Eur Arch Psychiatry Clin Neurosci (2012) 262:107–115
DOI 10.1007/s00406-011-0224-4

ORIGINAL PAPER

General and domain-specific neurocognitive impairments in deficit and non-deficit schizophrenia

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Received: 7 March 2010 / Accepted: 7 July 2011 / Published online: 27 July 2011

Abstract Earlier studies suggested more severe overall cognitive impairments in deficit versus non-deficit schizophrenia; however, the specific contribution of different cognitive domains to this overall cognitive impairment remains unclear. The purpose of this study was to compare the two subtypes in general cognitive functioning as well as in individual cognitive domains using the composite score approach. One hundred and forty-three patients fulfilling the criteria for the deficit syndrome were compared with 123 patients diagnosed with non-deficit schizophrenia. Neurocognitive functioning was assessed by a neuropsychological test battery measuring the domains of sustained vigilance/attention, working memory, short-term memory, verbal memory, cognitive flexibility, and ideation fluency. Using the raw neuropsychological measures, we calculated a global index of cognitive impairment and domain-specific composite *z*-scores. Association between these composite scores and the deficit syndrome was examined by logistic regression analysis. After adjusting for relevant covariates including sex, age, education, smoking, and antipsychotic dose, results indicated a significant increase in the likelihood of deficit syndrome as a function of global (OR = 5.40; 95% CI 3.02–9.65) as well as domain-specific impairments (OR > 2 for all individual domains except for short-term memory). Cognitive flexibility was an independent predictor (OR = 2.92; 95% CI 1.47–5.80), whereas other cognitive domains demonstrated no unique contribution to the general cognitive impairment. Patients with deficit schizophrenia suffer from a more severe degree of neurocognitive impairment, which is qualitatively similar to the dysfunction seen in non-deficit schizophrenia. However, our results indicate that cognitive flexibility is specifically impaired in deficit versus non-deficit patients and may therefore represent a core feature of this subtype.

Keywords Schizophrenia · Deficit syndrome · Neurocognitive dysfunction · Cognitive flexibility · Composite score approach · Antipsychotic medication

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Introduction

The deficit syndrome, a subgroup within schizophrenia, is characterized by enduring, idiopathic negative symptoms, including flattened affect, anhedonia, poverty of speech, curbing of interest, lack of sense of purpose, and diminished social drive. These features are continuously present during periods of clinical stability and are not secondary, i.e., not explainable by depression, anxiety, medication side effect, positive symptoms, substance abuse, or psychosocial deprivation. Since the introduction of the concept by Carpenter et al. [1], a substantial body of evidence has accumulated supporting the construct validity of the deficit syndrome as a pathophysiologically distinct subgroup within schizophrenia [2, 3].

Neurocognitive dysfunction is regarded as a core feature of schizophrenia that plays a major role in the functional outcome of the disorder [4]. Several studies that have examined neurocognitive functioning in these two subgroups of schizophrenia yielded conflicting results.

Buchanan et al. [5] reported differences in executive functioning in conjunction with a lack of difference in "temporal-lobe specific" performance. Similarly, two subsequent studies [6, 7] found poor performance in deficit schizophrenia (SZ-D) in executive functioning. Galderisi et al. [8] reported worse cognitive functioning in general, with specific dysfunction of complex motor tasks in the SZ-D group compared to the non-deficit schizophrenia (SZ-ND) group, suggesting that SZ-D patients suffer from specific frontoparietal dysfunction. However, the most recent results from a separate study and a meta-analysis of Cohen et al. [9] do not support the frontoparietal hypothesis of SZ-D. In their study comparing 20 SZ-D and 25 SZ-ND patients, the deficit group did not perform worse than the non-deficit group in frontal and parietal domain scores, although both reached lower scores compared to healthy controls. In the meta-analysis of 13 previous studies, results demonstrated more severe global neuropsychological impairment in deficit patients, with the specific contribution of olfaction, social cognition and language, but no specificity of neuropsychological processes connected to the frontal and parietal lobes.

The extensive use of neuropsychological tests in psychiatric disorders, especially in schizophrenia, has uncovered compelling results about the neurocognitive deficits observable in endogenous psychoses. On the other hand, these studies have raised several methodological controversies. As Jaeger et al. [10] summarize, such analyses often require data reduction techniques to avoid multiple comparisons and the grouping of neuropsychological tests according to conventional cognitive domains. This grouping of tests is often arbitrary and does not take into account the overlapping of different measures between domains. A statistical method to overcome this shortcoming is the composite score approach, using the *z*-transformation of variables to generate comparable data across domains [11].

Overall, due to the aforementioned methodological problems and shortcomings of previous studies including small sample size and variation of methodology across investigations, the specific neurocognitive profile of the deficit subgroup compared to non-deficit schizophrenia remains unclear. The aim of this study was to compare neurocognitive impairment and the specific contribution of cognitive domains in a large sample of SZ-D and SZ-ND patients using the composite score approach. The rationale for such a study is to reach a better understanding of the neurocognitive dysfunction in deficit schizophrenia and to further delineate the neurocognitive profile in patients suffering from this form of the disorder. Findings from such studies have the potential to promote further clinical, pharmacological, and genetic studies.

Methods

Participants

Participants included 266 patients between 18 and 65 years meeting DSM-IV criteria for schizophrenia [12] who were enrolled in a large-scale genetic study [13] and completed the neuropsychological test battery for the current investigation. The aim of the parent genetic study was to compare previously extensively investigated genetic markers in the deficit and non-deficit subgroups of schizophrenia. To achieve a balanced case–control design and optimal statistical power, we planned a two-center study, where the centers were selected in order to increase the likelihood of recruiting patients with deficit schizophrenia. The clinical diagnosis was confirmed by the Hungarian translation of the MINI 5.0 Neuropsychiatric Interview [14]; in ambiguous cases, decision about inclusion was taken by an expert panel of psychiatrists working at the study sites. All enrolled patients were treated at inpatient or outpatient units of two major psychiatric centers in Budapest, Hungary. Criteria for exclusion included severe comorbid conditions, such as neurological disorders, head trauma, mental retardation, or substance abuse. The study was approved by the Hungarian National Scientific and Ethical Committee (ETT TUKEB) and the Semmelweis University Institutional Ethical Board. All participants provided written informed consent.

Clinical, psychopathological, and neurocognitive assessment

Demographic and clinical data were assessed prior to the neuropsychological testing and included the following variables: age, sex, level and years of education, smoking, age at onset and duration of illness, number of hospitalizations, current antipsychotic therapy. The Positive and Negative Symptom Scale (PANSS) [15] and the Schedule for Deficit Syndrome (SDS) [16] were administered by trained staff members. Out of the 266 patients involved in the neuropsychological analyses, 143 fulfilled criteria for the deficit syndrome, demonstrating at least 2 of the 6 typical features at a clinically significant severity.

Inter-rater reliability and internal consistency (IC) of the Hungarian version of the SDS were assessed by calculating intra-class correlation coefficient (ICC) and Cronbach alpha for IC. Analysis of individual items yielded a median ICC value of 0.86, while there was full agreement among raters in the assessment of deficit/non-deficit status. The Cronbach alpha for the SDS scale based on the entire sample was 0.84. The current antipsychotic therapy of patients was converted into chlorpromazine (cpz)-

Table 1 Neuropsychological tests used in the study grouped by cognitive domain

Cognitive domain	Neuropsychological measures
Sustained vigilance/attention	Stroop words only and colors only scores [24], TMT-A [25]
Working memory	WAIS-R Digit Span Backward, WAIS-R Digit symbol score [26]
Short-term memory span	WAIS-R Digit Span Forward [26]
Verbal memory	RAVLT trials 1–5 total, RAVLT learning (5-1), RAVLT forget (7-5) [27]
Cognitive flexibility	WCST Perseverative errors percent, WCST # categories, WCST trials to complete set, WCST failure to maintain set [28], Stroop color/word interference score [24], TMT-B [25]
Ideation fluency	COWAT score [29], animal naming test score [17]

WAIS-R Wechsler adult intelligence scale, *WCST* Wisconsin card sorting test, *Stroop* color stroop test, *TMT A&B* trail making tests A&B, *RAVLT* Rey auditory verbal learning test, *COWAT* controlled oral word association test

equivalent values following the guidelines of Baldessarini and Tarazi [17] and Woods [18].

A battery of classical neuropsychological tests, covering a broad range of neurocognitive functions, was used for neurocognitive assessment (Table 1), following general testing guidelines [19]. The tests were selected on the basis of earlier results, showing their ability to assess neurocognitive impairment in schizophrenia.

To control for the overlap of the different neuropsychological tests (i.e., their "non-specificity") and to minimize multiple testing of neurocognitive variables across groups, we used the composite score approach as a data reduction technique. For this reason, measures of the different neuropsychological tests were grouped into cognitive functions a priori according to earlier results. Based on the conceptual model described by Jaeger et al. [10], the neuropsychological variables were assigned to the cognitive domains of sustained vigilance/attention, working memory, short-term memory capacity, verbal memory, set shifting/cognitive flexibility, and ideation fluency as seen in Table 1. The cognitive domains including these specific neuropsychological variables were used in the subsequent analyses.

Statistical procedures

The Statistical Analysis System (SAS) for Windows was used for all statistical analyses (version 9.1; SAS Institute, Cary, NC). Descriptive statistical data including demographic, clinical, and neurocognitive variables are presented as mean (SD) values for the SZ-ND and SZ-D subgroups. We used the chi-square test to compare the subgroups in case of categorical variables and the General Linear Model (GLM) analysis for continuous variables. In line with the composite score approach [11], all neuropsychological variables were standardized using z-transformation and adjusted for sign according to performance direction (with higher values indicating better performance for all variables). Similar to Bilder et al. [11], composite scores for each cognitive domain were calculated by summation of the z-transformed scores of the measures grouped into that specific cognitive domain. For the global index of cognitive impairment, all z-transformed neuropsychological variables were added.

Composite scores of the global index and each cognitive domain were compared between groups by effect size estimation [20] and univariate logistic regression analysis, where the deficit status was the dependent variable and the global or domain-specific z-scores the independent variables. To determine the unique domain-specific contribution of the different cognitive domains with respect to each other, we performed a multiple logistic regression analysis with all domain-specific z-scores added to the model as independent variables. The effects of sex, age, level of education, smoking, and antipsychotic medication (cpz-equivalents) were explored in ancillary analyses, where these variables were added to the multivariate logistic regression model as covariates. Covariates were chosen as possible sociodemographic and biological confounders, the most probable to affect cognitive functions. Statistical significance was defined at the level of 0.05. All calculated P values are two-tailed.

Results

Demographic and clinical results

Basic demographic and clinical data describing the two subgroups are summarized in Table 2. The SZ-ND and SZ-D subgroups demonstrated no significant differences in gender distribution, age, age at onset, and smoking. Chi-square and GLM analysis revealed significant differences in the level of education and years of education, number of hospitalizations, inpatient/outpatient ratio, duration of illness, and cpz-equivalent doses. As Table 2 indicates, SZ-ND and SZ-D patients differed significantly in their profile of psychopathological symptoms.

Table 2 Demographic and clinical characteristics of the non-deficit and deficit subgroups

Characteristic	SZ-ND ($n = 123$)	SZ-D ($n = 143$)	F/χ^2	P
Age (years)	36.0 (11.4)	38.7 (12.0)	3.34	0.068
Sex (M:F ratio)	58:65	64:79	0.15	0.7
Level of education (E:S:H ratio)	36:51:34	51:76:16	12.23	0.002[b]
Education (years)[a]	13.5 (3.1)	11.9 (2.8)	9.88	0.002[b]
Age at onset	28.4 (9.5)	28.8 (9.8)	0.12	0.73
Duration of illness (years)	7.5 (8.2)	10.1 (9.5)	5.34	0.021[b]
# of hospitalizations	5.4 (5.0)	7.0 (6.1)	5.32	0.022[b]
Inpatient/outpatient ratio	78:45	110:33	7.66	0.021[b]
PANSS positive (sum)	17.6 (4.8)	17.7 (5.1)	0.001	0.97
PANSS negative (sum)	16.9 (4.6)	22.4 (4.2)	101.13	0.0001[b]
PANSS general (sum)	36.7 (8.3)	43.1 (7.9)	40.7	0.0001[b]
PANSS total	71.3 (14.8)	83.1 (13.8)	45.3	0.0001[b]
SDS total	10.7 (1.9)	16.5 (2.8)	379.7	0.0001[b]
Smoking (%)	52.8	46.6	0.92	0.33
Antipsychotic therapy (cpz-equivalent dose in mgs)	394.5 (301.0)	507.0 (391.0)	7.1	0.008[b]
Typical antipsychotics (%)	13.1	16.2	0.56	0.45
Atypical antipsychotics (%)	95.4	96.8	0.35	0.55

SZ-ND Non-deficit schizophrenia, *SZ-D* deficit schizophrenia, *M* male, *F* female, *E* elementary, *S* secondary, *H* higher education, *PANSS* positive and negative symptom scale, *SDS* schedule for the deficit syndrome, *cpz-equivalent* chlorpromazine-equivalent

[a] Based on data of 155 patients

[b] Group differences significant at $P < 0.05$. Other group differences not statistically significant

Table 3 Descriptive statistics of raw neuropsychological measures

Neuropsychological measure	SZ-ND ($n = 123$[a])		SZ-D ($n = 143$[a])		F	P
	Mean (SD)	Q1–Q3	Mean (SD)	Q1–Q3		
WAIS-R Digit Span Backward	4.4 (1.3)	4–5	3.9 (1.3)	3–5	10.12	0.0016
WAIS-R Digit Span Forward	6.4 (1.4)	6–7	6.1 (1.4)	5–7	3.70	0.055
WAIS-R Digit Symbol Raw	34.1 (11.2)	26–41	25.6 (12.0)	16–33	32.97	<0.0001
Stroop words only	99.0 (29.9)	80–118	92.3 (29.6)	76–110	2.93	0.088
Stroop colors only	74.7 (20.3)	60–90	63.1 (22.8)	46–79	16.63	<0.0001
Stroop interference	45.3 (13.9)	37–54	36.4 (16.7)	24–48	18.54	<0.0001
Trail making A time	57.0 (25.9)	40–70	84.2 (55.7)	48–95	22.27	<0.0001
Trail making B time	107.4 (61.4)	65–134	150.1 (84.0)	90–189	20.61	<0.0001
COWAT total correct	11.4 (4.7)	8–14	8.9 (4.4)	6–12	19.66	<0.0001
Animal naming total correct	18.1 (6.6)	14–21	15.0 (5.8)	10–19	15.37	<0.0001
WCST Perseverative errors percent	15.8 (11.9)	7.8–11.6	25.5 (17.5)	11.8–33.6	26.26	<0.0001
WCST categories complete	4.8 (1.8)	3–6	3.3 (2.1)	2–6	33.92	<0.0001
WCST non-perseverative errors percent	14.0 (7.3)	8.1–12.5	17.8 (10.6)	10.9–22.7	11.35	0.0009
WCST trials to complete set	21.5 (23.9)	11–19	41.1 (42.6)	11–56	19.90	<0.0001
WCST failure to maintain set	1.0 (1.4)	0–2	1.0 (1.3)	0–2	0.03	0.85
RAVLT trials 1–5 total	45.3 (10.6)	38–53	37.3 (12.6)	30–46	30.59	<0.0001

SZ-ND non-deficit schizophrenia, *SZ-D* deficit schizophrenia, *SD* standard deviation, *Q1–Q3* interquartile range

[a] Sample size may vary due to missing data

Neurocognitive assessment

Results on neurocognitive performance indicated better performance in all measures of raw neuropsychological data in the SZ-ND group as compared to the SZ-D group. GLM analyses indicated that the differences between the two groups were statistically significant for all measures, except for the WAIS-R Digit Span Forward and the Stroop words only tests where the differences approached statistical significance. Raw neuropsychological data are summarized in Table 3, whereas the z-transformed cognitive domain scores and the global cognitive impairment index

Table 4 Descriptive statistics of domain-specific composite scores, effect sizes, and results of univariate and multivariate logistic regression analyses

Cognitive domain	SZ-ND		SZ-D		Effect size (Cohen's d)	Logistic regression			
						Univariate		Multivariate	
	Mean (SD)	Q1–Q3	Mean (SD)	Q1–Q3		OR	95% CI	OR	95% CI
Sustained vigilance/ attention	0.23 (0.68)	−0.23–0.71	−0.22 (0.93)	−0.64–0.38	0.55	2.01	1.36–2.97	0.81	0.47–1.37
Working memory	0.27 (0.80)	−0.35–0.78	−0.28 (0.88)	−0.81–0.28	0.65	2.35	1.59–3.47	1.29	0.70–2.36
Short-term memory span	0.13 (0.98)	−0.16–0.56	−0.11 (1.00)	−0.88–0.56	0.24	1.22	0.93–1.59	0.86	0.60–1.23
Verbal memory	0.27 (0.77)	−0.30–0.92	−0.24 (0.88)	−0.80–0.47	0.60	2.03	1.46–2.83	1.34	0.88–2.05
Cognitive flexibility	0.24 (0.58)	−0.06–0.67	−0.26 (0.72)	−0.64–0.21	0.77	3.23	2.04–5.10	2.92	1.47–5.80
Ideation fluency	0.27 (0.91)	−0.25–0.64	−0.25 (0.78)	−0.78–0.36	0.60	2.25	1.52–3.33	1.42	0.87–2.30
Global cognitive impairment	0.23 (0.46)	−0.09–0.60	−0.24 (0.59)	−0.64–0.17	0.88	5.40	3.02–9.65	–	–

SZ-ND non-deficit schizophrenia, *SZ-D* deficit schizophrenia, *SD* standard deviation, *Q1–Q3* interquartile range, *OR* odds ratio, *95% CI* 95% confidence intervals

are shown in Table 4. Comparison of the global cognitive impairment index and cognitive domain scores by effect size estimation revealed low to medium Cohen's d values.

Logistic regression analyses

Univariate logistic regression analysis was used to test the predictive power of the global cognitive impairment index as the independent variable for the patients' dichotomous classification with respect to deficit status (Table 4). The test revealed a highly significant increase in the likelihood of deficit syndrome as a function of global neuropsychological impairment (OR = 5.40; 95% CI 3.02–9.65), after adjustment for sex, age, and antipsychotic medication doses. We performed similar univariate analyses to test the individual domain-specific *z*-scores in predicting deficit status. Results demonstrated significant odds ratio values in all cognitive domains, except for the domain of short-term memory (OR = 1.22; 95% CI 0.93–1.59) with the highest odds ratios for cognitive flexibility (OR = 3.23; 95% CI 2.04–5.10) and working memory (OR = 2.35; 95% CI 1.59–3.47). Results are shown in Table 4 and Fig. 1.

To test the effects of education and smoking, as possible confounders on the association of the global cognitive impairment index and deficit status, we performed additional exploratory logistic regression analyses where either the level of completed education (elementary, secondary, higher) or smoking status was added to the model as covariates. Correcting for education in the logistic regression analysis increased the predictive power of the global composite score (OR = 5.77; 95% CI = 3.12–10.68), conversely adjustment for smoking decreased the predictive factor, but the original association remained significant (OR = 5.00; 95% CI 2.73–9.17).

In the multivariate logistic regression analysis including all domain-specific *z*-scores in the model as independent variables, and sex, age, and antipsychotic medication dose as covariates, the independent effects of cognitive domains were not significant (Table 4), except for the cognitive flexibility domain (OR = 2.92; 95% CI 1.47–5.80). Including smoking in the multivariate analysis had no significant effect on the above results (OR = 2.74; 95% CI 1.30–5.80).

Discussion

Although the concept of the deficit syndrome has had a profound influence on schizophrenia research, the specific neurocognitive profile of the deficit subgroup in comparison with non-deficit schizophrenia is still under debate. In this study, patients with deficit schizophrenia demonstrated significantly lower neurocognitive performance in general and in all cognitive domains except for the domain of short-term memory. The global cognitive impairment index, a composite measure of all neuropsychological measures, was found to have high predictive power (OR = 5.40; 95% CI 3.02–9.65) with regard to the two subtypes of schizophrenia. These results shed light on the "quantitative" differences in neurocognition between the two subgroups. When testing the "qualitative" differences in the cognitive profile of the two subgroups, i.e., the specific contribution of individual cognitive domains, we observed a significant difference in the cognitive flexibility (set shifting) domain independently of all other cognitive domains. The observed OR of 2.92 (95% CI 1.47–5.80) means that the composite score describing cognitive flexibility has a significant predictive power with respect to the

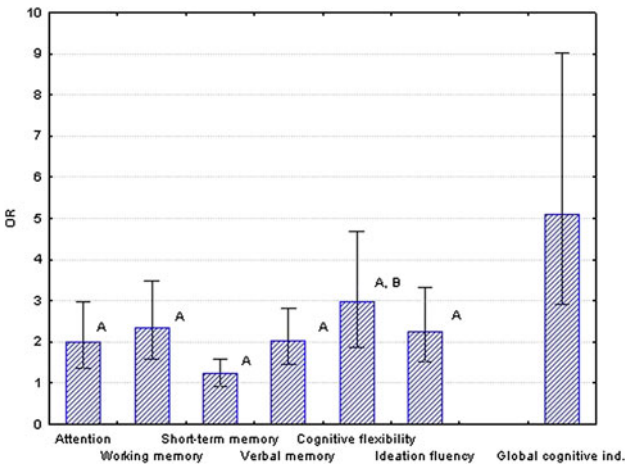

Fig. 1 Odds ratios of cognitive domains assessed by univariate logistic regression analyses. [A]Significant results in the univariate analyses. [B]Significant after multiple testing

SZ-ND and SZ-D classification, independently of all other measures.

Earlier research is contradictory concerning the "qualitative and quantitative" aspects of differences in neurocognitive performance of deficit and non-deficit schizophrenic patients. These studies suggested the specific impairment of frontoparietal cognitive functions [5] and more specifically of executive functions [6] in deficit schizophrenia. Recent meta-analytic data [9] have not confirmed the specificity of these functions, neither by examining individual tests nor by organizing the measures according to neuropsychological processes. Although no individual "lobe-specific" test or neuropsychological process was highlighted by the cited meta-analysis, results showed that the severity of neuropsychological impairments differs across cognitive functions. Notably, the most severe relative impairments in the deficit group were outside the prototypical set of schizophrenia neuropsychological impairments. It is important to note that earlier studies except for the aforementioned meta-analysis were limited by low statistical power due to small sample sizes and did not correct for the level of overall impairment while examining the contribution of specific neuropsychological domains.

Our results support the earlier findings with certain caveats and underscore the importance of both global cognitive impairments and the domain-specific impairment of cognitive flexibility. The deficit group demonstrated more severe cognitive dysfunction as captured by the global cognitive impairment index, and cognitive domains varied in their ability to distinguish the two groups. Notably, the domain of cognitive flexibility remained a significant explanatory factor after correcting for all other domains. Cognitive flexibility as a part of the prototypical neuropsychological impairments in schizophrenia is often defined as the ability to switch between behavioral responses according to the context of the situation, therefore contributing to efficient adaptation to task challenges. In their recently published twin-study, Owens et al. examined whether selective measures of executive processing are genetically linked to schizophrenia [21]. According to their results, genetic factors were the main source of the phenotypic correlations between schizophrenia and cognitive flexibility. Furthermore, their data suggest that mental flexibility is a specific cognitive process sharing very little common variance with general intellectual functioning. Thus, cognitive flexibility can be considered a relatively distinct domain and a possible endophenotype for future genetic studies focusing on the deficit syndrome.

Recent studies yielding findings that correspond to the results of this study should be mentioned. The study of Cascella et al. [22], also using the composite score approach, resulted in findings similar to ours. Their results pointed to the specific role of another executive function component, ideation fluency, but the unique contribution of cognitive flexibility was not supported by the analyses. Wang et al. [23] investigated neurocognitive functioning in SZ-D and SZ-ND patients of Chinese origin. They observed significant differences in two WCST measures and the TMT-B results between the two subgroups. Another important difference in the neuropsychological profile of the deficit patients is their specific impairment in procedural learning [24], suggesting the pathology of the striatal neurocircuitry. Finally, Szendi et al. [25], using systematic cognitive and symptomatological mapping and a cluster-analytic approach, were able to differentiate two subgroups within schizophrenia that partially overlapped with the SZ-D versus SZ-ND partition. Variables of cognitive flexibility and ideation fluency were the most sensitive predictors with regard to the two identified subgroups.

The composite score approach as a data reduction technique is a means to avoiding multiple comparisons and for the correction of the interdependency of neuropsychological measures. It is noteworthy that the studies using this methodology [9, 22],—including our data,—point to the importance of global differences between SZ-ND and SZ-D, rather than specific differences between cognitive domains. An analysis based on structural equation modeling has similarly come to the conclusion that cognitive deficit in schizophrenia is largely generalized across performance domains [26]. Moreover, a recent population-based study [27] investigated neurocognition patients with schizophrenia and bipolar disorder, representing a unique real-life approach. These results also point to the importance of the global cognitive impairment in patients with schizophrenia.

Structural brain imaging results do not provide a straightforward explanation for the more severe cognitive impairments in SZ-D. Structural brain imaging studies have actually shown more alterations (predominantly ventricular enlargement) in non-deficit schizophrenia compared to healthy controls [3]. Recently, Cascella et al. [28] have published structural MRI results about 19 SZ-D and 31 SZ-ND patients using voxel-based morphometry. These data also suggest that deficit patients have brain abnormalities (insula bilaterally, left superior frontal and middle temporal gyri) that differ from the prototypical schizophrenia brain alterations and seem to be associated with negative symptoms rather than neurocognitive dysfunction.

Sex, age, education, smoking status, and the daily dose of antipsychotic medication, tested as covariates, had no effect on the association of neurocognitive dysfunction and deficit status. The lack of effects of the sociodemographic variables corresponds to the concept of the deficit syndrome as described by Carpenter et al. [1], as independent of age, education, race. Cigarette smoking has been shown to partially remediate cognitive functions in schizophrenic patients [29, 30], but the presented results do not support a significant modulating effect of nicotine dependence on the robust association of neurocognitive dysfunction and deficit status. Since the two groups differed in terms of the daily dose of antipsychotic medication, it is conceivable that the cognitive side effect of these medications might have contributed to the difference in cognitive functioning between the two groups. Above average, excessive doses, and antipsychotic combinations have been associated with worsening cognitive functions in several domains,—visual memory, executive functions, delayed recall,—according to some studies [31, 32]. The introduction of cpz-equivalent daily doses in the analysis did not influence the observed differences, but we cannot rule out that extremely high antipsychotic doses or combinations in the SZ-D group contributed to the higher level of neurocognitive impairments according to a non-linear association.

Certain limitations and methodological issues of the study should be considered when interpreting the results. The composite score approach is an effective data reduction technique that bridges the problem of multiple testing; however, the a priori grouping of neuropsychological measures,—although based on previous studies,—is subject to debate and may mask differences in cognitive functions. Second, certain neuropsychological processes were not assessed in this study. Processing speed and social cognition are cognitive functions that could be important in distinguishing SZ-D and SZ-ND [33, 34]; moreover, they have been found to predict functional outcome in schizophrenia [35–39]. Our data do not provide results in this respect and might be biased by the lack of these measures. Third, data collection about the educational level of and the utilization of anticholinergic medications in the sample was incomplete or lacking. Finally, we did not include normal controls' results in the analyses, which would be informative about the overall magnitude of neurocognitive dysfunctions in affected individuals.

In conclusion, we have presented findings based on a large sample of schizophrenic patients and have shown evidence about the differences in neurocognitive functions of SZ-ND and SZ-D patients. Our results cast light on the deficit syndrome as a specific subgroup in terms of neurocognitive impairments, characterized by severe global impairment and unique dysfunction of executive functioning. Given the epidemiological findings about the worse long-term prognosis of the deficit syndrome [40, 41], and the recent positive results about the efficacy of cognitive remediation therapies in schizophrenia [42–44], a thorough description of the specific neurocognitive dysfunction in the deficit syndrome may offer the possibility to develop cognitive remediation techniques specifically designed to the needs of this patient group.

Acknowledgments We wish to thank the help of Drs. Csilla Bolyós, Márta Farkas, Zita Murai, Éva Rózsavölgyi, Tamás Kurimay, and Péter Pásztor in recruiting patients to the study and the assistance of Sarolta Komlósi and Krisztina Járvás in data collection. The study was supported financially by the Moravcsik Foundation and the OTKA-83876 Postdoctoral Grant.

Conflict of interest None.

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