ISSN 0362-1197, Human Physiology, 2016, Vol. 42, No. 4, pp. 371–375. © Pleiades Publishing, Inc., 2016.
Original Russian Text © I.S. Lebedeva, S.A. Karelin, T.An. Ahadov, A.S. Tomyshev, M.V. Ublinskiy, N.A. Semenova, A.N. Barhatova, V.G. Kaleda, 2016, published in Fiziologiya Cheloveka, 2016, Vol. 42, No. 4, pp. 27–31.

Microstructural Abnormalities of the Corpus Callosum and Fasciculus Uncinatus and Auditory Information Processing in Patients with Juvenile Paroxysmal Schizophrenia

I. S. Lebedeva[a], S. A. Karelin[a, b], T. An. Ahadov[c], A. S. Tomyshev[a], M. V. Ublinskiy[c], N. A. Semenova[c, d, e], A. N. Barhatova[a], and V. G. Kaleda[a]

[a] *Mental Health Research Center, Russian Academy of Medical Sciences, Moscow, 115522 Russia*
[b] *Moscow State University, Moscow, 119992 Russia*
[c] *Research Institute for Children's Emergency Surgery and Traumatology, Moscow Department of Healthcare, Moscow, 119180 Russia*
[d] *Emanuel Institute of Biochemical Physics, Russian Academy of Sciences, Moscow, 119334 Russia*
[e] *Semenov Institute of Chemical Physics, Russian Academy of Sciences, Moscow, 119991 Russia*
e-mail: Lebedeva-i@yandex.ru; stas.karelin@gmail.com

Received December 24, 2014

Abstract—One approach to the problem of determining the mechanisms coupling the structure and functions of the brain is studies in clinical populations aimed at assessing the presence or absence of congruence of anatomical/morphological and functional abnormalities. Magnetic resonance imaging (MRI), including structural MRI and diffusion tensor imaging with tractography, as well as the recording of auditory event-related potentials (ERPs) in the standard two-tone *oddball* paradigm and the *sensory gating* paradigm, was conducted in 26 male patients with paroxysmal juvenile schizophrenia and 26 mentally healthy men with no family history of mental illness. MRI abnormalities have been found in the genu of the corpus callosum and fasciculus uncinatus of the left hemisphere of the patients. Reduction of the fractional anisotropy in the genu of the corpus callosum was correlated with *P*300 reduction in the right temporal region.

Keywords: information processing by the brain, diffusion tensor imaging, tractography, event-related potentials, *oddball*

DOI: 10.1134/S0362119716040125

Despite decades of intense research, the mechanisms of structure–function relationship in the brain are far from being unambiguously identified.

Studies in clinical populations allowing the congruency between anatomical/morphological abnormalities and functional ones or the absence of this congruency to be established is an important approach to this issue.

Here, we used this approach when analyzing data on patients with paroxysmal juvenile schizophrenia, with special emphasis on the relationship between cerebral pathways and characteristics of auditory information processing.

At the current stage of research, these characteristics were estimated using two neurophysiological techniques: recording auditory event-related potentials (ERPs) using the *oddball* [1] and *sensory gating* paradigms (in a modification using the *N*100 wave) [2]. The results of numerous studies indicate that schizophrenia is accompanied by pathological changes in the ERP parameters recorded using both paradigms; these changes are regarded as markers of disturbance in the processes involved in selective attention, maintenance of working memory, and estimation of a completed action in the former case [3] and "filtration" of incoming information in the latter case [4].

Deviations of microstructural characteristics of cerebral pathways in schizophrenia has been described in many studies, the topography of abnormalities encompassing almost all main tracts, including the superior and inferior longitudinal fasciculi, corpus callosum, fasciculus uncinatus, and cingulum bundle [5–11].

The use of the corpus callosum as the object for analysis in this part of research was related both to the continuation of previous studies [12] and to the fact that microstructural abnormalities in this structure are among the most common findings in schizophrenic patients [7, 8, 13, 14]. In addition, we analyzed the microstructural characteristics of the fasciculus uncinatus connecting the frontal and temporal cortices, the areas that, first, are involved in the pathogenesis of

schizophrenia and, second, contain a number of generators of the ERP waves tested [15–18].

It should be emphasized that, judging by available publications (http://www.ncbi.nlm.nih.gov/pubmed/), few studies have addressed the relationships between the aforementioned anatomical and neurophysiological parameters. For example, Whitford et al. found the relationship between the characteristics of the generation of the *N*100 wave of auditory ERPs and fractional anisotropy of the fasciculus uncinatus in schizophrenic patients [19]. However, these authors used a different paradigm of neurophysiological studies.

METHODS

The study was carried out in compliance with the ethical principles stated by the Helsinki Declaration of the World Medical Association. All subjects signed an informed written consent to participate in the study.

The exclusion criteria in selecting the subjects included exacerbation of a somatic disease, hearing impairment, drug or alcohol addiction, a severe neuroinfection, or a history of head injury accompanied by an unconscious state for more than 5 min. All the subjects were right-handed.

Twenty-six male schizophrenic patients and 26 mentally healthy men (the control group) aged 16.5–28 years were enrolled in the study; there was no significant age difference between the groups (22.2 ± 3.1 vs. 22.6 ± 2.7 years; $t = -0.69$, $p = 0.50$).

We examined in- and outpatients of the Mental Health Research Center, Moscow, Russia, at the first stage of endogenous illness (no more than five years after the onset) who had experienced the first or repeated psychotic state in the course of schizophrenia (F20 according to the 10th revision of the International Classification of Diseases, ICD-10). Each patient received individually selected antipsychotic treatment. The patients were examined at the stage of reduction of active psychotic symptoms with alternating autochthonous and reactively provoked periods of exacerbation of psychotic symptoms and development of affective disorders, subpsychotic disorders accompanying gradual stabilization. The average severity of psychopathological disorders estimated by the positive and negative syndrome scale (PANSS) [20] was 59.5 ± 11.7 for the total scale and 11.0 ± 2.6 and 18.5 ± 5.1 for the total subscales of positive and negative syndromes, respectively. The clinical and neurophysiological examinations were performed a day before, or on the same day as, magnetic resonance imaging (MRI).

Auditory ERPs were recorded by means of a NeuroKM hardware and software suite (Statokin, Russia) coupled with an audio generator (MBN, Russia); the results were processed using the Brainsys software (Neurometrics, Russia). The samples that passed the neurophysiological examination were smaller (22 patients and 25 control subjects in the study using the *oddball* paradigm and 21 patients and 24 control subjects in the *sensory gating* study). In some cases, the numbers of the parameters compared were smaller because some ERP parameters were absent in a few derivations.

The bioelectrical brain activity was recorded from the F_3, F_4, T_3, C_3, Cz, C_4, and T_4 sites (the International 10–20 System), with linked earlobe electrodes serving as a reference electrode. The bandpass was 0.3–70 Hz (with subsequent offline filtration; range, 1.6–30 Hz); the sampling rate was 500 Hz in *oddball* studies and 1000 Hz in *sensory gating* studies.

The recording of auditory ERPs in the oddball paradigm was performed with a probability of presentation of the significant, target stimulus (a tone with a frequency of 2 kHz and an intensity of 60 dB) of 0.2 and that of presentation of the insignificant, non-target stimulus (a tone with a frequency of 1 kHz and an intensity of 60 dB) of 0.8. The interval between stimuli was 2 s (varying within 20%). The subject was instructed to press a button with his right thumb in response to the target stimuli and omit the non-target ones. A short training session was carried out at the beginning of examination.

After manual elimination of artifacts, we averaged the fragments of bioelectrical activity in response to the first 30 correctly recognized target stimuli and the first 115 correctly recognized non-target stimuli (separately for each subject). The epoch of analysis was 700 ms; the prestimulus interval (relative to which the data were corrected) was 200 ms. Peak latencies and amplitudes of the *P*300 and *N*100 waves (ERPs in response to target and non-target stimuli, respectively) were analyzed.

The recording of auditory ERPs in the sensory gating paradigm was performed using pairs of auditory stimuli (60 dB, 1000 Hz) at intervals within a pair and between pairs of 500 ms and 10 s, respectively (varying within 20%). The epoch of analysis was 500 ms; the prestimulus interval was 100 ms. For each subject, the ratio between the amplitudes of the *N*100 wave in the ERPs in response to the second and the first stimuli was analyzed.

The diffusion tensor imaging study was carried out using a Phillips Achieva magnetic resonance tomograph (Netherlands) with a magnetic field strength of 3 T equipped with a Dual Quasar gradient system and an eight-channel receiver radio-frequency coil for the head, with an in-built ViewForum software package.

An echoplanar impulse sequence was used (time of echo (*TE*), 70 ms; rotation angle, 90°; field of view, 240 mm; voxel size, $1.7 \times 1.7 \times 2$ mm; gap (section–section distance), 0). The diffuse gradients were applied in 32 noncollinear directions with a diffusion factor $b = 800$ s/mm^2 and in a single direction with $b = 0$.

The data were treated by means of a Philips Extended MR Workspace 2.6.3.4 workstation using

the *Fiber Track* option and superposition onto three-dimensional anatomical images.

We examined the corpus callosum (the genu and splenium regions) and the fasciculus uncinatus in the left and right hemispheres. In no case did the numbers of voxels in the area of interest in the patients and mentally healthy subjects differ significantly (22.2 ± 1.9 vs. 23.2 ± 3.2, $t = -1.5$, $p = 0.15$; 33.8 ± 6.6 vs. 33.9 ± 6.3, $t = -0.5$, $p = 0.98$; 925.2 ± 434.1 vs. 907.4 ± 417.9, $t = -0.16$, $p = 0.88$; 1005.9 ± 407.6 vs. 1152.0 ± 353.8, $t = -1.4$, $p = 0.16$, respectively). The fractional anisotropy index was used for analysis.

Statistical analysis was performed using the SPSS16.0 software. The Kolmogorov–Smirnov test was used to test the normality of distribution; Student's t test was used for intergroup comparisons; Spearman's rank-order correlation coefficient (r_{sp}), for correlation analysis. In this study, we performed intergroup comparison (patients versus mentally healthy subjects) with respect to the entire profile of the characteristics estimated (separately for each method); after that, we analyzed correlations between all parameters that were found to be significantly changed in the patients.

RESULTS AND DISCUSSION

The table summarizes the results of intergroup comparison; only the parameters that significantly differed ($p < 0.05$) in the patients and control subjects are shown. These were the fractional anisotropy, latent period and amplitude of the *P*300 wave, and amplitude of the *N*100 wave of the ERPs to insignificant stimuli in the *oddball* paradigm.

As seen from the table, the patients were characterized by a lower fractional anisotropy in the genu of the corpus callosum and the fasciculus uncinatus of the left hemisphere, longer latent periods of the *P*300 wave, a smaller amplitude of this wave in the right temporal area, and smaller amplitudes of the *N*100 wave of ERPs to non-target stimuli. No significant differences in the *sensory gating* index were found.

In the group of patients, the higher the fractional anisotropy index in the genu of the corpus callosum, the higher the *P*300 amplitude in T_4 was ($r = 0.63$, $p = 0.002$).

The profile of neurophysiological deviations in terms of ERPs recorded using the *oddball* paradigm found in schizophrenic patients (a decreased amplitude of the *N*100 wave of ERPs to insignificant stimuli and a decreased amplitude and an increased latency of the *P*300 wave of ERPs to significant ones) corresponds to published data and can be interpreted as a reflection of disturbed selective attention in this disease [3]. The absence of statistically significant deviations of the "sensory filter" index in schizophrenic patients has also been reported [21], although most studies have found such abnormalities [22, 23]. This discrepancy may be related to the relatively short duration of the disease and young age of the patients examined in our study (which suggests larger compensatory capacities of the brain and a smaller extent of structural and functional impairments). This also explains why we have detected deviations of *P*300 parameters (markers of the maintenance of working memory) only in a few derivations.

Structural abnormalities have been found in the genu of the corpus callosum and the fasciculus uncinatus of the left hemisphere of the patients, which also agrees with data published by other authors [7, 8, 13, 14, 24, 25] and, regarding the genu of the corpus callosum, with our earlier data [12]. A decreased fractional anisotropy is attributed to more poorly structured and/or fewer subunits of the tracts; therefore, the abnormalities detected are most likely to reflect microstructural changes in the aforementioned brain areas in this disease.

We found only one statistically significant interlevel (MRI–ERP) correlation: a decreased fractional anisotropy in the genu of the corpus callosum was accompanied by a lower *P*300 amplitude in the right temporal area. Probably, these two parameters were related because the fibers connecting the left and right prefrontal cortices, where a number of *P*300 wave generators are located, pass through the genu of the corpus callosum [15]. At the same time, it should be emphasized that this relationship has been found for only one derivation; hence, this result should be confirmed in a larger sample. It is also noteworthy that the sample of schizophrenic patients examined in this study consisted of young patients at early stages of the disease, whereas, as Premkumar et al. [26] showed in 2008, the correlations between structural and functional parameters are substantially stronger in chronic and older patients than in younger patients during the initial episode of the disease.

CONCLUSIONS

(1) Patients with juvenile paroxysmal schizophrenia are characterized by microstructural abnormalities of the genu of the corpus callosum and the fasciculus uncinatus of the left hemisphere, as well as smaller fractional anisotropy indices, larger peak latencies of the *P*300 wave of auditory ERPs, lower *P*300 amplitudes in the right temporal area, and lower amplitudes of the *N*100 wave to non-target stimuli compared to healthy subjects.

(2) The fractional anisotropy in the genu of the corpus callosum is significantly positively correlated with the *P*300 amplitude in the right temporal area.

ACKNOWLEDGMENTS

This study was supported by the Russian Foundation for Basic Research, project nos. 12-06-00284 and 15-06-05758.

Values of the parameters tested in the patients and control subjects and the results of comparison between the groups

Parameter	Patients	Control	Results of comparison
FA, the genu of the corpus callosum	0.69 ± 0.09	0.75 ± 0.04	$t = -3.04$, $p = 0.004$
FA, the fascilus uncinatus of the left hemisphere	0.39 ± 0.02	0.41 ± 0.03	$t = -2.14$, $p = 0.039$
LP of *P*300 (ms) in F_4	372 ± 35	347 ± 33	$t = 2.44$, $p = 0.019$
LP of *P*300 (ms) in *Cz*	365 ± 24	342 ± 35	$t = 2.74$, $p = 0.009$
LP of *P*300 (ms) in C_4	357 ± 32	336 ± 31	$t = 2.25$, $p = 0.030$
Amp of *P*300 (μV) in T_4	5.1 ± 2.6	7.2 ± 2.4	$t = -2.82$, $p = 0.007$
Amp of *N*100 (μV) in F_3	3.3 ± 1.7	4.3 ± 1.5	$t = -2.18$, $p = 0.035$
Amp of *N*100 (μV) in F_4	3.4 ± 1.6	4.9 ± 2	$t = -2.63$, $p = 0.012$
Amp of *N*100 (μV) in T_3	2.2 ± 1.2	3.1 ± 1.2	$t = -2.59$, $p = 0.013$
Amp of *N*100 (μV) in C_3	3.4 ± 2.1	4.8 ± 2	$t = -2.34$, $p = 0.024$
Amp of *N*100 (μV) in *Cz*	3.5 ± 2.1	5.5 ± 2.2	$t = -3.33$, $p = 0.002$
Amp of *N*100 (μV) in C_4	3.3 ± 1.9	5.4 ± 2.3	$t = -3.38$, $p = 0.002$
Amp of *N*100 (μV) in T_4	2.5 ± 1.1	3.9 ± 2	$t = -2.98$, $p = 0.005$

FA, fractional anisotropy; LP, latent period; Amp, amplitude.

REFERENCES

1. Squires, N.K., Squires, K.C., and Hillyard, S.A., Two varieties of long-latency positive waves evoked by unpredictable auditory stimuli in man, *Electroencephalogr. Clin. Neurophysiol.*, 1975, vol. 38, no. 4, p. 387.
2. Boutros, N.N., Belger, A., Campbell, D., et al., Comparison of four components of sensory gating in schizophrenia and normal subjects: a preliminary report, *Psychiatry Res.*, 1999, vol. 88, no. 2, p. 119.
3. Lebedeva, I.S., Neurophysiological markers of cognitive function disorders (based on data of auditory EPs in *oddball* paradigm), *Psikhiatriya*, 2009, vol. 39, no. 3, p. 48.
4. Cromwell, H.C., Mears, R.P., Wan, L., and Boutros, N.N., Sensory gating: a translational effort from basic to clinical science, *Clin. EEG Neurosci.*, 2008, vol. 39, no. 2, p. 69.
5. Kanaan, R.A., Kim, J.S., Kaufmann, W.E., et al., Diffusion tensor imaging in schizophrenia, *Biol. Psychiatry*, 2005, vol. 58, no. 12, p. 921.
6. Peters, B.D., de Haan, L., Dekker, N., et al., White matter fibertracking in first-episode schizophrenia, schizoaffective patients and subjects at ultra-high risk of psychosis, *Neuropsychobiology*, 2008, vol. 58, no. 1, p. 19.
7. Lee, S.H., Kubicki, M., Asami, T., et al., Extensive white matter abnormalities in patients with first-episode schizophrenia: a diffusion tensor imaging (DTI) study, *Schizophr. Res.*, 2013, vol. 143, nos. 2–3, p. 231.
8. Kochunov, P., Chiappelli, J., Wright, S.N., et al., Multimodal white matter imaging to investigate reduced fractional anisotropy and its age-related decline in schizophrenia, *Psychiatry Res., Neuroimaging*, 2014, vol. 223, no. 2, p. 148.
9. Kunimatsu, N., Aoki, S., Kunimatsu, A., et al., Tract-specific analysis of white matter integrity disruption in schizophrenia, *Psychiatry Res., Neuroimaging*, 2012, vol. 201, no. 2, p. 136.
10. Nakamura, K., Kawasaki, Y., Takahashi, T., et al., Reduced white matter fractional anisotropy and clinical symptoms in schizophrenia: a voxel-based diffusion tensor imaging study, *Psychiatry Res., Neuroimaging*, 2012, vol. 202, no. 3, p. 233.
11. Phillips, O.R., Nuechterlein, K.H., Kristi, A., et al., Fiber tractography reveals disruption of temporal lobe white matter tracts in schizophrenia, *Schizophr. Res.*, 2009, vol. 107, no. 1, p. 30.
12. Lebedeva, I.S., Sidorin, S.V., Akhadov, T.A., et al., Some structural-functional characteristics of the dorsolateral prefrontal cortex and the genu of the corpus callosum and auditory information processing (P300) in healthy subjects and patients with juvenile schizophrenia, *Neurosci. Behav. Physiol.*, 2014, vol. 44, no. 1, p. 9.
13. Henze, R., Brunner, R., Thiemann, U., et al., White matter alterations in the corpus callosum of adolescents with first-admission schizophrenia, *Neurosci. Lett.*, 2012, vol. 513, no. 2, p. 178.
14. Knöchel, C., Oertel-Knöchel, V., Schönmeyer, R., et al., Interhemispheric hypoconnectivity in schizophrenia: fiber integrity and volume differences of the corpus callosum in patients and unaffectedgen relatives, *NeuroImage*, 2012, vol. 59, no. 2, p. 926.
15. Kiehl, K. and Liddle, P., An event-related functional magnetic resonance imaging study of an auditory oddball task in schizophrenia, *Schizophr. Res.*, 2001, vol. 48, nos. 2–3, p. 159.

16. Näätänen, R. and Picton, T., The N1 wave of the human electric and magnetic response to sound: a review and an analysis of the component structure, *Phychophysiology*, 1987, vol. 24, no. 4, p. 375.

17. Boutros, N.N., Gjini, K., Urbach, H., and Pflieger, M.E., Mapping repetition suppression of the N100 evoked response to the human cerebral cortex, *Biol. Psychiatry*, 2011, vol. 69, no. 9, p. 883.

18. Mayer, A.R., Hanlon, F.M., Franco, A.R., et al., The neural networks underlying auditory sensory gating, *NeuroImage*, 2009, vol. 44, no. 1, p. 182.

19. Whitford, T.J., Mathalon, D.H., Shenton, M.E., et al., Electrophysiological and diffusion tensor imaging evidence of delayed corollary discharges in patients with schizophrenia, *Psychol. Med.*, 2011, vol. 41, no. 5, p. 959.

20. Kay, S.R., Fiszbein, A., and Opier, L., The positive and negative syndrome scale (PANSS) for schizophrenia, *Schizophr. Bull.*, 1987, vol. 13, no. 2, p. 261.

21. Bachmann, S., Weisbrod, M., Röhrig M. et al. MEG does not reveal impaired sensory gating in first-episode schizophrenia, *Schizophr. Res.*, 2010, vol. 121, nos. 1–3, p. 131.

22. Brockhaus-Dumke, A., Schultze-Lutter, F., Mueller, R., et al., Sensory gating in schizophrenia: P50 and N100 gating in antipsychotic-free subjects at risk, first-episode, and chronic patients, *Biol. Psychiatry*, 2008, vol. 64, no. 5, p. 376.

23. Smith, A.K., Edgar, J.C., Huang, M., et al., Cognitive abilities and 50- and 100-msec paired-click processes in shizophrenia, *Am. J. Psychiatry*, 2010, vol. 167, no. 10, p. 1264.

24. Price, G., Cercignani, M., Geoffrey, J.M., et al., White matter tracts in first-episode psychosis: a DTI tractography study of the uncinate fasciculus, *NeuroImage*, 2008, vol. 39, no. 3, p. 949.

25. Gasparotti, R., Valsecchi, P., Carletti, F., et al., Reduced fractional anisotropy of corpus callosum in first-contact, antipsychotic drug-naive patients with schizophrenia, *Schizophr. Res.*, 2009, vol. 108, nos. 1–3, p. 41.

26. Premkumar, P., Kumari, V., Corr, P.J., et al., Neuropsychological function-brain structure relationships and stage of illness: an investigation into chronic and first-episode schizophrenia, *Psychiatry Res.*, 2008, vol. 162, no. 3, p. 195.

Translated by V. Ushakov