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Regular Article

Estimated cognitive decline in patients with schizophrenia: A multicenter study

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Aim: Studies have reported that cognitive decline occurs after the onset of schizophrenia despite heterogeneity in cognitive function among patients. The aim of this study was to investigate the degree of estimated cognitive decline in patients with schizophrenia by comparing estimated premorbid intellectual functioning and current intellectual functioning.

Methods: A total of 446 patients with schizophrenia (228 male, 218 female), consisting of three sample sets obtained from 11 psychiatric facilities, and 686 healthy controls participated in this study. The Wechsler Adult Intelligence Scale-III (WAIS-III) was used to measure the participants' current full-scale IQ (FSIQ). The premorbid IQ was estimated using the Japanese Adult Reading Test-25. Estimated cognitive decline (difference score) was defined as the difference between the estimated premorbid IQ and the current FSIQ.

Results: Patients with schizophrenia showed greater estimated cognitive decline, a lower FSIQ, and a lower premorbid IQ compared with the healthy controls. The mean difference score, FSIQ, and

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estimated premorbid IQ were −16.3, 84.2, and 100.5, respectively, in patients with schizophrenia. Furthermore, 39.7% of the patients had a difference score of 20 points or greater decline. A discriminant analysis showed that the difference score accurately predicted 81.6% of the patients and healthy controls.

Conclusion: These results show the distribution of difference score in patients with schizophrenia. These findings may contribute to assessing the severity of estimated cognitive decline and identifying patients with schizophrenia who suffer from cognitive decline.

Key words: cognition, cognitive decline, intelligence, multicenter study, schizophrenia.

COGNITIVE IMPAIRMENT IS considered a core deficit of schizophrenia. A number of studies have reported that patients with the illness show a wide range of cognitive impairments (i.e., a 1–2-SD decline in performance on neuropsychological tests compared to a healthy population).[1,2] Because cognitive function is related to social functioning in patients with schizophrenia, various interventions, including cognitive remediation,[3–5] have been used to improve functional outcomes. A substantial proportion of patients exhibit cognitive disturbances after the onset of schizophrenia, although performance on cognitive batteries sometimes falls within the normal range.[6]

Cognitive decline refers to intra-individual differences in cognitive performance at different timepoints, such as premorbidity and post-morbidity. Generally, cognitive function has been demonstrated to decline from premorbid cognitive levels after illness onset.[7–9] To accurately determine the presence of cognitive decline, it would be ideal to assess cognitive performance before and after the onset of schizophrenia. In this context, an alternative approach is necessary to estimate cognitive decline in clinical settings.

Several cross-sectional studies[10,11] have reported strategies to identify patients who experience cognitive decline by estimating the premorbid IQ and current intelligence ability. This attempt is based on the assumption that the current intelligence alone is insufficient to estimate the severity of functional decline in individuals with schizophrenia. These previous studies also suggest that approximately half of patients experience cognitive decline.[10,11] However, distribution of cognitive decline per se has not been fully examined. Assessments of the cognitive decline in patients with schizophrenia, defined above, have been conducted by comparing the estimated premorbid IQ and current IQ.[12,13]

In this strategy, the premorbid IQ can be estimated using the Japanese version of the National Adult Reading Test (JART),[14] a measure of reading ability relatively intact in schizophrenia.[15] The National Adult Reading Test (NART) has been used to estimate premorbid IQ, and its validity in English-speaking patients with schizophrenia has been confirmed.[10,16–18] Likewise, the JART is widely used for Japanese patients, as an equivalent to the NART.[19–28] Currently, the full-scale IQ (FSIQ) is mostly measured using the Wechsler Adult Intelligence Scale-III (WAIS-III) in Japan.[29] Therefore, the aims of this study were to determine the degree and the distribution of estimated cognitive decline in a large sample of patients with schizophrenia, and to investigate the discriminative ability of such decline in patients in comparison with healthy control subjects.

METHODS

Subjects

A total of 446 patients with schizophrenia participated in this study. The patients were recruited from 11 psychiatric facilities (Osaka University Hospital, Hokkaido University Hospital, the University of Tokyo Hospital, Juntendo University Hospital, Kyushu University Hospital, Okayama University Hospital, Nagoya University Hospital, Kansai Medical University Hospital, Kyoto University Hospital, Fujita Health University Hospital, and Hizen Psychiatric Center) (Table S1). Data of the current study were collected from July 2007 to May 2015. Some data overlapped with those of our previous studies (Osaka).[4,30] In addition, 686 healthy control subjects were recruited from the community through

Table 1. Demographic variables, premorbid IQ, current IQ, and estimated cognitive decline in schizophrenia patients and healthy controls

Variables	Patients (n = 446)		Healthy controls (n = 686)		Statistics	
	Mean	SD	Mean	SD	χ^2 F	P-value
Sex (male/female)	228/218		340/346		0.26	0.61
Age	35.8	12.0	35.5	13.7	0.12	0.73
Education (years)	13.7	2.4	14.5	1.9	35.6	3.2×10^{-9}
Estimated premorbid IQ (JART-25)	100.5	10.7	108.2	7.6	196.5	2.8×10^{-41}
Current IQ (FSIQ)	84.2	17.7	111.6	12.2	947.1	1.5×10^{-151}
Estimated cognitive decline (difference score)†	−16.3	13.2	3.4	10.2	805.2	3.6×10^{-134}

†Difference score was calculated by subtracting the estimated premorbid IQ from the FSIQ.
FSIQ, full-scale IQ; JART-25: Japanese Adult Reading Test 25-item version.

local advertisements at Osaka University. The demographic data are shown in Table 1. Detailed information on subjects from each facility, including current psychiatric symptoms, chlorpromazine equivalents,[31] age at onset, and duration of illness, is shown in Supplemental Methods (File S1) and Table S2.

Written informed consent was obtained from all subjects after the procedures had been fully explained. This study was conducted in accordance with the World Medical Association's Declaration of Helsinki, and was approved by the research ethics committee at each institution.

Assessment of estimated cognitive decline

The current FSIQ was measured by the WAIS-III because the Japanese version of the WAIS-IV has not yet been released.[29,32] The current estimated IQ (EIQ) was calculated using two WAIS-III subtests (Similarities and Symbol Search). This short form was developed to estimate the FSIQ to reduce testing time while considering FSIQ predictability and the relation with functional outcomes.[30] The premorbid IQ was estimated using the JART-25 (a short form of the JART).[33] Ten patients recruited from Nagoya University Hospital and seven patients recruited from Juntendo University Hospital were assessed using the JART-50.[14] All intelligence tests were administered by expert psychologists at each site. The difference score was calculated by subtracting the estimated premorbid IQ (as measured by the JART) from the FSIQ, according to previously described methods.[12,13] Scores lower than −10 points were considered as cognitive decline, as suggested in previous studies.[10,11,34,35]

Statistical analysis

Statistical analyses were performed using SPSS 22.0 (SPSS Japan Inc., Tokyo, Japan). Analysis of variance (ANOVA) and the χ^2-test were used to examine differences in demographic variables between patients with schizophrenia and healthy controls. To examine the validity of the short form, an additional analysis was performed by substituting EIQ for FSIQ to estimate cognitive decline. The Kruskal–Wallis test was used to analyze the distribution of difference scores (i.e. FSIQ – estimated premorbid IQ and EIQ – estimated premorbid IQ) in patients.

Canonical discriminant analysis using the difference score was conducted to investigate its utility as a marker of schizophrenia. The inclusion and exclusion of variables was determined according to the Mahalanobis distance. Discriminant power was also assessed using a receiver–operator curve (ROC). Discriminant power was indexed by the area under the curve (AUC) with the 95% confidence interval (95% CI). The significance level was set at a two-tailed $P < 0.05$.

RESULTS

There were no differences in age or sex ratio between patients and healthy controls (P = 0.73, 0.61); however, years of education were significantly less for patients ($P = 3.2 \times 10^{-9}$) (Table 1).

Estimated cognitive decline

The difference score was significantly lower for patients compared to healthy controls (F = 805.2, $P = 3.6 \times 10^{-134}$). The estimated premorbid IQ and FSIQ were significantly lower for patients compared to healthy controls (F = 196.5, $P = 2.8 \times 10^{-41}$ and F = 947.1, $P = 1.5 \times 10^{-151}$, respectively) (Table 1). The mean difference score of the schizophrenic patients was −16.3 points. The proportion of patients who experienced cognitive decline, as defined by a difference score of −10 or less, was 69.3%. The proportion of patients who scored −20 points or less was 39.7% (Fig. 1).

The estimated premorbid IQ and the FSIQ of the total sample were 100.5 and 84.2, respectively. The mean FSIQ of patients was approximately 1 SD below that of the general population. The proportion of patients who scored less than 70 (2 SD below the general population) was 22.6% (Fig. S1a).

Validity of the EIQ for assessing estimated cognitive decline

The distributions of the FSIQ and EIQ were not significantly different for the total sample of patients (Kruskal–Wallis χ^2 = 0.9, P = 0.35) (Fig. S1a,b). A similar pattern of the difference score was observed when the analysis was completed using either the FSIQ or EIQ (Fig. S1c). The distributions of difference score calculated using the FSIQ and EIQ were not significantly different (Kruskal–Wallis χ^2 = 1.0, P = 0.33).

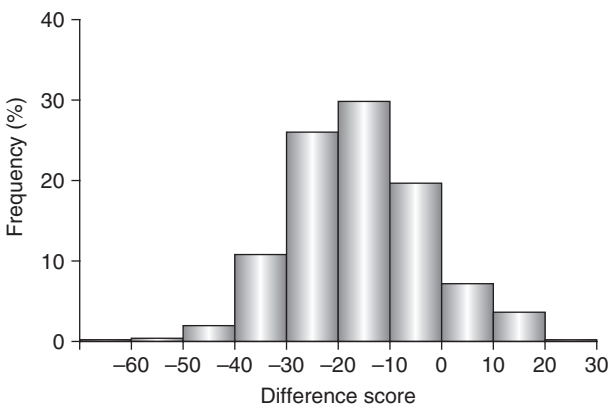

Figure 1. Distribution of the difference score in the patients with schizophrenia. Frequency (%, *y*-axis) distribution of the difference score (*x*-axis) of patients with schizophrenia.

Possible diagnostic utility of estimated cognitive decline

To evaluate the diagnostic utility of the difference score, discriminant analysis was performed using the total patient sample and healthy controls. Using the resubstitution method and the leave-one-out cross-validation method with an optimal cut-off value of −6.2, the correct rate of the discriminant analysis for the difference score was 81.6%.

ROC analysis for the difference score showed that sensitivity and specificity were 0.79 and 0.83, respectively. The AUC of the difference score was 0.88 (95%CI: 0.86–0.90), which suggests high sensitivity of this parameter to discriminate patients from healthy controls (Fig. 2).

DISCUSSON

The purpose of this study was to investigate estimated cognitive decline in a large sample of patients with schizophrenia. Patients showed marked estimated cognitive decline compared with the healthy controls. The results showed that cognitive decline is present in a large percentage of patients with schizophrenia, which is consistent with the results from

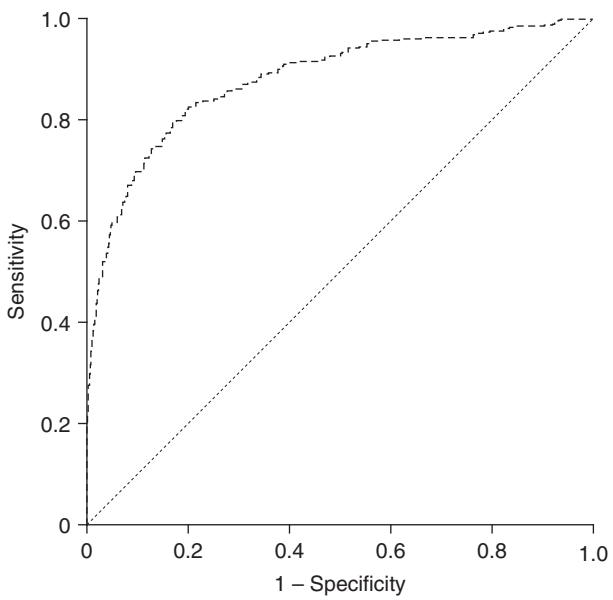

Figure 2. Receiver–operator curve (ROC) for the prediction of patients with schizophrenia. The area under the curve (AUC) of the difference score was 0.88 (95% confidence interval [CI]: 0.86–0.90), which suggests a good ability to discriminate patients from healthy controls.

previous studies.[36,37] To the best of our knowledge, this is the largest study showing the distribution and severity of estimated cognitive decline in patients with schizophrenia recruited from multiple facilities.

The present results showed that patients with schizophrenia experienced a 16.3-point decline in IQ from premorbid levels, which was not observed in the healthy controls. Approximately 70% of the patients had experienced cognitive decline according to the criteria suggested by a previous study (a decline of 10 points or greater in IQ),[10,11,34,35] and the remaining 30% of patients were considered cognitively preserved. Approximately 40% of the patients showed a decline in cognition of 20 points or greater, and 14% of the patients experienced a decline in cognition of 30 points or greater. Based on the distribution of the difference score, the severity of difference score in the present study could be interpreted as follows: a decline of 30 points or greater is severe (13.5%), a decline of 20–30 points is moderate (26.3%), a decline of 15–20 points is mild (15.9%), a decline of 10–15 points is borderline (13.7%), and a decline of less than 10 points is within the normal range (30.7%). These criteria may be useful for interpreting the difference score in patients with schizophrenia; however, the validity of these criteria should be confirmed in future studies.

Cognitive decline in this study was higher than that in previous studies.[10,11,34,35] Estimated premorbid IQ measured by JART was 100.5 in this study, which may be inconsistent with the preceding studies.[10,35] For example, Leeson *et al.* reported in a longitudinal study that approximately 25% of first-episode schizophrenic patients had lower premorbid IQ.[35] Our study basically excluded patients with schizophrenia who had lower premorbid IQ, such as mental retardation. This could explain the inconsistency in the proportion of degree of cognitive decline between our study and previous studies. We did not describe when the subjects received cognitive measures. Cognitive deficits may be improved by interventions, such as antipsychotic medication and psychiatric rehabilitation. For example, atypical antipsychotic drugs have been reported to mildly enhance cognition, as indicated by meta-analysis.[38,39] That may explain the relatively higher proportion of patients who experienced cognitive decline compared to previous findings.[10,11,34,35]

The distributions of the difference score using the FSIQ and EIQ were similar in our sample, which suggests the utility of the EIQ (the short form of the FSIQ) for estimating cognitive decline.[30] The difference score was able to accurately discriminate patients with schizophrenia from healthy individuals. The accuracy was comparable to that of other classification methods, such as classification by neurological soft signs and minor physical anomalies.[40] Therefore, the difference score should be considered a candidate auxiliary diagnostic to assist clinicians. A decline in intellectual ability may affect patients' functional outcomes, such as employment and social functioning; however, no study has elucidated a relation between these factors, and further investigation is needed to confirm a relation between estimated cognitive decline and functional outcomes in patients with schizophrenia.

Limitations

The major limitation of this study is that we could not obtain actual data concerning premorbid intelligence in the patients; however, we are aware that actual data are preferable.[9] Therefore, we cannot draw definite conclusions concerning the actual decline in IQ in patients because of the cross-sectional nature of the study. Second, we calculated the difference score using an estimated premorbid IQ and current IQ. Calculating a patient's IQ can result in measurement errors, which could affect the difference scores. Therefore, the difference score of an individual should not be interpreted as a value, but rather as a range. Third, we did not examine the relation between the difference score and psychiatric symptoms, medication dosage, and social functioning. Fourth, other multiple clinical factors, such as differences in the clinical characteristics of the patients, antipsychotic medications, treatment environment, and severity of psychopathology (e.g., depression), may affect the results.

Conclusion

We have demonstrated that marked estimated cognitive decline, as defined by the difference in the estimated premorbid IQ and current intellectual ability, was present in schizophrenia. These results provide useful information for interpreting cognitive deficit in patients with schizophrenia. The difference score could be an auxiliary tool for the diagnosis of schizophrenia.

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DISCLOSURE STATEMENT

We would like to disclose potential conflicts of interest regarding all financial support for the present study. H.F. reports grants from JPSP and Osaka University, during the conduct of the study. C.S. reports personal fees from CogState Co., Ltd., outside the submitted work. K.K. reports grants from MEXT and AMED, during the conduct of the study; as well as personal fees from Otsuka, Dainippon-Sumitomo, Yoshitomi, Sanofi, Ily Lily, Pfizer, Astellas, GSK, Janssen, Novartis, Daiichi-Sankyo, Meiji-Seika Pharma, and MSD, and grants from Dainippon-Sumitomo, Yoshitomi, Astellas, GSK, MSD, and Eizai, outside the submitted work. T.S. reports personal fees from Dainippon Sumitomo Pharmaceutical Co., Ltd., Otsuka Pharmaceutical Co., Ltd., Toyama Chemical Co., Ltd., Takeda Pharmaceutical Co., Ltd., Mochida Pharmaceutical Co., Ltd., Meiji Seika Pharma Co., Ltd., and NeuroCog Trials Co., Ltd., outside the submitted work. R.H. reports grants from JPSP, AMED, and Osaka University, during the conduct of the study. The other authors declare no financial or non-financial competing interests.

AUTHOR CONTRIBUTIONS

H.F. was critically involved in the collection and analysis of the data and wrote the first draft of the manuscript. C.S. and T.S. analyzed the data and contributed intellectually to the interpretation of the data and writing of the manuscript. Y.Y., H.Y., M. Fujimoto, M. Fukunaga, K.M., Y.T., N. Okada, S.I., N.K., A.T., H.K., M.I., K.O., Y.O., M.T., N.H., M.K., T. Onitsuka, T.U., T. Ohnuma, K.K., N. Ozaki, and O.I. were closely involved in the collection of the majority of the data and contributed intellectually to the interpretation of the data. R.H. supervised the entire project, collected the data, and was critically involved in the design, analysis, and interpretation of the data. All authors contributed to and have approved the final manuscript.

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SUPPORTING INFORMATION

Additional Supporting Information may be found in the online version of this article at the publisher's web-site:

File S1. Supplemental methods (text).

Table S1. Demographic variables, premorbid IQ, current IQ, and estimated cognitive decline in patients with schizophrenia (total sample and each facility).

Table S2. Age at onset, duration of illness, and psychiatric symptoms in patients with schizophrenia (total sample and each facility).

Figure S1. Distribution of the full-scale IQ (FSIQ), estimated IQ (EIQ), and difference score (estimated using the EIQ) in patients with schizophrenia. Frequency (%, *y*-axis) distribution of the scores in patients with schizophrenia.