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Broca's area intraoperative mapping with cortico-cortical evoked potentials

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ABSTRACT

Objective. Mapping of effective speech connections between the frontal and temporal lobes with cortico-cortical evoked potentials.

Material and methods. There were 3 patients with brain tumors in the left frontoparietal region. The neoplasms were localized in the dominant hemisphere near cortical speech centers and pathways. Cortico-cortical evoked potentials were intraoperatively recorded in response to bipolar stimulation with a direct current delivered through the subdural electrodes (single rectangular biphasic impulses with duration of 300 μs and frequency of 1 Hz). Stimulation intensity was gradually increased from 2 mA within 3–4 mA. Registration was carried out by averaging ECoG (30—50 stimuli in each session) in the 300-ms epoch after stimulus. Direct cortical stimulation was used to validate the results of cortico-cortical speech mapping with cortico-cortical evoked potentials.

Results. In our cases, we obtained cortico-cortical evoked potentials from inferior frontal gyrus after stimulation of superior temporal gyrus. In one case, this effective relationship was unidirectional, in the other two patients reciprocal. Mean latency of N1 peak was 65 ms (range 49.6—90 ms), mean amplitude 71 μV (range 50—100 μV). Cortico-cortical mapping data were confirmed by detection of Broca's area in 2 out of 3 cases out during direct cortical stimulation with maximum amplitude of N1 wave. «Awake craniotomy» protocol was applied. In one case, Broca's area was not detected during direct stimulation. No postoperative speech impairment was noted.

Conclusion. Initial results of cortical mapping with cortico-cortical evoked potentials in a small sample confirmed its practical significance for analysis of cortical projections of effective speech communications between the frontal and temporal lobes. Further study of this method in large samples is required.

Keywords: *cortico-cortical evoked potentials, neurooncology, glial tumors, speech function, connectome, Broca's area.*

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Abbreviations
CCEPs — cortico-cortical evoked potentials
fMRI — functional magnetic resonance imaging
ECoG — electrocorticography

Identification of structural and functional brain networks underlying cognitive functions is one of the main objectives of modern neurosciences. Moreover, their intraoperative mapping for prevention of damage is currently one of the most difficult and unresolved problems of neurosurgery for brain tumors. Analysis of these communications became widespread and resulted an appearance of new scientific field (Brain Connectomics) [1].

From the point of view of connectomics, brain is a complex of elements (cortical areas, subcortical nuclei) communicating through three types of connections — structural,

functional and effective. Structural connection is anatomical contact between the brain parts (conduction pathway, synapse, etc. **(Fig. 1)**). Comprehensive knowledge of anatomy of these connections, in particular, associative tracts, is a prerequisite for correct preoperative planning (selection of surgical approach) in neurosurgery of brain tumors.

However, knowledge of anatomy of structural connection is no longer sufficient at the present stage of neuroscience development. It is equally important to be aware of functional connections between various cortical areas.

Functional connection is a temporal correlation of activity in various brain structures underlying nervous activity, including such important domains as speech, praxis, memory, and emotions [2—7]. Simply put, if two brain structures function synchronously, they are functionally connected. These connections are available for analysis with functional brain imaging technologies, in particular, functional magnetic resonance imaging (fMRI), electroencephalography, electrocorticography (ECoG).

However, research of functional relationships also does not ensure a complete picture of connectome, since the cause-and-effect relationships «signal source — signal receiver" are not defined in this scientific paradigm. This important parameter characterizes the third type of connections — effective communication (targeted information flow between the brain structures) [6, 7].

In vivo research of effective connections is a complex interdisciplinary problem that can be partially resolved by so brain mapping method as cortico-cortical evoked potentials (CCEPs).

We report the first case in Russia of successful intraoperative mapping of effective speech connections between the frontal and temporal lobes with CCEPs registration in patients with glial tumors.

The purpose of the study was mapping of effective speech connections between the frontal and temporal lobes using cortical-cortical evoked potentials.

Material and methods

There were 3 CCEP-assisted interventions for glial tumors of the left frontal-parietal region for the period from June to November 2019 at the Burdenko Neurosurgery Center. Age of patients ranged from 29 to 61 years (median 45 years). Dominant hemisphere was determined using neuropsychological examination and fMRI data. The tumors were located in speech dominant hemisphere in close proximity to Broca's and/or Wernicke's areas, while their inner surface spread up to the arcuate fasciculus fibers. Histological structure of tumors was as follows: one anaplastic oligodendroglioma (WHO grade III), one oligodendroglioma (WHO grade II), one anaplastic astrocytoma (WHO grade III). All patients underwent preoperative MRI (GE Signa HDxt 3.0 T MRI scanner, GE Healthcare, USA). MRI protocol included standard modes (T1WI, T1 + C, 3D-T1-WI, T2-FLAIR, DWI), MR tractography and fMRI. Neurological and neuropsychological examination with Luria battery was carried out prior to surgery and 7 days later. Microsurgical resection of tumors was performed under awake craniotomy and monitored sedation in all cases.

CCEPs were intraoperatively recorded before tumor resection using a 32-channel intraoperative monitoring system "Neuro-IOM" ("Neurosoft", Russia) and two subdural strip electrodes. One electrode was placed within the frontal speech area (Broca's area) detected by direct cortical stimulation (2 cases) and inferior frontal gyrus (in this only case, Broca's area was not detected directly). The second electrode was placed within posterior segments of superior temporal gyrus. CCEPs were registered by averaging evoked responses (30—50 stimuli in each session) with an ECoG analysis epoch of 300 ms starting from the moment of stimulus. We registered at least two averaged curves each time to confirm the reproducibility of response.

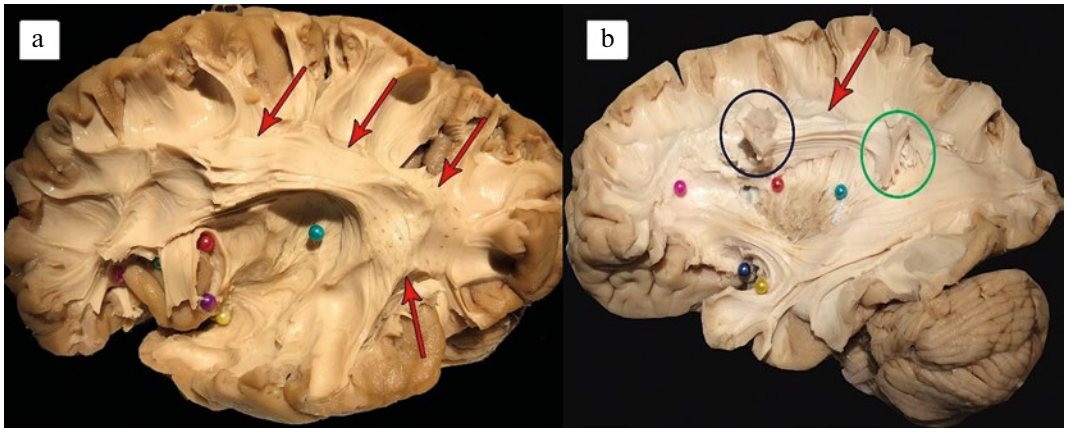


Fig. 1. **Specimens (Klingler's fiber dissection method) demonstrating structural connections of the frontal and temporal lobes.**

a — stage-by-stage dissection of the lateral brain surface: associative arcuate bundle connecting Broca's and Wernicke's areas (red arrow); b — stage-by-stage dissection of the lateral brain surface: arcuate bundle (red arrow), projection of its cortical endings in the frontal lobe (blue circle), temporal lobe (green circle).

ECoG was performed with quantization rate of 20 kHz. Pass filters were installed in the range of 5–1000 Hz. Monopolar registration was carried out from subdural electrode. Spiral subcutaneous electrode located within the contralateral mastoid process or frontal region was used as a reference electrode.

Cortical stimulation was carried out under bipolar mounting from two adjacent contacts of subdural electrode. Stimulation included single rectangular biphasic dc pulses with duration of 300 μs and frequency of 1 Hz. We gradually increased stimulation intensity over 2 mA until the paraphasic phenomena or epileptiform patterns were recorded. As a rule, effective range was 3–4 mA.

Results

Focal epileptic seizures with speech impairment was the main preoperative symptom in all patients.

Preoperative neuropsychological study revealed speech disorders with impaired understanding of complex logical and grammatical constructions only in 1 patient. Other patients had memory and dynamic praxis impairment.

We have intraoperatively obtained the speech effects typical for frontal lobe in 2 patients after their awakening and direct stimulation of inferior frontal gyrus (speech arrest, perseveration and paraphasia).

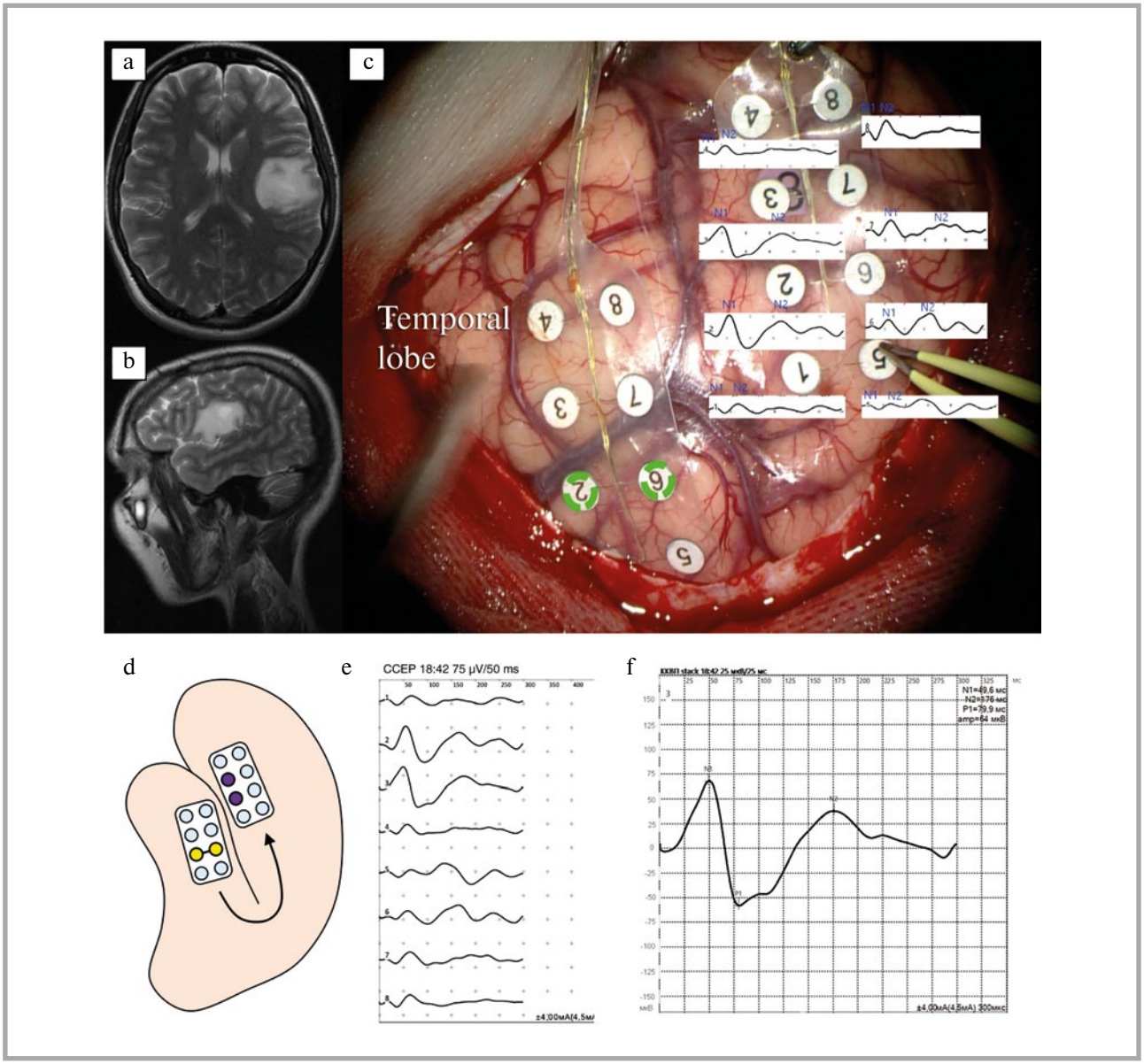


Fig. 2. Clinical case.

a, b — preoperative axial and sagittal MR scans, tumor of the left inferior frontal, pre- and postcentral gyri; c — intraoperative CCEPs. Two 8-channel subdural electrodes on the surface of the left frontal and temporal lobes. Temporal electrode stimulates Wernicke's area (green contacts), frontal electrode records responses. Maximum amplitude of N1 wave is obtained under the contacts # 2 and # 3; d — scheme, yellow contacts — bipolar stimulation, violet contacts — registration of CCEPs with maximum N1 wave amplitude, arrow — direction of CCEPs conduction; e — CCEP curves recorded in this case, contact # 3 demonstrates maximum amplitude of N1 wave — 64 μV; f — morphology of signal received from the contact # 3, early negative N1 wave, positive P1 wave and late negative N2 wave.

In the first case **(Fig. 2)**, fixation of the electrode on inferior frontal gyrus and stimulation from the temporal electrode resulted maximum amplitude of CCEPs under the contacts 2 and 3. Localization of these contacts coincided with Broca's area detected by direct cortical stimulation. Effective communication was unidirectional: superior temporal gyrus stimulation was followed by registration of responses from inferior frontal gyrus. There were no clear responses from the temporal electrode during frontal lobe stimulation.

In the second case, temporal lobe stimulation was followed by registration of response from inferior frontal gyrus. Maximum CCEP amplitude was located under the contacts 4 and 8 and did not coincide with Broca's area detected by direct stimulation. Broca's area was located under the contact 3. Response was also determined here, but an amplitude of N1 wave was not maximum. In contrast to the first case, CCEPs were recorded in two directions: responses arose under the contacts of the frontal electrode and vice versa upon temporal lobe stimulation.

In the third case, awake direct stimulation of inferior frontal gyrus resulted no speech effects typical for the frontal lobe. Therefore, Broca's area could not be directly detected. We tried to determine the cortex of inferior frontal gyrus that has effective connections with the cortex of superior temporal gyrus. We placed two 8-channel electrodes on the surface of frontal lobe and temporal lobe and recorded CCEPs.

We obtained CCEPs from the afferent electrode on inferior frontal gyrus upon stimulation with temporal electrode (contacts 1 and 5). Maximum amplitude of CCEP was noted under the contact 1 located 5 mm lateral to craniotomy (under the bone). We have checked this cortical area by direct stimulation that immediately resulted speech arrest. As in the second case, effective connection between inferior frontal and superior temporal gyri was bilateral.

Intraoperative seizures were not observed in any case. Postoperative neuropsychological examination revealed mild deterioration of baseline speech disorders in 1 patient **(Table)**.

Discussion

Various researchers have tried to determine local cortical response and activity of other brain structures upon stimulation by a single electrical stimulus since the 1960s (mainly in experimental studies) [8-10].

Initial researches devoted to analysis of functional connections of temporal and limbic lobes with evoked potentials were published in the late 80s and early 90s of the XX century [11, 12]. The authors studied distant response to stimulation of brain structures that made it possible to analyze the connections of distant brain regions.

At the beginning of the XXI century, scientists at the Cleveland Clinic [13], the University of Iowa [14] and the King's College London [15] developed the methods of cortical stimulation with a single impulse, as well as analysis of evoked potentials. These trials revived scientific interest in these signals. In the modern literature, these signals are usually denoted as cortico-cortical evoked

Clinical and electrophysiological data of patients.

Variable	Patient		
	1	2	3
Tumor localization	Left inferior frontal gyrus, left pre- and postcentral gyri	Left inferior frontal gyrus	Left inferior frontal gyrus, left pre- and postcentral gyri, left supramarginal gyrus
Age, years	61	29	46
Sex	Female	Male	Male
Histology	Anaplastic oligodendroglioma, IDH1-mutant with codeletion 1p/19q, WHO Grade III	Anaplastic astrocytoma, IDH1-mutant, WHO Grade III	Oligodendroglioma, IDH1 R132 H — mutant. WHO Grade II
Amplitude of N1 potential, μV	64	100	50
Latency of N1 potential, ms	49,6	58	90
Number of contacts with registered CCEPs	2, 3	4, 8, 5	1, 5
Type f CCEP wave	N1-P-N2	N1-P-N2	N1
Direction of impulse conduction	Wernicke's area → Broca's area	Broca's area ↔ Wernicke's area	Broca's area ↔ Wernicke's area
Impulse strength, mA	4	3	4
Preoperative speech function	Speech functions, including writing, reading, counting, are normal	Speech functions, including writing, reading, counting, are normal	Impaired understanding the complex logical and grammatical constructions. Speech apraxia test — single errors (dysarthria type). Impaired repetition of words with opposition sounds.
Postoperative speech function	No significant deterioration in speech function compared to preoperative status	No significant changes in speech function	Persistent preoperative disorders

Note. CCEP — cortico-cortical evoked potentials.

potentials. Scientists from the Cleveland introduced this concept into clinical practice [13].

CCEP is a burst of activity in one cortical zone caused by stimulation of another cortical zone. Cortical stimulation by a single impulse results two types of responses in other cortical areas (early and late) immediately after stimulation artifact [13, 15].

Early response was described in the 60s of the XX century [11, 12, 16, 17]. A. Valentín et al. first described delayed response with a latency of more than 100 ms in 2002. The authors determined significance of this response for identifying the epileptogenic zone in patients with temporal lobe epilepsy [15].

Early response is the first negative wave (distinguishable from the stimulation artifact) that is usually denoted as N1 wave. Delayed response (N2) is the second higher negative wave preceded by a positive peak (P1). Peak latency of N1 wave ranges from 10 to 100 ms, latency of N2 wave — from 70 to 300 ms [13, 18, 19]. Some authors describe a slight positive deviation of the curve before the N1 peak as P1 component [20, 21].

To date, several variants of CCEP waves have been described. Instead of N1wave, a positive potential can be recorded. N1 latency can exceed 100 ms. Moreover, only N2 component with a latency of more than 100 ms can be observed [22, 23].

In addition to conventional waves, S. Umeoka et al. identified 3 types of responses (N-P, N and P). N-P type includes a sequence of early negative and early positive waves [24]. Type N is only negative and type P is only positive. Thus, CCEP morphology is actually variable. The mechanism of emergence and conduction of CCEP is currently unclear and, most likely, orthodromic. However, antidromic activation of axons comprising associative fibers is also possible [25].

An important and fundamental question arises. What pathways conduct an impulse during cortical stimulation?

Two main options are discussed in the literature: direct conduction of an impulse through associative pathways and indirect conduction through subcortical structures.

The most logical assumption may be applied for Broca's and Wernicke's area. Stimulation of one of these zones is followed by impulse conduction through an arcuate bundle as the most powerful associative fascicle connecting these zones. Diameter of most axons in the brain is 0.8 — 2 μm, action potential conduction rate — 15 — 120 ms. Mean distance between Broca's and Wernicke's areas is 10 — 12 cm. Thus, an estimated conduction time between these zones will be approximately 1—10 ms that can correspond to N1 peak latency. However, N1 peak latency exceeding 10 ms (10–100 ms) is often recorded. This can be associated with oligo- or polysynaptic nature of responses or local delay (jitter) of synaptic transmission within stimulation and registration areas [25].

Direct conduction of cortico-cortical impulse is evidenced by linear correlation of N1 peak latency and distance between the electrodes reported by R. Matsumoto et al. In other words, greater distance between cortical areas is accompanied by longer conduction tracts, greater impulse transit time and N1 latency) [26].

The studies comparing CCEP and MR tractography data confirmed this hypothesis. C.R. Conner et al. combined CCEP with diffusion tensor imaging. They found that N1 wave amplitude is directly proportional to the number of fibers connecting the areas of stimulation and registration. At the same time, peak latency is inversely proportional to this parameter [27].

Similar results were obtained in one of the latest studies in 2020. The authors revealed a direct correlation between associative fiber length (according to MR tractography) and N1 peak latency, as well as an inverse correlation between pathway length and N1 peak amplitude. N1 wave conduction rate directly correlated with fractional anisotropy (reflects nerve fiber myelination) of associative bundles and was higher in associative fibers compared to U-fibers [14].

CCEPs are actively used in scientific practice. The most common form is searching for effective connections between the brain structures. Currently, these connections are impossible to be identified with intravital methods.

This method was used to study the connections between Broca's and Wernicke's areas [13, 23, 27, 28], Broca's area and additional motor zone (oblique frontal bundle) [29], connections between motor centers [23], including commissural ones [20], frontal operculum and insula [28].

CCEPs are also used in research of epilepsy, in particular, activity of brain connections and compensatory reorganization of functional centers [30–32].

The researchers demonstrate a significant difference in the CCEP amplitude in those brain regions effectively associated with ictal zone compared to the regions not associated with this area [30, 33].

Activity of abnormal connections is increased in ictal period and decreased in interictal period compared to normal parameters [25].

In neurosurgery, CCEPs can be used to preserved normal connections during resection of brain tumors and other lesions affecting nerve fibers [34–36]. On the other hand, this approach is valuable to determine functionally important cortical centers that was demonstrated in our research. Our initial results showed practical significance of CCEPs in determining the cortical projections of effective speech connections between the frontal and temporal lobes.

In 2 cases, impulse conduction was reciprocal (in two directions). In one case, CCEP was obtained only from inferior frontal gyrus upon stimulation of superior temporal gyrus. Mean N1 peak latency was 65 ms (49.6 — 90 ms), mean amplitude — 71 μV (50 –100 μV). Data of cortico-cortical mapping were confirmed by detection of Broca's area during awake cortical stimulation in all cases.

Currently, awake craniotomy is a standard for intraoperative mapping of speech function [37–40]. This method is effective and safe. However, this approach is contraindicated in some patients (baseline speech disorders, previous mental illness, severe scars and adhesions after previous surgery). Perhaps, CCEPs as a "passive" method of mapping will be applied in patients with contraindications to awake craniotomy and "active" brain mapping.

CCEP has own limitations despite significant possibilities and advantages. One of the disadvantages is impossible detection of exact anatomical pathway of impulse conduction from one cortical zone to another one. Several direct cortico-cortical and cortico-subcortical specialized pathways and neural networks involved in syntactic, phonological and articulatory processes ensure speech function. These pathways work as a single system.

Moreover, significant variability of CCEPs complicates standardized quantitative assessment of potentials and their physiological interpretation while stimulation artifact can interfere CCEP registration and mask early wave components. The methods of machine learning and mathematical analysis could solve this problem in the future.

Conclusion

Initial results of CCEP in small sample showed its practical importance in determining the cortical projections of effective speech connections between the frontal and temporal lobes. Further study of this method on large samples with machine learning methods and analysis of large databases is required.

Authors' participation:
Concept and design of the study — Bykanov A.E., Pitskhelauri D.I., Titov O.Yu.
Collection and analysis of data — Titov O.Yu., Ming-Chin Lin, Gulaev E.V., Ogurtsova A.A., Maryashev S.A., Zhukov V.Yu., Buklina S.B., Beshplav Sh.T., Konakova T.A., Lubnin A.Yu.
Writing the text — Bykanov A.E., Pitskhelauri D.I., Titov O.Yu.
Editing — Bykanov A.E., Pitskhelauri D.I., Titov O.Yu., Pronin I.N.

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No conflict of interests to declare.

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Commentary

Intraoperative neuromonitoring for surgical interventions associated with high risk of brain damage is currently the world standard. Neuromonitoring reduces postoperative morbidity, recovery time and improve satisfaction with surgical outcome in physicians and patients. Functional cortical mapping (sensory and motor areas, speech centers) is one of the most interesting capabilities of intraoperative neuromonitoring for a neurosurgeon. Preservation of speech function in postoperative period does not require additional actualization. This problem occupies a separate place among the main objectives of intraoperative neuromonitoring all over the world. Anatomical and func-

tional organization of speech in humans suggests certain difficulties and limitations in survey of this problem. Application of new methods of intraoperative neuromonitoring determine the relevance of this research. The authors described mapping of effective speech connections between the frontal and temporal lobes using cortico-cortical evoked potentials (CCEPs). The authors emphasize that this is initial experience in Russia with small sample size. Selection of patients for intraoperative speech mapping is a tangible problem due to the need for intraoperative awake protocol and some tests. The manuscript is interesting due to not only detailed description of this technique as important neurophysiological approach, but also comprehensive analysis of functional and effective speech connections. Own results are described in detail; each case is analyzed and sufficiently illustrated. Special attention is paid to the history of evoked cortical potentials, modern researches devoted to this problem are analyzed, and the main "blank spots" of speech mapping are reflected. The authors determined CCEPs as a "passive" method for mapping in patients with contraindications for awake craniotomy. Undoubtedly, this approach expands the possibilities of speech mapping and is of great interest. The authors analyzed the shortcomings and limitations of CCEPs as the basis for further development of this issue. This manuscript is relevant and characterized by obvious scientific novelty.

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