Diagnosis of the phenomenon of ‘covert cognition’ in patients with prolonged disorders of consciousness: clinical cases

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In recent decades, our understanding of patients with prolonged disorders of consciousness (PDOC) has expanded significantly thanks to the description of the phenomenon of ‘covert cognition.’ An individual approach is important in its diagnosis, involving the comparison of behavioural and instrumental data for each patient. In our country, research into this phenomenon is only just beginning to develop, which makes it important to accumulate cases of successful detection of various ‘covert’ signs of consciousness. This article presents clinical observations of two patients with PDOC. According to clinical assessment using specialised scales, the first patient was in a vegetative state/had unresponsive wakefulness syndrome. Using functional magnetic resonance imaging (fMRI) with a specially designed set of paradigms, the phenomenon of ‘covert cognition’ was detected in her (cerebral activation, partially correlated with the norm, in response to passive somatosensory, auditory non-verbal and verbal stimuli). The second patient, according to the clinical assessment, corresponded to a minimally conscious state ‘minus’. As a result of fMRI examination, instrumental confirmation of the preservation of certain aspects of consciousness (cerebral activation in response to auditory non-verbal and auditory verbal paradigms) was obtained. The use of a comprehensive multimodal personalised approach to the diagnosis of the phenomenon of ‘covert cognition’ and the possibilities of neurorehabilitation of patients based on the data obtained with its help are discussed.

Keywords: *prolonged disorders of consciousness; vegetative state / unresponsive wakefulness syndrome; minimally conscious state ‘minus’; ‘covert cognition’; paradigms; fMRI.*

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Diagnosis of the "covert cognition" phenomenon is one of the most important challenges faced by specialists studying patients with prolonged disorders of consciousness (PDOC). This phenomenon refers to a discrepancy between clinical assessment data for these patients, including those obtained with the use of specialized scales, and instrumental diagnostic data on their brain activation when presented with passive and/or active paradigms (tasks). Passive paradigms involve exposing patients to stimuli of various modalities, while active paradigms involve prompting patients to follow instructions [1].

Most of the research into the "covert cognition" phenomenon has been conducted abroad. In our country, the number of such studies is gradually increasing [2]. At the Russian Center of Neurology and Neuroscience in collaboration with a group of neuropsychologists from the Faculty of Psychology of Moscow State University, a set of nine passive (somatosensory, auditory non-speech and speech) and three active paradigms was developed and tested on healthy volunteers under the control of functional magnetic resonance imaging (fMRI) to detect the "covert cognition" phenomenon based on data from general psychology and neuropsychology [3, 4]. A study was then conducted using the developed set of paradigms in 10 patients with PDOC [six of whom were in a vegetative state / had unresponsive wakefulness syndrome (VS/UWS) and four of whom were in a minimally conscious state "minus" (MCS-)]. The results were published in this journal [5]. Among six patients in the VS/UWS there was one patient who demonstrated the "covert cognition" phenomenon, and in all four patients in the MCS-instrumental confirmation of the preservation of individual aspects of consciousness was obtained.

The aim of this study is to analyze the clinical cases of the patient in the VS/UWS with the Тcovert cognitionУ phenomenon and the patient in the MCS-, who had significant results confirming the presence of consciousness, in the largest number of fMRI paradigms.

Clinical observation 1

***Patient M.**, a 54-year-old woman, was admitted to the Russian Center of Neurology and Neurosciences with a primary diagnosis of encephalopathy (metabolic, post-hypoxic), sequelae of pontine and extrapontine myelinolysis, two months after suffering a brain injury. The ICD-10 diagnosis code was G93.8. Clinically, the level of consciousness corresponded to VS/UWS. Multiple assessments on the Coma Recovery Scale-Revised (CRS-R) yielded the best result, a total of 5 points (1–1–1–0–0–2). The patient's scores on other specialized scales are reflected in the following indicators:*

- *Nociception Coma Scale-Revised (NCS-R) – 3 points (1–0–2);*
- *Comorbidities Coma Scale (CoCoS) – 15 points (1–2–3–0–0–2–0–2–0–0–0–1–0–0–0–0–2–1–2 –0–0–0–0);*
- *Disability Rating Scale (DRS) – 24 points (0–3–4–3–3–3–5–3);*
- *Glasgow Outcome Scale-Extended (GOSE) – 2 points.*

Electroencephalography (EEG) revealed no alpha rhythm, and there was an unresponsive recording during functional tests. Acoustic brainstem evoked potentials (ABEPs) revealed intact primary components of the auditory brainstem structures, with increased V peak latency on both sides (6.28 ms on the left and 6.5 ms on the right). Cognitive evoked potentials (CEPs) revealed increased P300 peak latency (495 ms); the amplitude was 5.5 μV. Structural MRI data were consistent with metabolic changes (pontine and extrapontine myelinolysis) with signs of cerebral atrophy. Endoscopic assessment of swallowing revealed incompetent swallowing, penetration and aspiration syndrome. According to follow-up data, the patient died one month after completing her hospitalization.

According to the results of the fMRI study with the set of paradigms developed by the authors, the patient demonstrated significant activation in response to seven of them. Two paradigms (the auditory speech paradigm "Listening to narratives in Russian and Japanese" and the active paradigm, including the instruction "Singing to yourself the traditional Russian Christmas song") did not reveal significant activation clusters in a group analysis of data from healthy volunteers [4], therefore, a comparison of the patient's clusters with normative ones is not possible. In the first paradigm, activation is observed only in the right cerebellar hemisphere, while in the second, there is one small cluster in the right lingual gyrus and precuneus and a peak of activation in the left putamen.

For the remaining five paradigms, it is possible to compare activation with the average normative group data. In the auditory non-speech paradigm "Listening to the Wedding March (Mendelssohn)" the patient demonstrated a cluster only in the brainstem, which is not significant for our purposes. We present the data for the remaining paradigms in detail (Fig. 1):

- *in the somatosensory paradigm «Writing the letter "M" on the abdomen», the patient's activation is in the frontal cortex in the left hemisphere (precentral, superior/middle frontal gyri) and in the posterior cingulate cortex;*
- *in the auditory non-speech paradigm «Listening to the alarm clock sound», activation was observed in the right superior temporal gyrus, as well as in subcortical structures (chiasm, brainstem and putamen of the left hemisphere);*
- *the auditory speech paradigm "Listening to one's own name as part of the «cocktail party» effect" revealed activation in the temporal regions bilaterally (a cluster was detected in the right superior and middle temporal gyri, a peak of activation in the left superior temporal gyrus), as well as in the insula and posterior part of orbital gyrus of the right hemisphere, in the middle part of cingulate cortex, cerebellum and brainstem;*
- *in the auditory speech paradigm "Listening to audio fragment from the film with obscene language" activation was demonstrated in the convexital regions of the temporal lobes (right superior and middle temporal gyri and left superior temporal gyrus), deep temporal structures (left hippocampus, right parahippocampal gyrus), in some gyri of the frontal lobe (right precentral and middle frontal gyri, posterior part of the orbital gyri bilaterally), parietal lobe (right postcentral and supramarginal gyri) and occipital lobe (right fusiform and lingual gyri), in the right insula, as well as in a number of subcortical structures (brainstem, cerebellum and right thalamus).*

Clinical observation 2

***Patient B.**, a 28-year-old man, was admitted to the Russian Center of Neurology and Neurosciences with a primary diagnosis of severe posthypoxic encephalopathy. The ICD-10 diagnosis code was G93.1. His medical history revealed that 7 months earlier, with increasing signs of respiratory failure, he experienced sudden cardiac arrest. Cardiopulmonary resuscitation was performed (sinus rhythm was restored after 8 minutes). His clinical level of consciousness corresponded to MCS-. Repeated CRS-R scores reached a maximum of 9 points (1–1–3–2–0–2). The patient's scores on other specialized scales included the following:*

- *NCS-R – 7 points (3–1–3);*
- *CoCoS – 10 points (0–0–0–1–2–0–0–0–0–0–0–0–0–0–0–0–1–1–1–2–0–0–2–0);*
- *DRS – 20 points (0–3–1–3–3–3–4–3);*
- *GOSE – 2 points.*

EEG revealed no alpha rhythm and unresponsive recordings to functional tests, although physiological patterns of stage I and II sleep were identified. ABEP recordings revealed intact primary components of brainstem acoustic responses with some parameter changes, including increased V peak latencies on both sides (6.23 ms on the left and 5.9 ms on the right); increased interpeak intervals on both sides (2.55 ms on the left and 2.45 ms on the right). CEP recordings revealed increased P300 peak latency (475 ms in the first and 563 ms in the second significant series) and decreased amplitude in the first significant series to 3.1 μV. Structural MRI data indicated changes in both cerebral hemispheres, most likely due to global cerebral ischemia. It's worth noting that the patient was bilingual (Russian and Chechen). Endoscopic assessment of swallowing revealed incompetence. X-ray examination of swallowing revealed an oropharyngeal phase disorder. Follow-up data could not be collected due to the lack of telephone communication.

According to the results of the fMRI study with the set of paradigms developed by the authors, the patient demonstrated significant activation in response to seven of them. Three paradigms (the auditory non-speech paradigm "Listening to a child's laughter" and active paradigms aimed at following instructions – "Imagining cleaning teeth " and "Singing to yourself the traditional Russian Christmas song") did not reveal significant activation clusters in a group analysis of data from healthy volunteers [4], therefore, a comparison of the patient's clusters with normative ones is impossible. In the paradigm including imagining cleaning teeth, a small cluster of *activation is distinguished in the parieto-occipital region of the left hemisphere (superior and middle occipital gyri, angular gyrus). In the paradigm aimed at singing a song, activation clusters are present only in the right and left hemispheres of the cerebellum. A paradigm involving listening to a child's laughter revealed volumetric clusters in the superior temporal gyri of both hemispheres, left transverse temporal gyrus (Heschl gyrus) and outside the temporal lobes in the frontal (right middle and inferior frontal gyri) and parietal (left supramarginal gyrus) cortex (Fig. 2).*

For the remaining four paradigms, it is possible to compare the detected activation with the average group data of healthy volunteers. What is particularly important within the framework of this comparison is that in all four paradigms, the patient has clusters that overlap with the normative ones [4]. We will describe the observed activation in detail (see Fig. 2):

- *in the auditory non-speech paradigm «Listening to the Wedding March (Mendelssohn)» activation is revealed in the transverse temporal gyri (Heschl gyri) and superior temporal gyri bilaterally, as well as in the parietal regions (supramarginal gyrus bilaterally, right angular gyrus with the involvement of the right superior parietal lobule);*
- *in the auditory non-speech paradigm «Listening to the melody of the traditional Russian Christmas song» activation occurs in the superior temporal gyri bilaterally, in the occipital cortex of the left hemisphere (inferior occipital gyrus and fusiform gyrus), in the areas of the right frontal pole and the left parietal operculum;*
- *in the auditory speech paradigm «Listening to one's own name as part of the "cocktail party" effect» a peak of activation is observed in the left superior temporal gyrus;*
- *the auditory speech paradigm «Listening to audio fragment from the film with obscene language» also revealed a peak of activation in the left superior temporal gyrus.*

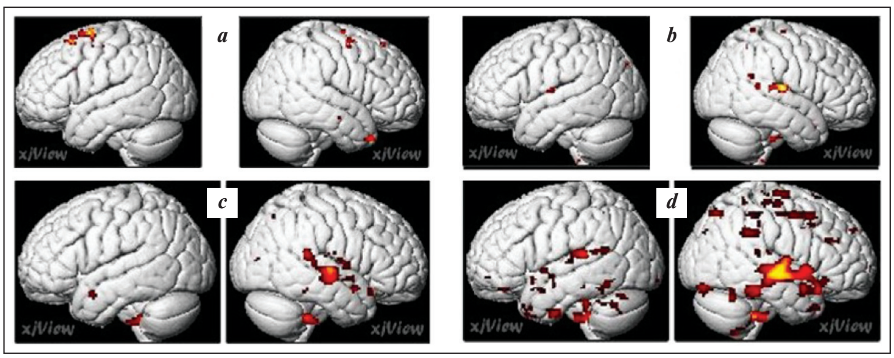

Fig. 1. *The activation revealed in the patient in VS/UWS corresponds to: a – paradigm "Writing the letter 'M' on the abdomen"; b – paradigm "Listening to the alarm sound"; c – paradigm "Listening to one's own name as part of the 'cocktail party' effect"; d – paradigm "Listening to audio fragment from the film with obscene language")*

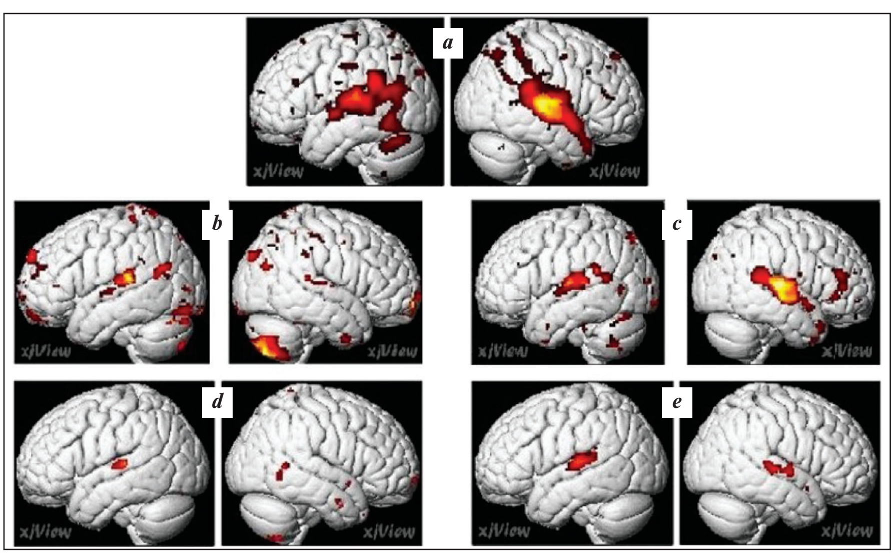

Fig. 2. *The activation revealed in the patient in MCS-corresponds to: a – paradigm "Listening to the Wedding March (Mendelssohn)"; b – paradigm "Listening to the melody of the traditional Russian Christmas song"; c – paradigm "Listening to a child's laughter"; d – paradigm "Listening to one's own name as part of the 'cocktail party' effect"; e – paradigm "Listening to audio fragment from the film with obscene language"*

Discussion

Let's analyze the case of the first patient. Clinical assessment revealed no signs of consciousness (only eye opening without stimulation, abnormal posturing, visual and auditory startle were observed), which was confirmed by assessments using specialized scales. Her level of consciousness corresponded to VS/UWS. However, according to the fMRI study data, significant clusters of activation were detected in her in response to passive somatosensory, auditory non-speech and speech paradigms, which were available for correlation with the activation observed in healthy volunteers [4].

In the somatosensory paradigm of "Writing the letter "M" on the abdomen" the patient's activation does not correspond to the average group norm, represented in the parietal and temporal regions of the right hemisphere, as well as in the right hemisphere of the cerebellum, but does occur in the frontal cortex of the left hemisphere (precentral, superior/middle frontal gyri) and in the posterior cingulate cortex. The absence of activation in the somatosensory areas of the brain may indicate limitations in the processing of cutaneous-kinesthetic information. However, the cluster in the indicated regions of the frontal cortex may reflect a motor response to stimulation. The posterior cingulate cortex, whose activation is present in the patient, is an important component of networks necessary for awareness and may be involved in maintaining a balance between the internal and external focus of attention [6].

In the auditory non-speech paradigm "Listening to the alarm clock sound" in contrast to the average activation in the left temporal lobe for the group, the patient (in addition to a cluster in subcortical structures) demonstrated activation in the right superior temporal gyrus. This is consistent with clinical neuropsychological data on the involvement of this area in the perception of non-verbal acoustic material [7].

In the auditory speech paradigm "Listening to one's own name as part of the “cocktail party” effect" the patient's name was presented within salient sentences (e.g., "Do you know what I learned about Ivan?") against a backdrop of party noise that was not clearly recognizable as speech. Similar to the average for the group of healthy volunteers, the patient demonstrated activation in the temporal lobes bilaterally, but with a greater representation in the right hemisphere. In contrast to the average normative data, the patient did not demonstrate activation in the left inferior frontal gyrus (Brodmann area 45). However, even in individual analysis in healthy individuals, the reproducibility of this area was low (noted in 1 out of 10 volunteers) [4]. The activation of the patient's temporal lobes corresponds to the perceptual level of processing auditory-speech information described in the works supervised by A.M. Owen and registered in a small proportion of patients in the VS/UWS (according to one of the large studies, in 6 out of 22 patients) [8]. The identified clusters may act as hubs of the language network [9]. In addition, the patient exhibited activation in the insula and posterior orbital gyrus of the right hemisphere, in the mid-cingulate cortex, the cerebellum and the brainstem. One fMRI study showed that the involuntary perception of one's own name as part of the "cocktail party" effect may be primarily ensured by the ascending attention network, consisting of structures of the auditory cortex, precuneus, insula, thalamus and brainstem [10], some of which were activated in the patient. Another series of studies demonstrated that the perception of self-related stimuli is closely linked to structures in the anterior cingulate cortex, including in patients with PDOC [11]. This partially overlaps with the activation of the cingulate cortex in our patient when presented with her own name.

The auditory speech paradigm "Listening to audio fragment from the film with obscene language" revealed fairly extensive activation in the patient. First, we will designate bilateral clusters in the temporal lobes (the right superior and middle temporal gyri and the left superior temporal gyrus), which intersect with the average group data of healthy people and can reflect the processes of perception of auditory and auditory speech information. Since the paradigm used scanner noise as a control condition, they are difficult to differentiate. In addition to activation of the convexital regions of the temporal lobes, clusters are present in deep temporal structures, in individual gyri of the frontal, parietal and occipital lobes, in the right insula and in a number of subcortical structures. Such a broad representation of zones may be due to the type of stimulation presented. Film excerpts are used in so-called "naturalistic" paradigms aimed at capturing similar conscious experiences in people when perceiving complex information over time. This requires the engagement of a number of high-level cognitive processes and the corresponding integrative activation in both modality-specific areas and supramodal frontal and parietal cortex [12]. The paradigm we used cannot be fully classified as "naturalistic" because it had a block design and did not include an assessment of the dynamics of the recorded parameters over the course of the plot. Nevertheless, the film excerpt contained within it could elicit similar extensive activation, which is what we observed in our patient. The inclusion of obscene language in the paradigm, which has not previously been used in studies of "covert cognition", could have contributed to increased involuntary involvement in the perceptual process, evoking an emotional response and, consequently, a broader cerebral response.

Most notably, activation consistent with normative levels was observed in auditory speech paradigms, which were found to be the most effective in healthy subjects [4]. It is worth noting that the identified clusters were predominantly represented in the patient's right hemisphere. This may be due to alterations in the functional systems responsible for processing presented information, given structural brain damage, or to the right hemisphere's dominance in speech. These data suggest that this patient, with a clinically established diagnosis of VS/UWS, exhibits the phenomenon of "covert cognition".

Let's discuss the second patient. Behavioral assessment revealed minimal signs of consciousness, including localization to noxious stimulation and vocalization. Otherwise, he exhibited eye opening without stimulation, visual and auditory startle, as assessed using specialized scales. His level of consciousness corresponded to MCS-. Moreover, fMRI data showed significant and, crucially, partially normative activation in response to passive auditory non-speech and speech paradigms.

In the auditory non-speech paradigm "Listening to the Wedding March (Mendelssohn)", the patient's activation corresponds to the activation of healthy volunteers in the right transverse temporal gyrus (Heschl gyrus) and the right superior temporal gyrus. In addition, it takes place in similar temporal structures of the left hemisphere and in the parietal areas (supramarginal gyrus bilaterally, right angular gyrus with the involvement of the right superior parietal lobule). Clusters in the temporal lobes are consistent with existing clinical and neuroimaging data on the perception of musical stimuli [13, 14]. The role of the parietal lobes (especially the inferior parietal lobule), whose activation is present in the patient, in the perception of music has also been shown in a number of studies. In particular, the cortex of these areas is involved in the perception of high-order characteristics of music, in tracking the flow of music that dynamically unfolds over time, in the recognition of music and associated memories [15].

In the auditory non-speech paradigm "Listening to the melody of the traditional Russian Christmas song", the patient's activation overlaps with that of healthy volunteers in the superior temporal gyri bilaterally. On average, across the group of healthy volunteers, clusters in the temporal lobes are more widely represented, and are also present outside of them in the right putamen, the left postcentral gyrus and the left anterior/middle cingulate gyrus. The patient also showed clusters of activation outside the temporal structures, but in other areas of the brain: in the occipital cortex of the left hemisphere (the inferior occipital gyrus and fusiform gyrus), in the right frontal pole areas and the left parietal operculum. The role of the parietal cortex in music perception has already been mentioned; the anterior prefrontal cortex may be involved in focusing attention on a musical stimulus and retaining it in working memory [15]. The involvement of occipital regions may reflect the involvement of intermodal interaction in the patient's perception of music.

Let us dwell separately on the auditory non-speech paradigm "Listening to a child’s laughter." It was not possible to obtain average group normative data for this paradigm [4]. Nevertheless, the patient exhibited volumetric clusters in the superior temporal gyri of both hemispheres, the left transverse temporal gyrus (Heschl gyrus), as well as in the frontal and parietal cortex. Clusters in the temporal cortex correlate to varying degrees with the expected activation based on other fMRI studies on the perception of laughter in healthy individuals [16, 17], as well as with clinical neuropsychological data on the involvement of the temporal lobe cortex, predominantly of the right hemisphere, in the recognition of emotional and prosodic components of speech [18].

In the "Listening to one's own name as part of the «cocktail party» effect" paradigm, the patient exhibited a peak in activation in the left superior temporal gyrus. No other activation, similar to the normative one (in the right temporal cortex and the left inferior frontal gyrus) was observed. Taking into account the control condition of the paradigm in the form of party noise, the activation observed in the patient may partially correspond to the perceptual level of processing auditory speech information described in the works led by A.M. Owen [8]. The identified cluster may act as a hub of the language network [9].

The "Listening to audio fragment from the film with obscene language" paradigm also showed a peak in activation in the left superior temporal lobe and an absence of the normally observed activation in the right temporal structures. This activation may reflect the perception of auditory and auditory speech information. Since scanner noise was used as a control condition in the paradigm, it is difficult to differentiate between them.

It's worth noting that activation clusters in response to paradigms focused on speech perception are present in the patient's left hemisphere, consistent with the concept of interhemispheric organization regarding left hemisphere dominance for speech. These results provide instrumental confirmation of the preservation of certain aspects of consciousness in this patient with a clinically established diagnosis of MCS- and expand our understanding of these aspects.

According to a large meta-analysis, the presence of a cerebral response to passive stimuli is present in 26% of patients in the VS/UWS and 55% in the MCS- [1]. Most studies presented in the literature used paradigms aimed at perceiving stimuli (single or hierarchical) within one of the modalities [1, 2], which may reduce the likelihood of identifying "covert cognition" and does not allow a more complete description of the profile of presumably preserved aspects of mental activity of patients with PDOC. In our study, a comprehensive multimodal personalized approach was applied using 12 fMRI paradigms, based on which it was possible to broadly cover the "covert" manifestations of consciousness. The patient in the VS/UWS was shown to be able to perceive somatosensory (tactile), auditory non-speech (household noises) and auditory speech (own name, obscene vocabulary) stimuli. The patient in the MCS- demonstrated the ability to perceive auditory non-speech (melodies without words) and speech (own name, obscene vocabulary) information.

A group of authors from Israel [19] previously conducted a similar fMRI study using a comprehensive multimodal personalized approach. Passive paradigms aimed at perceiving auditory, auditory speech, and visual information, as well as active paradigms aimed at mental representations, were used. The tasks were personalized (e.g., paradigm with the presentation of the patient's name versus neutral words and paradigm with the presentation of information spoken by a familiar voice versus the same information spoken by an unfamiliar voice were used). Among 11 patients with PDOC (six in the VS/UWS and five in the MCS-), activation was found in response to simple auditory stimuli in nine, speech in five, their own name in six, a familiar voice in three and visual stimuli in three patients. Regarding the active paradigms, one patient demonstrated corresponding activation in one task, two in two tasks, one in three tasks, and one in four mental representation tasks. The authors highlight the case of a patient in the VS/UWS who demonstrated activation in auditory, auditory speech and active paradigms. They note that the use of such a broad range of paradigms increased the sensitivity of the method and allowed for a profile of each patient's preserved capabilities. Our set of paradigms was aimed at achieving similar aims in the Russian-speaking sample of patients with PDOC, whose cases are presented in this article.

The practical significance of diagnosing "covert cognition" is related to the potential prognostic value of identifying this phenomenon, which is currently being studied. It has been shown that patients with "covert" signs of consciousness, especially in VS/UWS of traumatic etiology, may have a higher rehabilitation potential [20]. Unfortunately, in the current study, one of the patients presented rapidly died, and in the other, follow-up data could not be collected. Nevertheless, accumulating data on outcomes in patients with suspected signs of "covert cognition" is extremely important.

Furthermore, the proposed personalized approach, based on clinical case analysis, provides information for the development of neurorehabilitation programs for patients with PDOC. The obtained data on brain activation in response to stimuli of various modalities, including emotionally charged and personalized ones, can serve as a basis for the development of individualized psychostimulus therapy programs within the framework of neuropsychological rehabilitation [21, 22]. These programs can prioritize those types of stimulation to which patients have demonstrated a cerebral response, with a gradual expansion of the stimulus repertoire.

It is also possible to take into account data on «covert» signs of consciousness when deciding on the use of transcranial magnetic stimulation in patients with PDOC (since patients with such signs, as noted above, may have a higher rehabilitation potential), as well as when selecting stimulation targets based on the presence of preserved activation clusters, including in protocols combining cognitive rehabilitation and non-invasive neuromodulation, which requires further research [23].

Conclusion

The presented clinical observations illustrate the application of a comprehensive multimodal and personalized approach to diagnosing the phenomenon of "covert cognition" using fMRI paradigms. They add to the limited data available on identifying "covert" features of consciousness in a Russian-speaking sample of patients with PDOC.

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