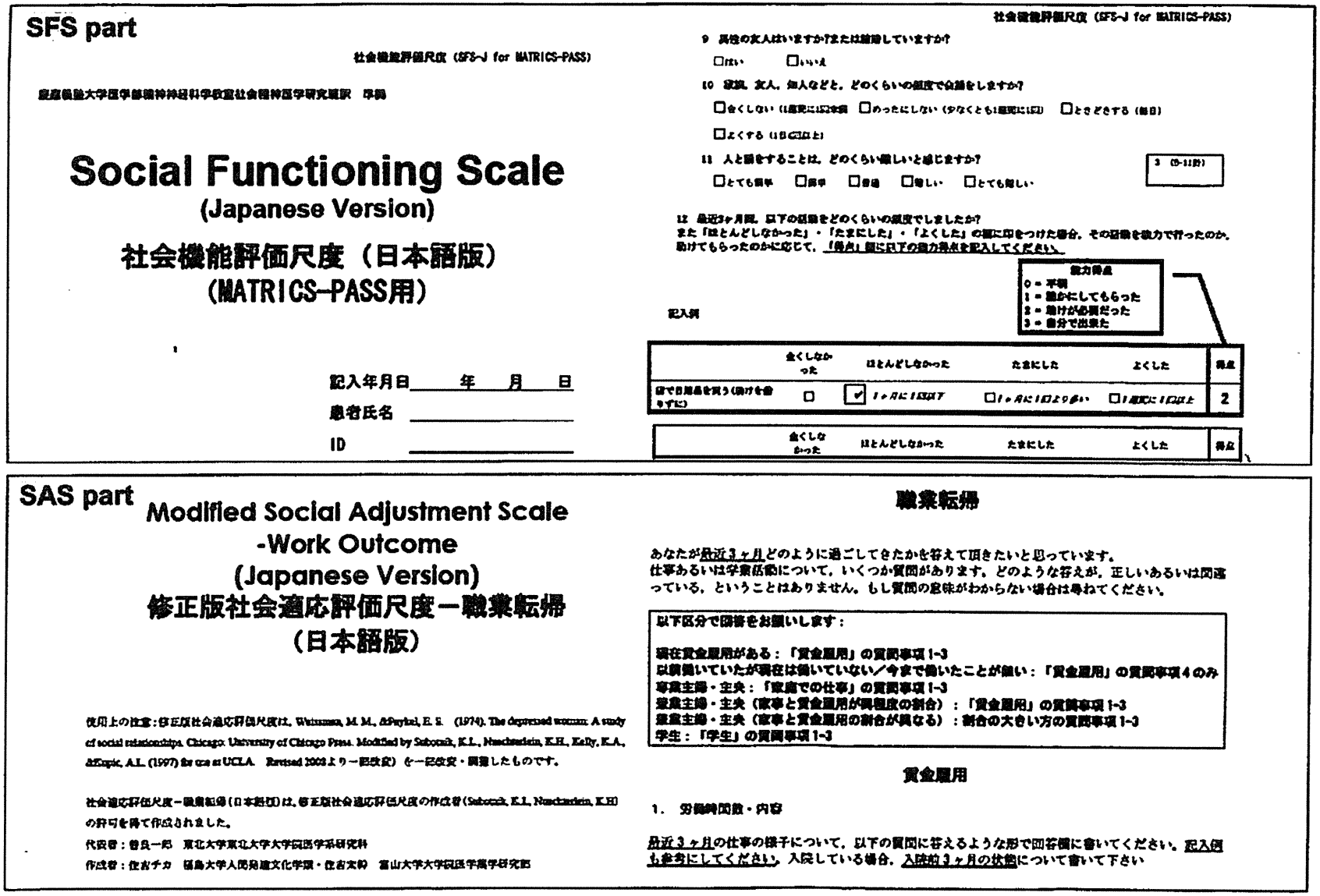

SFS part

社会機能評価尺度（SFS-J for MATRICS-PASS）

慶應義塾大学医学部精神神経科学教室社会精神医学研究班訳　作製

Social Functioning Scale
(Japanese Version)
社会機能評価尺度（日本語版）
(MATRICS-PASS用)

記入年月日＿＿年＿＿月＿＿日

患者氏名＿＿＿＿＿＿＿＿

ID＿＿＿＿＿＿＿＿

社会機能評価尺度（SFS-J for MATRICS-PASS）

9 異性の友人はいますか？または結婚していますか？

□はい　□いいえ

10 家族，友人，知人などと，どのくらいの頻度で会話をしますか？

□全くしない（1週間に1回未満）　□めったにしない（少なくとも1週間に1回）　□ときどきする（毎日）

□よくする（1日に2回以上）

11 人と話をすることは，どのくらい難しいと感じますか？　3（5-11計）

□とても簡単　□簡単　□普通　□難しい　□とても難しい

12 最近3ヶ月間，以下の活動をどのくらいの頻度でしましたか？
また「ほとんどしなかった」・「たまにした」・「よくした」の欄に印をつけた場合，その活動を独力で行ったのか，助けてもらったのかに応じて，「得点」欄に以下の能力得点を記入してください。

能力得点
0＝不明
1＝助かにしてもらった
2＝助けが必要だった
3＝自分で出来た

記入例

	全くしなかった	ほとんどしなかった	たまにした	よくした	得点
店で日用品を買う（助けを借りずに）	□	☑ 1ヶ月に1回以下	□1ヶ月に1回より多い	□1週間に1回以上	2

	全くしなかった	ほとんどしなかった	たまにした	よくした	得点

SAS part

Modified Social Adjustment Scale -Work Outcome (Japanese Version)
修正版社会適応評価尺度ー職業転帰（日本語版）

使用上の注意：修正版社会適応評価尺度は，Weissman, M. M., &Paykel, E. S. (1974). The depressed woman: A study of social relationships. Chicago: University of Chicago Press. Modified by Sabourin, K.L., Nuechterlein, K.H., Kelly, K.A., &Espic, A.L. (1997) for use at UCLA. Revised 2003より一部改変）を一部改変・翻訳したものです。

社会適応評価尺度ー職業転帰（日本語版）は，修正版社会適応評価尺度の作成者（Sabourin, K.L, Nuechterlein, K.H）の許可を得て作成されました。

代表者：曽良一郎　東北大学東北大学大学院医学系研究科

作成者：住吉チカ　福島大学人間発達文化学類・住吉太幹　富山大学大学院医学薬学研究部

職業転帰

あなたが最近3ヶ月どのように過ごしてきたかを答えて頂きたいと思っています。
仕事あるいは学業活動について，いくつか質問があります。どのような答えが，正しいあるいは間違っている，ということはありません。もし質問の意味がわからない場合は尋ねてください。

以下区分で回答をお願いします：

現在賃金雇用がある：「賃金雇用」の質問事項1-3
以前働いていたが現在は働いていない／今まで働いたことが無い：「賃金雇用」の質問事項4のみ
専業主婦・主夫：「家庭での仕事」の質問事項1-3
兼業主婦・主夫（家事と賃金雇用が同程度の割合）：「賃金雇用」の質問事項1-3
兼業主婦・主夫（家事と賃金雇用の割合が異なる）：割合の大きい方の質問事項1-3
学生：「学生」の質問事項1-3

賃金雇用

1．労働時間数・内容

最近3ヶ月の仕事の様子について，以下の質問に答えるような形で回答欄に書いてください。記入例も参考にしてください。入院している場合，入院前3ヶ月の状態について書いて下さい

図4　Modified SFS/SAS for MATRICS-PASS_J.

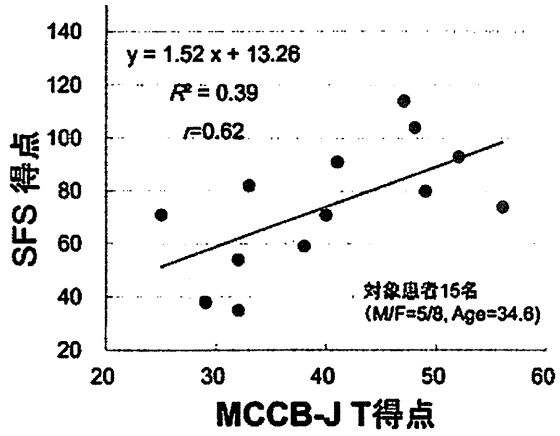

図5 MCCBとSFS for MATRICS-PASS Jの関連.

IV. 機能的転帰測度の移植

MATRICS-CTは，その名称が示すように，co-primary measuresの検討とともに，MCCBの各国（言語）への導入を図ってきた．同組織はまず，優先度の高い言語として，ドイツ語，ロシア語，ヒンディー語（インド），中国語（simplified Chinese），スペイン語（スペインと中南米のSpanish dialects 2種），の5言語（8バージョン）への翻訳を行った（http://www.matrics.ucla.edu/matrics-ct/）．ついで商業ベースでの導入として，クロアチア，ヘブライ語，日本語（商業版），イタリア語への翻訳が進められた．またアカデミック版として，ポーランド，トルコ，デンマーク，オランダ，ブラジル（Portuguese），日本語（アカデミック版）への導入も進められてきた．（http://www.matrics.ucla.edu/matrics-ct/）（Harvey et al, 2010）．

MCCBの国際的な普及に伴い，co-primary measures，およびcommunity functioning measuresについても，各国（言語）に翻訳され，併せて利用されていくと考えられる．しかし機能的転帰の評価尺度・バッテリーの他言語への移植は，MCCB以上に難しい作業となる可能性がある．Neuropsychological performanceレベルの検査バッテリーでさえ，使用言語・文化の影響を免れないが（例えばMCCBにおける語音整列課題や情動管理能力課題など，Harvey et al, 2010），機能的転帰の測定対象は，患者の生活環境に密接な認知機能や行動に置かれる．このため，社会・文化の影響は一層大きくなると考えられる．

社会生活・日常生活で必要とされる技能（したがってその遂行に要する認知機能）が社会・文化的に普遍でないため生じる問題の例として，例えばUPSA（原版）の課題で使用されている「小切手の使用」「電力・ガス等の請求書」「病院の診察予約」等の制度や概念そのものが欠如している場合，が挙げられる（http://www.matrics.ucla.edu/matrics-ct/）（Harvey and Velligan, 2011）．また，Modified SFS/SASのようなcommunity function measuresを移植する際，SFSパートに含まれる「娯楽」や，SASパートの「就労」の在り方は，社会・文化的背景により大きく異なる可能性がある（Burns and Patrick, 2007）．

普遍性の問題は，1）開発者が（原版に加えて）国際版を作成する，2）翻訳者が等価な課題に置き換える等の工夫により，ある程度コントロールし得るものと思われる．筆者らが翻訳したUPSA-B_J（住吉ら，2011b）においても，金銭管理課題で使用する請求書等は，日本の電力会社が実際に用いているものに基づき作成した（図2右参照；他詳細は本号の兼田ら参照）．またModified SFS/SASについては，日本における主婦/夫の役割の大きさを考慮し，PASS版では省かれていた主婦/夫の労働時間も評価に含める修正を施している．

V. おわりに

本総説では，統合失調症患者の機能的転帰について，その概念，評価方法，および各国へ移植する際の問題について概観した．筆者らのグループは，日本語版MCCB（MCCB-J）の開発に携わるとともに，MATRICS開発プロジェクトの手法を追う形で，MCCBと連動する機能的転帰の評価の手法も検討してきた（住吉ら，2011a）．先に述べたUPSA-B，Modified SFS/SAS for MATRICS-PASSについて，co-primary measureあるいはcommunity functioning measureとしての有効性を，本邦で確認していくことが今後の課題である．

先に，co-primary measureをfunctional performanceに据えるのが困難な理由として，治療者・薬がコントロールできない環境・社会要因が介在変数として影響するためだと述べた．これら介在変数は，MCCBと連動した機能的転帰を評価する点では望まれないかもしれないが，充実した支援・教育・経済援助等が，プラスの介在変数，すなわちneuropsychological performanceの改善を増幅するように働くのであれば，患者の社会的予後にはむしろ望ましいものと言える．また患者の社会認知も，心理教育や地域社会の成熟，福祉の向上など環境の整備により，改善を図ることが可能だと推察される．機能的転帰に対しプラスに働き得るこのような介在変数は，その社会の成熟度を示す指標ともいえ，心理・看護・福祉領域のコメディカル・スタッフとの協働のもと，その充実を図ることが望まれる．

本総説の作成にあたり，富山大学医学薬学研究部神経精神医学講座・住吉太幹准教授に助言と校正をいただきました．

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Abstract: Chika SUMIYOSHI (Faculty of Human Development and Culture, 1 Kanayagawa, Fukushima, 960-1296 Japan) *Functional outcome in schizophrenia: Relation to the MATRICS consensus cognitive battery.* Jpn. J. Neuropsychopharmacol., 31: 251-257 (2011).

Functional outcome includes a wide range of abilities from successful performance on neurocognitive tests to managing independent living in the community. Assessment of functional outcome has been one of the main concerns in the Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS), as it is supposed to mirror the cognitive improvement on the primary measure (i.e. MATRICS Consensus Cognitive Battery; MCCB). The first step was to identify an optimal level of functional outcome; functional capacity was specified as co-primary measures for MCCB. Subsequently, appropriate co-primary measures were explored both in performance-based and interview-based approaches. To study a higher level of functional outcome, functional performance has also been considered, which predicts the ability of patients to adjust themselves to the community. Among the community functioning measures developed recently, the Modified SFS/SAS for MATRICS-PASS (Social Functioning Scale/Social Adjustment Scale for MATRICS-Psychonomic and Standardization Study) was introduced, based on its ability to predict social functioning in patients with schizophrenia. Finally, the author discussed several issues concerning the translation of functional outcome measures into non-English languages.

Key words: Schizophrenia, MATRICS Consensus Cognitive Battery, Functional outcome, Co-primary measures, Community functioning measures

(Reprint requests should be sent to C. Sumiyoshi)

Psychiatry Research 169 (2009) 178–179

Contents lists available at ScienceDirect

Psychiatry Research

journal homepage: www.elsevier.com/locate/psychres

Brief report

Determinants of work outcome in schizophrenia and schizoaffective disorder: Role of cognitive function

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ARTICLE INFO

Article history:
Received 20 July 2008
Accepted 21 August 2008

Keywords:
Schizophrenia
Cognition
Employment
Verbal working memory

ABSTRACT

Cognitive impairment has been reported to be more important than clinical symptomatology as a determinant of work and social function in schizophrenia. In a retrospective analysis of a group of 152 patients with chronic schizophrenia or schizoaffective disorder, performance on a battery of neuropsychological tests was contrasted in employed (32, 21.1%) versus unemployed subgroups. As predicted, neurocognitive performance was more important than clinical symptoms in predicting employment status. Among neurocognitive functions, verbal working memory (as reflected by the Consonant Trigram Test) was the strongest predictor of employment status.

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1. Introduction

There has been considerable research into why people with schizophrenia are unable to obtain and keep competitive employment. Cognitive impairment, a core feature of schizophrenia, has been reported to be the most important determinant of work and social function in schizophrenia (**Meltzer et al., 1996; Green et al., 2000; McGurk and Meltzer, 2000**). Among several domains of cognitive function, verbal memory and executive function appear to be the cognitive functions that most affect work and social function (**Meltzer et al., 1996; Green et al., 2000; McGurk and Meltzer, 2000**). By contrast, most studies find that psychotic symptoms are not significantly associated with functional outcome (**Green et al., 2000**). However, several recent studies have suggested that psychopathology, and in particular positive symptoms, may be as important as, or more important than, cognitive dysfunction with regard to functional outcome (**Ertugrul and Ulug, 2002**). The purpose of this cross-sectional study was to test the hypotheses that specific types of cognitive impairment in patients with schizophrenia, but not psychotic symptoms, would predict work status.

2. Methods

Data from a previous study were used, and the subjects consisted of 152 patients with a DSM-III-R (**American Psychiatric Association, 1987**) diagnosis of chronic schizophrenia or schizoaffective disorder. Among the patients, 28 (18%) were women; the patients had a mean age of 42.7 (SD = 11.2), and a mean age at onset of 23.0 years (SD = 7.8). The assessments were performed using the Brief Psychiatric Rating Scale (BPRS; **Overall and Gorham, 1962**) for psychotic symptoms. Work status was defined as follows: (1) employed = full-time (minimum of 30 h/week or full-time student status) or part-time (1–29 h/week or part-time student status); and (2) unemployed = unemployed and not in school. The cognitive test battery consisted of measures addressing the following functions: (1) psychomotor speed and attention [Continuous Performance Test (CPT; **Loong, 1991**)]; (2) verbal [Consonant Trigram Test (CTT; **Peterson and Peterson, 1959**)] and spatial working memory [Spatial Working Memory Test (SWMT; **McGurk et al., 1996**)]; (3) verbal fluency [Controlled Word Association Test (CWAT; **Benton et al., 1983**)]; (4) verbal learning and memory [California Verbal Learning Test (CVLT; **Delis et al., 1987**) total words recalled for list A1–5, and long delay free recall (LDFR)]; and (5) executive function [Wisconsin Card Sorting Test (WCST; **Berg, 1948**) category (CAT) and percent perseveration (PP)].

3. Results and discussion

Of the 152 patients, 32 (21.1%) were employed. The age ($t = 2.75$, $df = 147$, $P < 0.01$) and duration of the illness ($t = 3.15$, $df = 71$, $P < 0.01$) were significantly lower in employed patients. Comparison of employed and unemployed groups showed significantly better CPT [$F(1,63) = 5.9$, $P = 0.01$], CTT [$F(1,122) = 9.2$, $P < 0.01$], SWMT [$F(1,95) = 8.2$, $P < 0.01$], BPRS Total [$F(1,119) = 4.9$, $P = 0.02$], and BPRS Positive [$F(1,119) = 6.1$, $P = 0.01$] scores in the employed group. When the analysis was repeated after covarying the duration of the illness, the results were virtually identical. A logistic regression analysis with a forward stepwise procedure indicated that the CTT score ($\chi^2 = 7.64$, $df = 1$, $P < 0.01$) was the strongest predictor of employment status.

As predicted, neurocognitive performance was more important than clinical symptoms in predicting employment status. Among neurocognitive functions, verbal working memory was more

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0165-1781/$ – see front matter © 2008 Elsevier Ireland Ltd. All rights reserved.
doi:10.1016/j.psychres.2008.08.003

important than other types of cognitive function for employment outcome. Treatment that enhances cognitive function, especially verbal working memory, may lead to better employment outcome in patients with schizophrenia or schizoaffective disorder. A further longitudinal study should be carried out to confirm the results of the present study.

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Verbal Working Memory Impairment in Patients With Current Episode of Unipolar Major Depressive Disorder and in Remission

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Abstract: In this naturalistic cross-sectional study, the author tested the hypothesis that verbal working memory (WM) in major depressive disorder (MDD) persists even after remission. The subjects consisted of 54 adult clinic outpatients and 54 age- and sex-equated healthy comparison subjects. The author found that the digit sequencing task scores for verbal WM were significantly less in both patients with a current episode of MDD and patients in remission than in the controls. Also, there were no significant correlations between the digit sequencing task scores and the dose of antidepressants or benzodiazepines in patients experiencing remission. It is suggested that WM/central executive function in MDD might be impaired, and thus verbal WM might be, at least to a degree, trait related.

Key Words: cross-sectional study, major depressive disorder, verbal working memory

(Clin Neuropharm 2009;32: 346Y347)

Patients with major depressive disorder (MDD) have been reported to perform less well in neurocognitive tests than healthy controls, even after their depression is successfully treated with modern antidepressants.[1,2] In a recent report, Gualtieri and Morgan[3] reported that substantial numbers of patients with depression are cognitively impaired. Despite evidence indicative of an MDD-associated deficit in verbal working memory (WM) function,[4] there have been comparatively few investigations of verbal WM in MDD after remission. The purpose of this study was to assess the hypothesis that verbal WM in MDD persists even after remission.

EXPERIMENTAL PROCEDURES

Sample

The subjects for this naturalistic cross-sectional study consisted of 54 adult clinic outpatients (aged 21Y59 years): 22 patients who met the Diagnostic and Statistical Manual of Mental Disorders-IV[5] criteria for a current episode of unipolar MDD (nonpsychotic) and 32 patients who were in remission (full/partial), and 54 age- and sex-equated healthy comparison subjects. The patients had no comorbid psychiatric disorders and no medical, neurological, or developmental conditions that might affect cognition (eg, attention-deficit/hyperactivity disorder, brain injury, mild cognitive impairment, and chronic pain). The investigation was carried out in accordance with the Declaration of Helsinki, and the informed consent was obtained from all subjects. In both the patients and the controls, 35 (65%) were women; the patients and the controls had a mean (SD) age of 41.0 (10.6), and the patients had a mean age at onset of 37.7 (11.7) years. Seven (32%) of the 22 patients with a current episode of MDD were given antidepressants, and 6 (27%) of them were given benzodiazepines. Twenty-eight (88%) of the 32 patients who were in remission were given antidepressants, and 16 (50%) of them were given benzodiazepines (Table 1).

Clinical Assessments

The assessments were performed using the HAM-D7[6] for severity of depression and remission; full remission was defined as an HAM-D7 score of 3 or less and partial remission as a score of 10 or less. The BACS[7] digit sequencing task (patients are presented with clusters of numbers in random order of increasing length, and they are asked to tell the experimenter the numbers in order, from lowest to highest) was used for verbal WM. The BACS digit sequencing task has been validated in the healthy controls.[7]

Data Analysis

The JMP (Version 8.0.1, Tokyo, Japan) for Macintosh was used to perform the analysis. For numerical variables, the t test procedures for independent group comparison were used to compare the differences in variables between 2 groups, and the differences between 3 groups were compared using the analysis of variance (ANOVA), followed by post hoc comparisons. The Pearson product moment correlation was used to examine the relationships between 2 numerical variables.

RESULTS

First, a comparison of the digit sequencing task scores between all patients (mean [SD], 17.1 [4.4]) and the controls (mean [SD], 20.6 [4.5]) revealed that the scores in the patients were significantly lower than those in the controls (P G 0.0001). When the analysis was repeated after covarying the education level, the results were virtually identical. Second, when we further compared the differences in the digit sequencing task scores between the 3 groups V the patients with a current episode of MDD (mean [SD], 17.2 [4.3]), the patients in remission (mean [SD], 17.0 [4.5]), and the controls, significant differences were found ($F_{2,105}$ = 8.39, P G 0.001); the digit sequencing task scores were significantly less in both patient groups than in the controls. Controlling for age and education level indicated that the results were virtually identical. Third, an examination of the relationship between depression and digit sequencing task scores revealed that there were no significant correlations between them in either patients with a current episode of MDD or patients in remission. In addition, there were no significant correlations between the digit sequencing task scores and the dose of antidepressants (r = j 0.03, df = 31, P = 0.86) or benzodiazepines (r = j 0.33, df = 31, P = 0.07) in patients experiencing remission.

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DOI: 10.1097/WNF.0b013e3181b130a0

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TABLE 1. Demographic Data

	n (F/M)	Age, yr	Education, yr	Age at Onset, yr	Duration of the Illness, yr	Dose of Antidepressants, mg/d*	Dose of Benzodiazepines, mg/d†	HAM-D7 (Total)	BACS Digit Sequencing Task Score
Healthy	54 (35/19)	41.0 (10.6)	13.6 (1.9)	V	V	V	V	V	20.6 (4.5)
Patients in acute depression	22 (13/9)	37.1 (9.0)	11.9 (2.0)	32.2 (11.2)	4.4 (5.3)	13.2 (22.8)	9.8 (16.0)	15.2 (1.9)	17.2 (4.3)
Patients in remission	32 (22/10)	43.7 (10.9)	12.2 (2.3)	41.1 (10.8)	2.1 (2.2)	22.5 (21.7)	8.7 (12.7)	6.9 (2.9)	17.0 (4.5)
Total No. Patients	54 (35/19)	41.0 (10.6)	12.0 (2.2)	37.7 (11.7)	3.0 (3.9)	18.7 (22.4)	9.1 (14.0)	10.4 (4,.8)	17.1 (4.4)

Data are given as mean (SD).
*Paroxetine equivalent.
†Diazepam equivalent.
BACS indicates Brief Assessment of Cognition in Schizophrenia; F/M, female/male; HAM-D7, 7-item Hamilton Rating Scale for Depression.

DISCUSSION

These findings therefore suggested that an MDD-associated deficit in verbal WM indeed existed in acute depression and even after remission. These findings are consistent with those of Nebes et al[8] who found that verbal VM dysfunction persisted in older patients with depression even after their mood disorder had responded to antidepressant medications. The observations in this study may be explained by an impairment of WM/central executive function in MDD supported by Rose and Ebmeier[4] because executive function impairment is considered to be, at least to a degree, trait related.[9] However, still the possibility of influence of antidepressants/benzodiazepines[10,11] on the results cannot be ruled out. Another limitation in this study was that patients with full and partial remissions were combined for statistical analyses mainly because there were few patients with full remission. Therefore, a further longitudinal study using patients in remission without medication might be necessary to confirm the results of the present study.

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The World Journal of Biological Psychiatry, 2009; 10(4): 591–594

BRIEF REPORT

Verbal working memory and functional outcome in patients with unipolar major depressive disorder

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Abstract

In this naturalistic cross-sectional study, the author tested the hypothesis that verbal working memory (WM) in major depressive disorder (MDD) would predict functional outcome. The subjects consisted of 54 clinic adult out-patients. The author found that, in the patients with current episode of MDD, functional outcome was significantly correlated with depressive scores, but not with Digit Sequencing Task scores. Meanwhile, in a sample of full remitted or partial remitted (mildly depressed) patients, functional outcome was significantly correlated with both Digit Sequencing Task scores and depressive scores. Moreover, in a sample of full remitted or partial remitted (mildly depressed) patients, the Digit Sequencing Task score significantly contributed to the prediction of the functional outcome, but the depressive score did not. The findings in this study suggested that enhancement of verbal WM function may be useful to achieve normalization of functioning as an important component of remission in addition to symptomatic remission.

Key words: *Cross-sectional study, functional outcome, major depressive disorder, verbal working memory*

Introduction

Major depressive disorder (MDD) is a significant health problem with economic implications, and estimates of the economic burden of depression range from $52 billion in 1990 to $83 billion in 2000 (Malone 2007). Among several factors, employment is considered to have a great impact on the societal costs of depression, due to lost income, lost productivity, and disability income payments.

In a previous report (Kaneda et al. in press), the author demonstrated that neurocognitive performance, particularly verbal working memory (WM), was more important than clinical symptoms to predict employment status in patients with schizophrenia. Patients with major depressive disorder also have been reported to perform less well in neurocognitive tests than normal controls, even after their depression is successfully treated with modern antidepressants (Gualtieri et al. 2006; Reppermund et al. 2008). In a recent report, Gualtieri and Morgan (2008) reported that substantial numbers of patients with depression are cognitively impaired, and the author also demonstrated that a depression-associated deficit in verbal WM existed even after remission (Kaneda in press). However, little emphasis has been placed on relation between neurocognitive function and psychosocial or functional outcome in studies of depression to date. The purpose of this study was to test the hypothesis that a specific type of cognitive impairment, namely verbal WM, in patients with MDD would predict functional outcome.

Experimental procedures

Sample

The subjects for this naturalistic cross-sectional study consisted of 54 clinic adult out-patients (aged 21–59 years): 22 patients who met DSM-IV (American Psychiatric Association 1994) criteria for current episode of unipolar MDD (nonpsychotic) and 32 patients who were in full remission or partial remission (mild depression). Patients had no comorbid psychiatric disorders and no medical, neurological or developmental conditions that might affect cognition. The investigation was carried out in accordance with the Declaration of Helsinki and the informed consent was obtained from all subjects.

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(Received 8 March 2009; accepted 20 June 2009)

ISSN 1562-2975 print/ISSN 1814-1412 online © 2009 Informa UK Ltd. (Informa Healthcare, Taylor & Francis AS)
DOI: 10.3109/15622970903183705

Thirty-five (65%) were women; the patients had a mean age of 41.0 (SD = 10.6), and a mean age at onset of 37.7 (11.7) years. Seven out of 22 (32%) patients with current episode of MDD were on antidepressants, and six (27%) of them were on benzodiazepines. Twenty-eight out of 32 (88%) remitted patients were on the antidepressants, and 16 (50%) of them were on benzodiazepines.

Clinical assessments

The assessments were performed using the seven-item Hamilton Rating Scale for Depression (HAM-D7; McIntyre et al. 2002) for severity of depression and remission: full remission defined as an HAM-D7 of 3 or less, and partial remission (mild depression) as a score of 10 or less, and Brief Assessment of Cognition in Schizophrenia (BACS; Keefe et al. 2004) Digit Sequencing Task (patients are presented with clusters of numbers in random order of increasing length, and they are asked to tell the experimenter the numbers in order, from lowest to highest) for verbal WM. The BACS Digit Sequencing Task has been validated in normal controls (Keefe et al. 2004). Digit Sequencing Task scores for each depression group were normalized against their respective age-matched control group (data available upon request). Functional outcome (productivity), such as working, doing household chores, or going to school was assessed by the author based on the interviews with patients and their partners/parents/children, and was defined as follows: 0=non-impaired, 1=mildly impaired, 2=moderately impaired, 3=severely impaired). Demographic data are presented in Table I.

Data analysis

JMI (Version 5.1.2) for Macintosh was used to perform the analysis. For numerical variables, the *t*-tests procedures for independent group comparison were used to compare the differences in variables between two groups, and the differences between three groups were compared by the analysis of variance (ANOVA), followed by *post hoc* comparisons. Pearson's correlation was used to examine the relationships between two numerical variables. A logistic regression model with forward selection criteria was used to predict the functional outcome using the demographic variables, depressive and verbal WM scores.

Results

First, as reported elsewhere (Kaneda in press), Digit Sequencing Task scores were not significantly different between the two groups of patients with

Table I. Demographic data.

	N (F/M)	Age (years)	Education (years)	Age at onset (years)	Duration of the illness (years)	Dose of antidepressants (mg/day)[1]	Dose of benzodiazepines (mg/day)[2]	HAM-D7 (Total)	BACS Digit Sequencing Task score (raw)	BACS Digit Sequencing Task score (*z* score[3])
Total patients	54 (35/19)	41.0 (10.6)	12.0 (2.2)	37.7 (11.7)	3.0 (3.9)	18.7 (22.4)	9.1 (14.0)	10.4 (4.8)	17.1 (4.4)	−0.75 (1.3)
Patients in acute depression	22 (13/9)	37.1 (9.0)	11.9 (2.0)	32.2 (11.2)	4.4 (5.3)	13.2 (22.8)	9.8 (16.0)	15.2 (1.9)	17.2 (4.3)	−0.97 (1.5)
Patients in remission	32 (22/10)	43.7 (10.9)	12.2 (2.3)	41.1 (10.8)	2.1 (2.2)	22.5 (21.7)	8.7 (12.7)	6.9 (2.9)	17.0 (4.5)	−0.59 (1.2)

[1]Paroxetine equivalent data are given as mean (SD).
[2]Diazepam equivalent data are given as mean (SD).
[3]*z* scores were calculated using the age-matched control group means and standard deviations.
BACS, Brief Assessment of Cognition in Schizophrenia; HAM-D7, seven-item Hamilton Rating Scale for Depression.

current episode of MDD and in full remission or partial remission (mild depression), even after controlling for the education level.

Second, examination of the relationships between functional outcome and Digit Sequencing Task and depressive scores in the two groups, patients with current episode of MDD and in full remission or partial remission (mild depression), the results were different between the two: in the patients with current episode of MDD, functional outcome was significantly correlated with depressive scores ($r=0.45$, $df=21$, $P<0.05$), but not with Digit Sequencing Task scores ($r=-0.14$, $df=21$, $P=0.54$). Meanwhile, in a sample of full remitted or partial remitted (mildly depressed) patients, functional outcome was significantly correlated with both Digit Sequencing Task scores ($r=-0.43$, $df=31$, $P<0.05$) and depressive scores ($r=0.38$, $df=31$, $P<0.05$).

Third, in a multiple regression analysis with a forward stepwise procedure, the depressive score in the group of patients with current episode of MDD ($F=5.1$, $df=1$, $P<0.05$) significantly contributed to the prediction of the functional outcome, but the Digit Sequencing Task score did not. Meanwhile in a sample of full remitted or partial remitted (mildly depressed) patients, the Digit Sequencing Task score ($F=4.5$, $df=1$, $P<0.05$) significantly contributed to the prediction of the functional outcome, but the depressive score did not.

Fourth, examination of the relationships between Digit Sequencing Task and depressive scores revealed that Digit Sequencing Task scores were not significantly correlated with depressive scores in either patients with current episode of MDD ($r=-0.03$, $df=21$, $P=0.89$) or in full remission or partial remission (mild depression) ($r=-0.32$, $df=31$, $P=0.08$). In addition, there were no significant correlations between Digit Sequencing Task scores and the dose of antidepressants ($r=-0.13$, $df=31$, $P=0.49$) or benzodiazepines ($r=-0.30$, $df=31$, $P=0.09$) in a sample of full remitted or partial remitted (mildly depressed) patients.

Discussion

These findings in this study suggested relations between MDD-associated deficit in verbal WM and functional outcome in a sample of full remitted or partial remitted (mildly depressed) patients. The findings seems to be inconsistent with those of Kennedy et al. (2007), who reported, in their review, that residual symptomatology after remission from depression may lead to enduring psychosocial impairment, as may subtle neurocognitive deficits. Nonetheless, the findings in this study do not underscore the importance of clinical remission from depression, which is defined objective outcome indicated by a quantifiable score with a depressive symptom measurement tool. On the contrary, symptomatic full remission should be always achieved as the primary goal of treatment, since it is the optimal outcome in depression (McIntyre et al. 2005; Möller 2008). Meanwhile, the findings in this study suggested that enhancement of verbal WM function by, e.g., cognitive rehabilitation may be useful to achieve normalization of functioning as an important component of remission (Zimmerman et al. 2006) when symptomatic full remission is failed to achieve. Besides, the possibility of influence of medications, particularly benzodiazepines (Stewart 2005), on the verbal WM dysfunction cannot completely be ruled out. Another limitation in this study was that patients in full remission and partial remission (mild depression) were combined for statistical analyses, mainly because there were few patients in full remission. Therefore, a further longitudinal study using patients without benzodiazepines might be necessary to confirm the results of the present study.

Acknowledgements

None.

Statement of interest

None.

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Psychiatry Research 178 (2010) 57–62

Contents lists available at ScienceDirect

Psychiatry Research

journal homepage: www.elsevier.com/locate/psychres

Determinants of work outcome in neuroleptic-resistant schizophrenia and schizoaffective disorder: Cognitive impairment and clozapine treatment

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ARTICLE INFO

Article history:
Received 28 September 2008
Received in revised form 29 March 2009
Accepted 15 April 2009

Keywords:
Adult
Open studies
Pharmacotherapy
Verbal working memory

ABSTRACT

There is considerable evidence that cognitive impairment is a better predictor of work and social function in schizophrenia than are positive and negative symptoms. Atypical antipsychotic drugs have been shown to improve cognitive function in schizophrenia patients, but it is unclear whether this improves patients' ability to gain employment. Data from a prospective longitudinal study was used to test the hypotheses that (1) clozapine treatment would improve employment outcome in treatment-resistant schizophrenia or schizoaffective disorder patients, and (2) specific cognitive functioning at baseline and after treatment would predict work status at baseline and change in work status. Employment status and cognitive assessment data were collected in 59 treatment-resistant schizophrenia or schizoaffective disorder patients. Forty-seven of 59 (79.7%) patients were unemployed at baseline. Over a 12-month period, 23 (48.9%) additional patients were able to gain paid or volunteer jobs, or attend school. As predicted, neurocognitive performance was a better predictor of employment status and ability to gain of employment than clinical symptoms. Improvement in verbal working memory was found to be a better predictor of employment outcome than other cognitive functions. Treatment that enhances cognitive function, especially verbal working memory, may lead to better employment outcomes in treatment-resistant schizophrenia or schizoaffective disorder patients.

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1. Introduction

Before the introduction and widespread use of atypical antipsychotic drugs such as aripiprazol, clozapine, olanzapine, quetiapine, risperidone and ziprasidone, no more than 15% of patients with schizophrenia in developed countries were reported able to obtain competitive employment (Mulkern and Manderscheid, 1989). In agreement with this, Mueser et al. (2001) reported that the competitive employment rates in patients with chronic schizophrenia were only 21–23%. There are few studies examining whether atypical antipsychotic drugs are helpful in increasing this low rate of employment. Factors influencing employment have a strong bearing on the societal costs of schizophrenia, due to lost income, lost productivity and disability income payments. Together these account for about US $46 billion (nearly 70% of a total of almost US$65 billion) of the total cost of schizophrenia in the United States (Anonymous, 1996).

There has been a considerable amount of research examining why people with schizophrenia are unable to obtain and keep competitive employment. Cognitive impairment, a core feature of schizophrenia (Saykin et al., 1994; Mohamed et al., 1999), has been reported to be the most important determinant of work and social function in schizophrenia (Green, 1996; Meltzer et al., 1996; Meltzer and McGurk, 1999; Green et al., 2000; McGurk and Meltzer, 2000; Bell and Bryson, 2001; Goldberg et al., 2001; Gold et al., 2002; Bryson and Bell, 2003). Among several domains of cognitive function, verbal memory and executive function appear to be the cognitive functions which most affect work and social function (Jaeger and Douglas, 1992; Lysaker et al., 1995; Green, 1996; Meltzer et al., 1996; Bryson et al., 1998; Meltzer and McGurk, 1999; Green et al., 2000; McGurk and Meltzer, 2000; Bell and Bryson, 2001; Martinez-Aran et al., 2002; Smith et al., 2002; Bryson and Bell, 2003). In contrast, most studies have found that psychotic symptoms (Mueser et al., 2001) are not significantly associated with functional outcome (Green, 1996; Green et al., 2000). However, several recent studies have suggested that psychopathology may be equally or more important than cognitive dysfunction with regard to functional outcome (Norman et al., 1999; Ertugrul and Ulug, 2002; Mohamed et al., 2008).

Recent reports have suggested the potential value of atypical antipsychotic drugs for improving cognitive impairment in patients with schizophrenia (Keefe et al., 1999; Meltzer and McGurk, 1999; Harvey and Keefe, 2001; Percudani et al., 2004; Woodward et al., 2005). Although there have been some exceptions (e.g. the CATIE Trial; Keefe et al., 2007), atypical antipsychotic drugs may be expected to improve employment outcome. Among the atypical antipsychotic drugs, clozapine has been most studied. Clozapine has been reported to produce improvements in treatment-resistant patients in attention,

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0165-1781/$ – see front matter © 2009 Elsevier Ireland Ltd. All rights reserved.
doi:10.1016/j.psychres.2009.04.001

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verbal fluency and some types of verbal learning and memory and executive function, but not working memory (Hagger et al., 1993; Lee et al., 1994; Lee et al., 1999; Meltzer and McGurk, 1999).

The goal of this prospective study was to test the hypotheses that (1) the clozapine treatment would improve employment outcome in treatment-resistant patients with schizophrenia or schizoaffective disorder, and (2) specific types of cognitive impairment but not psychotic symptoms in patients with schizophrenia would predict work status and that improvement in verbal memory and executive function in particular would predict improvement in employment status. In this study, treatment-resistant patients were chosen because clozapine use has generally been restricted to treatment-resistant patients with schizophrenia or schizoaffective disorder due to its ability to cause agranulocytosis.

2. Methods

2.1. Subjects

This study was conducted at Vanderbilt University. Data available from a prior prospective longitudinal study was used to test our hypotheses. Fifty-nine patients who met Diagnostic and Statistical Manual of Mental Disorders, third edition, Text Revision (DSM-III-R) (American Psychiatric Association, 1987) criteria for schizophrenia or schizoaffective disorder were included in this study. History of patients' response to antipsychotic treatment was assessed at the outset through intensive interviewing of the probands, first-degree relatives and other informants, as well as a review of hospital records. Treatment-resistance status was determined according to the criteria of Kane et al. (1988). Patients with a significant current history of substance abuse/dependence, seizure or radiologically confirmed head injury/malformation were excluded from the study. The patients were interviewed with the Schedule for Affective Disorders and Schizophrenia Lifetime (SADS-L) and Change (SADS-C) versions (Endicott and Spitzer, 1978) to establish diagnoses. The Brief Psychiatric Rating Scale (BPRS) (Overall and Gorham, 1962; 0–6 scales) was also employed to evaluate severity of psychopathology. Work status was defined as follows: 1. Employed = full-time (minimum of 30 h/week or full-time student status) or part-time (1–29 h/week or part-time student status); and 2. Unemployed = unemployed and not in school. Before admission to the study, informed written consent was obtained from all patients after the procedure had been fully explained. Demographic data are presented in Table 1.

Forty-eight (81.4%) patients were drug-free at least 5 days before baseline evaluation. Baseline assessments of the measures described above and cognitive function were performed. Patients were subsequently treated with clozapine. All patients were evaluated with the same measures after 12 months.

2.2. Treatment

2.2.1. Drug treatment

The drug treatment was carried out on an open basis because of the unreliability of maintaining masking during clozapine treatment. Thirty-one of 59 (52.5%) patients required concomitant medications; 10 (16.9%) patients received benztropine, 13 used lorazepam for psychomotor agitation, two received clonazepam and two received phenytoin for seizures, two required antihypertensive medications (atenolol and hydrochlorothiazide), one received chloral hydrate for insomnia, one received dicyclomine for irritable bowel syndrome and one patient received ranitidine for ulcers. Four patients received fluoxetine, two patients received divalproex, two patients received triptophan, one patient received sertraline and one patient received anafranil in addition to antipsychotic agents. The dosages of clozapine at 12 months were 422.4 (SD = 190.4) mg/day.

2.2.2. Psychosocial treatment

Patients received an intensive psychosocial treatment programme, which included group and multifamily therapy on a weekly basis throughout the course of the study. The nurse therapist who led these groups also provided a work readiness-training programme on both an individual and group basis for the treatment-resistant subjects. This included obtaining clerical tasks needed by the hospital and supervising the work of the patients in carrying out these jobs.

Table 1
Demographic information at baseline ($n = 59$).

	Mean (SD)
Age (yrs)	35.6 (8.9)
Gender (Female/male)	15/44
Race (African American/Caucasian/others)	8/50/1
Age of illness onset (yrs)	19.6 (4.7)
Duration of illness (yrs)	16.0 (7.8)
Years of education (yrs)	12.4 (2.3)
Number of times hospitalised	8.6 (6.4)
IQ	90.8 (15.8)

2.3. Cognitive tests

We used a cognitive test battery as described elsewhere (Kenny and Meltzer, 1991), consisting of the following measures: (1) a measure of psychomotor speed and attention {Wechsler Adult Intelligence Scale-Revised (WAIS-R) Digit Symbol Substitution Test (DSST; Wechsler, 1981)}; (2) verbal working memory {Consonant Trigram Test (CTT; Peterson and Peterson, 1959)}; (3) verbal fluency {Controlled Word Association Test (CWAT; Benton et al., 1983) and the Category Instance Generation Test (CIGT; Talland, 1965)}; (4) verbal learning and memory {Verbal List Learning (VLL) Immediate Recall (VLL-IR) and Delayed Recall (VLL-DR; Buschke and Fuld, 1974)}; and (5) executive function {Wisconsin Card Sorting Test (WCST) category (CAT) and perseveration (PP; Berg, 1948); Wechsler Intelligence Scale for Children-Revised (WISC-R) Maze (Wechsler, 1974)}. The neuropsychological tests were factor analysed into three factors: memory (CTT, VLL-IR, VLL-DR and WISC-R Maze), attention (DSST, CWAT and CIGT) and executive function (WCST) (Meltzer et al., unpublished results). These tests were administered by a psychologist who was not blind to the nature of drug treatment. An estimated intelligence score was obtained using WAIS-R.

2.4. Statistical methods

Data analysis was conducted using the SAS (Version 8.2, SAS institute, 1999) software. The comparison of categorical responses to employment groups was carried out using chi-square tests. *T*-test analyses for independent group comparisons were used to compare differences in psychopathology and cognitive variables on employment status at baseline and at 12 months between two groups of patients (patients who remained unemployed and patients who gained employment). Moreover, the differences in psychopathology and cognition variables at 12 months between three groups of patients (patients that remained unemployed, patients that remained gained non-competitive employment and patients that gained competitive employment) were compared by analysis of variance (ANOVA), followed by *post hoc* comparisons. Improvement of psychopathology and cognition over time across groups was analysed using a repeated-measure ANOVA model. A logistic regression model with forward selection criteria was used to predict employment status and change in employment at different time points (dichotomous response) using demographic variables, improvement in psychopathology and cognitive measures. A *P*-value of less than 0.05 was considered significant, and the statistical tests were two-sided.

3. Results

3.1. Changes in employment status

After 12 months, employment outcome had significantly improved from 20.3% (12/59) at baseline to 50.8% (30/59) [$\chi^2 = 12.0$, $df = 1$, $P < 0.001$]. Out of 47 patients, 23 (48.9%) who were unemployed at baseline became employed during the 12 months period. One, eight and 12 patients gained paid full-time jobs, paid part-time jobs and unpaid volunteer work respectively. One patient went back to school as a part-time student, and one patient undertook a vocational education programme. When the patients with unpaid employment (i.e., volunteer) were excluded, 15 (25.4% vs. 16.9% at baseline) patients had become competitively employed. Meanwhile, five of 12 (41.7%) patients employed at baseline became unemployed during the 12-month period.

3.2. Differences in baseline variables between unemployed and employed patients at baseline

Patients who were unemployed at baseline were significantly older [$t = 2.64$, $df = 38$, $P = 0.01$] and showed a trend towards a longer duration of illness [$t = 1.99$, $df = 57$, $P = 0.05$] than those who were employed (Table 2). Comparisons of these two groups revealed significantly better baseline scores in the employed group for the BPRS total [$t = 2.02$, $df = 52$, $P = 0.04$] and positive scores [$t = 2.85$, $df = 52$, $P < 0.01$]. There was a trend towards a higher WISC-R Maze score in the employed group [$t = -1.65$, $df = 52$, $P = 0.10$].

3.3. Predictors of work status at baseline

The logistic regression analysis used a forward stepwise procedure to predict work status at baseline from variables including baseline

neurocognitive and symptom measures. The results of the analysis indicated that the baseline BPRS positive scores were significantly associated with baseline employment [$\chi^2 = 6.85$, $df = 1$, $P < 0.01$]. Neither age nor duration of the illness was significantly associated with baseline employment status.

3.4. Changes in cognitive and clinical measures during the study

There were significant time effects (improvement) at 12 months for: (1) DSST [$F(1,32) = 12.3$, $P < 0.01$]; (2) CWAT [$F(1,31) = 10.2$, $P < 0.01$]; (3) CIGT [$F(1,31) = 15.8$, $P < 0.01$]; (4) VLL-IR [$F(1,32) = 10.1$, $P < 0.01$]; (5) VLL-DR [$F(1,31) = 5.6$, $P = 0.02$]; (6) WISC-R Maze [$F(1,31) = 15.0$, $P < 0.001$]; (7) memory factor [$F(1,30) = 5.7$, $P = 0.02$]; (8) attention factor [$F(1,31) = 26.6$, $P < 0.001$]; (9) BPRS total [$F(1,45) = 30.6$, $P < 0.001$]; and (10) BPRS positive [$F(1,45) = 26.9$, $P < 0.001$]. There was no significant time by group (remained unemployed vs. gained employment) interactions. However, when the duration of the illness and baseline scores were controlled for, an analysis of covariance (ANCOVA) indicated that the only significant time by group interaction was for the CTT score [$F(1,23) = 4.65$, $P = 0.04$]. This interaction was due to a significantly greater improvement in the patients who gained employment compared with those who remained unemployed.

3.5. Differences in variables at 12 months between patients who remained unemployed and patients who gained employment

The average age [$t = -2.16$, $df = 45.0$, $P = 0.03$] and duration of the illness [$t = -2.33$, $df = 39.7$, $P = 0.02$] were significantly less in patients who gained employment during the 12 months of treatment than in those who remained unemployed (Table 3). Comparisons of these two groups revealed that patients who gained employment showed significantly better scores on DSST [$t = 2.25$, $df = 27.0$, $P = 0.03$], CTT [$t = 4.31$, $df = 27.0$, $P < 0.001$], CIGT [$t = 2.10$, $df = 27.0$, $P = 0.04$], WCST-PP [$t = -2.17$, $df = 27.0$, $P = 0.03$], memory [$t = 2.60$, $df = 27.0$, $P = 0.01$] and attention factors [$t = 2.85$, $df = 27.0$, $P < 0.01$]. Moreover, there was a trend towards higher Executive Function factor scores in patients who gained employment [$t = 1.73$, $df = 27.0$, $P = 0.09$]. When the analysis was repeated using the duration of illness as a covariate, the results were largely unchanged. However, there were no significant differences between the two groups on BPRS total, positive or negative scores.

When we further compared the differences in variables at 12 months between patients who remained unemployed ($n = 24$), patients who gained non-competitive ($n = 13$), and patients who competitive employment ($n = 10$), we found significant differences in the duration of illness [$F(2,44) = 3.65$, $P = 0.03$], CTT[$F(2,26) = 9.16$, $P < 0.01$], memory [$F(2,26) = 3.40$, $P = 0.04$] and attention factor scores [$F(2,26) = 5.24$, $P = 0.01$]: duration of illness was significantly less in patients who gained competitive employment than in those who remained unemployed [$P = 0.01$]. The CTT [$P < 0.001$] and attention factor scores [$P = 0.01$] were shown to be significantly better in patients who gained competitive employment than in those who remained unemployed. The CTT scores for patients who gained non-competitive employment were significantly better after 12 months of treatment [$P < 0.01$] than those for patients who remained unemployed. Furthermore, there was a trend towards a difference between the three groups of patients in the DSST [$F(2,26) = 2.65$, $P = 0.08$] and CIGT scores [$F(2,26) = 2.66$, $P = 0.08$]: there was a trend towards better DSST [$P = 0.03$] and CIGT scores [$P = 0.02$] in patients who gained competitive employment than in those who remained unemployed. When the analysis was repeated including duration of illness as a covariate, the results were virtually identical. However, again there were no significant differences between the three groups on BPRS total, positive or negative scores.

Table 2
Differences in baseline variables between the groups of patients who were unemployed ($n = 47$) and employed ($n = 12$) at baseline.

	Unemployed	Employed	P (t/χ^2, df)[a]
Age	36.6 (9.4)	31.6 (4.5)	0.01 (2.64, 38)
Gender (female/male)	13/34	2/10	0.43 (0.61, 1)
Race (African American/Caucasian)	8/38	0/12	0.12 (2.42, 1)
Age of illness onset	19.6 (5.1)	19.5 (2.8)	0.93 (0.09, 33)
Duration of illness	17.0 (8.0)	12.1 (5.7)	0.05 (1.99, 57)
Years of education	12.4 (2.5)	12.5 (1.5)	0.84 (−0.20, 50)
Number of times hospitalised	8.6 (6.4)	7.6 (6.5)	0.54 (0.61, 57)
BPRS total	33.8 (14.2)	24.9 (9.9)	0.04 (2.02, 52)
BPRS positive	13.2 (5.1)	8.3 (5.6)	<0.01 (2.85, 52)
BPRS negative	4.3 (3.0)	4.6 (2.1)	0.75 (−0.31, 55)
IQ	89.3 (15.1)	97.6 (18.1)	0.17 (−1.37, 43)
Cognitive function			
Attention (DSST)	5.7 (2.2)	6.0 (1.8)	0.69 (−0.39, 54)
Verbal working memory (CTT)	25.4 (9.0)	26.8 (10.1)	0.66 (−0.44, 54)
Verbal fluency			
CWAT	30.1 (13.1)	31.7 (14.5)	0.72 (−0.35, 54)
CIGT	36.8 (15.0)	38.9 (10.2)	0.65 (−0.45, 54)
Verbal learning memory			
VLL-IR	7.1 (2.2)	7.6 (2.0)	0.50 (−0.67, 55)
VLL-DR	5.8 (3.2)	7.2 (2.9)	0.17 (−1.37, 54)
Executive function			
WCST-Category	2.5 (2.3)	3.4 (2.5)	0.24 (−1.17, 55)
WCST-Perseveration	23.4 (16.7)	16.3 (12.5)	0.17 (1.38, 55)
WISC-R Maze	6.6 (3.5)	8.6 (4.2)	0.10 (−1.65, 53)
Memory Factor	−7.5 (4.7)	−5.7 (4.7)	0.25 (−1.14, 52)
Attention Factor	−4.8 (2.6)	−4.5 (2.1)	0.70 (−0.38, 53)
Executive Fx Factor	−3.0 (3.0)	−1.6 (2.9)	0.15 (−1.43, 55)

Data are given as mean (SD). BPRS = Brief Psychiatric Rating Scale.; CIGT = Category Instance Generation Test; CTT = Consonant Trigram Test; CWAT = Controlled Word Association Test; DSST = Digit Symbol Substitution Test; VLL-DR = Verbal List Learning Delayed Recall; VLL-IR = Verbal List Learning Immediate Recall; WISC-R = Wechsler Intelligence Scale for Children-Revised; WCST = Wisconsin Card Sorting Test.
[a] chi-square tests/t-tests.

3.6. Predictors of work status for patients who gained employment at 12 months

The logistic regression analysis with a forward stepwise procedure indicated that work status after 12 months of treatment for patients who gained employment was significantly associated with CTT scores at 12 months [$\chi^2 = 11.17$, $df = 1$, $P < 0.001$] and at baseline [$\chi^2 = 4.74$, $df = 1$, $P = 0.02$], but not with positive or negative symptoms. None of the score changes after 12 months in cognitive and clinical measures were significantly associated with employment status at 12 months for patients who gained employment.

4. Discussion

The major finding of this study of treatment-resistant schizophrenia or schizoaffective disorder patients was that neurocognitive performance, but not clinical symptoms, was indicated to be the major factor differentiating patients who gained employment during 12 months of treatment from those who remained unemployed. Among neurocognitive functions, verbal working memory and attention were suggested to be the important factors related to improving employment outcome. To our knowledge, this is the first longitudinal study indicating an association between cognition and employment outcome in treatment-resistant schizophrenia or schizoaffective disorder. This relationship was not evident in prior cross-sectional studies. However, the possibility that obtaining work improved cognitive performance rather than the reverse cannot be entirely ruled out.

In this study, prior to treatment, 20.3% of patients were employed, and 16.9% were employed in competitive positions. This rate of employment was similar to that reported in the recent paper by Mueser et al. (2001). After intensive psychosocial and clozapine treatment, employment outcomes had improved significantly when

Table 3
Differences in variables at 12 months between the groups of patients who remained unemployed ($n=24$) and gained employment ($n=23$).

	Remained unemployed	Gained employment	P (t/χ^2, df) [a]
Age at baseline	39.4 (10.1)	33.7 (7.8)	0.03 (−2.16, 45.0)
Gender (female/male)	6/18	7/16	0.67 (0.17, 1)
Race (African American/ Caucasian)	5/19	3/19	0.52 (0.41, 1)
Age of illness onset	19.9 (3.8)	19.3 (6.3)	0.71 (−0.37, 35.9)
Duration of illness at baseline	19.5 (9.0)	14.3 (5.9)	0.02 (−2.33, 39.7)
Years of education at baseline	12.2 (2.2)	12.5 (2.8)	0.74 (0.33, 38.0)
Number of times hospitalised at baseline	9.6 (7.5)	8.1 (5.2)	0.43 (−0.79, 45.0)
BPRS Total	24.3 (8.5)	21.8 (11.0)	0.41 (−0.82, 38.0)
BPRS Positive	10.3 (4.1)	9.9 (5.1)	0.76 (−0.30, 38.0)
BPRS Negative	3.4 (2.5)	2.7 (3.2)	0.41 (−0.82, 38.0)
Cognitive function			
Attention (DSST)	6.0 (1.8)	7.8 (2.6)	0.03 (2.25, 27.0)
Verbal working memory (CTT)	19.5 (8.6)	32.7 (7.2)	<0.001 (4.31, 27.0)
Verbal fluency			
CWAT	33.8 (11.8)	40.8 (11.4)	0.12 (1.59, 27.0)
CIGT	40.4 (10.2)	48.6 (10.6)	0.04 (2.10, 27.0)
Verbal learning memory			
VLL-IR	7.4 (2.8)	8.5 (1.6)	0.23 (1.21, 27.0)
VLL-DR	6.4 (3.1)	7.2 (2.2)	0.48 (0.71, 27.0)
Executive function			
WCST-Category	1.6 (2.2)	2.3 (2.6)	0.45 (0.76, 27.0)
WCST-Perseveration	32.1 (18.7)	18.0 (14.7)	0.03 (−2.17, 27.0)
WISC-R Maze	6.9 (4.2)	8.8 (3.6)	0.19 (1.32, 27.0)
Memory Factor	−8.3 (5.1)	−3.9 (3.5)	0.01 (2.60, 27.0)
Attention Factor	−4.2 (1.7)	−2.2 (1.9)	<0.01 (2.85, 27.0)
Executive Fx Factor	−4.5 (3.2)	−2.5 (2.9)	0.09 (1.73, 27.0)

Data are given as mean (SD).
[a] chi-square tests/t-tests.

measured in a 12-month follow-up: 50.8% of the patients were now employed, and of these patients, 25.4% were competitively employed. The employment outcome was similar to that achieved by a group of patients with schizophrenia who received an intensive employment support program (Lehman et al., 2002). So far, seven published studies have investigated the effect of clozapine on employment (Meltzer et al., 1990, 1993; Aitchison and Kerwin, 1997; Lindström and Lundberga, 1997; Buchanan et al., 1998; Lindström, 1988; Drew et al., 1999). These studies showed clozapine to have a positive effect. In accord, we found a beneficial effect of clozapine on employment outcome, even in treatment-resistant patients. While clozapine is known to be the most effective treatment for treatment-resistant schizophrenia (Meltzer, 1997), it is likely that the combined efficacy of clozapine and the probable beneficial effects of the intensive work-oriented psychosocial programme together might contribute to the improvement.

The present results show that verbal working memory was the strongest determinant of employment outcome. Verbal working memory was better than clinical symptoms at predicting which patients found non-competitive or competitive employment after 12 months. This finding was further supported by the stepwise regression analysis, which revealed that CTT scores at 12 months contributed to differences in employment status at this time. Only a time by group (remained unemployed vs. gained employment) interaction was found to be significant for the CTT by ANCOVA. These findings provide additional support for a link between specific types of cognitive function and employment outcomes in patients suffering from treatment-resistant schizophrenia or schizoaffective disorder. The findings indicate a relation between verbal working memory and improvement in employment status. This relationship was not evident in prior cross-sectional studies. Our finding is, however, at least partially consistent with a recent prospective study by Smith et al. (2002). In addition, McGurk and Mueser (2002) reported that, besides positive symptoms, working memory was an important factor for distinguishing independently employed clients from those who were employed with supports.

CTT scores at baseline also contributed to differences in employment status at 12 months, although there was no significant difference in the CTT at baseline between the groups of patients who were unemployed and employed at baseline. Considered together, these findings suggest that patients with better verbal working memory are likely to have benefited more from clozapine medication than those with poorer verbal working memory. In this case, the interaction between intensive psychosocial treatment and clozapine may have facilitated the effect of clozapine. McGurk et al. (2003) reported that clients in supported employment programmes that had worse working memory and more severe positive symptoms required more vocational services per hour of work than less impaired clients. Our results appear to be consistent with this finding. Overall, the current findings support the conclusion that verbal working memory is an important factor involved in improving in employment outcomes. To further clarify the causal relationship between verbal working memory and employment outcome, a future study will investigate whether psychosocial rehabilitation, cognitive training and medications that enhance verbal working memory similarly lead to better employment outcomes.

Other than verbal working memory, attention and executive function were also indicated to have a role in obtaining and maintaining employment. Attention was particularly related to competitive employment. These findings are in accord with the view that these cognitive measures have an importance influence on employment outcome (Jaeger and Douglas, 1992; Lysaker et al., 1995; Green, 1996; Green et al., 2000; McGurk and Meltzer, 2000; Bell and Bryson, 2001; Gold et al., 2002; Palmer et al., 2002; Martinez-Aran et al., 2002; McGurk et al., 2003; Milev et al., 2005).

Besides cognitive function, positive symptoms were also found to be associated with employment status at baseline. Psychopathology has been found to predict employment outcomes in some studies (Beiser et al., 1994; Daradkeh and Karim, 1994; Slade and Salkever, 2001). Other studies have suggested that psychopathology may be more important than cognitive dysfunction (Breier et al., 1991; Norman et al., 1999; Ertugruland Ulug, 2002; Mueser, 2002), or that both psychopathology and cognitive function are associated with employment status and social functioning in schizophrenia (McGurk and Meltzer, 2000; Suslow et al., 2000; Martinez-Aran et al., 2002; Meyer et al., 2002; Palmer et al., 2002; Smith et al., 2002; Hoffmann et al., 2003; McGurk and Mueser, 2003; McGurk et al., 2003; Milev et al., 2005). More recently, after reanalysing CATIE data, Mohamed et al. (2008) reported that symptoms (negative and positive) and neurocognitive functioning were both independently significant correlates and predictors of vocational functioning. Taken together, both psychopathology and cognitive functioning may be predictive of employment outcomes. Neurocognitive status, however, appears to be the more robust predictor of successful rehabilitation (Green, 1996; Green et al., 2000).

Age was significantly different between patients who were unemployed and employed, and between patients who remained unemployed and those who gained employment. These findings are consistent with previous reports (Goldberg et al., 2001; Mueser et al., 2001). The duration of the illness was different between patients who remained unemployed and those who gained employment. It is considered that the difference was largely due to older age in the patients who remained unemployed compared with those who gained employment. Work history has been reported to be a predictor of employment and work functioning (Mueser et al., 2001). However, in this study, employment status at baseline was not associated with employment status at 12 months. Five of 12 patients employed at baseline became unemployed during the 12-month period. It has been reported that only 50% of patients with schizophrenia maintain their jobs for more than 6 months even when receiving supported

employment services (McHugo et al., 1998) Our result may reflect the difficulties faced by treatment-resistant schizophrenia or schizoaffective disorder patients in maintaining employment.

Overall, the present results showed a strong effect of clozapine on cognitive functioning. Among nine cognitive measures, six (DSST, CWAT, CIGT, VLL-IR, VLL-DR and WISC-R Maze) were significantly improved after 12 months of treatment. Similar findings have previously been reported for some of the subjects in this study (Hagger et al., 1993; Lee et al., 1994), and the current results provide additional support for the use of clozapine (Hagger et al., 1993; Lee et al., 1994; Lee et al., 1999; Meltzer and McGurk, 1999).

The current study involved several methodological limitations. The relatively small sample size, non-blind administration of tests and drug treatments and the inability to link improvements in employment status exclusively to clozapine should be considered in further studies.

Acknowledgement

Part of the data in this study were presented at the XXIVth Collegium Internationale Neuro-Psychopharmacologicum (CINP) Congress.

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紹介

統合失調症認知評価尺度日本語版 (SCoRS-J)*

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Key words

Cognitive function, Japanese version, Neuropsychology, Psychometrics, Schizophrenia, Schizophrenia Cognition Rating Scale (SCoRS)

はじめに

統合失調症患者の社会機能に及ぼす影響に関しては，その中核症状ともいえる認知機能障害が，精神病症状以上に重要な要因であると考えられている[4,5]。統合失調症の認知機能障害は広範囲な領域におよび，注意・遂行機能・記憶・言語機能・運動機能などの領域が特に注目されている。認知機能の評価においては，これまで，各認知機能領域を評価する幾つかの検査を目的に応じて組み合わせた神経心理学的テストバッテリー(NTB)が用いられてきた。しかし，NTBを用いた評価は，通常専門的な知識を要し，高価で時間を要するものであった。一方，統合失調症の主要な認知機能領域を簡便に評価し得る尺度は，日常臨床および研究において有用と思われる。

我々は認知機能の客観的評価のため，統合失調症認知機能簡易評価尺度(Brief Assessment of Cognition in Schizophrenia；BACS)の日本語版(BACS-J)を過去に作成した[7,8]。一方，このような認知機能の変化に加え，機能的予後に対する表面的妥当性を持つ評価尺度(co-primary measure)の候補として，Measurement and Treatment Research to Improve Cognition in Schizophrenia(MATRICS)委員会[10]は，エキスパートの推薦に基づき，4つの評価尺度を提言した。そ

* The Schizophrenia Cognition Rating Scale Japanese Version (SCoRS-J)

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0488-1281/10/¥500/論文/JCOPY

表1 統合失調症認知評価尺度日本語版(SCoRS-J)

1. 知人あるいは面識のある人の名前を覚える
2. 場所への行き方を覚える
3. テレビ番組の筋を追う
4. 物を置いた場所を覚える
5. 用事や責務を覚える
6. 道具や機器の使用法を学び，使う
7. 与えられたばかりの情報および，あるいはまた教示を覚える
8. 言おうとしていたことを覚えておく
9. お金を管理する
10. 混乱せずに話す
11. 集中して新聞あるいは本を読む
12. 慣れた作業を行う
13. 集中を持続させる
14. 新しいことを学習する
15. 考えを言葉にして，思ったとおり迅速に話す
16. 物事を迅速に行う
17. 日課の変更に対応する
18. 話かけられていることの意味を理解する
19. 他人が物事をどう感じているか理解する
20. 集団の中で会話についていく

のうち，社会的能力の評価尺度としてMaryland Assessment of Social Competence (MASC)[2]とUniversity of California at San Diego (UCSD) Performance-Based Skills Assessment (UPSA)[12]の2つが，また，面接に基づく認知機能評価尺度としては統合失調症認知評価尺度(Schizophrenia Cognition Rating Scale, SCoRS)[9]と統合失調症における認知機能障害の臨床的総合評価尺度(Clinical Global Impression of Cognition in Schizophrenia；CGI-CogS)[13]の2つが選択された。また，これら評価尺度の計量心理学特性は，いずれも容認できるものであったと報告された[6]。このうちSCoRSは，患者用，介護者用および評価者用フォームの3部で構成され，記憶，学習，注意，ワーキングメモリ，問題解決，処理/運動速度，社会認知および言語の8つの領域を評価する20項目と全般評価からなり，各項目はそれぞれ4段階で評価される。今回我々は，SCoRSの臨床応用への有用性に着目し，原著者の許可を得たうえでその日本語版(SCoRS-J)を作成した。なお，SCoRS-Jのcopyrightは，Duke University Medical Centerが所有している。

方法

まず，表1に，SCoRS-Jの評価項目を示した。原則として，原文に忠実に翻訳を行ったが，必要に応じ著者らの許可を得て修正した。

次に，SCoRS-Jの信頼性と妥当性を検討するため，我々は，SCoRS-Jを用いて慢性期の統合失調症患者の認知機能を評価した。対象は，主に徳島大学病院，富山大学附属病院，および弘前大学病院に入院あるいは通院中で，米国精神疾患の診断・統計マニュアル(DSM-IV)[1]の診断基準を満たす慢性統合失調症患者64名であった。Helsinki宣言に準拠し，研究に先立ち，研究の主旨を説明したうえで，同意が得られた者を被験者とした。表2に患者背景を示した。

精神症状評価には，簡易精神症状評価尺度($BPRS_{1-7}$；18項目)[11]を使用し，認知機能評価にはSCoRS-Jとともに BACS-Jを用いた。

SCoRS-Jは，評価マニュアルに基づき，3つの別々の評価を行う。すなわち，患者とのインタビュー，患者の介護者(家族，友人，ソーシャルワーカー，その他)とのインタビュー，そして，患者と介護者に評価を実施した評価者による評価である。各項目は，アンカー・ポイントを持っており，それに基づき，「なし」「軽度」「中等度」あるいは「重度」と判定する。20の質問終了後，評価者は各インタビューに基づいて，患者の認知機能障害の総合的なレベルに対する評価者の印象を示すように，1～10の全般評価尺度上に印をつける。SCoRS-Jを完成させるには，約30分を要する。

統計処理には，JMP-8.0.1J for Macを使用し，2組の定量的変数間の直線的関係をみるために，Pearsonの偏差積率相関係数を求めた。なお，統計学的有意水準は$p<0.05$とした。

結果

(1) SCoRS-J評価者版で，内的整合性の指標

表2　患者背景

	全体(n=64)	徳島(n=15)	富山(n=29)	弘前(n=20)
年齢(年)	36.7(13.8)	52.0(14.1)	29.1(8.3)	36.3(9.5)
罹病期間(年)	13.2(12.5)	25.6(14.6)	5.1(4.8)	15.4(9.5)
教育年数(年)	13.1(2.4)	12.0(3.3)	14.1(2.2)	12.3(1.0)
BPRS(総得点)	38.0(9.6)	34.8(10.3)	39.5(9.4)	38.9(9.1)
SCoRS-J(評価者全般評価)	4.0(1.8)	2.7(1.1)	3.8(1.7)	5.2(1.7)

値は，平均(標準偏差)
BPRS；簡易精神症状評価尺度
SCoRS-J；統合失調症認知評価尺度日本語版

である Cronbach の α 係数[3]は 0.95 あった。また，20 項目中どの項目を除外しても，α 係数は 0.01 以上大きくはならなかった。

(2) SCoRS-J 評価者用全般評価得点と 20 項目の平均得点との間には，統計学的に有意な相関を認めた(r=0.85, $p<0.0001$，表 3)。

(3) SCoRS-J 評価者用全般評価得点と，介護者(r=0.87, $p<0.00001$)および患者(r=0.82, $p<0.0001$)用全般評価得点との間に，統計学的に有意な相関を認めた。

(4) SCoRS-J 評価者用全般評価得点と BACS-J composite score(総合得点)間の相関係数は −0.33($p<0.01$)であった。一方，SCoRS-J 評価者用 20 項目の平均得点と BACS-J composite score 間の相関係数は −0.51($p<0.0001$)であった。SCoRS-J 評価者用全般評価得点と BACS-J composite score 間の相関係数は，施設別には，徳島 −0.53(n=15, $p<0.05$)，富山 −0.48(n=29, $p<0.01$)，そして弘前 −0.38(n=20, N.S.)であった。また，SCoRS-J 評価者用 20 項目の平均得点と BACS-J composite score 間の相関係数は，徳島 −0.47(N.S.)，富山 −0.48($p<0.01$)，そして弘前 −0.42(N.S.)であった(表 4)。

表3　SCoRS-J 評価者用全般評価得点と各項目および 20 項目平均得点間の相関

項目	r	項目	r
1	0.28*	11	0.57****
2	0.52****	12	0.55****
3	0.56****	13	0.68****
4	0.45***	14	0.63****
5	0.45***	15	0.67****
6	0.41***	16	0.67****
7	0.65****	17	0.73****
8	0.55****	18	0.73****
9	0.60****	19	0.65****
10	0.75****	20	0.68****
		20 項目平均	0.85****

*$p<0.05$, **$p<0.01$, ***$p<0.001$, および****$p<0.0001$

考察

以上より，SCoRS-J は，原版同様の信頼性および妥当性を有することが示された。SCoRS-J 評価者用全般評価得点と BACS-J composite score 間の相関係数は，3 施設を合計した場合，施設ごとに算出した場合よりも低かった。これは，全般評価において明確なアンカーポイントが示されていないことが大きな要因と考えられる。SCoRS を用いた多施設間での共同研究などにおいては，評価者間の信頼性を向上させることが必要である。一方，今回の結果からは，SCoRS-J 評価者用全般評価を評価者用 20 項目の平均得点で代用することが有用であることが示唆された。今後，より多くのサンプルでの再テスト信頼性などの検討をする必要があろう。

おわりに

我々は，統合失調症患者の日常生活機能と関連する認知機能を面接に基づき評価する SCoRS[9]の日本語版である SCoRS-J を作成し，計量心理学特性につき検討した。本研究の結果は，SCoRS-J