ORIGINAL ARTICLE

Patterns and Clinical Correlates of Neuropsychologic Deficits in Patients with Schizophrenia

*Shi-Kai Liu,[1,2] Ming-Hsin Hsieh,[1] Tzung-Jeng Huang,[1,3] Chi-Ming Liu,[1,3] Cheng-Chung Liu,[1,3] Mau-Sun Hua,[4] W.J. Chen,[1,5] Hai-Gwo Hwu[1,3]**

Background/Purpose: Neuropsychologic deficits are prevalent among schizophrenic patients and are closely associated with pathogenesis and outcome. The pattern, extent, severity and contributing factors to such deficits remain to be examined in Taiwanese schizophrenic patients.

Methods: A total of 122 schizophrenic patients and 94 healthy subjects for comparison were assessed by a comprehensive neuropsychologic test battery covering the eight cognitive domains of verbal ability, visual spatial ability, abstraction/execution, verbal memory, visual memory, perceptual/motor ability, mental control and attention. The relationships among cognitive deficits, demographic characteristics, clinical historical variables and clinical symptoms were further explored by multivariate regression analysis.

Results: A pattern of selective deficits superimposed on a generalized deficit was found for schizophrenic patients as a group. The mean overall deficit was 1.93 standard deviations below the control mean, and abstraction/execution, verbal memory, visual memory and attention were relatively impaired among the eight cognitive domains. However, there was also marked heterogeneity in individual performances in that 24.2%, 46.2% and 29.5% of patients performed at within normal range, moderately impaired and severely impaired levels, respectively. Duration of illness substantially affected the profile and severity of the deficits, suggesting a progressive deteriorating course in neuropsychological performance. The major predictors of cognitive deficits were number of formal years of education achieved and concurrent severity of disorganization symptoms.

Conclusion: In a large sample of schizophrenic patients who underwent comprehensive neuropsychologic evaluation, the current results confirmed that cognitive deficits were prevalent but not a universal feature within schizophrenia. The selective impairment pattern also confirmed that such deficits were mainly in frontal and frontotemporal related functions. Despite evidence suggesting that disease chronicity entailed a decline in selective cognitive domains, the trajectory of the neuropsychologic deficits remains to be examined by further longitudinal studies. [*J Formos Med Assoc* 2006;105(12):978–991]

Key Words: disorganization symptom, duration of illness, neuropsychologic deficits, schizophrenia

Schizophrenia is a chronic psychotic illness with significant social function impairment, and social function outcome has been found to be associated with impaired cognitive performances.[1] It is strongly recommended that cognitive assessments should be incorporated into individual-based specific pharmacologic and rehabilitation programs.[2] On the other hand, cognitive deficits, such as sustained attention, working memory, verbal memory, and perceptual processes, are potential

[1]Department of Psychiatry, National Taiwan University Hospital; [2]Department of Psychiatry, Far Eastern Memorial Hospital; Departments of [3]Psychiatry and [4]Psychology, and [5]Institute of Epidemiology, College of Public Health, National Taiwan University, Taipei, Taiwan.

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***Correspondence to:** Professor Hai-Gwo Hwu, Department of Psychiatry, National Taiwan University Hospital, 7 Chung-Shan South Road, Taipei 100, Taiwan.
E-mail: haigohwu@ha.mc.ntu.edu.tw

endophenotypic markers and useful probes for the complex genetics of schizophrenia.[3]

The literature shows that cognitive deficits are present in a substantial proportion of both recent onset and chronic schizophrenia patients, and almost all cognitive domains are affected. These cognitive deficits show a pattern of specific deficits superimposed on a background of generalized deficits.[4] It has also been reported that the first episode and chronic patients demonstrate comparable levels of deficits.[5–9] The clinical variables of current age, age at onset, duration of illness and level of initial neuropsychologic impairment do not seem to systematically affect cognitive performance.[5] Although certain clinical symptoms tended to parallel the levels of neurocognitive deficits, the improvements in cognitive performances could not be accounted for by changes in symptoms.[7,8] The cognitive deficits observed in schizophrenic patients thus seemed stable and were largely independent of extraneous factors, hence possible the manifestations of a "static encephalopathy".[10]

Nevertheless, as schizophrenia is markedly heterogeneous in its clinical manifestations, disease courses and social functions, analysis of schizophrenia as a group might have misleadingly obscured the heterogeneity in the severity and profile of neurocognitive performances.[9,11,12] We wanted to investigate whether or not such deficit patterns are robust for subgroups of schizophrenia patients across disease stages or levels of cognitive impairment. Based on these data, we could then hypothesize on whether the cognitive deficits are the result of a static encephalopathy or a degenerative process. Furthermore, it is important to address how cognitive performances are affected by individual and disease-associated factors, as substantial variations in the severity of deficits have been found across functional domains both within and between individual patients.[4]

Up to now, although relationships of selected cognitive domains, including sustained attention and executive function, have been reported for schizophrenic patients in Taiwan,[13] there have been no systematic description of cognitive performances in schizophrenia. The extent, profile and severity of cognitive deficits and potential contributing factors remain to be delineated. Over the years, we have followed up a substantial sample of community dwelling schizophrenic patients after their index admissions with yearly neuropsychologic assessments, using a comprehensive neuropsychologic test battery covering the major cognitive domains. As the patients varied widely in their demographic characteristics, disease course, durations of illness, clinical symptoms and treatment history, we were able to examine the effects of demographic and clinical variables on initial cognitive manifestations and subsequent change patterns. This report will focus on the initial cross-sectional cognitive performance, and the longitudinal changes will be reported separately. The main issues covered in this report thus include: (1) the pattern and magnitude of deficits in global and domain-specific performances of patients with schizophrenia, hence, to examine whether there are selective impairments among the functional domains; (2) the associations of cognitive deficits with a broad range of demographic and clinical characteristics, especially disease chronicity and severity, hence, to provide descriptive information for factors contributing to the cognitive deficits.

Patients and Methods

Subjects

Subjects in the current study were participants of the Taiwan Psychopathology Study of Schizophrenia (TPSS). The TPSS was a prospective follow-up study of schizophrenic patients spanning from August 1993 to June 1998 (TPSS stage 1; previously reported as the Multi-dimensional Psychopathological Group Research Projects[14]), and which was then extended from July 1998 to December 2001 (TPSS stage 2). The recruitment of subjects, psychopathologic instruments/assessments employed and follow-up methods/data schedules for TPSS have been described in detail elsewhere.[13,14] Briefly, during TPSS stage 1, consecutively admitted schizophrenic patients were recruited from the National Taiwan University Hospital and the

university-affiliated Provincial Taoyuan Psychiatric Center, and Taipei City Psychiatric Center to study their historical characteristics, clinical manifestations, treatment response and post-hospitalization course. Recruited subjects all met the diagnostic criteria of the Diagnostic and Statistical Manual, 4th edition (DSM-IV) of schizophrenia and gave their written informed consent. The diagnosis was confirmed at discharge by three senior psychiatrists independently, using all available caregiver reports, previous medical records, observations made during the index admission, and data gathered by structural interview using the Chinese version of the Diagnostic Interview for Genetic Study (DIGS-CH).[15] If there was any doubt, the final diagnosis was reached through a consensus meeting. Patients with a history of electroconvulsive therapy during the previous 6 months, mental retardation, trauma-related change in consciousness, psychoactive substance abuse, or physical illness that might cast doubt on the diagnosis were excluded. Clinical assessments of clinical symptoms, treatment response, drug-related adverse effects, and psychosocial function were performed at admission, on discharge and at 3, 6 and 12 months after discharge, and then yearly thereafter.

A total of 234 schizophrenic patients were enrolled during TPSS stage 1, who had been followed-up for 2–4 years at the conclusion of TPSS stage 1. At the start of TPSS stage 2, attempts were made to re-contact all TPSS stage 1 participants; those who renewed their consent were followed-up yearly for a further 2.5 years. In addition to the clinical assessments administered during TPSS stage 1, a comprehensive neuropsychologic test battery (described below) was further incorporated into the yearly assessments. Of the original 234 TPSS subjects who were successfully traced and who completed at least two neuropsychologic evaluations during the follow-up period, 122 (52.1%) were subjects of this report. Comparisons between the 122 cases included and the 112 cases who failed to be approached or who completed less than two neuropsychologic evaluations showed that there was no significant difference in sex ($\chi^2 = 0.07$, $p = 0.79$), age ($t = -1.26$, $p = 0.22$), education ($t = 0.33$, $p = 0.74$) and severity of initial clinical symptoms (for all symptom factors, $p > 0.05$).

For comparison and to provide estimates of the degree of deviation of schizophrenic patients' neuropsychologic performances, 94 healthy subjects were recruited through advertisements and announcements within the hospitals. Although the demographic characteristics could not be matched individually, attempts were made to include controls as closely matched in age, sex composition and education levels as possible. The clinical and neuropsychologic assessments of the control subjects followed the same protocol as those for the schizophrenic subjects. Evaluation using the DIGS-CH interview was done to rule out neuropsychiatric illness, DSM-IV axis I disorders and axis II schizophrenia-related personality disorders, mental retardation, and alcohol/psychoactive substance use within the past 1 year. The groups had nearly equal gender distribution (48.9% males *vs.* 50% males for comparison subjects *vs.* schizophrenic patients, respectively). Compared to schizophrenic patients, comparison subjects were younger (mean age ± standard deviation [SD], 28.61 ± 10.98 years *vs.* 32.89 ± 7.14 years for comparison subjects *vs.* schizophrenic patients respectively, $p < 0.05$) and better educated (mean years of education, 13.52 ± 2.96 *vs.* 11.17 ± 2.82 for comparison subjects *vs.* schizophrenic patients, respectively, $p < 0.05$). As the differences in basic characteristics might have confounded the estimation, we made statistical adjustments to account for the possible effects of age, sex and education in standardizing patients' neurocognitive performance scores (described below).

Clinical assessments

Baseline information regarding age at onset of psychiatric symptoms, duration of illness and history of previous medication and hospitalization were collected systematically. The Chinese version of the Positive and Negative Syndrome Schedules (PANSS),[16] having sufficient interrater reliability,[17] was used by trained senior research psychiatrists to assess the clinical psychopathology at baseline and at follow-ups. Antipsychotic-induced movement disorders were assessed by the Extrapyramidal

Syndrome Rating Scale,[18] which provided global severity measures for tardive dyskinesia (ESRS–TD) and Parkinsonism (ESRS–EPS) on a 0–7-point Likert scale.

Considering that the current sample consisted mainly of community living outpatients with mild clinical symptoms, and most of the general psychopathology subscale items of PANSS showed rare occurrences and little variation in ratings, we used seven positive subscale items and seven negative subscale items for symptomatologic analyses. Our previous factor-analytic study showed that the 14 PANSS positive and negative subscale items regrouped into four symptom dimensions, i.e. the negative (blunted affect, emotional withdrawal, poor rapport, passive apathetic social withdrawal), disorganization (conceptual disorganization, difficulty in abstract thinking, stereotyped thinking), delusion/hallucination (delusions, hallucinatory behavior, suspiciousness/persecution), and excitement (excitement, hostility) factors. These symptom dimensions were reported to be more related to cognitive performance than the original PANSS subscales.[13] We selected these 14 positive and negative subscale items to generate the four mean factor scores for analyses in this study.

Neuropsychologic tests and construction of neurocognitive functional domain

The neuropsychologic test battery consisted of the Wechsler Adult Intelligence Scale–revised (WAIS–R), Wechsler Memory Scale–revised (WMS–R), Wisconsin Card Sorting Test (WCST) computerized version, Continuous Performance Test (CPT) undegraded AX version, and Trail-making test parts A and B (Trail-A, B). The complete neuropsychologic evaluation took about 2.5 hours and was completed in the same day. As the tests were of composite nature and probably measured overlapping neuropsychologic processes, individual items of the tests were re-categorized into constructs of cognitive functional domains that hypothetically reflected basic cognitive processes.[11] According to Kremen et al, the cognitive domains and their components included the following: (1) verbal ability (VA) = information, similarity, comprehension (WAIS–R); (2) visual/spatial ability (VS) = block design, picture arrangement (WAIS–R); (3) abstraction/execution (ABEX) = category achieved, perseverative response (WCST), Trail-B; (4) verbal memory (VEM) = verbal paired association, immediate and delayed; (5) visual memory (VIM) = visual reproduction, immediate and delayed (WMS–R); (6) perceptual/motor (PEMO) = Trail-A, digit–symbol (WAIS–R); (7) mental control (MC) = arithmetic, digit span backward (WAIS–R); (8) attention (ATTN) = sensitivity index d' (CPT), digit span forward (WAIS–R).

To adjust for the effects of age, sex and education on cognitive performance, the predictive scores of individual cognitive test items of a subject were calculated by using the regression coefficients obtained from the regression of the cognitive scores on age, sex and education among the 94 comparison subjects. The difference between the raw score and the predictive score was then standardized by the root mean error of the regression and was defined as the adjusted z score of the individual test item. The comparison group's mean standardized z scores of the cognitive domains were adjusted to a mean of 0 and SD of 1. The standardized z scores of the schizophrenic patients thus provided the extent of the deviation from the comparison group and the direction of the z scores was adjusted so that higher scores indicated better performances. From individual item z scores, cognitive domain z scores could be generated by the summed average of the individual z scores of component items within each domain. In turn, an overall neuropsychologic performance index (NPI) was calculated for each subject by the summed average of the individual domain z scores. To examine the meaning of clinical heterogeneity in cognitive performance, study subjects were further classified according to the NPI into three severity subgroups: (1) those within normal limits (WNL), NPI > -1 ($n = 32$, 24.2%); (2) those moderately impaired (MI), NPI between -1 and -2.5 ($n = 61$, 46.2%); (3) those severely impaired (SI), NPI < -2.5 ($n = 39$, 29.5%).

Data analysis

Variables significantly associated with cognitive performances were examined by comparisons between subgroups defined according to specific variables (sex, illness duration, type of antipsychotics used, NPI). The correlations among demographic, clinical variables and cognitive domain scores were also examined. The χ^2 test was used for categorical variables and the independent *t* test or univariate analysis of variances (ANOVA) with Scheffe's *post hoc* analysis for continuous variables Correlations among demographic, clinical history, psychopathologic variables and cognitive impairments were examined by Pearson's correlational analysis. For variables with non-normal distributions, root square transformation was undertaken before the correlational analyses. Further multiple regression analyses were used to explore the effects of the demographic and clinical variables on the cognitive variables. NPI and individual cognitive domain mean z scores were regressed on a set of variables that were considered possibly contributing to the cognitive performances, including selective demographic variables (current age, sex, education), clinical historical variables (age at onset, duration of illness), concurrent neurologic status (presence of tardive dyskinesia and the severity of EPS) and the scores of the four symptomatologic dimensions. Statistical analyses were performed using SPSS version 10.0 (SPSS Inc., Chicago, IL, USA).

Results

Table 1 shows the descriptive data of clinical historical variables, symptomatologic dimensions, medications, extrapyramidal side effects and performances in cognitive domains of the patients. Since the current study was an extension from a previous longitudinal follow-up study, no subject was experiencing his/her first episode, and duration of illness spanned a wide range (2–30 years) with a mean ± SD of 10.09 ± 5.86 years. They were mildly symptomatic as indicated by the low mean PANSS factor scores. All patients were receiving neuroleptics with a mean ± SD dose of 821.00 ± 526.92 mg chlorpromazine equivalents, and 27.0% of subjects were receiving atypical antipsychotics (including 13% using clozapine). Patients had poor WAIS–R verbal IQ (mean ± SD = 87.22 ± 16.04, compared with the 111.88 ± 13.26 of the comparison subjects, $p < 0.05$) and global NPI (mean NPI = −1.93, one sample *t* test, $p < 0.05$). When classified by their NPIs, 24.2% ($n = 32$) of subjects could be considered as performing within the normal range (WNL group); 46.2% ($n = 61$) were moderately impaired (MI group); and 29.2% ($n = 39$) were severely impaired (SI group). Patients were substantially impaired across all individual domains (Table 1), with deficits (in z score units, reflecting the number of standard deviations below the mean of comparison subjects) ranging from −1.08 (visual/spatial ability) to −2.49 (verbal memory). Verbal ability and visual/spatial ability were relatively preserved with domain z scores around −1. In contrast, verbal memory, visual memory, abstraction/execution, and attention showed more severe impairments with deviations around 2.5 SD. Male and female schizophrenic patients did not reveal significant difference in demographic and clinical characteristics and severity of clinical symptoms and extrapyramidal side effects (Table 1). Female patients outperformed male patients in verbal ability, visual/spatial ability and verbal memory, with verbal memory showing the greatest gender difference. No significant difference was found between patients using traditional antipsychotics and those using second generation antipsychotics (comparisons across the eight neuropsychologic domains were not significant, all $p_s > 0.05$).

Figure 1 reveals the performances in the eight cognitive domains of patient groups with different durations of illness. Patients were subgrouped into those with illness duration < 5 years, i.e. the short duration group (SG, $n = 30$); those with between 5 and 10 years of illness duration, i.e. the medium duration group (MG, $n = 48$); and those longer than 10 years of illness duration, i.e. the long duration group (LG, $n = 44$). There was a general pattern of deterioration in all eight cognitive

Table 1. Descriptive data of clinical historical variables, symptomatologic dimensions, extrapyramidal symptoms and cognitive performances in schizophrenic patients*

	Male ($n=61$)	Female ($n=61$)	Total ($n=122$)
Clinical history variables			
Current age (yr)	32.69 ± 6.69	33.08 ± 7.61	32.89 ± 7.14
Education (yr)	10.93 ± 2.61	11.41 ± 3.02	11.17 ± 2.82
Age at onset (yr)	21.92 ± 6.01	23.95 ± 6.69	22.94 ± 6.42
Duration of illness (yr)	10.79 ± 6.58	9.39 ± 5.00	10.09 ± 5.86
Symptomatologic dimensions			
Negative symptoms	2.46 ± 1.14	2.46 ± 1.27	2.46 ± 1.20
Delusion-hallucination symptoms	2.52 ± 1.24	2.34 ± 1.21	2.45 ± 1.22
Cognitive symptoms	2.85 ± 1.20	2.69 ± 1.53	2.81 ± 1.37
Excitement symptoms	1.44 ± 0.71	1.50 ± 0.80	1.50 ± 0.78
Medication			
Neuroleptics (mg/d)	883.33 ± 598.75	760.12 ± 444.57	821.00 ± 526.92
Anticholinergics (mg/d)	10.31 ± 5.17	10.89 ± 3.82	10.67 ± 2.34
Extrapyramidal system side effects			
ESRS–tardive dyskinesia	0.34 ± 0.87	0.37 ± 6.80	0.35 ± 0.83
ESRS–Parkinsonism	1.31 ± 1.10	1.38 ± 1.22	1.34 ± 1.16
Cognitive performances			
NPI	−2.11 ± 1.08	−1.78 ± 1.17	−1.93 ± 1.13
Verbal ability†	−1.40 ± 0.99	−0.93 ± 1.00	−1.16 ± 1.01
Visual-spatial ability†	−1.35 ± 0.91	−0.75 ± 1.05	−1.08 ± 1.01
Abstraction/execution	−2.38 ± 1.11	−2.27 ± 1.07	−2.32 ± 1.12
Verbal memory†	−3.04 ± 2.73	−2.04 ± 2.63	−2.49 ± 2.71
Visual memory	−2.53 ± 2.30	−2.33 ± 2.16	−2.41 ± 2.19
Perceptual/motor	−2.19 ± 1.70	−1.74 ± 2.08	−1.95 ± 1.89
Mental control	−1.85 ± 0.81	−1.64 ± 0.79	−1.72 ± 0.81
Attention	−2.21 ± 1.69	−2.54 ± 2.17	−2.38 ± 2.00

**Data presented as mean ± standard deviation; †significant difference between male and female (p = 0.05). ESRS = Extrapyramidal Syndrome Rating Scale; NPI = overall neuropsychologic performance index.*

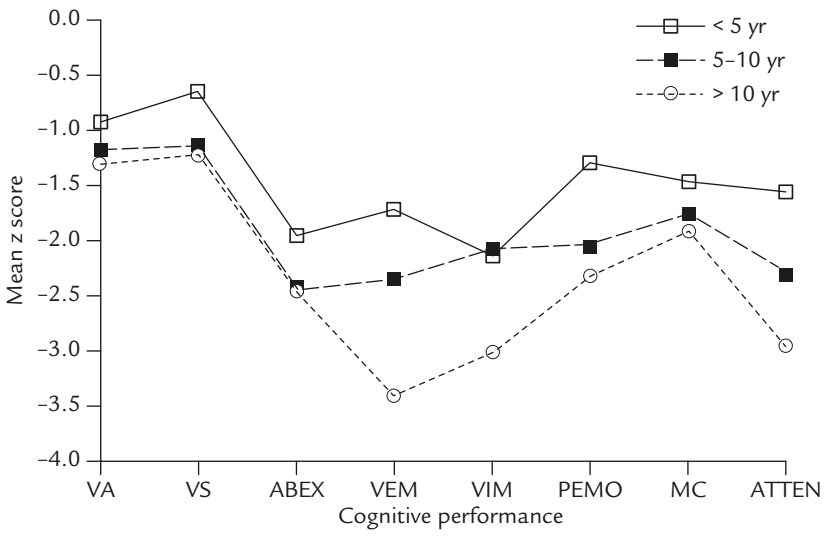

Figure 1. Deficits in eight cognitive domains by groups of patients with short duration (< 5 years), medium duration (5–10 years) and long duration (> 10 years) of illness. VA = verbal ability; VS = visual-spatial ability; ABEX = abstraction/execution; VEM = verbal memory; VIM = visual memory; PEMO = perceptual/motor ability; MC = mental control; ATTEN = attention.

domains in the disease course in that patients with longer duration of illness tended to have poorer performances in the majority of cognitive domains (Figure 1). Among the domains, verbal memory, visual memory and attention showed overt progressive deteriorations with increased chronicity, with z scores of −1.72 to −3.34, −2.34 to −3.02, and −1.56 to −2.96 respectively. The other two domains that showed a mild degree of decline were perceptual/motor and mental control. The corresponding z score changes were z values of −1.30 to −2.32, and −1.42 to −1.96, respectively. Although the overall pattern of relative deficits in abstraction/execution, visual memory, verbal memory and attention were largely preserved across subgroups, it was notable that verbal ability, visual/spatial ability and abstraction/execution were almost identical for the MG and SG subgroups, indicating no further worsening in subjects in the later disease stages. The results suggest that although abstraction/execution was affected in patients in the early phase of the disease, it remains stationary and does not further deteriorate as the disease progresses to the later stages. In contrast, verbal memory, visual memory and attention performances declined with the passage of time, probably in the first 5 years within disease onset.

Figure 2 shows the performance in the eight cognitive domains of patient groups with different degrees of impairment in overall NPI. Across subgroups with different severities of cognitive deficits, the differences in each cognitive domain were, as expected, significant among the three subgroups (ANOVA with Scheffe's *post hoc* comparisons, all $p_s < 0.01$). However, it was notable that differences among the subgroups in magnitudes of deficits in verbal ability, visual/spatial ability and abstraction/execution were relatively small, while large relative deficits in verbal memory, visual memory and attention were found. The deficits in these three domains were most profound in the SI group (Figure 2), which gave rise to the overall relative deficit pattern of the profile of the total sample. WNL patients and SI patients were further compared for possible differences in clinical history variables, treatment-related side effects and clinical symptom profiles. The WNL group was significantly better educated ($t = 4.46$, $p < 0.001$), with older age at disease onset ($t = 2.20$, $p = 0.03$), shorter duration of illness ($t = -2.13$, $p = 0.04$), less severity of EPS ($t = -2.34$, $p = 0.02$), lower antipsychotic dosage ($t = -2.72$, $p = 0.009$), and with fewer negative and disorganized symptoms ($t = -2.78$, $p = 0.007$; $t = -5.10$, $p < 0.001$, respectively).

Table 2 reveals the correlations among clinical historical variables, clinical symptoms and deficits in individual cognitive domains. The data showed that there was a general pattern that poorer performances were associated with less education, longer duration of illness, severer clinical negative, disorganization symptoms and EPS. It was notable that current age, age at onset, positive and

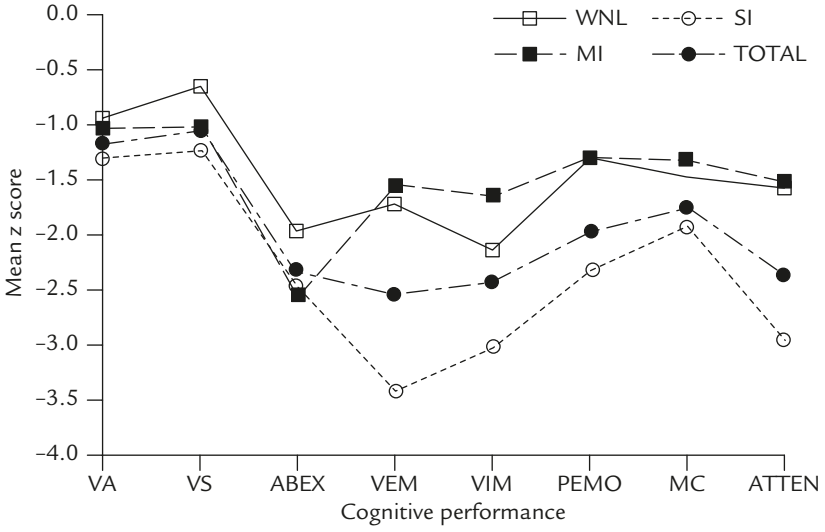

Figure 2. Deficits in eight neurocognitive domains by subgroups of patients with normal performance (WNL), mild impairment (MI) and severe impairment (SI) in overall neuropsychologic performance index. VA = verbal ability; VS = visual-spatial ability; ABEX = abstraction/execution; VEM = verbal memory; VIM = visual memory; PEMO = perceptual/motor ability; MC = mental control; ATTEN = attention.

Table 2. Correlations among demographic, clinical variables and z scores of performances in the eight cognitive domains

	Verbal ability	Visual-spatial ability	Abstraction/ execution	Verbal memory	Visual memory	Perceptual/ motor	Mental control	Attention
Age	–0.06	–0.004	–0.18	–0.14	–0.17	0.07	–0.05	0.12
Education	0.51*	0.07	–0.21†	0.43*	0.37*	0.22†	0.29*	0.40*
Duration of illness	–0.12	–0.18†	–0.24†	–0.25*	–0.20†	–0.11	–0.13	–0.24*
Age at onset	0.09	0.24	–0.01	0.10	0.02	0.26	0.14	0.12
EPS severity	–0.22†	–0.21†	–0.11	–0.10	–0.23†	–0.23†	–0.31*	–0.31*
Negative	–0.20†	–0.15	–0.13	–0.20†	–0.22†	–0.13	–0.18†	–0.28*
Cognitive	–0.42*	–0.36*	–0.15	–0.31*	–0.28*	–0.28*	–0.29*	–0.39*
Positive	–0.12	–0.14	–0.08	–0.07	–0.11	–0.15	–0.17	–0.18†
Excitement	–0.01	–0.09	0.02	0.12	–0.03	–0.05	–0.13	–0.17

$p < 0.005$; †$p < 0.05$. EPS severity = severity of extrapyramidal side effects from antipsychotic medications.

excitement symptoms were not associated with any cognitive performance.

Table 3 shows the predictive variables of cognitive deficits using multivariate regression analysis. The predictive variables included demographic characteristics (age, sex, education), duration of illness, motor side effects (severity of EPS and tardive dyskinesia) and the four clinical symptom dimensions. The analytical model was significant for all cognitive domains ($R^2 = 0.22–0.42$) except abstraction/execution ($R^2 = 0.16$, $p = 0.08$). Many of the variables with significant correlations in univariate analyses were not significant on multivariate analysis, indicating complex intercorrelations among the variables. Disorganization symptoms and education were the two most robust contributing factors to cognitive domain performances in terms of the number of domains involved (five and four domains respectively) and the relatively large regression coefficients. Duration of illness, gender and severity of EPS also had scattered associations with verbal ability, visual/spatial ability, perceptual/motor and attention.

Discussion

This study described in detail the profiles of cognitive deficits in 122 community living stable schizophrenic patients. The results showed that schizophrenic patients as a group had significant impairments in neuropsychologic function with a mean global deficit of 1.93 SDs relative to the comparison subjects, after adjusting for age, sex and education (Table 1). The mean deficits of around 2 SDs in the current schizophrenic sample are comparable to those reported in chronic schizophrenic patients,[19] but larger in magnitude than the 0.5–1.5 SDs reported for patients experiencing their first episode.[20] We thus emphasize that there might be cognitive function deteriorations along the clinical course in schizophrenic patients, which is substantiated by the data shown in Figure 1, where a progressive pattern of cognitive function impairment was clearly shown, especially in verbal memory, visual memory, perceptual/motor, mental control and attention. A relative deficit pattern was also found in that more severe impairments could be observed in verbal memory, visual/spatial memory, abstraction/execution and attention functions (mean z scores around –2.5) than in verbal ability and visual/spatial ability (mean z scores around –1).

The generalized deficits with disproportionate impairments in attention, frontal-based executive functions, and temporal-based memory found in the current study replicate those reported in the literature[20–23] and this also supports that cognitive impairments in schizophrenia might be characterized by selective involvement of frontotemporal functions superimposed on a generalized disability.[4,20,21] The functional deficits were also associated with changes in prefrontal and temporal structure and volume in schizophrenic patients.[23–25]

Table 3. Predictive variables of cognitive deficits using multivariate regression analysis*

	NPI	Verbal ability	Visual-spatial ability	Abstraction/ execution†	Verbal memory	Visual memory	Perceptual/ motor	Mental control	Attention
					Adjusted R^2				
	0.38§	0.42§	0.24§	0.16	0.29§	0.22§	0.21§	0.25§	0.38§
					Standardized regression coefficient β‡				
Age	–	–	–	–	–	–	–	–	–
Sex	–	0.16‖	0.26‖	–	–	–	–	–	–
Education	0.33§	0.43§	–	–	0.32§	0.34§	–	0.25§	0.37§
Duration of illness	–0.21‖	–	–0.20‖	–	–0.18‖	–	–0.25‖	–0.19‖	–0.20‖
EPS	–0.20‖	–0.19‖	–	–	–	–	–	–0.32§	–0.25§
TD	–	–	–	–	–	–	–	–	–
Negative	–	–	–	–	–	–	–	–	–
Disorganization	–0.37§	–0.38§	–0.37§	–	–0.23‖	–	–0.24‖	–	–0.27‖
Delusion/hallucination	–	–	–	–	–	–	–	–	–
Excitement	–	–	–	–	–	–	–	–	–

**Individual neurocognitive domain performance was regressed on demographic characteristics (age, sex, education), duration of illness and current pathologic manifestations (severity of EPS, severity of TD, and the four clinical symptom dimensions); †the overall model was not statistically significant so the regression coefficients are not shown; ‡only the statistically significant ($p < 0.05$) standardized βs are shown; §$p < 0.005$; ‖$p < 0.05$. NPI = overall neuropsychologic performance index; EPS = extrapyramidal system side effects from antipsychotic medications; TD = tardive dyskinesia symptoms.*

Despite the evidence, there remains concern that as the difficulty and complexity levels of the tasks for individual cognitive domains were often unmatched, the relative deficit pattern might have simply reflected the difficulty levels rather than genuine domain-specific impairments. Moreover, a generalized deficit or a slowing in general processing speed, rather than possible domain-specific or task-specific deficits could have accounted for the uneven performance pattern,[26] since tasks with selective attention/inhibition components and those with a lexicon component were demonstrated to be affected by the general processing speed to a greater extent than those without in schizophrenic patients.[27,28] Indeed, negative symptoms and severity of extrapyramidal symptoms, both clinical indicators for possible psychomotor slowing, was associated with poorer performances in those neurocognitive domains that were time-bound and speed-dependent.

There are reasons to believe that the pattern of differential deficits revealed by the current study is not likely to be an artifact, as schizophrenic and comparison subjects were equally exposed to the task-difficulty effects which were controlled for by the standardization of the cognitive data. The comparisons of the z scores within schizophrenia thus reflected the degree of relative domain-specific differences after weighting against comparison subjects rather than direct comparisons between the domain performances within schizophrenia subjects. In addition, neurocognitive ability was considered as a composite construct of complex cognitive processes, hence not likely to be explained by a general ability.[29] Besides, the parsing of neurocognitive function into distinct independent dimensions has been verified psychometrically by previous factor or cluster analytic studies[30] and external validity was provided through their differential associations with historical variables and clinical characteristics, especially the negative and disorganization symptoms.[29,31,32] More specifically from the current study, the cognitive domains did show differential patterns of associations with other noncognitive factors, supporting their relative independence.

Analysis of schizophrenia as a group might have misleadingly obscured the heterogeneity in severity and profile of cognitive performances.[11,12] Indeed, schizophrenic subjects in the current study varied greatly in global severity of cognitive impairments. Around 24.2% ($n=32$) could be described as performing without over impairment, 46.2% ($n=61$) as moderately impaired, and 29.2% ($n=39$) as remarkably impaired. The relative deficit pattern of the entire group was less conspicuous among subgroups with less global impairments and became apparent in those with the most severe global impairments due to the very poor performances in verbal memory, visual memory and attention. Subgroups defined by subjects' length of illness also revealed a similar pattern of selective deficits. In the group with remarkable impairment, the association of severe cognitive impairments with lower educational achievement, earlier age at onset, longer duration of illness, more severe EPS, negative and disorganized symptoms, provided evidence for a separate subtype within schizophrenia, e.g. the deficit type of schizophrenia.[33] Another intriguing finding was that these subgroups also differed in their deficit profiles. For those with least impairments, selective impairment was most apparent for the abstraction/execution function, while for those with more severe global deficits, the deficits in abstraction/execution remained at about the same level as those less severely impaired, and the worst performances were found in verbal memory, mental control and attention. Ceiling effects in abstraction/execution might have accounted for the findings.

In multivariate analyses, sex, education, duration of illness, disorganization symptoms and severity of extrapyramidal symptoms were found to contribute to individual domain performances except for the domain of abstraction/execution, independently. The pattern of relative abstraction/execution, verbal memory/visual memory and attention impairments was largely preserved for all groups with different disease chronicity. Moreover, the poorer performances in verbal memory, visual memory and attention manifested by patients with longer duration of illness suggested that decline

in performances in these domains might have occurred over the passage of time. The possible decline might not be simply age-related, since current age and age at onset were not associated with performance. The duration effects remained robust for visual/spatial ability, verbal memory, perceptual/motor, mental control and attention after potential confounding factors were controlled for in multiple regression analysis. The findings were in contrast to results from first episode patients that performances in most neurocognitive domains remained stable or even improved.[22,34] Considering that first episode subjects were mainly younger aged with follow-up periods limited to the immediate post-psychotic years, the evaluation might have missed the critical period of cognitive decline.[35] The current finding of possible neurocognitive declines was nonetheless limited by its cross-sectional nature; further longitudinal studies of patient samples stratified according to disease chronicity and followed-up for sufficient periods of time are required to solve this issue. Moreover, should there be true decline, it should not be taken as direct evidence of an ongoing neurodegenerative process, since natural age-related decline in cognitive functions, cumulated treatment-related side effects and environmental factors might complicate the picture.[36]

Disorganization symptoms were the only clinical symptoms showing consistent associations with cognitive domain deficits in the current study. Despite the attempts to explain clinical symptoms in terms of cognitive dysfunction, they nevertheless exhibited complex relationships and the findings were inconsistent. Variability in the nature of cognitive domains under investigation, clinical characteristics of the subjects, symptom definition and classifications might have contributed to the inconsistent findings.[37,38] Studies in first episode cases did not reveal consistent associations with clinical symptoms even with large sample size up to 301 subjects,[9,34] but during subsequent follow-up, associations with negative symptoms were observed,[7,39] indicating that clinical symptoms in the early stage might be poorly representative of cognitive deficits, while persistent symptoms manifested in stable clinical states are related to underlying cognitive dysfunction. This is supported by findings in stable patients with longer duration of illness that correlations with severity of negative and disorganized symptoms were more consistently reported.[37,40,41] Nevertheless, the correlations were modest at best, and clinical symptoms contributed to only 10–15% of the variance in cognitive performances, and the longitudinal development of cognitive dysfunction did not parallel the change in clinical symptoms, suggesting that psychopathology and cognitive deficits in schizophrenia only partially overlap and might be caused by distinct pathophysiologic processes.[42]

In the current study, negative symptoms were associated with cognitive measures in primary analysis but not in multivariate analysis. It is plausible that the negative symptoms were defined relatively narrowly, focusing on aspects of diminished affective expression, diminution in interpersonal contacts and social interests, while those more directly reflective of cognitive dysfunction, such as positive formal thought disorder, language performances and abstract thinking ability, were categorized as disorganization symptoms. In this regard, the results concurred with previous reports that syndromes of alogia, attentional impairment, and positive formal thought disorder that reflected primarily a disorganization of thought are more closely associated with cognitive performances than syndromes of affective flattening, avolition/apathy, and anhedonia.[43] Another possibility is that it was often difficult to distinguish between primary negative symptoms and extrapyramidal symptoms. This appeared to be the case in the current study, since negative symptoms and extrapyramidal symptoms were moderately correlated ($r = 0.47$, $p < 0.001$) and the profiles of associations with cognitive deficits in primary analyses were rather similar.

As expected, patients with better education performed better in most domains except perceptual/motor and abstraction/execution. One plausible explanation was that levels of academic achievement simply reflected differences in premorbid intellectual ability, hence the differences in cognitive

performances. However, it is complicated by the fact that schizophrenia often develops insidiously during critical periods of academic achievement and that some attenuation is expected and the degree of decrement cannot be exactly determined.[44] In the current study, when the 22 (12.5%) subjects who developed schizophrenia before completing their highest education were excluded, the results of analysis were similar to those obtained from the whole sample, indicating that the effects of possible underestimation of baseline intellectual ability by their educational achievement did not significantly influence the results. In addition, the association between verbal IQ, which is considered to be relatively well preserved in schizophrenia and approximates premorbid intellectual ability,[4] and education was modest ($r = 0.55$). Education thus might have independent contributions to cognitive performances other than general intellectual ability. It might be hypothesized that performances in tasks with at least some components that are well learned before the onset of disease are associated with education, such as verbal ability and verbal memory, whilst those involving mainly visual-spatial ability and perception are not. The unexpected finding of the negative contribution of education to abstraction/execution remains to be further explored.

The selective versus generalized issue might not be of mere academic interest. Although the relationships between cognitive domain performances and subsequent psychosocial functioning in the current sample are yet to be reported, as types and severity of individual cognitive domain deficits were associated with unique functional outcome dimensions, they were important targets of clinical assessments and treatment.[45] Generally, cognitive deficits did predict subsequent social functioning, independent daily living and disability level,[46–48] and measures of cognitive functioning accounted for more variance in functional capacity than did psychiatric ratings of symptoms.[47] More specifically, verbal memory was associated with all types of functional outcome;[49] vigilance was related to social problem solving and skill acquisition;[50] and executive function predicted community functioning but not social problem solving.[49] Since the current sample showed overt deficits in all these domains, it would be possible to examine whether they are indeed associated with different aspects of social and community functions and predicted subsequent functionality.

In conclusion, this study has provided information on the severity and profile of neurocognitive deficits in schizophrenic patients. Heterogeneity in neurocognitive capacity was clearly demonstrated and several potential contributing factors were found. Subjects with different durations of illness manifested specific patterns of deficits, and memory-related functions seemed to deteriorate with the passage of time, implying different trajectories taken by individual domains. The further development of neurocognitive deficits awaits confirmation from the results of longitudinal follow-up studies.

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