Spatial working memory deficit correlates with disorganization symptoms and social functioning in schizophrenia

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Abstract

Aim: Both spatial working memory deficit and disorganization symptoms have been considered significant components of schizophrenic impairment which are involved with the dorsolateral prefrontal cortex. In the present study, we investigated the relationships among spatial working memory, psychiatric symptoms including disorganization symptoms, and social functioning in schizophrenia.

Methods: Fifty clinically stable patients with schizophrenia and thirty-four healthy controls participated in the study. Patients were rated with the Brief Psychiatric Rating Scale and the Rehabilitation Evaluation Hall and Baker. The Advanced Trail Making Test was used to evaluate spatial working memory.

Results: Patients demonstrated significantly reduced spatial working memory compared to that of healthy controls. Spatial working memory in patients correlated significantly with social functioning such as self-care skills, community skills and speech disturbance, and with disorganization symptoms. Disorganization symptoms also correlated with these aspects of social functioning.

Conclusions: We suggest that both spatial working memory deficit and disorganization symptoms, which are impairments involved with the dorsolateral prefrontal cortex dysfunction, can serve as effective predictors of social functioning.

Key words: cognition, schizophrenia, social adjustment, spatial memory disorder, symptoms

INTRODUCTION

Working memory is the process of actively holding information "on-line" in the mind's eye and manipulating information in the service of guiding behavior [1]. Daily activities, such as mentally rehearsing a phone number or considering alternative perspectives and outcomes, might depend on working memory. After Goldman-Rakic[2] suggested that working memory impairment might underlie various cognitive deficits observed in patients with schizophrenia, a number of studies have identified spatial working memory (SWM) deficits in schizophrenia.[3-5] The SWM deficit is present during the acute psychotic stage of the illness as well as during the remission.[6] Non-psychotic first-degree relatives of patients with schizophrenia[7] have also been found to show SWM deficits. These studies suggest that SWM deficit constitutes an effective phenotypic marker for schizophrenia.

Recently, several studies have suggested the relationship between SWM deficit and disorganization symptoms.[8,9] In addition, Perlstein *et al.*[10] reported that the dorsolateral prefrontal cortex dysfunction was associated with both SWM and disorganization symptoms. Disorganization symptoms[11,12] and specific domains of neurocognition[13,14] are considered to be related to certain aspects of social functioning in patients with schizophrenia. Evaluation of social functioning and its related impairments in patients with schizophrenia is important to support their deinstitutionalization by providing them with appropriate psychosocial skills training and social welfare services. However, to the best of our knowledge, no study has investigated relationship between SWM and social functioning in patients with schizophrenia.

The purpose of this study is to investigate the relationships among SWM, psychiatric symptoms including disorganization symptoms, and social functioning in patients with schizophrenia. The subjects were clinically stable inpatients and were preparing for their social rehabilitation after their impending hospital discharge.

MATERIALS AND METHODS

Subjects

The subjects participated in this study were 50 patients with schizophrenia and 34 normal controls. The patients were hospitalized at a private psychiatric hospital, and all were diagnosed with schizophrenia according to the criteria in the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV).[15] Our diagnostic approach used information from the Structured Clinical Interview for DSM-IV[16] supplemented by information from family informants, psychiatrists, and medical records. The patients were 25 males and 25 females with an average (± SD) age of 36.7 (± 11.3) years, education of 12.2 (± 2.4) years, and illness duration of 14.1 (± 10.6) years (mean age of onset, 22.6 ± 6.1 years). All patients were stabilized with neuroleptic medication at the time of the testing. The mean dose of chlorpromazine-equivalent units per day[17] was 953.7 (± 762.2) mg, with 41 patients taking atypical antipsychotic medications (risperidone, quetiapine, and olanzapine), and nine patients typical antipsychotic medications (mostly haloperidol). Forty-two patients were being treated with anti-parkinsonian agents. Side effects in the form of extrapyramidal symptoms were insignificant in all patients. Every patient was clinically stable and had not undergone a change in medication for at least the previous two weeks.

The control group consisted of 12 males and 22 females with a mean age of 33.5 (± 10.1) years and education of 13.7 (± 1.8) years. The patient and control groups did not significantly differ in age distribution ($t = 1.17$, 83 df, $p = .247$) or gender ($\chi^2 = 2.21$, 1 df, $p = .137$), while the patients had a significantly lower educational level ($t = 3.09$, 83 df, $p = .003$) than the healthy controls.

For the patients with schizophrenia, all subtests of the Wechsler Adult Intelligence Scale, Revised (WAIS-R)[18] were administered to evaluate Full-Scale IQ. Full-Scale IQ of healthy controls was estimated with the four-subtest (Information, Picture Completion, Similarities, and Digit Symbol) short form of the WAIS-R.[19] Estimated Full-Scale IQ of healthy controls was 110.0 (± 10.7) on average, and the mean Full-Scale IQ of the patients was 83.1 (± 15.4), with the latter having a significantly lower IQ (t = 9.41, 83 df, $p < .001$).

Patients and controls were only included in the study if they had no history of alcohol or other substance dependence, neurologic disease or other illness or trauma, the pathologic features of the treatment which could influence their cognitive performance. Only controls who had never met the DSM-IV

Axis I or II criteria and had no family history of schizophrenia were included in the study.

The present study was carried out in accordance with Declaration of Helsinki. All subjects were provided a complete description of the purpose of the study and gave written informed consent before study participation. Subjects were required to demonstrate an understanding of study demands, risks, and their rights to withdraw in response to probe questions before signing consent documents. No subject refused to participate in the study, and all of them completed the procedures. Patient anonymity was protected in all instances.

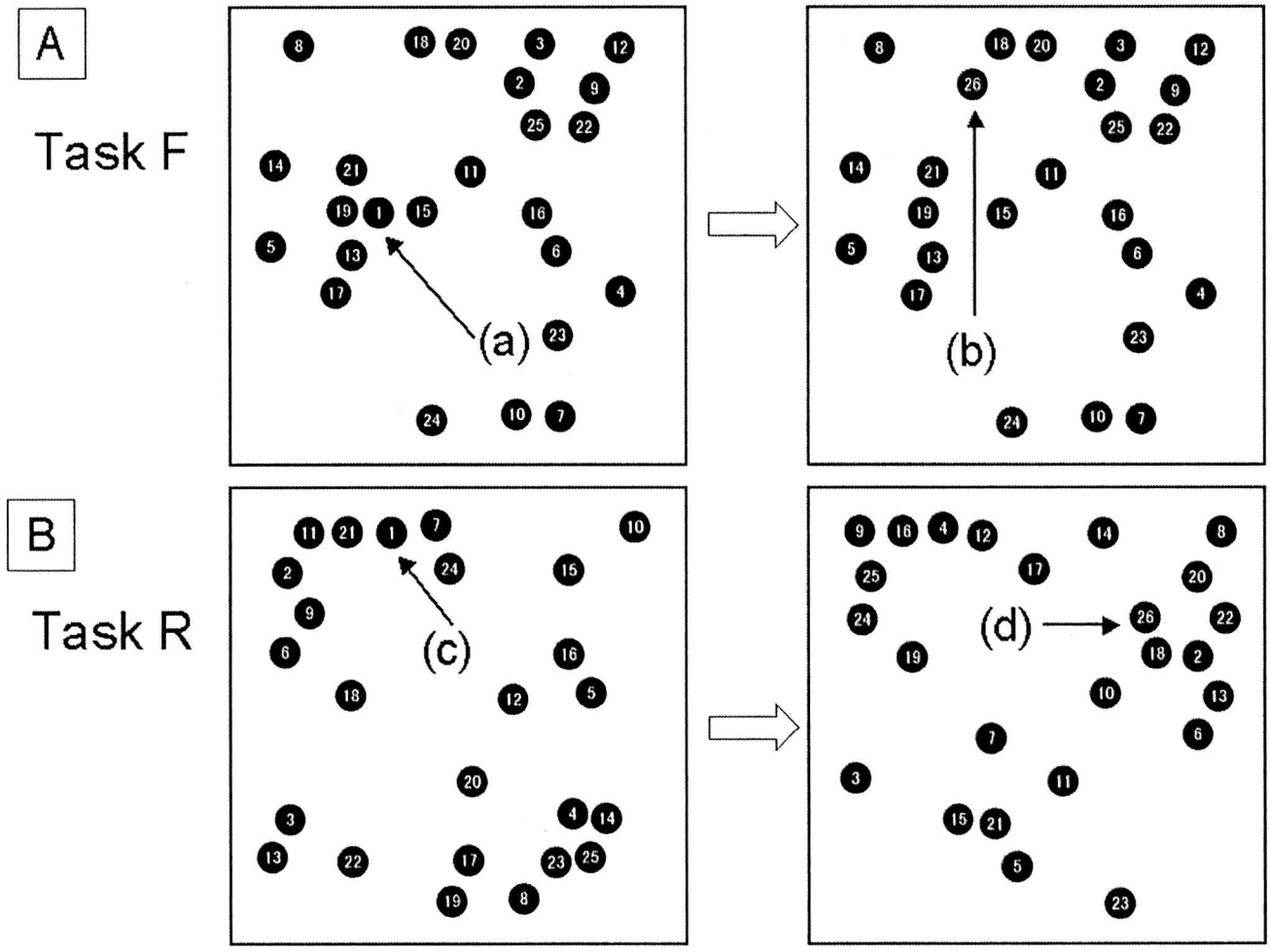

Figure 1. Summary of tasks of the Advanced Trail Making Test

(A) In task F of the ATMT, when the subject touches circle number 1 (arrow a), it disappears and the circle number 26 (arrow b) appear in a different location on the ATMT screen. Locations of other circles remain the same. (B) Task R of the ATMT was identical to task F in that one circle was added in a different location (arrow d) when the target circle had been touched (arrow c) and disappeared. The difference was that the location of all other circles changed at random when the target circle had been touched.

Measures

Spatial working memory

In order to evaluate SWM of the subjects with a wide variety of ages, intelligence and levels of severity of psychopathology, we used the Advanced Trail Making Test (ATMT).[20,21] The ATMT is a computerized task modified from the original Trail Making Test,[22] which consists of two sheets of paper, each with 25 circles containing numbers or letters. The ATMT was administered on a 15-inch display monitor (CV515PJ; Totoku Electric, Tokyo, Japan), which was fitted with a touch-sensitive panel. The display monitor was connected to a standard laptop personal computer, which had Advanced Trail Making Test software™ (Soiken, Inc., Toyonaka, Japan) installed. All ATMT tasks were performed on an 18cm square ATMT screen displayed on the monitor. Subjects were placed in a fixed position at the center of the ATMT screen, with their eyes approximately 40cm from the monitor. The calibration procedure involved touching two reference points on the touch-sensitive panel.

The ATMT consisted of two tasks, task F (Fixed) and task R (Random). These tasks included only a series of numbered circles (Figure 1). Each circle was black with a white number, had a diameter of 1cm.

In task F of the ATMT, circles numbered from 1 to 25 were first randomly located on the ATMT screen (Figure 1A). Subjects were required to touch these circles in sequence, starting with circle number 1. When the subject touched the first target circle, it disappeared and circle number 26 appeared in a different location on the ATMT screen. The locations of the other circles remained the same. Next, touching of, for example, circles 2, 3 and 4 resulted in their disappearance and the addition of circles 27, 28 and 29 on the ATMT screen, so that the number of circles seen on the screen always remained 25. In theory, the task could thus be performed in perpetuity. Subjects could memorize the locations of other circles while searching for the target circle (dual task) and shorten their reaction time (RT) of circle touching.

Task R of the ATMT was identical to task F in that one circle was added in a different location when the target circle had been touched and disappeared. The difference was that the position of all other circles changed at random when the target circle had been touched (Figure 1B). Since the locations of the circles changed every time the subject touched the target circle and every target circle had to be found in a new arrangement, this task required no memorization. The performance of task F required visual search and SWM, while task R required only visual search. The RT for circle touching could be shortened by SWM in task F, whereas SWM had no effect on the performance of task R.

In order to evaluate SWM used in task F, we computed the SWM utilization rate for task F (SWM-R: %) with the following procedure. The RT for the touching of any given circle was measured as the time lag between touching that target and the previous one. First, we determined the top 5 percent RT for touching circles in task R ($RT_{5\%}$) of each subject, which denoted the minimal RT for visual search of the target circle. Next, if RT for touching circles in task F was shorter than $RT_{5\%}$, then we assumed that SWM had been used when the circle was touched. The rate of SWM utilization for touching circles for task F was computed in percentage terms.

In both task F and R, every set consisted of a sequence of touching circles numbers 1 to 99. Each task was administered twice for a total of four sets. The order of task administration was fixed as R-F-F-R. Subjects administered these sets at intervals of sixty seconds between sets. The locations of the circles differed for each set.

In task F, if the target circle was near the previous target, the subject could have found the target by chance, and touched it as soon as the previous target had been touched without necessarily using SWM. We therefore excluded the target circle from the analysis if the distance from the previous target circle was less than half the side of the ATMT screen in both task F and R. In addition, as circles with a single digit (1 to 9) were easy to find, these circles were also excluded from the analysis. For each task, approximately 50 percent of all target circles were included in the analysis.

After the calibration, subjects were instructed to touch the target circle as rapidly as they could with the index finger of their dominant (right) hand. Prior to starting the ATMT task, a practice test of circle touching from 1 to 25 was performed for both tasks to ensure that all subjects understood the procedure. Subjects were informed that if they memorize the locations of other circles while searching for the target circle in task F, they could shorten their RT of circle touching. When subjects were ready to begin, they touched the ATMT screen showing

"Touch to Start" to initiate a trial.

The following outcome variables of ATMT were determined. The mean RT for touching circles in task F (RT-F: milliseconds [ms]) and in task R (RT-R: ms) were calculated. The SWM utilization rate for task F (SWM-R: %) was computed with the procedure described above.

Social functioning

Level of social functioning was measured with the Rehabilitation Evaluation Hall and Baker (REHAB).[23] For our study, the REHAB was completed by a trained psychometrician and ratings were based on behaviors and events that occurred during the week before the evaluation. The full scale is divided into two sections, "Deviant Behavior" and "General Behavior (GB)". We included only the GB rating, which consists of 15 items plus a 16th that assesses overall functioning. The score for an item ranges from 0 to 9 where 0 denotes the highest level and 9 the lowest level of functioning. Scores on the items were combined to yield total scores for five subscales derived from factor analysis: Social Activity (mixing on ward, mixing off ward, use of leisure, activity level, amount of speech, initiation of speech), Speech Disturbance (speech sense, speech clarity), Speech Skills (amount of speech, initiation of speech), Self-Care Skills (table manners, washing, dressing, care of possessions, need for prompting), and Community Skills (use of money, community facilities), plus a total score for all GB items, which includes the rating given to the overall functioning item.

The total for all GB items of the REHAB can be used to identify patients in a long-stay hospital who might be suitable for transfer to community services.[23] Patients with a GB score of less than 40 (out of a total score of 144) can be expected to be able to live independently in the community but it is likely to be quite difficult to deinstitutionalize patients with a GB score of more than 65. The average score for all GB items for patients with schizophrenia in our study was 63.18 (± 28.08).

Psychiatric symptoms

Psychiatric symptoms of patients with schizophrenia were assessed with the 18-item Brief Psychiatric Rating Scale (BPRS).[24] The BPRS was scored by an experienced psychiatrist, who was trained before the start of the study. Each item was rated on a 7-point severity scale (1 = symptom is not present, 7 = symptom is present to an extremely severe degree). Scores on the items were combined to yield total scores for five subscales based on a factor-analytic study.[25] The items constituting the symptom dimensions were 'negative' (emotional withdrawal, motor retardation, and blunted affect), 'positive' (somatic concern, grandiosity, suspicion, hallucinatory behavior, and unusual thought contents), 'disorganization' (conceptual disorganization, mannerisms and posturing, and disorientation), 'belligerence' (hostility, uncooperativeness, and excitement), and 'affect' (anxiety, guilt, tension, and depression).

Procedure and statistical methods

The assessment protocol consisted of two sessions, conducted in a fixed order. During session one, subjects completed WAIS-R after completing the diagnostic assessment and BPRS. During session two, ATMT was administered to the subjects after they had been assessed with REHAB. Session two was conducted one week after session one. Each assessment was conducted by an experienced examiner. Healthy controls were not subjected to BPRS or REHAB. Examiners were blind to the results of measurements assessed by other examiners.

Differences in measured variables between groups were determined by independent *t*-test. Correlational analyses using Pearson's coefficient were performed to assess the relationships among the measured variables in patients with schizophrenia. Unless specified, two-tailed tests were applied for all the statistical analyses. All results with a *p*-value of less than .05 were considered significant.

RESULTS

Means and standard deviations for the social functioning and the psychiatric symptoms of patients with schizophrenia are given in Table 1.

Comparison between spatial working memory of patients with schizophrenia and of healthy controls

The RT-F and the RT-R were significantly slower ($t = 8.02$, $df = 59$; $p < .001$ and $t = 8.14$, $df = 63$; $p < .001$, respectively) for patients with schizophrenia (4271.87 ± 1554.13 ms for

RT-F and 5329.30 ± 1545.00 ms for RT-R) than for healthy controls (2419.74 ± 416.76 ms for RT-F and 3421.54 ± 500.12 ms for RT-R). The patients registered a significantly reduced SWM-R (24.08 ± 8.28 %; $t = 5.90$, $df = 83$; $p < .001$) compared to healthy controls (35.38 ± 9.25 %).

Correlations between spatial working memory and other measured variables in schizophrenia

Correlation coefficients between SWM-R and other measured variables for schizophrenia are shown in the matrix in Table 2. The SWM-R proved to be related with the REHAB subscales, Speech Disturbance, Self-Care Skills, Community Skills and the Total for all GB items. The SWM-R showed a negative correlation with BPRS subscales, disorganization symptoms and the total BPRS score.

Correlations between psychiatric symptoms and social functioning in schizophrenia

We further analyzed relationships between psychiatric symptoms and social functioning in patients with schizophrenia. Correlation coefficients for the subscales of BPRS and REHAB are shown in the matrix in Table 3. Negative symptoms correlated significantly with Social Activity and Speech Skills, while disorganization symptoms displayed significant correlations with Speech Disturbance, Self-Care Skills, Community Skills and the Total score for all GB items. The REHAB subscales did not correlate significantly with psychiatric symptoms of BPRS total score, positive, belligerence and affect symptoms.

Correlation between general intelligence and other measured variables in schizophrenia

In the case of the patients, we further analyzed relationships between general intelligence and other measured variables (SWM, social functioning and psychiatric symptoms). SWM-R showed significant correlation with three IQ items assessed with WAIS-R ($r = 0.432$, $df = 98$; $p = 0.002$ for Full-Scale IQ, $r = 0.471$, $df = 98$; $p = 0.001$ for Verbal IQ and $r = 0.368$, $df = 98$; $p = 0.011$ for Performance IQ). Disorganization symptoms correlated negatively with Verbal IQ ($r = -0.306$, $df = 98$; $p = 0.037$). No other significant relationship was detected between psychiatric symptoms and the three IQ items.

TABLE 1. *Social functioning and psychiatric symptoms of patients with schizophrenia (n=50)*

		Mean	(SD)
REHAB	Total for all GB items	63.18	(28.08)
	Social Activity	28.42	(10.93)
	Speech Disturbance	7.06	(3.10)
	Speech Skills	8.64	(3.67)
	Self-Care Skills	16.40	(12.61)
	Community Skills	7.62	(5.64)
BPRS	Total Scores	40.86	(7.60)
	Negative	7.82	(3.44)
	Positive	13.52	(3.36)
	Disorganization	5.66	(1.86)
	Belligerence	5.58	(2.00)
	Affect	8.28	(2.93)

TABLE 2. *Correlations between Spatial Working Memory and other measured variables in schizophrenia (n=50, 98 df)*

		SWM-R	
		Pearson *r*	*p*-value
REHAB	Total for all GB items	- .362	.009**
	Social Activity	.135	.351
	Speech Disturbance	- .370	.008**
	Speech Skills	.265	.063
	Self-Care Skills	- .373	.008**
	Community Skills	- .385	.006**
BPRS	Total Scores	- .310	.029*
	Negative	-.156	.280
	Positive	-.162	.260
	Disorganization	- .367	.009**
	Belligerence	-.228	.111
	Affect	-.011	.938

**: $p < .01$, *: $p < .05$

Table 3. *Correlations between Psychiatric symptoms and Social functioning in Schizophrenia* † *(n=50, 98 df)*

	BPRS	Negative		Disorganization	
		Pearson *r*	*p*-value	Pearson *r*	*p*-value
REHAB	Total for all GB items	-.243	.089	.363	.009**
	Social Activity	.343	.015*	-.054	.708
	Speech Disturbance	-.211	.141	.400	.004**
	Speech Skills	.316	.025*	-.194	.177
	Self-Care Skills	-.104	.472	.412	.003**
	Community Skills	-.145	.316	.424	.002**

† The REHAB subscales did not correlate significantly with psychiatric symptoms of BPRS total score, positive, belligerence and affect symptoms. **: $p < .01$, *: $p < .05$

DISCUSSION

Patients with schizophrenia demonstrated significantly greater SWM deficit (assessed as SWM-R) compared to healthy controls. The SWM correlated with several aspects of social functioning such as self-care skills, community skills and speech disturbance, and with disorganization symptoms. Disorganization symptoms were also related to these aspects of social functioning. These results suggest that the dorsolateral prefrontal cortex dysfunction is involved with effective phenotypic markers for schizophrenia, which relate to the basic aspects of social functioning.

Since working memory has been hypothesized to be a temporary store whose contents are continually updated, scanned and manipulated in response to immediate information processing demands,[1] several activities in our daily life might depend on working memory. However, to the best of our knowledge, no study has investigated the relationship between SWM and social functioning in schizophrenia.

In order to evaluate SWM, we used the ATMT tasks. Since the ATMT can be accomplished whether the subject uses memory or not, it differs from the standard SWM task such as the delayed-response task. However, subjects reduce their RT for circle touching in task F when they memorize the location of the next circle while searching for the target circle (dual task) and, in this regard, SWM as evaluated by ATMT can be viewed as the equivalent of memory storage used unconsciously in daily activities. In addition, since the tasks involve simply touching the numbered circles in order and requires only few instructions, we could administer the tasks to subjects with a wide variety of ages, intelligence and levels of severity of psychopathology.

Our study identified relations between SWM-R and several subscales of REHAB (Speech Disturbance, Self-Care Skills, Community Skills and the total for all GB items). These findings indicate that social functioning in terms of speech disturbance, self-care and community skills requires SWM. On the other hand, SWM-R did not correlate with the activity of interpersonal exchange assessed by Social Activity and Speech Skills. We speculate that these aspects of social functioning require cognitive functions other than SWM.

The present study found that social functioning was also related to psychiatric symptoms in schizophrenia. Subscales of social functioning, such as Speech Disturbance, Self-Care Skills, Community Skills and the total for all GB items were associated with disorganization symptoms. All of these subscales were associated with SWM. On the other hand, the activity of interpersonal exchange assessed by Social Activity and Speech Skills correlated with negative symptoms but not with disorganization symptoms. No other psychiatric symptoms were related to social functioning.

Several studies have been devoted to the relationships between social functioning and psychiatric symptoms, and most of them reported that social functioning was correlated with negative symptoms.[26,27] Since the adequacy of the

dichotomous model of positive and negative symptoms of schizophrenia was questioned, factorial analytic studies have resulted in models with more than three syndrome clusters,[28,29] and disorganization symptoms were suggested to predict social functioning.[11,12] Our results support the findings of past studies that negative symptoms and disorganization symptoms were associated with social functioning.

The SWM-R was found to be related to disorganization symptoms. The SWM deficit in schizophrenia has been reported to be associated with negative symptoms.[3,30] However, in another study,[6] the relation between SWM and negative symptoms turned out to be inconsistent over time. During the acute state, SWM deficit and negative symptoms showed significant correlation, but 4 months later, this was no longer the case. After the development of tri-syndromic models, some studies suggested the existence of a relationship between SWM deficit and disorganization symptoms.[8,9] In addition, Perlstein *et al.*[10] reported that the dorsolateral prefrontal cortex dysfunction was associated with both disorganization symptoms and SWM. In our study, the SWM of clinically stable patients with schizophrenia correlated with disorganization symptoms but not with other symptoms. This result supports the findings of past studies conducted after the development of tri-syndromic models.

We could demonstrate that SWM assessed with ATMT were related to general intelligence measured with the WAIS-R. The SWM can be considered basic cognitive functions necessary for more complex cognitive measurements. However, the three IQ items evaluated by WAIS-R showed no relationship with social functioning in patients with schizophrenia. Several studies have investigated the relationship between social functioning and cognitive functions using the scaled scores of several subtests of WAIS-R.[26, 31, 32, 33, 34] These studies generally showed no significant relationships except that several composite measures were related to problem solving skills.[26, 34] The results of our study are consistent with these studies, indicating that IQ measurements are relatively ineffective for predicting social functioning of schizophrenia patients.

CONCLUSIONS

The SWM might predict several basic aspects of social functioning in schizophrenia, including self-care, community skills and speech disturbance, and these aspects of social functioning were also related to disorganization symptoms. Both spatial working memory deficit and disorganization symptoms have been considered significant components of schizophrenic impairment which are involved with the dorsolateral prefrontal cortex. It is clear that further studies are needed to clarify the relationships among SWM, disorganization symptoms and social functioning.

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REFERENCES

1. Baddeley A. *Working Memory.* Oxford University Press, New York, 1986.
2. Goldman-Rakic PS. Prefrontal cortical dysfunction in schizophrenia: The relevance of working memory. In: BJ Carroll, JE Barrett (ed.). *Psychopathology and the brain.* Raven Press, New York, 1991; 1-23.
3. Carter C, Robertson L, Nordahl T, Chaderjian M, Kraft L, O'Shora-Celaya L. Spatial working memory deficits and their relationship to negative symptoms in unmedicated schizophrenia patients. *Biol. Psychiatry* 1996; **40**: 930-932.
4. Keefe RS, Roitman SE, Harvey PD *et al.* A pen-and-paper human analogue of a monkey prefrontal cortex activation task: spatial working memory in patients with schizophrenia. *Schizophr. Res.* 1995; **17**: 25-33.
5. Park S, Holzman PS. Schizophrenics show spatial working memoy deficits. *Arch. Gen. Psychiatry* 1992; **49**: 975-982.
6. Park S, Puschel J, Sauter BH, Rentsch M, Hell D. Spatial working memory deficits and clinical symptoms in schizophrenia: a 4-month follow-up study. *Biol. Psychiatry* 1999; **46**: 392-400.
7. Park S, Holzman PS, Goldman-Rakic PS. Spatial Working memory deficits in the relatives of schizophrenic patients. *Arch. Gen. Psychiatry* 1995; **52**: 821-828.
8. Cameron AM, Oram J, Geffen GM, Kavanagh DJ, McGrath JJ, Geffen LB. Working memory correlates of three symptom clusters in schizophrenia. *Psychiatry Res.* 2002; **110**: 49-61.
9. McGrath J, Chapple B, Wright M. Working memory in schizophrenia and mania: correlation with symptoms during the acute and subacute phases. *Acta.*

Psychiat. Scand. 2001; **103**: 181–188.

10. Perlstein WM, Carter CS, Noll DC, Cohen JD. Relation of prefrontal cortex dysfunction to working memory and symptoms in schizophrenia. *Am. J. Psychiatry* 2001; **158**: 1105-13.
11. Sakiyama S, Iida J, Minami Y, Kishimoto T. Factors of good outcome after discharge from support house (engoryou) for schizophrenia. *Psychiatry Clin. Neurosci.* 2002; **56**: 609-15.
12. Norman RM, Malla AK, Cortese L *et al.* Symptoms and cognition as predictors of community functioning: a prospective analysis. *Am. J. Psychiatry* 1999; **156**: 400-405.
13. Green MF, Kern RS, Braff DL, Mintz J. Neurocognitive deficits and functional outcome in schizophrenia: are we measuring the "right stuff"? *Schizophr. Bull.* 2000; **26**: 119-136.
14. Nakamura M, Matsushima E, Ohta K, Ando K, Kojima T. Relationship between attention and arousal level in schizophrenia. *Psychiatry Clin. Neurosci.* 2003; **57**: 472-7.
15. American Psychiatric Association. *DSM-IV: Diagnostic and Statistical Manual of Mental Disorders, 4th Edition.* The American Psychiatric Press, Washington, DC, 1994.
16. First MB, Spitzer RL, Gibbon M, Williams JBW. *Structured Clinical Interview for DSM-IV Axis I Disorders - Patient Edition (SCID-I/P, Version 2.0).* Biometrics Research Department, New York State Psychiatric Institute, New York, 1995.
17. Meltzer HY, Fatemi SH. Schizophrenia. **In**: MH Ebert, PT Loosen, B Nurcombe (ed.). *Current diagnosis & treatment in Psychiatry.* McGraw-Hill, New York, 2000; 260–277.
18. Wechsler D. *WAIS-R Manual: Wechsler Adult Intelligence Scale-Revised.* Psychological Corp, New York, 1981.
19. Misawa G, Kobayashi S, Fujita K, Maekawa H, Dairoku H. *Japanese Wechsler Adult Intelligence Scale-Revised – Short Forms.* Nihonbunkakagakusha, Tokyo, 1993 (in Japanese).
20. Iwase M, Takahashi H, Nakahachi T, Kajimoto O, Shimizu A, Takeda M. The assessment of visuospatial working memory using Advanced Trail Making Test (ATMT). *Seishin Igaku* 2003; **45**: 1291-1296 (in Japanese).
21. Kajimoto O. Technique for assessment of degree of fatigue. *Igaku no Ayumi* 2003; **204**: 377-380 (in Japanese).
22. Reitan RM, Wolfson D. *The Halstead Reitan Neuropsychological Test Battery: Theory and Clinical Interpretation.* Neuropsychology Press, Tucson, Az, 1993.
23. Baker R, Hall JN. *REHAB: Rehabilitation Evaluation of Hall and Baker.* Vine Publishing, Aberdeen, 1984.
24. Overall JE, Gorham DR. The Brief Psychiatric Rating Scale. *Psychol. Rep.* 1962; **10**: 799-812.
25. Harvey PD, Davidson M, White L *et al.* Empirical evaluation of the factorial structure of clinical symptoms in schizophrenia: effects of typical neuroleptics on the brief psychiatric rating scale. *Biol. Psychiatry* 1996; **40**: 755-760.
26. Addington J, Addington D. Neurocognitive and social functioning in schizophrenia: a 2.5 year follow-up study. *Schizophr. Res.* 2000; **44**: 47-56.
27. Van der Does AJ, Dingemans PM, Linszen DH, Nugter MA, Scholte WF. Symptom dimensions and cognitive and social functioning in recent-onset schizophrenia. *Psychol. Med.* 1993; **23**: 745-53.
28. Bilder RM, Mukherjee S, Rieder RO, Pandurangi AK. Symptomatic and neuropsychological components of defect states. *Schizophr. Bull.* 1985; **11**: 409-419.
29. Liddle PF. The symptoms of chronic schizophrenia. A re-examination of the positive-negative dichotomy. *Br. J. Psychiatry* 1987; **151**: 145-151.
30. Pantelis C, Harvey CA, Plant G *et al.* Relationship of behavioural and symptomatic syndromes in schizophrenia to spatial working memory and attentional set-shifting ability. *Psychol. Med.* 2004; **34**: 693-703.
31. Ikebuchi E, Nakagome K, Tugawa R *et al.* What influences social skills in patients with schizophrenia? Preliminary study using the role play test, WAIS-R and event-related potential. *Schizophr. Res.* 1996; **22**: 143-150.
32. Brekke JS, Raine A, Ansel M, Lencz T, Bird L. Neuropsychological and psychophysiological correlates of psychosocial functioning in schizophrenia. *Schizophr. Bull.* 1997; **23**: 19-28.
33. Dickerson F, Boronow JJ, Ringel N, Parente F. Social functioning and neurocognitive deficits in outpatients with schizophrenia: a 2-year follow-up. *Schizophr. Res.* 1999; **37**: 13-20.
34. Addington J, McCleary L, Munroe-Blum H. Relationship between cognitive and social dysfunction in schizophrenia. *Schizophr. Res.* 1998; **34**: 59-66.

特集・統合失調症と認知機能—最近の話題

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精神疾患における応用可能性について

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特集　統合失調症と認知機能―最近の話題*

Advanced Trail Making Test(ATMT)による Visuospatial Working Memoryの測定**

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Key words

Advanced Trail Making Test(ATMT), Visuospatial working memory, Reaction time, Schizophrenia

はじめに

Trail Making Test(TMT)とは，1枚の紙に書かれた1から25までの数字などの指標を順に鉛筆でなぞるという簡易な認知機能検査である[4)]。TMTは1950年代に開発され神経内科領域で主に前頭葉機能を評価するために使用されてきた。

TMTは従来脳障害の判定に有用であるといわれており，左半球障害者や前頭葉障害者などではカテゴリーチェンジのないTMT-Aに比してカテゴリーチェンジのあるTMT-Bの成績が極端に悪くなると考えられている。TMT-A，B課題双方ともに成績が低下する場合には，情報処理あるいは注意力の全般的機能障害が示唆される。統合失調症患者においてもA，B課題双方ともに成績が低下し，A課題の障害に比してB課題の障害が高度であるという報告が多い。

梶本らはタッチパネルディスプレイを用いてTMTをコンピュータ化したAdvanced Trail Making Test(ATMT)を開発した[2)]。ATMTは原版のTMTを改変して，visuospatial working memory(VWM)の定量評価を可能にした。ATMTは原版のTMTと比べいくつかの利点がある。(1)タッチパネル上に表示された数字ボタンに直接指で触れて課題を遂行するようにし，1回のボタン押しごとの反応時間測定を可能にした。(2)数字ボタンを25までに限定せず長時間の

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** The Assessment of Visuospatial Working Memory using Advanced Trail Making Test(ATMT)in Psychiatric Disorders

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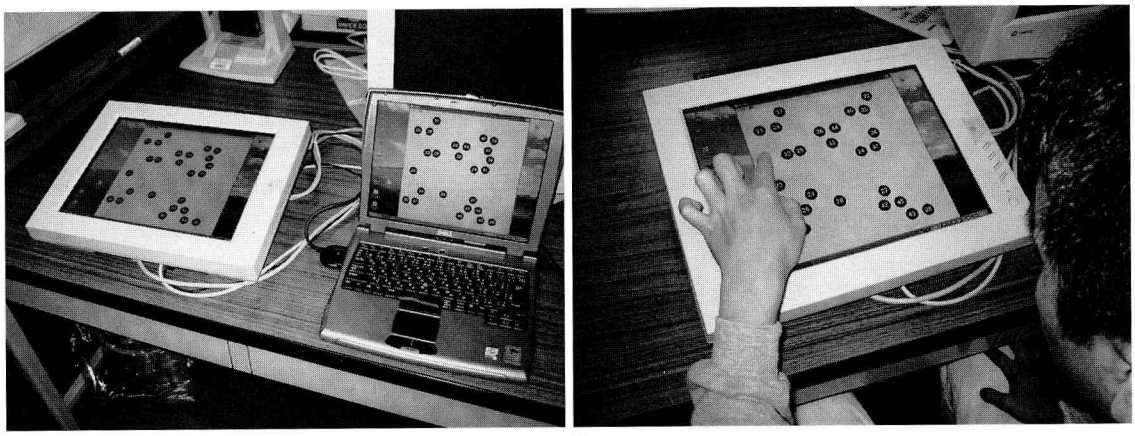

A　　B

図1　A；ATMTの使用機器。15インチ-タッチスクリーンディスプレー CV 515 PJ（東京特殊電線製），ノート型パソコン（RS 232 C端子を要するPC），ATMTソフトウェアの組み合わせで施行可能である。B；ATMTの施行風景。タッチパネルディスプレイ上に表示された丸い数字ボタンを1から順番に指で触れていく課題を施行中。

連続測定を可能にした。(3)数字ボタンの位置が固定され，VWMにより成績向上が可能な課題(ATMT-B課題)と数字ボタンの位置が1回のボタン押しごとに変化し，課題の遂行が視覚的探索のみによる課題(ATMT-C課題)とを作成し，両者の比較によりVWMの定量評価を可能にした。ATMTは短時間で大量かつ定量性の高いデータを得られる上に，課題の教示がほとんど不要なため容易に検査を施行でき，小児から高齢者までさまざまな精神疾患へ応用可能と考えられる。

本論文では，ATMTによるVWMの評価方法を概説する。さらに，健常者と統合失調症患者の少数例でVWMの評価を予備的に開始しており，その結果について述べる。

対象と方法

1．対象

DSM-IVにより診断された統合失調症30名(男/女：16/14，平均年齢38.4±12.2歳，教育年数12.2±2.4年)，健常被験者17名(男/女：10/7，平均年齢34.8±8.5歳，教育年数17.1±3.2年)を対象とした。なお本研究の実施に先立ち，ヘルシンキ宣言の趣旨に基づき，個々の被験者より書面にて自由意志による参加の同意を得た。対象となった患者は，病歴の長い慢性期の患者が中心であった。健常被験者は現時点では統合失調症群と年齢，教育年数はマッチされていない。統合失調症患者では年齢，教育年数のほかに背景情報を調査した。統合失調症患者においては発症年齢22.7±5.8歳，罹病期間15.7±11.6年，服薬量1,408±2,867 mg(クロルプロマジン換算量)，精神症状23.8±8.1点(BPRS総得点)，錐体外路症状0.57±0.82点(DIEPSS概括重症度)であった。BPRSは18項目からなる精神症状評価尺度であるが，症状項目の因子分析研究[3]に基づいて陽性症状10.7±5.3点(思考解体・衒奇的な行動や姿勢・敵意・疑惑・幻覚・思考内容の異常)，陰性症状5.4±4.0点(感情的引きこもり・運動減退・非協調性・情動鈍麻もしくは不適切な言動)，躁症状2.3±3.4点(誇大性・高揚気分・精神運動興奮)，うつ症状5.3±3.5点(心気的訴え・不安・罪業感・緊張・抑うつ気分)をそれぞれ評価した。

2．測定機器

実験に使用したのは15インチ-タッチスクリーンディスプレー CV 515 PJ（東京特殊電線製），RS 232 C端子を要するノート型パソコン(PC)，それからATMTソフトウェアである。これらを組み合わせて実際に実験している様子を図1-A，Bに示した。このように簡単な機器の組み合

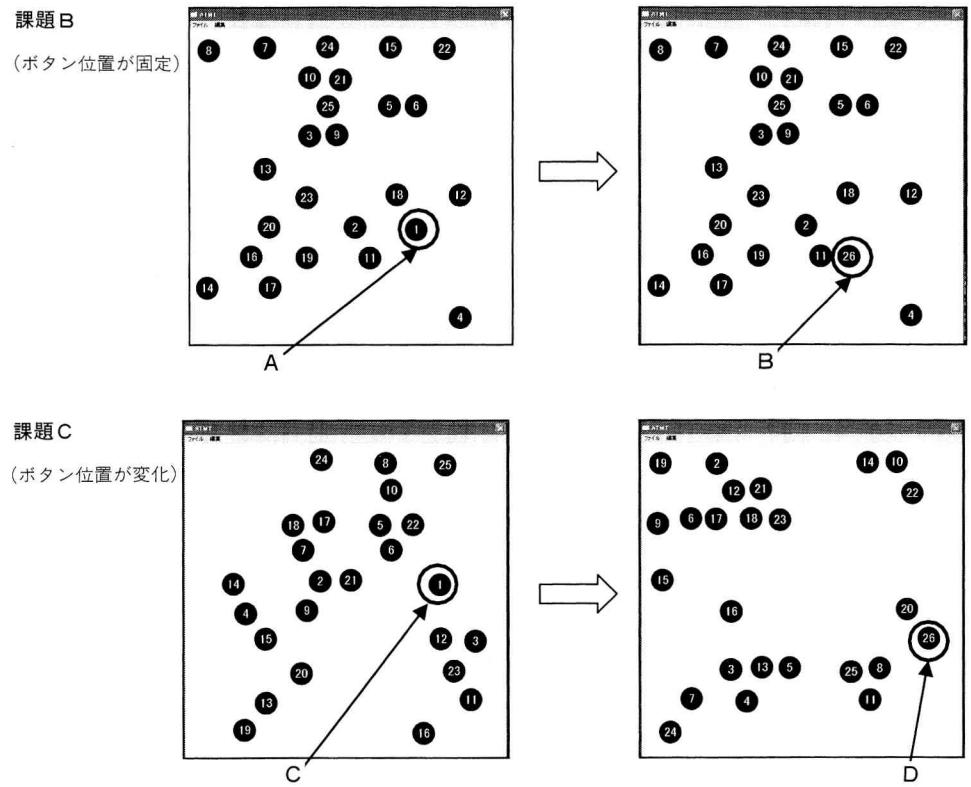

図2　B課題では，最初1から25までの数字ボタンがスクリーンディスプレー上にランダムに配置されている。これらのボタンを1から順番に押していく。被験者がボタン1を押す(矢印A)とそれが消え，新たにボタン26が画面上の任意の位置に追加される(矢印B)。このとき，残りのボタンの位置は固定されたままである。以下2，3，4と順番に消えていき，新たに27，28，29，とボタンが追加される。画面上には常に25個のボタンが表示される。被験者はターゲットを探索しながら他のボタンの位置を覚えること，つまりVWMの利用によりボタン押しの反応時間を短縮できる。C課題でもB課題同様に1から順番に数字押しを行う。ボタン1を押す(矢印C)とそれが消え，ボタン26が任意の位置に追加される(矢印D)。その際残りのボタンもすべて再配置される。したがって，被験者は絶えず新しい配置の中からターゲットを探索しなければならず，VWMの利用は不可能である。

わせにより容易に検査の施行が可能であり，なおかつ検査機器の携帯性もあるため応用範囲が広い検査法である。

3．課題の概要

ATMTはA課題・B課題・C課題の3種類の課題からなる。今回，課題を簡便にするためにいずれの課題も数字のみを扱い，カテゴリーチェンジは採用しなかった。A課題は原版のTMTのA課題とほぼ同様の課題である。このA課題では数字ボタンは1から25までに限られるが，B・C課題では数字ボタンを25までに限定せず任意の回数まで行うことができ，長時間の連続測定が可能である。ATMTにおけるこれらB・C課題を用いてVWMを評価した。以下これらの課題について説明する(図2)。

ATMT-B課題では，最初1から25までの数字ボタンがスクリーンディスプレー上にランダムに配置されている。これらのボタンを1から順番に押していく。被験者がボタン1を押すとそれが消え，新たにボタン26が画面上に追加される。このとき，残りのボタンの位置は固定されたままである。以下2，3，4と順番に消えていき，新たに27，28，29，とボタンが追加される。画面上には常に25個のボタンが表示される。被験者は

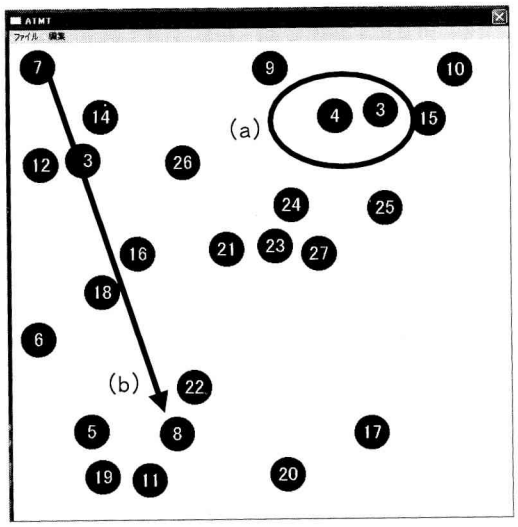

図3　課題Bでの VWM による反応時間短縮効果と注意視野の関係について。(a)次のボタンが注意視野内にある場合，反応時間の短縮は VWM によるものか，偶然近くにあったボタンをすぐに見つけたためかは判定不能。(b)次のボタンが注意視野外にある場合，反応時間の短縮は VWM によるものと考えられる。

ターゲットを探索しながら他のボタンの位置を覚えることによりボタン押しの反応時間を短縮できる。ATMT-C 課題でも B 課題同様，1つのボタンが消えると新たに数字ボタンが追加されるが，その際残りのボタンもすべて再配置される。したがって，被験者は絶えず新しい配置の中からターゲットを探索しなければならない。両課題を遂行するにあたり，できるだけ早く課題を遂行してもらうように教示した。ただし，B 課題ではボタン位置を覚えながら遂行することで時間の短縮が可能なことをあらかじめ知識として与えた。B，C 課題それぞれ1から25までのボタン押しを練習として行った後，実際の測定を行った。測定の際には1から99までのボタン押しを1ブロックとして，C－B－B－C 課題の4ブロックを施行し，この4ブロック内で VWM の測定を行った。測定に要する時間は20分前後であり，患者に過剰な負担を強いることなく検査可能であり，B，C 課題ともに約200ボタン押しのデータが得られるため十分な定量性が得られている。

以上のように個々の課題遂行に必要な認知的要素は，B 課題では視覚探索＋VWM，C 課題では視覚探索のみが考えられる。そのため B 課題の反応時間は VWM により C 課題の反応時間よりも短縮される。しかし B 課題での反応時間短縮効果は，たとえば図3でボタン3の次にボタン4を押す(a)の場合のように次のボタンが注意視野内にある場合，反応時間の短縮は VWM によるものとは限らないが，(b)のように次のボタンが注意視野外にある場合，反応時間の短縮は VWM によるものと考えられる。したがって，VWM 測定の前提条件として注意視野外のボタン押しに絞って解析を行う必要がある。注意視野の広さは予備実験の結果から大体 ATMT の画面の半分よりやや小さい程度であると推定しており，今回は，画面の大きさの半分の距離よりも遠い位置にあるボタンは注意視野の外にあると仮定して，結果の解析を行った。

4．B 課題における VWM 利用率の算出方法

以上の前提に基づいて，B 課題における VWM 利用率を次に解説するように算出した。図4は，一人の健常被験者について長時間 ATMT を施行したデータである。まず C 課題における注意視野外にあるボタン押しの反応時間の分布から上位5％での反応時間を決定する。これは視覚探索により，次のボタンが見つかる早さの上限を決定するための操作である。次に B 課題において注意視野外にあるボタン押しの反応時間が C 課題の上位5％より早い場合，そのボタン押しに VWM を利用したと定義する。注意視野外にある B 課題の全ボタン押しのうち，VWM を利用したボタン押しが何％存在したかを算出する。例えば図4において，C 課題における注意視野外にあるボタン押しの反応時間の分布から上位5％での反応時間は1,080 ms である。注意視野外にある B 課題の全ボタン押し2,553個のうち VWM を利用したと考えられるのは反応時間が1,080 ms より短い1,065個であるので VWM 利用率は1,065／2,553×100＝41.7％となる。これと同様の作業を C－B－B－C 課題の4ブロックについて行い，VWM 利用率の算出を行った。

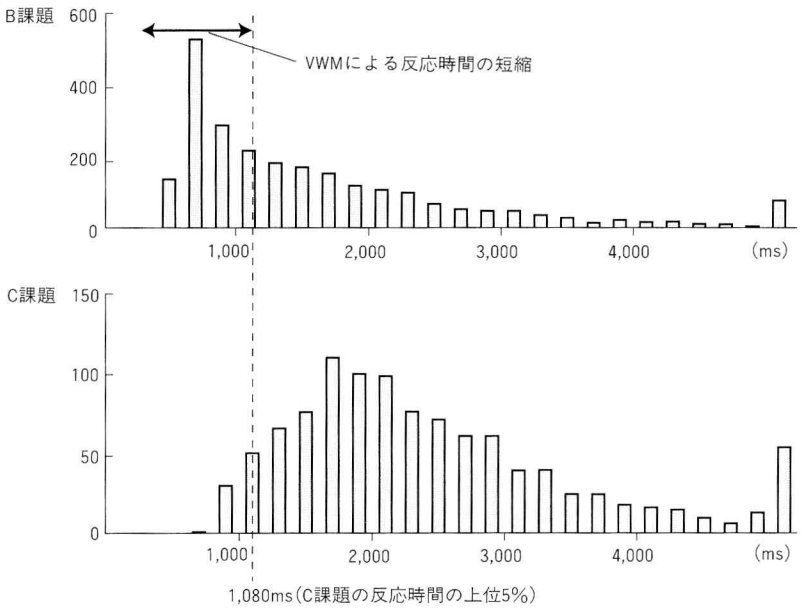

図4　課題BでのVWMによる反応時間短縮効果の算出。上下のグラフはB・C課題のボタン押し数のヒストグラムであり，横軸は反応時間，縦軸はボタン押しの度数を示している。C課題における注意視野外にあるボタン押しの反応時間の分布から上位5％の反応時間はこのデータでは1,080 msである。注意視野外にあるB課題の全ボタン押し2,553度数のうち反応時間が1,080 msより短いものが1,065度数あり，これらのボタン押しはVWMを利用したと考えられるのでVWM利用率は1,065／2,553×100＝41.7％となる。

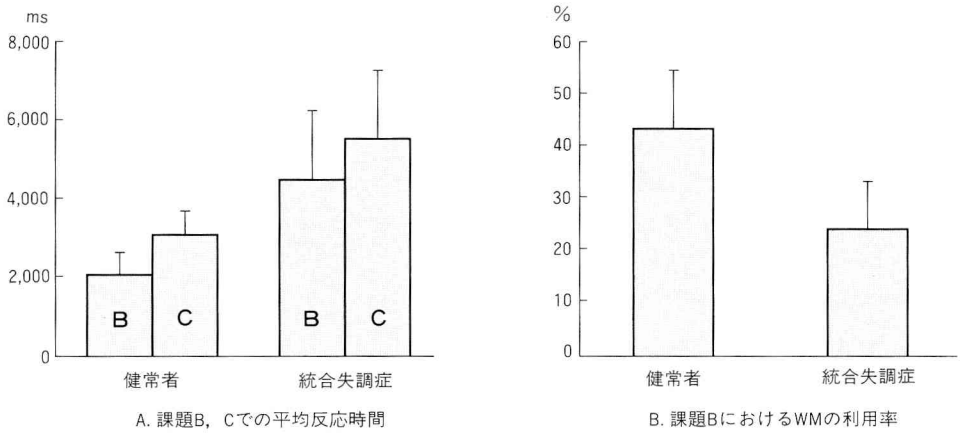

図5　健常者のB・C課題の反応時間，VWM利用率の平均±標準偏差はそれぞれ，2,081.1±555.7 msec・3,080.5±611.1 msec・42.9±11.5％，統合失調症患者のB・C課題の反応時間，VWM利用率はそれぞれ，4,481.8±1,726.7 msec・5,531.9±1,711.2 msec・24.1±8.9％であった。A；統合失調症患者の反応時間は健常被験者と比べ，B・C課題ともに有意に延長していた。統合失調症患者においても健常被験者同様B課題はC課題と比べ反応時間が短く，VWMによる反応時間の短縮効果がみられたが，この結果からは両群のWMの差は判然としない。B；各ボタン押しごとにVWMの利用を判別した解析では，健常者ではVWM利用率が40%前後であるが，統合失調症では20%前後となり，両群のVWM利用率の違いが明確に示された。

結果

健常者のB・C課題の平均反応時間，VWM利用率の平均±標準偏差はそれぞれ，2,081.1±555.7 msec・3,080.5±611.1 msec・42.9±11.5%，統合失調症患者のB・C課題の平均反応時間，VWM利用率はそれぞれ，4,481.8±1,726.7 msec・5,531.9±1,711.2 msec・24.1±8.9%であった(図5)。統合失調症患者の平均反応時間は健常被験者と比べ，B・C課題ともに有意に延長していた。統合失調症患者も健常被験者もB課題はC課題と比べ平均反応時間は1,000 msほど短縮されており，VWMによる反応時間の短縮がみられた(図5-A)。しかし，この結果だけでは統合失調症患者と健常者のVWMの差は明確ではない。前述した方法によりVWM利用率を比較した場合，統合失調症患者ではB課題のボタン押しにVWMを使用した頻度はボタン押し全体の24.1%であり，健常被験者の42.9%と比べ著明に低下していた(図5-B)。

考察

ATMTを使用したVWMの測定法を考案し，報告した。ATMTは結果変数として，B・C課題の反応時間およびB課題でのVWM利用率が得られる。B課題の平均反応時間は作業速度とVWMの両方を，C課題の平均反応時間は作業速度を，B課題でのVWM利用率は課題施行中のWM容量を反映している。ATMTのB課題はWMを全く利用しなくても遂行が可能であり，この点は情報の一時保持を確実に行わなければ正解できない従来のWM課題とは若干性質が異なる。B課題ではWMを使用しなくてもよいが，使用したほうが課題の遂行速度を上げることが可能である。つまり，ATMTで測定しているWMは，日常の作業で無意識に使っている情報の保持容量の測定となり，より自然な状況での情報処理容量を評価していると考えられる。

統合失調症患者では健常者と比べ，注意視野内外を含めボタン押しの平均反応時間(B・C課題)は有意に延長していた。課題BでのWM利用率は健常者では40%前後であるが，統合失調症では20%前後と著明に低下していた。一方，課題B，Cの平均反応時間の単純な比較では統合失調症のWM障害は明確にできず，我々の考案したWM評価の有用性が示唆された。統合失調症患者では健常者と比べ有意に反応時間が延長し，WM容量も著明に低下していた。統合失調症の基本的な認知・行動特性として課題の種類に関係なく作業速度が低下していること，情報処理容量が限られていることはよく知られており[1]，本研究の結果もこの見解と一致している。今後，対象数を増やして今回の知見をさらに確立していくとともに，知能，精神症状，社会生活技能などの患者の状態を反映する指標とATMTの成績にどのような関連が存在するのかを明らかにし，患者の状態評価の簡易な検査法としてのATMTの有用性を検討していく必要があると思われた。

ATMTの利点として理解力の乏しい重症の患者にも施行可能であると考えられる。今後は統合失調症だけでなく痴呆や発達障害，気分障害など他の精神疾患へも対象を広げて作業速度とVWMの定量評価を行い，患者の状態を反映する各指標との関連を調査し，ATMTの臨床上の有用性を検討していく必要がある。またATMTは長時間の連続施行が可能であり，健常者においてもストレス，疲労に伴う作業能力低下の評価などに応用可能と考えられる。

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文献

1) 昼田源四郎：分裂病者の行動特性．金剛出版，1989
2) 梶本修身，山下仰，高橋丈生，他：Trail-Making-Testを改良した「ATMT脳年齢推測・痴呆判別ソフト」の臨床的有用性．新薬と臨床 49：448-459，2000
3) 北村俊則，杠岳文，森田昌宏，他：オックスフォード大学版BPRSの下位尺度の作成とその妥当性．精神科診断学 1：101-107，1990
4) LeZak MD：Neuropsychological Assessment，3 rd ed. Oxford University Press, London, 1995

Reduction of serotonin transporters of patients with chronic fatigue syndrome

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To assess the involvement of serotonin in the symptoms of chronic fatigue syndrome, we investigated the serotonergic neurotransmitter system of chronic fatigue syndrome patients by the positron emission tomography (PET). Here we show that the density of serotonin transporters (5-HTTs) in the brain, as determined by using a radiotracer, [^{11}C](+)McN5652, was significantly reduced in the rostral subdivision of the anterior cingulate as compared with that in normal volunteers. This subdivision is different from that in the dorsal anterior cingulate in which binding potential values of individual patient showed a weak negative correlation with self-reported pain score of the patients. Therefore, an alteration of serotonergic system in the rostral anterior cingulate plays a key role in pathophysiology of chronic fatigue syndrome. *NeuroReport* 15:2571–2574 © 2004 Lippincott Williams & Wilkins.

Key words: Anterior cingulate; Chronic fatigue syndrome; Fatigue; Positron emission tomography (PET); Serotonin transporter

INTRODUCTION

Chronic fatigue syndrome is a disorder characterized by profound disabling fatigue that persists for at least 6 months without relief, being unsatisfied by ordinary rest [1]. Musculoskeletal pain or nonpsychotic depression often accompanies chronic fatigue syndrome. Although no effective somatic treatment for chronic fatigue syndrome has been established yet, selective serotonin reuptake inhibitors (SSRIs) have often been prescribed and have been reported to be effective in non-depressed patients as well as or better than in depressed patients though this effect was not confirmed when one of SSRIs, fluoxetine, was tried [2]. Our recent treatment study with fluvoxamine demonstrated the improvement in 36% of patients [3]. Serotonergic abnormalities have also been reported from endocrinological studies that showed a high sensitivity of serotonin (5-HT) neurotransmission in chronic fatigue syndrome patients [4,5]. In addition, a study on polymorphism of the promoter region of the 5-HT transporter (5-HTT) gene revealed a difference in genotype distribution between chronic fatigue syndrome patients and controls [6]. The role of the serotonergic system in chronic pain has been highlighted [7], especially, in the patients with fibromyalgia, a disease closely related to chronic fatigue syndrome in which pain is more centered than in chronic fatigue syndrome.

A PET study with [^{18}F]-FDG PET reported that chronic fatigue syndrome patients showed a significant hypometabolism in right mediofrontal cortex and brain stem in comparison with the healthy controls [8]. Siessmeier *et al.* [9] also demonstrated by PET that 12 of 26 patients examined showed hypometabolism bilaterally in the cingulate gyrus and the adjacent mesial cortical areas. Our previous PET studies on patients showed that hypoperfusion and decrease in uptake of the acetyl moiety of acetyl-L-carnitine as measured with [2-^{11}C]acetyl-L-carnitine (an indicator of glutamate biosynthesis) occurred in several regions of the brains of the patient group, namely, in the prefrontal (Brodmann's area 9/46d) and temporal (Brodmann's area 21 and 41) cortices, anterior cingulate (Brodmann's area 24 and 33), and cerebellum [10].

These lines of evidence led us to investigate the 5-HT neurotransmission in the brain of chronic fatigue syndrome patients. Here, we measured the density of 5-HTTs by using PET with [^{11}C](+)McN5652, which binds specifically to the 5-HTT molecule and is widely used to study 5-HTTs in the brains of Ecstasy abusers [11] and patients with obsessive-compulsive disorder [12].

MATERIALS AND METHODS

Subjects: Ten patients with chronic fatigue syndrome (six women and four men, 35.7±8.0 years old) determined by the clinical diagnostic criteria [1] and 10 age-matched healthy controls (five women and five men, 36.9±10.1 years old) participated in this study. Patients with a major depressive disorder determined by diagnostic and statistical manual (DSM-IV) of mental disorders and taking drugs affecting 5-HT neurons within 1 month before the start of the study were excluded. Eight of the patients were naive for SSRIs; and the other two, who had been prescribed

paroxetine, had not been medicated within 1 month before the experimental day. The study was approved by the Ethics Committee of Hamamatsu Medical Center. All participants agreed to the present study with their written informed consent. Patients filled out a questionnaire about their extent of fatigue [expressed by the visual analogue scale], pain scales of headache, sore throat, myalgia, and arthralgia (pain scale: 0, none; 1, mild; 2, moderate; and 3, severe), attention score calculated by thinking difficulty, inability to concentration, impairment in memory, and absence of alertness (each scale: 0, none; 1, mild; 2, moderate; and 3, severe), and duration of disease. The total sum of the pain scale values and attention scores with four items was used as the pain and attention score for each group, respectively. Depression scale was assessed using the 17-item Hamilton Depression Rating Scale (HDRS-17) [13].

MRI and PET experiments: MRI acquired by a 0.3 T scanner (MRP7000AD, Hitachi, Tokyo, Japan) of each subject revealed no apparent morphological abnormalities. The specific radioactivity ranged from 46.6 to 88.2 GBq/μmol. After a bolus injection of [^{11}C](+)McN5652 (390.7±71.9 MBq), PET scan was performed with a duration of 92 min (4 × 30 s, 20 × 1 min, and 14 × 5 min), using a SHR12000 (Hamamatsu Photonics KK, Hamamatsu, Japan) scanner in 3D.

PET data analysis: We generated parametric images of the binding potential (BP) by a simplified reference tissue model based on pixel-wise kinetic modelling [14] using a time-activity curve of bilateral white matter as an input function. We normalized the images spatially within the standard Montreal Neurological Institute (MNI) brain space by using SPM99. The resultant images were smoothed using a Gaussian filter of 8.0 mm FWHM. We performed two-tailed *t*-tests between patients and controls, and conducted correlation analysis between the BP value and the clinical symptomatic scores of the patients. We gave the threshold of significance as voxels that had the peak height corrected, $p<0.05$ for the two-tailed *t*-tests. For the correlation analysis, we also searched the brain regions which shows tendency of significance by a threshold of $p<0.001$.

RESULTS

As shown in Table 1, fatigue scores, as indexed by visual analogue scale, were in a narrow range both in patients and controls (7.3±1.6 *vs* 2.7±1.0, respectively). In contrast, the pain scores for the chronic fatigue syndrome group were scattered (from 2 to 11, 5.8±3.0), and those for the controls were almost 0 or 1 (0.3±0.5). The attention score showing less attentive feature was 6.7±1.7 and 2.5±2.5 in the patients and controls, respectively. Fatigue, pain, and attention scores were significantly higher for the chronic fatigue syndrome patients than for the controls ($p<0.0001$, $p<0.0005$, and $p<0.0005$, respectively). The depression score (HDRS-17) was ranged from 5 to 22 in the patient group (11.5±5.3). Although the score was rather high in chronic fatigue syndrome patients, the main source of higher scores was derived mostly from higher scores on work and activities, and the somatic items such as somatic symptoms general, anxiety somatic, and hypochondriasis (date not shown). However, there were no significant correlation among visual analogue scale and other three clinical scores (pain, attention, and depression).

The PET results of the two-tailed *t*-test showed a significant reduction of the BP in the rostral subdivision of anterior cingulate (BA24/32) in chronic fatigue syndrome patients (Fig. 1a–c). The BP in the rostral anterior cingulate was decreased by 26.5% in the chronic fatigue syndrome patients, with its mean values for controls and patients being 0.82±0.04 and 0.61±0.08, respectively (Fig. 1d).

Correlation analysis using various clinical scores in chronic fatigue syndrome patients showed that no correlation was significant at the corrected level of $p<0.05$. If the tendency was followed by lowering the statistical threshold to uncorrected $p<0.001$, pain score showed a negative correlation with the BP in anterior cingulate (Fig. 2a,c) and other areas related to pain sensation, including cuneus/precuneus (BA18, Z=4.8), orbitofrontal cortex (BA11/47, Z=3.76), posterior cingulate (BA31, Z=3.64), and insular cortex, Z=3.32; Fig. 2a,b). The locus in the anterior cingulate was however in the dorsal subdivision (Fig. 2a,b), an apparently different region from the rostral subdivision. All the other scores and values of clinical symptoms such as depression, attention, and duration of disease showed no

Table 1. Summary of demographic data in 10 patients with chronic fatigue syndrome (CFS) and normal controls.

Group	Patient no.	Age	Sex	EP	DD	Comorbidity	Antidepressant	HDRS-17	VAS	Attention score[2]	Pain score[3]
CFS	1	45	M	18	6	CD	–	5	6.1	8	3
	2	46	M	16	5	None	+[1]	17	7.8	8	8
	3	30	M	12	3	None	–	7	9.6	7	3
	4	27	M	16	3	None	–	13	6.4	6	5
	5	46	F	16	15	usd	–	9	6.4	8	10
	6	27	F	16	8	usd	–	14	9	3	4
	7	37	F	14	0.5	None	–	9	4.8	5	2
	8	27	F	12	13	usd	+[1]	22	5.6	8	11
	9	39	F	16	11	None	–	13	7.8	8	6
	10	33	F	18	4	None	–	6	9.1	6	6
	Mean	35.7		15.4	6.9			11.5	7.3	6.7	5.8
	SD	8		2.1	4.8			5.3	1.6	1.7	3
Normal	Mean	36.9	5M	15.6					2.7	2.5	0.3
	SD	10.1	5F	2.1					1	2.5	0.5

EP, education period (years); DD, disease duration (years); HDRS-17, the 17-item hamilton depression rating scale; VAS, visual analogue scale; CD, conversion disorder; usd, undifferentiated somatoform disorder.

[1]Patient no.2 was medicated by SSRIs, fluvoxamine and paroxetine for 12 months and 15 months, respectively. Patient no. 8 was medicated by paroxetine for 13 months.

[2]Thinking difficulty, inability to concentrate, impairment in memory, and absence of alertness scales (0, none; 1, mild; 2, moderate; and 3, severe) were summed up as the attention score.

[3]Headache, sore throat, myalgia, and arthralgia scales (0, none; 1, mild; 2, moderate; and 3, severe) were summed up as the pain score.

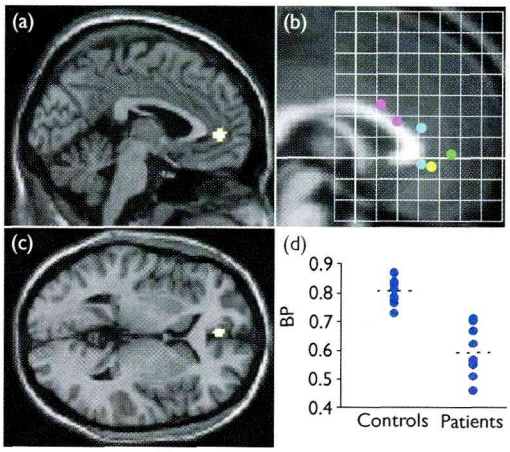

Fig. 1. The region showing a significant reduction in the BP of 5-HTT in chronic fatigue syndrome patients. (**a**) Sagittal and (**b**) horizontal views of statistical parametric maps superimposed on a normalized brain MRI. BP of the rostral subdivision of anterior cingulate (BA24/32) was significantly reduced (corrected $p=0.008$, $Z=4.95$) in chronic fatigue syndrome patients. The cluster consisted of 39 voxels extending from the MNI brain space coordinates (x −2, y 46, z 2). (**c**) The coordinates of the cluster observed in the present study (green circle) is compared with those of previous PET studies demonstrating a reduction in the rCBF shown by blue circles [10], regional standard uptake value of [2-^{11}C]acetyl-L-carnitine shown by purple circles [10], and regional glucose metabolism shown by a yellow circle [9]. (**d**) Plots of BP in the rostral anterior cingulate of controls and chronic fatigue syndrome patients.

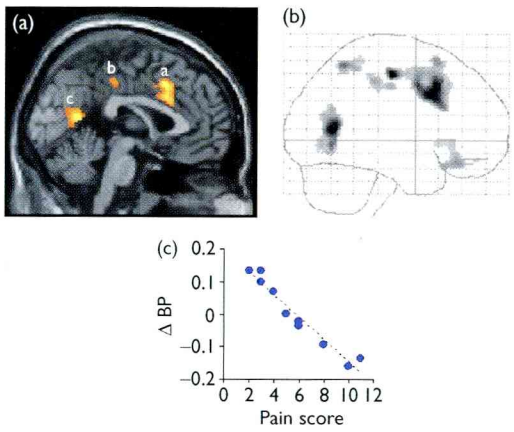

Fig. 2. The region showing a negative correlation between the BP of 5-HTT and the pain score. (**a**) Sagittal view of statistical parametric maps superimposed on a normalized brain MRI, and (**b**) sagittal view of standard SPM-glass brain. BP in the dorsal subdivision of anterior cingulate (BA24) was negatively correlated (uncorrected $p<0.0001$, $Z=4.71$) with the pain score. The cluster consisted of 1058 voxels extending from the MNI brain space coordinates (x 4, y 16, z 42). (a) Dorsal anterior cingulate (BA24/32); (b) posterior cingulate cortex (BA31); (**c**) cuneus/precuneus (BA18). (**c**) Scatter plots showing the negative correlation between the BP and the pain score in the dorsal anterior cingulate.

significant correlation at any brain regions including anterior cingulate, even under lowered statistical threshold.

DISCUSSION

Alteration of 5-HTT density occurred selectively in the rostral subdivision of anterior cingulate in patients with chronic fatigue syndrome. Previous histological examination showed dense serotonergic projections from the dorsal raphe nucleus to the anterior cingulate [15]. Lower than normal 5-HTT density was also detected by single-photon emission-computed tomography (SPECT) in the brain of patients with major depression [16] and in postmortem studies [17,18], mostly related to the suicide; but the affected regions were dominantly the prefrontal cortex and midbrain including the dorsal raphe nucleus. The reduction of 5-HTT specifically in the discrete region of anterior cingulate might be linked to the pathophysiology of non-depressed chronic fatigue syndrome patients in this study.

BP (k3/k4) of [^{11}C](+)McN5652 calculated by compartment model is considered to be related with the B_{max}/K_d to the 5-HTT molecule. Therefore, reduction of BP observed in the anterior cingulate might be associated with decrement of density of 5-HTT and/or affinity. A possible interpretation of the data is that the reduction in BP is due to the increase in 5-HT in the synaptic cleft, as shown in the case of [^{11}C]raclopride for increase in endogenous dopamine release [19]. In a study of Ecstasy abusers, McCann *et al.* [11] reported the reduction of density of 5-HTT in the nerve terminals. The other interpretation is the degeneration of the nerve terminals themselves. To solve this question, the PET study using [^{11}C]5-HTP in chronic fatigue syndrome patients is currently under progress in our laboratory.

Concerning expression of 5-HTT in diseases, even in the case of major depressive disorder, the results from the PET imaging studies and those from the biochemical studies on postmortem brain tissues from patients [20], mostly suicidal ones, are still controversial. Recently, our colleagues [6] found a difference between chronic fatigue syndrome patients and controls in the distribution of polymorphism of the 5-HTT gene promoter. Association between polymorphism of the 5-HTT gene promoter and the expression of 5-HTT protein in the brain is unclear yet [21]. It is of very importance to further study on the association between genotype and phenotype in chronic fatigue syndrome patients.

The anterior cingulate consists of functionally heterogeneous regions, and the rostral subdivision is thought to be involved in the processing of emotional information [22]. The rostral anterior cingulate, in which BP values of 5-HTT were significantly reduced in chronic fatigue syndrome patients, is distinct from the dorsal anterior cingulate associated with the cognitive information processing. Comorbidities of chronic fatigue syndrome which are closely related to emotional aspects might be associated with the loss of modulatory function of 5-HT released possibly from 5-HT nerve-terminals in the rostral subdivision. The locus in the dorsal subdivision that was not significantly but by lower threshold correlated negatively with the pain score of chronic fatigue syndrome patients is close to the locus of pain processing found in the previous PET studies [23,24]. Concerning other brain regions, although none of the brain regions reached to the statistically significant level at $p<0.05$ (corrected), most of the regions negatively correlated with the pain score at lower threshold ($p<0.001$, uncorrected; Fig. 2) were consistent with those which were suggested to be involved in several aspects of pain information processing by recent fMRI and PET experiments [24], indicating the role of 5-HT neurotransmission of these regions in pain-related features of chronic fatigue syndrome patients. Therefore, reduced 5-HTT in the rostral anterior cingulate of the chronic fatigue syndrome patients might be related to the pathogenesis of the disease, not to the non-specific symptom of pain, although we should be careful about the discrimination of

chronic fatigue syndrome patients from the patients who are suffering mostly with stronger pain, fibromyalgia.

Figure 1c shows loci of anterior cingulate observed in this study and previous PET studies on chronic fatigue syndrome. These loci associated with chronic fatigue syndrome totally converged in the anterior cingulate. Apart from the dorsal subdivision, the hypoactivity, hypometabolism, and dysfunction of 5-HT neurotransmission concomitantly occurred in the rostral subdivision. Therefore, these findings strongly suggest that an abnormality of 5-HT neurotransmission, especially the reduction in the density of presynaptic terminals of the serotonergic system in the projection area of the anterior cingulate, might be closely associated with the pathophysiology of chronic fatigue syndrome.

Although regional cerebral blood flow (rCBF) of chronic fatigue syndrome patients was not measured in the present study, the decreased BP value of 5-HTT may be partly affected by the hypoperfusion in anterior cingulate reported in the previous PET study [10]. However, decreases in rCBF were also significant in several regions such as middle occipital gyrus, putamen, insula, and so on, while a significant decrease in BP value of 5-HTT in the present study was only observed in the rostral part of anterior cingulate. Therefore, the decrease in BP value might be more likely due to the decrease in density and/or affinity of 5-HTT.

As described in the Introduction, the results of clinical treatment of chronic fatigue syndrome patients with SSRIs are still controversial. Several detrimental effects, such as nausea, headache, and nervousness often disturb and mask the beneficial effects of SSRIs at the beginning of a clinical trial. In addition, increment of risk of suicide by use of SSRIs has been issued recently as a considerable public warning, especially in teenager patients. Therefore, quantitative PET imaging analysis for measuring the brain 5-HTT density with a specific radiotracer, such as [^{11}C]McN5652 used in this study, is feasible for both judging and monitoring the medication of individual chronic fatigue syndrome patients.

CONCLUSION

The density of 5-HTTs was significantly reduced in the rostral subdivision of anterior cingulate in chronic fatigue syndrome patients. An alteration of the 5-HTergic system in the rostral anterior cingulate plays a key role in pathophysiology of the chronic fatigue syndrome.

REFERENCES

1. Fukuda K, Straus SE, Hickie I, Sharpe MC, Dobbins JG and Komaroff A. The chronic fatigue syndrome: a comprehensive approach to its definition and study. International Chronic Fatigue Syndrome Study Group. *Ann Intern Med* 1994; **121**:953–959.
2. Vercoulen JH, Swanink CM, Zitman FG, Vreden SG, Hoofs MP, Fennis JF *et al.* Randomised, double-blind, placebo-controlled study of fluoxetine in chronic fatigue syndrome. *Lancet* 1996; **347**:858–861.
3. Kuratsune H. The current treatment for patients with chronic fatigue syndrome: fluvoxamine, amantadine and herbal medicine. *J Chronic Fatigue Syndr*, in press.
4. Bakheit AM, Behan PO, Dinan TG, Gray CE and O'Keane V. Possible upregulation of hypothalamic 5-hydroxytryptamine receptors in patients with postviral fatigue syndrome. *Br Med J* 1992; **304**:1010–1012.
5. Cleare AJ, Bearn J, Allain T, McGregor A, Wessely S, Murray RM *et al.* Contrasting neuroendocrine responses in depression and chronic fatigue syndrome. *J Affect Disord* 1995; **35**:283–289.
6. Narita M, Nishigami N, Narita N, Yamaguti K, Okado N, Watanabe Y *et al.* Association between serotonin transporter gene polymorphism and chronic fatigue syndrome. *Biochem Biophys Res Commun* 2003; **311**:264–266.
7. Grothe DR, Scheckener B and Albano D. Treatment of pain syndromes with venlafaxine. *Pharmacotherapy* 2004; **24**:621–629.
8. Tirelli U, Chierichetti F, Tavio M, Simonelli C, Bianchin G, Zanco P *et al.* Brain positron emission tomography (PET) in chronic fatigue syndrome: preliminary data. *Am J Med* 1998; **105**:54S–58S.
9. Siessmeier T, Nix WA, Hardt J, Schreckenberger M, Egle UT and Bartenstein P. Observer independent analysis of cerebral glucose metabolism in patients with chronic fatigue syndrome. *J Neurol Neurosurg Psych* 2003; **74**:922–928.
10. Kuratsune H, Yamaguti K, Lindh G, Evengård B, Hagberg G, Matsumura K *et al.* Brain regions involved in fatigue sensation: reduced acetylcarnitine uptake into the brain. *Neuroimage* 2002; **17**:1256–1265.
11. McCann UD, Szabo Z, Scheffel U, Dannals RF and Ricaurte GA. Positron emission tomographic evidence of toxic effect of MDMA ("Ecstasy") on brain serotonin neurons in human beings. *Lancet* 1998; **352**:1433–1437.
12. Simpson HB, Lombardo I, Slifstein M, Huang HY, Hwang DR, Abi-Dargham A *et al.* Serotonin transporters in obsessive-compulsive disorder: a positron emission tomography study with [^{11}C]McN 5652. *Biol Psychiatry* 2003; **54**:1414–1421.
13. Williams JB. A structured interview guide for the Hamilton Depression Rating Scale. *Arch Gen Psychiatry* 1988; **45**:742–747.
14. Buck A, Gucker PM, Schönbächler RD, Arigoni M, Kneifel S, Vollenweider FX *et al.* Evaluation of serotonergic transporters using PET and [^{11}C](+)McN-5652: assessment of methods. *J Cerebr Blood Flow Metab* 2000; **20**:253–262.
15. Wilson MA and Molliver ME. The organization of serotonergic projections to cerebral cortex in primates: regional distribution of axon terminals. *Neuroscience* 1991; **44**:537–553.
16. Malison RT, Price LH, Berman R, van Dyck CH, Pelton GH, Carpenter L *et al.* Reduced brain serotonin transporter availability in major depression as measured by [^{123}I]2 beta-carbomethoxy-3 beta-(4-iodophenyl)tropane and single photon emission computed tomography. *Biol Psychiatry* 1998; **44**:1090–1098.
17. Arango V, Underwood MD, Gubbi AV and Mann JJ. Localized alterations in pre- and postsynaptic serotonin binding sites in the ventrolateral prefrontal cortex of suicide victims. *Brain Res* 1995; **7**:121–133.
18. Mann JJ, Huang YY, Underwood MD, Kassir SA, Oppenheim S, Kelly TM *et al.* A serotonin transporter gene promoter polymorphism (5-HTTLPR) and prefrontal cortical binding in major depression and suicide. *Arch Gen Psychiatry* 2000; **57**:729–738.
19. M. Imaging synaptic neurotransmission with *in vivo* binding competition techniques: a critical review. *J Cerebr Blood Flow Metab* 2000; **20**:423–51.
20. Stockmeier CA. Involvement of serotonin in depression: evidence from post-mortem and imaging studies of serotonin receptors and the serotonin transporter. *J Psych Res* 2003; **37**:357–373.
21. Collier DA, Stober G, Li T, Heils A, Catalano M, Di Bella D *et al.* A novel functional polymorphism within the promoter of the serotonin transporter gene: possible role in susceptibility to affective disorders. *Mol Psychiatry* 1996; **1**:453–460.
22. Shioe K, Ichimiya T, Suhara T, Takano A, Sudo Y, Yasuno F *et al.* No association between genotype of the promoter region of serotonin transporter gene and serotonin transporter binding in human brain measured by PET. *Synapse* 2003; **48**:184–188.
23. Bush G, Luu P and Posner MI. Cognitive and emotional influences in anterior cingulate cortex. *Trends Cogn Sci* 2000; **4**:215–222.
24. Rainville P, Duncan GH, Price DD, Carrier B and Bushnell MC. Pain affect encoded in human anterior cingulate but not somatosensory cortex. *Science* 1997; **277**:968–971.
25. Peyron R, Laurent B and Garcia-Larrea L. Functional imaging of brain responses to pain. A review and meta-analysis (2000). *Neurophysiol Clin* 2000; **30**:263–288.

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