DOI: 10.5455/bcp.20131213040431

Neuropsychological Assessment in Patients with Paranoid and Non-Paranoid Schizophrenia

Serhat Citak[1], Ebru T. Cakici[2], Mehmet Cakici[2], Samet Kose[3]

ÖZET:

Paranoid ve non-paranoid şizofreni hastalarında nöropsikolojik değerlendirme

Amaç: Şizofrenide bilişsel bozulmalar şizofreninin değişik belirti alt tipleriyle bağlantılıdır. Paranoid tip şizofrenide bilişsel işlevlerin daha iyi korunduğu öne sürülmüştür. Bu çalışmada, nöropsikolojik ölçümlerin, paranoid şizofreni hastalarını paranoid olmayanlardan ayrıştırıp ayrıştırmadığının değerlendirilmesi amaçlanmıştır.

Yöntemler: Bu çalışmaya DSM-IV ölçütlerine göre 26 paranoid tip ve 27 non-paranoid tip şizofreni tanısı konan hastalar dahil edilmiştir. Ortalama yaş paranoid hastalarda 38.0±9.1, non-paranoid hastalarda 39.8±16.4 idi. Tüm olgulara, dikkat, yürütücü işlevler, bellek, lisan ve karmaşık algısal işleme gibi işlevleri değerlendirmek üzere tasarlanmış bir dizi testten oluşan geniş ölçekli bir nöropsikolojik test bataryası uygulanmıştır.

Bulgular: Paranoid tip şizofreni hastalarının, seçici dikkat/ yürütücü işlevler (Stroop Renk Kelime Testi) (F=6.07, p<0.01) ve öğrenme /bellek işlevleri (Sayı Dizisi Öğrenme Testi) (F=8.43, p<0.00) açısından, non-paranoid hastalara gore daha yüksek bir performans sergiledikleri bulunmuştur.

Sonuç: Bulgularımız, bilişsel farklılıkların altta yatan nörokognitif süreçleri yansıtabileceğini ve şizofreni alttiplerini ayrıştırabileceğini düşündürmektedir.

Anahtar sözcükler: bilişsel işlevler, nöropsikolojik testler, paranoid şizofreni

Klinik Psikofarmakoloji Bulteni 2013;23(4):294-304

ABSTRACT:

Neuropsychological assessment in patients with paranoid and non-paranoid schizophrenia

Objective: Cognitive impairments in schizophrenia are associated with different symptom subtypes of schizophrenia. It has been suggested that cognitive functions in the paranoid type of schizophrenia were better protected. Here, we examine how neuropsychological measures jointly differentiate patients with paranoid schizophrenia from non-paranoid patients.

Methods: Fifty-three patients with schizophrenia, 26 paranoid and 27 non-paranoid, were included in the study. The mean age was 38.0±9.1 in the paranoid patients and 39.8±16.4 in the non-paranoid patients. A comprehensive test battery was administered to evaluate a broad range of cognitive functions including attention, executive functions, memory, language, and complex perceptual processing.

Results: Patients with paranoid schizophrenia demonstrated higher performance than non-paranoid patients on measures of selective attention/executive function (Stroop Color-Word Interference Test) (F=6.07, p<0.01) and learning/memory functions (Serial Digit Learning Test) (F=8.43, p<0.00).

Conclusion: Our findings suggest that cognitive differences might reflect underlying neurocognitive processes and may differentiate subtypes of schizophrenia.

Keywords: cognition, neuropsychological tests, paranoid schizophrenia

Bulletin of Clinical Psychopharmacology 2013;23(4):294-304

[1]Associate Professor of Psychiatry, Erenköy Training and Research Hospital for Psychiatric and Neurological Diseases, Istanbul - Turkey
[2]Associate Professor of Psychiatry, Near East University, Psychology Department, Lefkosa, Turkish Republic of Northern Cyprus
[3]Assistant Professor of Psychiatry, The University of Texas Medical School at Houston, Department of Psychiatry and Behavioral Sciences, Houston, Texas, USA

Address reprint requests to:
Serhat Citak, M.D., Ph.D.
Erenköy Training and Research Hospital for Psychiatric and Neurological Diseases, Istanbul - Turkey

Phone: +90-216-356-0503

E-mail address:
drserhat@hotmail.com

Date of submission:
July 24, 2013

Date of acceptance:
December 13, 2013

Declaration of interest:
S.C., E.T.C., M.C., S.K.: The authors reported no conflict of interest related to this article.

INTRODUCTION

Schizophrenia is a complex and debilitating psychiatric illness with different subtypes. The neuropsychological basis of different syndromes and the specific symptoms of schizophrenia have been investigated. A widely accepted classification system for distinguishing different subtypes of schizophrenia emphasizes the presence of negative or positive symptoms. Studies investigating neuropsychological performance in positive and negative clinical subtypes have revealed that performance in the positive symptom subtype was better than in the negative subtype on different neuropsychological measures (1-3).

Another classification approach has been to classify schizophrenia as either paranoid or non-paranoid subtypes. It has been accepted that patients with paranoid schizophrenia demonstrate less impairment of neurocognitive functions compared to non-paranoid patients (4-6). However, other studies have failed to demonstrate differences between subtypes in schizophrenia (7-9).

In a review of studies from 1975 to 1995 examining the neurocognitive differences between paranoid and non-paranoid schizophrenia, the authors reviewed a total of 32 studies in which the two subtypes had been compared in terms of general intellectual functioning, executive functions, attention, memory, verbal abilities and visual-spatial and motor skills (10). There was little empirical support for the hypothesis suggesting a higher IQ in the paranoid subtype. Similarly, no consistent findings were found for subtype differences in verbal abilities or visual-spatial skills. Limited support for neuropsychological differences favoring the paranoid group was found in executive functioning, attention, memory, and motor skills. The review offers only modest support for the notion of cognitive differences associated with paranoid and non-paranoid schizophrenia. The authors noted the factors limiting the reliability of studies such as methodological variability, and subject variables such as severity of illness, clinical state, medication effects, and sampling biases.

Studies attempting to clarify the patterns of neuropsychological differences in schizophrenia subtypes may lead to a better understanding of underlying pathophysiological processes. Here, we aimed to examine the cognitive differences between paranoid and non-paranoid schizophrenia subtypes. We hypothesized that paranoid schizophrenia patients would demonstrate higher neuropsychological performance compared to non-paranoid patients. Our hypothesis may reveal the importance of subtype-associated cognitive differences in schizophrenia, in association with the results of previous studies indicating the distinguishing clinical symptoms and neuroanatomical features.

METHODS

Subjects

Fifty-three inpatients meeting the DSM IV criteria for schizophrenia were included in this study. Patients were recruited from consecutive admissions to the psychiatric wards of Bakırköy Training and Research Hospital for Psychiatric and Neurological Diseases. Subjects were excluded from the study if they:

(1) had a history of a neurological or medical disorder that would affect neuropsychological functioning, (i.e., seizures, head trauma with loss of consciousness, stroke, brain tumor, meningitis etc.)
(2) had documented evidence of mental retardation,
(3) had a history of alcohol or substance abuse/dependence, or
(4) had been treated with ECT within the previous 6 months.

Demographic data were obtained by interviews with patients and family members. A comprehensive neuropsychological test battery was administered to both groups.

Socio-demographic and clinical characteristics of the 53 patients are presented in Table 1. Twenty-six subjects (all male) were paranoid schizophrenic and 27 were non-paranoid schizophrenia patients (18 men, 9 women; 14 undifferentiated, 9 residual, and 4 disorganized subtypes). Mean age, duration of illness and number of previous hospitalizations in the paranoid patients were 38.0±9.1; 13.4±9.5; 6.0±3.8, respectively. These values in non-paranoid patients were 39.8±16.4; 15.3±12.9; 7.2±6.9, respectively. There were no significant differences between the two groups with respect to age, duration of illness or number of previous hospitalizations. The average duration of education was higher in the paranoid group when compared to the non-paranoid group. One possible explanation might be the earlier onset of illness in the non-paranoid patients; although, our results did not support any difference between the groups in duration of illness.

Group differences in demographic variables were examined with the Mann-Whitney U test for continuous data and the Chi-square test for categorical data. A multivariate analysis of variance (MANOVA) was performed with group as the between-group factor and cognitive domain (attention, learning and memory, executive function, language, and visuo-spatial perception) as the within-group factor in order to determine whether there was an interaction of group by cognitive functions. The average duration of education was higher in the paranoid group. Previous studies have clarified the effects of education on neurocognitive performance (11-13). Group differences in neuropsychological performance were evaluated using a stratified t - test. Stratification was done into 3 educational groups (0-5 years, 6-8 years, 9 years or more) to adjust for the confounding effect of education. To investigate the possible effects of the duration of education on the group differences of cognitive performance, a two-factor factorial ANOVA was performed. Since there were 9 females in the non-paranoid group, the possible differences on cognitive tasks might be related to a gender effect. To clarify the effect of gender on neuropsychological performance in the non-paranoid group, we performed a MANOVA. Subjects provided informed consent in a matter approved by the Bakırköy Training and Research Hospital for Psychiatric and Neurological Diseases Institutional Review Board. This study was conducted in accordance with the Declaration of Helsinki.

Instruments

A comprehensive neurocognitive test battery was designed to evaluate a broad range of cognitive domains. These assessments focused on measures of attention, learning and memory, executive functions, language, and visuo-spatial perception. The battery included 11 tests that would assess these domains. These tests have been described extensively in prior researche (2,14-22). The neurocognitive domains and the tests that were included in these domains were as follows:

1. Attention
   - 1.1. Continuous Performance Test (CPT) (23)
   - 1.2. Cancellation Test (reliable and valid Turkish version) (21,24,25)
2. Learning and Memory
   - 2.1. Serial Digit Learning Test (SDLT) (reliable and valid Turkish version) (21,26)
   - 2.2. Rey Auditory Verbal Learning Test (RAVLT) (27)
   - 2.3. Wechsler Memory Scale III (WMS-III) Visual Reproduction Subtest (reliable and valid Turkish version) (21,28)
3. Executive Functions
   - 3.1. Category Fluency Test (29)
   - 3.2. Wisconsin Card Sorting Test (WCST) (reliable and valid Turkish version) (21,30)
   - 3.3. Raven Progressive Matrices Test (RPMT) (reliable and valid Turkish version) (21,31)
   - 3.4. Stroop Color Word Interference Test (reliable and valid Turkish version) (21,32)
4. Language
   - 4.1. Boston Naming Test (33)
5. Visuo-spatial Perception
   - 5.1. Benton Judgment of Line Orientation Test (reliable and valid Turkish version) (21,34)

Table 1: Socio-demographic and clinical variables

Variable	Paranoid (n=26)		Non-paranoid (n=27)		Mann-Whitney U	
	mean	SD	mean	SD	U	p
Age	38.00	9.18	39.89	16.49	340.5	0.85
Education	11.69	4.12	8.52	3.27	198.5	**0.00***
Number of hospitalizations	6.08	3.88	7.27	6.93	325.5	0.81
Duration of disease	13.42	9.59	15.35	12.92	322.0	0.76
Chlorpromazine equivalent dose (mg)	859.65	362.23	788.86	286.47	299.0	0.44

0.00*: Significant between-group difference

Table 1a: Mann Whitney U median values (25%-75%)

Variable	Paranoid (n=26)		Non-paranoid (n=27)		Mann-Whitney U	
	25%	75%	25%	75%	U	p
Age	31.00	44.00	25.00	58.50	340.5	0.85
Education	10.00	14.75	5.00	11.00	198.5	0.00*
Number of hospitalizations	4.50	22.75	3.50	27.00	325.5	0.81
Duration of disease	3.00	8.00	1.00	13.50	322.0	0.76
Chlorpromazine equivalent dose (mg)	500.00	1000.00	500.00	1000.00	299.0	0.44

0.00*: Significant between-group difference

Procedure

Following the clinical interview, the neurocognitive test battery was administered by study investigators trained in standardized assessment and experienced in working with psychotic patients. The test administrators were supervised by the principal investigator (SC). The test battery took about 2 hours to complete. Testing took place in a quiet room in sessions of about an hour each, at times when the patients were most cooperative and alert. Neuropsychological assessments were administered after patients had confirmed to be psychiatrically and medically stable for at least 2 weeks. At neuropsychological testing, 61.5% of paranoid and 77 % of non-paranoid patients were receiving haloperidol; 38.5% of paranoid and 23% of non-paranoid patients were receiving clozapine. There were no significant differences between groups according to the type of antipsychotic medication (chi-square=3.11, p=0.21) and according to the chlorpromazine (CPZ) equivalent dose (Table 1).

Statistical Analysis

All statistical analyses were performed using the SPSS 10.0 for Windows (SPSS, Inc., Chicago, IL) and STATA data analysis and statistical software program. (StataCorp LP, Texas). An alpha level of 0.05 was considered to be statistically significant. Significance was evaluated by a two-tailed test. Group differences were examined by using Mann-Whitney U, Chi-square and the stratified t-test. Multivariate analysis of variance (MANOVA) and two-factor factorial ANOVA methods were used to determine main effects or interactions between the two groups in the test phase.

RESULTS

All comparisons between the paranoid and non-paranoid groups were made after adjustment for education by the stratified t-test. The results are presented in Tables 1, 1a and 2. The patients in the paranoid group performed significantly better than those in the non-paranoid group on measures of executive functions and learning/memory. On the Stroop test, paranoid patients made significantly fewer errors than non-paranoid patients. They did not differ in the number of corrections. On the SDLT, patients with paranoid schizophrenia learned the digits earlier than their non-paranoid counterparts. In the paranoid group, the average

Table 2: Neuropsychological test scores

Variable	Paranoid (n=26)		Non-paranoid (n=27)		Stratified t-test	MANOVA
	Mean	SD	Mean	SD	t	F (df =1)
Attention						
Continuous performance test total score	22.15	2.68	20.15	4.85	1.72	2.04
Cancellation test						
right score	111.78	8.79	108.10	16.73	0.66	0.90
leftscore	114.22	4.48	109.05	17.25	0.78	1.94
Learning and memory						
Serial digit learning test						
No of trials for exact learning	5.78	3.21	9.17	3.80	-3.62 **	8.43 **
total score	12.25	8.06	6.12	8.41	2.34 *	5.58 *
Rey AVLT immediate learning	4.69	1.67	4.04	1.83	0.16	1.77
No of trials for exact learning	9.04	1.89	11.59	8.68	-0.45	2.68
total learning	96.23	20.88	80.15	22.11	1.64	3.48
WMS-III visual memory subtest						
immediate learning	26.73	8.36	20.74	9.77	1.36	3.01
Executive functions						
Category fluency test	16.28	4.85	14.56	5.94	0.07	1.07
Wisconsin Card Sorting Test						
Number of categories attained	2.00	2.43	0.96	1.25	0.69	3.35
Number of perseverative errors [%]	39.08	22.51	49.42	19.63	-1.17	3.59
Raven Progressive Matrices score	23.72	10.11	19.36	8.83	0.45	1.95
time for completion [minutes]	22.68	9.94	20.91	10.05	0.00	0.34
Stroop test						
number of errors	1.36	1.70	6.96	10.34	-2.58 *	6.07 **
number of corrections	2.32	2.34	3.77	3.49	-1.53	3.01
Language						
Boston naming test	17.85	2.54	17.41	1.93	0.02	0.63
Visuo-spatial perception						
Benton Judgment of line orientation test	18.77	5.69	14.00	6.89	1.52	2.31

p<0.05, **p<0.01: significant between-group differences
Group differences on neuropsychological performance were evaluated using the stratified t - test. To evaluate whether there was a significant interaction of group (paranoid vs non-paranoid) by condition (5 domains of cognitive function), we performed aMANOVA.

number of trials for exact learning was significantly fewer and the average total score was significantly higher than in the non-paranoid group. There were no significant differences between the two groups on other measures of executive functions and memory, or on measures of language and visuo-spatial perception functions.

To evaluate whether there was a significant interaction of group (paranoid vs non-paranoid) by condition (5 domains of cognitive function), we performed a MANOVA. First, we determined the overall multivariate-F (Wilks' Lambda F) of the 5 domains of cognitive function. The Wilks' Lambda (WL), significance (p) and hypothesis degree of freedom (df) values for the 5 cognitive function domains were as follows: for attention, WL was 1.32, p was 0.28, df was 3.0; for learning and memory, these values were 2.56, 0.04, 6.0; for executive functions, 3.90, 0.01, 7.0; for language, 0.11, 0.89, 2.0, and for visuo-spatial functions, 1.70, 0.14, 3.0. Since the overall multivariate-F values were significant for learning and memory and executive functions, separate univariate analyses were performed to determine the group differences on these cognitive domains (Table 2). Our findings revealed significant group differences on the Stroop test and the SDLT results. Patients with paranoid schizophrenia performed better on the Stroop testand on the SDLT exact learning and total scores.

To evaluate whether these differences were attributable to group differences in educational level, a two-factor factorial ANOVA was performed. As a result, no differences were found between the groups in terms of educational level, except for the RAVLT. In the 0-5 year educational level, paranoid

patients performed better on the RAVLT total score. ($p<0.01$, $F=4.72$) Although the performances of the paranoid patients were higher in this analysis, it seemed to be balanced when the overall group performance was analyzed by using the MANOVA. To evaluate the effects of gender on cognitive functions in the non-paranoid group, a MANOVA was performed. The results indicated that gender did not seem to have any effect on neurocognitive performance of the patients. There were no differences in performance between males and females on the measures of neuropsychological functioning in the non-paranoid patients. However, there was a trend toward differences on the RAVLT test ($p=0.06$, $F=3.62$), the category fluency test ($p=0.07$, $F=3.35$), the WCST ($p=0.06$, $F=3.77$), and the Stroop test ($p=0.06$, $F=3.72$).

DISCUSSION

The main finding of this study was that patients with paranoid schizophrenia performed significantly better on executive and learning / memory functions compared to non-paranoid patients. There were no significant differences on other measures of neuropsychological functioning. Statistical analyses suggested that the observed group performance differences were not due to education or gender. When the education factor was statistically controlled, the non-paranoid group was still more severely impaired on executive and memory functions. These findings support previous studies which found that patients with paranoid schizophrenia performed significantly better than non-paranoid patients (35-40).

The first significant group difference was observed in the number of errors onthe Stroop Test. This would be consistent with reports of studies demonstrating that patients with paranoid schizophrenia performed better on the Stroop Task (37,41).

There were no significant differences between the two groups on other measures of executive function (Category Fluency Test, WCST and Raven Progressive Matrices Test). Our findings were similar to those of Kremen et al. , who found no differences between the two groups on WCST performance (9). There are some studies indicating that paranoid patients performed better on the WCST compared to non-paranoid patients (5,39). However, Abburezze et al. found that paranoid patients made a higher number of perseverative errors on the WCST compared to non-paranoid Patients (42). Taken together, as Zalewski et al. pointed out, the findings of the WCST studies do not strongly support subtype differences (10).

The second significant group difference was observed on the Serial Digit Learning Test. In patients with paranoid schizophrenia, the number of trials for exact learning was lower and the total score was higher. Bornstein et al. have found that paranoid patients were less impaired than non-paranoids on both verbal and non-verbal components of the WMS-R (5). Kremen et al. have reported higher verbal memory skills in patients with a history of systematized delusions, as compared with patients without systematized delusions (9). Contrary to these results, Kolb and Whishaw Hvw found no differences between paranoid and non-paranoid participants on visual or auditory memory (7).

There were no group differences on other measures of memory such as the Rey Auditory Verbal Learning Test and the WMS-III Visual Reproduction Subtest. Our findings were consistent with Seltzer et al.'s findings that both paranoid and non-paranoid groups were equally impaired on the Rey AVLT (39). On measures of non-verbal memory, Bornstein et al. did not find any differences between the two groups (5). Similarly, Kremen et al. failed to demonstrate subtype differences on the WMS-R visual reproduction test (9).

We found that patients with paranoid schizophrenia did not differ from non-paranoid patients on spatial distribution of attention, language, and visuo-spatial perception functions. Previous studies that have assessed attentional and verbal skills don't suggest subtype differences. As Zalewski et al. indicated, there was little evidence

to suggest that subgroups differed on measures of visuo-spatial ability (10). Kremen et al. found no differences between groups on the CPT and the Cancellation test (9). Our findings are consistent with previous reports (9,10).

The Stroop Test has been defined as a measure of executive function (19). It has also been reported to be a means of assessing attentional matrix, specifically selective attention (17). Studies of neurocognitive functioning in schizophrenia have considered the Stroop task as a measure of selective attention (43-46). It has been hypothesized that the Stroop Test was associated with the focus-execute component of attention (47). In a study of construct validity of various verbal and visual memory tests, Larrabee and Curtiss found that the Serial Digit Learning Test was more closely associated with attention/ information processing than with general memory (48). In our study, the main group differences were observed on the Stroop Test and the Serial Digit Learning Test. If we consider these two tests as measures of selective attention, we might suggest that patients with paranoid schizophrenia demonstrated higher performance on selective attention tasks compared to non-paranoid patients.

The current study has several limitations. First, our sample size was relatively small. This probably decreased the power of the statistical analysis. Second, we couldn't measure the illness severity, general IQ, and clinical status in our patient groups. Another issue was the chronicity of illness. Even though there were no significant differences on duration of disease between the two groups in our sample, we cannot estimate the impact of institutionalization on cognitive abilities especially in the non-paranoid group. There were also trends toward gender differences on measures of executive functions in the non-paranoid group. Although these differences were not significant, could potentially confound the results. We could have also considered the possible effects of medications on our findings. Although the subgroups did not differ statistically according to the type of antipsychotic medication, we cannot exactly estimate the effects of neuroleptic and anticholinergic drugs on neurocognitive performance. Our study sample did not include healthy subjects as a control group. We compared the cognitive functions between paranoid and non-paranoid schizophrenia in a cross-sectional study design, therefore we were not able to follow up the prognosis of these functions. Because of these limitations, our results are suggestive rather than conclusive.

Schizophrenia should not be regarded as a homogenous disorder with respect to cognitive skills. There may be significant differences among diagnostic subgroups in the degree of neuropsychological functioning. Cognitive differences might reflect the underlying neurocognitive processes in schizophrenia subtypes. These differences may also be related with lower illness severity and better prognosis in paranoid subgroups.

In summary, we have found evidence of differential performance on selective attention/ executive function and learning/ memory measures in patients with paranoid and non-paranoid schizophrenia. These differences were not attributable to either educational level or gender. Patients with paranoid schizophrenia seem to focus more selectively and be less susceptible to the confounding effects of Stroop interference. They also tend to record numerical information more quickly and seem to learn numerical information better than verbal information. These results might suggest that paranoid patients might have a better cognitive ability to focus on, to record, and recall information selectively.

A major obstacle to the identification of the neurobiological correlates of schizophrenia is the substantial clinical heterogeneity present in this disorder. Dividing schizophrenia into "paranoid" and "non-paranoid" subtypes may reduce heterogeneity and facilitate identification of neurobiological markers of disease.

Neuroimaging studies in schizophrenia have revealed distinguishing findings amongst subtypes and predominant symptoms. Schizophrenic patients showed a decrease in the N-acetylaspartate/creatine (NAA/Cr) ratio in the

left medial temporal lobe, and patients with the disorganized subtype of the illness showed significantly lower NAA/Cr and choline/creatine (Cho/Cr) ratios than those with paranoid schizophrenia. These findings suggest that patients with the disorganized and undifferentiated subtypes had greater impairments in neuronal integrity or function in the left medial temporal lobe than patients with other subtypes of schizophrenia (49). P300 amplitude when viewing a photograph of a smiling baby was the smallest registered of three photographs for healthy subjects and paranoid type patients with successively greater amplitudes for neutrality and sadness. These results suggest that the P300 amplitude was influenced by viewing emotionally moving facial expressions and that the effect is different for different subtypes of schizophrenia (50).

Schneiderian symptoms may be associated with morphological abnormalities in the limbic-paralimbic regions such as the cingulate gyrus and parahippocampal gyrus (51). The findings of a voxel-based morphometry study revealed volume loss in the right superior temporal gyrus, right middle temporal gyrus, and right anterior cingulate gyrus among antipsychotic-naive first-episode schizophrenia patients. In addition, the functional networks involving the right superior temporal gyrus and middle temporal gyrus were associated with positive symptom severity (52). The findings of an MRI study suggest that temporal and parietal cortical abnormalities might be associated mainly with positive symptoms, while medial temporal and ventricular system abnormalities may be associated with both positive and negative symptoms (53). Regional abnormalities in brain structure may offer an account for some impaired cognitive domains in patients with schizophrenia (54,55). Schizophrenic patients with high negative symptoms had generalized prefrontal white matter reductions that were most severe in the orbitofrontal subregion. The convergence of findings for schizophrenic patients regarding the prefrontal region, negative symptoms, psychomotor speed and cognitive flexibility suggests that schizophrenic negative symptoms might involve disruption of frontal-subcortical connections (56,57).

The results of our study suggest that, current diagnostic classifications might not be the most useful factors for studies of the cognitive correlates of schizophrenia.

The DSM-5, as noted in its own appendix, has made several amendments in its section on Schizophrenia Spectrum and Other Psychotic Disorders. These amendments include the elimination of the older Kraepelinean sub-types such as paranoid or disorganized, and the de-emphasis of bizarre positive symptoms, which previously were on their own sufficient for a diagnosis, but now must be accompanied by at least one other core symptom. It seems possible that the DSM-5 has been pointing to future manuals in which there will be increasing efforts to make the pieces of this disorder easier to recognize, but with less concern for core psychopathological processes such as those proposed by Bleuler, which allow us to make sense of how schizophrenia spectrum disorders represent as a unique set of disorders. With regard to the diagnostic criteria for schizophrenia, changes include the elimination of the special attribution of bizarre delusions and first-rank auditory hallucinations according to Schneider's criteria. The traditional sub-typing of schizophrenia into paranoid, disorganized (hebephrenic), catatonic, undifferentiated, and residual forms is also now being discarded altogether, based on the view that sub-types were diagnostically unstable, unreliable, and invalid. In fact, auditory hallucinations in the form of commenting voices and other first-rank symptoms are 'core' to all early recognition manuals, including the most widely used Structured Interview for Psychotic Symptoms (SIPS) or the Comprehensive Assessment of At-Risk Mental States (CAARMS). It was the explicit goal of the early protagonists in psychiatry such as Kahlbaum and Kraepelin to describe clinical 'entities' based on symptomatology (which at the time included not just the subjective aspect of symptomatology, but also non-verbal and paraverbal abnormalities in expression), course and outcome. Many

clinicians probably share the view that an insidious early onset of schizophrenia, rapid development of negative symptoms, poor insight, and behavioral abnormalities (that is, hebephrenia) were generally associated with a poorer prognosis respecting recovery, social functioning, and quality of life, compared with patients with acute paranoid schizophrenia (58).

Future studies should focus on selective attention, learning/memory and information processing functions in schizophrenia by using more specific measures. These studies might include larger sample sizes with different control groups. Symptom severity and illness chronicity should be evaluated. Possible confounding effects of education, gender, and medication should be considered. These will be crucial in the development of a neuropsychological understanding of the cognitive impairments observed in schizophrenia subtypes.

Acknowledgments

The authors would like to commemorate their deceased colleague and mentor Oğuz Arkonaç, MD with respect and gratitude.

References:

1. Berman I, Viegner B, Emerson A, Allan E, Pappas D, Green AI. Differential relationships between positive and negative symptoms and neuropsychological deficits in schizophrenia. Schizophr Res 1997;25(1):1-10.

2. O'Leary DS, Flaum M, Kesler ML, Flashman LA, Arndt S, Andreasen NC. Cognitive correlates of negative, disorganized and psychotic symptom dimensions of schizophrenia.J Neuropsychiatry Clin Neurosci 2000;12(1):4-15.

3. Brazo P, Marie RM, Halbecq I, Benali K, Segard L, et al. Cognitive patterns in subtypes of schizophrenia. Eur Psychiatry 2002;17(3):155-62.

4. Philips ML, David AS. Cognitive impairments as causes of positive symptoms in schizophrenia. In: Sharma T, Harvey P (eds.). Cognition in Schizophrenia Impairments, Importance and Treatment Strategies. Oxford University Press, New York, 2000; 211-28.

5. Bornstein RA, Nasrallah HA, Olson SC, Coffman JA, Torello M, Schwarzkoph SB. Neuropsychological deficit in schizophrenic subtypes: paranoid, non-paranoid, schizoaffective subgroups. Psychiatry Res 1990;31(1):15-24.

6. Langell ME, Purisch AD, Golden CJ. Neuropsychological differences between paranoid and non-paranoid schizophrenics on the Luria-Nebraska Battery. Int J Clin Neuropsychol 1987;9(1):88-95.

7. Kolb B, Whishaw IQ. Performance of schizophrenic patients on tests sensitive to left or right frontal, temporal or parietal function in neurological patients. J Nerv Ment Dis 1983;171(7):435-43.

8. Paulman RG, Devous MD, Gregory RR, Herman JH, Jennings L, Bonte FJ, et al. Hypofrontality and cognitive impairment in schizophrenia: dynamic single photon tomography and neuropsychological assessment of schizophrenic brain function. Biol Psychiatry 1990;27(4):377-99.

9. Kremen WS, Seidman LJ, Goldstein JM, Fanaone SV, Tsuang MT. Systematized delusions and neuropsychological function in paranoid and non-paranoid schizophrenia. Schizophr Res 1994;12(3):223-36.

10. Zalewski C, Johnson-Selfridge MT, Ohriner S, Zorrella K, Seltzer JC. A review of neuropsychological differences between paranoid and non-paranoid schizophrenia patients. Schizophr Bull 1998;24(1):127-45.

11. Clark CR, Paul RH, Williams LM, Arns M, Fallahpour K, et al. Standardized assessment of cognitive functioning during development and aging using an automated touchscreen battery. Arch Clin Neuropsychol 2006;21(5):449-67.

12. Gomez-Perez E ,Ostrosky-Solis F. Attention and memory evaluation across the life span: heterogeneous effects of age and education. J Clin Exp Neuropsychol 2006 28(4):477-94.

13. Brucki SM, Rocha MS. Category fluency test: effects of age, gender and education on total scores, clustering and switching in Brazilian Portuguese-speaking subjects. Braz J Med Biol Res 2004;37(12):1771-7.

14. Çıtak S, Çakıcı ET, Çakıcı M. Neuropsychological assessment in schizophrenic patients treated with haloperidol or clozapine. Klinik Psikofarmakoloji Bulteni-Bulletin of Clinical Psychopharmacology 2009;19(1):5-14. (Turkish)

15. Nuechterlein KH, Green MF, Kern RS, Baade LE, Barch DM, et al. The MATRICS Consensus Cognitive Battery, part 1: test selection, reliability and validity. Am J Psychiatry 2008;165(2):203-13.

16. Rund BR, Melle I, Friis S, Larsen TK, Midboe LJ, Opjordsmoen S. et al. Neurocognitive dysfunction in first episode psychosis: correlates with symptoms, premorbid adjustment and duration of untreated psychosis. Am J Psychiatry 2004;161(3):466-73.

17. Miler P, Ho BC, Arndt V, Andreasen NC. Predictive values of neurocognition and negative symptoms on functional outcome in schizophrenia: A longitudinal first-episode study with 7-year follow up. Am J Psychiatry 2005;162(3):495-507.

18. Weintraub S. Neuropsychological Assessment of Mental State. In: Mesulam MM (ed.). Principles of Behavioral and Cognitive Neurology. Oxford University Press, New York, 2000; 121-164.

19. Lezak MD. Neuropsychological Assessment (3rd ed.). Oxford University Press, New York, NY, 1995; 110-43.

20. Sharma T, Harvey P. Cognition in Schizophrenia: Impairments, Importance and Treatment Strategies. Oxford University Press, New York, NY, 2000.

21. Karakaş S, Başer E. Standardization of neuropsychological tests in Turkish population according different age and educational level. Kriz Dergisi 1995;3(1):177-84. (Turkish)

22. Karakaş S. BILNOT Battery Handbook: Research and Development Studies for Neuropsychological Tests (2nd ed.). Hacettepe University Press, Ankara, 2006. (Turkish)

23. Cornblatt BA, Risch NJ, Faris G, Friedman D, Erlenmeyer-Kimling L. The Continuous Performance Test, identical pairs version (CTP-IP): I.New findings about sustained attention in normal families. Psychiatry Res 1988;26(2):223-38.

24. Mesulam MM. Principles of Behavioral and Cognitive Neurology (2nd ed.). Oxford University Press, New York, NY, 2000.

25. Lowery N, Ragland JD, Gur RC, Gur RE, Moberg PJ. Normative data for the symbol cancellation test in young healthy adults. Appl Neuropsychol 2004;11(4):218-21.

26. Benton AL, Hamsher K de S, Varney N, Spreen O. Contributions to Neuropsychological Assessment: A Clinical Manual (2nd ed.). Oxford University Press, New York, NY, 1998.

27. Rey A. L' examen Clinique en Psychologie. Presses Universitaires de France, Paris, 1964; 1-222.

28. Wechsler D. Wechsler Memory Scale III. The Psychological Corporation, San Antonio, Texas, 1987.

29. Morris JC, Heyman A, Mohs RC. The Consortium to Establish a Registry for Alzheimer's disease (CERAD). Part I, Clinical and neuropsychological assessment of Alzheimer's disease. Neurology 1989;39(9):1159-65.

30. Grant DA, Berg E. The Wisconsin Card Sort Test Random Layout: Directions for Administration and Scoring. Wells Printing, Madison, Wisconsin, 1980.

31. Raven JC. Guide to the Standart Proggressive Matrices. H.K.Lewis', London, 1960.

32. Stroop JR. Studies of interference in serial verbal reactions. J Exp Psychol 1935;18:643-62.

33. Kaplan E, Goodglass H, Weintraub S. The Boston Naming Test. Lea and Febiger, Philadelphia, 1983; 1-61.

34. Benton AL, Varney NR, Hamsher KD. Visuospatial judgement A clinical test. Arch Neurol 1978;35(6):364-7.

35. Palmer BW, Dawes SE, Heaton RK. What do we know about neuropsychological aspects of schizophrenia? Neuropsychol Rev 2009;19(3):365-84.

36. Goldstein G, Shemansky WJ, Allen DN. Cognitive function in schizoaffective disorder and clinical subtypes of schizophrenia. Arch Clin Neuropsychol 2005;20(2):153-9.

37. Hagh-Shenas H, Toobai S, Makaremi A. Selective, sustained and shift in attention in patients with diagnoses of schizophrenia. Percept Mot Skills 2002;95(3):1087-95.

38. Hill SK, Ragland JD, Gur RC, Gur RE. Neuropsychological differences among empirically derived clinical subtypes of schizophrenia. Neuropsychology 2001;15(4):492-501.

39. Seltzer J, Conrad C, Cassens C. Neuropsychological profiles in schizophrenia: paranoid versus undifferentiated distinctions. Schizophr Res 1997;23(2):131-8.

40. Dillon C, Taranago F, Sarasola D, Iturry M, Serrano C, Raczkowski A, et al. Cognitive performance in schizophrenia(paranoid vs residual subtype). Vertex 2007; 18(73):170-5.

41. Carter C, Robertson LC, Nordahl TE, O'Shora-Celaya LJ, Chaderjian MC. Abnormal Processing of irrelevant information in schizophrenia: the role of illness subtype. Psychiatry Res 1993;48(1):17-26.

42. Abburezze M, Ferri S, Scarone S. Performance on the Wisconsin Card Sorting Test in Schizophrenia: perseveration in clinical subtypes. J Psychiatry Res 1996;64(1):27-33.

43. Henik A, Salo R. Schizophrenia and the Stroop effect. Behav Cogn Neurosci Rev 2004;3(1):42-59.

44. Filbey FM, Toulopoulou T, Morris RG, McDonald C, Bramon E, Walshe M, et al. Selective attention deficits reflect increased genetic vulnerability to schizophrenia. Schizophr Res 2008;101(1-3):169-75.

45. Barch DM, Carter CS, Hachten PC, Usher M, Cohen JD. The benefits of distractibility: mechanisms underlying increased Stroop effects in schizophrenia. Schizophr Bull 1999;25(4):74-62.

46. Perlstein WM, Carter CS, Barch DM, Baird JW. The Stroop task and attention deficits in schizophrenia: a critical evaluation of card and single-trial Stroop methodologies. Neuropsychology 1998;12(3):414-25.

47. Buchanan RW, Strauss ME, Breier A, Kirkpatrick B, Carpenter WT. Attentional impairments in deficit and non-deficit forms of schizophrenia. Am J Psychiatry 1997;154(3):363-70.

48. Larrabee GJ, Curtiss G. Construct validity of various verbal and visual memory tests. J Clin Exp Neuropsychol 1995;17(4):536-47.

49. Fukuzako H , Kodama S , Fukuzako T , Yamada K , Doi W, Sato D, et al. Subtype-associated metabolite differences in the temporal lobe in schizophrenia detected by proton magnetic resonance spectroscopy. Psychiatry Res 1999;92(1): 45-56.

50. Ueno T , Morita K , Shoji Y , Yamamoto M , Yamamoto H , H Maeda. Recognition of facial expression and visual P300 in schizophrenic patients: differences between paranoid type patients and non-paranoid patients.Psychiatry Clin Neurosci 2004;58(6):585-92.

51. Suzuki M, Zhou SY, Hagino H, Niu L, Takahashi T, Kawasaki Y, et al. Morphological brain changes associated with Schneider's first- rank symptoms in schizophrenia: a MRI study. Psychol Med 2005;35(4):549-60.

52. Lui S, Deng W, Huang X, Jiang L, Ma X, nGhen H, et al. Association of cerebral deficits with clinical symptoms in antipsychotic-naive first-episode schizophrenia: an optimized voxel-based morphometry and resting state functional connectivity study. Am J Psychiatry 2009; 166(2):196-205.

53. Çıtak S, Çakıcı M, Çakıcı ET, Aker AT. The association of negative and positive symptoms with structural brain imaging findings in schizoprenia: an MRI study. Düşünen Adam 2009;22(1-4):18-26. (Turkish)

54. Wolf RC, Höse A, Frasch K, Walter H, Vasic N. Volumetric abnormalities associated with cognitive deficits in patients with schizophrenia. Eur Psychiatry 2008;23(8):541-8.

55. Antonova E, Kumari V, Morris R, Halari R, Anilkumar A, Mehrotra R, et al. The relationship of structural alterations to cognitive deficits in schizophrenia: a voxel-based morphometry study. Biol Psychiatry 2005;58(6):457-67.

56. Sanfilipo M, Lafargue T, Rusinek H, Arena L, Loneragan C, , Lautin A, et al. Volumetric measure of the frontal and temporal lobe regions in schizophrenia: relationship to negative symptoms. Arch Gen Psychiatry 2000;57(5):471-80.

57. Sanfilipo M, Lafargue T, Rusinek H, Arena L, Loneragan C, Lautin A, et al. Cognitive performance in schizophrenia: relationship to regional brain volumes and psychiatric symptoms. Psychiatry Res 2002;116(1-2):1-23.

58. Nemeroff CB, Weinberger D, Rutter M, Macmillan HL, Bryant RA, Wessely S, et al. DSM-5: a collection of psychiatrist views on the changes, controversies, and future directions. BMC Medicine 2013;11(202):1-19.