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Working memory dysfunction in patients suffering from schizophrenia and their first-degree relatives*

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Summary

Working memory deficits are considered to play an important role affecting not only the pathogenesis but also the course of schizophrenia. Numerous studies of schizophrenic patients and their first-degree relatives suggest that this impairment may be an indicator of susceptibility to developing schizophrenia.

Aim. A comparison of selected working memory indicators in patients with schizophrenia, their first-degree relatives, and healthy controls.

Subjects. 99 patients with the diagnosis of schizophrenia (according to the ICD-10-DCR criteria) in an early period of remission, their healthy first-degree relatives (N = 42), relatives with a history of psychiatric disorder (N = 14), and a control group of those (N = 54) unrelated to the subjects and with no psychiatric history were the participants of the study.

Methods. Selected tests from the computer-aided Vienna Test Battery were used, measuring reaction time (RT) in a task that required choosing among complex stimuli of two modalities, a tendency to perseveration (PERSEV), and immediate visuospatial memory span (CORSI).

Results. Schizophrenic patients' performance was found to be significantly inferior to that of controls on all the cognitive tests related to working memory: they had longer reaction time in forced choice tasks, elevated perseverative tendencies and reduced immediate visuospatial memory span. Moreover, healthy relatives of schizophrenic patients performed significantly poorer than did the controls, both as regards perseverative tendencies and visuospatial memory span. Schizophrenic patients did not differ significantly from their close relatives in the degree of visuospatial memory span impairment.

Conclusions. The findings indicate that working memory deficits as assessed by the tests used in the study may be related to familial susceptibility to schizophrenia. Therefore, the dysfunction may be taken into account in the capacity of endophenotype of such susceptibility.

Key words: schizophrenia, working memory deficits, first-degree relatives.

Introduction

It was already Kraepelin [1] who emphasised the clinical importance of early-appearing neurocognitive deficits for the further course of the disease and for the weak-

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ening of the intellectual efficiency of patients suffering from schizophrenia (dementia precox). Nowadays, these deficits are often rated among the basic features of schizophrenia, significant for its pathogenesis as well as for the patient's functioning in life and for the clinical aspects of the disease (such as its course, prognoses, the patient's awareness of the disease) [2, 3, 4, 5]. Evident neurocognitive deficits increase during the period of two years before the first episode of psychosis, and during the episode itself they already reach intensity of a considerable degree [6, 7, 8]. In many patients they can increase together with disease duration and impair the patients' functioning in the society [9]. Cognitive deficits diagnosed at the beginning of the disease can both affect coping abilities and constitute an indicator of further prognosis [10]. Schizophrenia is characterised by a variety of cognitive function deficits, affecting attention, memory, visuospatial functions, language abilities and the general level of intelligence. Cognitive deficits related to problem solving, planning and abstract thinking, known as executive functions, are of special importance [11].

In recent years, working memory in healthy people and in people suffering from various psychic disturbances has been frequently focused on in studies. It is becoming a widespread view that the disturbances of working memory and executive functions belong to the most important cognitive dysfunctions in schizophrenia [4, 12, 13, 14]. They are usually accompanied by abnormalities located in the anterior region of the brain, i.e. in anterior cortical associative region (prefrontal cortex) [12, 14, 15]. In their work, some authors explicitly call schizophrenia a "working memory disease". Silver et al [14] compared patients with stable chronic schizophrenia treated with atypical neuroleptics with a group of healthy unrelated participants; the results of neurocognitive tests indicated larger working memory deficits as compared to other cognitive functions. In studies on working memory deficit, Bertolino et al [15] used magnetic resonance spectroscopic imaging in schizophrenic patients who were doing the N-back working memory test; the results suggested neuronal pathology in the hippocampal area and the dorsolateral prefrontal cortex, which can be related to the schizophrenic patients' poorer performance on working memory tasks. On this basis, it was concluded that the working memory deficit is the core deficit in schizophrenia and probably is also a factor limiting the efficiency of other cognitive functions.

Baddeley [16] as well as Baddeley and Hitch [17] presented a dynamic working memory model, describing it as the limited capacity of "working space" of information processing. According to Baddeley, working memory is the ability to temporarily store important information in memory and manipulate them [16]. It is a system which in the process of thinking temporarily retains selected current events and integrates them with past experience. It constitutes the basis for intended, planned actions and for inducing long-term memory, especially the autobiographical one. This happens because of what is known as online processing [18]. Working memory is the basis for executive functions necessary for planning, problem solving, orientation and reaction in complex situations, flexibility and the ability to adjust one's behaviour to the situation.

It has been stated in many works that cognitive dysfunctions of various intensity and frequency occur also in schizophrenic patients' first-degree relatives [19, 20], in particular, but not exclusively, in those showing schizotypal personality disorders [21,

22]. It has been noted that working memory dysfunction occurs also in schizophrenic patients' healthy monozygotic twins. The studies suggest that genetic susceptibility to developing schizophrenia can refer to biological mechanisms connected with working memory and executive functions [23]. This leads to the belief that cognitive deficits revealed by means of neuropsychological methods can belong to the important indicators of this susceptibility, and can be an element of schizophrenia phenotype (known as endophenotype) that in pathogenetic studies is more useful than the complex clinical picture of schizophrenia. Working memory deficits are used in genetic studies as an endophenotypic marker for this disease [23, 26]. Glahn et al [26], after examining spatial working memory of probands and their mono- and dizygotic twins, stated that working memory dysfunction occurring in these groups can be an actual endophenotypic marker for schizophrenia [26].

The term "working memory" is not used consistently, so that it is possible to distinguish different ways of defining it as well as various study methods [14, 16]. There is no standard test battery. Apart from those tests that are most frequently mentioned by works in English, such as: *Wisconsin Card Sorting Test* (WCST) [27], *N-back Test*, *Trail Making Test–B* (TMT-B), "tower" tests, e.g. *Tower of London, ...of Hanoi*, there are also in use many other simple tests known from various batteries used for studying lesions of the central nervous system [13, 28, 29].

Aim

The aim was to compare nature and intensity of neuropsychological working memory dysfunctions revealed in the study using tests from Vienna Test Battery [29] in schizophrenic patients and their first-degree relatives. The basic research question was as follows:

– Do selected tests related in various degrees to working memory make it possible to claim that there are cognitive functioning differences in this respect between schizophrenic patients and their first-degree relatives on the one hand and healthy participants on the other?

A positive answer to this question would be an argument supporting the claim that a working memory dysfunction is not only an indicator of disease "condition", but also an indicator of the "feature" of susceptibility to developing schizophrenia, occurring in both schizophrenic patients and in their healthy relatives. In this way, a working memory dysfunction would become one of the relatively simple indicators which could be recognised as the endophenotype of the susceptibility to developing schizophrenia.

Subject

The studied group included patients with schizophrenia diagnosed according to ICD-10 criteria, and their family members, first-degree relatives. The control group included healthy participants with no schizophrenia symptoms and no psychic dis-

turbances in their medical history. The study included altogether 209 subjects, whose basic social-demographic characteristics are presented in Table1.

Table 1.

The social-demographic characteristics of the subjects

Analysed variables		Schizophrenic patients (n=99)	Healthy first-degree relatives (n=42)	Healthy participants (n=54)	First-degree relatives with a history of psychiatric disorder (n=14)
Sex[1]	females	41 (41%)	29 (69%)	10 (71%)	36 (67%)
	males	58 (59%)	13 (31%)	4 (29%)	18 (33%)
Age (years)[2]	mean standard deviation	33.8 ±11	48.5±14	44.79±15.7	29.8±8
	range	18-62	23-76	17-75	20-53
Education[3]	primary	30 (30%)	7 (17%)	6 (43%)	7 (13%)
	secondary	51 (52%)	15 (36%)	6 (43%)	31 (57%)
	higher	18 (18%)	20 (47%)	2 (14%)	16 (30%)

1. 5 χ^2=1.24; p<0.002
2. F=27.88; p<0.000
3. χ^2= 20.45; p<0.02

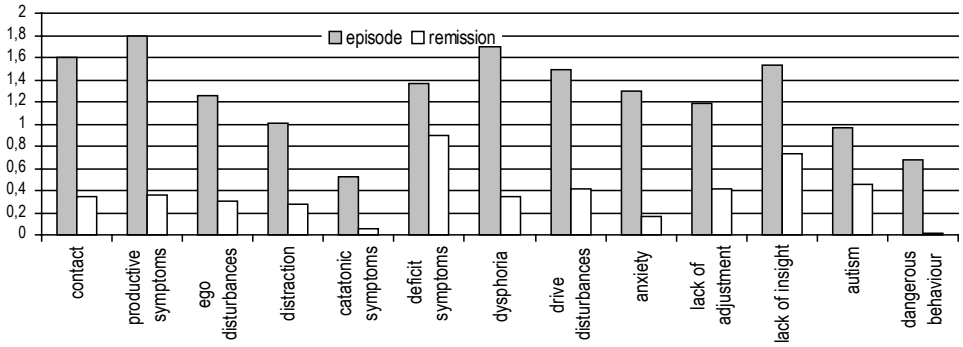

Figure 1. **The comparison of the average intensity of 13 symptom groups, assessed according to the KOSS-W scale, during the developed episode of disturbances and during the period of remission. Neuropsychological examination was conducted during the remission period.**

Patients

The study included 99 patients receiving treatment in various wards of the Department. There were two inclusion criteria: the diagnosis of schizophrenia, according to the criteria of the tenth version of International Classification of Diseases (ICD-10) and the condition of an early period of symptoms remission. The initial level of symptoms, assessed by means of the PANSS scale [30], was 77 points on average, and 45 points at the moment of the study (improvement indicator approximately 45%), with the positive sum score 16 → 9, the negative sum score 22 → 14, and the general sum

score 40 → 22, respectively. Psychopathological profile described by means of the KOSS-W scale [31] is presented in Fig. 1. At the time of the study (remission) it was marked by a low level of most of the symptoms, with a relative higher level of deficit symptoms, slowness and autism. Mental condition was assessed by doctors conducting treatment. There were slightly more male patients (58%) and people with secondary education (54.8%). All the patients had been treated with antipsychotics, and 30% of the patients had been taking new generation medicines.

Families

The study included 56 family members: first-degree relatives of the patients participating in the study. Some of them (14 participants) had received medical treatment beforehand due to psychotic disturbances in the past. In the group of 42 healthy relatives there were more females (69%) and subjects with higher education (48%), whereas in the group of relatives with medical record there were more females (72%) and subjects with secondary education (43%). The two groups: that of the patients and that of the patients' relatives could not be made equal in number. The reason for this was the fact that many relatives, who were clearly afraid of the results confirming their potential susceptibility to developing schizophrenia, refused to participate in the study.

Control group

The study included 54 healthy participants, volunteers, who during their lifetime had not received psychiatric treatment, and with no psychic disturbances revealed either in their medical history or at the time of the study. The participants were mainly members of the Institute staff, trainee doctors and medical students, i.e. mostly female groups; as a result, in control group females outnumbered males (86%).

Methods

Selected tests from the Vienna Test System [WTS, *Wiener Test System*, 29] were used in the study as indicators of working memory functions. It is a system of computer-aided psychological tests, by means of which it is possible, for example, to study cognitive function deficits. The subjects found it very attractive that the tests were computer-aided, which proved to be of considerable importance. The tests, presented on the computer screen, were done with either a light pen or the keyboard.

Reaction time tests (RT). Reaction test consists in reacting (pressing an appropriate key) as quickly as possible after a given constellation of visual and/or acoustic stimuli has been presented. The subject holds the finger on the rest key, which he/she releases (R) upon noticing a relevant stimulus (S) on the screen, and then presses the reaction key (K) as quickly as possible. The programme measures reaction time (t_R-t_S) and motor time (t_K-t_R). The measured reaction time requires therefore, among others, efficient working memory, since in order to react appropriately the subject has to recognise the perceived stimulus combination of two modalities (sight, hearing) and store it temporarily in memory as well as compare it to the established model, remembered beforehand. In order to do the test correctly, the ability to switch from one stimulus

combination into another is required. Various forms of the RT test were used. In the S3 form the task is simpler: reaction to yellow light or sound. In the S5 form the task is more difficult, as the reaction is expected upon noticing either the yellow light and sound or yellow and red lights. The basic variables recorded are median reaction time and median motor time (milli-seconds), resulting from a number of trials.

Perseveration test (PERSEV) assesses the tendency to perseveration, i.e. stereotypical reaction. The computer screen displays nine randomly positioned circles (Fig. 2A), which the subject presses in a possibly random way. Each circle has its identifier, and the frequency with which the subject presses various circles is measured automatically. On this basis, the redundancy indicator is established; it expresses the probability of non-random choice (repetition, preference) of certain circles. The higher the redundancy indicator value, the greater the tendency to perseveration, i.e. to react in a stereotypical manner. Redundancy of the second degree, expressing the frequency of the preference for individual combinations of two circles, is considered to be a significant indicator of the dysfunction of the flexibility of reaction.

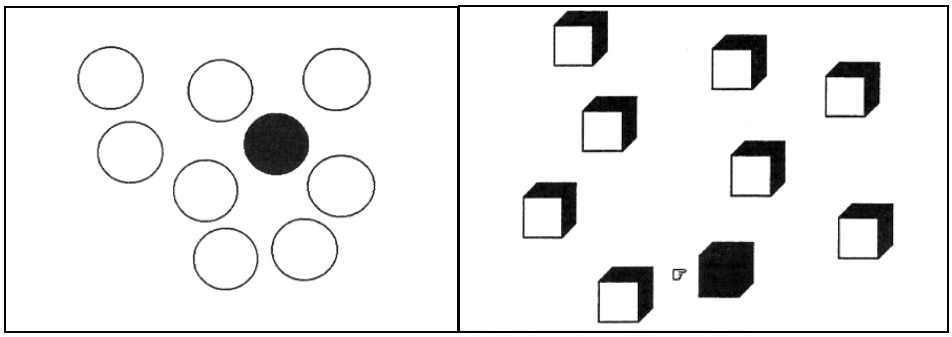

Figure 2. **A sample view of the screen in (A) the persevaration test (PERSEV) and (B) the Corsi test (CORSI).**

Corsi test (CORSI) assesses the capacity (span) of immediate visuospatial memory. During the test a few (3 to 8) cubes appear for a short time on the computer screen and then disappear. After the cubes have been displayed, the subject is to point with a light pen at the previously displayed cubes, maintaining their order of appearance. The basic measured value is the mean number of cubes stored in the memory (and pointed correctly). According to the authors of the test, this value corresponds to the efficiency of the visuospatial aspect of working memory.

Statistical analysis involved methods available in SPSS statistical package (version 10 PL), mainly simple measures of statistical description and hypotheses testing using the mean difference test (Student's t-test) for non-correlated groups.

Results

Average values of all recorded results of particular tests in the compared groups of subjects are presented in table 2, while basic findings of the study, revealing significant differences between the compared groups of subjects are listed in Table 3.

Table 2

Results (means, standard deviations) of the tests used in the study in the examined groups of patients, their first-degree relatives and healthy controls.

Test variables	Average values (meanstandard deviation) in the compared groups			
	schizophrenic patients (n=99)	healthy first-degree relatives (n=42)	control group of healthy participants (n=54)	first-degree relatives with a history of psychiatric disorder (n=14)
RT: S3 form – test of choice reaction time (choice reaction to yellow light or sound)				
median of reaction times	487.35±167.79	436.76±78.45	424.93±72.73	504.79±74.13
median of motor times**	270.13±110.10	253.40±90.31	203.24±63.36	278.93±82.45
distribution* of reaction times	27.28±15.95	24.083±8.96	22.15±7.67	21.295±7.31
distribution* of motor times**	38.67±117.37	18.867±7.27	18.95±10.03	15.759±6.59
correct reactions	15.65±1.60	16.00±0.0	15.98±0.14	15.86±0.54
no reaction	0.30±1.55	0	0	0.14±0.54
incomplete reactions	0.04±0.20	0	0.02±0.14	0
incorrect reactions	0.71±2.20	0.21±0.57	0.07±0.26	1.71±4.36
RT: S5 form – test of choice reaction time to yellow light and sound or yellow and red lights				
median of reaction time	611.51±153.6	543.29±92.6	520.46±75.1	623.14±118.2
median of motor time**	285.23±158.9	262.76±87.7	197.80±63.0	271.21±72.8
distribution* of reaction time	36.21±26.1	36.778±16.1	26.02±8.0	36.554±28.4
distribution * of motor time**	27.82±25.2	26.879±32.8	24.00±17.9	19.139±10.3
correct reactions	15.14±2.3	15.71±0.8	15.81±1.0	15.50±1.2
no reaction	0.65±1.9	0.24±0.7	0.15±0.8	0.36±1.1
incomplete reactions	0.21±0.6	0	0.04±0.2	0.14±0.4
incorrect reactions	0.74±2.4	0.12±0.4	0.06±0.23	0.43±0.9
PERSEV – test of flexibility of psychic processes				
redundancy of the first degree	1.46±2.3	2.23±6.3	1.14±1.7	1.26±1.8
redundancy of the second degree	53.86±24.0	41.80±20.5	33.77±18.9	47.77±26.0
omitted reactions	0	0	0	0
multiple reactions	3.09±11.8	2.24±10.8	0.91±3.8	7.71±21.5
CORSI – test of short-term visuospatial memory span				
immediate memory span	5.13±1.0	5.36±1.0	5.94±1.0	4.86±1.2
correct answers	7.26±2.7	7.90±2.6	9.33±2.4	6.93±3.2
incorrect answers	4.32±1.2	4.57±1.3	4.61±1.4	3.71±0.8
performance time	3.32±1.3	3.75±1.4	4.24±1.5	3.01±1.4

Table 3

Statistically significant differences between mean values of selected attention tests in the groups of: patients, relatives and controls (Student's t-test)

Tests used in the study and examined variables	Compared groups of subjects								
	patients vs. control group			patients vs. their healthy relatives			healthy relatives vs. control group		
	patients (mean)	control group (mean)	test (t)	patients (mean)	healthy relatives (mean)	test (t)	healthy relatives (mean)	control group (mean)	test (t)
RT-S3: choice reaction to yellow light or sound									
reaction time (median)	487.4	424. 9	3.135**	487.4	436.8	2.421*	436.8	424.9	Ns
RT- S5: choice reaction to yellow light and sound or yellow and red lights									
reaction time (median)	611.51	520.46	4.881***	611.51	543.29	3.224**	543.29	520.46	Ns
PERSEV – test of flexibility of psychic processes									
indicator of redundancy of the second degree	53.86	33.77	5.704***	53.86	41.80	2.846**	41.80	33.77	1.993*
CORSI – test of short-term visuospatial memory span									
immediate memory span	5.13	5.94	-4.96***	5.13	5.36	ns	5.36	5.94	-2.88**

Level of significance: ns-no significance; * p=0.05; ** p=0.01; *** p=0.001

RT test. The time of choice reaction to a simple (RT: s3) and more complex (RT: s5) combination of stimuli proved to be longer for the patients, as compared to both the group of healthy relatives and the control group. In the group of the relatives the time was insignificantly longer than in the control group. This means that the patients, as compared to healthy participants (both related and unrelated) needed more time for the choice and reaction to a stimulus combination requiring the ability to switch from one stimulus combination into another.

Reaction times (s3, s5) did not correlate with sex, although they did correlate slightly and insignificantly with age (s3: rho = 0.24; s5: rho = 0.25). In the case of the simpler form of the RT test, the analysis of variance did not reveal any correlation between the test results and education (RT: s3, p = 0.1); such correlation, however, was revealed in the case of the more complex form (RT: s5, p = 0.03).

In the *Perseveration test*, the highest indicators of redundancy of the second degree were observed in the group of patients, the lowest – in the control group of healthy participants, and medium – in the group of healthy relatives. Differences among all groups proved to be statistically significant.

According to the analysis of variance, the indicator of redundancy of the second degree did not correlate with sex, and correlated with education only in a limited degree (p = 0.053). A slight and insignificant correlation with age (rho = 0.13) also suggests that these two variables are not significantly interrelated.

In the *Corsi test* the average immediate visuospatial working memory span proved to be significantly larger in healthy controls, as compared to both the patients and the patients' close relatives. On the other hand, the differences between the patients and their healthy relatives proved to be statistically insignificant. The analysis of variance

did not reveal any correlation between memory span and sex ($p = 0.83$) or education ($p = 0.08$). However, this variable correlated slightly and negatively with age (rho = -0.27).

The results of the tests used in the study did not reveal any significant differences between the group of schizophrenic patients (N = 99) and the group of their relatives (N = 14) who were selected during the examination of families and whose medical history suggests a mental disease (schizophrenia or similar disturbances but with no current symptoms requiring hospitalisation).

Discussion

The assessment of the intensity of working memory deficit in schizophrenic patients seems to be important since various studies indicate that it is the main deficit, affecting other cognitive functions [14]. The deficit has been observed in schizophrenic patients and their first-degree relatives [19, 20].

The results, achieved in this study, of the assessment of working memory cognitive processes in schizophrenic patients, their healthy first-degree relatives and the control group of unrelated participants, prove that the groups differ in the level of correctness in doing selected tests and the time needed to complete them. These results are compatible with the findings of other authors [14, 15, 20, 26] and they confirm that the group of patients always achieve the poorest, dysfunctional results, as compared with other groups involved in the study [32, 33, 34, 35].

The tasks testing the time of choice reaction require from the subject to store two different sequences in working memory, which allows switching the processed information from one stimulus combination into another. The results of the reaction time tests which required the choice between two different simple stimuli (yellow light or sound) were significantly different in the group of schizophrenic patients and the control group: the reaction time was considerably longer for schizophrenic patients. The reaction to two different complex sequences (yellow light and sound or yellow and red lights) revealed even more significant differences between the patients and the controls. In both cases, moreover, the time of choice reaction has been considerably longer for the patients, as compared to their healthy relatives. However, between the patients' healthy relatives and healthy controls no significant differences in reaction time have been found. The results have revealed, then, that this aspect of working memory dysfunction is characteristic, above all, of the subjects suffering from the disease. No specific reaction pattern for sight or hearing analysers has been found in this group; the results suggest a similar performance pattern for both modalities. Other authors have reached similar conclusions, too [17].

The results make it possible to conclude that immediate visuospatial memory span in schizophrenic patients included in the study, is indeed reduced. The results of the Corsi test revealed significant differences between the groups of both the patients and their healthy relatives on the one hand, and the control group on the other. The difference between the patients and their healthy relatives turned out to be statistically insignificant. It has been found by other authors as well [19, 20, 25] that schizophrenic

patients and their first-degree relatives perform poorer on various tasks requiring efficient (and therefore capacious) working memory. It seems that they have difficulties with the correct use of information depending on the circumstances, with the short-term storage of information concerning the present activity, and with the correct switching into new rules of action [36]. The upper limit of the short-term memory span has been determined in the studies at the level of 72 elements [37]. In our study, as a rule, the patients did not reach the limit of 7 elements, stopping most often at 4-5 elements. It is this feature of the working memory dysfunction, out of all these analysed in our study, which makes the patients and their close relatives the most similar. Reduced working memory span makes it difficult to learn new material, solve problems, make decisions, think abstractly. Randolph, Goldberg and Weinberger [38], discussing various neuropsychological deficits diagnosed in patients suffering from schizophrenia conclude that memory impairment can be fundamental for the disease.

Impaired processes of coding, storing and reconstructing memory traces can result in impaired ability to learn new material, which, in turn, can make the adjustment to the changing circumstances more difficult [39, 40, 41]. In our study, interesting differences among the compared groups have been found, as regards perseverative tendencies, which have been the most elevated in schizophrenic patients, weaker in their healthy relatives and the weakest in healthy controls. The differences among all these groups have been statistically significant, which suggests that dysfunctional tendency to stereotypical reaction in the PERSEV test (expressed by redundancy of the second degree) can be an important diversifying characteristic. High redundancy can be interpreted as the expression of rigid cognitive processes and reduced ability to change the reaction criterion, caused by stereotypical resorting into the reaction already learned. Rigidity of psychic processes can impair the efficiency of executive functions, such as planning, organised searching and using feedback information from the environment. Furthermore, it makes it difficult to change the rules of the choice, to perform deliberate actions and to control impulsive reactions [27, 29, 42]. The subjects undergoing the test are not able to successfully adjust their reactions to the needs (instructions), which results in the rigidity in task solutions and behaviour [39, 43]. All observed deficits of working memory cognitive functions (longer reaction time when taking complex decisions is required, reduced immediate visuospatial memory span, elevated tendency for perseveration) can be interesting indicators of the dysfunction related to the present condition of the disease, as they allow to differentiate subjects suffering from schizophrenia from the healthy participants.

However, some of these deficits (reduced immediate visuospatial memory span and perseverative tendencies) allow also to differentiate healthy subjects closely related to schizophrenic patients from healthy unrelated subjects (control group), which can lead to the belief that these aspects of the dysfunction indicate not only the present schizophrenia condition but also familial susceptibility which increases the risk of developing schizophrenia. This suggests that working memory dysfunction could presumably be taken into account as an endophenotypic feature of this susceptibility [26, 44, 45, 46]. Interestingly, the deficit revealed in the test most directly related to the concept of working memory (the Corsi test) practically does not provide any dif-

ferences among related participants, regardless of their condition (i.e. whether they are healthy or not).

In spite of the relatively large group of subjects the final conclusions should be formulated cautiously and further study is recommended, since it was difficult to make the compared groups equal as far as sex, education and age were concerned. It should be emphasised, however, that the results of the tests used in the study did not significantly correlate with the above-mentioned social-demographic variables.

Conclusions

1. Working memory tests, which were used in the study, revealed poorer results of the schizophrenic patients, as compared to unrelated healthy subjects (control group): longer reaction time in tasks requiring a complex choice while the modalities of the stimulus were crossing, elevated tendency to perseveration and reduced immediate visuospatial memory span. It indicates a working memory dysfunction in these patients.
2. Two of the dysfunction indicators which were examined: perseverative tendencies and reduced visuospatial memory span, revealed lower values in the schizophrenic patients' close relatives than in the control group. It can be then suggested that those aspects of the dysfunction which are familial and which increase the risk of developing the disease manifest themselves in these subjects.
3. Immediate visuospatial memory span deficit does not significantly differentiate the schizophrenic patients from their healthy relatives, which stresses how important this particular dysfunction indicator is for the familial susceptibility to developing the disease.
4. The findings suggest that working memory dysfunction can be interpreted as an endophenotypic feature of the susceptibility to developing schizophrenia, while the results of some of the tests used in the study can be regarded as the indicator of this feature.

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