

## Integrative Neuropsychological Characteristics of Subcortical-Frontal Brain Regions as a Schizophrenia Liability Factor

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In order to study neuropsychological characteristics of subcortical-frontal brain regions function and assessment of their relation with vulnerability to schizophrenia 59 patients and 23 controls were investigated using Luria's neuropsychological methods. The analysis established bilateral abnormalities of the function of prefrontal and profound frontal lobe zones in patients as compared with controls. These abnormalities were more predominate in the left hemisphere. Point biserial correlation coefficients of determined integrative neuropsychological indicators with liability to schizophrenia were  $0.39 \pm 0.11$  and  $0.28 \pm 0.09$ , for the left and right brain zones respectively. The obtained data permits discussion of the integrative neuropsychological indicators of subcortical-frontal brain regions as potential markers of liability to schizophrenia and confirms the role of structural and functional brain asymmetry in the pathogenesis of schizophrenia.

*Keywords:* neuropsychology, subcortical-frontal regions, schizophrenia, liability

Para estudiar las características de las regiones cerebrales subcortico-frontal, se investigaron la función y la evaluación de su relación con la vulnerabilidad a la esquizofrenia en 59 pacientes y 23 controles, empleando los métodos neuropsicológicos de Luria. El análisis estableció anomalías bilaterales de la función de las zonas lobulares prefrontal y frontal profunda en pacientes comparados con los controles. Estas anomalías eran más predominantes en el hemisferio izquierdo. Los coeficientes de correlación punto-biserial de algunos indicadores neuropsicológicos integrativos con la vulnerabilidad a la esquizofrenia eran de  $0,39 \pm 0,11$  y  $0,28 \pm 0,09$ , respectivamente. Los datos obtenidos llevan a la discusión de los indicadores neuropsicológicos integrativos de regiones subcortical-frontales del cerebro que se revelan como marcadores potenciales de vulnerabilidad a la esquizofrenia y confirma el papel de la asimetría estructural y funcional del cerebro en la patogénesis de la esquizofrenia.

*Palabras clave:* neuropsicología, regiones subcortico-frontales, esquizofrenia, vulnerabilidad

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Data on distinct functional brain abnormalities in patients with schizophrenia identified by neuropsychological methods has been reflected in the number of studies (among others, Tkachenko & Bocharov, 1991; Koren, Seidman, Harrison, & Lyon, 1998; Touloupoulou, Morris, Rabe-Hesketh, & Murray, 2003). Impairment of memory, attention, insufficient executive control and its organization and difficulties with auditory and visual gnosis are considered among the most typical manifestations of the “neuropsychological deficit” in schizophrenia. Certain interrelations between neuropsychological features and the severity and clinical peculiarities of negative schizophrenia symptoms, and its course duration have been established (Tkachenko & Bocharov, 1991; Sweeney, Haas, & Li, 1992). However, in some reports, similar higher psychological anomalies have been noted in patients’ healthy relatives (Savina & Orlova, 2003; Cornblat & Keilp, 1994; Faraone et al., 1999; Touloupoulou et al., 2003), which may indicate to their hereditary nature and defines the need to study them as factors of vulnerability to the disease. However, this issue remains poorly studied due both to the limited quantity and volume of study samples, and to the fact that most of the works employ methods that are insufficient to study the features of brain function and damage topography in detail (the Wisconsin Card Sorting Test of Grant and Berg, 1948, binaural listening, and others). The most prospective of such studies is the use of A. R. Luria’s methods (1963), which allows to perform the detailed neuropsychological analysis of higher brain functions relative to brain structures. Scientific literature has limited studies using such methods in schizophrenia. In these studies (Tkachenko & Bocharov, 1991), it was shown that subcortical-frontal brain region dysfunction reflects features of a neurocognitive defect that is typical for schizophrenia. In our preceding studies, using familial material (Orlova et al., 2004a, 2004b), it was established that, although brain functional deficiency in patients and family members has complex nature and affects the entire brain, the characteristics of the function of subcortical-prefrontal regions are the most informative, permitting the differentiation of patients, relatives (high-risk group for schizophrenia), and healthy controls (low-risk group for schizophrenia).

The purpose of the present study was to research the neuropsychological features of the subcortical-frontal brain regions in patients with schizophrenia and to assess their significance as markers for liability to the disease.

Vulnerability or liability (predisposition, disposition) is a concept introduced in genetics by Falconer (1960) that implies a totality of genetic and environmental causes leading to the manifestation of multifactor traits. The appropriateness of using this concept arose during the analysis of the results of epidemiologic studies of multifactor diseases (including schizophrenia), which can reveal that individuals with relatively high (or low) indices of certain traits are more vulnerable to disease than other individuals. The present report analyses such qualitative traits as the neuropsychological characteristics of subcortical-frontal brain regions.

## Method

### *Participants*

The study was carried out on 59 patients with schizophrenia (44 males, 15 females) and 23 healthy control subjects (14 males, 9 females) without family history of schizophrenia. The mean age of the patients was 23.5 years; healthy control’s mean age was 36.1 years. All the subjects were right-handed.

Clinical diagnosis was made in accordance with Russian systematic endogenous psychiatric disorders criteria (Tiganov, 1999) and the *International Statistical Classification of Diseases* (ICD-10, World Health Organization, 1990). Eight patients were diagnosed with paranoid continuous schizophrenia, 20 were diagnosed with paranoid episodic schizophrenia, 10 were diagnosed with paranoid remitted schizophrenia, and 21 were diagnosed with slow progressive (schizotypal disorder) schizophrenia. The mean age at disease onset was 14.7 years; mean disease duration was 8.7 years. At the time of the study, all the patients were under out-patient observation at the Mental Health Research Center of the Russian Academy of Medical Sciences.

### *Measures and Procedure*

All the participants (patients and healthy controls) underwent neuropsychological assessment according to A. R. Luria’s method (1963). General and specific topography symptoms of the left and right subcortical-frontal structures were examined.

Among the neuropsychological peculiarities characterizing the functions of the right subcortical-frontal region such audio-lingual memory parameters as recall order, selective recall, and the presence of contamination in recalled material were evaluated.

The following neuropsychological parameters characterizing the functions of the left subcortical-frontal regions were studied:

1. Parameters of audio-lingual memory: learning in conditions of interference, delayed recall after homogeneous and heterogeneous interference, delayed recall of a semantic fragment;
2. Attention parameters: stability in conditions of prolonged concentration;
3. Praxis parameters: formation of a motor program, formation of choice reaction.

The following neuropsychological features that characterize the functions of both the left and right subcortical-frontal regions were studied: dynamic activity parameters (freezing, impulsiveness, inertia, slowness) and parameters of the regulation of fine motor action (tremor, synkinesis, propulsion).

The values of the separate neuropsychological symptoms (in scores) were entered in a formalized data protocol. The adopted data-processing algorithm was assigned by the form used for order scales, specifically summarizing the points of

neuropsychological features of the preceding level to form the corresponding value for the following level. The final (integrative) neuropsychological scores of the functions of the left and right subcortical-frontal regions were formed as the summation of the scores of the features of audio-lingual memory, attention and praxis. The above shows that the integrative neuropsychological scores of the functions of subcortical-frontal zones of both the left and right hemispheres included general and specific left- or right-hemisphere parameters.

The significance of the difference of mean values of the integrative neuropsychological scores studied in patients with schizophrenia and healthy controls was calculated with Student's *t*-test.

The evaluation of the integrative neuropsychological parameters of subcortical-frontal function as disease liability factors was defined by calculating the point biserial correlation coefficients on the basis of the means and standard deviations of patients' and healthy controls' features, taking into account the prevalence of schizophrenia in the common population. For this purpose, the method developed by Falconer (1960) was used. Errors in the obtained coefficients were calculated according to Sokal and Rohlf (1981). The significance of these correlation coefficients was assessed by calculating the confidence intervals of these coefficients using the formula  $R \pm u_p S_R$  (where *R* is the correlation coefficient,  $u_p$  is equaled as the 1.96 percentile of order  $p = .05$ , and  $S_R$  is the correlation coefficient error). The correlation coefficients were considered to be significant at the 5% level of the value of the two-sample test if the result calculated was within the zero to one interval.

## Results

As shown by the study, in contrast to healthy control subjects, patients with schizophrenia had disorders of higher

brain functions related to the activity of subcortical-frontal brain regions. The patients had symptoms indicating to the dysfunction of subcortical-frontal structures of the left hemisphere. A decrease in voluntary regulation level of mnestic activity was noted in various modalities. The consequence of this decrease was related to maximal deficit of verbal and verbal-logic thought processes, in the form of difficulty for understanding the meaning of narratives, popular sayings with non-adequate interpretation determined by symptoms such as impulsiveness and fragmentary assessment of subject content. Memory impairment symptoms manifested as impaired learning in conditions of interference, delayed recall following homogeneous and heterogeneous interference, and delayed recall of a semantic fragment. Attention impairment was defined in conditions of prolonged concentration. Dynamic and kinesthetic apraxia (a type of presumable impairment of voluntary regulation of activity) was also noted.

Dysfunction of the subcortical-frontal structures of the right hemisphere was indicated by impairment of audio-lingual memory such as contamination, confabulation (disruption of recall order), and selective (contextual) recall in patients with schizophrenia.

Neuropsychological symptoms characterizing impairment of both left and right subcortical-frontal structures were revealed in dyspraxic disturbance. Patients showed dynamic activity parameter deficiency (freezing, impulsiveness, inertia, slowness) and disturbance of fine motor action (tremor, synkinesia, propulsion).

The mean values of the integrative neuropsychological symptoms studied in the group of patients with schizophrenia significantly differed ( $p < .01$ ) from the values obtained in the healthy control group. The mean values of the studied integrative neuropsychological parameters of the left subcortical-frontal regions were greater than the corresponding characteristics of the right subcortical-frontal regions ( $p < .01$ ), as shown in Table 1.

Table 1

*Mean Values and Standard Deviations of the Studied Integrative Neuropsychological Characteristics (in Scores) in Patients with Schizophrenia and Healthy Controls*

Characteristics of regions	Patients	Controls
Left subcortical-frontal	3.22±2.32*	0.78±0.83**
Right subcortical-frontal	2.44±1.75*	1.09±0.83**

\* $p < .05$  in comparison of values of the left and right indices in patients. \*\* $p < .01$  in comparison of values in patients and healthy controls

Table 2

*Point Biserial Correlation Coefficients of the Studied Integrative Neuropsychological Characteristics with Liability to Schizophrenia and their Errors*

Characteristics of regions	Correlation Coefficient and Error $R \pm S_R$
Left subcortical-frontal	0.39 ± 0.07
Right subcortical-frontal	0.28 ± 0.08

\* $p < .05$  (see explanation in text).

Point biserial correlation coefficients of the integrative characteristics of the left and right subcortical-frontal regions with liability to schizophrenia reached  $0.39 \pm 0.07$  and  $0.28 \pm 0.08$ , respectively, as shown in Table 2. These values indicate to a significant moderate correlation between liability to schizophrenia and the characteristics of the left subcortical-frontal regions and a significant but weak correlation with the right regions.

## Discussion

The present study confirmed data revealing the fact that patients with schizophrenia have neuropsychological deficit symptoms that manifest as memory and attention impairment, insufficient activity control and organization (Savina & Orlova, 2003; Tkachenko & Bocharov, 1991; Touloupoulou et al., & Murray, 2003). The data about the disturbance of the function of the subcortical-frontal region revealed by neuropsychological assessment support the "hypofrontality" hypothesis (Ingvar, 1987; Weinberger, Berman, & Illowsky, 1988), explaining the mechanisms of brain damage in schizophrenia.

Praxis disorders in the form of difficulty in the formation of motor program and choice reactions, as well as dynamic parameters and exquisite motor action regulation, were also revealed in the patients with schizophrenia in the present study. These findings were partially reported in our previous publications (Orlova et al., 2004a, 2004b).

The results of the present study can be considered as the evidence of greater dysfunction focused on the subcortical-frontal regions of the left hemisphere in comparison to the corresponding regions of the right hemisphere, as we reported previously (Orlova et al., 2004a, 2004b).

Disorders of higher brain function are directly linked to changes in the brain substrate. Therefore, it is necessary to note the parallelism of the obtained neuropsychological data and the results of studies of brain morphology in schizophrenia. Despite the variety of structural change findings in the brains of patients with schizophrenia, anomalies of subcortical and frontal regions are the most typical characteristics for this disease (for reviews, see Gur & Pearlson, 1993; Pearlson & Marsh, 1999). It is noteworthy that part of the subjects of the study sample (30 patients) who underwent tomographic imaging had increased parameters of the frontal horns and central parts of the lateral ventricles as well as of the third ventricle indirectly indicating hypoplasia of subcortical structures and deep-lying regions of the frontal lobes (Orlova, Vavilov, Trubnikov, & Belova, 1994; Orlova et al., 1999). In these families, correlation was revealed between the characteristics of the brain ventricles and the severity of audio-lingual and visual memory impairment, the anomaly of emotionality and attention, and the severity of positive and negative disorders (Orlova, Vavilov, Trubnikov, & Belova, 1994; Orlova et al., 1998,

1999; Savina et al., 1998). The presented data provides evidence of the correlation between morphologic and neuropsychological features of schizophrenia endophenotypes.

Note that several neuroimaging reports have shown greater severity of structural anomaly of the left frontal regions compared to the corresponding right regions in schizophrenia. This concept concerns the decrease of the dimension of the anterior cingulate and medial frontal gyri (Sigmundsson et al., 2001), the frontal lobe of male patients (Highley et al., 1998), subcortical nuclei (caudate, lentiformis) (Efanova et al., 2005), and the increase of the lateral ventricle frontal horn volume (DeLisi, Sakuma, & Kushner, 1997). Most frequent in schizophrenia is the location of cortical atrophy in the left frontal region compared to the right frontal region (Vovin, Golenkov, & Ivanov, 1991).

The study of brain metabolism and perfusion using in vivo visualization has revealed greater left-sided dysfunction of the basal ganglia (globus pallidus) (Early, Reiman, Raichle, & Spitznagel, 1989), and the frontal lobe in patients with schizophrenia (Deicken, Merrin, Floyd, & Weiner, 1995).

Note that in several tomographic studies, reduction of frontal and subcortical structures correlated with the risk of schizophrenia manifestation (Efanova et al., 2005; McDonald et al., 2004).

Thus, the present neuropsychological study together with our previous data on the morphologic and functional characteristics of the brain in families of patients with schizophrenia (Orlova et al., 1998; Orlova et al., 2004a, 2004b; Orlova, Savina et al., 2004) and the literature data, allow us to assume that disturbance in the interaction of subcortical structures and frontal regions (with a focus on left-sided lateralization) plays an important role in the pathogenesis of schizophrenia. This disturbance may explain previous experimental-psychological data related to psychological changes of mental activity in families of patients with schizophrenia. In particular, the decrease in formal dynamic indices of mental activity, attention disorders, and impairment of the selectivity of mental activity in patients with schizophrenia and their relatives (Savina & Orlova, 2003) may be related to the examined anomalies of subcortical-frontal interaction playing a significant role in providing activeness and conditions for complex programmed activity and its control (Khomskaya, 1972; Luria, 1966).

The results of the present study, showing greater severity of subcortical-frontal dysfunction in the left hemisphere in schizophrenic patients and its significance as a marker of liability to the disease may be also considered as confirmation of data on the significance of the pathology of genes controlling brain asymmetry for the development of disease (Crow et al., 1989; Orlova, Trubnikov, Savvateeva, & Lebedeva, 2000).

Further studies of the revealed integrative characteristics of the left subcortical-frontal regions as complex neuropsychological predictors of schizophrenia for medical genetic consulting are prospective.

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