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Sustainability of Cognitive Improvement in Schizophrenic Patients with a Neuropsychological Educational Approach

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Objectives : This study aimed to investigate the effects of the Neuropsychological Educational Approach to Cognitive Remediation (NEAR) in improving cognitive function and its sustainability in patients with schizophrenia or schizoaffective disorders.

Methods : The *z*-scores of the Brief Assessment of Cognition in Schizophrenia (BACS) of patients who had experienced NEAR during psychiatric day care in the past were compared using results at the baseline, post-NEAR, and a follow-up evaluation. To investigate changes in cognitive function over time, a correlation analysis was conducted between the number of days from post-NEAR to follow-up and the degree of change in *z*-scores. Living conditions were compared between the group with maintained *z*-scores and the group with declined *z*-scores.

Results : 34 patients (22 men) participated. Repeated-measures analysis of variance showed that participants had significantly higher *z*-scores at the post-NEAR stage than at the baseline ($p<.01$). The follow-up evaluation showed a slow decline in *z*-scores. Participants in the group that had declined *z*-scores tended to be younger and had a longer follow-up period. Of them, 52.94 % were admitted to a psychiatric hospital during the follow-up period.

Conclusion : The increase in *z*-scores post-NEAR suggests that NEAR is effective in improving cognitive function. Decline in cognitive function during the follow-up period was slight and gradual over subsequent years. In the case of participants whose *z*-scores had decreased, it is likely that unstable disease conditions had affected the decline in their cognitive function because over half of them were hospitalised during the follow-up period.

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Key words : schizophrenia, cognitive rehabilitation, Neuropsychological Educational Approach to Cognitive Remediation (NEAR)

I Introduction

In recent years, cognitive impairment has been acknowledged as the core symptom of schizophrenia[1)2)]. In a study of patients with first-episode schizophrenia, 59 % showed moderate to severe levels of cognitive impairment on the standardized neurocognitive battery (MATRICS Consensus Cognitive Battery ; MCCB) (1.5 standard deviations below the performance of healthy individuals), and only 17 % were in the non-impaired range[3)]. Therefore, most schizophrenic patients demonstrate clinically significant impairment of cognition overall at the onset, with a decline in memory function being especially conspicuous[4)]. Reports have shown that antipsychotic drugs have only limited effects against cognitive impairment and that atypical antipsychotic

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drugs do not improve cognitive impairment[5]. Furthermore, their improvement effects are no different from those of typical formulations[6]. However, there is some evidence that antipsychotics may partially improve cognitive function in schizophrenia, and the effects of antipsychotics on cognitive function are not entirely clear[7]. Researchers have also noted that the social outcomes of schizophrenia (for example, employment, school attendance, participation in community activities, etc.) are more strongly related to cognitive impairment than positive symptoms such as hallucinations and delusions. Additionally, the severity of cognitive impairment is a predictive factor for long-term prognosis[8][9]. This improves cognitive function, a vital goal in the rehabilitation of patients with schizophrenia.

According to the Measurement and Treatment Research to Improve Cognition in Schizophrenia Project, the significant cognitive impairments of patients with schizophrenia are within the following seven areas—working memory, attention/vigilance, verbal learning and memory, visual learning and memory, reasoning, and problem-solving speed of processing, and social cognition[10]. Of these, the first six are collectively called neurocognition. This is different from social cognition, which is related to understanding other people's intentions and feelings, such as theory-of-mind and attribution bias[11].

The Neuropsychological Educational Approach to Cognitive Remediation (NEAR) is a neurocognition training program. NEAR has educational psychology and ethology as its basic theories, and cognitive correction therapy normally implements it in the form of 6-month-long group counseling sessions[12][13]. The program includes computer and language sessions that last 60 minutes each. In the computer sessions held twice a week, participants tackle tasks that stimulate cognitive function. In the once-a-week language sessions, they learn about the relationship between cognitive function and daily living.

Several studies on the effects of NEAR have been published. Medalia et al.[13] conducted NEAR with 12 individuals with mental illness referred from a housing support program for homeless people. They reported that the participants' speed of processing, reaction time, and memory improved significantly. Choi and Medalia[14] conducted NEAR with 48 outpatients with a mood disorder and reported that their processing speed and attention improved significantly. Hodge et al.[15] performed a multicenter RCT targeting 40 patients with schizophrenia and found that in the NEAR group, attention, speed of processing, executive function, verbal memory, and visual memory improved significantly, and the effects remained even after four months. In a Japanese study, Ikezawa et al.[16] conducted NEAR with 51 patients diagnosed with either schizophrenia or schizoaffective disorder and reported that compared to the control group, those in the NEAR group had a more significant improvement in their overall cognitive function, verbal memory, working memory, verbal fluency, attention, and processing speed. A meta-analysis found that the size of cognitive remediation effects against schizophrenia was about 0.45, and the program had no impact on mental symptoms[17].

Although studies show that NEAR can improve cognitive function, it is not evident how long this improvement lasts. Several follow-ups have shown that cognitive improvement persists after cognitive remediation therapy, but follow-up periods are usually within 6 months to 1 year[18)-22]. For further long-term effects, a two-year follow-up study has shown that cognitive rehabilitation training may reduce recurrence rates, improve employment rates, and improve social functioning in schizophrenia[23]. Furthermore, it has been pointed out that the combined use of cognitive remediation therapy and a standard rehabilitation program may sustain the improvement of cognitive function for 5 years. Then the continuation of the standard rehabilitation program may improve the quality of life[24]. However, NEAR was not used in these follow-up studies[18)-24]. Therefore, the long-term effects of NEAR on cognitive improvement remain unclear.

Once the duration of sustained cognitive improvement through NEAR is known and the factors that influence cognitive decline, strategies for maintaining cognitive function can be formulated, leading to

further rehabilitation for patients diagnosed with schizophrenia and/or schizoaffective disorder. We specifically investigate two hypotheses—1) Cognitive function decreases as the duration of the post-NEAR period increases ; 2) Cognitive function is maintained by those who find employment and those who are satisfied with their lives. This study aimed to investigate the sustainability of neurocognitive function after NEAR in patients with schizophrenia or schizoaffective disorder and to explore the factors associated with cognitive decline.

Ⅱ Methods

A Participants

Participants were recruited from current and previous patients who have undergone NEAR in the Kyoto Prefectural Rakunan Hospital Day Care. The inclusion criteria were—(1) at least six months elapsed since the completion of NEAR ; (2) aged between 14–60 years, (3) diagnosed with schizophrenia or schizoaffective disorder according to the diagnostic criteria of DSM-5[25] and (4) agreed to participate in our follow-up survey. Moreover, patients diagnosed with intellectual disability, substance abuse and dependence, dementia, epilepsy, head injury, and complications of cerebrovascular diseases, as well as those judged unfit by the psychiatrists or occupational therapists in charge were excluded. We explained the study's objectives to the participants, both orally and in writing, and obtained their consent. This study was conducted after receiving the approval of Shinshu University's Medical Ethics Committee (Approval No. : 4443) and the Ethical Review Board of Kyoto Prefectural Rakunan Hospital (Approval No. : Gen-4).

B Procedures and study design

This was a single-arm longitudinal study. Baseline data were collected between March 2010 and January 2019, post-evaluation data were collected between September 2010 and August 2019, and the follow-up evaluation was conducted between October 2019 and March 2020. Before implementing NEAR, the participants' cognitive function tests were treated as the baseline evaluation. Those conducted after completing NEAR were designated as the post-evaluation, and tests performed during follow-up surveys were designated as the follow-up evaluation. All evaluations were conducted for individual participants between 15 : 00–16 : 00. To investigate the secular changes in cognitive function, we established the period from the post-evaluation after completion of NEAR to the follow-up evaluation as the follow-up period. A correlation analysis was conducted using the scores of cognitive function tests that had changed during this period. The degree of change in the composite score of cognitive function tests was divided into half at the median-the participants were divided into a cognitive function-maintained group and a cognitive function-declined group. The scores of the baseline information and follow-up evaluation scales were then compared.

C Measurements

The primary outcome was the Brief Assessment of Cognition in Schizophrenia Scale or BACS[26], which includes six subscales-verbal memory, working memory, motor speed, verbal fluency, attention, and executive function. They were evaluated according to age group-specific standardized scores that set the average score of healthy adults as zero. The higher the *z*-score, the higher was the level of cognitive function. The composite score was the average of the *z*-scores of the six domains. The data of the baseline and post-evaluations were obtained from the day care facilities' medical records.

The secondary outcomes were psychosocial function, subjective well-being, self-efficacy, and living conditions during the follow-up period. The psychosocial function was measured using the Global Assessment of Functioning (GAF) (APA, 2000) (range : 0–100). Subjective well-being was measured using the Subjective Well-being under Neuroleptic drug treatment Short form (SWNS)[27], which involves answering 20 questions on a six-point scale. The higher the score, the higher is a person's subjective sense of well-being (range : 20–120). Finally, self-efficacy was measured using the Self-Efficacy for Community Life Scale (SECL)[28]. SECL requires a patient with a mental disability to answer, using an 11-point scale, how

much confidence they have in the 18 actions and behaviors needed to perform while living in a regional community. The higher the score, the higher is the person's sense of self-efficacy (range : 0-180). In addition to basic information such as age and sex, an occupational therapist interviewed the participants to understand their living conditions better. Data collected for the follow-up period included the presence or absence of cohabitation, main places of activities (for example, home, office, welfare center, etc.), presence or absence of employment and hospital stays, the use of medical care services, medication compliance, satisfaction with life and living, and living expenses.

D Statistical analysis

We first confirmed the normality of data to compare BACS *z*-scores at the baseline, post-, and follow-up evaluations. We then used repeated-measures analysis of variance (ANOVA) and multiple comparisons (Bonferroni). Next, Pearson's correlation coefficient was used to conduct a correlation analysis between the follow-up period and the degree of change in BACS *z*-scores. Additionally, the participants were divided into two groups based on BACS *z*-scores—the cognitive function-maintained and cognitive function-declined groups. Either the *t*-test or the χ^2-test was used to compare these groups. Finally, we employed the Bell Curve for Excel (version 3.21) to perform statistical analysis, with the two-sided level of significance set at 5 % or below.

Ⅲ Results

A Participant demographic information

In all, 90 patients had previously undergone NEAR at a psychiatric day care center. After assessing the eligibility of these individuals, we excluded 56 survey participants. These included 29 patients who had been diagnosed with diseases other than schizophrenia or schizoaffective disorder, six who had declined to participate, and 21 for other reasons (for example, changed physicians, duration was less than six months after completion of NEAR, difficulty taking tests, etc.). Ultimately, 34 individuals (22 men and 12 women ; 30 with schizophrenia and 4 with schizoaffective disorder) participated in the follow-up evaluations **(Fig. 1)**.

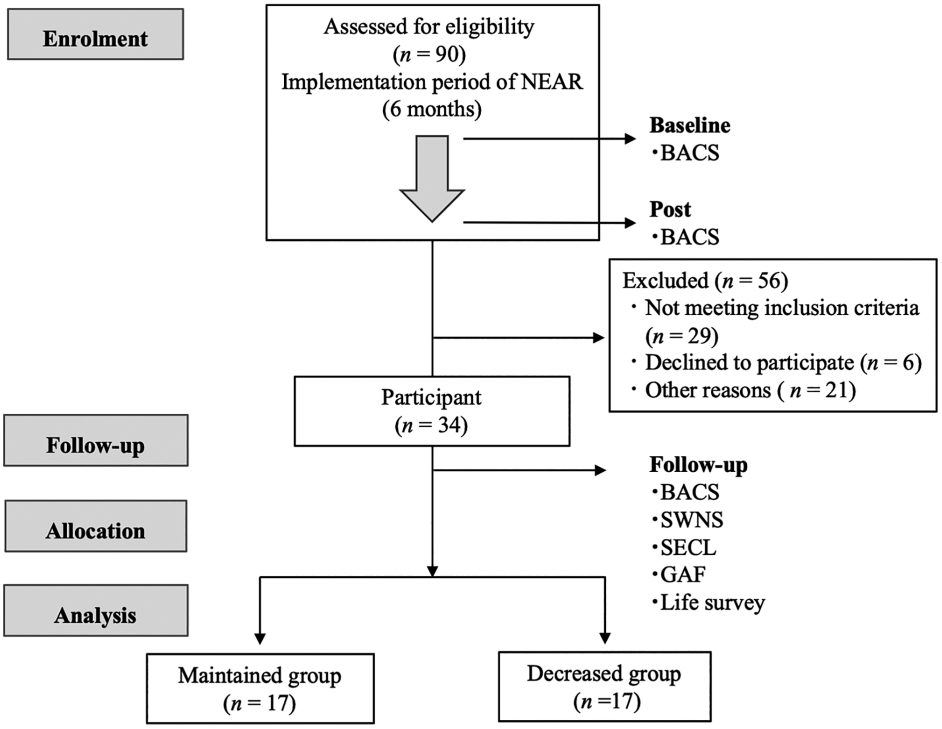

Fig. 1 Flowchart of research participants
Data collection period : Baseline (March 2010-January 2019), (September 2010-August 2019), Follow-up (October 2019-March 2020). Follow-up period : 1639.29 ± 990.18 days

Table 1 shows the basic information of the 34 participants that had been collected at the follow-up evaluation. Additionally, during the six months when NEAR was implemented, some participants had used other day care programs in which they engaged in sports, psychology education, employment preparation, and group or individual activities. There was no significant difference in daily antipsychotic use between Baseline and Follow-up.

B Changes in BACS *z*-score

At baseline, all subscales and composite scores showed mild to moderate cognitive impairments **(Table 2)**. The results of repeated-measures ANOVA showed a significant difference in all subscales (p <.001); the variance ratio of the total scores of BACS (F) was 84.14, and the effect size (η^2) was .20. A large

Table 1 Participants' demographic characteristics (N=34)

Variable	Frequency/ Mean (*SD*)
Age (years), *mean (SD)*	42.65 (8.57)
Sex (Male / Female)	22 / 12
Diagnosis (F20 / F25)	30 / 4
Disease period (years), *mean (SD)*	18.68 (9.07)
Number of hospital stays (times), *mean (SD)*	3.68 (3.41)
Participation rate in NEAR sessions (%), *mean (SD)*	95.9 (0.03)
Antipsychotic (mg/day)[a], *mean (SD)*	
・Baseline	947.44 (716.91)
・Follow-up	857.68 (573.28)
Follow-up period (days)	1639.29 (990.18)
Living conditions during the follow-up period	
・Cohabitant (with / without)	23 / 11
・Main places of activity (Home / Other)	5 / 29
・Employment (Yes / No)	24 / 10
・Hospital stays (Yes / No)	9 / 25
・Outpatient visit (Yes / No)	34 / 0
・Use of day care (Yes / No)	13 / 21
・Use of home-visit nursing (Yes / No)	11 / 23
・Use of home help service (Yes / No)	3 / 31
・Life satisfaction *mean (SD)*	3.21 (1.25)

[a] Chlorpromazine equivalent dose

Table 2 Comparison of BACS *z*-score at baseline, post-NEAR and at follow-up

Subscales	Baseline *Mean (SD)*	Post *Mean (SD)*	Follow-up *Mean (SD)*	F	p	η^2
Verbal memory	−1.21 (1.18)	−0.47 (1.16)	−0.70 (1.33)	15.64	<.001	.07
Working memory	−0.74 (1.11)	0.09 (1.24)	−0.46 (1.32)	21.33	<.001	.08
Motor speed	−1.33 (1.15)	−0.31 (1.22)	−0.79 (1.21)	19.61	<.001	.14
Verbal fluency	−0.25 (0.95)	0.39 (1.00)	0.45 (1.16)	22.07	<.001	.10
Attention	−1.37 (0.79)	−0.75 (0.89)	−1.20 (0.79)	24.58	<.001	.11
Executive function	−0.48 (1.32)	0.64 (0.76)	0.47 (0.78)	24.34	<.001	.28
Composite score	−0.90 (0.73)	−0.07 (0.68)	−0.37 (0.75)	84.14	<.001	.20

N=34

Repeated-measures ANOVA

Estimated effect size (η^2): .01 (small), .06 (medium), .14 (large)

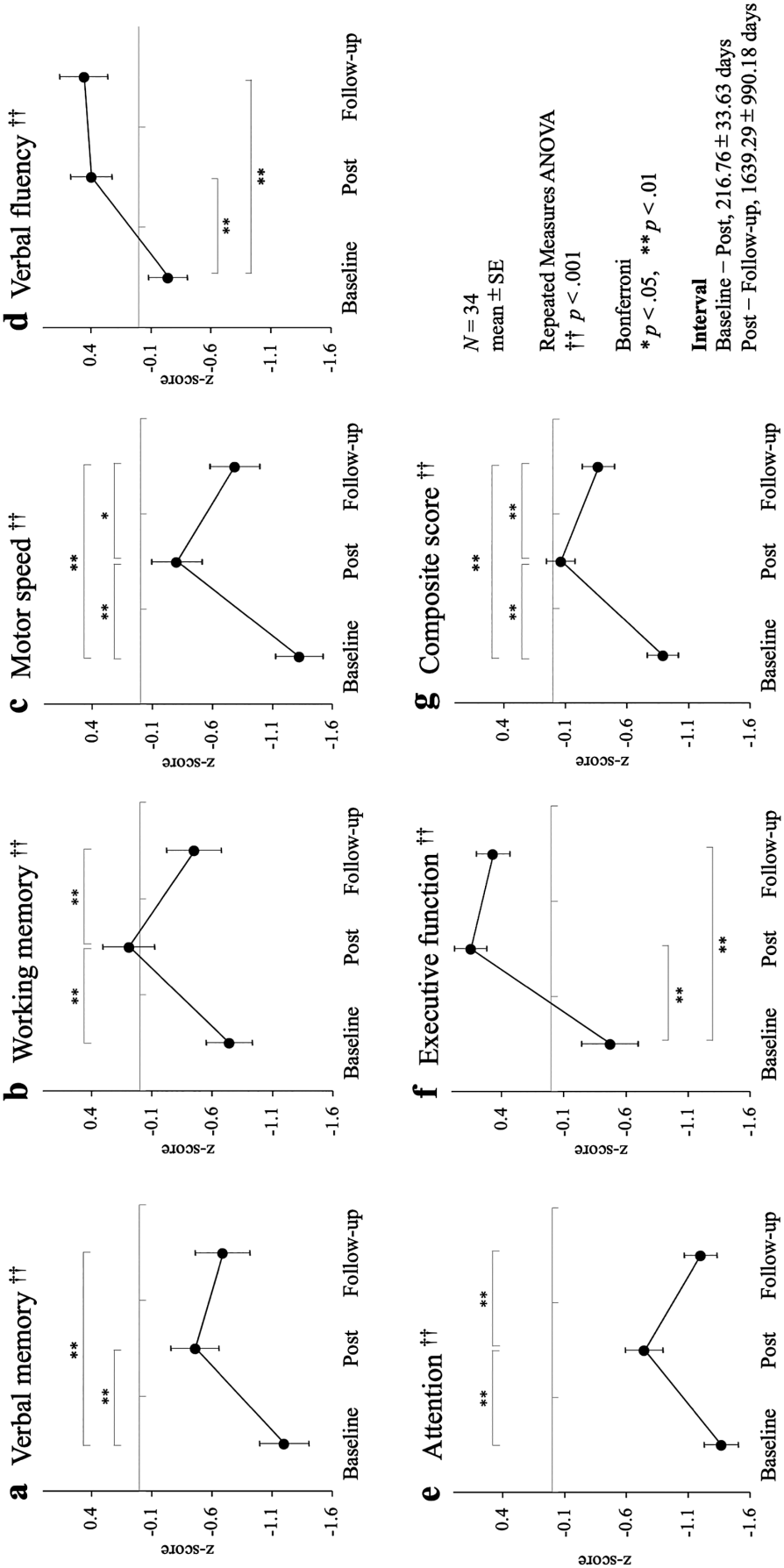

Fig. 2 Changes in BACS z-score at baseline, post-NEAR and at follow-up

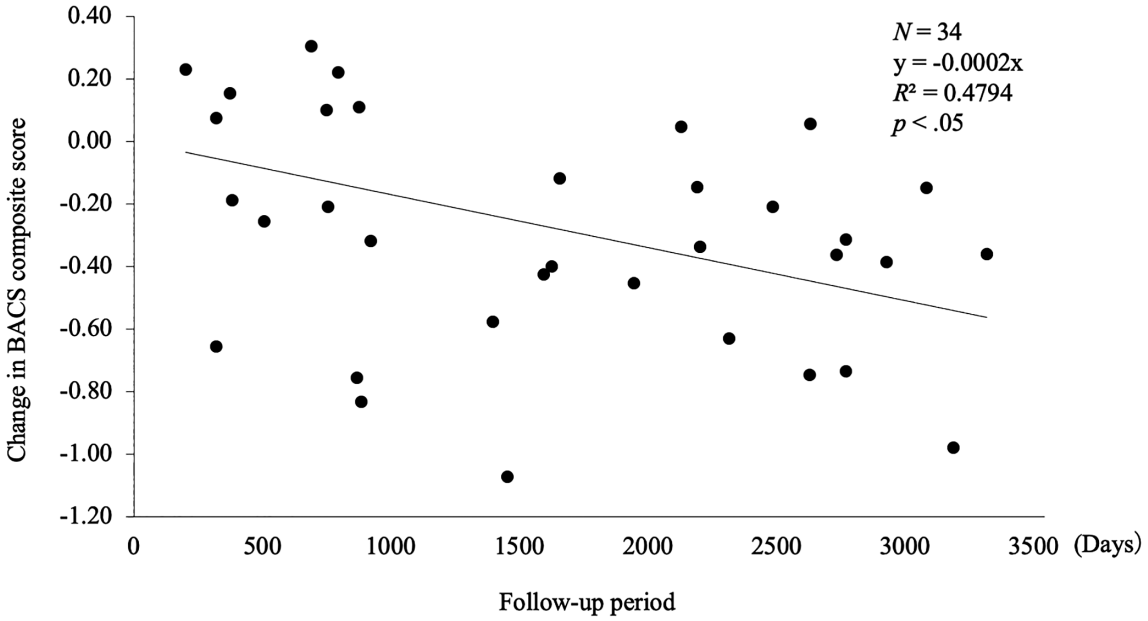

Fig. 3 Correlation between follow-up period and cognitive function

increase in *z*-scores was seen in multiple comparisons between the baseline and post-NEAR periods; a significant difference was seen in all subscales (p <.01). Further, an effect size of r = .845 was seen in terms of increases in composite scores. During the follow-up period, *z*-scores declined in all subscales except verbal fluency with significant differences seen in working memory (p<.01), motor speed (p <.05), attention (p<.01), and composite score (p<.01). **Fig. 2** shows the results of multiple comparisons (Bonferroni).

The duration of the follow-up period, BACS composite scores (differences), and Pearson's correlation coefficients were calculated. The regression equation $y = -0.0002x$, $R^2 = 0.4794$ (p<.05) was obtained from a linear approximation with a fixed zero intercept, which revealed that the longer the period after the completion of NEAR, the lower was the BACS composite score **(Fig. 3)**.

C Comparison between the cognitive function-maintained and the cognitive function-declined groups

Table 3 compares the basic information between the cognitive function-maintained and the cognitive function-declined groups. Notably, age was significantly higher in the cognitive function-maintained group (p = .03), and the cumulative number of hospital stays was considerably higher in the cognitive function-declined group (p = .00). No other significant differences were observed between the two groups.

No differences were seen in GAF, SECL, or SWNS scores between the two groups **(Table 4)**. However, the BACS scores tended to be higher in the cognitive function-maintained group, with a significant difference in the composite scores (p<.05).

Ⅳ Discussion

As indicated by the findings of the evaluations at baseline, the participants in this study were patients with schizophrenia or schizoaffective disorder and mild to moderate cognitive impairment. As a result of NEAR, which they had undergone for six months at a psychiatric day care center, their *z*-scores were found to have increased in all the BACS subscales. Namely verbal memory, working memory, motor speed, verbal fluency, attention, and executive function. Their composite scores had increased to the standard score (0) post-evaluation. As with previous studies[13)-16)], this increase in scores appeared to have been caused due to NEAR's cognitive function improvement effects. However, in the follow-up evaluation, cognitive function declined in all areas except the verbal fluency category in BACS. The average follow-up period was long — 1,639.29 (SD = 990.18)

Table 3 Demographic characteristics of the cognitive function-maintained and the cognitive function-declined groups

Variable	Maintained group ($n=17$)	Declined group ($n=17$)	p
Age (years), *mean (SD)*	45.24 (6.70)	40.06 (9.61)	.03*
Sex (Male / Female)	12 / 5	10 / 7	.47
Participation rate in NEAR sessions (%), *mean (SD)*	96.2 (0.020)	95.6 (0.034)	.56
Antipsychotic drugs dosage (mg/day)[a], *mean (SD)*	876.47 (685.31)	838.88 (455.46)	.85
Disease period (years), *mean (SD)*	19.71 (9.77)	17.65 (8.49)	.51
Number of hospital stays (times), *mean (SD)*	3.94 (3.92)	3.41 (2.90)	.65
Follow-up period (days)	1330.64 (1000.23)	1947.94 (905.15)	.06
Living conditions during the follow-up period			
・Cohabitant (with / without)	11 / 6	12 / 5	.71
・Main places of activity (Home / Other)	3 / 14	2 / 15	.63
・Employment (Yes / No)	11 / 6	13 / 4	.45
・Hospital stays (Yes / No)	0 / 17	9 / 8	.00**
・Outpatient visit (Yes / No)	17 / 0	17 / 0	—
・Use of day care (Yes / No)	7 / 10	6 / 11	.72
・Use of home-visit nursing (Yes / No)	4 / 13	7 / 10	.27
・Use of home help service (Yes / No)	2 / 15	1 / 16	.55
・Medication adherence (Yes / No)	16 / 1	14 / 3	.29
・Life satisfaction, *mean (SD)*	3.29 (1.40)	3.12 (1.24)	.68
・Living expenses			
Family income, *n*	7	4	.66
Own income, *n*	4	5	
Disability pension, *n*	4	4	
Livelihood protection expenses, *n*	2	4	

t-test, *$p<.05$
Chi-squared test, **$p<.01$
[a] Chlorpromazine equivalent dose

days or approximately 4 years and 6 months. Variations were seen within the range of 6 months to 9 years. However, the change in BACS composite scores during the follow-up period was only 0.3 on average. The regression equation of a linear approximation with a fixed zero intercept was $y=-0.0002x$, confirming the gradual decline in cognitive function over time after the completion of NEAR. To the best of our knowledge, this is the first study to investigate the long-term sustainability of cognitive function after the implementation of NEAR.

In a comparison between the cognitive function-maintained and the cognitive function-declined groups (created based on the change in the BACS composite score during the follow-up period), those in the cognitive function-declined group tended to be significantly younger ($p=.03$) and had a slightly more extended follow-up period ($p=.06$), with 9 out of 17 participants (53 %) having experienced either hospitalization or re-hospitalization during the same period. No differences were observed between the two groups in their scores related to living conditions such as main places of activity, employment status, use of home-visit nursing and home help services, dosage of antipsychotic drugs, and medication compliance, and scales such as psychosocial function,

Table 4 Comparison between cognitive function-maintained group and cognitive function-declined group

Scales and subscales	Total ($n=34$)		Maintained group ($n=17$)		Declined group ($n=17$)		p
	Mean	(SD)	Mean	(SD)	Mean	(SD)	
GAF	61.5	(11.03)	62.65	(11.16)	60.35	(11.11)	.55
BACS							
Verbal memory	−0.70	(1.33)	−0.37	(1.25)	−1.02	(1.35)	.15
Working memory	−0.46	(1.32)	−0.16	(1.36)	−0.75	(1.25)	.19
Motor speed	−0.79	(1.21)	−0.43	(1.05)	−1.15	(1.28)	.08
Verbal fluency	0.45	(1.16)	0.81	(1.23)	0.10	(1.00)	.07
Attention	−1.20	(0.79)	−0.98	(0.70)	−1.43	(0.82)	.08
Executive function	0.47	(0.78)	0.64	(0.82)	0.29	(0.73)	.20
Composite score	−0.37	(0.75)	−0.08	(0.66)	−0.66	(0.75)	.02*
SECL							
Daily life	63.47	(21.77)	65.53	(14.41)	61.41	(27.58)	.59
Treatment behaviour	73.53	(22.09)	75.15	(18.08)	71.91	(25.96)	.67
Symptom coping	62.21	(24.35)	65.59	(19.42)	58.82	(28.66)	.42
Social life	66.19	(26.43)	69.22	(18.88)	63.16	(32.63)	.51
Interpersonal relations	50.15	(28.46)	47.35	(27.05)	52.94	(30.37)	.57
Total score	115.91	(38.53)	119.29	(27.11)	112.53	(47.99)	.61
SWNS							
Mental function	14.24	(3.92)	14.12	(3.06)	14.35	(4.73)	.86
Self-control	15.18	(4.39)	14.82	(4.28)	15.53	(4.60)	.64
Emotional regulation	15.18	(4.20)	15.41	(3.14)	14.94	(5.13)	.75
Physical function	15.35	(4.54)	15.12	(4.70)	15.59	(4.50)	.77
Social integration	14.41	(3.87)	13.88	(3.86)	14.94)	(3.93)	.43
Total score	74.35	(18.67)	73.35	(16.65)	75.35	(5.08)	.76

t-test, *$p<.05$

GAF, Global Assessment of Functioning ; BACS, Brief Assessment of Cognition in Schizophrenia ; SECL, Self-Efficacy for Community Life Scale ; SWANS, Subjective Well-being under Neuroleptic drug treatment Short form. BACS shows the result of follow-up evaluation.

subjective well-being, and sense of self-efficacy. Thus, the results did not support our hypothesized relationships between cognitive function and employment or life satisfaction. The decrease in cognitive function seen in the cognitive function-declined group may have been related to changes in the participants' disease condition as shown by age, length of the follow-up period, and high hospitalization rate. A meta-analysis investigating the non-specific effects in the improvement of cognitive function in schizophrenia[29] showed that the improvement was negatively correlated with age, suggesting that people in the younger age groups might have reacted more sensitively to cognitive interventions. The cognitive decline group included more individuals from younger age groups who may have responded sensitively to cognitive intervention by NEAR and the removal of cognitive intervention. Further, given that over half of the participants in the cognitive function-declined group had experienced hospital stays during the follow-up period, it is likely that the instability of their disease and behavioral restrictions during hospitalization promoted a decline in cognitive function.

Limitations

This study has several limitations. First, there was a selection bias in recruiting participants. The decision to undergo NEAR at a day care center depended on the patients' desire to participate and their availability in real life, which were not controlled for. Moreover, patients who participated in the follow-up survey mainly were those who had continued to undergo outpatient treatment. Further, they did not include those who discontinued their treatment. Second, it could not be asserted that the improvement of cognitive function seen in the post-evaluation was the sole effect of NEAR. Multiple rehabilitation programs are sometimes used simultaneously at day care centers ; there is a possibility that participants' cognitive function had improved due to program(s) other than NEAR. Third, there was a considerable variation in the participants' follow-up period, and the patients' course during the follow-up period was not monitored in detail. For example, items on starting work, entering school, taking other training programs, and the frequency of actions and behaviors when playing ordinary social roles might also support the maintenance of the participants' cognitive function. This study could not thoroughly investigate the underlying factors related to the maintenance and improvement of cognitive functions. Therefore, the "relationship between employment and/or life satisfaction and maintenance of cognitive function" that we hypothesized remains unclear and needs further investigation. Fourth, psychiatric symptoms were not included as a secondary endpoint. More than half of the cognitive function-declined group were hospitalized during the follow-up period and may have had worsening psychiatric symptoms. Deterioration of psychiatric symptoms can affect cognitive function, so psychiatric symptoms had to be considered to assess the sustainability of cognitive improvement. Finally, due to the small sample size, the generalization of the results was limited. In future studies, it will be necessary to pay full attention to these limitations, carry out RCTs and prospective cohort surveys using a control group, ensure a sufficient sample size, and identify factors related to the maintenance of cognitive function.

V Conclusion

The findings suggested that there was a slight decline in cognitive function after NEAR. However, the follow-up period was as long as 1,639.29 (SD = 990.18) days, and it was not possible to identify the factors that contribute to the maintenance of cognitive function. Compared to the group whose cognitive function had been maintained, participants in the group that showed a decline in cognitive function during the follow-up period tended to be significantly younger. Further, they had a slightly more extended follow-up period. Moreover, 53 % of them were either hospitalized or re-hospitalized during the study period. However, it remains unclear whether cognitive decline affected recurrence or readmission. Cognitive improvement by NEAR and its persistence should be demonstrated by RCTs with controls. Therefore, further research is needed to obtain sufficient sample size and identify factors that influence the maintenance or decline of cognitive function.

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Declarations of conflicting interest

The authors declare that there is no conflict of interest.

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