Full title：

「The effect of cognitive remediation therapy using The Frontal/ Executive Program for autism spectrum disorder」

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Abstract

Objective- The cognitive features and treatment of autism spectrum disorder (ASD) have been the subject of much debate in recent years. Therapeutic approaches to date have focused on skills acquisition, support tailored to the characteristics of ASD, and interventions in social cognitive functioning; there have been few reports describing interventions aimed at neurocognitive dysfunction. In this study we focus on impairment of executive functioning in ASD patients and investigate improvements in executive functioning and their generalization to social functioning. Method- The intervention adopted for this study was cognitive remediation therapy using the frontal/executive program (FEP). To investigate the effectiveness of FEP, 15 subjects who consented to participate in the study were randomly assigned to an intervention group or control group. FEP was administered to the intervention group for about 6 months. Both groups were evaluated using the same scales: BACS-J, WCST and CPT for cognitive assessment, SCoRS-J, GAF and LASMI for social functioning, and GSE for self-efficacy. Results- Both groups had lower scores for cognitive functioning than normal individuals at baseline. After completion of FEP, the intervention group showed improved performance on BACS-J for overall score, digit sequencing, verbal fluency, and Tower of London tasks. Improvements were also seen on SCoRS-J and LASMI scales of

social functioning. Conclusions- This was the first study to use FEP to focus on neurocognitive dysfunction in ASD patients. FEP is effective in improving impaired executive functioning in ASD patients and may also lead to improvements in some aspects of social functioning.

Key Words

Cognitive Disorders, Autism Spectrum Disorder, Executive Function, Rehabilitation

Introduction

Autism spectrum disorder (ASD) is characterized by persistent deficits in social communication and interpersonal interactions and repeated patterns of restricted behaviors, interests, and activities. These symptoms appear in the early stages of development and lead to severe impairments later on in the social and work domains [1]. According to a survey by Kim et al., the prevalence of ASD is 2.6% and gradually increasing [2].

In addition to the basic impairments described above, ASD also includes cognitive deviations in a wide range of areas. For example, patients with Asperger's syndrome and high-functioning autism may have impaired visuospatial cognition that prioritizes awareness of the details while failing to grasp the overall picture [3]. Patients may also exhibit diminished semantic utilization in the organization of verbal memory [4], or impairments in complex executive functioning such as planning, performance, and monitoring capabilities required to effectively perform a series of actions [5]. Other impairments such as difficulty in reading facial expressions may also be present [6, 7].

Much of the treatment and support of ASD patients is related to improving basic characteristics such as communication and behavior characteristics such as social skills and social cognition [8]. Support in Japan is focused on the period until the child is

around 12 years old; children diagnosed with ASD receive little support after adolescence, which has a significant impact on their social life.

Cognitive remediation therapy (CRT) has received attention in recent years as an intervention for cognitive dysfunction. CRT is based on behavioral training and was developed to improve cognitive processes (attention, memory, executive function, social cognition, or metacognition) with the goals of durability and generalization [9]. Research on the effects of CRT has increased since the 1990s. Meta-analysis has shown that CRT produces mild improvement in cognitive performance in schizophrenia patients, and that these neurocognitive improvements lead to improved psychosocial functioning [10].

The present study focuses on disturbance of executive functioning in adult ASD patients, with the objective of investigating whether the use of the frontal/executive program (FEP) as a CRT intervention leads to improvements in the cognitive and social functioning of adult ASD patients. This study was the first attempt to use FEP in ASD patients.

Methods

Subjects

The subjects were outpatients of the psychiatric department at Asahiyama Hospital who were defined as ASD in DSM-5 based on infant developmental history carefully taken using Pervasive Developmental Disorders Autism Society Japan Rating Scale (PARS) [11]. The inclusion criteria were that the patient be no more than 60 years old and have had no less than 9 years of formal education; the exclusion criteria were dementia, drug dependence, alcohol dependence, and organic brain disease. The 15 subjects were randomly assigned to either an intervention group who underwent FEP for about 6 months, or a control group who underwent their normal supportive psychotherapy, drug treatment, and twice-weekly occupational therapy over the same period but did not undergo FEP. Of the 15 subjects, 7 were assigned to the intervention group (3 males, 4 females, mean age 36.1±8.1 years), 7 were assigned to the control group (5 males, 2 females, mean age 37.7±11.4 years) and 1 subject dropped out.

Details of intervention

The FEP used for this study was developed by Delahunty and published in Japan in a translation by Matsui et al [12]. The FEP consists of three modules: cognitive flexibility, working memory, and planning. It is designed so that the tasks become progressively more difficult as the sessions proceed. Each module is made up of tasks focusing on eye movement and perception, organization of information, fine motor

movements, and so on. The therapist encourages the subject to verbalize problem-solving methods and gives instruction on the use of effective strategies. In this way, the FEP system encourages subjects to execute tasks as correctly as possible. The FEP consists of 44 sessions in total, and each session includes training mainly using paper-and-pencil but also includes the use of building blocks (tokens) and fine hand movements. The subjects have two one-on-one sessions a week with the therapist, each lasting 1 hour.

For this study, the intervention group underwent FEP as described above. The participants were also assessed for cognitive functioning, social functioning, and self-efficacy before starting FEP and after completion of the program. The control group received their normal treatment (supportive psychotherapy, drug treatment, occupational therapy twice a week) over the same period. These participants were assessed in the same way as the intervention group before and after treatment. This study was conducted with the approval of the Ethics Committee of the Faculty of Health Sciences, Hokkaido University (13-84), and the Ethics Committee of Asahiyama Hospital (13-12), and with the written informed consent of all subjects.

Assessment

Cognitive functioning

The Brief Assessment of Cognition in Schizophrenia-Japanese version (BACS-J) [13], Wisconsin card sorting test (WCST) [14], and Continuous Performance Test (CPT) [15] were used to assess cognitive functioning. BACS-J was devised by Keefe et al. [16] and the Japanese version was created by Kaneda et al [17]. It is used to assess cognitive functioning in schizophrenia patients based on scores in six cognitive function domains and a composite score. The assessment score is determined by calculating z-scores derived by comparison with the mean of normal individuals. The WCST is a test of frontal lobe function involving abstraction and set-shifting, in which subjects must select a response card according to one of the three categories of color, shape, and number. The assessment is based on calculation of the number of categories achieved and perseveration errors. The CPT measures the ability to sustain attention by concentrating on letters randomly displayed on a computer screen and giving responses according to certain rules. Assessment is based on response time and number of errors.

Social functioning

This was assessed using the Schizophrenia Cognition Rating Scale-Japanese version (SCoRS-J) and the Life Assessment Scale for the Mentally Ill (LASMI). SCoRS-J is an assessment scale recommended by the United States MATRICS (Measurement and Treatment Research to Improve Cognition in Schizophrenia) Neurocognition

Committee as a suitable scale for functional prognosis with face validity. It was devised by Keefe et al. [18] and the Japanese version was created by Kaneda et al [19]. This scale assesses cognitive functioning related to day-to-day functioning, and consists of 20 questions in the 8 domains of memory, learning, attention, working memory, problem-solving, processing/motor speed, social cognition and language. The questions are answered by the patient, an evaluator and the patient's carer, and the overall assessment is based on the mean score of all three respondents and the global score.

Self-efficacy

The Generalized Self-Efficacy Scale (GSE scale) was used to assess self-efficacy. The GSE scale is a 23-item scale in which higher scores indicate greater self-efficacy. The lowest possible score is 23 points and the highest possible score is 115 points [20].

Data Analysis

The 14 subjects in the intervention group and control group were included in the analysis, and the dropout was excluded. A χ^2 test was applied to the basic information on the sex of the subjects, and unpaired t-test was applied to age, years of education, amount of antipsychotic medication, and IQ (WAIS-III). A t-test was also applied to each assessment item in order to investigate whether there were any intergroup differences in cognitive functioning, social functioning and self-efficacy before the intervention.

Mann-Whitney's U test was also applied to the assessment items for each function before and after the intervention in order to investigate the effectiveness of FEP. SPSSver20.0 (IBM) was used for the statistical analysis and the significance level was set at 0.05.

Results

Basic information and functioning characteristics of each group before intervention

Basic information on the groups is shown in Table 1. There were no significant intergroup differences in age, years of education, amount of antipsychotic medication, sex, or IQ.

-Insert Table 1here-

Baseline cognitive functioning, social functioning, and self-efficacy measures before intervention are shown in Table 2. There were no significant intergroup differences in the BACS-J, WCST and CPT cognitive assessments and the GSE self-efficacy scale. However, in the task performance subscale on the LASMI assessment of social functioning, the control group had significantly higher scores than the intervention group at baseline ($p<.012$).

-Insert Table 2 here-

Comparison of each function in both groups before and after intervention

A comparison of each functional assessment before and after intervention is shown in Table 3. In the BACS-J assessment of cognitive functioning, the composite scores were significantly higher in the intervention group than in the control group ($p<.018$).

The intervention group also performed significantly better on the subscales of digit sequencing ($p<.018$), verbal fluency ($p<.008$), and Tower of London task ($p<.012$). There were no significant intergroup differences in the CPT and WCST scales for frontal lobe functioning and attention.

In social functioning, the intervention group showed significant improvements in SCoRS-J in the carer's overall assessment ($p<.002$) and the evaluator's overall assessment ($p<.012$). The intervention group also showed significant improvements in LASMI on the subscales of daily activities ($p<.027$), interpersonal relations ($p<.018$) and task performance ($p<.005$). There were no significant differences in the GSE scale of self-efficacy.

-Insert Table 3 here-

Discussion

Improvement in cognitive functioning

Both groups performed more poorly at baseline than normal individuals in the BACS-J, but the intervention group had significantly better composite scores and scores on the subscales of digit sequencing (working memory), verbal fluency and Tower of London task.

According to Baddeley's definition, working memory is a system involving the temporary storage of multiple pieces of information (phonological loop and visuospatial scratchpad) and the cognitive processing activities that use this information (central executive system) [21]. The BACS-J digit sequencing task used in this study requires the storage of phonological information and also manipulation of that information by reordering. The improvements seen in this test were thought to be because the accurate verbalization of problems-solving methods, writing down of thought processes and internalization of learning strategies taught through FEP were effective for the storage and manipulation of phonological information, as was reported in previous research on schizophrenia by Wykes et al [22-24].

Verbal fluency is the ability to examine and retrieve words from long-term memory storage in accordance with the conditions, and is thought to reflect executive functioning and semantic processing. FEP includes a number of tasks that promote categorization of information, and was therefore thought to be effective in improving

verbal fluency in terms of semantic processing. As with the improvements in working memory, it is also possible that FEP's promotion of encoding through verbalization of problem-solving methods helped to reinforce phonological memory and encourage smooth retrieval.

The Tower of London task reflects planning, working memory and problem solving function. FEP essentially consists of the three modules of cognitive flexibility, working memory and planning, in which the therapist helps the patient to find effective strategies through the teaching of efficient information processing and verbalization of problem-solving methods. The working memory module also helps to enhance information storage and processing; the planning module consists of tasks that require the planning of a sequence of actions to achieve a goal. The similarity between the FEP target tasks and the Tower of London task may explain the improved performance on this task.

These results suggest that FEP is effective in improving frontal lobe functions such as working memory, verbal fluency and planning in ASD patients.

Improvements in social functioning and self-efficacy

Improved social functioning was seen on LASMI in daily activities, interpersonal relations and task performance. The improvements in daily activities and task

performance were thought to be due to FEP's promotion of goal-oriented behavior, while the improvements in interpersonal relations were attributed to confidence in interpersonal interactions resulting from the experience of repeated verbalization.

Subjects showed improvements on SCoRS-J according to the assessment of carers and evaluators. SCoRS-J has been found to correlate with BACS-J, and is used to assess social function, which is closely connected to cognitive function. It was therefore thought that the subject's improved cognitive functioning led to improved social functioning as assessed objectively by an external observer.

The intervention group did not significantly improve on the GSE scale of self-efficacy, although their scores after intervention increased by 11.29 points from baseline. This trend for improvement was attributed to the subject's recognition of improved task performance through repeated successful completion of a task, and the confidence acquired through a sense of achievement and through positive feedback.

Significance of the study

This study was the first attempt to use FEP in ASD patients. We demonstrated that FEP improves cognitive and social functioning in ASD patients, and can thus be considered as a new intervention for ASD patients with impaired frontal lobe function.

Limitations

It is difficult to draw firm conclusions about the effectiveness of FEP because of the small sample size, and further investigation in a larger sample size is therefore needed. Follow-up investigation is also necessary to determine the persistence of the effect of FEP on our subjects.

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Table 1. Key demographic and clinical characteristics of participants at entry to the study

	FEP group (n=7)	Control group (n=7)	P
	Mean (SD)	Mean (SD)	
age	36.14 (8.78)	37.71 (12.34)	0.9
Years of education	11.71 (2.36)	12.79 (1.41)	0.38
Antipsychotic medication (chlorpromazine equivalents)	82.14 (186.37)	215.00 (274.61)	0.54
Gender (%male)	42.86	71.43	0.28
IQ (WAIS-Ⅲ)	80.43 (16.39)	81.71 (14.51)	0.81

Table 2. Characteristics of neurocognitive function, social function and self-efficacy at baseline

	FEP group (n=7)		Control group (n=7)		p
	Mean	SD	Mean	SD	
BACS-J (Z-score)*					
Composite Score	-0.69	1.36	-1.4	1.43	0.62
Verbal Memory	-0.31	1.66	-0.87	1.13	0.535
Digit Sequencing	-0.69	1.36	-1.4	1.43	0.62
Token Motor Task	-0.74	0.81	-0.77	0.79	0.902
Verbal Fluency	-0.71	1.47	-1.13	0.76	0.71
Symbol Coding	-0.13	1.56	-0.82	1.51	0.456
Tower of London	-0.74	0.81	-0.77	0.79	0.805
WCST					
Categories	5.14	0.69	4.14	2.34	0.71
PEN	2.29	1.6	6.14	6.91	0.71
PEM	1.29	1.89	4.29	5.71	0.383
CPT					
Reaction time	449.16	7.072	521.9	78.93	0.073
Errors	3.71	3.04	4	1.83	0.535
GAF	42.14	5.67	42.86	9.06	0.902
SCoRS-J					
Global Ratings (Patient)	4.71	1.6	4.86	2.27	0.902
Global Ratings (Informant)	4.14	1.21	4	1.15	0.71
Global Ratings (Interviewer)	5.29	0.76	5.71	1.11	0.456
LASMI					
Daily living	1.23	0.54	1.62	0.64	0.535
Interpersonal relations	1.73	0.68	1.62	0.64	0.805
Work	1.23	0.54	1.9	0.29	0.011
Endurance & stability	3.86	0.94	3.57	1.3	0.71
Self-recognition	0.95	0.28	1.29	0.75	0.383
GSE	53.14	13.99	60.29	15.81	0.383

* Values were normalized using the data of a healthy person

BACS-J; Brief Assessment of Cognition in Schizophrenia-Japanese version

WCST; Wisconsin card sorting test

CPT; Continuous Performance Test

GAF; Global Assessment of Functioning Scale

SCoRS-J; Scizophrenia Cognition Rating Scale-Japanese version

LASMI; Life Assessment Scale for the Mentally Ill

GSE; Generalized Self-Efficacy Scale

Table 3. Change of each function before and after intervention

			FEP group (n=7)			Control group (n=7)			p
			Beaseline	Post-treatment	Difference	Beaseline	Post-treatment	Difference	
BACS-J (Z-score)*	Composite Score	Mean	-0.69	0.51	1.2	-1.4	-1.38	0.02	0.017
		SD	1.36	1.14		1.43	1.22		
	Verbal Memory	Mean	-0.31	0.8	1.11	-0.87	-0.55	0.32	0.053
		SD	1.66	1.13		1.13	1		
	Digit Sequencing	Mean	-0.69	0.51	1.2	-1.4	-1.38	0.02	0.017
		SD	1.36	1.14		1.43	1.22		
	Token Motor Task	Mean	-0.74	0.47	1.21	-0.77	-0.45	0.32	0.209
		SD	0.81	0.27		0.79	0.99		
	Verbal Fluency	Mean	-0.71	0.08	0.79	-1.13	-1.54	-0.41	0.007
		SD	1.47	1.13		0.76	0.82		
	Symbol Coding	Mean	-0.13	0.16	0.29	-0.82	-0.75	0.07	0.383
		SD	1.56	1.38		1.51	1.4		
	Tower of London	Mean	-0.74	0.47	1.21	-0.77	-0.45	0.32	0.011
		SD	0.81	0.27		0.79	0.99		
WCST	Categories	Mean	5.14	5.86	0.72	4.14	5	0.86	0.165
		SD	0.69	0.38		2.34	1.41		
	PEN	Mean	2.29	0.43	-1.86	6.14	3	-3.14	0.318
		SD	1.6	0.53		6.91	5.07		
	PEM	Mean	1.29	0.29	-1	4.29	1	-3.29	0.259
		SD	1.89	0.49		5.71	1.15		
CPT	Reaction time	Mean	449.16	408.99	-40.17	521.9	512.91	-8.99	0.053
		SD	7.072	82.06		78.93	103.54		
	Errors	Mean	3.71	3	-0.71	4	5	1	0.62
		SD	3.04	1.53		1.83	4.83		
GAF		Mean	42.14	55.43	13.29	42.86	42.86	0	0.128
		SD	5.67	13.34		9.06	7.56		
SCoRS-J	Global Ratings (Patient)	Mean	4.71	4.29	-0.42	4.86	4.43	-0.43	0.902
		SD	1.6	1.8		2.27	1.51		
	Global Ratings (Informant)	Mean	4.14	2.57	-1.57	4	6.29	2.29	0.001
		SD	1.21	1.13		1.15	1.38		

	Global Ratings (Interviewer)	Mean	5.29	3.57	-1.72	5.71	5.71	0	0.011
		SD	0.76	0.79		1.11	1.38		
LASMI	Daily living	Mean	1.23	0.74	-0.49	1.62	1.59	-0.03	0.026
		SD	0.54	0.37		0.64	0.41		
	Interpersonal relations	Mean	1.73	0.92	-0.81	1.62	1.59	-0.03	0.017
		SD	0.68	0.43		0.64	0.41		
	Work	Mean	1.23	0.74	-0.49	1.9	1.46	-0.44	0.004
		SD	0.54	0.37		0.29	0.4		
	Endurance & stability	Mean	3.86	2.61	-1.25	3.57	3.64	0.07	0.259
		SD	0.94	0.76		1.3	1.14		
	Self-recognition	Mean	0.95	0.76	-0.19	1.29	1.01	-0.28	0.318
		SD	0.28	0.66		0.75	0.39		
GSE		Mean	53.14	64.43	11.29	60.29	55.57	-4.72	0.456
		SD	13.99	17.88		15.81	16.98		