Neurocognitive Expression of Hypofrontality in Long Term Schizophrenia

Marek Krzystanek¹, Irena Krupka-Matuszczyk¹ and Adam Klasik²
¹Department of Psychiatry and Psychotherapy, Medical University of Silesia in Katowice
²The Institute of Psychology, Opole University
Poland

1. Introduction

Despite over a century of studies on schizophrenia, its pathogenesis still remains unexplained. In particular, cognitive dysfunctions, related to a decrease of prefrontal cortex activity in the human brain represent one of the main symptoms of schizophrenia. The cognitive dysfunctions usually precede, by a few years, the first acute episode of the disease. These dysfunctions are present in approximately 70% of persons suffering from schizophrenia, and can be maintained at a stable level over the rest of their lifetime (Rund et al., 2006). For instance, majority of patients enrolled in the CATIE study suffered from the cognitive disorders (Lieberman et al., 2005a).

According to Javitt (2010), the cognitive deficits are the key symptoms of schizophrenia, which usually precede an onset of some other symptoms of this disease. Due to that, the cognitive disorders can represent the leading concept among hypotheses, related to etiology of schizophrenia. The main component of these disorders is the deterioration of attention concentration and operative memory deficits, including the difficulty of holding some elements in short-term memory (Goldman-Rakic, 1999) that in turn translates into some cognitive dysfunctions. These disorders include also memory, learning abilities, and executive functions (Meltzer & McGurk, 2004). The cognitive dysfunctions related to hypofrontality consist of deterioration of the activity of prefrontal brain cortex (Carter et al., 1998).

In majority of patients, the cognitive deficits begin prior to their first disease episode, in the prodromal stage (Fuller et al., 2002). Individuals with prodromal schizophrenia symptoms often present deficits, ranging in intensity from almost normal conditions to the ones, resembling mental status of patients with the first episode of their disease (Lencz et al., 2006). In this aspect, neurocognitive disorders can be considered as the initial schizophrenia symptoms (Javitt, 2010). Due to these reasons, the cognitive disorders appear to be closely connected with the etiology of schizophrenia (Kantrowitz & Javitt, 2010b).

In schizophrenia, the cognitive dysfunctions and hypofrontality are associated with hypofunction of NMDA receptors (NMDA-R) (Marek et al., 2010), and according to Carlsson (2006), an abnormal function of NMDA-R is the main cause of schizophrenia. These cognitive disorders, mostly in form of concentration deterioration, and deficits of operative memory are results of prefrontal cortex dysfunctions, which are related to the
deficit of glutamergic transmission, caused by the NMDA-R hypofunction (Thomsen et al., 2009).

There are two pharmacological models of the NMDA-R (receptor) hypofunction – acute and chronic (Pratt et al., 2008). Acute receptor antagonist model relates to a short-term administration of the NMDA-R antagonist. In this situation, blocking the NMDA-R causes disinhibition of neurotransmission and so called hyperfrontality that means increased glutamergic activity in the areas of prefrontal cortex (Homayoun & Moghaddam, 2007). There is indirect evidence that some cerebral metabolic disorders, in the acute phase of schizophrenia, resemble the changes that were observed experimentally, during administration of the NMDA-R antagonists, directly to different areas of the brain (Bubeníková-Valesová et al., 2008). Also, a significant increase of the glutaminic acid concentration in the cingular area has been noted both in patients with an early psychosis (Théberge et al., 2002), and with prodromal schizophrenia symptoms (Stone et al., 2009).

Pratt et al. (2008) proposed a chronic psilocybine (PCP) model, which explains a relation between the NMDA receptors hypofunction and hypofrontality. Chronic administration of the PCP to rats caused a reduction of glucose metabolism in their prefrontal cortex, and a decrease in the expression of protein marker of gamma aminobutyric acid (GABA) interneuron’s’ activity. In schizophrenia patients, similarly to chronic PCP abusers, the hypofrontality symptoms and GABA interneuron’s deficits have been noted. According to the Pratt’s model, hypofrontality represents neuroadaptation, created during a period of long-term glutamergic hyperfunction, caused by a chronic blockage of the NMDA-R, related to GABA interneurons.

Based on some studies, the cognitive deficits appear a few years prior to the onset of schizophrenia (Fuller et al., 2002; Kantrowitz et Javitt, 2010b), but there is no convincing evidence that they are present since early childhood (Paz et al., 2008; Perkins et al., 2005). A 28-year observational study by Seidman et al. (2006) has revealed that the patients with schizophrenia displayed some minor concentration disorders already at the age of 7 years. These disorders are subsequently aggravated, with the development of the disease. However, the exact moment of aggravation is still unknown. It is possible that the disorders’ exacerbation can occur just before the first schizophrenia episode.

2. Study design

Our unpublished study results indicate the persistence of cognitive dysfunctions in schizophrenia, and are convergent with some recent research data in this area.

In our study, cognitive functioning was assessed with neuropsychological tests, included in the Vienna System Tests. Functions of attention, operational memory, learning and motor reactions were also examined. A battery of Cognition (COG), Block Taping Test (CORSI), SIGNAL and Reaction Test (RT) tests was performed in all of our paranoid schizophrenia patients.

3. Study group

We studied a group of 162 paranoid schizophrenics, treated with 3 different neuroleptics, or treatment-resistant patients (Figure 1).

Patients who were recruited to this study were diagnosed with paranoid schizophrenia, and treated in monotherapy with one of the following neuroleptics: haloperidol, clozapine or
olanzapine. Subjects in the study group met the contemporary criteria of symptomatic remission in schizophrenia. The study covered also a group of chronically ill schizophrenic subjects, who were resistant to the pharmacologic treatment, and did not have the remission.

Fig. 1. Percentages of paranoid schizophrenia patient’s sub-groups, treated with haloperidol, clozapine, olanzapine, and treatment-resistant. Results are shown as percentages (%) of the entire study group.

The gender characteristics of the study patients are shown in Figure 2.

Fig. 2. Gender of patients in the study groups. Results are expressed as percentages (%) of the entire study group.

The mean age of patients was 46.1 years. The age of patients in the study groups is shown in Figure 3.
An average disease onset was at the age of 27.4 years (mean age) (Figure 4), and the mean period of the disease duration was 19.3 years (Figure 5).

Fig. 3. Age of patients in the study groups. Results are expressed as the mean ± standard deviation (SD).

Fig. 4. The age of schizophrenia onset in the study groups of patients. The results are shown as means ± standard deviation (SD).
The duration of the disease in the study groups of patients is shown in Figure 5. The results are shown as means ± standard deviation (SD).

The mean numbers of hospitalizations of the study patients are shown in Figure 6. The results were analyzed statistically using non-parametric Kruskal-Wallis test and Tukey HSD test for unequal sample sizes. NIR post-hoc test was also applied. Confidence interval (CI) was established at the level of 95%. The results were established as statistically significant at $p<0.05$. 

Fig. 5. The duration of the disease in the study groups of patients. The results are shown as means ± standard deviation (SD).

Fig. 6. The number of hospitalizations in the study groups of patients. The results are shown as means ± standard deviation (SD).
4. Results

The intensity of negative symptoms was significantly below, as compared to the results of patients treated with neuroleptics. It was shown both in the global results of Negative Symptom Assessment Scale (NSA-16) (Figure 7) and in its sub-scales assessing alogy (Figure 8), blunted affect (Figure 9), asociality-anhedonia (Figure 10) and avolition-apathy (Figure 11).

The intensity of negative symptoms, measured with NSA-16 was 32% lower in the group of patients treated with neuroleptics, as compared with the treatment resistant subjects (Figure 7).

![Fig. 7. Results of NSA-16 scale, in paranoid schizophrenia study groups of patients. Results are shown as means with standard deviation (SD). $H_{3,162}=84.7$, $p=0.00001$, $\eta^2_p=0.53$.](image1)

![Fig. 8. Results of NSA-16 alogy subscale, in paranoid schizophrenia study groups of patients. Results are shown as means with standard deviation (SD). $H_{3,162}=70.7$, $p=0.00001$, $\eta^2_p=0.43$.](image2)
Fig. 9. Results of NSA-16 blunted affect subscale, in paranoid schizophrenia study groups of patients. Results are shown as the means with standard deviation (SD). $H_{3,162}=65,6$, $p=0,00001$, $\eta^2_{p}=0,49$.

Fig. 10. Results of NSA-16 asociality-anhedonia subscale in paranoid schizophrenia study groups of patients. Results are shown as the means with standard deviation (SD). $H_{3,162}=60,3$, $p=0,00001$, $\eta^2_{p}=0,35$. 
In the avolition-apathy subscale of NSA-16, the intensity of symptoms was 39.7% lower in the group of treatment resistant schizophrenic patients (Figure 8).

In the blunted affect subscale of NSA-16, the intensity of symptoms was 26.1% lower in the patients treated with neuroleptics (Figure 9).

The intensity of symptoms, according to asociality-anhedonia subscale of NSA-16, was 35.3% higher in the treatment resistant schizophrenic patients group (Figure 10).

An analysis of the avolition-apathy subscale of NSA-16 revealed that the intensity of symptoms was 34.7% higher in the treatment resistant schizophrenia patients (Figure 11).

A clinical state of the study patients was assessed with the Clinical Global Impression–Severity (CGI-S) scale. Comparison of global clinical picture between the patients without remission and the patients effectively treated with neuroleptics revealed the significant difference (Figure 12).

In patients with remission, the intensity of the disease was assessed as minimal, but in the group of patients with residual symptoms, the intensity measured with CGI-S was moderate to severe.

An analysis of Person’s correlation coefficient has revealed that in the group of patients without remission, the severity of the symptoms correlated with the intensity of negative symptoms, measured with NSA-16 scale ($R=0.65$, $p=0.0001$). The intensity of both positive ($R=0.58$, $p=0.0001$) and negative ($R=0.37$, $p=0.0001$) symptoms, in the study groups of patients was assessed, according to Positive and Negative Syndrome Scale (PANSS).

In patients treated with haloperidol, the severity of the disease correlated significantly ($R=0.33$, $p=0.03$) with the intensity of extrapyramidal symptoms, assessed with Simpson-Angus Extrapyramidal Symptoms Scale.
Cognitive dysfunctions of various intensity were present in all groups of the study patients. They included disturbances of: attention, operational memory, learning mechanisms, and reaction time. These dysfunctions were present, even though the patients met the criteria of functional remission, and were treated with neuroleptics.

An analysis of logistic regression has indicated that the cognitive deficits in subjects with schizophrenia depended on the intensity of negative symptoms and are related to the schizophrenic process. However, these symptoms did not depend on the duration of the disease, and on the age of schizophrenia onset.

5. Discussion

Many authors indicate the steady persistence of cognitive dysfunctions, during the entire schizophrenia course.

In the study by Klingberg et al. (2008), alterations of cognitive functioning among schizophrenia patients were noted over the period of 15 months. Despite improvement of memory and concentration, comparing to the beginning of the disease, after a successful treatment of the acute episode, the patient’s cognitive functioning, during the entire observation period did not return to normal level.

Also, in their 5-year study, Albus et al. (2006) indicated that the cognitive dysfunctions in schizophrenia were present from the beginning of the disease, and then, they remained stable, over the consecutive years. Both classical and atypical neuroleptics did not have any significant influence on these cognitive deficits, except from verbal fluency.

Likewise, the study by Kurtz et al. (2005), conducted on a small group of patients, indicated the presence of persistent deficits of cognitive functioning in schizophrenia, during the observation period of 10 years. Another 10-year observation conducted by Stirling et al. (2003) has revealed that the deterioration of cognitive functioning in schizophrenia remained at a similar level during the entire duration of the disease. According to the same author, the deficit of executive
functions was present already at the onset of the disease, and did not increase over the next 10-12 years. According to a 10-year observation by Hoff et al. (2005), it was found that the cognitive deficits had arisen prior to the first hospitalization, and subsequently lasted, without any significant deterioration, over the entire disease period. Based on the study by Øie et al. (2010), the cognitive disorders among schizophrenic patients, especially in the spectrum of verbal memory, attention, and information processing speed, remained almost unchanged, despite a 13-year period of treatment. These cognitive deficits were present, despite the improvement of clinical symptoms, over a few years, after the first schizophrenia episode (de Mello Ayres et al., 2010).

The above research findings indicate that the cognitive disorders among patients with schizophrenia appear at the beginning of the disease, or even before the stage of full-blown disease, and then, they can be stable chronically. According to contemporary standards of schizophrenia treatment, neuroleptics play the main role in therapy. Treatment starts at the beginning of acute schizophrenia episode, when a patient meets diagnostic criteria of the disease, including fully expressed positive schizophrenia symptoms. A hypothesis of the NMDA receptors’ hypofunction and the associated cognitive disorders in schizophrenia indicate that the moment of treatment initiation is delayed by a few years. Contemporary knowledge about cognitive disorders in schizophrenia reveals that they arise approximately 3-4 years before the first schizophrenia episode, and then, they last over the entire lifespan, at a stable level. Our study findings have confirmed the above results. The intensity of cognitive disorders among our study patients was not related to the duration of the disease. Despite an effective treatment, in patients suffering from this disease for many years, the attention disorders, operative memory deficits, as well as learning and reaction speed abnormalities persisted.

It seems that the primary cause of schizophrenia is closely related to the hypofunction of NMDA receptors. Pathogenetic process, dependent on the hypofunction of these receptors is initiated by disinhibition of neurotransmission in the OUN and hyperfrontality. Long-term effects of the glutamergic hypofunction in the OUN lead to hypofrontality, through mechanisms of neuroadaptation. Chronic persistence of cognitive dysfunctions, despite the effective symptomatic treatment indicates that the currently used neuroleptics do not normalize functions of glutamergic system. This lack of normalization of the glutamergic system activity with the neuroleptics, explains their unsatisfactory therapeutic effect on the cognitive dysfunctions in schizophrenia. Treatment of these symptoms represents a very important pharmacotherapy goal in psychiatry, because the patients’ quality of life depends mostly on the level of cognitive deficits, and intensity of negative symptoms.

According to a model of hypofunction of the NMDA receptors in schizophrenia, the treatment should already be started at the stage, in which the first cognitive disorders appear. Since the primary cause of glutamergic malfunction in schizophrenia is the hypofunction of NMDA receptors, related to GABA-ergic interneurons, the initial stage of therapy should include their stimulation, which can cause the return of inhibition of this neurotransmission in OUN. One of the considered medications in this area is acamprosate – a GABA-ergic agent, which normalizes the NMDA receptor functions and the release of glutamate (De Witte et al., 2005). In the second stage of the disease, characterized by hypofrontality and cognitive dysfunctions, the treatment should be focused on increasing
the activity of glutamergic system. In the meantime, as indicated by our study results, the
neuroleptics, through altering composition of different subunits of the NMDA receptor, can
reduce its activity.
It appears that the treatment strategy, which considers the model of NMDA receptor
hypofunction, can create a new direction of research in psychiatry.
Some proglutamergic agents, which are now under clinical investigation, may become a
new generation of anti Schizophrenic drugs, in the future. They may also, like D-cycloserine
- act as agonists of the NMDA receptor, or like sarcosice - inhibit the reverse uptake of
glycine (Krzystanek et al., 2009).

6. Conclusion
The presented results strongly support an argument that schizophrenia may not be related
to a degenerative process. The cognitive dysfunctions, as the first line of schizophrenic
symptoms, can remain in schizophrenic patients for their lifetime, despite achieving clinical
remission.

7. Acknowledgment
The study was funded by grant for scientific research (No KNW6-272/06) from the Ministry
of Science and Higher Education in Poland. The cost of the publication was sponsored by
Polpharma Biuro Handlowe Sp. z o.o.

8. References
schizophrenia: results of a prospective 5-year follow-up study. European Archives of
0940-1334
schizophrenia in humans and animals based on inhibition of NMDA receptors.
Neuroscience and Biobehavioral Reviews, Vol.32, No.5, (July 2008), pp.1014-1023, ISSN
0149-7634
Vol.39, Suppl.1, (February 2006), pp.10-14, ISSN 0176-3679
hypofrontality and working memory dysfunction in schizophrenia. American
Journal of Psychiatry, Vol.155, No. 9, (September 1998), pp.1285-1287, ISSN. 0002-
953X
de Mello Ayres, A.; Scazuflca, M.; Menezes, P.R.; Nakano, E.Y.; Regina, A.C.; Schaufelberger,
functioning in subjects with recent-onset psychosis from a low-middle-income
environment: multiple-domain deficits and longitudinal evaluation. Psychiatry
Research, Vol.179, No.2, (September 2010), pp.157-164, ISSN 0165-1781


Neurocognitive Expression of Hypofrontality in Long Term Schizophrenia


Due to their prevalence, pervasiveness and burden inflicted on men and women of today, psychiatric disorders are considered as one of the most important, sever and painful illnesses. This impairment of cognitive, emotional, or behavioural functioning is in some cases tragic. Aside from knowing the physical organic factors, such as infections, endocrinal illnesses or head injuries, the aetiology of psychiatric disorders has remained a mystery. However, recent advances in psychiatry and neuroscience have been successful in discovering subsequent pathophysiology and reaching associated bio-psycho-social factors. This book consists of recent trends and developments in psychiatry from all over the world, presented in the form of multifarious and comprehensive articles. The first two sections of the book are reserved for articles on schizophrenia and depression, two major illnesses present in this field. The third section of the book is reserved for addiction psychiatry, related not only to socio-cultural but also biological alterations. The last section of the book, titled Biological Neuropsychiatry, consists of three topics - updated molecular biology, fundamental neuroscience and clinical neuropsychiatric conditions. Doubtlessly, this book will be fruitful for future developments and collaboration in world psychiatry.