に対する効果検証を開始した。次年度には引き続き、MCT-J の介入を行い、介入の前後における参加者のメタ認知、心の理論、結論への性急な飛躍バイアス、抑うつについてのデータ収集と解析を行う予定である。

F. 研究発表

1. 論文発表

なし

2. 学会発表

なし

G. 知的財産権の出願・登録状況

1. 特許取得

なし

2. 実用新案登録

なし

3. その他

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Ⅲ．　研究成果の刊行に関する一覧表

研究成果の刊行に関する一覧表

書籍

著者氏名	論文タイトル名	書籍全体の編集者名	書　籍　名	出版社名	出版地	出版年	ページ
花川 隆	小脳の機能イメージング	西澤正豊	小脳と運動失調 小脳は何をしているのか	中山出版	東京	2013	99-106

雑誌

発表者氏名	論文タイトル名	発表誌名	巻号	ページ	出版年
Pu S, Nakagome K, Yamada T, Ikezawa S, Itakura M, Satake T, Ishida H, Nagata I, Mogami T, Kaneko K	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.	Schizophrenia Research	153(1-3)	87-95	2014
Kanie A, Hagiya K, Ashida S, Pu S, Kaneko K, Mogami T, Oshima S, Motoya M, Niwa SI, Inagaki A, Ikebuchi E, Kikuchi A, Yamasaki S, Iwata K, Roberts DL, Nakagome K	A new instrument for measuring multiple domains of social cognition: Construct validity of the Social Cognition Screening Questionnaire (Japanese version).	Psychiatry Clin Neurosci			in press
Ban H, Yamamoto H, Hanakawa T, Urayama S, Aso T, Fukuyama H, Ejima Y	Topographic representation of an occluded object and the effects of spatiotemporal context in human early visual areas motional-affective modulation in adults	J Neurosci	33(43)	16992-17007	2013

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Hosoda C, Tanaka K, Nariai T, Honda M, Hanakawa T	Dynamic neural network reorganization associated with second language vocabulary acquisition	J Neurosci	33(34)	13663-13762	2013
池淵恵美	統合失調症の社会機能をどのように測定するか	精神神経学雑誌	115巻6号	570-585	2013
根本隆洋、水野雅文	精神病発症危険状態への薬物療法について	精神科治療学	28	901-908	2013
Kou Murayama, Madoka Matsumoto, Keise Izuma, Ayaka Sugiura, Richard M. Ryan, Edward L. Deci Kenji Matsumoto	How Self-Determined Choice Facilitates Performance: A Key Role of the Ventromedial Prefrontal Cortex	Cerebral Cortex			in press
Kawano N, Awata S, Ijuin M, Iwamoto K, Ozaki N	Necessity of normative data on the Japanese version of the Wechsler Memory Scale-Revised Logical Memory subtest for old-old people.	Geriatr Gerontol Int	13 (3)	726-30	2013
Aleksic B, Kushima I, Ohye T, Ikeda M, Kunimoto S, Nakamura Y, Yoshimi A, Koide T, Iritani S, Kurahashi H, Iwata N, Ozaki N	Definition and refinement of the 7q36.3 duplication region associated with schizophrenia.	Sci Rep	2	2587	2013
Aleksic B, Kushima I, Hashimoto R, Ohi K, Ikeda M, Yoshimi A, Nakamura Y, Ito Y, Okochi T, Fukuo Y, Yasuda Y, Fukumoto M, Yamamori H, Ujike H, Suzuki M, Inada T, Takeda M, Kaibuchi K, Iwata N, Ozaki N	Analysis of the VAV3 as Candidate Gene for Schizophrenia: Evidences From Voxel-Based Morphometry and Mutation Screening.	Schizophr Bull	39(3)	720-8	2013

Ⅳ．　研究成果の刊行物・別刷

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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.

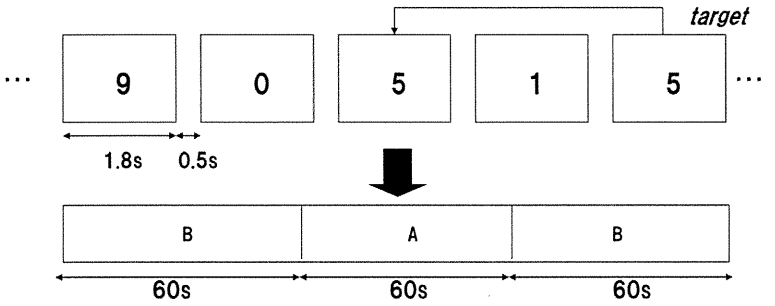

Fig. 1. The task design of 2-back task. A: Activation condition: 2-back. B: Baseline condition: 0-back, "9" as target.

(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

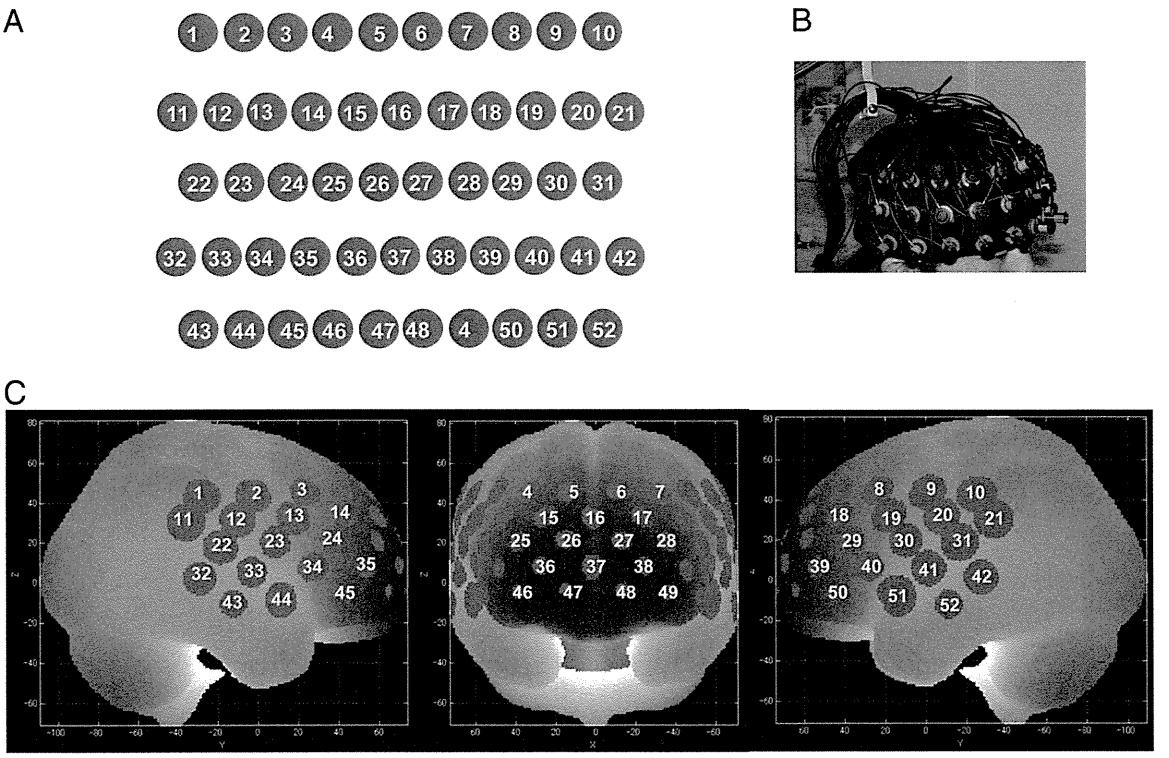

Fig. 2. Probe setting and measurement points for 52-channel near-infrared spectroscopy (NIRS). (A) The 52 measuring areas are labeled ch1 to ch52 from the right posterior to the left anterior. (B–C) The probes with 3 × 11 thermoplastic shells were placed over a subject's bilateral prefrontal and superior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

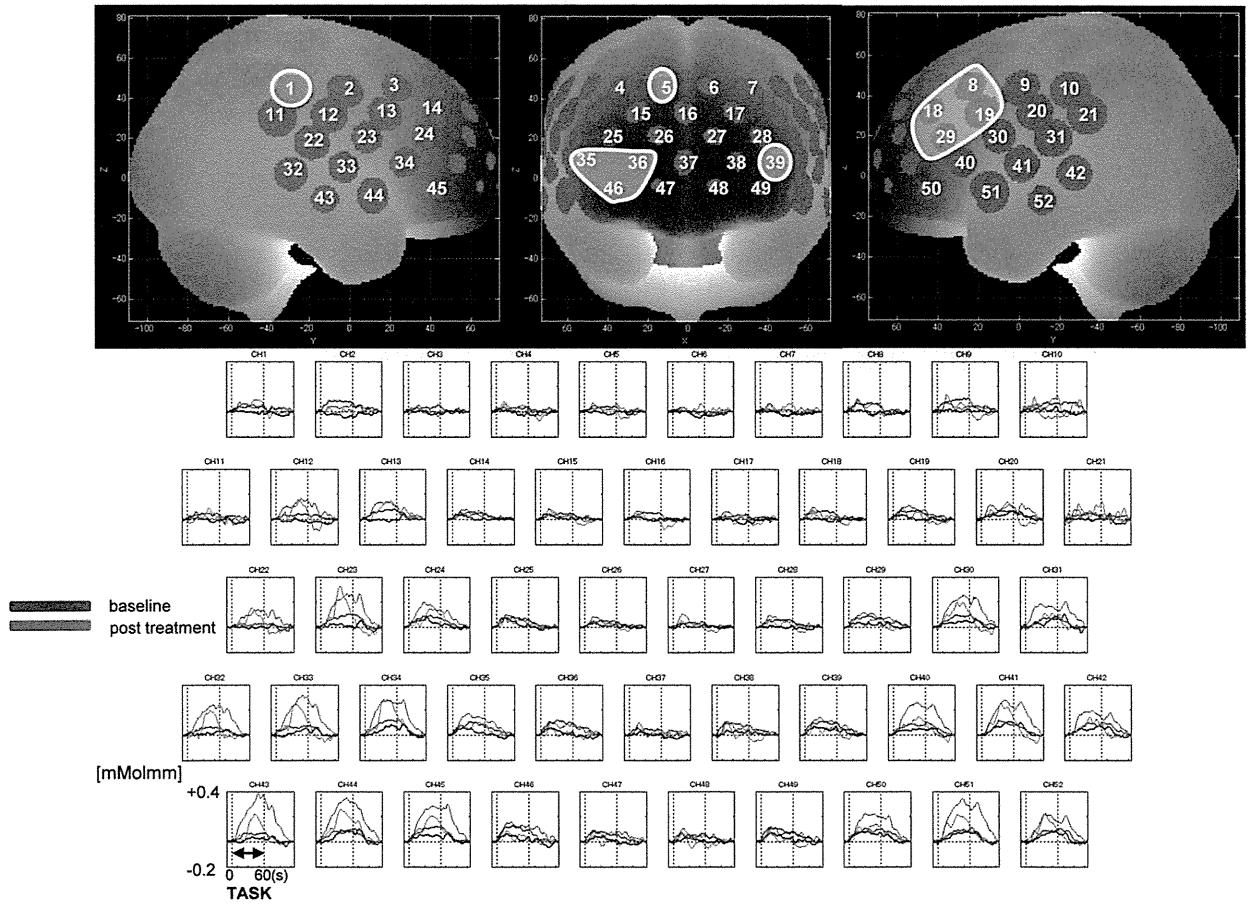

Fig. 3. Above: Brain area in yellow corresponds to the NIRS channels with significantly increased [oxy-Hb] in the after completing NEAR than in the before beginning NEAR. The locations of NIRS channels were probabilistically estimated and anatomically labeled in the standard brain space in accordance 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

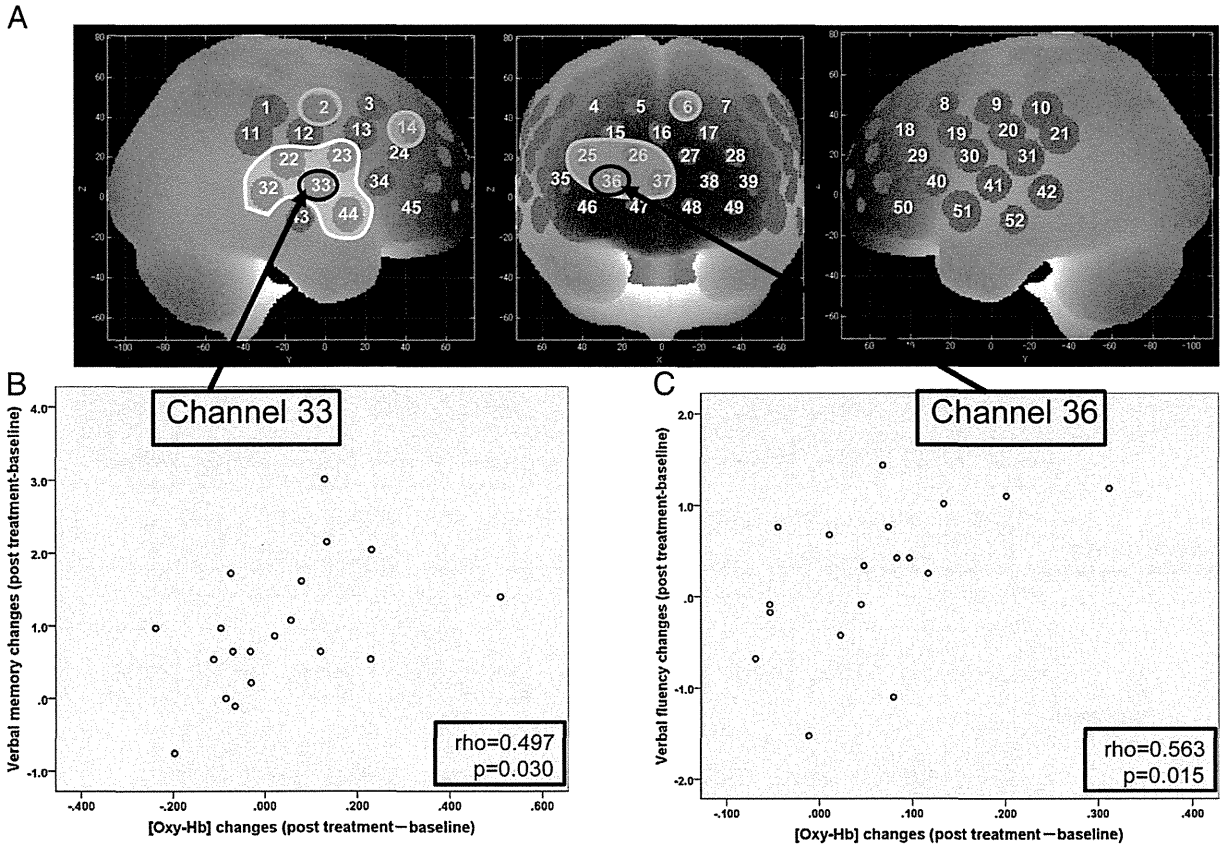

Fig. 4. (A) The relationship between cognitive function and changes in [oxy-Hb] associated with working memory tasks before and after NEAR. Green and yellow represent verbal memory and verbal fluency changes in the BACS-J, respectively. (B) Scatter diagrams showing the relationship between verbal memory 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.

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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

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

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