

# CORRELATION ANALYSIS BETWEEN THE MORPHOMETRIC CHARACTERISTICS OF THE HEAD OF NUCLEUS CAUDATUS AND THE INTENSITY OF PSYCHOTIC MANIFESTATION IN SCHIZOPHRENIA

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**Abstract: Introduction:** One of the significant functional disorders of the central nervous system in patients with schizophrenia is the increased activity of the mesolimbic dopaminergic system. By the nigrostriatal pathway, the caudate nucleus is closely related to other dopaminergic systems of the brain. Since the function of caudate nucleus relies on the action of dopamine in the brain; the role of this anatomical structure in the pathogenesis of schizophrenia is not sufficiently clarified. The aim of this paper was to examine whether the caudate nucleus participates in the modulation of the intensity of psychotic manifestations in schizophrenia. **Patients and Methods:** The study included a total of thirty-one patients with schizophrenia. Diagnosis of the schizophrenia was based on the DSM-IV criterion (Diagnostic and Statistical Manual of Mental Disorders, fourth edition), and the intensity of psychotic manifestations was evaluated by using Brief Psychiatric Rating Scale (BPRS). The size of the caudate nucleus was determined on axial non-contrast CT images on the surface of the largest cross-section using AutoCAD 2007 digital morphometry. The statistical data were processed by the SPSS 16.0 program package. The statistical conclusions are presented on the basis of two-tail  $p < 0.05$ . **Results:** In this study, we have observed a negative correlation between the area as well as the perimeter of the left caudate nucleus head section and the intensity of the psychotic manifestations (area: regression coefficient  $B = -0.17$ ,  $p = 0.050$ , perimeter: regression coefficient  $B = -0.010$ ,  $p = 0.012$ ). On the right hemisphere of the brain we observed only a negative correlation of the intensity of the

psychotic manifestations from the perimeter of the head section of caudate nucleus (regression coefficient  $B = -0.013$ ,  $p = 0.011$ ). **Conclusion:** In our research we found that the higher intensity of psychotic manifestations in schizophrenia was accompanied with the smaller area and the perimeter of left caudate head as well as the smaller perimeter of the head of right caudate nucleus. The finding of the dependence of the intensity of psychotic manifestations on the perimeter of the right caudate head and not on its area speaks in favor of the caudate head surface deformations as one of the markers of intensity of psychotic manifestations in patients with schizophrenia.

**Key words:** caudate nucleus, schizophrenia, analysis, correlation.

## INTRODUCTION

One of the significant functional disorders of the central nervous system in patients with schizophrenia is the increased activity of the mesolimbic dopaminergic system (1, 2). Caudate nucleus belongs to the subcortical gray masses of the brain i.e. to basal ganglia. By the nigrostriatal pathway, the caudate nucleus is closely related to other dopaminergic systems of the brain. Since the function of caudate nucleus relies on the action of dopamine in the brain; the role of this anatomical structure in the pathogenesis of schizophrenia is not sufficiently clarified. The aim of this paper was to examine whether the caudate nucleus participates in the modulation of the intensity of psychotic manifestations in schizophrenia.

## PATIENTS AND METHODS

The study encompassed a total of thirty-one persons with schizophrenia (F20): 15 females and 16 males. Schizophrenia diagnosis was based on the DSM-IV criterion (3), and the intensity of psychotic manifestations was evaluated using the Brief Psychiatric Rating Scale (BPRS) (4). The intensity of psychotic manifestations in this scale is scored by the values from 1 to 7 (1 = symptoms not present, 2 = very mild, 3 = mild, 4 = moderate, 5 = moderately strong, 6 = strong and 7 = extremely strong). More BPRS score values reflect higher intensity of the psychotic manifestations.

The size of the caudate nucleus was determined on axial non-contrast CT images (layer thickness of 5 mm) on the surface of the largest cross section. The area and the perimeter of the caudate head were determined using the AutoCAD digital planimetry (Figure 1). AutoCAD 2007 for PC Windows (developed by Autodesk, Inc. San Rafael, California, U.S.) belongs to a group of software packages designed for drawing, designing and other aspects of computer application engineering practice. This software package can also be used to measure surfaces of irregular geometric figures, such as central nervous system structures (5).

Patients with severe comorbid states (cardiac decompensation, unstable angina pectoris, myocardial infarction in the previous and the year of the study, infectious diseases, malignant and chronic immune diseases) were excluded from the study because of the confounding effect. Also, the study did not include patients with other psychiatric disorders diagnoses, neurological disorders and patients with the history of stroke.

The statistic data are processed in the SPSS 16.0 program package. The hypotheses of the regression



**Figure 1.** Display of the AutoCAD digital morphometry of the largest cross-section of the right caudate nucleus head: area 141.18 mm<sup>2</sup>, perimeter 48.802 mm

models used were tested. The statistical conclusions are presented on the basis of two-tail  $p < 0.05$ .

## RESULTS

Examination of the correlation between intensity of psychotic manifestations in patients with schizophrenia comparing the gender and age of respondents is shown in Table 1.

Since the deviation of BPRS scores from the normal distribution was observed (Shapiro-Wilk test  $p = 0.044$ ), in the correlation of psychotic manifestations intensity regarding the gender and age of respondents the generalized linear model of the subclass gamma with the log link (robust estimator) was used. Negative correlation i.e. higher intensity of symptoms of psychotic manifestations in younger persons was observed (regression coefficient  $B = -0.00036$ ,  $p < 0.001$ ) (Table 1). By incorporating only one parameter i.e. age of the respondents in the examined model, the aforementioned correlation was also confirmed (regression coefficient  $B = -0.00040$ ,  $p < 0.001$ ).

Examining the correlation of the intensity of psychotic manifestations (BPRS score) of patients with

**Table 1.** Dependence of the intensity of psychotic manifestations of patients with schizophrenia regarding the gender and the age of respondents

Parameter Estimates							
Parameter	B	Standard Error	95% Wald Confidence Interval		Hypothesis Test		
			Lower	Upper	Wald Chi-square	df	p
(Intercept)	4.254	0.0530	4.150	4.358	6433.764	1	< 0.001
Years	-0.00036	0.00009	-0.0005	-0.0002	16.217	1	< 0.001
[Male]	0.075	0.0738	-0.069	0.220	1.042	1	0.307
[Female]	0 <sup>a</sup>						
(Scale)	0.045 <sup>b</sup>						

BPRS: Brief Psychiatric Rating Scale

Dependent Variable: BPRS score

a. This parameter is set to zero because it is redundant.

b. Calculation based on the Pearson's Chi-Squared test.

*Table 2. Examination of the dependency of the intensity of psychotic manifestations from the largest cross section area of the left caudate nucleus head*

Parameter Estimates							
Parameter	B	Standard Error	95% Wald Confidence Interval		Hypothesis Test		
			Lower	Upper	Wald Chi-Square	df	p
(Intercept)	6.631	1.2016	4.276	8.986	30.453	1	< 0.001
Years	-0.054	0.0291	-0.111	0.003	3.429	1	0.064
Cross-sectional area of the left caudate head (mm <sup>2</sup> )	-0.017	0.0087	-0.034	-0.00004	3.858	1	0.050
Years *Cross sectional area of the left caudate head	0.00039	0.0002	-0.00003	0.001	3.370	1	0.066
(Scale)	0.042 <sup>a</sup>						

BPRS: Brief Psychiatric Rating Scale

Dependent Variable: BPRS score

a. Calculation based on the Pearson's Chi-Squared test.

*Table 3. Examination of the dependency of the intensity of psychotic manifestations from the largest cross section perimeter of the left caudate nucleus head*

Parameter Estimates							
Parameter	B	Standard Error	95% Wald Confidence Interval		Hypothesis Test		
			Lower	Upper	Wald Chi-Square	df	p
(Intercept)	4.747	0.1950	4.365	5.129	592.721	1	< 0.001
Years	-0.00047	0.00008	-0.0006	-0.0003	37.224	1	< 0.001
Cross-sectional perimeter of the left caudate head (mm)	-0.010	0.0038	-0.017	-0.002	6.357	1	0.012
(Scale)	0.042 <sup>a</sup>						

BPRS: Brief Psychiatric Rating Scale

Dependent Variable: BPRS score

a. Calculation based on the Pearson's Chi-Squared test.

schizophrenia and the age and the area of the largest cross section of the left caudate nucleus head we found greater intensity of psychotic manifestations in persons with smaller caudate head area (regression coefficient  $B = -0.17$ ,  $p = 0.050$ ) (Table 2). For the examination of statistical significance, the generalized linear model of the subclass gamma with the log link (robust estimator) was used.

Examining the correlation between intensity of psychotic manifestations (BPRS score) of patients with schizophrenia and the age and the perimeter of the largest cross section of the left caudate nucleus head we found greater intensity of psychotic manifestations in younger persons (regression coefficient  $B = -0.00047$ ,  $p < 0.001$ ) with smaller caudate head perimeter (regression coefficient  $B = -0.010$ ,  $p = 0.012$ ) (Table 3). For the

examination of statistical significance, the generalized linear model of the subclass gamma with the log link (robust estimator) was used.

Examining the correlation between the intensity of psychotic manifestations (BPRS score) of patients with schizophrenia and the age and the area of the largest cross section of the right caudate nucleus head we did not certain correlation between the intensity of psychotic manifestations and caudate head area (regression coefficient  $B = -0.002$ ,  $p = 0.404$ ) (Table 4). For the examination of statistical significance, the generalized linear model of the subclass gamma with the log link (robust estimator) was used.

Examining the correlation between the intensity of psychotic manifestations (BPRS score) of patients with schizophrenia and the age and the perimeter of

**Table 4.** Examination of the dependency of the intensity of psychotic manifestations from the largest cross section area of the right caudate nucleus head

Parameter Estimates							
Parameter	B	Standard Error	95% Wald Confidence Interval		Hypothesis Test		
			Lower	Upper	Wald Chi-Square	df	p
(Intercept)	4.640	0.4095	3.837	5.443	128.398	1	< 0.001
Years	-0.0005	0.000084	-0.0006	-0.0003	29.959	1	< 0.001
Cross-sectional area of the right caudate head (mm <sup>2</sup> )	-0.002	0.0028	-0.008	0.003	0.695	1	0.404
(Scale)	0.046a						

BPRS: Brief Psychiatric Rating Scale

Dependent Variable: BPRS score

a. Calculation based on the Pearson's Chi-Squared test.

**Table 5.** Examination of the dependency of the intensity of psychotic manifestations from the largest cross section perimeter of the right caudate nucleus head

Parameter Estimates							
Parameter	B	Standard Error	95% Wald Confidence Interval		Hypothesis Test		
			Lower	Upper	Wald Chi-Square	df	p
(Intercept)	4.906	0.2470	4.421	5.390	394.367	1	< 0.001
Years	-0.0005	0.00008	-0.0006	-0.0003	34.615	1	< 0.001
Cross-sectional perimeter of the right caudate head (mm)	-0.013	0.0052	-0.023	-0.003	6.448	1	0.011
(Scale)	0.040 <sup>a</sup>						

BPRS: Brief Psychiatric Rating Scale

Dependent Variable: BPRS score

a. Calculation based on the Pearson's Chi-Squared test.

the largest cross section of the right caudate nucleus head we found greater intensity of psychotic manifestations in younger persons (regression coefficient  $B = -0.0005$ ,  $p < 0.001$ ) with smaller caudate head perimeter (regression coefficient  $B = -0.013$ ,  $p = 0.011$ ) (Table 5). For the examination of statistical significance, the generalized linear model of the subclass gamma with the log link (robust estimator) was used.

## DISCUSSION

In terms of morphology of caudate nucleus and its association with psychotic manifestations in schizophrenia results in the literature are different. Thus, for example, Rich AM et al. did not observe the morphometric caudate nucleus alterations in patients with chronic and early schizophrenia (6). Brugger SP et. Howes OD in meta-analysis also did not indicate the

modified caudate nucleus in patients with the first episode of schizophrenia (7). Authors (8) came up with a similar conclusion. On the other hand, Ebdrup BH et al. indicated a reduction in volume and smaller caudate nucleus in patients with the first episode of schizophrenia without the use of antipsychotics (9). Also, Stegmayer K et al. in patients with schizophrenia and significant emotional dysregulation indicate the reduction of gray mass in ventral striatum and caudate nucleus (10). Li Y et al. in meta-analysis showed reduction of grey mass of the left caudate nucleus (11), and Brandt GN et Bonelli RM (12) emphasize, besides the reduction of caudate nucleus in the first episode of schizophrenia, to the increased caudate nucleus in chronic phase, as a consequence of the antipsychotic application.

The authors (13) also point out to the smaller caudate nucleus in early schizophrenia in comparison to a healthy population, with a subsequent increase in the

size of the caudate nucleus after ordering antipsychotic therapy. Zampieri E et al. emphasize the importance of antipsychotics to the increase of caudate nucleus too (14). However, in this case, different findings are also depicted in the literature. Emsley R et al. do not only challenge the smaller caudate nucleus in patients with early schizophrenia, pointing to their findings of a larger caudate nucleus of schizophrenic patients, but also negating the increase of the caudate nucleus after administration of antipsychotics such as risperidone and flupentixol (15). In support of the aforementioned larger caudate nucleus in patient with schizophrenia refer also the studies (16, 17). Regarding the increase of caudate nucleus after ordering antipsychotics, Mouchlianitis E et al. cited different findings in meta-analysis i.e. three studies where antipsychotic clozapine led to caudate nucleus reduction, not increment (18). However, in the later case, there are literature counterparts that point to the increased metabolism of caudate nucleus after the administration of clozapine (19). So, the issues are not completely settled yet.

In our study, we found a negative correlation between intensity psychotic manifestations from the size of the cross section of caudate nucleus head; on the left brain hemisphere from the both i.e. area and perimeter (Table 2 and 3), and from the perimeter on the right brain side (Table 5). Greater intensity of psychotic manifestations in patients with smaller head size of cauda-

te nucleus was also noted by the authors (20). Our finding of the dependence of the intensity of psychotic manifestations on the perimeter of the right caudate head and not from its area speaks in favor of the deformations of the surface of caudate nucleus head in patients with schizophrenia, as indicated by the study (21).

## CONCLUSION

In our research we found that the higher intensity of psychotic manifestations in schizophrenia was accompanied with the smaller area and the perimeter of left caudate head as well as the smaller perimeter of the head of right caudate nucleus. The finding of the correlation between intensity of psychotic manifestations on the perimeter of the right caudate head and not on its area speaks in favor of the caudate head surface deformations as one of the markers of intensity of psychotic manifestations in patients with schizophrenia.

## DECLARATION OF INTEREST

The authors declare that there are no conflicts of interests.

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## Sažetak

# ANALIZA KORELACIJE MORFOMETRIJSKIH KARAKTERISTIKA GLAVE REPATOG JEDRA I INTENZITETA PSIHOTIČNIH MANIFESTACIJA KOD SHIZOFRENIJE

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**Uvod:** Jedan od značajnih funkcionalnih poremećaja centralnog nervnog sistema kod pacijenata sa shizofrenijom je povećana aktivnost mezolimbickog dopaminergičkog sistema. Preko nigrostrijatnog puta repato jedro je usko funkcionalno povezano sa drugim dopaminergičkim sistemima mozga. Budući da se funkcija nc. Caudatusa naslanja na djelovanje dopamina u mozgu, uloga ove anatomske strukture u patogenezi shizofrenije nije dovoljno razjašnjena. Cilj ovog rada je bio da se ispita da li repato jedro učestvuje u modulaciji intenziteta psihotičnih manifestacija kod shizofrenije. **Ispitanici i metode:** Istraživanje je obuhvatilo ukupno trideset i jednu osobu obolelu od shizofrenije. Dijagnoza shizofrenije je postavljena na

osnovu DSM-IV kriterijuma, a intenzitet psihotičnih manifestacija je procenjivan primenom skale za procenu psihotičnih poremećaja - BPRS (Brief Psychiatric Rating Scale). Veličina glave repatog jedra određivana je na aksijalnim nekontrastnim CT snimcima na površini najvećeg poprečnog preseka primenom AutoCAD 2007 digitalne morfometrije. Statistički podaci su obrađivani u SPSS 16.0 programskom paketu. Statistički zaključci izneseni su na osnovu dvostranog  $p < 0.05$ . **Rezultati:** U ovom istraživanju uočili smo negativnu korelaciju površine i obima preseka leve glave repatog jedra i intenziteta psihotičnih manifestacija (površina: regresioni koeficijent  $B = -0.17$ ,  $p = 0.050$ , obim: regresioni koeficijent  $B =$

-0.010,  $p = 0.012$ ). Na desnoj hemisferi mozga uočili smo negativnu korelaciju intenziteta psihotičnih manifestacija samo od obima preseka glave repatog jedra (regresioni koeficijent  $B = -0.013$ ,  $p = 0.011$ ). **Zaključak:** U našem istraživanju uočili smo da je veći intenzitet psihotičnih manifestacija kod pacijenata sa shizofrenijom bio praćen manjom površinom i obimom glave levog nc. Caudatusa i manjim obimom

glave desnog kaudatusa. Nalaz zavisnosti intenziteta psihotičnih manifestacija od obima glave desnog kaudatusa, a ne i od površine govori u prilog prisutnih deformacija na površini glave repatog jedra kao jednog od korelata intenziteta psihotičnih manifestacija kod pacijenata sa shizofrenijom.

**Cljučne reči:** nc. caudatus, shizofrenija, analiza, korelacija.

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