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Review

Methodological aspects of studying the mechanisms of consciousness

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ABSTRACT

There are at least two approaches to the definition of consciousness. In the first case, certain aspects of consciousness, called *qualia*, are considered inaccessible for research from a third person and can only be described through subjective experience. This approach is inextricably linked with the so-called "hard problem of consciousness", that is, the question of why consciousness has *qualia* or how any physical changes in the environment can generate subjective experience. With this approach, some aspects of consciousness, by definition, cannot be explained on the basis of external observations and, therefore, are outside the scope of scientific research. In the second case, a priori constraints do not constrain the field of scientific investigation, and the best explanation of the experience in the first person is included as a possible subject of empirical research. Historically, in the study of cause-and-effect relationships in biology, it was customary to distinguish between proximate causation and ultimate causation existing in biological systems. Immediate causes are based on the immediate influencing factors [1]. Proximate causation has evolutionary explanations. When studying biological systems themselves, such an approach is undoubtedly justified, but it often seems insufficient when studying the interaction of consciousness and the brain [2,3]. Current scientific communities proceed from the assumption that the physical substrate for the generation of consciousness is a neural network that unites various types of neurons located in various brain structures. Many neuroscientists attach a key role in this process to the cortical and thalamocortical neural networks. This question is directly related to experimental and clinical research in the field of disorder of consciousness. Progress in this area of medicine depends on advances in neuroscience in this area and is also a powerful source of empirical information. In this area of consciousness research, a large amount of experimental data has been accumulated, and in this review an attempt was made to generalize and systematize.

1. Introduction

Consciousness research has always faced serious difficulties. The very definition of consciousness is rather vague and includes many interdisciplinary aspects related to psychology and philosophy. There is no generally accepted definition of consciousness, but most modern researchers agree that consciousness in its simplest form is “a feeling or awareness of internal or external existence” [4–6]. Until about the 20th century, the concept of consciousness was defined as "inner life", the introspection of personal thoughts, imagination and will. Today, most scientists include in the concept of consciousness individual experience, cognition and perception. It is also generally accepted that there may be different levels or orders of consciousness, as well as different types of consciousness, but assessing the level of consciousness is a non-trivial task. A separate question is whether only humans possess consciousness, or at least some animals also possess consciousness.

The founder of the concept of neuro-darwinism, Gerald Edelman, believed that it is necessary to distinguish between primary consciousness and higher (superior) consciousness [7]. Primary consciousness is a multimodular structure that brings together various sources of information. In contrast to the primary, higher consciousness develops in parallel with the acquisition of language, and continuously structures the experience gained by the individual. While primary consciousness links memory to current perception, higher consciousness directs the synthesis between memory patterns distributed over time. Edelman’s model implies that the integrative activities required for higher consciousness arise at the border between the thalamocortical system and other areas of the brain. It is an autonomous dynamic nucleus that cannot be identified either as the brain as a whole or as a specific part of the brain [7,8].

Numerous studies, including with the use of modern imaging technologies, have been undertaken to answer the question "what happens in the brain when the awareness of the surrounding world disappears?" So, in a recent study, a change in the consciousness of an experiment was

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carried out with a simultaneous analysis of brain activity using positron emission tomography (PET, PET). Measurements of brain activity were carried out during wakefulness, under the influence of various anesthetics, as well as during non-rapid eye movements (non-REM) sleep [6]. The deep stage of general anesthesia, when the subsequent report on mental content did not contain any signs of awareness of the surrounding world, was considered as a confirmed lack of consciousness [6]. The level of consciousness of the test subjects was regulated by propofol or dexmedetomidine with a stepwise increase in the concentration of the drug [6].

Decades of research have led to a certain consensus based on the fact that consciousness, like numerous forms of complex behavior, are network-level phenomena, that is, a phenomenological product of a neural network [9,10]. Highly organized social behavior requires high-level integration of various sensory inputs, synchronization of many motor patterns, and coordination of their activities within large-scale neural networks. Consequently, the accumulation of data on the functioning of neural networks contributes to the formation of a number of testable hypotheses regarding the neural foundations of cognitive functions, memory, and motivated behavior.

Currently, the study of consciousness consists of three main directions of levels: the search for neural correlates of consciousness, the mechanisms of functioning of these correlates and the reproducibility of the hypotheses put forward [11].

This manuscript is intended for neuroscientists, psychologists-clinicians, as well as other scientists involved in the field of relationship between consciousness and its brain substrate. Our aim was to more accurately formulate the main conclusions reached by experimental neurobiology while investigating the problem of the regulation of the mechanisms of consciousness by the human brain. It was used data from the last quarter of the previous century up to the present time.

2. Neural correlates of consciousness

Functional brain mapping is a critical area of neuroscience that has applications in both clinical and fundamental fields. In the latter case, functional mapping is directly related to the search for neural correlates of consciousness (NCC). In other words, this is a search for that hypothetical minimum set of neurons, without which the emergence of consciousness is impossible. On the other hand, even minimal changes in the functioning of the NCC should inevitably lead to a change in the state of consciousness or its temporary shutdown.

It is generally accepted that there are brain structures, without which consciousness is completely impossible. First of all, these include the reticular system of the medulla oblongata, which provides the proper level of activation in different areas of the brain. However, in the discourse of "neurobiology of consciousness" it does not occupy a key position, since it is not sufficient for the emergence of consciousness and does not affect its context, i.e., content of thoughts and images.

It is critical that the neurons of this structure give rise to an ascending reticular activating system (ARAS): the reticular formation of the medulla oblongata connects with some nuclei of the thalamus and hypothalamus, and this whole structure controls the overall level of wakefulness and the transition from sleep to vigor [12]. Over the past decades, most neuroscientists have held the view that consciousness requires the correct functioning of several subcortical structures and that its normal functioning is accompanied by the activity of neurons in certain areas of the cerebral cortex [13,14]. The neurons of the reticular formation, and especially the neurons of the ascending reticular system, play a vital role in maintaining behavioral arousal and consciousness [15,16].

Based on numerous clinical data, it was concluded that consciousness is awareness of oneself and the environment. This awareness is achieved through the action of the ARAS on the brainstem and cerebral cortex [17]. It is known that ARAS consists of several neural circuits that connect the brain stem to the cortex. These neural connections originate in the reticular formation (RF) of the brainstem and are projected through neurons in the intralaminar nucleus of the thalamus into the cerebral cortex [17,18]. The ARAS system also includes some nuclei of the brainstem (pedunculopontine nucleus, parabrachial nucleus), nonspecific thalamic nuclei, hypothalamus, and basal forebrain [18,19].

ARAS neurons reach the cortex via the ventral pathway (hypothalamus, basal forebrain) and via the aminergic nuclei of the dorsal pathway (thalamus). Switching between paradoxical sleep (rapid-eye movements, REM sleep) and slow sleep is regulated by the reticular formation, and the transition from sleep to wakefulness lies in the hypothalamus [11]. Data obtained in recent years indicate that dopaminergic neurons located in the nucleus accumbens are also involved in the regulation of sleep and are involved in the regulation of consciousness [20]. Probably, this regulation can be, to one degree or another, under the control of the limbic system. fMRI data suggests that the amygdala is directly involved in the regulation of consciousness through its connection to the reticular formation [21].

The brain contains phylogenetically ancient neural systems that maintain wakefulness at a certain period, regardless of sensory stimuli. These systems are localized in subcortical structures and through ascending projections they cause the activation of the cortex, characterized by high-frequency gamma and low-frequency theta activity [15]. Through descending projections into the spinal cord, they stimulate muscle tone. Morphologically, these systems mainly consist of neuronal assemblies of the reticular formation of the brainstem, thalamus, and posterior hypothalamus (Fig. 1, B). The neurons of the reticular formation predominantly use glutamate as a neurotransmitter and induce cortical activation by exciting neurons in the thalamocortical loops. Cholinergic neurons of the ponto-mesencephalic operculum and basal forebrain provide activation of the cortex during wakefulness, as well as during rapid eye movement sleep (REM Sleep). Dopaminergic ventral mesencephalic neurons control highly motivated behavior during wakefulness, but also maintain a high level of activity during REM sleep [15]. In contrast, blue spot neurons promote arousal wakefulness and prevent both REM sleep and slow wave sleep (SWS sleep) [15]. Suture serotonergic neurons promote restful wakefulness, which, while not including REM sleep, may promote SWS sleep. Histaminergic neurons in the posterior hypothalamus act as noradrenergic neurons to induce wakefulness and are joined by neurons containing orexin, a neuropeptide recently shown to maintain wakefulness and is responsible in absentia for narcolepsy and some sleep pathologies [22,23]. These multiple excitation systems are parallel and seemingly redundant, but they are highly differentiated, since each plays a specific role in the regulation of wakefulness and sleep. During SWS sleep, they are subjected to the inhibitory effect of certain GABAergic neurons distributed in the cortex and subcortical structures, as well as concentrated in the basal forebrain [15].

This is not the case with cortical structures. Traumatic or surgical loss of the frontal lobes usually leads to a serious mental defect: the patient's emotional reactions lose their adequacy, and often there are problems with speech and with a number of motor functions. However, consciousness as such is preserved, and often for many years. On the contrary, the loss of fragments of the posterior (including the occipital, parietal and temporal lobes) cortex leads to much more serious consequences: the loss of recognition of faces and familiar images, which destroys normal communication with society and is often considered a violation of consciousness. The question of the functional differences between the frontal and posterior cortex remains open, and certainly one of the most important in neurobiology [12].

3. Cortical and subcortical hypothesis

It can be assumed that modern neurobiology considers two subcortical structures - the thalamus and the claustrum, and two cortical systems as the main candidates for the role of NCC, and two cortical systems: the so-called "posterior cortical hot zone, PCHZ" - "posterior hot

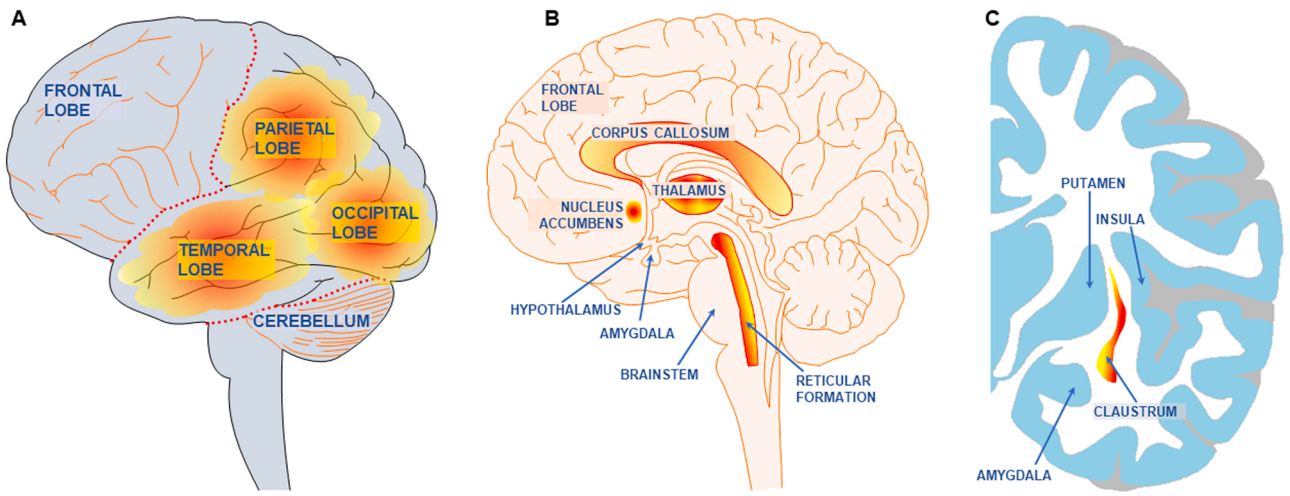

Fig. 1. A. Posterior hot zone (PHZ) of the brain (depicted by the red dotted line). Each experience of awareness corresponds to a specific set of neural activities called neural correlates of consciousness (NCC). The neurons participating in this experience are located in the (PHZ). This part of the cortex consists of the parietal, occipital, and temporal lobes of the cerebral cortex. The level of complexity of organizing patterns neuronal activity after a stimulating magnetic impulse allows to assess the level of human consciousness. B, C. Some cortical and subcortical structures associated with the regulation of consciousness shown in the sagittal and coronal sections, respectively. The claustrum directly innervates the PFC, and possibly plays an important role in the regulation of consciousness. The ascending reticular activating system (ARAS) has been considered as a main neural structure for consciousness. ARAS transmits nerve impulses from the reticular formation of the midbrain up through the thalamus to all parts of the cerebral cortex.

area" - a large area of the cortex at the junction of the parietal, the occipital and temporal lobes and the fronto-parietal cortical attention system - intraparietal sulcus (IPS) of the superior parietal lobe (SPL).

The term "posterior hot zone of the cortex (PCHZ) was coined to describe a zone of the neocortex, which is possibly the minimum cortical substrate required for conscious perception (Fig. 1 A) [12,24]. It is a collective term that includes sensory cortical areas in the parietal, temporal, and occipital lobes. Thanks to modern methods of functional brain mapping, we know quite a lot about the organization of this area of the cortex. In short, the sensory component (shape, color, texture, tonality) of any object stored in long-term memory is encoded by PCHZ neurons as part of the corresponding neural ensembles [25,26]. When accessing this object in memory, the corresponding area is activated in the PCHZ, which leads to the conscious perception of the object. Hebb's principle "cells that fire together wire together" explains the perception of a familiar object, but does not explain the infinite number of new objects that a person can imagine [27,28]. It is likely that a cortical neural network can combine the individual properties of objects stored in memory almost indefinitely. If this combination occurs consciously, the process can be called cognitive synthesis, or prefrontal synthesis. If this process is carried out unconsciously, it can be viewed as a dream or hallucination.

Another hypothesis states that consciousness first appears at the level of integrative circuits in the parietal and temporal lobes [29]. This hypothesis introduces the concept of central representation (CR, CP, central representation) [30,31]. Based on functional mapping of the human brain, it can be concluded that the role of IPL as an anatomical substrate for "central representation" (CR), i.e., the center of integration, continuously creating consciousness [31]. It is assumed that CR is present in all mammals and reaches its maximum development in humans [30].

The sensory nuclei of the thalamus carry a relay function, maintaining communication between organs - receptors and the sensory cortex. However, in addition to this, the thalamus contains a large number of neurons through which communication between different cortical zones is carried out. The idea that the thalamus plays a key role in the management of states of consciousness gained popularity in the second half of the 20th century. The reticulothalamic system consists of two parts, corresponding to their thalamo-cortical connections [32]: (1) specific pathways (SP), carriers of afferent information going to the cortex. First of all, these include the lateral geniculate nucleus (LGN), which is part of the visual system (2) non-specific pathways (NSP) that do not transmit information to the cortex, but have modulating effects on the cortex.

There is strong physiological evidence to support this hypothesis. There is clinical evidence demonstrating that the thalamus is directly involved in controlling the state of consciousness. It has been shown that neurons in the thalamus largely control the alternations between sleep and wakefulness [33]. Generally acting anesthetics have a common target in the NSP thalamus [34,35]. Damage to the NSP thalamus often causes unconsciousness in patients, even if the SP system remains intact [36]. Based on these data, many believe that the NSP-thalamus modulates the state and level of consciousness [8]. The thalamocortical theory of consciousness suggests that consciousness is based on interactions between thalamic nuclei and areas of the cortex. According to this theory, there is no specific area of the cortex that regulates consciousness. The continuous interaction of the cortex with the thalamus is key.

The basic fact about consciousness is that a state of consciousness can never be separated from the content of consciousness. It is impossible to perceive the taste or understand the word, being in an unconscious state [32]. Conversely, it is impossible to be in a conscious state without being aware of anything. In other words, the content of consciousness and the state of consciousness constitute a single whole [32]. The state of consciousness cannot be separated from the content of consciousness. In other words, it is impossible to be aware of a sensory stimulus while in an unconscious state [37–39]. One of the theories of consciousness assigns the role of the physiological substrate of consciousness to the thalamo-cortical loop [32].

More recently, a hypothesis has been proposed that both the state and the content of consciousness depend on the pyramidal cells of the cortical layer V (Layer 5 pyramidal, L5p) [32]. These neurons connect the cortical-cortical and thalamo-cortical loops with each other [32]. It has been suggested that functionally this connection corresponds to the connection between the state and the content of consciousness. The authors conclude from this that any processing of information in the cortex that does not include L5p neurons will be unconscious. Or, which is the same as the fact that L5p neurons play a central role in the mechanisms of consciousness [32].

Numerous studies agree that layer V cortical pyramidal neurons (L5p) play a central role in the mechanisms underlying consciousness. A

feature of these neurons is extensive connections with the thalamus, as well as with other cortical neurons. These cortical-cortical and thalamocortical loops form the thalamo-cortical translating system, in which neurons L5p play a central role [40,41]. Here is why this is so: both the state and the content of consciousness depend on the activity of the L5p neurons [40,41] (Fig. 2). The idea that the thalamus plays a key role in managing states of consciousness emerged in the second half of the 20th century. It was believed that in this case, two types of thalamo-cortical pathways: (1) specific pathways (SP) that function as carriers of afferent information to the cortex [for example, the lateral geniculate nucleus (LGN) for vision]; and (2) nonspecific pathways (NSPs), which do not transmit information to the cortex, but are capable of modulating the state of the cerebral cortex [42,43]. Later, however, it turned out that the division into NSP and SP is not absolute [44]. This modulation has been shown experimentally. Therefore, for example, stimulation the ventromedial thalamic nucleus awakens mice from non-REM (Rapid Eye Movements) sleep and anesthesia [45]. General anesthetics have common targets in the NSP thalamus despite different physiological mechanisms [46]. These results are in agreement with the fact that injuries and tumors localized in the thalamus of the NSP often cause the absence of consciousness in patients, despite the fact that SP system has

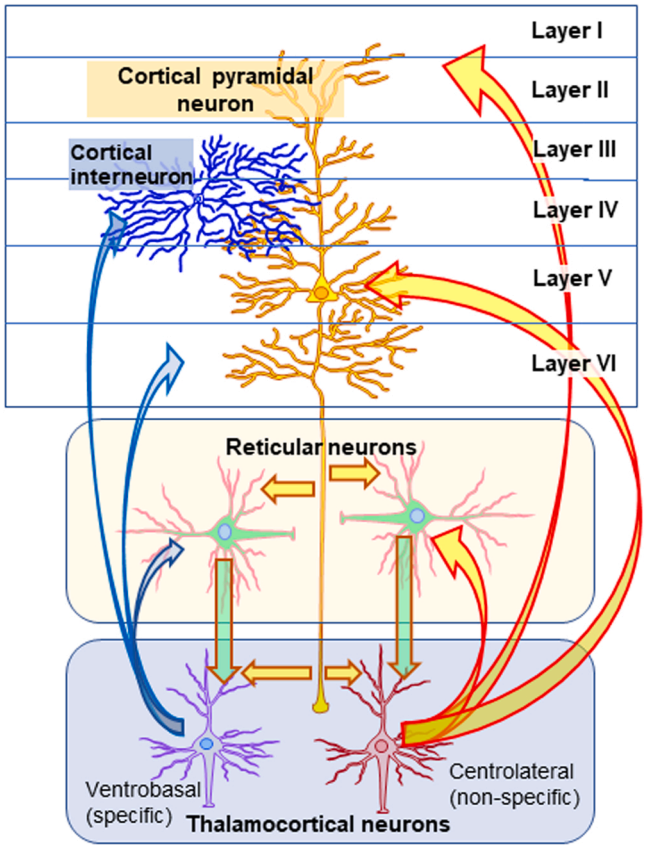

Fig. 2. Simplified depiction of specific and non-specific thalamocortical pathways. Pyramidal neurons in the deep layers of the cortex are involved in both the thalamo-cortical and cortical-cortical loops. It is assumed that by connecting these loops, they functionally connect the state and content of consciousness [40]. Recovery of consciousness, including recovery from the coma state, includes the restoration of excitatory neurotransmission through corticocortical and thalamocortical connections, both intrahemispheric and transcallosal [140]. Thalamocortical circuits are the target of general anesthesia, in addition, damage to these circuits due to trauma or disease often leads to coma. But many studies using functional imaging of the brain place key areas of regulation of consciousness in the cerebral cortex. Possible, both thalamocortical and cortical-cortical circuits are involved in the regulation of consciousness. These circuits intersect via L5p neurons.

remained relatively intact. Taken together, these results show that it is highly likely that the thalamus actually modulates state and level of consciousness [47,48]. Thalamocortical theory of consciousness suggests that conscious experience is based on the interaction between the nuclei of the thalamus and the cerebral cortex. At the same time, it is impossible to distinguish a specific area of the cortex: the key role belongs to the interaction of the cortex with the thalamus [41].

All of the data is fully consistent with the data obtained from fMRI and electrophysiological experiments on primates [49]. It has been shown that consciousness is directly dependent on thalamocortical and corticocortical interactions. It was found that neurons in the thalamus and deep cortical layers are most sensitive to changes in the level of consciousness. Deep layer activity is supported by interaction with central lateral thalamus. The practical implication of these experiments is that targeted deep brain stimulation can alleviate impaired consciousness [49].

In recent decades, several strategies have been proposed for using neurostimulation to improve impaired consciousness in patients [50]. Recent studies of centromedian-parafascicular (CM-Pf) thalamic nuclei and rostral intralaminar thalamic nuclei in patients in a vegetative state of minimal consciousness showed encouraging results [51]. So, it has been shown to improve in almost 50% of patients from a vegetative state after stimulation of the (CM-Pf). Unfortunately, in such clinical trials, it is rather difficult to implement adequate control [50,52].

With severe damage to the cortex, neurostimulation is meaningless. Most neuroscientists believe that consciousness is usually retained in people without a cerebral cortex, but is lost when the brainstem system is damaged [53]. This is due to the hierarchical relationship between the cortical and stem functions of the forms: the stem functions support the cortical. It is almost certain that any damage to the parabrachial nucleus, the smallest area of the brain, will impair consciousness and cause coma [53–55]. The parabrachial nucleus maintains the multiparticulate systems of the brain at the required level, as well as controls the state of the body, maintaining the level of oxygen, temperature and glucose in the blood you need, in other words, it maintains homeostasis [56].

If the body does not maintain the required level of homeostasis, it ceases to exist as an organism. This shows why there is a basic form of consciousness: it constantly evaluates the state of the organism within the biological scale of values, prompts the forebrain to take actions aimed at preserving existence [54]. The parabrachial nucleus is a self-organizing system consisting of several subsystems responsible for certain physiological functions. One of these functions is the management of many forms of cortical activity, and it is this that determines the role that the parabranchial nucleus plays in the regulation of consciousness [57].

Associated with the parabrachial nucleus, the peripeduncular area, or peripeduncular nucleus is bordered by substantia nigra and the nuclei of the medial geniculate body. Peripeduncular the zone, is bilaterally connected with the limbic system and basal ganglia [58,59]. Relatively little is known about the functions of this structure, but there is evidence of the important role of neurons in the peripeduncular area in the regulation of behavior. There is indirect evidence that this structure may have a regulatory effect on the structures of the forebrain, and may be a point of application for the search for new strategies in the treatment of diseases such as Parkinson's disease [60,61]. This assumption is supported by data obtained from epileptic studies on animals [62]. Probably, with an electroshock seizure, direct connections between the lateral part of the substantia nigra and the adjacent peripeduncular the area is critical for the transmission of anticonvulsant influence [62].

Dorsolateral prefrontal cortex (DLPFC) is thought to be related to working memory and selective attention [63,64]. It is likely that this area also supports cognitive selection of sensory information and responses [65,66]. Thus, it can influence emotional reactivity by altering the systems of perception, and possibly by mediating the level of consciousness. Numerous studies in both humans and primates have shown that when the DLPFC is deactivated during sleep, the conscious is absent

even if the rest of the brain remains active [67]. Deactivation of DLPFC during sleep correlates with activation of the anterior cingulate cortex (ACC). These opposite states are associated with specific modulation of acetylcholine via the m2 muscarinic receptors [68]. There is a number of evidence that indicates that the DLPFC is a powerful source of neural correlates of consciousness [67,69,70]. It is likely that through the system of intercortical connections between ACC and DLPFC, the cholinergic system is involved in the regulation of consciousness.

4. Claustrum as a candidate for the role of a key structure in the formation of consciousness

In addition to the thalamus, the claustrum (fence) is considered as a candidate for the role of the minimum necessary anatomical carrier of consciousness [71,72]. Claustrum is a vertical curved plate of gray matter up to several millimeters thick (Fig. 1 C). The claustrum is part of the limbic system and is located lateral to the shell of the lenticular nucleus and medially under the insular cortex. Claustrum is found in the brain of all mammals [73].

A feature of claustrum is a large number of gap junctions that connect neurons directly, rather than through synapses [73]. Gap junctions are intercellular contacts that provide direct transfer of ions and small molecules between neighboring cells. Gap junctions' channels consist of two parts - connexons. Each connexon consists of six protein subunits. The permeability of the gap junctions is not constant and is regulated by opening and closing the gates of the channel under the influence of various factors.

Francis Crick, in his hypothesis, suggested that consciousness is supported by the activity of a limited number (~ 105) neurons [74,75]. According to his hypothesis, these neurons should:

(1) not belong directly to the sensory or motor areas of the cortex
(2) integrate sensory inputs from multiple sensory systems on oneself
(3) correlate with conscious experience

Crick and his co-authors suggested that a particular part of the brain should contain a large number of such neurons. These authors concluded that, based on clinical and experimental data, a large number of such neurons contain claustrum [8,73,74,76].

Electrical stimulation of various subcortical structures of the brain (deep brain stimulation, DBS) is widely used for therapeutic purposes. Electrical stimulation of the claustrum has been shown to lead to a complete cessation of volitional behavior, insensitivity to sensory stimuli, and amnesia without additional negative symptoms [77]. The impairment of consciousness did not last longer than stimulation and did not cause epileptiform discharges. These results most likely confirm that at least part of the claustrum is an important part of the neural network that controls consciousness [77].

The claustrum hypothesis has strong psychopharmacological confirmation [75]. The psychedelic *Salvinorin A*, the main component that affects humans when consumed with the psychedelic plant *Salvia divinorum*, causes changes in human consciousness [75,78]. When *Salvinorin A* acts on the corresponding receptors, the excitability of cells decreases due to an increase in potassium currents [79]. *Salvinorin A* is a selective, highly potent agonist of the kappa opioid receptor (KORr) and thus utilizes the KOPr system to regulate cognitive and perceptual effects. The claustrum has the highest level of KOR in the brain, yet its roles not been elucidated [80]. KORr plays an important role in regulating reward and mood processes. Current evidence suggests that KORr modulates overlapping neural networks linking monoaminergic nuclei of the brainstem with limbic structures of the forebrain. In addiction studies, KORr is considered to represent a biological substrate of comorbidity, in which life experience is combined with general brain mechanisms, increasing the risk of various but interacting psychopathologies [81]. Simultaneously, *Salvinorin A* reduces N-type calcium currents, which, by decreasing presynaptic Ca^{2+}, decrease excitation and facilitate the release of inhibitory neurotransmitters [79]. Thus, the effects of KORr are inhibitory [75].

The distribution of KORr in the brain was measured by determining the mRNA density of the receptor, and by detecting receptor-mediated metabolism of radioactively labeled precursors of the secondary messenger [82]. A high density of KORr has been found especially in the claustrum. In fact, this was the only area of the brain in which almost all cells have a very high concentration of κ-opioid receptors [82]. The unique high density of κ-opioid receptors in claustrum makes it an especially good candidate for *Salvinorin A* to alter consciousness [75]. For *S. Divinorum*, subjective reports indicate marked differences between the experiences associated with it and other psychoactive drugs [83].

There is a hypothesis that claustrum plays a global role in perception and consciousness, which requires the integration of information within this structure. This integration can be largely due to gap junctions between claustrum cells [84].

Claustrum is found in all species from insectivores to humans, mammals, although its shape and connections vary from species to species [85]. The claustrum receives information from almost all areas of the cortex and is projected back into almost all areas of the cortex, while its function remains unclear. There are few types of neurons in the claustrum. From a functional point of view, with some approximation, it seems possible to speak of the presence of an auditory, visual zone and an area not related to these two in the claustrum. [86]. Neurons, called type 1, have a large soma, but their shape varies considerably. Their dendrites have spines, and their axons these neurons often leave the claustrum. Other claustral neurons do not have spines on their dendrites, and their body size varies greatly. The axons of these cells does not leave the claustrum, so they are classified as interneurons [74]. Claustrum neurons have extensive connections with many parts of the cortex, both ipsi- and contralateral. It has been hypothesized that the claustrum is involved in crossmodel processing [74]. It would be naive to assume that claustrum is some kind of hypothetical center where mind and brain meet and consciousness arises. Crick and Koch believe that the conductor is coordinating performers in the orchestra, and the cluster constantly coordinates the work different areas of the cerebral cortex [74]. Synchronized activity of the claustrum' interneurons, based on gap junctions connections between them, can be crucial for synchronizing remote populations of cortical neurons [74]. It is assumed that a key property of conscious sensations is their integrated nature [74]. An Inherent property of almost all neural theories consciousness is the need for constant interaction dispersed neurons [74]. Such interaction expressed in continuous flow conscious perception, including images and thoughts. This seems to be most clearly described in the concept of a dynamic core [8].

5. Epilepsy as a source of information about the state of consciousness

In clinical neurobiology, epilepsy provides a rich material for the study of consciousness, since an epileptic seizure and an epileptic aura are accompanied by a change or loss of consciousness [87]. At the same time, before and after the attack, the brain is in a normal state [88,89]. The seizures that actually cause impaired consciousness are very diverse in terms of behavior and physiology. Historically, epileptic seizures are often associated with religious beliefs and are interpreted as spirit possession [90].

Advances in neuroimaging technology and physiological research in the clinic and in animal models have allowed a new look at the impairment of consciousness in epilepsy. It is likely that in any type of epilepsy, pathological activity affects the fronto-parietal associative cortex and thalamus. Here, undoubtedly, there are clear parallels with the cortical and thalamic hypothesis of consciousness [89]. Impaired consciousness in epilepsy differs from other disorders of consciousness only in that they are temporary. Recently, a "network inhibition hypothesis" has been proposed to explain the loss of consciousness caused

by focal seizures of epilepsy in the temporal lobe [91,92]. Consciousness is usually supported by mutual interactions between the cortical and subcortical components of the consciousness system. Focal epileptic activity causes pathologically synchronized discharges in the temporal lobe. Corticothalamic connections transmit pathological activity to subcortical structures, especially to the reticular nucleus of the thalamus. Removal of thalamic excitation leads to pathological slow-wave activity in the fronto-parietal associative cortex, causing impairment of consciousness [93].

The epileptic aura is directly related to the neurobiological correlates of consciousness. From a clinical point of view, an epileptic aura is any sensation or experience that regularly precedes an epileptic seizure or is an independent seizure. The manifestations of the aura are varied and depend on the location of the epileptic focus. The aura proceeds with intact consciousness and is accompanied by the patient's subjective sensations, lasting from several seconds to several minutes. The patient's consciousness at the moment of the aura is preserved, but the changes in consciousness are quite typical. In most cases, the patient retains a memory for the experienced sensations. Usually in clinical practice somatosensory, visual, auditory, olfactory, gustatory, psychic auras (including oneiric states and depersonalization states), autonomic, abdominal and nonspecific auras are distinguished.

Despite the differences between absence, tonic-clonic and focal forms of epilepsy, they all have a common feature - a change or loss of consciousness. Consequently, an epileptic seizure includes at least some of the regions such as the frontal and parietal associative cortex, cingulate gyrus, claustrum, thalamus (especially the medial, median, and intralaminar nuclei), and activating systems located in the basal forebrain. These regions can be defined as the "system of consciousness" [91,92,94].

It has been shown that absence seizures, generalized tonic-clonic seizures and focal impaired consciousness seizures (FICS) are associated with the same general anatomical regions of the "system of consciousness". All three types of epileptic seizures cause abnormal increases in activity in the upper brainstem and medial thalamus. However, the dynamics of these changes are not so simple. Generalized tonic-clonic seizures show an increase in cerebral blood flow (CBF) in most areas of the frontal and parietal associative cortex during an attack, but the medial frontal zones and cingulate cortex show a marked decrease [89,93].

In all regions, there is a decrease in CBF in the postictal period, after a tonic-clonic seizure, when consciousness usually remains seriously impaired. Seizures in the temporal lobe show an ictal decrease in CBF in the frontal and parietal associative cortex, which coincides in time with impaired consciousness in the postictal period [91].

6. Von Economo neurons

Many researchers link regulation of consciousness with von Economo neurons, discovered and described in the early 20th century. Von Economo neurons (VENs) - spindle-shaped brain cells, named after the scientist who first described them, are found only in humans, apes, and some other highly social mammals. Apparently, these cells are present mainly in the anterior cingulate cortex (ACC) and in one frontal islet (FI). Moreover, ACC is a rather unique structure of the brain in terms of the number and density of VEN in it.

ACC and FI have been shown to be especially active when people are experiencing emotion [95,96]. From a morphological point of view, VENs are characterized by their large size and small dendrites. In humans, VEN has long been shown in the entorhinal cortex, hippocampus, cingulate cortex, and rostral part of the islet. Later, VFNs were found in other areas of the brain, albeit in smaller numbers. All areas of the brain containing VFNs are associated with cognitive and social. In the right hemisphere, the number of VFNs is significantly greater than in the left [97].

It was hypothesized that the brain monitors and responds to "internal sensations" arising as a result of internal processes as well as social interactions [96]. Thus, there is supposedly a connection between self-control and awareness of others that allows a person to understand the feelings of others. In other words, self-awareness and social awareness are part of the same functional brain system.

It is highly likely that von Economo neurons are responsible for the communication between ACC and FI with the rest of the brain. Clinical studies have shown that damage to a small area of the brain — the anterior insula (AI) and the pregenual anterior cingulate cortex (pACC) — are often associated with coma [98].

From a functional point of view, the ACC is divided into the pregenual (pACC) and subgenic (sACC) parts [99,100]. According to the currently accepted view, sACC is associated with the processing of negative valence stimuli and emotions, and pACC supports the processing of positive valence stimuli [100]. One of the pACC zones, called the "gyral component" or area p24ab, is associated with interoception, and most likely, with the mechanisms of consciousness regulation [100,101]. The role of the right pACC in the formation of emotional behavior and empathy has also been proven [102].

These areas of the cortex correspond to the distribution of von Economo neurons. It has also been shown that impaired communication between AI and pACC is observed in patients with impaired consciousness. Logically, it was concluded that a neural network heavily based on neurons von Economo based in the cortical regions of AI and pACC may play an important role in maintaining human consciousness [103].

7. Astrocytic syncytium as a regulator of consciousness

In accordance with the "astrocentric" hypothesis, cortical and subcortical astrocytes, connected to each other through gap junctions, form numerous mosaic domains with a three-dimensional structure [104,105]. Together with adjacent neurons, these domains are a matrix for expressing consciousness and binding sensory information to consciousness, as well as for storing memories [104].

With the help of gap junctions, astrocytes form astrocytic syncytium - a globally distributed network of astrocytes. It has been shown that astrocytic syncytium consists of domains that are contiguous and contiguous [106,107]. These domains cover the entire neocortex with a three-dimensional geometric pattern [105,107]. Gap junctions between astrocyte domains allow small molecules, many of which are important for information processing and metabolic homeostasis, to be distributed throughout the syncytium. These molecules are relatively small and include glutamate, glucose, lactate, ATP, cyclic AMR, ions, microRNA, and other small molecules [107,108]. Studies of astrocytic syncytium have led to the formation of a rather bold hypothesis that it is he who is the main substrate of consciousness [107].

Astrocytic syncytium can represent a specialized "analog" intercellular signaling system (an alternative to "binary" interneuronal communication), which, using the intercellular diffusion of many molecules, can provide a second level of information processing in the central nervous system [107–110]. Such a binary/analog hybrid system has been proposed as a characteristic of consciousness [107,111]. Probably, astrocyte gap junctions can exist in a quasicrystalline form and are capable of crystallizing [112]. This fact is the basis for the hypothesis that consciousness arises when gap junctions are activated by synaptic activity [107].

The transition of the gap junction to the crystalline form corresponds to the transition of the information pattern to the form of long-term memory, and the reconsolidation of memory occurs with a return to the crystalline state, after invoking a certain memory. Memories are formed when gap junctions are transformed into a crystalline configuration. The type of explicit memory (iconic, short-term, long-term) depends on the time interval between the initial conscious moment and the return to the quasi-crystalline state [107,110].

Metaphorically, consciousness is a movie screen of an analog movie projector that projects visual and auditory information that is perceived

sequentially as frames move [105]. However, if this is so, the real situation is much more complicated. However, the proposal is much more complicated. Astrocyte gaps represent billions of "pixels" on a hypothetical screen, which requires tremendous visual acuity of the observer. Continuous perception of what is happening on this metaphorical screen generates consciousness [105].

This hypothesis is supported by the fact that, unlike neurons, which differ little from neurons in other mammals, human astrocytes have changed greatly during evolution [105]. There are at least three primate-specific astrocyte types [105,106]. This hypothesis has only indirect confirmation, mainly obtained as a result of experiments on animals. Thus, an extremely important organ of information perception in rodents is the vibrissal system. The somatotopic organization of the vibrissal system is preserved at all levels, including the ventral-posterior thalamic nucleus (VPM) and the barrel field (BF) of the primary somatosensory cortex. Thalamic barreloids contain gap junctions between astrocytes and oligodendrocytes. It has been shown that the propagation of tracers through the panglial astrocyte – oligodendrocyte network in the VPM is strongly dependent on neuronal activity and is limited by barreloid boundaries [113].

In addition, it was found that each barreloid contains such a panglial network within its own boundaries, and its cells do not have gap junctions with the cells of neighboring barreloids [104,113]. Unlike neurons, glial cells do not generate or propagate action potentials. It has been suggested that astrocytes associated with gap junctions represent a functional syncytium in which large-scale Ca^{2+} waves can propagate, which can modulate interneuronal communication [114–116].

8. Coma and minimally conscious state

Generally under the term "coma" there are three stages of the disorder of consciousness (DoC). DoCs include coma, vegetative state (VS), and minimal consciousness state (MCS). The Glasgow Coma Scale is commonly used immediately after a coma is diagnosed, in the emergency department, and during admission [117,118]. This scale helps track improvements and deterioration in brain recovery and predict recovery. A fully conscious person has a Glasgow coma score of 15, and a deep coma patient has a Glasgow coma score of 3 [119].

Clinical medicine distinguishes between coma, minimal consciousness, sustained vegetative state, and brain dead. Almost always in a coma, the thalamus or brainstem, or much of the cerebral cortex is damaged. Patients cannot be woken up and do not respond to sensory and pain stimuli. Unlike coma, in a minimally conscious state (MCS), patients are periodically aware of their surroundings and can respond to commands. In a persistent vegetative state, patients show no signs of perception, communication, or self-awareness. Because brain stem functions remain intact, patients can breathe spontaneously and experience cycles of sleep and wakefulness. A persistent vegetative state can last for decades and most scientists believe that there is no consciousness in this state. Since thalamocortical communication and reticular nuclei of the thalamus is responsible for the regulation of consciousness, impairment of this system often leads to a state of coma. Usually, the level of coma correlates with the degree of damage to the thalamocortical system [120].

The problem of consciousness is inextricably linked with the state of coma, i.e. prolonged unconsciousness. In a coma, a person cannot be awakened, does not respond to sensory and painful stimuli, and does not go through the normal cycle of changing wakefulness and sleep. Usually, a person is considered to be in a coma if their Glasgow Coma Scale (GCS) score is less than 8–10 and this state lasts at least 6 h. Coma can be caused by various causes, but one of the most common causes is damage to the reticular activating system (RAS), especially ascending part of it (ARAS). ARAS neurons produce acetylcholine, and with the help of this neurotransmitter, they activate neurons in various brain structures. Any disruption in the functioning of ARAS leads to impairment of consciousness. It seems that the coma is always accompanied by impaired ARAS functioning.

Focal lesions of the brain stem often lead to coma. Extensive research aimed at pinpointing the location of such lesions has been undertaken recently. It turns out that damage to a small area on the left side of the bridge, next to the medial parabrachial nucleus, causes a coma [121]. This region of the brainstem, like other areas affected by coma, is associated with the left agranular, anterior insula (AI), and the pregenual anterior cingulate cortex (pACC) [103]. These areas of the cortex correspond to the distribution of von Economo neurons (VENs). These results indicate that coma-causing lesions disable some of the brain's unique neural network. It has been hypothesized that this network may represent a neuroanatomical substrate linking arousal and awareness, two major components of human consciousness [121].

The hypothesis about the role of VENs in the formation of consciousness is supported by the fact that people develop the ability to recognize the self in the mirror image between the ages of 18 and 24 months. At the age of up to 4 years, speech is mainly formed. This completely coincides with the development of the VEN development [96].

For a better understanding of the neural correlates of consciousness, the data on the use of deep brain stimulation (DBS) to stimulate the consciousness of patients in coma are extremely interesting [122]. Electrical stimulation of the thalamus and globus pallidum likely stimulated the improvement of the patient's condition after prolonged exposure to a coma, but the small amount of data does not allow us to speak about this with certainty [122]. Indirectly, this is supported by the rather small amount of data on the use of deep brain stimulation to recover patients out of coma. Thus, DoC patients underwent unilateral DBS electrode implantation into the centromedian parafascicular complex of the thalamic intralaminar nuclei. Consciousness recovery was confirmed and brain MRI volumetric measurements were done prior to the procedure, then a year after, and finally 7 years after the implementation of the electrode. It was shown that limbic cortices and insula demonstrated a volume increase 1 and 7 years after DBS [118,123]. It can be concluded that DBS stimulated recovery from coma, and at the same time normalization of functions and regeneration processes in some brain structures. These results are very interesting, but unfortunately these studies were not randomized. It cannot be ruled out that fundamentally new brain stimulation technologies may be useful in this area in the future [124–127].

These findings are in line with the recent findings of a study based on extensive clinical material: Cerebral PET with F-FDG can be successfully used as a predictor of the state of patients with mental disorders. To a lesser extent, the same can be said about fMRI [128].

According to the "astrocentric" hypothesis of consciousness, astrocytes are the last stage of conscious information processing [129]. From a physiological point of view, astrocytes are assumed to bind sensory information to consciousness and are able to store encoded memories for a long time [129].

Consciousness is an ambiguous concept, but in practice, severe acquired brain injuries leading to disorder of consciousness (DoC) provide a model from which to refine our understanding of consciousness [130]. Progress in the treatment of patients with DoC is inextricably linked to our improved understanding of how brain injury leads to these disorders [131,132].

Usually "loss of consciousness" (LoC) and "regain of consciousness" (RoC) in clinical practice is determined using behavioral correlates. But physiological correlates of LoC and RoC also very important, so these correlates were investigated in volunteers in controlled loss of consciousness caused by propofol and the presence of autonomic biomarkers of loss and recovery of consciousness during general anesthesia has been demonstrated. These biomarkers are likely more accurate than tracking behavior [133].

Thus, general anesthesia causes a clear change EEG, primarily a gradual increase in low-frequency high-amplitude activity as the level of general anesthesia deepens. However, different anesthetics, as well as

their combinations, have different physiological effects. Clinical and animal studies have shown that anesthetics induce unconsciousness by altering neurotransmission in many areas of the cerebral cortex, brainstem, and thalamus [117].

In vivo and *in vitro* studies have shown that NMDA and GABA-A receptors in the cortex, thalamus, brainstem, and striatum are major targets for many anesthetics. [117]. Since a small number of inhibitory interneurons control a large number of excitatory pyramidal neurons, increased inhibition of GABA-A can inactivate many circuits and cause loss of consciousness [117].

With general anesthesia, different anesthetics act on different molecular targets and different neural circuits, causing different brain conditions [134]. These conditions can be differentiated using the EEG. The use of techniques based on the combination of EEG analysis and patient behavioral responses has entered the practice of anesthesiology. However, using EEG, it is not possible to estimate the depth of anesthesia with high accuracy, especially in pediatric practice.

By *in vivo* animal experiments it was shown that alpha oscillations (10–15 Hz) caused by propofol are synchronized between the thalamus and the medial prefrontal cortex. It was also shown that with deep general anesthesia, coherent thalamocortical oscillations with a frequency of 1–5 Hz develop. The structure of these patterns in the cortex and thalamus is very similar to those observed on the electroencephalogram of a person during loss of consciousness caused by propofol [135].

Coma is a state of complete unresponsiveness, usually resulting from traumatic brain injury, toxic effects, or other factors. Patients in a coma do not respond to sensory stimulation, but they can retain elements of motor activity. [117]. EEGs in comatose patients depend on the degree of brain damage and often resemble the high-amplitude, low-frequency activity seen in patients under general anesthesia. General anesthesia is often viewed as a reversible pharmacological coma [117].

Refractory status epilepticus (RSE) is a life-threatening condition that can be treated with pharmacologically induced coma (PIC) achieved by continuous infusion of anesthetics [136]. Needless to say, this requires maintaining a balance between sufficient brain inactivation and minimizing the coma-related risks. The problem of measuring the degree of brain inactivation is particularly acute here. An empirical and well-established method of EEG analysis is commonly used [136,137]. On the basis of these algorithms closed-loop systems work quite effectively, which allow you to maintain an optimal level of PIC [138]. The findings of the animal study establish the feasibility of using a closed-loop anesthetic delivery systems to achieve in real time reliable and accurate control of the level of anesthesia [138]. In very promising study developed a robust closed-loop anesthesia delivery (CLAD) system to control the burst suppression probability (BSP) was developed [137]. In practice, the use of EEG-based algorithms for automated assessment of the patient's condition is much more difficult due to the high degree of interindividual differences [136].

Currently, an extensive study undertaken by the Curing Coma Campaign identified three fundamental gaps in DoC research: (1) lack of mechanistic integration between structural brain damage and abnormal brain function in DoC; (2) the absence of translational bridges between neural phenomena at the micro and macro levels; and (3) incomplete exploration of possible synergies between data-driven and theory-driven approaches [131]. Despite these problems, the accumulation of empirical data on the treatment of DoC is constantly growing [139].

The latest brain imaging data show that so called covert consciousness or cognitive motor dissociation (CMD) is present in 15–20% of patients with DoC [130,140]. In CMD patients, brain activity appears in response to stimulus presentation, but because they lack motor and cognitive functions, they are often thought to be in a vegetative state [140]. Some modern therapies are likely to be more effective in patients with CMD [140]. For example, DBS and ultrasound brain stimulation have shown encouraging results [139,141]. Pharmacological interventions in the treatment of DoC patients are aimed at increasing the level of brain arousal and restoring consciousness [142]. In recent years, amantadine and zolpidem have proved to be quite promising, and in some cases the use of these drugs has led to dramatic improvements, although the mechanism of their action remains unclear [142–145]. Amantadine is currently the only pharmacological drug that has been shown to be effective in restoring consciousness in a randomized controlled trial of patients with subacute traumatic DoC [140,146].

9. Divided mind and the separated hemispheres

Since its inception more than fifty years ago, split-brain research has continually found itself on the edge of the needle in the development of psychology and neuroscience. The term "split brain" was coined in the mid-20th century to describe the result of a callosotomy, a surgical incision of the corpus callosum to relieve severe epilepsy in patients. During this procedure, the corpus callosum - the bundle of nerve fibers that connects the left and right hemispheres of the brain - is cut to prevent the spread of epileptic activity between the two hemispheres (Fig. 1 B). This procedure eliminates almost all communication between the hemispheres, which leads to the so-called "division of the brain". Callosotomy is often successful in reducing, and in some cases, completely eliminating seizures. Many split-brain patients report that they feel normal after surgery and do not feel that their brain is "split".

Sufficiently extensive clinical material has shown that in most cases, callosotomy does not affect the functioning of patients, however, some differences were observed between patients with split-brain and normal subjects. This unique state, combined with the technique of independently presenting verbal and non-verbal stimuli to each hemisphere, continues to bring new insights into neuroscience. However, this area also continues to generate much debate.

Sperry and Gazzaniga found that split-brain patients can only respond to stimuli in the right visual field with the right hand and vice versa [147]. This was taken by many researchers as proof that the dissection of the corpus callosum causes each hemisphere to acquire its own consciousness.

A well-known patient received a callosotomy at the age of ten due to severe epileptic seizures [148]. This patient was tested using techniques that allowed verbal tests to be presented independently to the left and right hemispheres [148]. The results obtained suggested that the right hemisphere has a distinct consciousness that differs from that of the left hemisphere [148].

On the other hand, there is also evidence of unity of consciousness in split-brain patients [149]. Pinto's research shows that even if the two hemispheres are completely isolated from each other, the brain as a whole is still capable of producing only one conscious agent [149,150]. Pinto and his colleagues argue against the prevailing view in split-brain research: once the corpus callosum has split, visual information cannot be transmitted through other fibers from one hemisphere to the other [151,152]. Moreover, they suggest that the two hemispheres are not separately conscious after surgery [150]. According to this view, in split-brain patients, visual perception remains divided, but consciousness is not divided.

The authors call this concept "phenomenal splitting" combined with "unity of consciousness" [150–152]. This model asserts that the divided brain is a single consciousness that is influenced by two parallel, non-integrated flows of information [150]. To date, the question of the possibility of the existence of two consciousnesses in one individual has not been proven or refuted.

10. Technical aspects of assessing the level of consciousness

The neurobiological aspects of the problem of consciousness have direct application in clinical practice. The advances in resuscitation medicine make the request for a certain technical "consciousness meter" - a fairly reliable technique based on tracking physiological correlates of mental activity [12]. Such a technique still does not exist, and until

recently, the patient's level of consciousness was assessed on the basis of his ability to interact with society.

Indeed, observing purposeful behavior, adequate behavioral responses to sensory, primarily verbal, stimuli, it is easy to draw a conclusion about the consciousness of the studied subject. However, consciousness can be present even in the absence of any interaction with the outside world. Until now, there is no objective and reliable measure for assessing the level of consciousness.

An attempt to introduce a technically objective element into the assessment of the level of consciousness was undertaken in the current decade [153,154]. Transcranial magnetic stimulation (TMS) has been used in combination with electroencephalography to quantify the complexity of brain activity during wakefulness, sleep, pharmacological anesthesia, and during pathological loss of consciousness due to brain trauma [153]. It has been shown that the EEG response to transcranial magnetic stimulation of an awake person differs significantly from the response of a person in deep sleep, anesthesia, and vegetative state after severe traumatic brain injury [153]. This technique, called "zap and zip", has been tested in clinical practice [153].

The authors of the method proceeded from the fact that consciousness requires the coexistence of integration and storage of information in the thalamocortical network [153]. This network, as a system for processing and storing information, must have the following properties: 1. Have a large set of available states 2. Be integrated, that is, the network cannot be decomposed into a number of independent subsystems.

Measuring the amount of information in biological systems is a nontrivial and hardly solvable task in an absolute form, but it is quite possible to draw some general conclusions. For example, the extinction of consciousness during the transition from wakefulness to the phase of slow wave sleep should be associated either with a decrease in integration within the main thalamocortical complex. Or with the reduction of information (the repertoire of available states should be reduced). In simpler terms, the complexity of information processing should be high when consciousness is present and low when consciousness is lost.

The authors of this concept undertook an experimental study in which systematic measurement of cortical-cortical EEG in response to direct TMS was carried out, and the 60-channel EEG derivation made possible a certain functional mapping. The results obtained showed that EEG responses to TMS differ for patients in a state of wakefulness, sleep, "locked-in syndrome" (LIS), "minimally conscious state (MCS), coma", non-REM sleep, sedation with midazolam, anesthesia with xenon and propofol.

There is no doubt that consciousness is associated with thalamocortical neural networks, but it is unclear what contribution the neurons of different cortical layers and thalamic nuclei make [49]. To a large extent, animal experiments have clarified the situation. The neurons of the lateral thalamus and deep cortical layers were found to be the most sensitive to changes in the level of consciousness [49]. Electrical stimulation of neurons in the centrolateral nucleus of the thalamus in anesthetized macaques effectively restored the awake state of the nervous system, and this effect depended on the location of the electrode and the stimulation parameter [49]. Awakening from anesthesia or sleep occurred instantly, and also instantly disappeared when the stimulation was stopped [49]. This suggests that thalamocortical correlates of consciousness depend on the location of key neurons. It is likely that targeted deep stimulation of the lateral thalamus can be used to alleviate impairment of consciousness in clinical practice [49].

The medial nuclei of the thalamus are part of the higher order thalamus. Their neurons receive little sensory information, but they form extensive thalamocortical loops. A growing body of evidence supports a general role for the thalamus in controlling cortical information transmission and cognitive processing, and hence consciousness [49,155].

In the waking brain, with intact interneuronal connections, such monitoring of the electrical activity of various regions in response to TMS shows a high mathematical complexity of the response in most of the cortex. This answer can be described as a kind of dynamic pattern that is neither completely predictable nor completely random. The degree of its complexity is expressed by the perturbational complexity index (PCI) [153,156]. PCI can be calculated at different times and in different parts of the brain [156]. This mathematical technique is borrowed from computer science and forms the basis of the popular zip file compression algorithm. If the brain barely responds to magnetic stimulation - for example, because cortical activity is suppressed - PCI will be close to zero, and the maximum response complexity corresponds to PCI close to one. The higher the PCI, the more varied the brain's response to a magnetic impulse [24,153,156]. In practice, it is possible to measure the extent to which a signal recorded at one point in the skull makes it possible to predict changes in the signal at another point. In the presence of consciousness, this degree should be greater, and the temporal difference between activity at different points should be more variable, since in the presence of consciousness there are many active connections between areas of the brain. These connections are continuously increasing and weakening, which is reflected in the temporal difference [157].

Striking Similarities Between TMS-Induced EEG Responses during sleep, under anesthesia and in coma patients suggests common neural mechanisms. During slow wave sleep (non-REM), the lengthening of the response may be caused by an increased level of K^+ leakage caused by a decrease in cholinergic activity. In addition, inhalation anesthetics, including nitrous oxide and isoflurane, significantly potentiate the activity of the two-pore K^+ channels. On the other hand, increased inhibition in thalamocortical networks can play a decisive role in the case of the use of anesthetics that act primarily (propofol, etomidate) or exclusively (midazolam) on GABA receptors.

It seems highly probable that in such experiments imaging technologies can, to one degree or another, successfully replace multichannel EEG recording. When working with animal models, it can use VSDi or IOS, and when working with humans - fNIRS and similar technologies, called evoked response optical signal (EROS) [158,159].

The question of whether spontaneous EEG changes characterizing various states of consciousness are epiphenomena that have little functional significance, or whether they can be considered physiological correlates of consciousness, has been considered since the second half of the 20th century. This question is especially related to the low frequency rhythms (0.5–15 Hz) that define slow non-REM sleep [160]. Previously, this condition was considered associated with global inhibition of the cerebral cortex and subcortical structures [161–163]. It has been suggested that these low-frequency rhythms are associated with the influence of the reticular activating system. Further research in this area led to the concept of sleep as an active process directly related to the state of consciousness [162]. With further progress in the study of thalamocortical connections, data appeared on the specific contribution of these connections both to the regulation of states of consciousness and to the formation of physiological correlates of consciousness. Thus, conceptual parallels were formulated between Mountcastle's work on cortical columns and Edelman's concept of populations of neurons functioning as processors in a brain system based on the principles of selection rather than learning [8,164]. Earlier, a model was proposed in which the source of neuromodulation of the activated areas of the brain depends on the state of consciousness [165–167]. This concept was further developed in the works of the end of the last - the beginning of the current century [24].

From the point of view of neurobiology, there are two key characteristics of consciousness: (1) the state of consciousness (that is, wakefulness) and (2) the content of consciousness (that is, awareness) [168–170]. From the point of view of clinicians, more attention is paid to wakefulness than awareness, since disturbance of this state can lead to coma [171]. The ability to be awake and aware of the external world is a characteristic that is inextricably linked with consciousness. [169]. Consequently, the presence of consciousness is inseparable from wakefulness, the physiological opposite of which is a coma. However, the

state of consciousness differs both from sleep and from coma, and there are various forms of sleep and coma that are quite clearly differentiated according to physiological characteristics.

It is generally accepted that at least either the thalamus or the brain stem is damaged in a coma. In this case, the patient does not respond to sensory and painful stimuli and does not experience transitions from sleep to wakefulness and back. Moreover, damage to the lower part of the brainstem often necessitates mechanical ventilation. A vegetative state is different from a coma, although patients show no signs of perception or self-awareness. However, since brain stem functions remain unchanged, patients can breathe on their own and move from sleep to wakefulness. If a patient is in a coma for several weeks, which is rare, they are considered to be in a persistent vegetative state that may become permanent. Without consciousness, patients can remain in this state for decades.

While the borderline between coma and vegetative state is based on physiological indicators, then the border between minimum conscious state and vegetative state is more based on verbal and motor responses. Diagnostics, prognosis and therapy of such conditions is precisely the area where the question of consciousness, its neurological substrate and its physiological correlates is of the greatest practical importance.

At the same time, it is generally accepted that a neural network is an integral physical substrate of consciousness. Consequently, the continuously changing set of excitations of numerous elements of this network is what displays consciousness to the maximum extent. Even if the original point of view about the physical substrate turns out to be incomplete, studying the correlations between the neural network and consciousness will ultimately give us the most detailed description of consciousness. There is no doubt that this area in the near future will be at the forefront of neurobiological research using a wide arsenal of laboratory and clinical methods.

11. Conclusion

One of the main questions of neurobiology is the question of localization within the neural circuits of the brain, which is the carrier of consciousness. In other words, neuroscientists have long attempted to figure out where the individual's ability to experience internal and external sensations is localized in the brain. Probably, certain brain structures play a key role in these processes. The question of the structures of the brain that are critical for the functioning of consciousness is a particular case of a broader line of neurobiological research - the question of the localization of functions in the nervous system.

In recent years, extensive research has been carried out that has led to the identification of many candidates for neural correlates of consciousness (NCC). However, this colossal amount of work has not yet led to the creation of a generally accepted theory of consciousness.

The concept of sleep induction and regulation of consciousness by the caudal part of the brain stem was introduced in the middle of the last century [172]. Subsequently, the concept of reticular activating system (ARAS) as a reticular excitation system consisting of various interacting components grew out of this concept [119]. It is generally accepted that the impact of the ARAS on the cerebral cortex is responsible for achieving consciousness.

Among the anatomical structures of the brain that play a key role in the regulation of consciousness, several cortical and subcortical structures are usually distinguished. As for the cortical, the extensive clinical material gives grounds to single out the temporal, parietal and occipital regions as the "posterior hot zone", which, apparently, plays a direct role in clarifying the content of consciousness. Among the subcortical structures, the thalamus and claustrum are usually ascribed a key role. For the most part, clinical materials are based on the study of coma, vegetative state, state of minimal consciousness, delirium and various forms of epileptic seizures. All of these disturbances at the level of consciousness arise from disturbances affecting the subcortical excitation systems or corticothalamic networks, or both.

Previously, researchers had high hopes for studying patients after callosotomy, since it was assumed that their hemispheres could function completely independently. However, the last research disproves the concept that split-brain patients have split consciousness. The search for NCC at the cellular level also includes the hypothesis of the role of astrocytic syncytium in the regulation of consciousness. At the center of this hypothesis is the thesis of the glial-neuronal units that generate consciousness. However, at present, the possibility of testing such a model by biological methods is at least seriously limited.

Research in this area is greatly limited by the weakness of the methodological base. The creation of a methodology for assessing the level of consciousness, or, in other words, the creation of a "meter of consciousness" is an important issue for both neurobiological research and clinical practice [173]. This problem has not yet been radically resolved, but the achievements of recent decades, considered in this review, give rise to hope that it will be resolved in the foreseeable future.

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