就労機能改善の効果が示されており，認知機能改善については治療終了6カ月後の持続が確認されている．認知矯正療法全体のメタ分析では，認知機能改善に対して中程度の効果サイズ（d＝.41），社会機能の改善に対してはやや小さめの効果サイズ（d＝.36）が報告されている（McGurk et al, 2007）．

2）効果の対象となる領域とその意義

認知矯正療法の効果を評価する際の留意点として，効果指標の違い，効果サイズ，対照条件の違いがある．効果研究で検討される領域や用いられる効果指標は多様であることは指摘され，メタ分析では領域別に効果が示されている（Grynszpan et al, 2011; Medalia and Choi, 2009; McGurk et al, 2007）．効果を評価する際に効果サイズなどの数値だけでなく，領域が機能的転帰に対してもつ意義を加味することが必要である．評価領域として，認知矯正療法で直接的に標的とする神経認知とも呼ばれる認知機能の改善だけでなく，神経認知を基盤とする社会認知や，さらにそれらの応用が求められる社会技能があげられる．より具体的には，他者の表情や感情を的確に読み取り，一定時間内または場面に応じて適切な反応を，言語的または非言語的にするためには，注意や集中，処理速度などの認知機能を用いることが必要になるということである．社会場面や対人場面での反応が適切であることが自立生活を送るためにしばしば必要になるため，精神疾患の機能的転帰を考える上でも，認知矯正療法をどの領域への効果から評価するのかは，重要である．逆に，認知機能障害は，精神症状とはほとんど関連していないことから，認知矯正療法も精神症状の改善を目的としていないことが多い．精神症状の中でも陰性症状は認知機能障害と関連すると考えられているが，その関連はわずかなものであり，陰性症状により認知機能障害が生じるわけではないことも指摘されている（Medalia and Choi, 2009）．ただし，全体的な機能水準の改善が認められる際に，精神症状の若干の改善が報告されている場合がある（Medalia and Choi, 2009）．

3）認知矯正療法の効果の評価ポイント

認知矯正療法の効果研究を評価するには，いくつかのポイントに留意する必要がある．海外の研究では，患者が受ける対照条件の性質の違いにより，active control，passive control に分類されている．対照条件が active control である場合には，認知矯正療法に参加していなくても同じ時間別の種類の治療に参加し，治療者に関わっているのが通常であるのに対し，passive control では，時間数は同じでも，治療者からの積極的な関わりを受けることはない．認知矯正療法の効果研究の評価では，薬物を使用した治療法に関する研究とは対照条件の定義がやや異なる点に注意が必要である．ただし，精神疾患を持つ患者は薬物療法を受けていることが多いため，認知矯正療法の効果研究では，特に処方されている向精神病薬の内容が示されていることが望ましい．

他に直接的には影響を与えないかもしれないが，認知矯正療法の媒介要因として，治療者側また患者側の要因があることが指摘されている．例えば，治療者側の要因としては，治療者の受けた精神衛生に関する訓練や教育年数があげられる．人的な要因ではないが，治療要因として認知矯正療法が実施される頻度や期間が治療効果に影響を与えることが指摘されている．患者側の要因としては，多様な要因が治療効果に影響を与えるのではないかと論じられているが，Choi らによる論文（Choi and Medalia, 2005）では，年齢や認知矯正療法への出席率が関与していることが示されている．これらの指摘からは，必ずしも高機能の患者のみが認知矯正療法による恩恵を受けるわけではないことが窺える．

認知矯正療法は，その程度は手法により異なるが，観察を通じた脆弱認知領域の特定，肯定的フィードバック，般化の促しなど人的介入が必要であるため，臨床スタッフの事前の訓練がある程度必要になる．コンピューターを用いる手法でも，臨床スタッフの存在が必要であり，用いない手法ではさらにその必要性が高まると考えられる．

認知矯正療法は集団形式で実施するものが多い．一対一の対面形式で実施する場合はその限りではないが，集団形式特有の集団力動の存在や，患者同士の競争心などを建設的に治療に用いることが求められる．認知矯正療法を学習活動になぞらえ，学習は孤立してではなく他者との関係において行うときにこそ効果的であるとする立場もある（Medalia and Choi, 2009）ことから，認知矯正療法が集団形式で行われることが多いのは理にかなっているといえる．つまり，認知矯正療法は認知機能の改善に特化した治療法ではあるが，臨床スタッフの存在や集団形式での療法を実施する能力を差し引いては治療評価が困難だということである．

また，認知矯正療法は精神科デイケアなど包括的な精神疾患リハビリテーションと組み合わせて実施するのが望ましい．これは，認知矯正療法を通じて改善した認知機能を，他の療法や訓練を受けて日常生活に般化させることが求められるためである．精神疾患からの回復には認知機能の改善だけでなく，生活機能の改善が重要であり，改善した認知機能がよりよく生活場面で発揮されることが望まれる．患者の機能水準により，般化に必要な介入の水準が異なると考えられる．

2. 一般的に用いられる効果指標

認知矯正療法の効果は，認知機能の変化と社会機能の変化により評価される．Primary 指標として神経心理検査，Co-Primary（機能的転帰）指標として社会技能尺度，自立生活技能尺度，就労技能尺度などを用いる．認知矯正療法

は認知機能を直接治療標的にしており，認知機能障害は，精神症状の悪化や改善にはあまり影響を受けないため，精神症状尺度は認知矯正療法の主たる効果尺度としては用いられない．

複数ある認知矯正療法の効果研究で，手法を問わず治療で扱う課題に類似している認知課題を効果指標とすれば，非常に大きい効果が示され，治療で扱う課題とは別の種類の神経心理検査では，示される効果の大きさはやや減少することが示されている．機能的転帰指標で示される効果はさらに減少するが，潜在的な能力を測定する尺度と，real-world functioningと呼ばれる生活場面でのパフォーマンスを測定する尺度では，後者で示される効果の大きさはさらに減少する．これは，認知矯正療法で標的としている認知機能から機能的な距離が開くほど応用的な側面が高まり，影響を与える要因が増えるためだとされている（Medalia and Choi, 2009）．

認知矯正療法の効果指標には，実施者が特に着目している領域や，患者の臨床像にとってより重要な領域を中心に，適宜個別の認知機能を測定する神経心理検査を組み合わせて用いる（McGurk et al, 2007）．そのため，認知矯正療法で使用される効果指標は効果研究間で統一されていないが，以下に代表的なものをあげる．注意機能検査としてContinuous Performance Test（CPT），処理速度検査としてTrail Making Test A，作業記憶検査としてWechsler数唱検査，言語学習と記憶検査としてWechsler Memory Scale論理言語記憶，視覚記憶検査としてWechsler Memory Scale視覚再認と再生検査，遂行機能検査として「ハノイの塔」，Wisconsin Card Sorting Test（WCST），Trail Making Test Bが主として使用されるようである．

これら既存の神経心理検査のうち，統合失調症で重要な指標を測定する検査を組み合わせてバッテリー形式の検査が考案された．代表的なバッテリー形式の神経心理検査としてBrief Assessment of Cognition in Schizophrenia（BACS）（Keefe et al, 2008），Measurement and Treatment Research to Improve Cognition in Schizophrenia Consensus Cognitive Battery（MCCB）（Green et al, 2004）があげられる．BACSでは，6つの下位検査により言語記憶，作業記憶，運動速度，言語流暢性，注意，遂行機能を測定し，実施に要する時間は30～40分と簡便である．MCCBは処理速度，注意/覚醒，作業記憶，言語学習，視覚学習，推論と問題解決，社会・感情認知と，より広範囲の機能測定が可能だが，実施には90～100分を要する．これらの検査の日本語版は既に作成されており，特にBACSはその簡便さから臨床場面で好まれることが多いようである．

Co-Primary（機能的転帰）指標には，患者本人または患者をよく知る人物の面接により，患者の潜在的な能力を測定する面接形式と，電話をかけるなどロールプレイや模擬，あるいは実際の生活場面での行動観察を通じて実際のパフォーマンスを測定する形式がある．面接形式尺度の代表例であるSchizophrenia Cognition Scale（SCoRS）では，記憶，学習，注意，作業記憶，問題解決，処理／運動速度，社会認知および言語の8つの認知機能に関連した日常生活機能を測定する（Keefe et al, 2006）．SCoRSでは患者本人，主たる介護者の面接と，尺度を実施する評価者と三方向からの評価を用いるため，バイアスの少ない複合的な評価が可能である．また，MCCBで測定する認知機能領域と内容が対応しており，海外のデータでは有意な相関が報告されていることも長所にあげられる（Keefe et al, 2006）．

もう1つの面接形式尺度の例であるSocial Functioning Scale（SFS）では，ひきこもり，対人関係，社会参加，余暇活動機能，自立生活機能，就労機能などを測定し，面接を通じてこれらの機能が評価されるが，自己記入式でも実施が可能である（Birchwood et al, 1990）．SCoRS，SFSには日本語版が準備されている．

パフォーマンスを測定する尺度の例にはSocial Skills Performance Assessment（SSPA）（Patterson et al, 2001），University of California San Diego Performance-based Skills Assessment（UPSA）（Patterson et al, 2001）があり，ロールプレイを通じてコミュニケーションや金銭管理能力などを測定する．これら尺度は一部日本語版が作成されているが，社会的状況のもつ意味，ニュアンスや要求される課題が文化により異なることから，国内で結果解釈基準を定着させることが課題になっている．

V. 結　論

認知矯正療法の効果研究におけるRCTの対照条件では通常通りの治療などがあり，条件の種類にかかわらず認知矯正療法は有意な効果を示しているが，治療者暴露時間を統制して検討することが今後必要である．認知矯正療法の効果に影響を与える要因としては，治療条件，患者要因，治療者要因などが検討されており，手法によっても異なる．今後，わが国でも精神科領域で認知機能リハビリテーションがますます一般的になることが望ましいと考えられる．

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Abstract: Tamiko MOGAMI[*1], Satoru IKEZAWA[*2,3], Koichi KANEKO[*1], Shenghong PU[*1] and Kazuyuki NAKAGOME[*3] ([*1] Department of Clinical Psychology and [*1] Division of Neuropsychiatry, Faculty of Medicine, Tottori University, 86 Nishi-cho, Yonago, 683-8503 Japan; [*2] Yowa Hospital; [*3] Yale School of Medicine, Department of Psychiatry, Connecticut Mental Health Center; [*3] National Center of Neurology and Psychiatry) *Outcome studies of cognitive remediation for schizophrenia*. Jpn. J. Neuropsychopharmacol., 31: 245-249 (2011).

Cognitive remediation purports to improve the cognitive dysfunction of schizophrenia, and has many forms. Eighty percent of people with schizophrenia suffer from cognitive dysfunction. The impact of cognitive dysfunction on everyday activity is widespread. Cognitive remediation as a non-pharmaceutical, psychosocial treatment modality for cognitive dysfunction has received attention as medical treatment has been able to make only limited gains. The ultimate goal of cognitive remediation is to improve the functional outcome. The increased interest in cognitive remediation resulted in numerous reports of outcome studies and meta-analysis. This paper reports different methods of cognitive remediation, evaluations of outcome studies, and various outcome indices. Cognitive remediation differs according to whether specific cognitions are targeted, and whether a method takes a compensatory or restorative approach. This paper briefly reviews methods of cognitive remediation which demonstrated their effect through RCT: IPT, NEAR, CET, and NET. Cognitive remediation often includes sessions that aim for transfer of the gained learning, such as verbal sessions or vocational skills training. Cognitive remediation is considered most effective when included as part of a comprehensive rehabilitation program. It is important to note that various studies report different outcome indices, control groups, and effect sizes in evaluating the effect of cognitive remediation.

Key words: Schizophrenia, Cognitive dysfunction, Rehabilitation, Psychosocial intervention, Functional outcome

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A multi-channel near-infrared spectroscopy study of prefrontal cortex activation during working memory task in major depressive disorder

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ABSTRACT

Many neuropsychological studies demonstrate impairment of working memory in patients with major depressive disorder (MDD). However, there are not enough functional neuroimaging studies of MDD patients seeking for the underlying brain activity relevant to working memory function. The objective of this study is to evaluate prefrontal hemodynamic response related to working memory function in patients with MDD. Twenty-four subjects with MDD and 26 age- and gender-matched healthy subjects were recruited for the present study. We measured hemoglobin concentration changes in the prefrontal and superior temporal cortical surface areas during the execution of working memory task (WM; 2-back, letter version) using 52-channel near-infrared spectroscopy (NIRS), which enables real-time monitoring of task-related changes in cerebral blood volumes in the cortical surface areas. MDD patients showed a smaller increase in lateral prefrontal and superior temporal cortex activation during the 2-back task and associated poorer task performance than healthy controls. The results coincided with previous findings in terms of working memory deficits and prefrontal cortex dysfunction in MDD patients, but contradicted with some previous fMRI studies that suggested increased cortical activity during the working memory task in patients with depression. The contradiction may, in part, be explained by a relatively low level of cognitive demand imposed on the subjects in the present study.

1. Introduction

Working memory is an extensively researched psychological concept related to the temporary storage and processing of information (Baddeley, 1992, 2003). Intact working memory is essential for everyday functioning. Working memory tasks require several cognitive processes, such as online monitoring, continuous updating, manipulating stored information, and decision making, which might all be affected by major depressive disorder (MDD). Many neuropsychological studies demonstrate impairment of working memory in patients with MDD (Rose and Ebmeier, 2006; Harvey et al., 2004; Porter et al., 2003; Landro et al., 2001; Nebes et al., 2000; Elliott et al., 1996; Beats et al., 1996; Channon et al., 1993). However, some other studies failed to find significant differences between patients with MDD and normal controls (Elderkin-Thompson et al., 2003; Sweeney et al., 2000; Zakzanis et al., 1998; Purcell et al., 1997). The inconsistency presumably owes much to the difference in the patients' clinical characteristics, the cognitive demand of the various neuropsychological tests applied in the studies.

The hemodynamic responses related to the neural activity underlying working memory processes have been widely investigated using neuroimaging (fMRI and PET) techniques (Owen et al., 2005; Wager and Smith, 2003). In healthy subjects, the *n*-back task activated a bilateral network consisting of ventrolateral prefrontal cortex (VLPFC) and dorsolateral prefrontal cortex (DLPFC), frontal poles, lateral premotor cortex, dorsal cingulate and medial premotor cortices, and medial and lateral posterior parietal cortices (Owen et al., 2005). Recently, a number of studies have used fMRI and other imaging techniques to study brain activation associated with working memory function in patients with MDD. However, the findings have been inconsistent. There is one study that demonstrated significantly greater activation in the dorsolateral cortex in MDD patients than in healthy controls (Matsuo et al., 2007), whereas another study showed no difference in the prefrontal activation between MDD patients and healthy controls (Barch et al., 2003). Interestingly, in both studies, there was no significant between-group difference in the performance level. Moreover, a number of neuroimaging studies targeting working memory have demonstrated *load-related* hyperfrontality in MDD patients com-

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pared with that in healthy controls (Harvey et al., 2005; Walsh et al., 2007; Fitzgerald et al., 2008), namely, MDD patients showed more increased cerebral activation in association with a higher level of complexity than healthy controls. The authors suggest that patients with MDD require greater resources to maintain task performance with increasing cognitive demand. Walter et al. (2007) assessed patients' neural response to correct trials only in a working memory task and found increased DLPFC activation. In their study, however, patients with MDD showed less accurate performance than healthy controls in a task with higher complexity and increased activation was not seen when incorrect trials were included in the analysis. This result suggests that increased cortical response is associated with matched performance level and may enable identification of where patients' performance is impaired.

In this regard, it is noteworthy that better working memory performance is associated with increased prefrontal activation in healthy subjects (Courtney et al., 1998; Ungerleider et al., 1998; Courtney et al., 1996; Leung et al., 2002; Sakai et al., 2002). Although the relationship between working memory performance and prefrontal activation in patients with MDD is not so clear, cortical response may be attenuated compared with that in healthy controls as a function of the extent of impaired performance of the patients.

In this study, we examined hemodynamic response in the fronto-temporal regions during engagement in working memory task in patients with MDD using multi-channel near-infrared spectroscopy (NIRS). Multi-channel NIRS (ETG-4000, Hitachi Medical Co.), a recently developed functional neuroimaging technology, enables the non-invasive detection of spatiotemporal characteristics of brain function near the brain surface using near-infrared light (Strangman et al., 2002a; Boas et al., 2004). NIRS has enabled bedside measurement of the concentrations of oxygenated ([oxy-Hb]) and deoxygenated hemoglobin ([deoxy-Hb]) in micro-blood vessels. Assuming that hematocrit is constant, the changes in [oxy-Hb], [deoxy-Hb] and also [total Hb] (summation of [oxy-Hb] and [deoxy-Hb]) are correlated with the changes in the regional cerebral blood volume (rCBV) as shown by simultaneous NIRS and positron emission tomography (PET) measurements (Hock et al., 1997; Villringer et al., 1997; Ohmae et al., 2006). In contrast to other neuroimaging methodologies such as fMRI, PET, electroencephalography (EEG) and magnetoencephalography (MEG), NIRS can be measured under a more restraint-free environment that is especially suitable for psychiatric patients. Indeed, NIRS has been used to assess brain functions in many psychiatric disorders (Matsuo et al., 2003; Suto et al., 2004; Kameyama et al., 2006). Moreover, unlike fMRI, which mainly represents the blood oxygenation level-dependent (BOLD) effect in the draining vein, NIRS is more likely to measure the changes in rCBV in distensible capillary vessels. Although the two methods target distinct aspects of hemodynamic response, the findings in terms of cortical activation obtained by simultaneous recordings of fMRI and NIRS are generally in agreement (Lee et al., 2008; Strangman et al., 2002b).

The goal of this study was to compare brain activation, measured by NIRS, as well as behavioral performance in patients with MDD and age- and gender-matched healthy controls during engagement in working memory task. From the hypothesis that patients with MDD require more resources to maintain the task performance, we predicted that patients with MDD would show either (1) increased prefrontal activation associated with comparable task performance or (2) decreased or equivalent activation associated with impaired task performance compared with the healthy controls.

2. Subjects and methods

2.1. Subjects

Twenty-four patients with MDD and 26 healthy controls participated in the study (Table 1). The patients were recruited from the outpatients at Tottori University Hospital, and were diagnosed using the criteria of Diagnostic and Statistical Manual of Mental Disorders, the fourth edition, text revision (DSM-IV-TR, American Psychiatric Association 2000).

To obtain detailed information on psychiatric symptoms, the participants were questioned using a structured interview, the Mini-International Neuropsychiatric Interview (MINI) (Sheehan et al., 1998). None of the subjects had clinical evidence of other central nervous system disorders based on history and medical examination. Patients with previous head trauma, stroke, electroconvulsive therapy, and current or previous history of substance abuse were excluded from the study. Twenty-four individuals (12 male and 12 female) meeting these criteria participated in the investigation. All the patients with MDD were in a depressed mood state. Within the MDD sample, 13 patients were taking selective serotonin reuptake inhibitors (SSRIs), 8 were taking serotonin noradrenaline reuptake inhibitors (SNRIs) and 3 were taking tricyclic antidepressants.

Individuals who were appropriate age and gender matches for the MDD patients participated as controls in the present study. Inclusion criteria for controls were similar to those for the patient sample, although controls were additionally required to have no previous or current psychiatric illnesses. Twenty-six individuals

Table 1
Demographic characteristics of the subjects and scores of BDI, HAMD and task performance (given values are means with standard deviations in parentheses).

	Major depression disorder ($N=24$)	Normal controls ($N=26$)	Group difference P-value
Gender (f/m)	12 f/12 m	18 f/8 m	0.16
Age (years)	47.9 (13.9)	42.4 (9.3)	0.10
Duration of illness (years)	4.0 (4.9)	N/A	
Age of onset (years)	43.0 (14.3)	N/A	
Number of depressive episodes	1.8 (1.4)	N/A	
Beck Depression Inventory (BDI)	22.1 (12.7)	8.0 (8.0)	<0.001
Hamilton Depression Rating Scale (HAMD)	20.3 (9.2)	N/A	
Task performance			
Reaction time (RT; ms)	739.4 (220.4)	678.1 (179.4)	0.32
Accuracy (%)	77.4 (0.30)	96.5 (0.08)	<0.01
Sensitivity A′	0.87 (0.28)	0.99 (0.02)	<0.05
Antidepressants (imipramine equivalents) (mg/day)	101.0 (57.1)	N/A	
Other drugs			
Anxiolytics	5	N/A	
Hypnotics	12		
Anxiolytics and hypnotics	3		

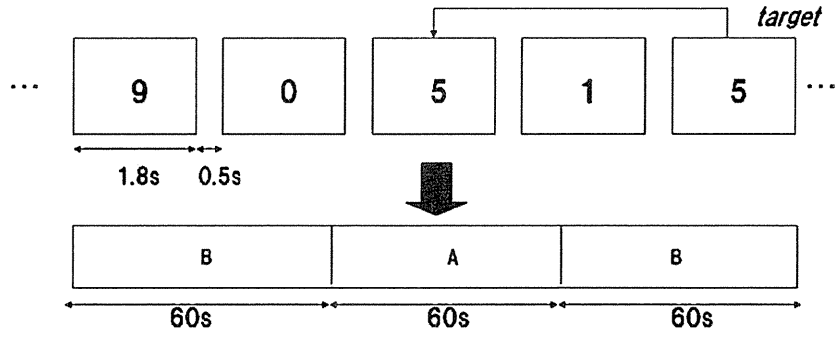

Fig. 1. The task design of 2-back task. A: Activation condition: 2-back. B: Baseline condition: 0-back, "9" as target.

(8 male and 18 female) meeting these criteria were selected to participate in the study.

All participants were right-handed with criteria of more than 80% by the Edinburgh Inventory Index (Oldfield, 1971). All subjects gave their consent in a written form after receiving comprehensive information on the study protocol. The study was approved by the ethics committee of Tottori University Faculty of Medicine.

2.2. Assessment of clinical evaluation

Prior to scanning, all subjects undertook a self-assessment of depression severity using the Beck Depression Inventory (BDI, Beck et al., 1961). In addition, only the patients were assessed for depression severity using the Hamilton Rating Scale for Depression (HAMD, Hamilton, 1960) by two trained psychiatrists.

2.3. NIRS measurements

2.3.1. Activation task

We used a 2-back task with a blocked periodic BA design (Fig. 1) to activate brain regions specialized for maintenance components of verbal working memory, 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 one meter 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. During the period of the activation (A) condition (2-back), 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 two trials previously (e.g., 5–1–5, but not 2–6–3–2 or 7–7). The working memory task consisted of a 60-s pre-task period (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 on 2-back task during measurement was monitored in terms of reaction time (RT) to target figures, accuracy (number of target figures correctly identified) and sensitivity A′ (Grier, 1971). All subjects received identical training prior to measurement.

2.3.2. NIRS machine

The 52-channel NIRS machine (ETG-4000) measures relative changes of [oxy-Hb] and [deoxy-Hb] using two wavelengths (695 and 830 nm) of infrared light on the basis of the modified Beer–Lambert law (Yamashita et al., 1996). In this system, these [Hb] values include differential pathlength factor (DPF). The distance between pairs of source-detector probes was set at 3.0 cm and each measuring area between pairs of source-detector probes was defined as 'channel'. It is considered that the machine measures points at 2–3 cm depth from the scalp, that is, the surface of the cerebral cortex (Okada and Delpy, 2003; Toronov et al., 2001). The probes of the NIRS machine were fixed with thermoplastic 3 × 11 shells, with the lowest probes positioned along the Fp1–Fp2 line according to the international 10–20 system used in electroencephalography. The arrangement of the probes enabled the measurement of [Hb] values from bilateral prefrontal and superior temporal cortical surface regions. The correspondence of the probe positions and the measuring area on the cerebral cortex has been reported elsewhere (Okamoto et al., 2004). It was approximated by superimposing the measuring positions on MRI of a three-dimensionally reconstructed cerebral cortex made by averaging 17 healthy volunteers' brain images normalized to the MNI152 standard template (Fig. 2).

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 just prior to 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 two baselines. A moving average method using a window width of 5 s was applied to remove any short-term motion artifacts. However, a moving average method alone could not remove all the artifacts and, thus, we applied a semi-automatic method for removing those data with significant artifacts. First, we applied the algorithm developed by Takizawa et al. (2008) that enables a fully automatic rejection of data with artifacts separately for each channel using quantitative evaluation, although the algorithm appeared to even reject data without artifacts. Therefore, in the next step, two researchers, who were both blind to the clinical background of the data, judged whether or not to save those data rejected by the algorithm through consultation. Consequently, the number of averaged data for each channel did not vary widely within and between the two diagnostic groups (MDD: N = 20–24 [mean = 22.7, SD = 1.28]; control: N = 23–26 [mean = 24.9, SD = 1.00]).

2.4. Data analysis

First, the performance level was compared between the two groups using the Wilcoxon rank sum test. Next, for the analysis of the hemodynamic response data, [Hb] variables, which are specifically [oxy-Hb], [deoxy-Hb] and [total Hb] concentrations, of each channel were averaged for the two time segments (pre- and post-task baseline and task period). We focused on [oxy-Hb] concentrations, since [oxy-Hb] change (task period – pre- and post-task baseline period) is assumed to more directly reflect cognitive activation than [deoxy-Hb] change as shown by a stronger correlation with blood-oxygenation level-dependent signal measured by fMRI (Strangman et al., 2002b). The mean [oxy-Hb] changes were compared between the two groups (MDD and control) for each channel using Student's t-test. Since we performed 52 t-tests,

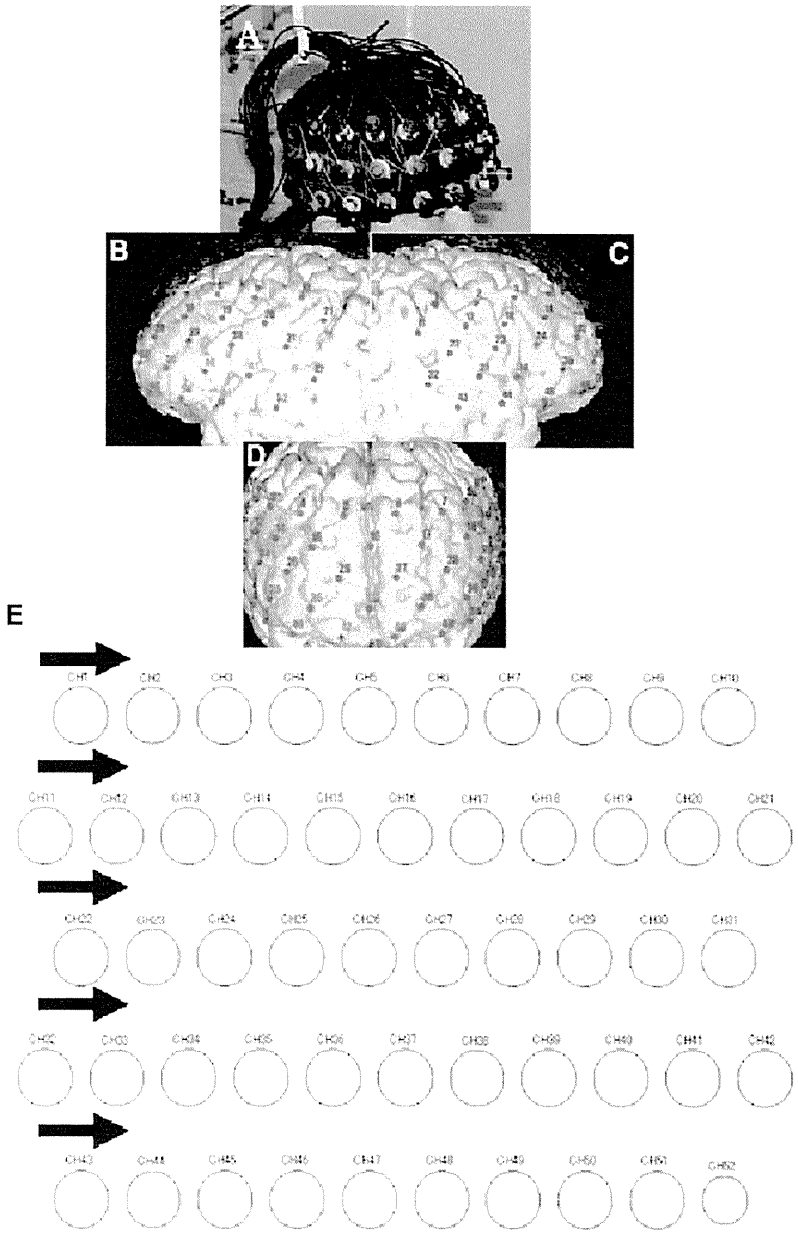

Fig. 2. Probe setting and measurement points for 52-channel near-infrared spectroscopy (NIRS). (A) The probes with 3 × 11 thermoplastic shells were placed over a subject's bilateral frontal regions. (B–D) The 52 measuring positions of the NIRS machine are superimposed on 3D-reconstructed cerebral cortical surface from magnetic resonance imaging (MRI) made by averaging 17 healthy volunteers' brain images normalized to the MNI152 standard template. The channel numbers are indicated above the measuring points. (E) The 52 measuring areas are labeled ch1–52 from the right posterior to the left anterior.

the correction for multiple comparisons was made using false discovery rate (FDR). We set the value of q specifying the maximum FDR to 0.05, so that there were no more than 5% false-positives on average (Singh and Dan, 2006). In case there was a significant between-group difference in the performance level (sensitivity A′), we performed additional analyses of co-variance (ANCOVA) using the performance level (sensitivity A′) as a covariate to the [oxy-Hb] changes, also applying FDR correction.

For MDD patients, Spearman's rhos were calculated for each channel to assess the relationship between the mean [oxy-Hb] changes and the clinical characteristics such as duration of illness, age of onset, number of depressive episodes, HAMD and BDI scores. We again adopted an FDR-based procedure for the multiple testing correction in correlational analyses for 52 channels and identified those channels for which r values reached a significance level of $P<0.05$ (FDR-corrected). Additionally, we investigated the relationship between [oxy-Hb] changes and performance level (reaction time, accuracy, sensitivity A′) and age in total samples using Spearman's rhos. Finally, we examined the relationship between [oxy-Hb] changes and the daily dose levels of antidepressants (imipramine equivalents) and also compared [oxy-Hb] changes between patients taking SSRIs and those taking SNRIs. Statistical analyses were performed using SPSS 13.0 software.

3. Results

3.1. Task performance

The response sensitivity A′ ($P<0.05$) and accuracy ($P<0.01$) on the 2-back task during NIRS measurement were significantly worse

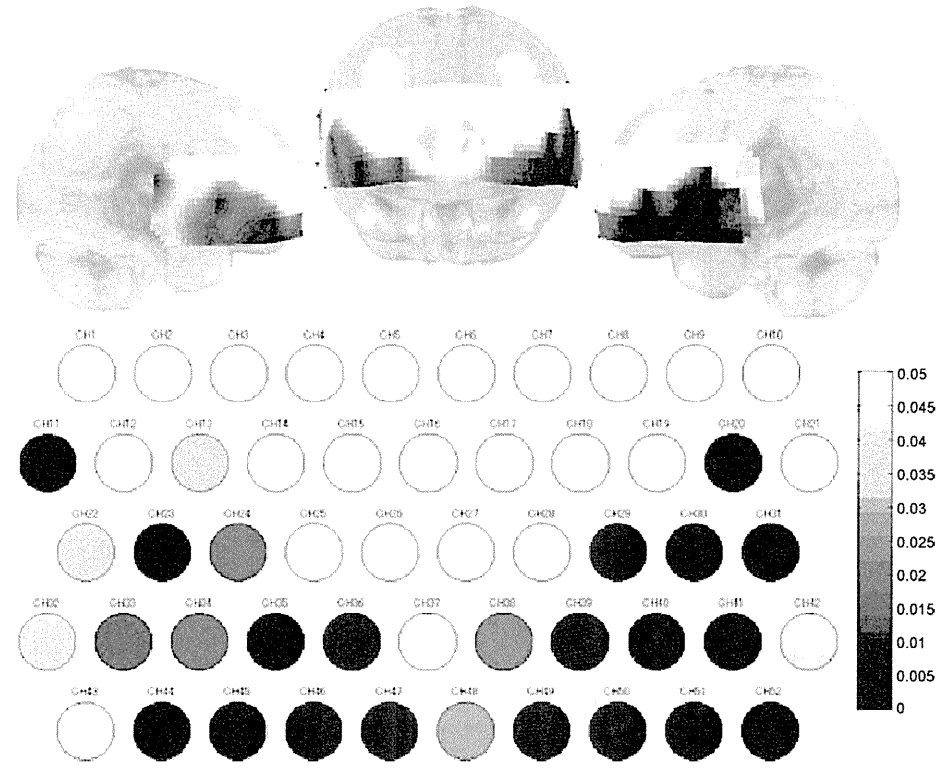

Fig. 3. *P*-value significance map of *t*-tests for [oxy-Hb] activation in patients with MDD compared with healthy controls using FDR correction. The numbered dots on the lower panel indicate 52 channels, which are projected to the 3D brain model in the upper panel.

in the MDD group than in the healthy controls. There was no significant between-group difference in reaction time (Table 1).

3.2. [Hb] changes during task (Fig. 3)

MDD patients were associated with a significantly smaller increase in [oxy-Hb] than controls at 29 channels (ch11, ch13, ch20, ch22–24, ch29–36, ch38–52; FDR-corrected *P*: 0.001–0.030). Fig. 3 is a *P* significance map of the *t*-tests, that is, MDD versus control, which shows significant group differences in a broad area.

The between-group differences in the [oxy-Hb] changes remained significant after correcting for performance levels in 22 channels (ch11, ch20, ch23–24, ch29–31, ch33–36, ch39–41, ch44–47, ch49–52; FDR-corrected *P*: 0.001–0.018) with ANCOVA using sensitivity A′ as a covariate to the [oxy-Hb] changes.

3.3. Correlations between [oxy-Hb] change and clinical variables, performance level, age and drugs

The mean [oxy-Hb] change in neither channel during the task period was significantly correlated with sensitivity A′ (rho = −0.16–0.28, n.s.), accuracy (rho = −0.14–0.30, n.s.), reaction time (rho = −0.33–0.39, n.s.), age (rho = −0.21–0.39, n.s.) for the total sample and also with age of onset (rho = −0.02–0.55, n.s.), duration of illness (rho = −0.61–0.14, n.s.), number of depressive episodes (rho = −0.42–0.19, n.s.), BDI (rho = −0.45–0.47, n.s.), HAMD (rho = −0.53–0.05, n.s.) for patients with MDD.

The mean [oxy-Hb] change in neither channel during the task period was significantly correlated with imipramine equivalents (mg/day). The mean [oxy-Hb] change in either channel did not significantly differ between the patients taking SSRIs ($n = 13$) and those taking SNRIs ($n = 8$) (Student's *t* test, $P = 0.06–0.99$, n.s.).

4. Discussion

The primary objective of this study was to examine whether the hemodynamic response in the fronto-temporal region during working memory processing differs between MDD patients and healthy subjects. Partially consistent with our prediction, we found that patients with MDD showed smaller hemodynamic response and worse task performance during engagement in working memory task than healthy controls. However, the finding contradicts several previous studies.

A number of previous studies demonstrated increased cortical activity in a depressed group using an *n*-back working memory task (Harvey et al., 2005; Walsh et al., 2007; Fitzgerald et al., 2008; Matsuo et al., 2007) and some demonstrated a higher linear load-response in patients with MDD than the normal controls, indicating that hyperfrontality in MDD was more evident in higher cognitive demanding condition. In addition, Barch et al. (2003) reported no significant difference between patients with MDD and normal controls in the neural response in the prefrontal cortex (PFC) elicited by the 2-back task using words, which was considered to be much easier than those adopted in the studies showing hyperfrontality presumed by the high performance level in both controls and patients with MDD. On the other hand, using a different cognitive task with high complexity ("Tower of London" task), Elliott et al. (1997) showed reduced neural response in cortical regions, particularly in VLPFC and DLPFC for patients with MDD compared with healthy controls, where patients' performance was impaired. It therefore seems to be an inverted-U relationship between neural response and cognitive demand in patients with MDD.

In the present study, there was no significant correlation between hemodynamic response and performance level, suggesting that the patients failed to recruit additional neural resources to attain higher performance level. As the patients with poor performance level showed similar degree of activation as those with

high performance level, it can also be assumed that the attenuated [oxy-Hb] change was not due to the patients' disengagement in the task per se. We speculate that the 2-back task adopted in the present study posed relatively small amount of cognitive load on the subjects, which can be presumed by the high performance level of the normal controls, and also the 2-back task using numerical figures (0–9) may well be considered simple, compared to the task using letters adopted in most studies showing hyperfrontality in patients with MDD. Moreover, the period of 2-back task to be engaged in was as short as 60 s, which also implies relatively small load on memory and attentional system. According to the inverted-U relationship between neural response and cognitive demand in patients with MDD, it was suggested that the attenutated [oxy-Hb] change in patients with MDD reflected the failure of recruiting neural resources to attain comparable performance as normal controls even in low cognitive demanding condition.

It is possible that the different results between the present study and previous studies arise from patient characteristics, age or severity of illness. In fact, the mean age of the subjects in the present study (47.9 ± 13.9) was older than those in the previous studies, which were mostly within the range of 30–40 years. Although this is highly speculative, poor vasomotor function associated with presumably higher incidence of microvascular dysregulation in older patients with MDD may have made it difficult to recruit additional neural resources. It may be assumed that NIRS, which mainly measures the rCBV in the distensible capillary vessels, is more sensitive to vasomotor function than fMRI (Matsuo et al., 2005). These issues should be addressed systematically in future research.

One of the shortcomings of NIRS is that it cannot measure the rCBV change in deeper region of the brain such as limbic regions. In depression, DLPFC is thought to inhibit emotional responses through its efferent connections to limbic regions. Previous fMRI studies using a cognitive challenge showed decreased activity in limbic regions including medial prefrontal cortex (MPFC) while DLPFC and other cognitive regions were activated (Pochon et al., 2002). Harvey et al. (2005) demonstrated a trend for a greater decrease of activity in MPFC in control subjects compared to patients with MDD. In the study, the activity gap between cortical and limbic regions increased as the task increased in complexity and the authors suggested that the activity gap may affect the processing efficiency. The hypofrontality as well as poorer performance level in patients with MDD in the present study may have been due to smaller activity gap between cortical and limbic regions, although we should await future studies using other neuroimaging methods to measure the neural activity in limbic regions.

Previous fMRI studies using 2-back task cited in our manuscript did not find significant relationship between neural response and clinical symptoms. We also failed to find any relationship between [oxy-Hb] change and BDI or HAMD scores, but not surprisingly because we speculate that [oxy-Hb] change should be related to cognitive function rather than mood state. A range of neurocognitive functions including verbal memory (Sternberg and Jarvik, 1976), attention (Porter et al., 2003), working memory (Barch et al., 2003; Elliott et al., 1996) and executive function (Elliott et al., 1997) have been shown to be affected in patients with MDD. Moreover, these deficits are now being recognized to be independent of the disturbance of mood, although not entirely. Because cognitive deficits exist even when patients are euthymic (Kennedy et al., 2007) and are closely linked to social function (Jaeger et al., 2006), interventions targeting these deficits seem to be urgently required. Further studies are warranted to elucidate the relationship between [oxy-Hb] change elicited by the 2-back task and cognitive function as well as social function using neuropsychological test batteries and social function measurements.

Contributors

S. Pu designed the study, wrote the protocol, collected the data, statistically analyzed the data, and wrote the first draft of the manuscript. T. Yamada was involved in patient recruitment and data collection; he also contributed to writing the final version of the manuscript. K. Yokoyama, H. Matsumura, H. Kobayashi and N. Sasaki were involved in working out the study design and data collection. H. Mitani and A. Adachi were involved in data collection. K. Kaneko contributed to writing the final version of the manuscript. K. Nakagome was involved in working out the study design, writing the protocol and contributed to writing the final version of the manuscript.

Conflict of interest

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

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Tottori University (Dr. Nakagome) and Hitachi Group (Advanced Research Laboratory, Hitachi Medical Corporation) have had an official contract for a collaborative study on the clinical application of near-infrared spectroscopy in psychiatric disorders since 2006. Hitachi Group has provided a material support. In addition, the present study has been funded by the Research Grant (20B-1) for Nervous and Mental Disorders from the Ministry of Health, Labour and Welfare.

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The pilot study of a Neuropsychological Educational Approach to Cognitive Remediation for patients with schizophrenia in Japan

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ABSTRACT

The main aim of this study is to demonstrate the feasibility and efficacy of a Neuropsychological Educational Approach to Cognitive Remediation (NEAR) in Japan on cognitive function. This multi-site study used a quasi-experimental design. 51 patients with schizophrenia or schizoaffective disorder participated. 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 6 months of NEAR sessions before being assessed. Moreover, taking into consideration the possible practice effect, we assessed 21 control patients twice with an interval of 6 months. We assessed cognitive function by using Japanese version of Brief Assessment of Cognition in Schizophrenia (BACS-J). Consequently, NEAR group showed significant improvement in overall cognitive function, and in comparison with control group, these findings were generally similar except for motor speed. Though there are not a few limitations about the present study, this study indicated that NEAR is feasible in Japan just as well as in Western countries.

1. Introduction

It is widely accepted that cognitive dysfunction in schizophrenia plays a major role in determining social function (Green et al., 2000). Although there have been numerous reports that indicate the effectiveness of atypical antipsychotics (AAPs) on cognitive function, the size of the effect of AAPs is generally about 0.2–0.5 standard deviations (S.D.) (Woodward et al., 2005; Keefe et al., 2007), while the extent of cognitive dysfunction in schizophrenia is about 1–1.5 S.D. below the level of healthy populations (Bilder et al., 2000; Heinrichs, 2004). To bridge this gap, other treatment methods, such as cognitive remediation, have been considered in Western countries.

In Japan, the "Services and Supports for Persons with Disabilities Act" was established in 2006. Although disabled persons' employment, deinstitutionalization, and socialization were promoted by this law, there are actually many people with psychiatric illnesses, including patients with schizophrenia, who still suffer from social dysfunction. With the aim of alleviating the many difficulties that they encounter in their lives, cognitive remediation therapy for patients with schizophrenia has gradually been launched in Japan (Nemoto et al., 2009).

We have become interested in one of the cognitive remediation therapies, namely, a Neuropsychological Educational Approach to Cognitive Remediation (NEAR) (Medalia and Freilich, 2008; Medalia et al., 2009), which is theoretically based on neuropsychology, educational psychology, learning theory, and cognitive psychology. After participating in one-week clinician training of NEAR, we started implementing NEAR in Japan. 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. Sessions are structured in a way to enhance intrinsic motivation and learning. The main aim of this study is to demonstrate the feasibility and efficacy of NEAR in Japan by assessing its effectiveness on cognitive function using neuropsychological indices as a primary endpoint.

2. Methods

This multi-site study used a quasi-experimental design. All participants were recruited from five psychiatric hospitals in the western region of Japan called 'San-in' district and were subjected to NEAR in each hospital. All participants were recruited on the basis of consecutive referrals.

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Table 1
Baseline demographic variables.

	NEAR group	Control group
Number of patients		
Sch:Schizophrenia	Sch:48	Sch:21
SchAf:Schizoaffective disorder	SchAf:3	SchAf:1
Gender	Male:31, Female:20	Male:14, Female:8
Mean age	36.1 ± 10.6 y.o.	41.1 ± 12.4 y.o.
Years of education	13.5 ± 2.5 years	12.5 ± 2.6 years
Duration of illness	13.8 ± 9.8 years	16.1 ± 10.8 years
Age at onset of illness	22.3 ± 6.6 y.o.	22.6 ± 6.3 y.o.
Total number of hospitalizations	2.8 ± 3.1 times	4.6 ± 5.2 times
Total months of hospitalization	19.4 ± 29.4 Months	39.3 ± 65.8 months
Mean dosage of antipsychotics (Chlorpromazine equivalent dose)	634.5 ± 364.9 mg/day	699.2 ± 569.2 mg/day
Treatment settings (Outpatient or inpatient) *	Outpatients:42 Inpatients:9	Outpatients:12 Inpatients:10
NEAR attendance rate	0.90 ± 0.11	
BACS-J z score; Verbal memory**	−1.09 ± 0.92	−2.00 ± 1.05
BACS-J z score; Working memory	−0.95 ± 0.95	−1.30 ± 1.08
BACS-J z score; Speed	−1.60 ± 1.37	−2.25 ± 1.74
BACS-J z score; Verbal fluency	−0.47 ± 1.00	−0.71 ± 0.89
BACS-J z score; Attention and speed of information processing	−1.24 ± 0.88	−1.56 ± 0.77
BACS-J z score; Executive function	−0.57 ± 1.42	−1.56 ± 2.15
[EX]**	−0.79 ± 0.59	−1.10 ± 0.59
BACS-J composite score**	−1.65 ± 1.27	−2.61 ± 1.51

* $p<0.05$ Fisher's exact test.
** $p<0.05$ Student's t test.
[EX] = −log[2 − (Executive function BACS-J z score)].

2.1. Subjects (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 made by two experienced psychiatrists 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) being recommended by their doctors. Exclusion criteria were patients (a) with active substance or alcohol abuse or having left detox within 1 month, or (b) with traumatic head injury within the past 3 years.

Sixty-two patients were referred and eleven patients dropped out of the program midway through it (the dropout rate was 17.4%). Among these eleven patients, five patients dropped out owing to a lack of motivation and five patients dropped out because of relapse of psychotic symptoms. One patient found a job and left the program. Six of the patients who withdrew left the program within the first half of the 6-month trial. Finally, fifty-one patients with schizophrenia or schizoaffective disorder completed the 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.

Moreover, we assessed 22 control patients twice with an interval of six 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. As for the clinical backgrounds, the treatment settings were significantly different between the two groups, with more inpatients being included in the control group than in the NEAR participant group.

In each computer session, patients engaged with some educational computer software that was related to various domains of cognitive function, including attention, memory, and executive function, taking into account the profiles of the patients' cognitive impairments. The software available in Japan is not identical to that in Western countries; however, it appeared to cover the relevant cognitive domains (Table 2).

The main aim of the group meeting sessions was to contextualize the computer training into their everyday activities. The process should lead to enhancing motivation and generalization of cognitive skills to real-life activities.

One of our co-authors is certified as a supervisor of NEAR and she supervised NEAR sessions periodically. In order to use consistent methods across sites, all clinicians participated in one-week clinician training of NEAR, and they attended trimonthly meetings.

Although the medications were changed throughout the whole period as little as possible, there were 16 patients whose medications needed to be changed because of clinical decisions. However, the change in the medication status of these 16 patients was only related to daily dosage levels.

2.2. Assessments

We assessed cognitive function using the Japanese version of Brief Assessment of Cognition in Schizophrenia (BACS-J) (Keefe et al., 2004; Kaneda et al., 2007). Z scores were calculated for each subcomponent score 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, working memory, 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. Statistical analysis

Two-tailed paired t-tests were performed for the assessment of change between the two measurements of BACS-J data, which were administered before (baseline) and after (post-treatment) the NEAR sessions. Each subcomponent score was normally distributed except for the executive function score. By performing a logarithmic transformation of the executive function score, the curve was modified to a normal distribution, described by [EX] = −log[2 − (Executive function BACS-J z score)]. Therefore, we used [EX] instead of "executive function BACS-J z score" for analysis.

Except for the treatment settings, baseline verbal memory, baseline [EX], and baseline composite scores, neither socio-demographic nor clinical variables differed significantly between the two groups (Table 1). Therefore, repeated measures analyses

Table 2
Sample educational computer software used in the computer sessions.

Task	Software	Activity	Target cognitive domain
The mail room	Monsters Inc.: Scream Team Training	Sort all the mail into the proper mailboxes before the clock hits 9 a.m.	Attention, speed
Lunch room	Monsters Inc.: Scream Team Training	Select food items and daily specials to serve to each monster in accordance with the figure presented on the lunch-order ticket.	Attention, speed
Moonfish	Finding Nemo: Nemo's Underwater World of Fun	Repeat the shape patterns made by the moonfish.	Working memory
Spark! Mejikara	Let's refresh your brain	Memorize the illustrations that appear one after another on the screen, and recollect them in order.	Working memory
Hustle memory	Let's refresh your brain	Memorize the character's clothes that are put on within ten seconds.	Visual learning and memory
Frippletration	Thinkin' Things 2	Visual and auditory memory matching game.	Visual / auditory learning and memory
Stocktopus	Thinkin' Things 3	Repeat trading items to get the items you need for your portfolio.	Working memory, executive function,
Build it	Factory Deluxe	Build up the presented goal product by selecting and using appropriate tools.	Executive function
The puzzles	Logical Journey Of The Zoombinis	Solve puzzles with various rules using as clues physical features of hair, eyes, nose, and feet of little creatures called Zoombinis.	Executive function

"Thinkin' Things 2", "Thinkin' Things 3", and "Factory Deluxe" were English versions; however, English ability was not necessary to accomplish the tasks. Other software programs were Japanese versions.

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Table 3
The result of paired *t* test on BACS-J data with NEAR participants.

	Baseline	Post treatment	*t*	*p*	Cohen's *d*
Verbal memory	−1.09±0.92	−0.13±0.99	8.80	<0.0001	1.01
Working memory	−0.95±0.95	−0.54±1.17	4.11	<0.0005	0.39
Motor speed	−1.60±1.37	−1.04±1.42	3.28	<0.005	0.41
Verbal fluency	−0.47±1.00	−0.14±1.10	3.41	<0.005	0.32
Attention and speed of information processing	−1.24±0.88	−0.99±0.96	3.19	<0.005	0.28
[EX]	−0.79±0.59	−0.55±0.55	3.02	<0.005	0.44
Composite score	−1.65±1.27	−0.79±1.33	8.96	<0.0001	0.67

[EX] = −log[2 − (Executive function BACS-J z score)].

of variance were performed on BACS-J data using 'group' (NEAR group, control group) and 'treatment settings' (inpatient, outpatient) as inter-individual factors, while 'time' (baseline, post-treatment) was used as an intra-individual factor. Moreover, in the analyses of verbal memory, [EX], and composite scores, baseline data were used as covariates.

3. Results (Tables 3, 4, Fig. 1)

3.1. The within-NEAR treatment change of BACS-J data

There were significant improvements in the scores of all subcomponents in BACS-J (Table 3).

3.2. In comparison with control patients

There were significant interactions between 'group' and 'time' in verbal memory, working memory, verbal fluency, attention and speed of information processing, [EX], and composite scores (Table 4). The improvement of these areas was significantly greater in the NEAR group than in the control group. There was no difference between groups in terms of the change in motor speed.

4. Discussion

In the present study, we found significant improvement for all cognitive domains related to BACS-J. According to the meta-analysis of the effectiveness of cognitive remediation in schizophrenia, neurocognitive benefit varied from small (Cohen's $d=0.2$) to very large ($d=1.2$) effect size (Medalia and Choi, 2009). Medalia et al. (2009) also suggested that heterogeneity of response to cognitive remediation might depend on instructional techniques, intellectual ability, and intrinsic motivation. In NEAR, instructional techniques are devised to enhance intrinsic motivation. It has already been shown that the use of NEAR educational software without an instructional approach did not achieve clinically meaningful change in neurocognitive capacity (Bellack et al., 2005; Dickinson et al., 2010). In our study, we complied with the principle of NEAR by attaching great importance to instructional approach and could find small to very large effect sizes in broad domains ($d=0.28$–1.01). In comparison with the control group, the positive findings remained significant except for motor speed. NEAR approach proved to be a feasible psychosocial therapy, even in Japan with its different cultural background and with the use of software programs that differ from those in Western countries.

In BACS-J, motor speed was assessed by "Token Motor Task". The task requires the participants to put 100 plastic tokens into a container bimanually as quickly as possible within 60 s, and the outcome measure is the total number of tokens put in the container (Keefe et al., 2004). In the NEAR session, participants were engaged in the computerized learning tasks selected to address specific domains of cognitive function (Medalia et al., 2009); however, we may have failed to include those tasks that required considerable motor speed to perform in the session. This may explain why the NEAR participants were not able to achieve greater improvement in motor speed than the controls.

In this study, the two groups were heterogeneous in many points, and although several subcomponent scores of the BACS-J were significantly lower in the control group than in the NEAR group, correlations between baseline BACS-J data and the improvement in

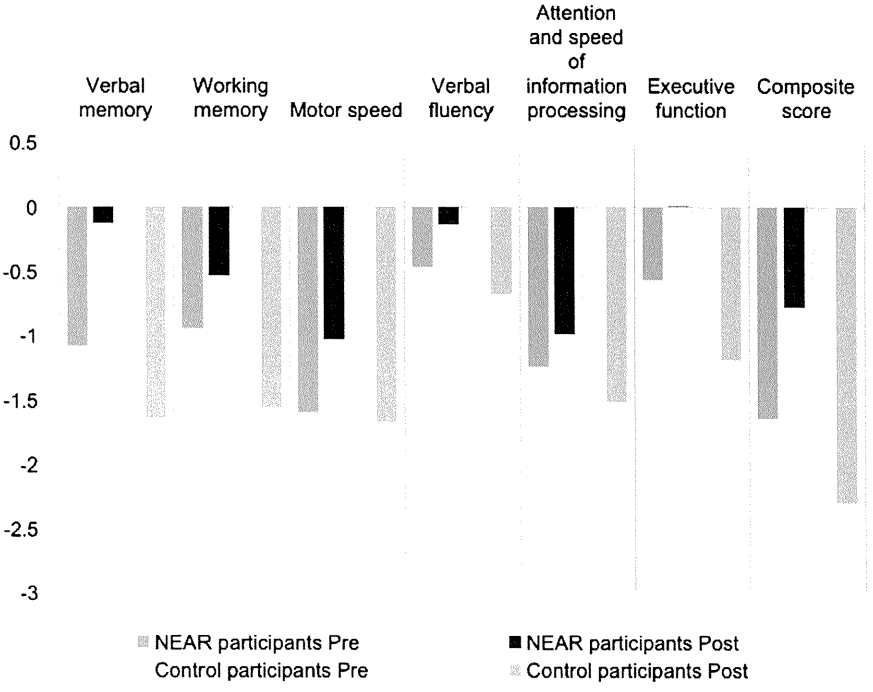

Fig. 1. Changes in cognitive function during 6 months period.

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Table 4
"Time × group" interaction effect on ANOVA with BACS-J data in comparison with control group.

	d.f.	F	p
Verbal memory#	1,69	16.1	<0.0005
Working memory	1,70	16.9	<0.0005
Motor speed	1,70	1.53	n.s.
Verbal fluency	1,70	4.39	<0.05
Attention and speed of information processing	1,70	5.79	<0.05
[EX]#	1,69	4.69	<0.05
Composite score#	1,69	19.1	<0.0001

# baseline data were used as covariates.
[EX] = −log[2 − (Executive function BACS-J z score)].

BACS-J data were negative ($r = -0.57$ to -0.06) in the NEAR group. This implies that the NEAR program is more effective when baseline neurocognition ability is weaker. Although it is possible that there was recruitment bias to include higher-function subjects in the NEAR group at baseline, it may be assumed that taking into account the difference in neurocognition would not negate the effect of NEAR.

There are several limitations of the present study. First, although only the difference in treatment settings between the NEAR participants and the controls appeared significant, clinical and demographic variables were not well matched between the two groups. Second, subjects were not randomly assigned to either of the groups. Third, some clinicians who managed the NEAR session also had to take a role as a tester of BACS-J. In order to resolve these issues, randomized control studies of NEAR program with testers being blinded to the treatment assignment are warranted. Moreover, while we focused on the neurocognitive effect of NEAR in Japan in the present report, we should also take into consideration its effectiveness on social function and/or quality of life in patients with schizophrenia.

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1 統合失調症の発症過程と認知機能

はじめに

Kraepelin と E. Bleuler の記述以来、認知障害は統合失調症の中核的病態として重視されてきた[30, 32]。近年、神経心理学、精神生理学、神経画像などの研究を背景に、認知障害研究が飛躍的に進展し[19, 31]、特に神経心理学の知見から統合失調症にみられる認知障害の特徴が次のようにまとめられている[21]。

1 記憶、注意、作業記憶、問題解決、処理速度、社会認知の機能領域で、健常者の平均値と比べて1.5～2倍の標準偏差(SD)以下の遂行障害を示す。
2 発症以前から存在し発症後も精神症状や薬物とは独立して持続する脆弱性指標の特徴を示す。
3 生活能力や機能的転帰に対して陽性症状や陰性症状と比べ強い影響力をもち将来的に治療標的となりうる。
4 疾患特異的な認知プロフィールを示す。

統合失調症の表現型としての陽性症状、陰性症状、解体症状などの精神症状と比べて、認知障害はより多くの患者に共通してみられ[35]、また患者家族の一部にも同様の異常が見られるため、中間表現型あるいはエンドフェノタイプ[14]の特性をもっていると考えられる。しかし、認知障害に基づいてこの疾患がもつ臨床的な多様性や異種性を説明できるまでに至っておらず、病因論、病態論、症候論における認知障害の位置づけもまだ明確になっていない[33, 35, 49]。また、統合失調症における脳構造変化と同様に認知障害のプロフィールは患者間でかなり異なり、さらに、もともとの認知予備能や疾病に対する脳の認知的代償反応という側面も考慮する必要があり[26, 51]、認知障害の議論は単純化できない。

近年、統合失調症を代表とする精神病性障害の早期介入研究が急速に進展しており、早期介入による疾患の経過や転帰への影響が重要な論点となっている[27, 36, 47]。冒頭で述べたように統合失調症の認知障害は発症以前から存在し、生活能力や機能的転帰に対して陽性症状や陰性症状と比べ強い影響力をもつことを考慮すると、発症前での認知機能の特徴を知ることは病因、病態のみならず治療や転帰の視点からも重要である[8, 30, 34, 35, 45]。本稿では、統合失調症の発症に至るまでの認知機能の特徴とその臨床的意義を、特に異種性を中心に考察したい。

A. 早期介入研究と臨床疫学研究から見えてきたこと

精神病の早期介入研究はこの15年間で飛躍的に進展し、統合失調症を中心とした精神病性障害に新たな臨床的知見が加わってきた[28, 36]。さらに一般集団を対象とした前方視的な臨床疫学研究や臨床遺伝学研究の進歩もめざましく、特にこれまで最も謎となっていた精神病発症前における“軌跡”が点から線へと繋がりつつある。例えば、一般若年集団において精神病様症状体験 psychotic-like experiences (PLEs) の頻度が予想以上に高いことから、精神病が患者と健常者との間でのある種の疑似的な連続体を構成していることが注目されている[55]。なお、疑似的な連続体というのは、健常集団自体が均一ではなく、精神病発症に関して健常集団の中に複数の下位群が推定されるためである。一方、双極性障害と精神病性障害の間などで共通の感受性遺伝子が発見され、疾患カテゴリー間の連続性も注目されている[9]。また、統合失調症の発症に遺伝子・環境相互作用が予想以上に大きな影響力をもっていることが明らかになりつつあり[56]、発症過程における環境因子、特に日常的なストレスと発症との関連などは治療にとっても、今後、重要な研究テーマとなるだろう[43, 44]。

こうした早期介入研究を中心とした発症過程や病態に関わる新たな研究領域の進展は、統合失調

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症をはじめとした精神病性障害の疾患概念、病態、症候、診断、治療のあらゆる領域に大きな影響を与えており、現在進行している精神疾患の国際診断基準の改訂作業でも活発に議論されている。さらに、精神病性障害に対して、精神病発症以前も含めて一般医学でも使用されている臨床病期モデルclinical staging modelの確立と、それに基づいた治療の進展が期待されている[38, 39, 48]。図1は重度の精神疾患の臨床病期の中でも、発症直前のリスク状態の病期について示しているが、非特異的な段階からより精神疾患に特異的な段階までのカスケードが想定されている[38, 39]。この臨床病期モデルでは、統合失調症に限らずいくつかの重度の精神疾患は、主観的苦痛や社会機能障害を伴いながら多様な精神症状（微弱な精神病症状、不安、抑うつなど）を示すような、ある種の共通路を通過し発展すると考えられる。ただし、図1にも示してあるようにどの段階からでも発展が途中で頓挫し治癒することがありうるような不連続性あるいは多能性の特徴をもっている。ちなみに、

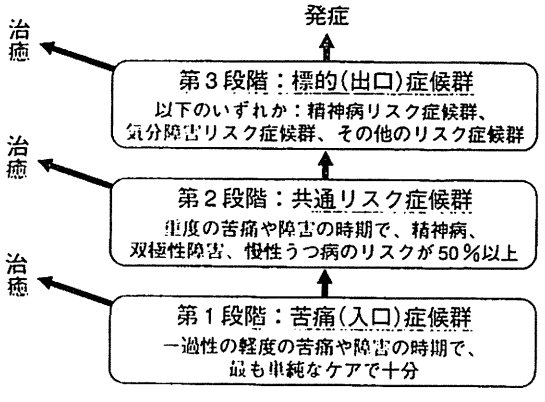

図1　精神疾患の臨床病期モデル：発症前のアットリスク精神状態　（文献38, 39を参考に作成）

重症の精神疾患（統合失調症をはじめとした精神病、双極性障害、慢性うつ病など）が発症するまでの発展段階を示しており、それぞれに特異的な治療法が対応するように3段階の臨床病期（苦痛症候群、共通リスク症候群、標的症候群）が示されている。各段階で微弱な精神病症状、不安、抑うつなどが混在するが、患者自身の苦痛や社会的機能障害を伴うためそれぞれの段階に特化したケアが必要となる。どの段階からでも、発症せずに治癒する場合がある。なお、発症後に関しても複数の臨床病期が想定されている。

後述する微弱な精神病症状を示すようなアットリスク精神状態（at-risk mental state, ARMS）では、当教室の専門外来でのインテーク時に、大半の症例に不安障害、気分障害、適応障害、解離性障害、身体表現性障害、広汎性発達障害、摂食障害などと多様な診断が該当することから[28, 40]、ARMSの症状、病態は非常に複雑であり、よりきめ細かな治療を行うためにも臨床病期モデルの視点が今後必要とされる[29]。

B. 精神病の早期介入と認知障害

精神病を顕在発症する前の発症リスク群に対する早期介入のための診断基準はいくつかあるが、メルボルンのPACE（Personal Assessment and Crisis Evaluation）クリニックでは、ARMSを診断するために以下の超ハイリスク（ultra high risk, UHR）基準によって3つの下位群を規定している。

①閾値下の微弱な陽性症状を呈する群，
②自然寛解する短期間欠性の精神病症状をもつ群，
③精神病に対する素因性の脆弱性を持ち、最近の機能低下を認める群[28]。

何らかの支援を求めて専門外来を訪れるARMSの中では、①が大半を占める。これらのリスク群に対する早期介入の意義は、支援サービスを求めてきたARMS群に対して、現在の症状による苦痛と負担を軽減し社会的障害を改善すること、精神病への移行率を低くすること、発症後の治療導入が容易となり社会的不利益を軽減することなどである。

筆者らの教室では、2004年にARMSの専門外来を立ち上げ、これまで100名以上の支援希求者の評価を行ってきた[28, 29, 40, 41]。その中で、ARMSと診断されたものは約60％で、12ヵ月転帰で10％程度が精神病へ移行した。早期介入の今後の課題として、いかに高い精度で精神病移行群を診断し適切な治療を行うかに加えて、社会機能に問題はあるが精神病に発展しない疑陽性例（元々発症しない群）と疑疑陽性例（発症を阻止した群）に対する新たな支援方法の開発も重要になっている。例えば、当教室の専門外来における

インテーク時の全体的評定尺度（GAF）得点は、精神病初回エピソード群で平均約38点であったが、ARMS群でも平均約46点、精神病初回エピソード患者を除く非ARMS群でも平均約51点とかなり低く、さらに生活の質はいずれの群も同様に低下していた[29]。

以上より、早期介入では精神症状と精神病移行を標的とした症状転帰の改善以上に、支援を求めて専門外来を訪れてきた若者における機能障害を標的とした機能転帰の改善がさらに重要である。そして、統合失調症の病態の中核が社会機能と最も関連性の深い認知障害であるとすれば、早期介入の本質は認知障害の予防と改善による予後と転帰の向上にあるといえる[8,25,30,47]。

C. 精神病発症前の社会機能障害と認知障害

一般若年集団を対象とした研究において、診断閾値下の軽微な陽性症状を示すPLEsの有病率が10％程度の比率で出現することが明らかになってきており（このうち3分の1程度が苦痛や支援希求行動を伴う）[55]、同様に診断閾値下の軽微な陰性症状／解体症状も一般若年集団に存在することがわかってきた。そして、一般若年集団を対象とした前方視的な約10年間の追跡研究[13]によって、閾値下陰性／解体症状が閾値下陽性症状の出現する数年前から先行して出現することが示され（図2左の“認知経路”）、比較的多くの統合失調症にみられる経時的な症状発現パターン[17]（後述）が支持された。認知障害と精神症状の間には深い関連があるが、それらの病態論的位置づけや評価方法には未解決の問題があり両者の関係は明らかになっていない[32～34,49]。しかし、その中でも認知障害と陰性／解体症状とは相互に独立的ではあるが、ある一定の関連性が指摘されている[12,52]。図2左の“認知経路”で発症する統合失調症は、基盤に早期神経発達障害の遺伝的リスクがあり、さまざまなレベルでの遺伝子・環境相互作用を通して[11,13,56]、認知障害さらに軽微な陰性／解体症状が出現し、最終的に精神病症状が惹起されると推定される[13,54]。

精神病の早期介入対象となるARMSの多くは発症に至らず、ARMSからの精神病移行率は最近では10％程度である[39]。発症の予測精度をあげる条件として、北米の研究グループは、社会機能障害、社会機能レベルの最近の悪化、疑惑／パラノイア、物質乱用の既往、普通でない思考内容を[5]、また、欧州の研究グループは、陽性症状、奇異な思考、睡眠障害、統合失調型障害、過去1年間での社会機能水準、教育年数の累積的影響を挙げている[50]。これらには、上述の“認知経路”で重要となる認知障害や陰性症状／解体症状との関連が示唆される項目が含まれ、さらにそれらの背景には言語性記憶・学習、作業記憶に関わる認知障害が推定されている[50]。

前述のようにARMS群では既に社会機能がかなり低下しており（当教室の調査では、GAFは平均46点[29]）、それは精神病症状の出現するか

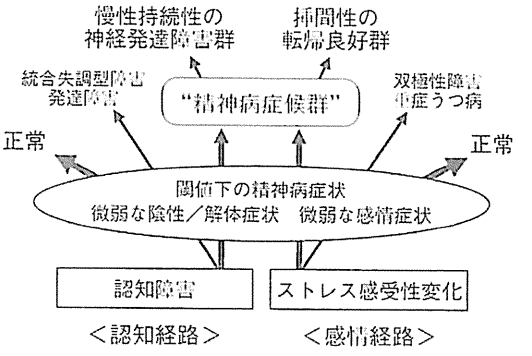

図2　精神病症候群に至る認知経路と感情経路
（文献43を参考に作成）

左の認知経路では遺伝子・環境相互作用の影響をさまざまなレベルで受けながら、神経発達障害に基づく認知障害を基盤にして、微弱な陰性／解体症状、閾値下の精神病症状を経て、慢性持続性の経過を辿る精神病症候群[56]を示す。精神病症候群に至らずに、統合失調型障害、発達障害に留まるか、あるいは正常化する場合もある。

右の感情経路も遺伝子・環境相互作用の影響を受け（特に小児期の心的外傷など）、ストレス感受性が変化し、それを基盤にして、微弱な感情症状を経て、挿間性の転帰良好な経過を辿る精神病症候群を示す。精神病症候群に至らずに、双極性障害、慢性うつ病になる場合や、あるいは正常化する場合もある。

なり以前から始まっていることが多くの研究で指摘されてきた[8, 17, 25, 36, 50]。例えば、米国で行われている早期介入研究の1つであるRAP（Recognition and Prevention）プログラムでは、精神病の早期危険因子として、認知障害、感情障害、社会的孤立、学校機能障害の4つを重視しており、それらを早期介入の標的としている[8, 36]。最近の出生コホートによる前方視的研究でも、精神病性障害になった患者の多くが、児童思春期、青年期に既にさまざまは精神・行動の障害を示していたことが明らかになっている[22]。

統合失調症の発症以前における認知障害それ自体に関する研究[4]では、後方視的な検討ではあるが、学業成績から推定すると（成績表をもとに各学年ごとに健常者群での到達検査得点を算出し、それと患者群を比較。学年が高くなるにつれ得点が直線的に高くなる）、小学1年生の時点で健常群の0.8～1.1学年相当分（精神病発症時点での認知障害の60％に相当）の成績低下が見られ、高校3年生の時点で1.5～1.8学年相当分の成績が低下していた。次に、大学進学適性検査でのデータからは、高校3年生の時点から、行動変化の出現（平均22.6歳）、精神病発症（平均24.3歳）を経過して検査時点（平均26.5歳）までの約8年間で、10ポイント程度のIQ低下を認めた。

Simonら[53]は、①精神病初回エピソード群、②超ハイリスク群、③基底症状群（主観的な認知障害）、④患者対照群での横断的研究ではあるが、認知障害の重症度が、①＞②＞③＝④であることを示した。したがって、認知障害が複数の段階を経て悪化することが推測される[36]。なお、脳の構造変化に関する研究からも、早期の神経発達障害（胎生期から周生期）、前駆期から発症までの移行時期と発症直後にまたがる後期の神経発達障害として、複数の連鎖的悪化過程が推定されている[36, 46]。

ARMSの前方視的な追跡研究では[20]、①精神病初回エピソード群、②後に精神病に移行したARMS群、③後に精神病に移行しなかったARMS群、④健常群を対象に神経心理学的検査を反復して施行したが、初回検査時点では②と③のARMS群（精神病への移行率は41％）は①と④の中間的な値を示したが、その後の反復検査時点では、②だけが認知悪化を認めた。これらの所見は、認知的悪化が、発症直前の時期に加えてそれ以前の時期との複数の段階を経ているというSimonsらの結果[53]を支持すると思われる。

以上より、認知障害は発症以前から先行して見られ、“認知経路”による発症を支持している。ところで、精神病初回エピソード患者での多くの前方視的転帰研究において、予後良好群と不良群はそれぞれ約半数ずつを占めており、少なくとも経過や転帰からして疾患異種性を考慮する必要がある[54]。認知障害が統合失調症の長期転帰に重大な影響を及ぼすことは多くの研究で指摘されてきており[15]、さらに認知障害は発症時点で既に存在し、多くの場合、その重症度は疾患の生涯経過を通して比較的安定したままである[18]。したがって、経過や転帰を規定するような疾患の異種性は少なくとも発症以前から存在する可能性があるが、この問題はほとんど明らかになっていない。以下では、発症以前での疾患の異種性と認知障害の関連について、現時点で推定されていることをまとめる。

D. 統合失調症の異種性と認知障害

1. 臨床経過における異種性

包括的ケアマネージメント、心理社会療法、薬物療法、精神病の早期介入などによって、統合失調症の寛解（症状寛解と機能寛解を含む）や回復への関心が高まっている[2, 10, 37, 58]。なお、臨床的回復モデルでは一定の評価基準で症状寛解と機能寛解が達成された場合を回復と定義している[37, 58]。これは治療計画を立てる際の重要な視点となるが、それは現在症の評価のみならず経過と予後を予測しつつ個別化医療を達成することが求められているからである。Wunderinkら[58]は、精神病初回エピソード患者（約半数が統合失調症）を対象に、症状寛解と機能寛解とを2週毎に評価し2年間追跡した。ここでいう機能評価は、自己ケア、家事、パートナー関係、家族関係、仲間関係、地域との関わり、学業・職業の7領域に渡る状態を

評価している．これによると、初発後2年時点で、症状寛解を示したのは52％であり、機能寛解を示したのは26.4％で、症状寛解と機能寛解の両方が達成された回復群は19.2％（統合失調症だけに限ると8.8％）であった（詳細は文献37を参照）．そして、回復の予測因子として、短い"精神病の未治療期間"（duration of untreated psychosis, DUP；精神病症状の起始から治療開始までの期間）とベースラインでの良好な社会機能状態が指摘された（ただし、本研究には認知機能評価は含まれていない）。

統合失調症の発症までの精神症状の経過に関して、構造化面接であるInstrument for the Retrospective Assessment of the Onset of Schizophrenia（IRAOS）[16]を用いた後方視的研究では、患者の7％は陽性症状で始まり、73％は陰性症状（集中困難、意欲低下、精神運動緩慢）または非特異的症状（落ち着きのなさ、不安、抑うつ）で始まり、20％は両症状が同時的（1ヵ月以内）に始まっていた[17]。多くを占める陰性症状や非特異的症状で始まる群は、前述の"認知経路"で発症する群に相当すると思われる。

2. 認知障害における異種性

冒頭でも述べたように統合失調症の認知障害はエンドフェノタイプ（中間表現型）としての特徴をもっていることから、精神症状などと比べて病態の異種性の指標として優れていると予想される[9, 14, 32]。ここでは認知障害から統合失調症の異種性を検討した試みをいくつか紹介する。

Ammariら[1]は、これまでの研究成果に基づいて、標準的な全般的認知機能検査から統合失調症と統合失調感情障害を以下の3群に分けて検討した：①重度の陰性症状と関連すると仮定される全般性認知障害群（知能、言語性記憶ともに異常）；②重度の精神症状と社会機能障害と関連すると仮定される言語性記憶障害群（知能は正常だが言語性記憶が異常）；③社会機能障害が目立たないと仮定される正常認知群（知能、言語性記憶ともに正常）。精神病症状に関しては3群間で同等であったが、正常認知群と比べて全般性認知障害群は陰性症状と社会機能障害が強く、両者は臨床的、機能的に異なる亜型である可能性が示唆された。言語性記憶障害群は他の2群間のようには明確に区別はできなかったが、正常知能に比して作業記憶の障害が目立ち、他の2群よりも雇用率が低く特異な1群が含まれている可能性が推定される。なお、統合失調感情障害は、②と③の群に多く含まれていた。

Weickertら[57]は、発症後の知能から発症前の知能を推定することで3つの経過類型を見出した（図3）。①知能温存群（知能は発症前後ともに正常範囲内。全体の25％を占める）；知能は正常だが、軽度の注意と実行機能の障害が存在する。②知能悪化群（発症前の知能は正常だが発症前後で低下。全体の51％を占める）；注意と実行機能に加え記憶と眼球運動の障害が存在し、おそらく発症前後での前頭・側頭機能の認知的悪化が推定される。③知能障害群（発症前後ともに知能低下。全体の23％を占める）；注意、実行機能、記憶、眼球運動、言語、視空間知覚の重度で広範な障害が発症前から存在し、おそらく早期の神経発達障害と関連する。これらより統合失調症での一定の認知障害は発症以前から程度の差はあるに

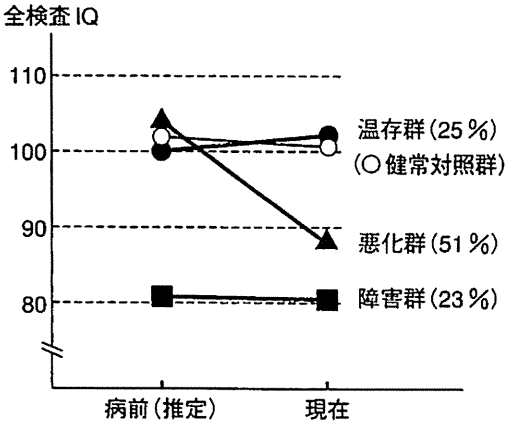

図3　慢性統合失調症患者における現在の知能から病前の知能を推定した場合の経過型（文献57を参考に作成）

知能温存型（図の●印）は全体の25％を占め、発症前後ともに知能が正常。知能悪化型（▲）は全体の51％を占め発症前知能は正常だが、発症後には悪化している。知能障害型（■）は全体の23％を占め、発症前後とも同様に知能障害が持続。参考までに健常対照群（○）のデータも示してある。3群の神経心理学的プロフィールは異なっている（本文参照）。

せよ既に存在しており、その重症度や経過が一様ではなく病態の異種性が推定される。

Niendam ら[45]は、精神病の超ハイリスク群に対してケースマネージメント、心理社会療法、薬物療法を含む包括的治療を行うことによって平均8.3ヵ月後で認知機能がどのように変化するのかを前方視的に検討した。被験者の約半数で20％以上認知機能が改善し、それに伴って短期的な社会機能や精神症状も改善した。一方で残りの半数は包括的治療にもかかわらず認知的には不変あるいは悪化を示し、認知機能の治療反応性に関しても異種性の存在が示唆された。なお、被験者の25％が精神病に移行したが、認知障害の変化からはそれを予測できなかった。

3. 精神病発症経路の異種性：認知経路と感情経路（図2）

先に述べた“認知経路”で発症する統合失調症は（図2左）、基盤に早期神経発達障害を伴う遺伝的リスクがあり、さまざまなレベルでの遺伝子・環境相互作用を通して、認知障害さらに軽微な陰性／解体症状が出現し、最終的に精神病症状が惹起されると推定される[13, 54]。この経路で発症する一群は、臨床経過と認知障害における異種性で述べたように、神経発達障害、重度の認知障害、陰性症状で特徴づけられる慢性持続性の経過を辿ると考えられる。

一方で、Myin-Germeys と van Os[43]は、“認知経路”とは異なる発症様式と臨床経過を示すような“感情経路”（図2の右）を介して発症する一群を想定している。この経路は、認知障害の程度とは関係なく[42]、日常生活上のストレスに対する情動反応性の過剰な高まりが、精神病症候群を惹起するというもので[43, 44]、発症後は挿間性の転帰良好な経過を辿る。おそらく情動反応性の亢進は、発症前に発生したストレスとなるライフイベント、虐待などの小児期の心的外傷などによって引き起こされた脳機能変化を通して形成されると考えられる[11, 43, 56]。また、日常的ストレスと情動反応性の関連については、Experience Sampling Method（ESM）を用い日常の出来事とその時の感情、思考の関連を検討したところ、対照群と比べて患者およびその第一度親族でのストレス感受性が用量反応性に変化していた[43, 44]。なお、感情経路では認知障害自体が精神病症候群の原因にはならないが、それはこの群での認知障害の存在を否定するものではない。

認知経路と感情経路の関連については未解決の点が多いが[3]、持続性の一次性陰性症状[6]を示す“欠陥型統合失調症”の概念は認知経路に重要な視点を提供している。この仮定された統合失調症の下位群は安定期の統合失調症の20～30％に見られ、非欠陥型と比べて、陽性の精神病症状の程度に関しては同程度ではあるが、より重度で広範にわたる認知障害を示し、気分症状や自殺の頻度は低い[7, 23, 24]。欠陥症状の中核的な構成要素の1つである“感情平板化”（情動体験以上に、情動表現と関連した症状）によって情動反応性が低下しており、むしろストレスの影響は低い可能性があり、感情経路とは相反する病態を示しているのかもしれない[43]。

おわりに

Kraepelin と E. Bleuler は精神病症状以上に認知障害を重視したが、現代の精神医学（国際診断基準も含めて）では、評価のしやすい精神病症状を偏重するようになった。しかし、精神病症状は程度に差はあるにせよ非感情性精神病圏以外の多くの疾患でも見られることから、さまざまな病態によって引き起こされる最終共通路としての疾患非特異的症状であるかもしれない。近年、早期介入研究が進展し精神疾患の発症以前の軌跡が明らかにされつつあり、精神病の超ハイリスク状態は正常化する場合も含めて異種性ないし多能性の状態とみなされている。さらに、統合失調症への異なる発展過程として認知経路と感情経路とが提唱されている。これらはとりもなおさず疾患の異種性を示す証拠であり、さまざまな転帰を示す統合失調症を中心とした精神病性障害においては、それらを単一の病態として扱うのではなく、ここで取り上げたようなエンドフェノタイプとしての認知障害を重視した病態論の発展が望まれる。これによって患者の経過や転帰を予測した個別化医療が精神疾患でも実現するであろう。