

## Figure legends

**Fig. 1.** Mean scores on 7 dimensions of TCI in schizophrenia males.

■, schizophrenia males; ▣, schizophrenia females; □, total controls (male and female combined). \*Only schizophrenia males significantly differed from controls; \*\*Both schizophrenia males and females significantly differed from controls.

Table 1

## Demographic and clinical characteristics of patients with schizophrenia and healthy controls stratified by gender

Characteristic	Schizophrenia patients ( <i>n</i> = 86)		Analyses (male vs. female patients)		Healthy controls ( <i>n</i> = 115)		Analyses (male vs. female controls)	
	Male ( <i>n</i> = 53)	Female ( <i>n</i> = 33)	statistics	<i>P</i>	Male ( <i>n</i> = 71)	Female ( <i>n</i> = 44)	statistics	<i>P</i>
			(male vs. female patients)				(male vs. female controls)	
Age, years: mean (S.D.)	41.5 (11.8)	41.9 (10.6)	$F(1,84) = 0.025$	0.87	41.2 (14.0)	41.6 (4.1)	$F(1,113) = 0.046$	0.83
Education, years: mean (S.D.)	13.6 (2.6)	13.1 (1.7)	$F(1,84) = 1.19$	0.28	17.3 (3.0)	14.4 (1.9)	$F(1,113) = 31.9$	< 0.001
Family history of psychiatric disease: Yes/No	20/33	9/24	$\chi^2(1) = 0.996$	0.32				
Age at illness onset, years: mean (S.D.)	23.6 (6.6)	25.1 (8.8)	$F(1,84) = 0.83$	0.36				
Duration of illness, years: mean (S.D.)	17.9 (11.4)	16.8 (10.1)	$F(1,84) = 0.22$	0.64				
CPZeq of total antipsychotics, mg/day: mean (S.D.)	974.5 (927.5)	837.6 (690.8)	$F(1,84) = 0.53$	0.47				
Number of hospitalizations, <i>n</i> : mean (S.D.)	2.3 (2.1)	2.2 (2.7)	$F(1,84) = 0.061$	0.81				
Outpatients/Inpatients, <i>n</i>	35/18	22/11	$\chi^2(1) = 0.0036$	0.95				

PANSS scores ( <i>n</i> = 53): mean (S.D.)	( <i>n</i> = 31)	( <i>n</i> = 22)
Positive subscale	13.3 (5.6)	15.8 (7.7)
		$F(1,51) = 1.79$ 0.19
Negative subscale	20.5 (6.9)	18.9 (7.0)
		$F(1,51) = 0.63$ 0.43
General subscale	29.0 (8.8)	30.1 (8.1)
		$F(1,51) = 0.20$ 0.66
Total score	62.8 (16.8)	64.8 (18.9)
		$F(1,51) = 0.16$ 0.69

CPZeq: Chlorpromazine equivalents.

PANSS: Positive and Negative Syndrome Scale (Kay et al., 1987).

Table 2  
Comparisons of TCI scores between patients with schizophrenia and control subjects

Variable	No. of items	Schizophrenia patients ( <i>n</i> = 86)	Healthy controls		ANOVA <sup>a</sup>		ANCOVA <sup>b</sup>	
			Mean (S.D.)	Mean (S.D.)	<i>F</i>	<i>P</i>	<i>F</i>	<i>P</i>
Novelty seeking	NS	17.4 (4.6)	20.6 (4.1)	26.69	<0.001	27.79	<0.001	
Harm avoidance	HA	22.7 (6.0)	16.9 (5.6)	48.4	<0.001	40.87	<0.001	
Reward dependence	RD	13.6 (3.5)	15.2 (3.7)	9.86	0.002	13.55	<0.001	

Persistence	PS	8	4.1 (1.9)	4.6 (1.7)	3.81	0.052	0.36	0.55
Self-directedness	SD	44	23.6 (6.6)	30.1 (5.8)	55.07	< 0.001	32.64	< 0.001
Cooperativeness	CO	42	26.7 (5.4)	28.5 (5.4)	5.38	0.02	5.18	0.02
Self-transcendence	ST	33	13.8 (7.5)	10.9 (5.1)	10.79	0.001	5.24	0.02

<sup>a</sup> Degrees of freedom = 1, 199.

<sup>b</sup> Education years was controlled for. Degrees of freedom = 1, 199.

**Table 3**  
**Correlations between TCI and PANSS scores**

	NS	HA	RD	PS	SD	CO	ST
Positive subscale	0.02	-0.14	-0.10	0.23	-0.17	-0.04	0.34*
Negative subscale	0.04	0.11	-0.34*	-0.27*	-0.25	-0.28*	-0.25
General subscale	0.26	0.004	-0.37**	0.03	-0.32*	-0.29*	0.16
Total score	0.15	-0.01	-0.35**	-0.01	-0.32*	-0.27	0.11

Each figure represents Pearson's *r*.

\*  $P < 0.05$ , \*\*  $P < 0.01$ .

Table 4

Comparisons of TCI results in schizophrenia patients and healthy controls between prior studies and ours

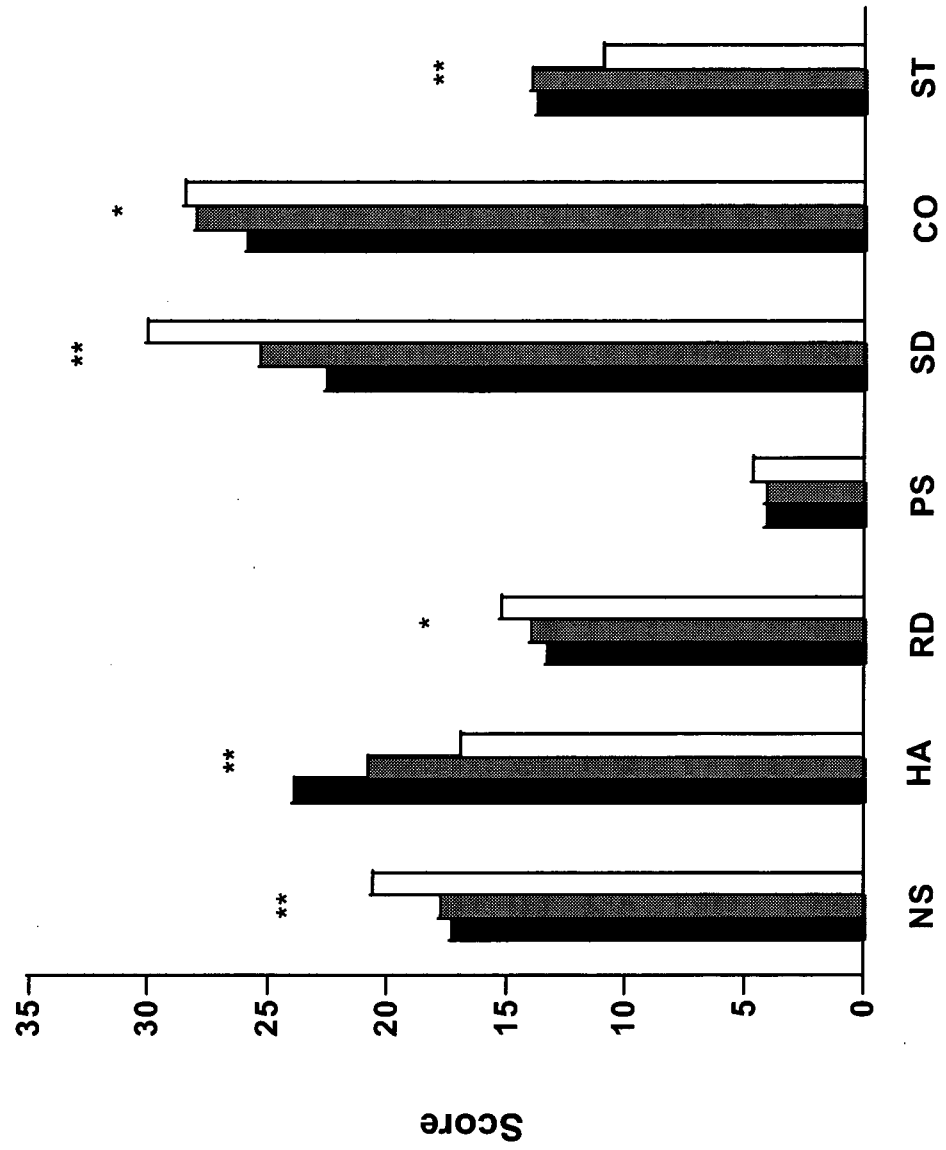
Country (City)	No. of sample		Matching status	TCI results (patients vs. controls) <sup>a</sup>						
	Patients	Controls		NS	HA	RD	PS	SD	CO	ST
The present study	86	115	age/gender	-3.2**	5.8**	-1.6**	-0.5	-6.5**	-1.8*	2.9**
Guillem et al. (2002)	52	25	age	-4.4**	8.1**	-0.9	-1.4*	-8.1**	-3.6**	2.4
Boeker et al. (2006)	22	22	age/gender	-0.4	2.9	0.4	-0.4	-5.9**	-2.8*	4.1*

<sup>a</sup> Differences in sub-dimensions of TCI between patients and controls of each study.

Each figure in these 7 columns was calculated as follows: &lt;mean of patients&gt; - &lt;mean of controls&gt;

\* : Patients showed a significant difference from controls ( $P < 0.05$ ).\*\* : Patients showed a significant difference from controls ( $P < 0.01$ ).

Fig. 1.



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Manuscript Draft

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

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**Abstract:** Schizophrenia is characterized by a series of serious mental disturbances, including social, cognitive, and emotional dysfunctions. Although motor dysfunctions as well as the cognitive impairments in schizophrenia have been noted since the Kraepelin era, little attention has been paid to motor dysfunctions until recently. Here, we examined the characteristics of motor dysfunctions and their relationship to other cognitive functions in schizophrenia. Subjects were 27 patients who met the DSM-IV criteria for schizophrenia and 49 healthy volunteers. A series of motor tests, i.e., pegboard, mirror drawing, normal drawing, and finger movement tests, were administered, and cognitive functions were assessed with the WAIS-R, the WMS-R and the WCST. The finger movement test is a novel motor test that we developed to assess motor dexterity independent of motor speed. A stepwise discriminant analysis revealed that the finger movement and delayed recall tests were able to distinguish patients and controls most effectively. The scores of these two tests showed no correlation. The education level was correlated with the delayed recall,



but not with the finger movement. A significant difference was observed in the finger movement test score between inpatients and outpatients. There was no significant correlation between dosage of antipsychotic drugs and finger movement in the patient group. The present results suggest that impairment in motor dexterity is a major characteristic of schizophrenia, which might be independent of cognitive functions.

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Thank you for your reply and for sending the reviewers' comments on our paper entitled "Impairment of motor dexterity in schizophrenia assessed by a novel finger-movement test" (PSY-D-06-00135). In the light of the comments, we have revised the paper extensively, and resubmit it herewith.

Enclosed are a paper of the revised version and a list of responses to the reviewers' comments and the changes that we have made.

We would be grateful if the manuscript could be reviewed and considered for publication in Psychiatry Research.

Yours sincerely,

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## Responses to Editor

### **Comment 1:**

*Please give more of the details of the study in the abstract, including number of patients and controls. Figure 3 adds little, so please omit.*

- Following your suggestions, we have added information on the number of patients and controls in the abstract, and have omitted the Figure 3.

### **Comment 2:**

*The following reference presents data on the importance of motor systems in psychosis and may be useful to cite.*

- We have cited several new references, following your suggestions (line 10 to 11, page 2).

### **Comment 3:**

*In addition to the critiques, please review carefully the following. (1) In series of citations enclosed within parentheses in the text, list papers in chronological order. (2) In the references list, important words in each journal title should have initial upper case letter.*

- We have reviewed and corrected the format carefully.

Responses to Reviewer #1:

**Comment 1:**

*It is unclear if the primary goal of this manuscript is intended to explore the broader issue of cognitive functions, or if it is primarily an attempt to validate the utility and sensitivity of this new test.*

- Our primary goal was to explore the broader issue of cognitive functions, paying much attention on motor dysfunction rather than to validate our newly developed test. We wrote the aims of the study in the last paragraph of the introduction as follows. *“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 discriminate patients and controls among several motor and cognitive tests.”* (line 24, page 2 to line 2, page3).

**Comment 2:**

*The patient subgroup is relatively small, and is adequately described in terms of medications, hospitalizations, etc. It would also be helpful to know the breakdown of subtypes of disease since numerous studies have shown that cognitive dysfunction is not equally associated with all forms of illness. It also was unclear if the schizophrenic subjects were all without history of neurological illness or substance abuse.*

- Following your suggestion, we have described the patients in more detail (Table 1).
- The majority of the patients were residual type of schizophrenia; however, we have not obtained accurate information about subtypes of all the patients.
- Participants were excluded from both the patient and control groups if they had prior medical histories of central nervous system disease or severe head injury, or if they met criteria for alcohol/drug dependence or mental retardation (line 20 to 22, page3).

**Comment 3:**

*The patient and control groups are poorly matched on demographic variables. These potential confounding variables are included as covariates in the analyses, although the extent of these differences raises some question as to whether ANCOVA adequately addresses these issues. It does not appear that antipsychotic medication dosage was included although this could also affect cognitive or motor performance.*

- We have performed additional analysis using a pair-wised method and we have obtained almost the same results when age and education level were controlled for (line 18, page 7 to line 3, page 8).

- We also considered that antipsychotic medication was one of the important factors for motor deficit; however, it is hard to analyze the data controlling for antipsychotic medication using an ANCOVA, because all patients took medication while control subjects did not. Furthermore, we found no significant correlation between medication dosage and motor function within the patient group (Table 4).

**Comment 4:**

*The discriminant function analysis employed 14 variables. Since there were only 27 schizophrenic subjects, this does not meet even minimal assumptions regarding subject/variable ration (typically this is at least 3 to 1). Therefore the results of the discriminant functions analysis are invalid. The correlational analyses are of limited value because the focus on the two cognitive measures is based on the discriminant function analysis.*

- According to your suggestion, we re-analyzed the data using major 7 out of the 14 variables. That is, two motor tests (finger movement test, pegboard), four indexes of memory and intelligence (general memory, attention and concentration, delayed recall, full scale IQ), and one executive test (completed categories of Wisconsin Card Sorting Test) were put into the stepwise discriminant analysis procedure. The results were essentially unchanged. Only two items were selected: delayed recall of the WMS-R and finger movement. In the first step, delayed recall test was selected. Next, delayed recall and finger movement tests were selected. We modified the method and result sections accordingly (line 5 to 15, page 8).

**Comment 5:**

*There may be some value in developing a motor test that is independent of speed and which can distinguish between schizophrenics and controls. It would be of greater value to know how such a test correlates with measures of disease (positive vs negative symptoms) and whether this is affected by psychotropic medications.*

- As you suggest, it is interesting to examine the possible relationship between motor function and symptoms. We would like to examine this point in the future with a longitudinal design.
- Concerning the effect of psychotropic medications, we found no significant correlation between motor performance and medications (Table 4).

## Responses to Reviewer #2:

### **Comment 1:**

*The first problem is that of the reliability and validity of the finger movement test. With respect to the reliability of the test: When the subject is asked to rotate each finger pair, the number of separations of the finger pairs is counted by an examiner. In my opinion this method gives room for many counting problems. To my, it seems very difficult to obtain reliable results. I would like to ask the authors which actions they have taken to ensure the reliability of the test results. According to me there are different solutions to overcome this reliability problem. First, a second examiner simultaneously counts the number of separations. Another solution is to obtain a videotape of the test performance which enables a verification of the scores afterwards. A third solution is to use computer-registration with actometers to obtain a more objective score. With respect to the validity: how sure are the authors that the finger movement test actually measures dexterity? How was the correlation between this test and the pegboard test? Is it possible that the finger movement test measures the rigidity of the fingers? A related problem with this finger movement test is that the performances are, to my opinion, dependent on the amount of force subjects apply while keeping the remaining fingers fixed. The more force the subject is applying the better (s)he will be able to keep the fingers fixed.*

- We did not feel that it is very difficult to count the number of leaving fingers accurately; however, it is surely possible that a single examiner without monitoring may yield inaccurate score. This point has been acknowledged as a limitation in *Discussion* (line 3 to 5, page 13).
- There was a significant correlation between finger movement and pegboard tests (Table 6), providing evidence for the validity of the finger movement measuring motor dexterity. As you point out, finger movement is likely to be affected by rigidity of fingers. This point was discussed (2nd paragraph, page 11).
- It is also possible that subject's force may influence test results. This point has also been described in *Discussion* (line 5 to 7, page 13).

### **Comment 2:**

*Another major problem is that the authors only used a restricted battery of cognitive and motor tests, whereas their conclusion (impairment in motor dexterity is a prominent characteristic of schizophrenia, which is relatively independent of cognitive functions) sounds very ambitiously. Moreover, the rationale of most of the motor as well as cognitive tests applied in this study is lacking. Why were the drawing tasks included in the study? Why was there a focus on memory tasks? Why not including other cognitive tests, particularly tests for executive functioning, a domain that is found relevant for schizophrenia and functional outcome (see Neuchterlein et al., 2004)? In case of the motor tasks a test for motor speed is*

*missing; many previous studies (see e.g. the work of Til Wykes) have shown the relevance of speed variables in schizophrenia.*

- According to your suggestion, we have added data on Wisconsin card sorting test (WCST) as a measure for executive function.
- The rationale for selecting tests has now been described in *Methods* (line 2 to 11, page 4).
- As you point out, we did not examine speed variable alone. It is surely possible that this variable might be important in schizophrenia, which has been acknowledged as a limitation (line 25, page 12 to line 3, page 13).

**Comment 3:**

*A third problem is that the conclusion of the study, which states that the finger movement test performances might be relevant for the functional outcome of patients, is too suggestive, as it is only based on the found differences between inpatients and outpatients. The assumption here is that outpatients have a better functional outcome than inpatients, which is however not examined in this study. Therefore, in my opinion, the authors give too much weight to this conclusion. The term functional outcome is even chosen as a keyword, which is not correct. The words that are mentioned here are not appropriate. I'm astonished that the authors forget to mention 'motor dexterity' and 'schizophrenia'. I would recommend removing 'functional outcome'.*

- We agree with your points that the possible relationship between finger movement test and functional outcomes remain to be speculative; thus we have deleted this point from the abstract and conclusions.
- Following your comment, we have removed 'functional outcome' and added 'motor dexterity' and 'schizophrenia' as key words.

**Comment 4:**

*Page 3: Instead of the first sentence "The study consisted of □" I would recommend to say "The participants in the present study were □".*

- Following your advice, we have rewritten the sentence (line 12, page 3).

**Comment 5:**

*The participants in the study were 27 patients with schizophrenia and 49 healthy controls. In Table 1 it is shown that these two groups differ significantly with respect to age, male/female distribution and educational level. Why not using two matched groups (on these three demographic features) with the same number of subjects?*

- 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 quit 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 too 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 Krapelin 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).