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VERBAL, VISUOSPATIAL AND FACE WORKING MEMORY IMPAIRMENT IN MULTIPLE EPISODE SCHIZOPHRENIA PATIENTS

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Abstract
Memory impairment has been acknowledged as a core cognitive deficit in schizophrenia, and it is present irrespective of specific features related to the patient or the evolution of the disorder. It is suggested that distinct functional subsystems of memory are differently impaired in these patients, hence the broad range of levels of functioning affected in this specific population. The aim of this study was to assess working memory performance in multiple episode schizophrenia patients. A group of patients diagnosed with schizophrenia and a control group of healthy subjects were comparatively evaluated with 3 neurocognitive tests which require the use of working memory subsystems. Our results indicate significantly poorer performance in the case of patients suffering from schizophrenia, in all three working memory tests - they displayed impaired face recognition abilities and used a significantly higher number of non-list words when asked to repeat a list of words, which may be particularly relevant for their social functioning. The neurobiological and genetic background of the memory impairment in schizophrenia have been acknowledged due to increasing body of evidence, and the current study supports the current data which state that working memory deficits in schizophrenia are consistent, stable and comprehensive. This is particularly relevant for the personal management, and also for the academic, interpersonal and social rehabilitation of schizophrenia patients.

Keywords: schizophrenia, working memory, impairment, cognitive tests

A great number of studies have revealed cognitive deficits in schizophrenia patients, irrespective of the stage of the disorder. Memory dysfunction has been identified through specific tests as a core feature of the cognitive impairment in schizophrenia, and research suggests that it is not correlated with intellectual performance or IQ levels in particular (Zihl et al, 1998, Leeson et al, 2008). Distinct aspects of implicit and explicit memory are

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differently impaired, according to the memory subtype underlying the specific task involved in the test (Danion et al, 2001, Perry et al, 2001).

Performances of schizophrenia subjects significantly depend on memory type and system employed for the task, and also on the memory task itself (Turetsky et al, 2002).

Working memory is limited in volume and time span, allowing the subject to operate with bits of recent information (Westen, 2006) – for example, retaining the digits of a telephone number, from its reading until the call is made (Twamley et al, 2006), or drawing a figure right after it was seen. It also entails temporary storage and manipulation of information necessary for complex cognitive tasks such as language comprehension, learning, abstract thinking (Twamley et al, 2006), problem-solving related to spatial tasks – spatial working memory (Westen, 2006), generating novel problem solving strategies, understanding the meaning of complex texts, planning oral communications, daily activities or a trip (Zihl et al, 1998). This cluster of functions was conceptualized as „executive function working memory" (Twamley et al, 2006), and it is suggested that prefrontal areas play a significant role in its functioning (Zihl et al, 1998). Verbal memory is also regarded as a distinctive type of working memory, underlying encoding through language (Ragland et al, 2004, Barch and Csernansky, 2007). Baddeley, who had a significant contribution to the coining of the term working memory in cognitive psychology, emphasizes that working memory has two subsystems: the visuo – spatial sketchpad and the phonological loop. The first one is represented by the working memory for visual and spatial information, and the second one – the short term memory for acoustic or speech-based information. The two aforementioned subsystems are under the control of a central executive system (Baddeley, 1996).

The hippocampus is the most important among the cortical areas contributing to the verbal declarative memory. Hippocampal and parahippocampal areas are involved in placing into proper context both verbal memory, and the processes associated with it, such as assessment of sensory information, context analysis and sensory selection. Studies in schizophrenia patients have revealed bilateral morphological anomalies of limbic structures of the temporal lobe, but also of the prefrontal areas (Stone and Seidman, 2008); however, some authors have described a left lateralization of the impairment (Bogerts, 1997). Verbal memory deficits significantly contribute to the impairment in independent functioning of the schizophrenia patients and their relationship with family and peers (Stone and Seidman, 2008). Research on primates revealed that the prefrontal cortex is the primary storage site for transient visuospatial information (Perry et al, 2001). A large body of evidence from neuroimaging studies through event-related functional magnetic resonance imaging (fMRI) showed bilateral activation patterns in the orbitofrontal cortex during working memory tasks (Steinberg et al, 1999, Hill et al, 2008) and confirmed that increased frontal activity is correlated with accuracy of working memory (Lee et al, 2008). Healthy subjects exhibit an increased activation in the right frontal, temporal and cingulate regions (Hill et al, 2008, Lee et al, 2008), while schizophrenia patients show greater activation in left dorsolateral prefrontal, frontal, temporal and parietal regions as well as in right frontal regions (Barch and Csernansky, 2007, Hill et al, 2008, Lee et al, 2008), precuneus, hippocampus, paracentral lobule, and putamen (Steinberg, 2007) during working memory tasks. These findings support the hypothesis that the major difference between healthy subjects and schizophrenia patients concerning working memory is functional asymmetry – the subjects diagnosed with schizophrenia recruited a more extensive, bilateral neuronal network to achieve the same level of working memory performance (Lee et al, 2008).

Working memory provides a crucial interface between perception, attention, memory, and action, due to its involvement in complex cognitive functions such as learning, reasoning and comprehension (Baddeley, 1996). Neuroimaging studies have ascertained that working memory, rather than being located to a single brain region, is probably supported by the functional interactions of the prefrontal cortex with other areas of the central nervous system (D'Esposito, 2007), and that different tasks involving working memory generate different patterns of brain activation (Wager and Smith, 2003). However, identifying specific tasks that only require the functioning of one specific working memory subsystem, and developing them into specific measurements that would independently test each working memory subsystem without any interference from the others is very difficult, because tests involving the phonological loop and those for visuo-spatial working memory, administered independently or combined, require the activation of the central executive in order to complete the putative tasks (Cocchini et al, 2002); also, the power of neuroimaging studies to differentiate between activated and not activated brain areas has been questioned (Wager and Smith, 2003).

Nevertheless, the assessment of working memory subsystems has been shown to provide invaluable information for the strategy of cognitive rehabilitation of schizophrenia patients, due to the fact that cognitive training exercises mainly involve working memory subsystems (Wexler et al, 2000; Wykes et al, 2002)

We conducted an assessment of a sample of multiple episode schizophrenia patients, in order to evaluate the degree of working memory impairment by means of a battery of specific neurocognitive tests. The individual level and pattern of impairment was regarded as clinically relevant for the management strategy of each specific patient, while the purpose of identifying common features of working memory dysfunction in this particular sample was deemed as significant for the association between working memory subsystems and the cognitive impairment in schizophrenia.

Methods

Participants

Forty schizophrenia inpatients (29 male and 11 female) were included in the study. All participants were Caucasian, had a mean age of 29.1 years (SD = 6.3) and averaged 13.1 years (SD = 2.6) of education. They were recruited from the acute-care psychiatric unit of the Cluj County Emergency Hospital in Cluj-Napoca, between 2005 and 2007.

All patients met the DSM-IV-TR criteria for schizophrenia or schizoaffective disorder. The mean age of illness onset was 22.2 years (SD = 3.8), with a mean duration of illness of 6.9 (SD = 4.8) and a number of previous hospitalizations ranging between 1 and 5. The IQ scores of patients, assessed by the Raven test, excluded the presence of mental retardation in the experimental group. The patients did not have a history of drug or alcohol use, head trauma, neurological or systemic conditions affecting the central nervous system, and they had not recently undergone electroconvulsive therapy. Also, all patients were treated with second generation antipsychotic medication and their therapy was not changed for at least three months prior to inclusion.

Thirty non-psychiatric comparison participants (11 men; mean age = 29.6; SD = 4.7) were recruited from the community. Individuals with a history of mental disorders and those who had a first degree relative with a history of mental disorders were excluded from this group.

The two groups were comparable for age (Mann-Whitney U = 688.5; p = .863) and sex (χ^2 = 3.413; p = .065). (See Table 1)

All participants signed an informed consent form prior to inclusion and the study was approved by the University of Medicine and Pharmacy "Iuliu Hațieganu" Cluj-Napoca, Romania Institutional Ethics Review Board.

Table 1. Demographic characteristics of study participants

	Patients with schizophrenia	Controls
Age (years)*	29.1 (6.3)	29.6 (4.7)
Gender (% male)	58.0	36.7
Ethnicity (% caucasian)	100	100
Education (years)*	13.1 (2.6)	18.2 (2.8)
Duration of illness (years)*	6.9 (4.8)	-
Age of illness onset (years)*	22.2 (3.8)	-
Number of previous hospitalizations	?	-

* Data presented as mean (standard deviation)

Assessment of psychopathology

The Severity of Illness subscale of the Clinical Global Impressions (CGI) scale (Guy, 1976), scored from 1 (not ill at all) to 7 (among the most extremely ill) was used for the baseline assessment of patients in the study group. The CGI is a standardized, public domain clinical tool, widely employed in clinical and research settings due to the fact that it is manageable and it only takes 1-2 minutes to score after the completion of the psychiatric assessment.

The 30-item Positive and Negative Syndrome Scale (PANSS) with its 3 subscales, Positive (7 items), Negative (7 items) and General Psychopathology (16 items) (Kay at al, 1987), developed in order to evaluate the severity of the positive and negative symptoms in adult subjects with schizophrenia, was also included in the baseline assessment of patients included in the study group.

The mean score of illness severity in the patient group was 5.2 (SD = 1.1) on the CGI scale. The mean score for positive symptoms was 26.4 (SD = 7.1) on the Positive subscale of PANSS, while the mean score on the Negative subscale of PANSS in the same group was 28.2 (SD = 8.1). Patients had a mean score of 53.4 (SD = 10.9) on the General pathology subscale of the PANSS, and a mean total PANSS score of 107.9 (SD = 21.2).

Table 2. Scores on psychopathology scales in study participants

	Patients with schizophrenia	Controls
Positive subscale of PANSS	26.4 (7.1)	-
Negative subscale of PANSS	28.2 (8.1)	-
General pathology subscale of PANSS	53.4 (10.9)	-
PANSS total score	107.9 (21.2)	-
CGI score	5.2 (1.1)	-

Neuropsychological Tests

All participants were assessed using the Word List Memory Test, the Face Memory Test and the Spatial Working Memory Test on a Cogtest Console (Cogtest, Inc.). The Cogtest system is a highly reliable, completely automatic, state of the art, precise cognitive assessment, scoring, and data management from a streamlined computer, similar to an electronic CRF. It has a broad range of indications and it is customized according to requirements, with a specific battery of tests of attention, working memory, and declarative memory, depending on the domains selected. Test features increase efficiency, reduce the cost of assessment, and include complexity manipulations to modify difficulty, which minimizes the total testing time for valid assessments.

The Word List Memory Test consists of 5 trials. In the first trial, the computer plays 20 recordings of 20 words in the native language of the subject.

After a short latency period the subject is asked to repeat these words. In the following trials the computer plays only the recordings of the words that the subject failed to repeat, but the subject is asked to say all the words (including those he remembered in the previous trial(s). The computer calculates the number of non-list words, a total learning score and trial-to-trial transfer percent.

In the Face Memory Test, the computer displays two series of 20 black and white images of neutral expression male faces that the subject is asked to memorize. After each series, the computer displays 20 pairs of images containing the same kind of faces, one face showed before and one new. For each pair of images displayed, the subject is asked to select the one he/she has seen before. The proportion of correct answers is calculated.

In the Spatial Working Memory Test the computer displays a stimulus in a random position on the screen for a short period of time. The subject is asked to memorize the position of that stimulus and then he/she is asked to touch the screen in the exact position where another stimulus is displayed. This other stimulus is displayed until the subject touches it for a small or large number of times (short or long trial, respectively). After that, the subject is asked to touch the screen in the position the original stimulus was displayed. The distance between the real position of the original stimulus and the position the subject pointed out is measured. Mean and median distances are calculated for the short and long trials, and also overall trials.

Results

The Kolmogorov-Smirnov Test showed that continuous data were not normally distributed ($p > 0.05$). Thus, Mann-Whitney U Test was used to test for differences between means.

Schizophrenia patients showed significantly poorer performance in all three working memory tests as compared to controls (see Table 3).

Word List Memory Test

The Word List Memory Test (WLM) evaluates verbal working memory, which depends both on the limits of auditory processing and the phonological loop, as previously shown by Baddeley (Baddeley, 1986).

As shown in table 3, schizophrenia patients showed a significantly higher rate of non-list words in their responses (4.38 ± 6.98 vs. 1.23 ± 1.79, $p = 0.004$), lower learning (42.65 ± 12.87 vs. 51.80 ± 14.31, $p = 0.006$) and trial-to-trial transfer capabilities (54.82 ± 25.29 vs. 87.21 ± 8.99, $p < 0.001$).

Face Memory Test

Face Memory Test entails temporary, short-term storage of a specific type of visual information. The anthropomorphic characteristics of the information required to be stored makes it different from other types of visual memory (shapes, colors, landscapes), and connects it to elements supported by episodic memory.

Schizophrenia patients showed significantly poorer performance in memorizing and recognizing faces, as showed by their lower correct answer proportion when compared to controls (0.66 ± 0.13 vs. 0.83 ± 0.09, $p < 0.001$) – see Table 3.

Spatial Working Memory

Spatial Working Memory Test involves both maintenance and manipulation of information, which deems it an assessment tool for the executive function of working memory.

Schizophrenia patients had a significantly poorer performance compared to controls (89.42 ± 55.42 vs. 49.37 ± 16.57, $p <0.001$) – see Table 3.

Table 3. Scores on neuropsychological tests for the two groups

Test	Score						Analysis	
	Patients with schizophrenia			Controls				
	N	Mean	SD	N	Mean	SD	Mann-Whitney U	p/sig
Word List Memory Test								
Total number of non-list words	40	4.38	6.98	30	1.23	1.79	363.00	<.05
Total learning	40	42.65	12.87	30	51.80	14.31	367.00	<.05
Trial-to-Trial Transfer (%)	40	54.82	25.29	29	87.21	8.99	116.00	< .01
Face Memory Test								
Proportion Correct	32	.66	.13	30	.83	.09	132.00	< .01
Spatial Working Memory								
Short Median	33	63.64	67.04	30	35.00	12.06	225.00	< .01
Short Mean	33	62.19	48.22	30	38.86	15.19	232.50	< .01
Long Median	33	96.27	61.18	30	54.37	22.97	198.00	< .01
Long Mean	33	116.65	68.60	30	59.81	23.74	184.00	< .01
Overall Median	32	67.06	52.39	30	39.80	13.13	151.50	< .01
Overall Mean	33	89.42	55.42	30	49.37	16.57	176.50	< .01

Discussion

Neurocognitive assessment in studies of schizophrenia has gained relevance, through several measures which not only cover domains implicated in pathophysiology, but are also linked to the neurobiological mechanisms underlying neurocognitive impairment connected with schizophrenia.

Furthermore, research performed on particular processes and domains suggests that the underlying neurocognitive systems are complex and interrelated. Factor analysis of previous evidence regarding separable neurocognitive dimensions in schizophrenia subjects hints that these areas are actually somewhat correlated rather than independent, which means that efficient multidimensional methods of integrating data within and across levels of analysis are necessary. Consecutively, rigorous and comprehensive measures related to brain function should allow researchers to better ascribe the diverse contributions to major behavioral domains (Gur et al, 2007).

The results for the memory tests employed in our study are similar to data from most of the studies performed so far on this issue. For instance, a meta-analysis of studies performed between 1997 and 1999 on memory in schizophrenia (Aleman et al, 1999) was focused on the correlation between schizophrenia and memory impairment and the potential modulating variables of this correlation. The collected data suggested that memory deficits and schizophrenia were significantly correlated (moderate – large size effects), which corroborates data from another meta-analysis of studies which assessed correlations between performances of schizophrenia patients and healthy subjects in several functional neurocognitive investigations, and revealed significant impairment in the studied parameters, including long-term verbal and non-verbal memory (Heinrichs, Zakzanis, 1998).

Our study focused on various aspects related to working memory, elicited by the specific task requirements of a battery of neurocognitive tests. The first one considered for assessment was the Word List Memory Test. Patients included in our study exhibited significantly lower performance in this test, when compared to the control group. The assessment of the test (trial-to-trial transfer) reveals that transient online maintenance memory function is impaired across consecutive processing sequences. This deficit is bound to generate dysfunctions in WLM Total learning – i.e., the implicit learning within the task entailed by the test. Concerning the total number of non-list words, they frequently interfere with the memorized material in schizophrenia patients. This generates perturbing factors of verbal working memory performance, and could mostly be the expression of psychopathology rather than of working memory processes.

The analysis of performance in subjects in the study group for the tasks required by the Face Memory Test emphasized that the proportion of incorrect answers in schizophrenia patients assessed expresses the manner in which this particular test evaluates functions ascribed to the storage buffers (rehearsal) mentioned in Baddeley's Working Memory model (Baddeley, 2000). According to latest studies, assessment of facial processing can advance the understanding of schizophrenia deficits (Gur et al, 2006).

The tasks entailed by the Spatial Working Memory test require adequate and efficient executive functions of working memory when information is transformed, encoded or protected from interference. Resistance to interference of working memory is significantly decreased in the studied patients, therefore suggesting trait-like features of schizophrenia in the studied group. As an additional comment, the impairment of this subtype of working memory exhibited by the studied group did not change across the duration of the disorder, unlike the

Face Memory Test, which revealed an increase of performance alterations across time.

Among possible moderator variables, only the negative symptoms appeared to influence the relationship schizophrenia – memory. Thus, negative symptoms were correlated with the degree of frontal lobe dysfunction – which in turn was correlated with the degree of impairment in information retrieval (Aleman et al, 1999). The memory impairment in schizophrenia patients is extensive and highly stable, irrespective of task variables (degree of support in the process of information retrieval, type of stimulus, retention interval), and it appears to have a pattern of generalized dysfunction, rather than one of differential deficits (Aleman et al, 1999).

Comprehensive assessment of distinctive areas of cognitive functioning (memory, attention, intelligence, executive functioning, verbal and motor performance) had the purpose of clarifying the generalized versus differentiated nature of neurocognitive impairment in schizophrenia (Heinrichs, Zakzanis 1998), and it was concluded that schizophrenia is characterized by an extensive cognitive impairment, with different degrees of deficit in various areas of functioning (Aleman et al, 1999).

The neurodevelopmental model for schizophrenia supports the hypothesis of later development of brain changes and suggests that the variable age at onset can be accounted for by late prenatal, genetic and environmental factors, with the mention that genes affecting the development of cognitive abilities operate more strongly in late adolescence, and also that genetic factors shape the brain throughout the entire lifetime (Rapoport et al, 2005).

The limitations of this study come from the fact that the tests were administered only to 40 schizophrenia patients, most of which had the diagnosis of paranoid schizophrenia. Therefore, a distinctive analysis of each clinical form of schizophrenia (e.g. simplex, non-differentiated, etc.) could not be performed. Of all working memory subsystems, verbal memory outlines the most clearly the learning difficulties of schizophrenia patients. The consequences of this deficit can explain, at least in part, the gradual impairment of both interpersonal skills, and personal management strategies in multiple episodes schizophrenia patients. The conclusion we wish to emphasize is that working memory is globally impaired. This specific cognitive dysfunction may lead to social withdrawal and loss of social connection through the impairment of learning mechanisms. Not taking into account this reality deprives the individual who experiences schizophrenia throughout the life span of the chance of correct and comprehensive therapy management.

Conflict of interest
Neither of the authors have any conflict of interest to report.

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