Results of the application of a set of functional MRI paradigms to diagnose "covert cognition" phenomenon in patients with prolonged disorders of consciousness

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In recent years, the development of instrumental diagnostics has made it possible to identify a subgroup among patients with prolonged disorders of consciousness (PDoC) in which the phenomenon of "covert cognition" occurs, characterized by a dissociation between the clinical assessment and the data of instrumental diagnostic methods. To identify this phenomenon, we used a set of diagnostic paradigms developed at the Scientific Centre of Neurology in collaboration with a group of neuropsychologists from M.V. Lomonosov Moscow State University and tested on a cohort of healthy volunteers (n=10) under the control of functional magnetic resonance imaging (fMRI).

Objective: *to evaluate the results of applying a set of paradigms to diagnose the phenomenon of "covert cognition" in a Russian-speaking cohort of patients with PDoC.*

Material and methods. *In this fragment of a prospective study, after analyzing the medical records of 138 patients, 10 individuals with PDoC of various etiologies were included. Patients underwent a thorough neurological examination and a comprehensive neurophysiological and imaging study with emphasis on fMRI with paradigms.*

Results. *When analyzing the fMRI data, significant activation clusters were detected in five patients in response to some passive paradigms, some of which were comparable to those of healthy subjects.*

Conclusion. *Using the proposed set of fMRI paradigms, we demonstrated the possibility of identifying the phenomenon of "covert cognition" in a Russian-speaking cohort of patients in vegetative state / with unresponsive wakefulness syndrome (1/6), and confirmed by instrumental methods preservation of individual aspects of consciousness in patients in minimally conscious state "minus" (4/4).*

Keywords: *paradigms; the phenomenon of "covert cognition"; cognitive-motor dissociation; prolonged disorders of consciousness; functional magnetic resonance imaging.*

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The field of prolonged disorders of consciousness (pDoC) is one of the youngest, but at the same time actively developing in modern neurology. Its origin was made possible thanks to the achievements of intensive care medicine [1]. Of course, the clinical approach to the diagnosis of pDoC has been and remains paramount. Detailed examinations of patients after coming out of a coma made it possible to introduce the basic terminology within the pDoC: vegetative state/unresponsive wakefulness syndrome (VS/UWS) [2], minimal consciousness state "minus" and "plus" (MCS- and MCS+) [3]. As clinical data accumulated, the criteria for diagnosing these conditions were gradually improved [4, 5]. A Russian working group on the problems of chronic disorders of consciousness was organized in our country. In 2020, based on the results of the first meeting of this group, a Russian-language list of terms for describing pDoC was compiled and the corresponding diagnostic criteria were identified [6].

Modern capabilities of instrumental methods have made it possible to identify another group of patients within the pDoC - patients with "covert cognition". The term "covert cognition" was first used by the British neuroscientist A.M. Owen in a 2007 publication [7]. A year earlier, under his leadership, a work describing this condition was published, which stirred up the world of researchers of disorders of consciousness. It presented a patient with VS/UWS, in whom, using the method of functional magnetic resonance imaging (fMRI), it was possible to identify the correct response (changes in the BOLD signal, similar to healthy volunteers) when presented with two instructions aimed at imagining playing tennis and moving around the house ("navigation") [8].

The concept of "covert cognition" is an umbrella term, which includes several modes of manifestation of consciousness and reflects the dissociation between the clinical assessment of the patient and the data of instrumental studies. It can take a variety of forms, from the basic processing of stimuli of a particular modality to the safe following of commands and communication. A variant of "covert cognition", which has received special attention in recent years, is cognitive motor dissociation (CMD). This term was introduced by the American scientist N. Schiff in 2015 to designate those patients who clinically fit the definition of VS/UWS or MCS, whereas neuroimaging or neurophysiological research methods demonstrate that they are able to follow instructions [9]. In Russia, a significant contribution to the development of this field and its terminology was made by a group of researchers led by A.A. Belkin, who demonstrated the effectiveness of navigational transcranial magnetic stimulation as a method of diagnosing CMD [10].

According to a recent meta-analysis, "covert" following commands is available to 14% of patients with VS/UWS and 32% with MCS, and the presence of a cerebral response to certain stimuli is present in 26% of patients with VS/UWS and 55% with MCS. The fulfillment of instructions is more often noted in traumatic brain injury than in non-traumatic brain injuries (32% vs. 19%) [11].

A large number of studies are being conducted to determine the standard for the diagnosis of "covert cognition". Currently, the prevailing method is event-related research, which means evaluating the dynamics of certain observed indicators against the background of proposed paradigms under the control of neurophysiological or neuroimaging monitoring.

Table 1. *A set of paradigms developed to diagnose the phenomenon of "covert cognition" in the Russian-speaking population of patients with pDoC*

№	The paradigm content	Characteristics
1	Pressing on the nail bed of the right hand index finger	Passive somatosensory
2	«Writing» the letter «M» on the abdomen	
3	Listening to the alarm sound	Passive auditory non-speech
4	Listening to the Wedding March (Mendelssohn)	
5	Listening to the melody of the traditional Russian Christmas song	
6	Listening to the child's laughter	
7	Listening to narratives in Russian and Japanese	Passive auditory speech
8	Listening to testee`s name within the «cocktail party» effect	
9	Listening to the fragment from the film with obscene language	
10	Imagining spatial navigation at testee`s home	Active
11	Imagining cleaning teeth	
12	Singing to yourself the traditional Russian Christmas song	

The paradigms (tasks) used for this purpose are divided into passive and active ones. The first group is aimed at detecting brain activation in response to stimuli of a particular modality (visual, auditory, somatosensory, gustatory, olfactory), and the second - in response to the urge to follow instructions. The importance of including in the paradigms stimuli that could evoke an emotional response and would be significant for the patient should be specially emphasized [12].

Since the emergence of interest in the "covert cognition" phenomenon, most research on the development and application of paradigms has been conducted abroad, mainly on the English-speaking population, taking into account its cultural characteristics, which makes it difficult to transfer these paradigms to the Russian-speaking population and requires preliminary validation research. The creation of new paradigms also remains relevant. To this end, on the basis of the Research Center of Neurology in collaboration with a group of neuropsychologists from the Faculty of Psychology of Lomonosov Moscow State University developed a set of diagnostic paradigms for patients with pDoC (Table 1). The development was carried out based on the analysis of foreign and domestic fMRI studies of "covert cognition" [13] and data from general psychology and neuropsychology [14].

The presented set of paradigms was tested on a sample of healthy volunteers (n=10) using the fMRI method. When analyzing the data for the group, significant activation clusters were noted in 6 passive paradigms (№ 2, 3, 4, 5, 8, 9). In an individual analysis, the auditory speech paradigms have proven themselves to be the best. These data are presented in detail in a separate article [15].

The aim of this publication is to present the results of the application of the proposed set of paradigms to identify the "covert cognition" phenomenon in a Russian-speaking sample of patients with pDoC under the control of fMRI.

Patients and methods. The recruitment of patients within the framework of this fragment of a prospective monocenter study was carried out on the basis of the Research Center of Neurology at the Department of Anesthesiology and Intensive Care in the period from June 2020 to June 2021. The neuroimaging study was performed at the Department of Radiation Diagnostics of the Research Center of Neurology.

The inclusion criteria were the formed pDoC in persons over 18 years of age from the time of completion of the prolonged impairment of consciousness and the signed informed consent of the patient's legal representatives. *The criteria for non-inclusion* were severe somatic pathology, the presence of contraindications and limitations for conducting MRI of the brain (pacemakers, programmable ventriculoperitoneal shunts, metal implants, and others), as well as mental disorders that limit the possibilities of research and rehabilitation treatment. *The exclusion criteria* were decompensation of somatic pathology during the study and refusal of the patient's legal representatives from further participation. The study was approved by the Local Ethics Committee of the Research Center of Neurology (Protocol No. 1-5/23 dated 01/25/2023).

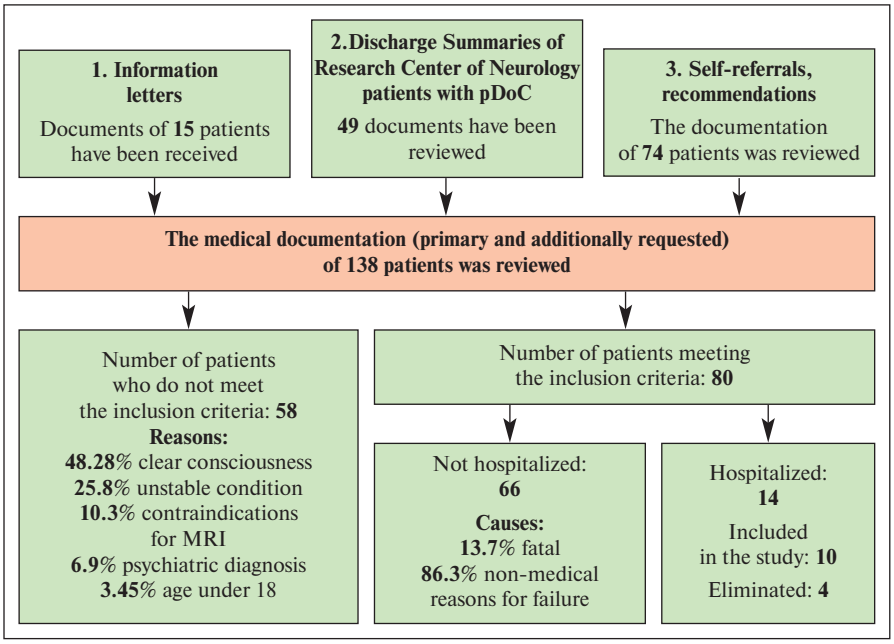
The staff of the Department of Anesthesiology and Intensive Care of the Research Center of Neurology analyzed the medical documentation (primary and additionally request-

ed) of 138 patients obtained through three channels (responses to information letters; discharge summaries of patients with pDoC who previously underwent inpatient treatment at the Research Center of Neurology; self-referrals). Eighty people met the inclusion criteria, 14 of them were hospitalized, 4 of whom dropped out of the study for medical and technical reasons (Fig.1).

Thus, 10 patients were included in the study (7 women, 3 men; average age 46.2 years, SD=13.8). Of these, 6 with VS/UWS and 4 with MCS-. The average duration of brain damage at the time of hospitalization was 16 months. In most patients (n=4), pDoC was formed as a result of anoxic brain damage. Metabolic etiology (n=2) and traumatic brain injury due to a traffic accident (n=2) were less common as the main causes of pDoC development. The rarest causal factors in this group were acute cerebrovascular accident (n=1) and acute multiple encephalomyelitis (n=1). According to the results of a thorough analysis of medical documentation and the findings of the brain MRI in the Department of Radiology of the Research Center of Neurology, a mixed etiology was revealed in one patient (secondary hypoxia was confirmed in a patient with a primary established traumatic cause of pDoC).

During hospitalization (2 weeks), patients underwent a thorough neurological examination, including multiple assessments on the Revised Coma Recovery Scale (CRS-R), the Nociception Coma Scale-Revised (NCS-R), the Comorbidities Coma Scale (CoCoS), Disability Rating Scale (DRS) and the Glasgow Outcome Scale-Extended (GOSE). A detailed description of the sample with scale data is presented in Table. 2. A neuropsychologist participated in the diagnosis of the current level of consciousness and various parameters of mental activity of the patients.

All patients underwent structural MRI and fMRI of the brain on a Siemens MAGNETOM Verio tomograph with a magnetic induction value of 3 T using an 8-channel head coil. The scanning protocol included the following pulse sequences: mode T2-weighted images in the axial projection and 3D T1-weighted images in the sagittal projection. In order to reduce the severity of artifacts from the sounds produced during the operation of the tomograph, and to present auditory stimuli within the



The scheme of patient recruitment to the study

Table 2. *Clinical characteristics of patients with pDoC*

Patient №	Gender	Age (years)	pDoC type	Term (months)	pDoC etiology*	CRS-R	NCS-R	CoCoS (total score)	DRS (total score)	GOSE
1	F	61	VS/UWS	5	1	5 (1-0-1-1-0-2)	2 (1-0-1)	18	23	2
2	F	29	VS/UWS	2	3	5 (1-0-2-1-0-1)	4 (2-0-2)	13	23	2
3	F	69	VS/UWS	1	4	5 (1-1-1-0-0-2)	3 (2-0-1)	19	23	2
4	F	54	VS/UWS	2	3	5 (1-1-1-0-0-2)	3 (1-0-2)	15	24	2
5	F	44	MCS-	8	1	10 (2-3-2-1-0-2)	6 (2-1-3)	13	22	2
6	M	28	MCS-	7	1	9 (1-1-3-2-0-2)	7 (3-1-3)	10	20	2
7	M	38	MCS-	15	6	11 (2-3-2-2-0-2)	4 (2-0-2)	11	23	2
8	M	35	MCS-	9	2	9 (2-3-2-0-0-2)	5 (2-1-2)	14	21	2
9	F	49	VS/UWS	114	1	7 (1-1-2-1-0-2)	1 (0-0-1)	5	23	2
10	F	55	VS/UWS	1	5	4 (1-1-0-0-0-2)	1 (1-0-0)	18	23	2

* 1 – anoxic, 2 – traumatic, 3 – metabolic, 4 – cerebrovascular accident, 5 – acute disseminated encephalomyelitis , 6 – mixed.

framework of the paradigms, special MR-compatible headphones were used. Patient э1 with myoclonic hyperkinesis in the muscles of the upper and lower extremities was sedated with continuous administration of dexmedetomidine at a rate of 1 mcg / kg/ h in order to minimize motor artifacts under the control of vital functions by monitoring blood pressure, pulse and saturation. The choice of dexmedetomidine was due to the data showing that of all drugs for anesthesia, it has the least effect on the level of consciousness [16].

During the fMRI study, patients were given a set of paradigms presented in Table 1. The sequence of tasks corresponded to the numbering in the table. Detailed characteristics of each paradigm (content of passive and active blocks, instructions for implementation, time parameters), as well as a description of fMRI data collection are given in the publication on testing paradigms on healthy volunteers and were the same for our patients [15].

The SPM12 software package (Statistical parametric mapping, Welcome Trust Centre for Neuroimaging, London, UK) was used to process fMRI data. Post-processing consisted of correction of the patient's head movements using a solid body transformation algorithm, co-registration of functional and anatomical data, spatial normalization according to the spatial coordinate system of the Montreal Neurological Institute and smoothing of functional data. A general linear model was used to compile activation maps by parallel comparison. The results show activation zones with only $p_{correct} < 0.05$ at the cluster level. A group analysis was not performed in relation to patients, since in order to identify the "covert cognition" phenomenon we were interested in the presence of significant activation clusters at the level of an individual subject, as well as in connection with the individual characteristics of brain damage in each case.

Results. In patients №1 and №9, it was not possible to conduct a reliable analysis of fMRI data due to extremely pronounced structural brain damage. The data of patient э10 were lost at the stage of their extraction.

The remaining patients were evaluated for the presence of significant activation clusters in response to each of the paradigms of the complex. Visual analysis excluded cases of registration of false activation in the projection of the upper sagittal sinus. The clusters identified in patients were compared with significant activation clusters obtained earlier in a group of healthy volunteers (for 6 passive paradigms that proved to be effective normally). The presence of clusters which partially correlated with the average group normative data in response to some passive paradigms was noted in 5 patients (1 with VS/UWS, 4 with MCS-) (Table 3).

Discussion. First, it is worth noting that, starting from early works, an approach has been formed in this area, implying a comparison of cerebral activation detected in patients with pDoC with activation recorded in healthy people in response to the same paradigms [8, 17]. Moreover, tasks that normally demonstrate not only the presence of group activation, but also its reproducibility at the individual level are considered the most effective [18]. In accordance with this approach, we have identified 6 passive paradigms that have proven to be useful in the group analysis of data from healthy volunteers; two of which are most effective at the individual level. Then, the fMRI data of patients was compared with the normative data for these 6 passive paradigms. As a result, 5 patients with pDoC were identified (1 in VS/UWS, 4 in MCS-), who demonstrated significant activation clusters, which partially correlated with the average normal group data, in response to some of these paradigms.

Table 3. *The results of presenting paradigms to patients with pDoC under the control of the fMRI method*

Patient №	Paradigm № 1	2**	3**	4**	5**	6	7	8**	9**	10	11	12
1	--	--	--	--	--	--	--	--	--	--	--	--
2	-	-	-	-	-	-	-	-	-	-	-	-
3	-	-	-	-	-	-	-	-	-	-	-	-/+
4*	-	+/-	+/-	+/-	-	-	-/+	+	+	-	-	-/+
5*	-/+	+	+/-	-	+	-	-	-	-	-	-	-
6*	-	-	-	+	+	-/+	-	+	+	-	-/+	-/+
7*	-	+/-	+	+	+	-/+	-/+	-	-	-	-	-
8*	-	+	+/-	+/-	-	-	-	-	-	-	-/+	-
9	--	--	--	--	--	--	--	--	--	--	--	--
10	--	--	--	--	--	--	--	--	--	--	--	--

«+» – the presence of significant activation clusters, which partially correlated with the average group data of healthy volunteers; «+/-» – the presence of significant activation clusters in areas other than the average group data of healthy volunteers; «-/+» – the presence of significant activation clusters in paradigms that proved ineffective in the group analysis of healthy volunteer data; «-» – absence of significant activation clusters; «--» – inability to analyze data. The numbers of paradigms in which significant activation clusters were identified in healthy volunteers during group analysis are highlighted in gray. The numbers of patients who demonstrated significant results when compared with the normative data are highlighted in black.

As mentioned earlier, the "covert cognition" phenomenon is heterogeneous. Passive paradigms are aimed at assessing the preservation of patients' ability to perceive stimuli of a particular modality, which can be determined on the basis of cerebral activation of secondary and tertiary associative regions of the brain. They are more applicable to patients with a clinically established diagnosis of VS/UWS. In the absence of signs of behavioral response to any stimuli, the presence of such activation demonstrates the "covert cognition" phenomenon. In our study, it was detected in 1 out of 6 patients with VS/UWS (16%).

Patients with MCS-, in accordance with diagnostic criteria, are able to respond behaviorally to certain external stimuli [6]. In their case, activation in response to passive paradigms acts more as an instrumental confirmation of the preservation of residual manifestations of cognitive functioning. In our work, such confirmation was received from each of the 4 patients with MCS- (100%). It is worth noting that not all passive paradigms turned out to be equally effective for them. Thus, the somatosensory para-

digm revealed activation clusters correlating with normative ones in 2 out of 4 patients with MCS (without taking into account the normative data – in 3 out of 4), auditory nonпspeech paradigms in 3 out of 4 (without taking into account the normative data – in all 4), and auditory speech paradigms in only 1 out of 4 patients (without taking into account the normative data – the same). This indicates the importance of applying paradigms aimed at different modalities. Further analysis of the clinical cases of these patients is needed to compare behavioral and instrumental reactivity to stimuli in order to better cover the preserved components of their cognitive sphere.

Let's pay attention to the fact that in the data of healthy volunteers there was a variation in the effectiveness of these passive paradigms at the individual level [15]. It may be related to the duration of the study (the total time for presenting paradigms was 40 minutes 42 seconds). Even normally, when performing the same type of tasks for a long time, people may experience satiety, exhaustion and fluctuations in attention. And for patients with pDoC, in addition, transitions from wakefulness to sleep are characteristic, as well as fluctuations in the level of conscious activity during the wakefulness period. As a result, the study could have been conducted at a time when the patient could not demonstrate his cognitive abilities to the fullest. In order to monitor a patient in a waking state, the use of an electroencephalography compatible with fMRI can be suggested as a recommendation for subsequent studies. In addition, it is necessary to take into account the fact of the presence of drug sedation, which, despite the chosen drug, can slightly affect the state of the cognitive sphere. In the presented fragment of the study, it was required by one patient with VS/UWS and did not play a significant role, since the fMRI data in her case turned out to be unavailable for processing due to gross brain damage. Structural changes in the brain due to primary lesions (hematoma area, ischemia, trauma) are another factor complicating the study in patients with pDoC. All these limitations can lead to the presence of false negative results in patients in response to certain paradigms or to the whole complex. Thus, the absence of activation cannot be used as the evidence of the absence of consciousness or some of its manifestations.

The discussed approach to the diagnosis of "covert cognition" is certainly important, but it leaves out of the scope of consideration cases of registration of activation that does not correspond to the normative one. At the same time, taking into account pronounced brain damage in patients with pDoC, there may be a change in the functional systems that ensure the implementation of a particular mental function and the involvement of other brain structures in the process. In addition, due to the absence of average group clusters and high interindividual variability in healthy volunteers, the remaining 6 paradigms of the complex (including 3 active ones) were out of focus of the analysis. Namely, active paradigms allow us to indicate the preservation of consciousness with a greater degree of certainty. According to the presented results, some patients demonstrated activation clusters in response to these paradigms, but it is impossible to compare them with the normative ones. Thus, the approach of comparing normal activation and activation in the presence of pDoC has a number of limitations, which requires the development of alternative ways to identify the "covert cognition" phenomenon and its variant of CMD. One of these methods in relation to active paradigms will be presented in subsequent publications by the authors.

Conclusions. As a result of the study, it was shown that it is possible to identify the "covert cognition" phenomenon in a Russian-speaking sample of patients with pDHC using the proposed complex of fMRI paradigms. In 1 out of 6 patients with a clinically established diagnosis of VS/UWS, signs of "covert cognition" were revealed. Instrumental confirmation of the preservation of certain aspects of consciousness was obtained in all 4 patients with a clinically established diagnosis of MCS.

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