- According to your comment, we have chosen 11 patients and 11 controls matched for age and sex and re-analyzed the data in addition to the ANCOVA. Results were essentially similar to those obtained from the ANCOVA analysis in the total subjects (Table 3).

Comment 6:

Page 5: The maximum score on the finger movement test is 25. It is not clearly stated whether a score of 25 is positive (no separations) or negative (25 separations). From the scores in Table 2 and 4 it seems that 25 is a positive score.

- A score of 25 indicates no separations (line 14, page 5).

Comment 7:

Page 6: The reason why the data of the mirror drawing task was excluded from further analyses seems arbitrary. The results that patients could not fulfill this task might be viewed as a major difficulty with visuo-motor coordination.

- We excluded the data of the mirror drawing task simply because more than half of the patients quitted the test before completing. (Since the score of the mirror drawing task is time of completing the test, no data were obtained for such patients.) As you point out, this may suggest a major difficulty with visuo-motor coordination in schizophrenia. We have acknowledged this point in the *Discussion* (line 21 to 24, page 11).

Comment 8:

Page 7: Figure 3 does not add extra information.

- Following your comment, we have deleted Figure 3.

Comment 9:

Page 8: Because the finger movement test performances were poorer in inpatients than in outpatients, motor dexterity may be related to gross functional outcome: See the previously mentioned third major problem. Functional outcome was not examined in the present study.

- Following your comment, we have deleted the 'functional outcome'.

Comment 10:

Page 8: In accordance with our results, schizophrenia is characterized by a substantial deterioration of memory functions. I would state 'deficit' in stead of 'deterioration'.

- We agree with this point. We have now used 'deficit' instead of 'deterioration'

Comment 11:

Page 9: | our data demonstrate that impairment in motor dexterity per se is one of the most prominent characteristics of chronic schizophrenic patients. | This conclusion can not be made as this study only examines a few aspects of the cognitive and motor deficits found in schizophrenia. Recently, Neuchterlein et al. (2004) distinguishes seven major neurocognitive domains in schizophrenia: speed of information processing, attention / vigilance, working memory, verbal learning and memory, visual learning and memory, problem solving and social cognition. The present study only examines motor dexterity / visuo-motor coordination, memory problems, attention / concentrations, and IQ.

- Neuchterlein et al. (2004) performed a meta-analysis of studies on neurocognitive functions in schizophrenia; however, their inclusion criteria were too strict to include many studies that focused on motor functions. This may be the reason why Neuchterlein et al. (2004) could not find motor dysfunction as a major neurocognitive deficit in schizophrenia. Our observations clearly suggest that impairment in motor dexterity is a major characteristic in schizophrenia patients. Although our study may be limited by the number of tests, the tests cover substantially comprehensive areas of neurocognitive domains. We administered full versions of WAIS-R and WMS-R. Even these two tests can measure a number of aspects of neurocognitive functions such as speed of information processing, attention/vigilance, verbal learning and memory, visual learning and memory, problem solving, i.e, virtually all the domains mentioned by Neuchterlein et al. (2004).

Responses to Reviewer #3:

Comment 1:

There are highly significant differences in the sample concerning age, education and gender. The authors state in the paper, that they have statistically corrected these variables. In my opinion, it would be interesting whether the baseline of the test results is artificially elevated in healthy controls. Therefore, I recommend to analyze pairwise matched subgroups in the most important test variables.

- Following your suggestion, we have performed additional analysis using matched pair-wise method (line 18, page 7 to line 3, page 8), and we have obtained similar results (Table 3).

Comment 2:

Another important point is that there might be a selection bias in the group of inpatients versus outpatients, what could be an explanation for the better test performance of the outpatients with schizophrenia. Several other important influences have to be mentioned in this part of the study. This question should be analyzed in a more theoretical way, more literature should be cited.

- According to the comment 3 of the Reviewer #2, we have refrained from stressing the difference in test performance between inpatients and outpatients, since it remains to be speculative that such difference reflects functional outcomes. The possible relationship between motor performance and functional outcomes should be examined in a more theoretical way in a future study.

Responses to Reviewer #4:

Comment 1:

Yet, there are some methodological problems. Most of them are quite typical and most studies in this field cannot avoid these problems, like the problem to differentiate between effects of schizophrenia itself from effects of antipsychotic treatment. These problems are common to the reader and correctly discussed in the article.

- We agree with this point. We have discussed this point in more detail adding some references. (line 8 to 20, page 11).

Comment 2:

The kind and dosage of antipsychotic medication should be given in detail, i.e. whether conventional or atypical antipsychotics have been used.

- Following your suggestion, additional information has been added in Table 1.

Comment 3:

For US- or European readers it seems strange that the 15 inpatient subjects have received a stable dose of antipsychotics during the last 3 months and were also clinically stable. Why have them been admitted to the hospital? or: are they patients who have been in a kind of long-term care unit? Please make clearer which group of patients you investigated.

- It is regrettable that Japanese mental health care system remains to be old-fashioned. Indeed, the mean duration of hospitalization in psychiatric patients is still more than 300 days, which may be surprising to Western people. This is due mainly to the lack of transitional facility and community care system. As a result, lots of people (approximately 70 thousands of schizophrenics) with poor social functioning (i.e., those who can not live alone and support themselves) remain to be hospitalized in Japan. The stable inpatients we investigated were such patients; they were surely under long-term care. We have described this point in Method (line 18 to 19, page 3).

Comment 4:

The discussion fails to discuss the topic of disturbed motor dexterity in schizophrenic patients controversially. In contrast to the presentation in the manuscript, data are quite conflicting in this field. This should be mentioned and underlined with some citations (f.ex. see discussion in Tigges et al.). The conclusion that "impairment in motor dexterity per se is one of the most prominent characteristics of chronic schizophrenic patients" is to strong without mentioning conflicting results. Also the statement that medicated and unmedicated patients are similarly

impaired in motor performance is far to strict in the context of the present findings (see f.ex. discussions in Putzhammer et al. 2004, 2005, 2006)

- As you point out, our conclusion might be strong and is far to strict in the context of the present findings. We had a rethink the effect of medication and modified *Discussion* citing several studies (line 8 to 20, page 11).

Comment 6:

The sentence "Whereas motor dysfunctions ... have been noted since the Kreapelin era, little attention has been paid to motor dysfunctions until recently" in the Introduction section is confusing. Maybe you should state that the attention has decreased with the introduction of antipsychotic drugs as motor dysfunctions were mainly interpreted as side-effects.

- We have modified this part, following your suggestion (line 6 to 9, page 2).

* Title Page showing full Author and Address Details

Impairment of motor dexterity in schizophrenia assessed by a novel finger-movement test

Akira Midorikawa[a,b,c], Ryota Hashimoto[d,e,f], Hiroko Noguchi[f], Osamu Saitoh[g], Hiroshi Kunugi[f], and Katsuki Nakamura [b,c,*]

[a] Department of Psychology, Chuo University, Tokyo, Japan

[b] Department of Animal Models for Human Disease, National Institute of Neuroscience, National Center of Neurology and Psychiatry, Tokyo, Japan

[c] CREST, Japan Science and Technology Agency, Saitama, Japan

[d] Osaka-Hamamatsu Joint Research Center for Child Mental Development, Osaka University Graduate School of Medicine, Osaka, Japan

[e] Department of Psychiatry, Osaka University Graduate School of Medicine, Osaka, Japan

[f] Department of Mental Disorder Research, National Institute of Neuroscience, National Center of Neurology and Psychiatry, Tokyo, Japan

[g] Department of Psychiatry, Musashi Hospital, National Center of Neurology and Psychiatry, Tokyo, Japan

* Corresponding author:

Department of Animal Models for Human Disease, National Institute of Neuroscience, National Center of Neurology and Psychiatry, 4-1-1 Ogawa-Higashi, Kodaira, Tokyo 187-8502, Japan

E-mail: katsuki@ncnp.go.jp; Tel/Fax: +81 42 346 1724

1. Introduction

Patients with schizophrenia have a wide spectrum of disturbances, including social, cognitive, and emotional dysfunctions. Of these, the most serious dysfunction may be cognitive impairment (Goldberg and Seidman, 1991), with the associated memory deficits (Saykin et al., 1991; Saykin et al., 1994; Heinrichs and Zakzanis, 1998). Whereas motor dysfunctions, as well as cognitive impairments, have been noted since the Kraepelin era (Kraepelin, 1919), the attention has decreased with the introduction of antipsychotic drugs as motor dysfunction were mainly interpreted as side-effects. Nevertheless, motor function of schizophrenia has been revisited by recent investigators (e.g. Rogowska et al., 2004; Jahn et al., 2006).

The most remarkable motor dysfunction in schizophrenia may be the deficit in fine motor skills (Rosofsky et al., 1982; Manschreck, 1986). To evaluate motor functions in patients, three tests have been generally applied: the reaction time test to evaluate the speed of initial timing, the finger tapping test to examine the speed of continued oscillatory movement, and the pegboard test to determine motor dexterity (King, 1958; Heinrichs and Zakzanis, 1998). However, the score of the pegboard test is thought to be affected by the motor speed as well as dexterity (Rosofsky et al., 1982). Therefore, the development of a motor test that can evaluate dexterity irrespective of motor speed would be beneficial. The examination of movement dexterity has recently received an increasing amount of attention since dexterity was shown to be associated with functional outcomes (Lehoux et al., 2003). Furthermore, some studies have found that deficits in dexterity were greater in familial schizophrenics than in sporadic patients (Sautter et al., 1997; Gschwandtner et al., 2005).

In this study, we attempted to elucidate motor dysfunction using some traditional and newly developed tests (finger movement test) in chronic schizophrenia. We also attempted to

elucidate which tests most discrimate patients and controls among several motor and cognitive tests.

2. Method

The research protocol was approved by the ethics committee of the National Center of Neurology and Psychiatry (NCNP), Tokyo, Japan. Written informed consent was obtained from all subjects.

2.1. Subjects

The participants in the present study were 27 patients who met the Diagnostic and Statistical Manual of Mental Disorders, 4th Edition (DSM-IV) criteria for schizophrenia and 49 healthy volunteers (Table 1). The patients were under treatment at the Department of Psychiatry, Musashi Hospital, NCNP. A consensus diagnosis of schizophrenia was made by at least two psychiatrists based on clinical interviews, observations, and case notes. Patients were clinically stable on a stable dose of antipsychotic medication for at least 3 months prior to the neuropsychological testing sessions. Among 27 patients, there were 15 inpatients under long-term care. Healthy volunteers from hospital staff and their associates who had no history of psychiatric treatment were recruited. The subjects had no history of central nervous system disease, severe head injury, alcohol/drug dependence, or mental retardation. They were biologically unrelated Japanese who resided in the same geographical area, the Western part of the Tokyo metropolitan area.

2.2. Procedures

We selected the following four motor function tests: pegboard, mirror drawing, normal drawing, and finger movement tests. The pegboard test has been widely used to evaluate motor dexterity (e.g. King, 1958; Heinrichs and Zakzanis, 1998). Mirror drawing test measures visuo-motor coordination and its procedure learning, which has been shown to be impaired in patients with schizophrenia (Scherer et al., 2003). To assess whether deficits in the mirror drawing test depend on the mirroring procedure, normal (non-mirror) drawing test using the same figure was also administered. In order to evaluate motor dexterity, excluding effect of motor speed, we developed the "finger movement test". In addition to motor domain, memory, intelligence, and executive functions were also examined, since such functions were impaired in schizophrenic patients (e.g. Bilder et al., 2000). The handedness of each subject was evaluated using the Edinburgh inventory (Oldfield, 1971). With the exception of the finger movement test, each motor test was performed with the dominant hand.

The pegboard test performed was the grooved pegboard test (Matthews and Klove, 1964) with minor modifications, *i.e.*, the subjects were asked to pinch aluminum rivet pins (3 mm in diameter, 1.5 cm in length) one by one and insert them into small holes arrayed in a 5 x 5 grid as fast as possible. The time (seconds) for completion was measured as the score. In the mirror drawing test (Milner et al., 1968), the subjects were asked to trace a shape, which was a modified hexagon with double lines, using a pencil (Fig. 1) while looking at it through a mirror apparatus (TAKEI Corp. Tokyo, Japan). The width between the lines was 3 mm. At the beginning of a trial, the examiner put the tip of the pencil at the starting position and asked the subject to trace the shape as fast as possible without deviating from the lines. If the subject moved the pencil tip from the space between the lines and could not return it within the lines by himself/herself, the examiner assisted in returning the tip to the lines. In the normal drawing test, the subjects were asked to trace the same hexagon. The subjects were asked to

trace the shape as fast as possible without deviating from the lines. In both the mirror and normal drawing tests, the subjects were asked to trace the shape clockwise for the right hand and anticlockwise for the left hand. The time (seconds) to complete the task with his/her dominant hand was recorded as the score for the mirror and normal drawing tests. Although the scores of these motor tests can estimate motor dexterity, they are also dependent on motor speed as mentioned above. Consequently, to examine motor dexterity, we developed the finger movement test, which was derived from a finger-movement exercise (Kurita, 1995). The subjects were asked to rotate each finger pair while keeping the remaining fingers fixed (Fig. 2). First, the subjects turned their right and left thumbs together in the same direction five times and then in the reverse direction. The subjects then similarly turned their second, third, fourth, and fifth fingers. An examiner counted the number of separations of the finger pairs that were supposed to remain fixed as a score. The performance for each finger pair was graded as follows: no separation, 5; 1–4 separations, 4–1; 5 or more separations or an inability to do the task, 0. The maximum score was 25 points for individuals who showed no separations. In this test, the time to complete the task was unrelated to the score, making this test independent of motor speed.

To examine cognitive functions, we administered the Japanese version (Shinagawa et al., 1990) of the Wechsler Adult Intelligence Scale Revised (WAIS-R) (Wechsler, 1981) and the Japanese version (Sugishita, 2001) of the Wechsler Memory Scale Revised (WMS-R) (Wechsler, 1987). To examine executive functions, we administered a computer version (http://cvddb.shimane-med.ac.jp/user/wisconsin.htm) of the modified Wisconsin card sorting test (WCST) (Kashima et al., 1987). We analyzed the following measures: the performance IQ, verbal IQ, and full scale IQ from the WAIS-R and the verbal memory, visual memory, general memory, attention and concentration, delayed recall from the WMS-R, and completed categories from the WCST.

2.3. Data analysis

Data were analyzed using SPSS for Windows version 11 (SPSS Japan Inc., Tokyo, Japan). Inter-group differences in means and proportions were assessed with a *t*-test and chi-square test, respectively. Correlation analysis was performed using Pearson's product moment correlation coefficient. Analysis of covariance (ANCOVA) was used when comparing means controlling for confounding variables. To select items that distinguish the patients from the healthy controls, we employed a stepwise discriminant function analysis using the Wilks' lambda method. The criterion for inclusion/exclusion *P* value was 0.05. Statistical significance was considered when the two-tailed *P* value was less than 0.05.

3. Results

The demographic and clinical data of the patients and controls are shown in Table 1. Mean age, sex ratio, and education level in years were significantly different between the two groups.

3.1. Motor tasks

More than half of the patients (13/23) gave up the mirror drawing test at an early stage (for example Fig. 1), whereas the remaining ten patients completed the test. By contrast, most of the control subjects (46/49) completed the test, and only three of them failed. This difference was statistically significant ($\chi^2 = 15.8$, $df = 1$, $P = 0.00007$). Therefore, although the mirror drawing test could distinguish the patients from the healthy controls, the data of the mirror drawing test were excluded from later analyses. Because significant differences were observed

between the patients and control groups concerning age, sex, and education level (Table 1), the performance in each test was compared between the two groups using an ANCOVA, controlling for these variables. As shown in Table 2A, there were highly significant differences between the two groups in the pegboard, normal drawing, and finger movement tests ($P = 3.0\times 10^{-5}$, 9.1×10^{-6}, 5.0×10^{-7}, respectively).

3.2. Cognitive tasks

Results of the cognitive tests in the total patients and controls are shown in Table 2B. The performance of the patients was significantly poorer than that of the healthy controls in the majority of the cognitive tests, even after controlling for age, sex, and education level in the analysis by ANCOVA. Among the cognitive tests, the delayed recall test was found to be most impaired in the patients. With respect to IQ, deficits in the performance IQ were greater than the verbal IQ in the patients. With respect to the WCST, test performance was lower in the patients than in the controls; the difference approached, but did not reach, statistical significance (p=0.051).

3.3. Pair-wised analysis

The observed differences in motor and cognitive tasks between patients and controls may be attributable to the differential distributions in age, sex, and education years between the two groups. Therefore we reanalyzed the two groups using a pair-wise procedure controlling for age, sex and education years. We selected each pair so that differences of age and education year could be within two years. Eleven matched pairs were selected. After pairwise procedure, there was no significant difference between two groups in age ($t\,(20) = 0.6, P = 1.0$), education

year (t (20) = 1.3, P = 0.2), and sex ratio (χ^2 (1) = 1.8, P = 0.2). Table 3 shows results of t test analysis of the matched pairs, which showed essentially similar results to the original analysis (Table 2).

3.4. Discriminant analysis

We performed a discriminant analysis to select items to distinguish between patients and controls. Two motor tests (finger movement test and pegboard), four memory and intelligence indices (general memory, attention and concentration, delayed recall, and full scale IQ), and one executive test (completed categories of WCST) were put into the stepwise discriminant analysis procedure. In the first step, delayed recall test was selected. Next, delayed recall and finger movement tests were selected. These two items correctly classified 96.1% of the originally grouped subjects (Wilks' λ = 0.28, $P = 4.9 \times 10^{-19}$). When the correlation between delayed recall and finger movement tests was examined within the patient group, there was no correlation (Pearson's r = –0.001, P = 1.0).

3.5. Relationship of demographic and clinical variables with delayed recall and finger movement

The correlations of the demographic and clinical variables (continuous variables) with the delayed recall and finger movement tests are shown in Table 4. While the education level was significantly correlated with the performance in the delayed recall test (r = 0.51, P = 0.01), there was no correlation between the education years and the performance in the finger movement test. No significant correlation was observed for the remaining variables.

Differences in performance in the delayed recall and finger movement tests between the

groups classified by categorical variables (sex, family history, and out- or inpatient status) are shown in Table 5. We found a significant difference in finger movement between out- and inpatients (t-test, $P = 0.014$). The scores of outpatients were significantly higher than those of inpatients in the finger movement test, although this difference was not observed for the delayed recall test. In regard to sex or family history, there was no significant difference in the scores in either test.

3.6. Relationship of motor and cognitive functions with delayed recall and finger movement

The correlations of the motor and cognitive functions with the delayed recall and finger movement tests are shown in Table 6. Finger movement was correlated with pegboard only, while delayed recall was correlated with many of the variables: normal drawing, indexes of WMS-R, and full scale IQ.

4. Discussion

By using a series of tests, we confirmed that both motor and cognitive functions are profoundly impaired in patients with chronic schizophrenia. The scores of all of the motor (pegboard, mirror drawing, normal drawing, and finger movement) and cognitive (WAIS-R and WMS-R) tests were significantly poorer in the schizophrenic patients than in the healthy control subjects even when sex, age, and education years were controlled for. A discriminant analysis revealed that the functions that most successfully distinguished patients and controls were delayed recall and finger movement among the tests. Because the finger movement test that we developed is independent of motor speed, our results suggest that motor dexterity is intrinsically impaired in chronic schizophrenia. Furthermore, the score of the finger

movement test did not correlate with that of the delayed recall, suggesting that these two functions are dimensionally different.

In accordance with our results, schizophrenia is characterized by a substantial deficits in memory functions (Saykin et al., 1991; Saykin et al., 1994; Censits et al., 1997). Among the subscales of WMS-R, the most impaired function was delayed recall in our patients (index score of 69.2), followed by visual memory (73.4), verbal memory (76.6), and attention and concentration (83.7). This order is not consistent with previous studies (Wechsler, 1987; Randolph et al., 1994; Hawkins et al., 1997). For example, Gold et al. (1992) studied 45 schizophrenic patients and reported that the subscale scores of WMS-R were similarly impaired (attention and concentration: 80.0; verbal memory: 81.8; visual memory: 81.5; delayed recall: 81.6). The inconsistency between previous studies and ours may be attributable to the ethnic difference or relatively older age of our subjects (mean age: 44 years). With respect to the WCST, the difference between patients and controls just failed to reach statistical significance ($p=0.051$), in spite that many studies have thus far shown that deficits in WCST are incontestable marker of schizophrenia (e.g. Franke et al., 1992; Scarone et al., 1993). The failure to reach statistical significance may be attributable to the small sample and relatively large inter-individual differences (i.e., a wide range of SD) in the test score.

In addition to memory functions, motor functions can be another factor to distinguish schizophrenic patients from healthy controls. The finger movement test we developed was found to have a highly discriminative power between patients and controls; this power might be even higher than that of the conventional motor tests, such as the pegboard test. Motor dysfunction in schizophrenia has been noted since the Kraepelin era (Kraepelin, 1919; King, 1958; Weaver and Brooks, 1964; Heinrichs and Zakzanis, 1998). Our present results further add evidence for this. The majority of previous studies employed the finger tapping and pegboard tests (Heinrichs and Zakzanis, 1998). Score of the latter test is, however, influenced

by not only dexterity but also motor speed (Rosofsky et al., 1982). Therefore, we developed the finger movement test to evaluate motor dexterity alone. There was a highly significant correlation between finger movement and pegboard tests, ensuring that the validity of the newly developed finger movement test as a tool to measure motor dexterity. Our observation that finger movement test had a highly discriminative power between patients and controls suggest that impairment in motor dexterity *per se* might be a major characteristic of chronic schizophrenia.

However, one might suspect that impaired motor dexterity might have been due to undesirable side effects of the antipsychotic drugs (*i.e.*, extrapyramidal symptoms). Finger rigidity, for example, may influence finger movement test results. Though we found no significant correlation between daily dose of antipsychotic drugs and performance in the finger movement test, there have been conflicting reports concerning the effect of antipsychotic medication. Some reports showed that motor deficit was independently of antipsychotics (Saykin et al., 1994; Tigges et al., 2000), but others showed that medicated patients were much worse than drug naïve patients (Putzhammer et al., 2004; Putzhammer et al., 2005). One plausible explanation was that drug naïve patient suffer from a primary motor deficit and antipsychotic medication (especially conventional one) worsens these primary deficit (Putzhammer and Klein, 2006). Taken together, poor performance observed in the finger movement test is unlikely to be attribute solely to side effects of antipsychotic medication.

With respect to the mirror drawing task, more than half of the patients did not complete it. So we excluded the results of mirror drawing task from further analysis; however, the observation that so many patients could not complete the task may suggest a major difficulty with visuo-motor coordination in schizophrenia.

There is some evidence that deficits in motor function or dexterity have developmental

origin and manifest before the onset of schizophrenia. Cannon et al. (1999) examined various activities of school age in individuals who later developed schizophrenia, and found that they were significantly poorer than control subjects only in nonacademic factors such as sports and handicrafts. Gschwandtner et al. (2005) reported that poorer fine motor functions as well as cognitive functions during childhood were crucial risk factors for later development of schizophrenia. Such deficits in motor functions may be related to genetic factors. Sautter et al. (1997) reported that familial patients were much worse than non-familial patients in the domain of motor function and frontal lobe function. In the present study, however, we obtained no evidence supporting this possibility.

In the present study, the inpatients were poorer in performance of the finger movement test than the outpatients. In line with this, Weaver et al. (1964) reported that scores in motor function tests were highly associated with the probability of discharge from a hospital. Lehoux et al. (2003) studied the relationship of several cognitive and motor tests with social functioning and revealed that the best fitting multivariate model to explain social functioning included fine motor dexterity and executive functioning. Sota and Heinrichs (2004) showed that motor dexterity was one of the crucial cognitive factors which predicted overall quality of life three years after initial measurement. These observations may suggest motor dexterity is related to functional outcomes.

Several limitations are present in this study. First, the sample size was not very large. There is a possibility that some factors to discriminate between patients and controls have been missed due to the small sample size (type II error). Second, the mean IQ and memory indices of our controls were relatively high (around 110); therefore, it is possible that motor functions might also be relatively higher than the general population. Thus, the differences in motor functions between patients and controls may have been overestimated in our study. Third, we did not administer a test for motor speed alone; the possibility remains that motor

speed may be an important factor in discriminating patients and controls. Indeed, deficits in motor speed have been reported in schizophrenics and individuals at risk for the illness (Niendam et al., 2006). Fourth, scoring of finger movement test was performed by a single examiner without monitoring by a second examiner or objective instrument; thus some scoring errors might have occurred. Furthermore, strength of the fixed finger might have had some influence on the finger movement test score; controlling for such strength should have been done in the test.

In conclusion, we demonstrated profound impairment in motor dexterity as well as cognitive impairment in chronic schizophrenia using a newly developed motor test, the finger movement test. Impaired motor dexterity is a major characteristic of schizophrenia, which is relatively independent of cognitive functions.

Acknowledgements

This study was financially supported by CREST of the Japan Science and Technology Agency (JST) and Health and Labor Science Research Grants (Research on Psychiatric and Neurological Diseases and Mental Health).

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