The Visceral Theory of Sleep

Article *in* Neuroscience and Behavioral Physiology · May 2014

DOI: 10.1007/s11055-014-9928-z

1 author:

Ivan N Pigarev
Russian Academy of Sciences

Neuroscience and Behavioral Physiology, Vol. 44, No. 4, May, 2014

The Visceral Theory of Sleep

I. N. Pigarev

UDC 612.821.7

Translated from Zhurnal Vysshei Nervnoi Deyatel'nosti imeni I. P. Pavlova, Vol. 63, No. 1, pp. 86–104, January–February, 2013. Original article submitted May 24, 2012. Accepted October 19, 2012.

This review addresses studies seeking experimental confirmation of the author's visceral theory of sleep, along with independent investigations whose results are consistent with this hypothesis. The visceral hypothesis suggests that during sleep, the central nervous system, particularly the cerebral cortex, switches from analyzing exteroceptive information to analyzing signals arriving from interoceptors distributed throughout all the systems of the body. Substitution of cortical afferentation during sleep implies a simultaneous substitution in the targeting of efferent cortical information streams. In waking, these streams are directed to structures supporting behavior in the environment. During sleep, they switch to structures supporting the efficient operation of all the visceral systems. Analysis of the visceral hypothesis of sleep shows that many pathological states associated with the sleep–waking cycle can be explained in terms of impairments to the synchronicity of the switching of information streams in the cerebral cortex going from waking from sleep and vice versa.

Keywords: sleep, sleep disorders, waking, visceral systems, behavior, cortical activity.

Sleep deprivation is known to lead to impairments in the visceral domain; complete lack of sleep leads to death in experimental animals [12, 21, 41, 45]. Many visceral disorders, especially of the gastrointestinal tract, are seen in sleep disorders in humans [26, 29, 39]. However, it is likely that because of clear changes in brain electrical activity accompanying the transition from waking to sleep, and the fantastic patterns of dreams, most basic studies and hypotheses on the functional importance of sleep have been focused on different aspects of brain functions. Reviews of these studies have been presented in a number of publications [2, 16, 18]. It is widely recognized that during slow-wave sleep, cortical neurons show characteristic changes in activity, transferring to a regime of rare, periodic bursts with pauses, reflected in slow EEG waves. Animals choose quiet, dark places for sleep, with soft litter, to decrease the level of activation of exteroceptors. Neuronal mechanisms increasing thresholds on the sensory information conduction pathways to the brain [28, 41] are also activated, while conduction of signals from the cortical motor zones to the body muscles are inhibited, i.e., so-called sleep atonia [17].

However, the following question remains: how could all the changes in brain activity listed above, which accompany the transition from waking to sleep, be associated with visceral health? We might hope that an understanding of the nature of this connection would finally allow sleep to be converted from a semi-mysterious state to a number of understood physiological phenomena.

With the aim of combining the cerebral effects accompanying the transition from waking to sleep and the visceral consequences of sleep deprivation into a single system, we proposed a simple but at first glance fantastical hypothesis. The essence of this hypothesis is that during sleep, the same cortical neurons which during waking analyze exteroceptive information of different modalities switch to analyzing interoceptive information arriving from a variety of visceral systems.

Theoretical analysis of this suggestion showed that the ambit of this approach includes explanations for many phenomena which appear to have escaped explanation to date. It becoems clear why cortical neuron spike activity does not decrease during sleep, but can even increase, despite active

A. A. Kharkevich Institute of Problems in Information Transmission, Russian Academy of Sciences, Moscow; e-mail: pigarev@iitp.ru.

blockade of the conduction of exteroceptive signals to the cortex. In sleep, this activity is maintained by the visceral afferent stream. Slow-wave cortical activity recorded at defined stages of sleep may result from interference between the periodic activities of the various visceral systems (gastrointestinal tract peristalsis, respiration, signals from the heart). The reason why the conduction of signals from the motor cortex to spinal cord motoneurons is blocked is understandable: this activity during sleep is associated with analysis of visceral information and must be directed not to the system organizing body movements but to the corresponding visceral system.

However, while this is an attractive approach, there is a major obstacle which is difficult to overcome – the complexity of the organization of the brain, as has become increasingly apparent over the last century. It is now widely recognized that different cortical zones are specialized processors. Thus, there are few who doubt that the visual zones process signals arriving from the retina, and many investigators find it difficult to accept that these neurons could be involved in analyzing signals arriving, for example, from the gastrointestinal tract. However, we should note that computers are based on the operation of universal, rather than highly specialized, processors. There is no doubt that the construction of manmade computers is much simpler than the organization of one of the most powerful known information processing devices – the animal brain. It is difficult to accept that the "universal processors" principle was not used in creating living brains. This led to the desire to seek experimental confirmation of the nontrivial predictions of the visceral hypothesis of sleep.

Most studies performed with the aim of confirming this hypothesis have been published [6, 30, 32, 33, 35], while some are conference presentations [7, 8, 31, 34, 38], and articles with detailed descriptions will appear soon. The present report provides a brief presentation and systematization of experimental results obtained with the aim of confirming this hypothesis. Most attention has been focused on new concepts of the organization of information streams in the brain during sleep and waking on the basis of these experimental data. This structure of information streams is expected to lead to an understanding of the mechanisms of normal and pathological states linked to sleep.

1. EXPERIMENTAL CONFIRMATION OF THE VISCERAL HYPOTHESIS OF SLEEP

The visceral hypothesis of sleep is based on the suggestion that those neurons which analyze signals from exteroceptors during waking switch to analyzing interoceptive information on the state of sleep. A natural approach to experimental confirmation of this hypothesis is to compare the responses of individual areas of the cerebral cortex to extero- and interoceptive stimulation during sleep and waking.

1.1. Responses of the Sensory Zones of the Cerebral Cortex to Electrical and Magnetic Stimulation of the Digestive Organs during Sleep and Waking. The first series of chronic experiments recorded activity from individual neurons in the primary visual cortex in cats in conditions of painless fixation of the head. In waking, these neurons responded to visual stimulation and had classical receptive fields. When the animals went to sleep, which was monitored in terms of changes in the EEG pattern and eye movements, they underwent transient intraperitoneal electrical stimulation of the stomach or small intestine areas. Stimulation parameters were selected such that stimuli would not wake the sleeping animals. Our results showed that electrical stimulation did not wake the cat, but, conversely, converted sleep to a deeper phase. Most simple and complex cells in the primary visual cortex were found to start responding to intraperitoneal stimulation in the state of slow-wave sleep. These neurons ceased to respond to electrical stimulation immediately after waking the cats and returned to the production of visual responses [30]. Similar experiments were performed with neurons in somatosensory field 5 of the cat cerebral cortex using active movements of the forelimbs. In slow-wave sleep, these animals showed responses to electrical stimulation of the intestine and stomach zones. Figure 1 shows a comparison of the responses of neurons in the primary visual (*A*) and somatosensory (*B*) cortex to visceral stimulation. During sleep, neurons in the visual and somatosensory areas of the cortex can be seen to generate clear responses to electrical stimulation. The shapes of these responses were different and their latent periods in the somatosensory cortex were significantly shorter. Responses to visceral stimulation were absent during waking and REM sleep.

Similar experiments were performed on monkeys with chronic EEG recording of activity in the occipital area above the visual cortex. Intraperitoneal stimulation in monkeys also evoked clear EEG responses during the slow-wave sleep phase, which disappeared in REM sleep and on waking [33].

Cortical evoked responses to magnetic stimulation of the abdomen in monkeys, recorded over the occipital cortex, behaved similarly [32]. The reactions of neurons in extrastriate visual zone V4 in response to the same stimulation were somewhat different, and in most cases were inhibitory. Short-latency phasic inhibition was followed with delays of 10–20 sec by tonic excitation, clearly apparent in some neurons, and still evident in the averaged population responses of the neurons studied (Fig. 2). Similar stimulation during waking never evoked visible changes in the mean baseline activity of these neurons.

Intraperitoneal electrical stimulation was also used in chronic experiments in rabbits [31] using recording of evoked responses over the visual and somatosensory areas of the cortex. All three rabbits showed responses to stimulation applied during the slow-wave sleep phase. Visceral stimulation-evoked responses over the somatosensory and visual cortex had different patterns and numbers of compo-

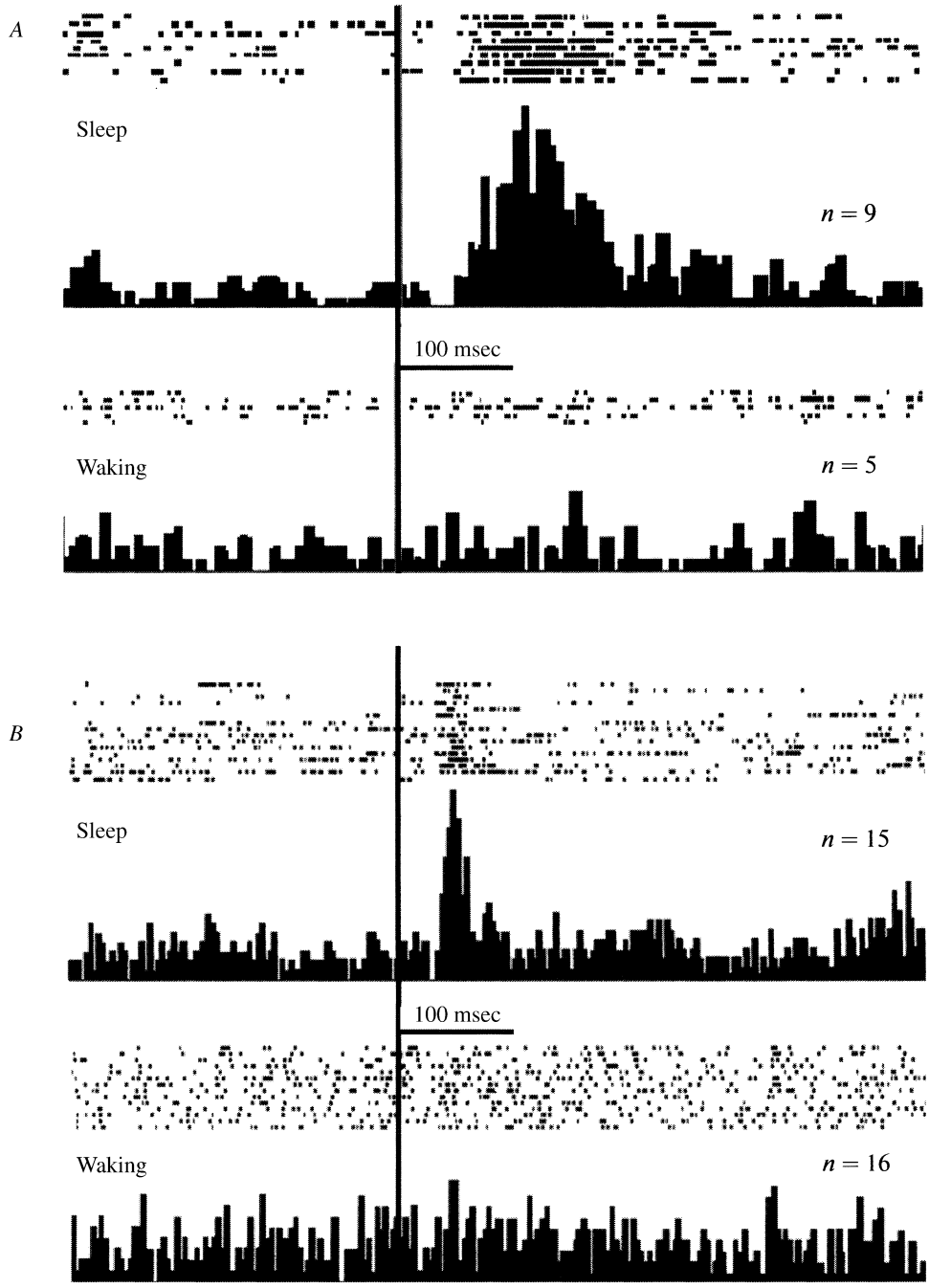

Fig. 1. Responses of visual zone V1 neurons (*A*) and somatosensory zone 5 neurons (*5*) in the cat cerebral cortex to electrical intraperitoneal stimulation during slow-wave sleep and waking. Vertical lines show the moment of stimulation. Raster plots for individual trials are shown above and averaged histograms are shown below; *n* is the number of trials.

nents (Fig. 3). The latent periods of responses, as in cats, were significantly shorter over the somatosensory cortex. During waking and REM sleep, there were no responses to visceral stimulation in either area of the cortex in rabbits.

1.2. Link between Neuron Activity in the Visual Areas of the Cortex and the Myoelectrical Activity of the Stomach and Duodenum during Sleep. It is abundantly clear that the experimental results described above have one weak point. The electrical stimulation used is not a natural element of physiological activity. Critics of the hypothesis have noted that these effects may also not reflect real natural mechanisms but are some kind of "nonspecific" effects.

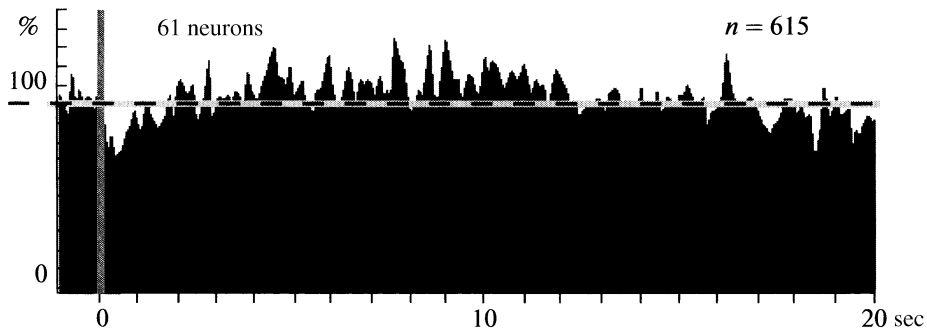

Fig. 2. Mean population responses of 61 neurons in visual zone V4 of the monkey cerebral cortex in the state of slow-wave sleep to magnetic stimulation of the abdomen. The vertical gray line shows the moment of stimulation. The horizontal dotted line shows the baseline activity level before stimulation, taken as 100%; *n* is the number of averaged stimuli.

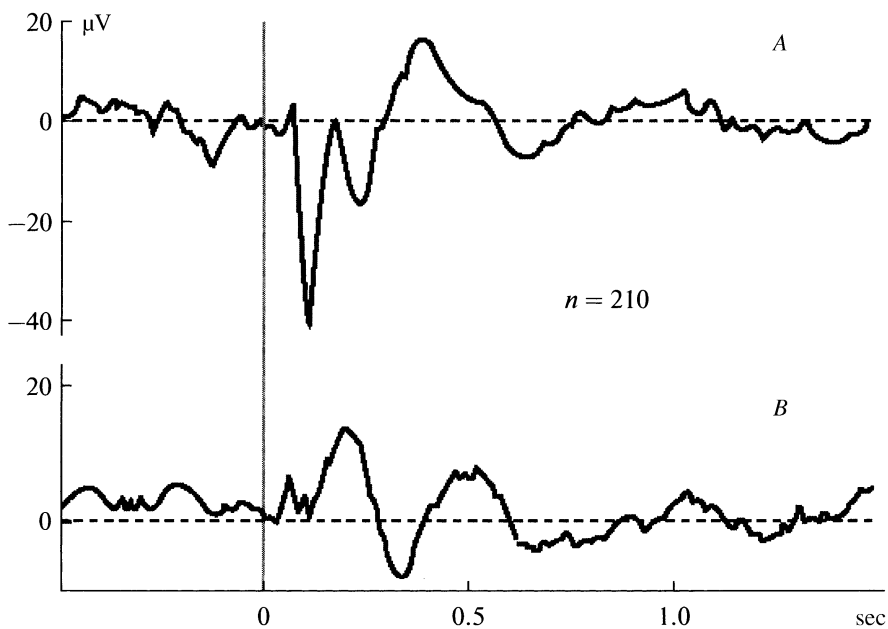

Fig. 3. Averaged evoked responses to intraperitoneal electrical stimulation during slow-wave sleep recorded over the somatosensory (*A*) and visual (*B*) areas of the cerebral cortex in a rabbit. The vertical line shows the moment of stimulation; *n* is the number of averaged trials.

We cannot completely accept this criticism, as a significant proportion of our knowledge of the functional organization of the nervous system has been obtained using electrical stimulation methods. However, demonstration of a link between the natural activity of the visceral system and the sensory zones of the cerebral cortex during sleep has become a significantly stronger argument in favor of the visceral hypothesis of sleep. These experiments were performed in collaboration with the late Professor V. A. Bagaev, director of the Laboratory for Corticovisceral Physiology, Pavlov Institute of Physiology and his colleague I. I. Busygina. Recording electrodes were implanted into the smooth muscle walls of the stomach and duodenum of cats, for recording of the natural myoelectrical activity of these organs in chronic experimental conditions. The natural activity of the gastrointestinal tract organs could be compared with the activity of cortical neurons and the overall EEG during waking and slow-wave and REM sleep. During uniform slow-wave sleep, the EEG was found to show episodes of transient desynchronization coinciding with so-called vagal myoelectrical complexes in the activity recorded from the stomach wall. These complexes, separated by intervals of 50–140 sec, reflect contractions of the stomach incompletely filled with food (Fig. 4).

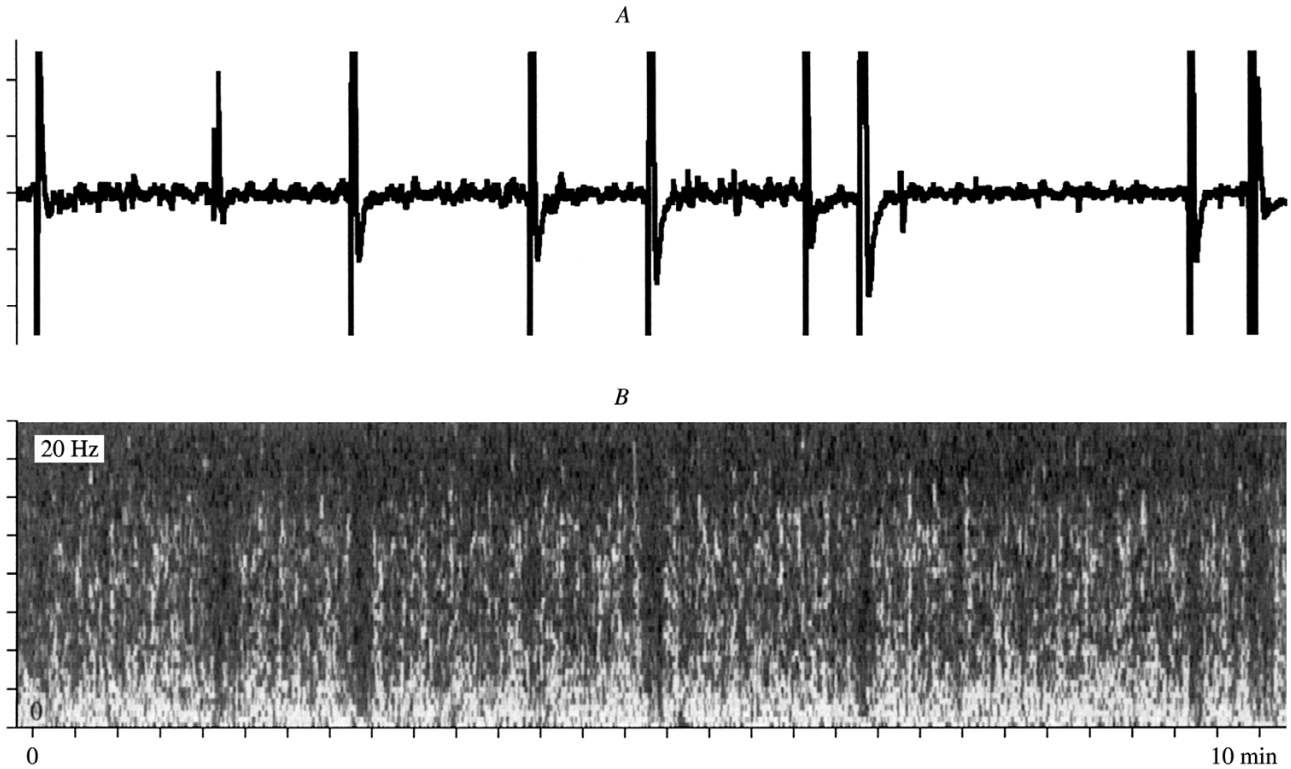

Fig. 4. Migrating myoelectrical complexes in the cat stomach (*A*) recorded simultaneously with the spectrogram of the cortical EEG during slow-wave sleep (*B*). Light parts on the spectrogram correspond to greater spectral power.

Analysis of the spike activity of 202 visual cortex neurons showed that 30% of neurons showed changes in spike frequency at particular periods of slow-wave sleep, which correlated with the rhythm of the myoelectrical activity of the duodenum. Furthermore, individual cortical neurons showed selectivity for rhythms of particular types (pure rhythms or rhythms with spike potentials). The spike activity of one third of cortical neurons showed a significant relationship with low-amplitude periodic changes in the recorded gastric activity. In waking, none of the study neurons displayed activity linked with gastric or intestinal myoelectrical activity [7, 34].

1.3. Relationship between the Structure of the Baseline Activity of Visual Cortex Neurons during Sleep and Changes in the Composition of the Intragastric Medium. These results led to the view that during sleep periods, the composition of the intragastric medium might be reflected both in the overall EEG and in the spike activity of individual cortical neurons. Confirmation of this hypothesis was sought by creating fistulas in cats for delivery of different substances directly into the gastric lumen during sleep. Warm water was given in the first experiments. This affected mechanoreceptors in the stomach walls and altered the acidity of the of the medium; this could alter the afferentation arriving from chemoreceptors. However, it would be surprising for a neutral substance – water – given into the stomach to have direct effects on the activity of neurons in the cortex. These experiments showed that administration of water into the stomach during the slow-wave sleep phase led to an immediate increase in the depth of the animal's sleep. The increase in the depth of sleep was primarily reflected in relaxation of the sleeping animal's posture – the eyes were tightly closed, and the animal was not woken by random sounds. Continuous slow-wave activity was recorded throughout periods with durations unusual for daytime sleep in cats. With time, the behavioral pattern deep sleep showed no change, though the overall EEG pattern did alter significantly, with appearance of a so-called intermediate sleep phase [22, 23]. Short periods of slow waves alternated with desynchronization reminiscent of the inclusions of REM sleep. This state could last up to 40 min. Analysis of the baseline activity of cortical neurons during periods of stable slow-wave activity after administration of water, as compared with analogous periods before administration, also showed significant rearrangements of spike activity structure in most neurons studied, while mean spike frequency was virtually unchanged [8].

The experiments described in sections 1.2 and 1.3 required special statistical analysis and large datasets, which are difficult to obtain during the relatively short peri-

ods of REM sleep. Thus, analysis is restricted to slow-wave sleep and waking.

We note that in the 1950s, cortical responses to stimulation of different visceral nerves were studied in the laboratory of Bykov and Chernigovskii; the results of these experiments and references to non-Russian studies have been reviewed in [1, 4, 10]. These data were obtained in acute experiments on anesthetized animals. However, when chronic experiments without anesthesia became possible, cortical responses to visceral stimulation could not be reproduced. Neurons in these cortical zones in conscious animals responded only to visual or somatosensory stimulation; they are now regarded as associative zones for the corresponding sensory modalities. Cortical responses to visceral stimulation came to be regarded as probably an artifact of anesthesia.

In natural conditions, without anesthesia, the cortical zones have been shown to establish connections with the visceral organs, though these connections are active only during sleep.

Our experiments have demonstrated conduction of signals from the digestive system organs to the cortex during slow-wave sleep. In REM sleep, conduction of these signals was again terminated. On the other hand, periods of REM sleep can be regarded as the deepest sleep, with the greatest threshold of arousal and the greatest level of muscular atonia. Within the framework of the visceral theory, we do not see these two states as being fundamentally different, but suggest that the cortex is occupied processing visceral information during both slow-wave sleep and REM sleep. So what defines the specific features of REM sleep, particularly in the disappearance of slow-wave activity from the EEG? It can be suggested that during a complete sleep cycle, including slow-wave and REM phases, the brain performs a sequential scan of all the body's life systems. This process starts with the digestive and respiratory organs and the heart, which have clearly rhythmic functions. Interference with the rhythmic activity of these systems also determines slow waves in the cortical EEG. Scanning then progresses to the organs without obvious rhythmicity, such as the liver, kidneys, vascular system, reproductive organs, muscles, and tendons. Finally, the brain itself is a body organ, whose physicochemical state also requires monitoring. The nonrhythmic stream of afferentation from these organs also leads to desynchronization of the EEG. Thus, sleep can be regarded as a single process associated with the involvement of the brain in analyzing all the body's visceral systems. The final section of this review will only address waking and sleep, without dividing these states into individual phases.

Periodic substitution of cortical afferentation during the sleep–waking cycle implies the need for modification of existing views as to the organization of the major information streams in the nervous system. The various aspects of this theme will be evaluated in the second part of the present work.

2. SWITCHING OF INFORMATION STREAMS IN THE NERVOUS SYSTEM DURING THE SLEEP–WAKING CYCLE

The main information streams in the central nervous system are shown schematically in Figs. 5–7. It is natural that regardless of functional state, all conducting pathways on the schemes remain in their places. However, these pathways are in some cases "open" for conducting signals. These active pathways are indicated in black. Blocked pathways, where signal conduction is terminated in certain situations, are indicated with light gray arrows. Structures blocking signal transmission are shown as circles, in which two parallel lines show the state of the gating elements. If the lines run parallel to the conducting pathways, then conduction is open; if they are perpendicular, then conduction is closed. Each gating element also has a second input, shown by the inclined thin line with a circle at the end. This is the input for the control signal which commands a given apparatus to transfer from the open state to the closed. In other words, this control input regulates the threshold for signal conduction. In the brain, the transition from the open state to the closed can occur gradually, extended over time. Structures with the properties of such gating elements are well known in neurophysiology. These include, for example, triadic synapses or synapses supporting presynaptic inhibition. The details of this are of no great interest here. The important point is that these mechanisms do in fact exist and that their use in the scheme is not just imagination.

This is of course an extremely simplified scheme. Its individual blocks are not associated with real brain structures. The single exception to this is the "cerebral cortex" block. This is to a considerable extent arbitrary. The cortex of the real brain is actually within this functional block. It is very likely that other brain structures may also be in this situation. We will now ask the reader not to focus on the simplification of the scheme, but on the main idea presented, which reflects the results of the experiments as presented.

Thus, Fig. 5, *A* shows the state of the conducting pathways of the nervous system in waking. Information on the environment or the state of the animal's body itself (the lower left corner of the scheme), transformed into nerve spikes by extero- and interoceptors, passes through open gating elements and is sent to the central "cerebral cortex" block for analysis. The results of this analysis are sent to the block driving behavior and motor activity. Output signals are transmitted in parallel, to the "Consciousness" block, activation of whose neurons leads to suppression of perception of the self and the environment. Many may feel justifiably confused. Traditionally, consciousness is linked with activity in the cerebral cortex. However, results from sleep studies have definitively demonstrated that this is not so. Consciousness is known to be active in waking and almost completely absent in sleep and under anesthesia. At the same time, the mean levels of activity in cortical neurons are not significantly different in these states. It appears to

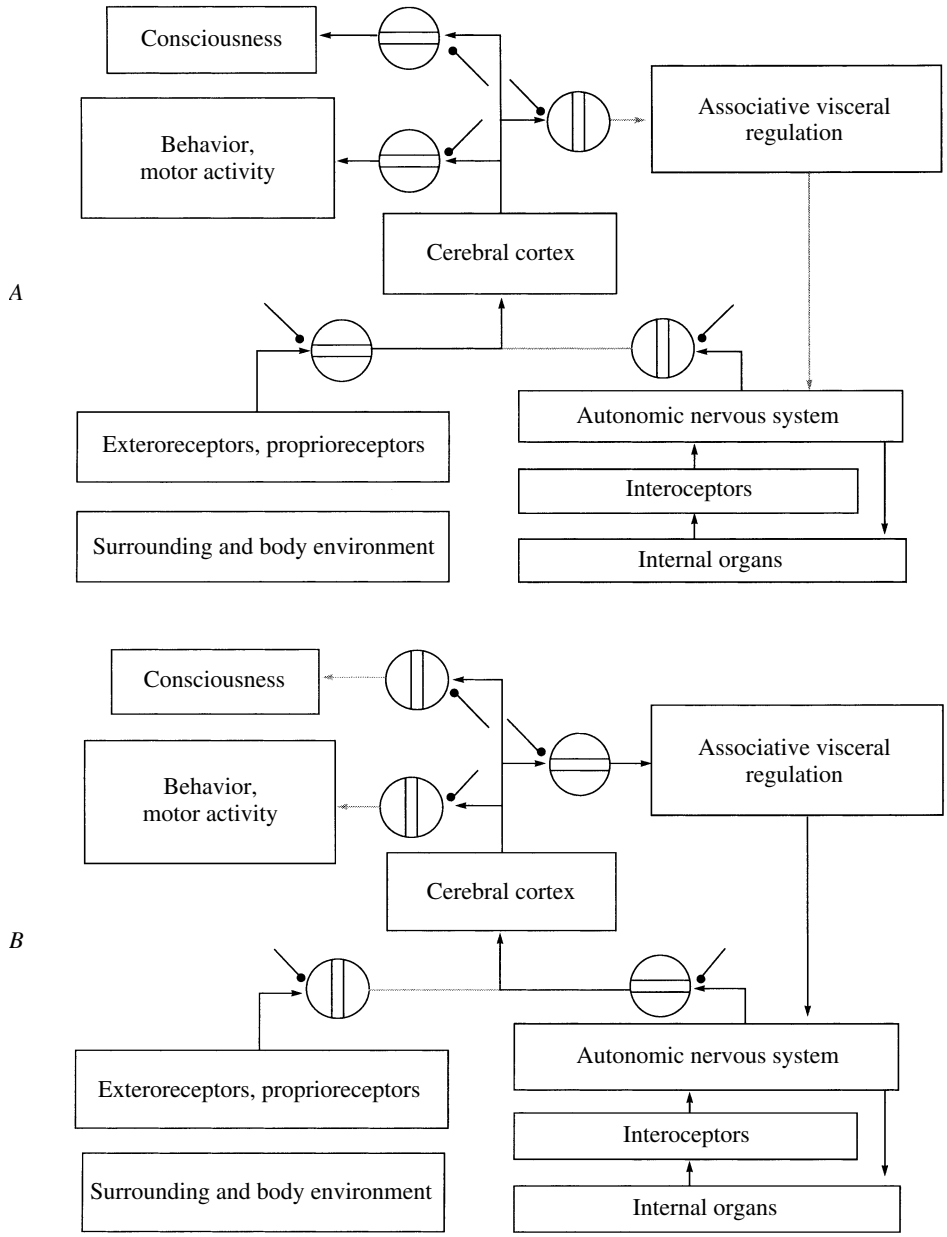

Fig. 5. Scheme showing information streams in animals' bodies in waking (*A*) and during sleep (*B*). Black and gray lines show active and blocked signal transmission channels, respectively. See text for explanation.

follow either that consciousness is not associated with the activity of cerebral neurons or that the structures associated with consciousness are in a different location. In the first of these, the question of the locations of structures associated with the processes of consciousness is entirely meaningless, at least at the current level of knowledge of the brain. The second possibility means that we can look for these structures. There is a simple experimental approach to answering this question. If consciousness is active during waking and inactive during sleep, the structures whose neurons behave in concert with this need to be found. However, this is not all. Structures which are candidates for the role of "substrates for higher brain functions" should have a wide circle of associative connections with the cortical zones leading the analysis of all types of exteroceptive and proprioceptive information. Such structures do in fact exist in the brain. The structures of the basal ganglia have associative connections with all cortical zones [42]. Furthermore, the excitatory cortical projections to neurons in the main nucleus of the basal ganglia, i.e., the caudate nucleus, are inactivated in the state of sleep. As a result, caudate nucleus neurons decrease their baseline activity during sleep, often to complete ces-

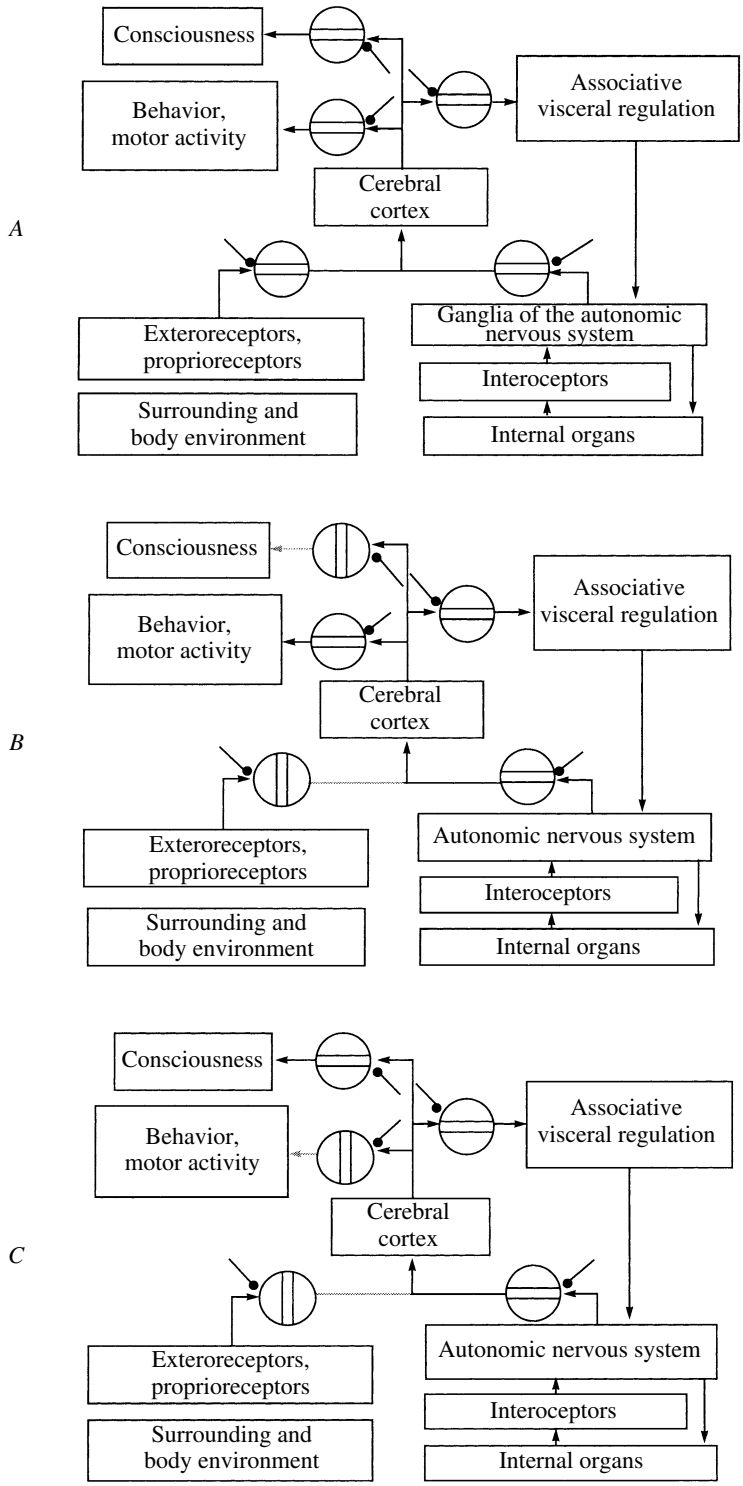

Fig. 6. Scheme showing proposed impairments of activation of information channels on the transition from waking to sleep leading to hypnagogic hallucinations (*A*), restless legs syndrome (*B*), and dreams (*C*).

sation [27, 37]. Large reductions in the level of baseline activity during sleep have also been demonstrated for another structure of the basal ganglia – the globus pallidus [19]. Positron emission tomography [11] in humans has shown that mean cortical activity does not change on the transition from waking to sleep, while the level of activation

of the basal ganglia decreases sharply. This is only a small proportion of the data casting doubt on the traditional views of the position of the cerebral cortex in the hierarchy of cerebral structures. However, detailed assessment of this question is the subject of a separate review. At this point we will simply note this structure for its connections and consider the extent to which it provides an explanation for a number of phenomena.

The right-hand side of the schemes presented here show the animal's body. During waking, information on the state of the internal organs, converted into nerve spikes by interoceptors, arrive in autonomic nervous system structures which at this time control the internal organs [5]. The segmental structure of the innervation of the internal organs does not support the transmission of information about some visceral systems to others. During waking, these systems effectively work under the local control of autonomic nervous system structures.

However, with time, local autonomic nervous system ganglia become unable to solve problems arising in the visceral domain independently. Interoceptors assessing the operating parameters of visceral organs start to send signals reflecting deviations in ongoing parameters from the genetically specified norms. These signals are evidence perceived by the animal as the feeling of tiredness, such that they start to look for a safe and comfortable place to sleep. The details of the process of the transition to sleep will be discussed below. We will now address the state of sleep.

During sleep, there is a radical change in information streams in the nervous system (Fig. 5, *B*). In the ideal case, after becoming able to sleep, all gating elements switch simultaneously to the opposite positions. During sleep, signal transmission from extero- and proprioceptors to the cerebral cortex is blocked. However, the same input channels to the cortex start to carry information on the state of the body's visceral systems.

In all probability, the main structure in which afferentation from extero- and proprioceptors is switched to interoception is the thalamus. This may also be the main functional load on the thalamus. Recent studies have shown that at the level of the lateral geniculate body, the main thalamic nucleus of the visual system, transmission of visual information to the cortex is blocked [28, 41]. The synapses of fibers running from the retina are known to make up one third of all synapses on relay nuclei in the lateral geniculate body. A second third consists of the synapses of collateral projections from the visual cortex, whose functions remain unknown. One third of the synapses is formed by fibers running from non-visual brain structures, particularly the pontine nuclei [24]. Activation of the pontine nuclei is known to induce characteristic bursts of neuron activity in the visual cortex during sleep. These are known as ponto-geniculo-occipital spikes [14]. The maximum numbers of these spikes are seen during REM sleep. The pontine nuclei lie on the paths of visceral information streams from the spinal cord. However, what activation of these spikes is associated with and what they reflect remain unclear.

In parallel with the shift in cortical afferentation from extero- to interoceptive, it is natural to expect changes in the efferent cortical projections. Output information streams from the cortex during sleep reflect the results of the cortical processing of visceral information and should not be addressed to structures associated with motor activity, behavior, or consciousness. On the scheme, the gating blocks on these pathways are closed during sleep. The fact that consciousness during sleep is detached from the surrounding world is well known to people on the basis of personal experience. In addition, we know that at the anatomical-physiological level, signal transmission from the cortex to spinal cord motoneurons is known to be blocked during sleep. This leads to relaxation of the body's muscles, which reaches a maximum during REM sleep [17]. It has already been noted above that the transmission of information from the cerebral cortex to structures of the basal ganglia – an important associative center of the brain – ceases during sleep.

At the same time, conduction via some new pathway from the cerebral cortex to structures associated with processing information from all the visceral systems must open up during sleep. The hypothalamus can be identified as a candidate for such an associative visceral regulatory system. However, the efficiency of cortical-hypothalamic connections during the sleep–waking cycle has not been studied.

When all visceral parameters are normalized as a result of the involvement of the cortex in visceral integration processes, the imperative to sleep is lifted, all gating elements switch to the opposite position, and the animal wakes.

We can thus see an ideal picture of the switching of information streams in the sleep–waking cycle. However, it should be noted that the main elements of this system are devices blocking conduction via one pathway or another – not electric relays, but chemical synapses. Their operating efficiency may depend on large numbers of conditions external to the synapse. Furthermore, the spike response of the postsynaptic neuron is determined not only by the efficiency of the control synapse, but also by the current threshold of the neuron itself. Neuron thresholds are known to depend on their previous activity. If a neuron has recently been highly active, its excitation threshold will decrease and, conversely, neurons which have been silent in the recent past will have increased thresholds. When analyzing this scheme, it must be borne in mind that real switching of gating elements in some, generally pathological, conditions may be extended over a significant period of time. The resulting nonsynchronicity of the switching of information streams may involve displacement of exteroceptive and interoceptive information at the input to the cerebral cortex. The output signals of the cerebral cortex may also be addressed to incorrect targets. The next section will consider some likely consequences of such addressing errors.

3. NONSYNCHRONIZATION OF THE SWITCHING OF INFORMATION STREAMS IN THE BRAIN AS A LIKELY CAUSE OF PATHOLOGICAL PHENOMENA ASSOCIATED WITH THE SLEEP–WAKING CYCLE

3.1. Hypnagogic Hallucinations. Hypnagogic hallucinations constitute a common but quite harmless pathology of the process of transition from waking to sleep [43], These hallucinations appear before falling asleep, at low illumination levels, and appear as various generally moving beings (large "beetles"). This may occur when the pressure of sleep opens the pathways for visceral afferentation to the cortex, though the conduction of visual information to the cortex is not blocked and the connection of the cortex with the behavior and consciousness blocks are retained (Fig. 6, *A*). An important condition is a low level of illumination. People continue to perceive the context around them. However, the intensity of visual afferentation is decreased in these conditions. The intensity of the opened visceral signals stream is comparable with that of the visual stream. Arriving in the consciousness block, bursts of spike activity from the visceral inputs can induce excitation of visual gestalts superimposed on the real visual scene which is still being perceived. It is also easy to explain the movement which is usually reported in these hallucinations. The onset of sleep has been shown to start in the visual cortex in the extrastriate zones [36]. This is how a movement analyzed in visual zone V5 appears. On going to sleep, visceral information will primarily be directed here, while the output signals of this zone, passing through the still open gating to the consciousness block, will naturally evoke the feeling of movement. This may also explain the hallucinatory movements not associated with the appearance of additional objects, which occurs in conditions of increasing pressure to sleep. This produces the sensation, for example, of wavelike movements of the floor or deformation of particular objects.

Turning on the light also eliminates hypnagogic hallucinations because of the increasing intensity of signals from the real visual scene on whose background "visceral" components become subthreshold, and also because of switching of the visceral inputs to the cortex due to the arousing action of bright light.

3.2. Restless Legs Syndrome. The transition from waking to sleep also produces another, more unpleasant, situation, reflected in Fig. 6, *B*. In this situation, the cortical input to the consciousness block switches normally, while switching of the output to structures associated with motor activity, is delayed. When sleep develops, activation in the motor areas of the cortex induced by what are now visceral inputs is not blocked but is switched to spinal cord motoneurons. Excitation of motoneurons leads to sudden limb movements, which interrupts the developing sleep. This provides a model of restless legs syndrome, which occurs quite commonly [20]. There are now medications which are quite effective in preventing the occurrence of such movements during sleep. When sleep deepens, conduction of visceral signals to the spinal cord is switched, such that there are no further problems sleeping. "Extraneous" support is all that is needed during the transition period.

Eye movements during sleep constitute a special case of this situation. Eye movements in the REM phase of sleep are well known. However, the eyes show smooth drift over very large angles from the central position during slow-wave sleep too, in some cases exceeding the normal amplitude of movements in waking [30]. As these movements are slow, they are often not seen on the electrooculogram. However, as information on eyeball position in the orbits does not reach consciousness even during waking and the eyes have an essentially perfectly spherical shape, their movements beneath the closed lids do not interfere with the onset of sleep. There are therefore no special mechanisms for the active suppression of these movements during sleep.

3.3. Dreams. Dreams can be regarded as the commonest and from time to time even comical "pathology" of sleep. A possible cause of dreams is outlined in Fig. 6, *C*. The gating on the pathway from the cortex to the consciousness block is not completely switched during sleep. The strongest output signals reflecting the results of the processing of visceral information also erroneously enter the consciousness block. However, the visceral systems are not represented in our consciousness. Thus, for consciousness, these signals are generally merely noise. Noise can excite those neurons which have the lowest response thresholds, i.e., those neurons which were operating the most actively during the preceding waking period. This phenomenon is reminiscent of the stochastic resonance principle, when addition of noise to a subthreshold signal has the result that it starts to be perceived in a threshold system. This mechanism provides a physiological basis for psychoanalytical approaches based on analysis of reports of dreams. In fact, the subject of dreams will in the first instance be items occupying the greatest proportion of consciousness during waking.

It can also be suggested that at particular time points, the spatial distribution of excitation running from the cortex and reflecting the results of analysis of visceral information is similar to the spatial profile of the gestalts of real objects formed during waking. As a result, the image formed by associative connections in the consciousness systems triggers the development of fantastic plots.

Dreams are probably are manifestations of the transitional period from waking to sleep or vice versa, when the gating on the input to the consciousness block is not yet completely closed or remains slightly ajar. Full closure probably occurs on transition to the stationary sleep state. Thus, this situation, although pathological, is harmless. However, less pleasant cases do occur, when the gating to the input to the consciousness block does not switch even after long periods of time. This produces the situation of persistent nocturnal nightmares which interrupt normal sleep. There are also cases of real and profound pathology.

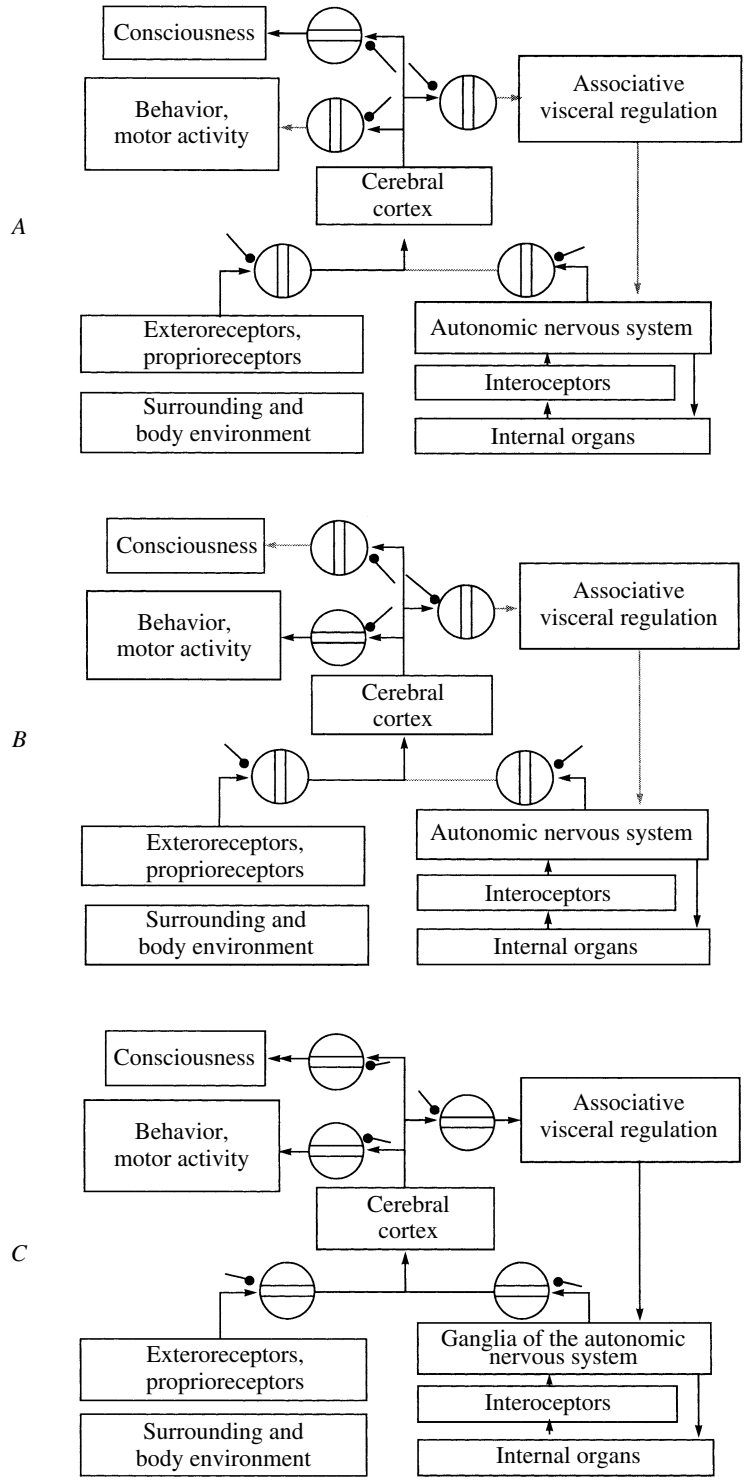

Fig. 7. Scheme showing d impairments of activation of information channels on the transition from sleep to waking leading to sleep paralysis (*A*),somnambulism (*B*), and visceral hallucinations (*C*).

It should be noted that the old legend that dreams are exclusively associated with the REM phase of sleep has not received support. People also describe dreams on waking from slow-wave sleep [15, 44]. As dreams can only be evaluated in terms of post-waking descriptions, it is very likely that they also appear during these transition periods.

However, the question of the time of occurrence of dreams cannot in principle be solved experimentally, and is thus not a question for science. This position is given a grounding in strict logic in Malcolm's book *The State of Sleep* [3].

Previous sections have assessed the possible consequences of impairments to the synchronicity of the switching of information streams during the transition from waking to sleep. We will now consider pathological situations occurring during the transition from deep sleep to waking.

3.4. Sleep Paralysis. A not uncommon phenomenon occurring on the transition from sleep to waking is so-called sleep paralysis. People normally wake up, have appropriate perception of the environment and their own body, but for some period of time (from several seconds to several minutes) are unable to perform any kind of voluntary movement. The likely cause of this phenomenon is simple, and is shown in the scheme in Fig. 7, *A*. There is a delay in the release of the blockade of the transmission line sending motor commands from the cortex to the behavior and motor activity block. This is the point at which consciousness has already been restored but the motor control system remains asleep.

3.5. Somnambulism. Directly opposite cases are also encountered, in which the pathway from the cortex to the behavior and motor activity block opens and the pathway to the consciousness block remains in the blocked state (Fig. 7, *B*). This is the phenomenon of somnambulism – which is quite common, especially in children. People get up from bed at night and walk trajectories of different lengths. The eyes are open while sleepwalking, people do not collide with obstacles, and their movements are well coordinated. At the end of the trajectory, the person often falls asleep again, and on waking has no memory of getting to the new location [25]. Somnambulism is a further argument supporting the conclusion that the consciousness block is separate from the cerebral cortex and structures programming body movements. It is difficult to say anything definite about connections between the visceral systems and the cerebral cortex during sleepwalking. It is entirely probable that the trigger for these episodes may consist of as yet undiscovered visceral information streams, inducing dreams en route to waking, which in turn provoke subsequent sleepwalking.

3.6. Visceral Hallucinations. The term "visceral hallucinations" has not, as far as we know, been used previously, and the existence of this phenomenon can be regarded as a prediction of the visceral theory of sleep. In the section on hypnagogic hallucinations we discussed the effects of perception evoked by mixed extero- and interoceptive information at the input to the cortex, a situation which can occur in the transitional periods between sleep and waking when some conducting pathways have yet to close completely and others have not completely opened. As a result, interoceptive signals are projected into real life situations and are perceived as hallucinations. In theory, these phenomena could also occur in the opposite direction. By analogy, we term these visceral hallucinations (Fig. 7, *C*). It can be suggested that under the pressure to sleep, the pathways connecting the visceral systems with the cerebral cortex start to open. However, rapid transition to sleep may not be possible under the pressure of the circumstances. The connection between the cortex and the exteroceptive inputs and outputs for consciousness and motor activity remain open. The results of analysis of exteroceptive signals may reach the visceral integration block and be assessed there as cortical signals arising from analysis of the visceral inputs. Control of the visceral systems will now occur by means of these "hallucinatory" signals, which cannot produce any kind of positive effect in the visceral domain.

The pernicious visceral consequences of acute stress probably operate by this mechanism. The same mechanism may also explain the occurrence of the visceral components (nausea, vomiting) of motion sickness. Rhythmic rocking and constantly reduced gravity, as in space flight, produce sharp changes in the afferent spike stream arriving from mechanoreceptors in the walls of the gastrointestinal tract organs. The urgent need for analysis of the causes of these unusual changes in afferentation generates pressure to go to sleep. The pressure of sleep exposes the cortical output to structures for visceral analysis and, possibly the input of visceral information to the cortex. However, the high levels of behavioral activity during this time prevent the transition to sleep and the cortex remains connected with the powerful exteroceptive input stream. This powerful exteroceptive signal stream arrives at the visceral information analysis blocks, where it exacerbates the unusual nature of the afferentation from the organs of the gastrointestinal tract. The natural response to this will be urgent clearing of the stomach to remove the sources of the "alarm" signals, i.e., vomiting.

As far as we know, the mechanism of these "visceral hallucinations" has not previously been addressed. It seems very likely that in a sleep-deprived society, the consequences of visceral hallucinations, which are pernicious for the visceral systems, may be large. Interference with extero- and interoceptive information on the pathway to the cerebral cortex and at the outputs from the cortex may be the cause of many psychosomatic illnesses.

4. THE SLEEP-TRIGGERING MECHANISM

The schemes presented in this report provide an understanding that the basic elements supporting the transition from waking to sleep and vice versa are gating elements opening or closing the conduction of extero- and interoceptive information in different directions. Changes in the states of these gates occur in response to control commands arriving from the sleep–waking centers. As these commands are simple and uniform in type for all the neurons to which they are addressed, it would appear that this involves a limited number of neurons with branched projections over the whole surface of the cerebral cortex. These are the properties of neurons in a number of identified "centers" regu-

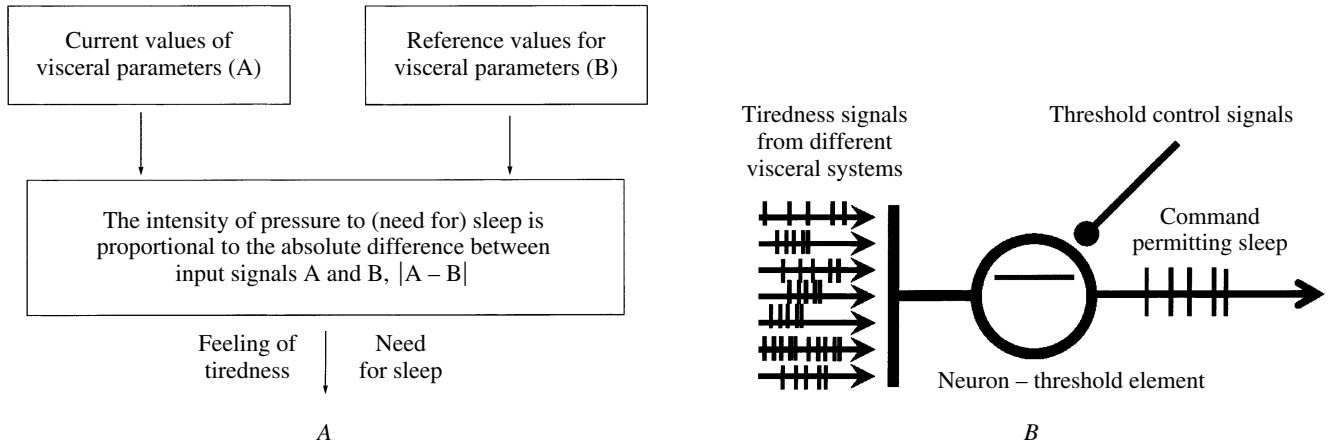

Fig. 8. Schemes explaining the first stage of the triggering of sleep, occurring independently in each visceral system and leading to pressure to sleep (*A*), and the second stage, permitting sleep (*B*). See text for explanation.

lating the transition from waking to sleep and vice versa [18]. It is now important to establish how the commands for these transitions are formed.

The first stage in this pathway must be performed in all visceral systems. The task of this level is to make a simple comparison between current values of parameters determining the ability of this system to function with their genetically determined standard values. This process is shown schematically in Fig. 8, *A*. The block determining the need for (or pressure to) sleep simply subtracts the standard values from the current visceral parameter values. The absolute size of this difference will also determine the level of tiredness or pressure to sleep. All visceral systems must have these elements for comparison. At the second stage of taking the decision to go to sleep (Fig. 8, *B*), tiredness signals from different visceral systems are summed in a threshold block designated on the schemes as "Neuron – threshold element." The output signal of the threshold element will also be the "Command to sleep," which converts the gating elements from the "state for waking" to the "state for sleep." This scheme shows that the final output signal from the threshold element is entirely determined by the summed "tiredness" signals. These signals determine only what we have repeatedly called the pressure to sleep. The second important element determining the command to trigger sleep is the threshold command signal. This signal accumulates information on the current state of the body as an element of the environment and on the state of the environment itself, reflecting the current assessment of the body's potential to go to sleep. In a safe environment with no other competing needs, the threshold will be low and the transition to sleep can occur with the first signs of tiredness. In conditions of sleep deprivation, there can be a significant increase in the threshold, such that even strong pressure to sleep may be insufficient to overcome it.

However, this does not restrict the sleep control system. There is at least one more important element determining the transition between sleep and waking – the circadian rhythm. It can be suggested that in some situations, the circadian rhythm operates as a signal directly controlled by some of the gating elements described above.

Over recent decades, sleep physiologists have discussed the model of sleep regulation proposed by Borbély [13]. This model is presented in Borbély's book *The Secrets of Sleep*, which has been translated into Russian and is available free of charge at www.sleep.ru. In this model, the transition from waking to sleep is determined by the interaction between two processes: the homeostatic and the circadian. The homeostatic process maintains a particular amount of sleep per day. The visceral theory of sleep gives the "homeostatic process" physiological content. In fact, here is a need to maintain homeostasis – not the abstract state of sleep, but the functional state of all the body's visceral systems, which occurs during sleep as a result of switching of the cerebral cortex to processing information regarding the state of these systems.

CONCLUSIONS

In summary, we can say that over the last 15 years, the visceral theory of sleep has received much direct support in experimental studies, which is unlikely to have happened without this theory to drive experimental work. In addition, the theory has proposed real physiological mechanisms for basic phenomena associated with the sleep–waking cycle, as well as novel mechanisms which may underlie psychosomatic illnesses. Numerous studies demonstrating relationships between sleep disorders and the occurrence of pathological deviations in all visceral systems in the human body [9] may represent an indirect argument supporting the visceral theory of sleep.

The author would like to thank M. L. Pigareva, V. B. Dorokhov, and E. M. Rutskova for critical comments.

This study was supported by the Russian Foundation for Basic Research (Grant No. 10-04-00844).

REFERENCES

1. K. M. Bykov, *Selected Works*, Vol. 2, *The Cerebral Cortex and the Internal Organs* [in Russian], Gos. Izd. Med. Lit., Moscow (1954).
2. V. M. Koval'zon, *Basic Somnology* [in Russian], Binom. Lab. Znanii, Moscow (2011).
3. N. Malcolm, *The State of Sleep* [Russian translation], IG Progress-Kultura, Moscow (1993).
4. S. S. Musyashchikova and V. N. Chernigovskii, *Cortical and Subcortical Representations of the Visceral Systems* [in Russian], Nauka, Leningrad (1973).
5. A. D. Nozdrachev, *Autonomic Nervous System Physiology* [in Russian], Meditsina, Leningrad (1983).
6. I. N. Pigarev, *Brain and Sleep. Science in Russia* [in Russian] (2005), Vol. 1, pp. 61–65.
7. I. N. Pigarev, V. A. Bagaev, I. I. Busygina, and N. G. Bibikov, "The state of sleep – the period of cortical control of visceral functions. Mechanisms of regulation of the body's physiological systems during adaptation to the environment," in: *Proc. All-Russ. Conf. Celebr. 85th Anniv. Found. Pavlov Institute of Physiological, Russian Academy of Sciences*, St. Petersburg, Dec. 7–9, 2010, Institute of Physiology, Russian Academy of Sciences (2010).
8. I. N. Pigarev, A. V. Bagaev, I. I. Busygina, et al., "Gastric and duodenal activity is reflected in cortical neuron discharges during sleep," *Ros. Fiziol. Zh.*, **90**, No. 8, 196 (2004).
9. I. N. Pigarev and M. L. Pigareva, "Sleep and the control of visceral functions," *Ros. Fiziol. Zh.*, **97**, No. 4, 374–387 (2011).
10. V. N. Chernigovskii, *Interoceptors* [in Russian], Medgiz, Moscow (1960).
11. T. J. Balkin, A. R. Braun, N. J. Wesensten, et al., "The process of awakening: a PET study of regional brain activity patterns mediating the re-establishment of alertness and consciousness," *Brain*, **125**, 2308–2319 (2002).
12. R. P. Barf, P. Meerlo, and A. J. W. Scheurink, "Chronic sleep disturbance impairs glucose homeostasis in rats," *Int. J. Endocrinol.* (2010), doi: 10.1155/2010/819414.
13. A. A. Borbély, "A two-process model of sleep regulation," *Hum. Neurobiol.*, **1**, 195–204 (1982).
14. D. C. Brooks and E. Bizzi, "Brain stem electrical activity during deep sleep," *Arch. Ital. Biol.*, **101**, 648–665 (1963).
15. C. Cavallero, P. Cicogna, V. Natale, et al., "Slow wave sleep dreaming," *Sleep*, **15**, No. 6, 562–566 (1992).
16. C. Cirelli and G. Tononi, "Is sleep essential?" *PLoS Biol.*, **6**, No. 8, e216.doi:10.1371/journal.pbio.0060216.
17. M. H. Chase, "Confirmation of the consensus that glycinergic postsynaptic inhibition is responsible for the atonia of REM sleep," *Sleep*, **31**, No. 11, 1487–1491 (2008).
18. S. Datta and R. R. MacLean, "Neurobiological mechanisms for the regulation of mammalian sleep-wake behavior. Reinterpretation of historical evidence and inclusion of contemporary cellular and molecular evidence," *Neurosci. Biobehav. Res.*, **31**, No. 5, 775–824 (2007).
19. L. Detary, G. Juhasz, and T. Kukorelly, "Neuronal firing in the pallidal region: firing pattern during a sleep-wakefulness cycle," *EEG Clin. Neurophysiol.*, **67**, No. 2, 159–167 (1987).
20. C. J. Farley, "Restless legs syndrome," *New Eng. J. Med.*, **348**, No. 21, 2103–2109 (2003).
21. C. A. Everson and A. Szabo, "Recurrent restriction of sleep and inadequate recuperation induce both adaptive changes and pathological outcomes," *Am. J. Physiol. Regul. Integr. Comp. Physiol.*, **297**, R1430–R1440 (2009).
22. C. Gottesman, "The transition from slow-wave sleep to paradoxical sleep: evolving facts and concepts of the neurophysiological processes underlying the intermediate stage of sleep," *Neurosci. Biobehav. Rev.*, **20**, No. 3, 367–387 (1996).
23. C. Gottesman, G. Gandolfo, C. Arnaud, and P. Gauthier, "The intermediate stage and paradoxical sleep in the rat: influence of three generations of hypnotics," *Eur. J. Neurosci.*, **10**, 409–414 (1998).
24. H. C. Hughes and W. H. Mullikin, "Brainstem afferents to the lateral geniculate nucleus of the cat," *Exp. Brain Res.*, **54**, No. 2, 253–258 (1984).
25. N. B. Kavey, J. Whyte, S. R. Resor, Jr., and S. Gidro-Frank, "Somnambulism in adults," *Neurology*, **40**, 749–752 (1990).
26. L. Keefer, E. J. Stepanski, Z. Ranjbaran, et al., "An initial report of sleep disturbance in inactive inflammatory bowel disease," *J. Clin. Sleep Med.*, **2**, 409–416 (2006).
27. A. A. Loshkarev, E. I. Rodionova, E. V. Levichkina, and I. N. Pigarev, "Inactivation of the excitatory cortical projections to caudate nucleus during sleep," *J. Sleep Res.*, **13**, Supplement 1, 614 (2004).
28. L. M. Mukhametov and G. Rizzolatti, "The responses of lateral geniculate neurons to flashes of light during the sleep–waking cycle," *Arch. Ital. Biol.*, **108**, No. 2, 325–347(1970).
29. W. C. Orr, "Esophageal function during sleep: Another danger in the night," *Sleep Med.*, **8**, 105–106 (2007).
30. I. N. Pigarev, "Neurons of visual cortex respond to visceral stimulation during slow wave sleep," *Neuroscience*, **62**, No. 4, 1237–1243 (1994).
31. I. N. Pigarev, I. Almirall, J. Marimon, and M. L. Pigareva, "Dynamic pattern of the viscero-cortical projections during sleep. Study in New Zealand rabbits," *J. Sleep Res.*, **13**, Suppl. 1, 574 (2004).
32. I. N. Pigarev, I. Almirall, and M. L. Pigareva, "Cortical evoked responses to magnetic stimulation of macaque's abdominal wall in sleep-wake cycle," *Acta Neurobiol. Exp.*, **68**, No. 1, 91–96 (2008).
33. I. N. Pigarev, I. Almirall, M. L. Pigareva, et al., "Visceral signals reach visual cortex during slow wave sleep. Study in monkeys," *Acta Neurobiol. Exp.*, **66**, No. 1, 69–73 (2006).
34. I. N. Pigarev, V. A. Bagaev, I. I. Busygina, et al., "Causal link between myoelectrical intestinal activity and cortical neuronal firing in sleep," *J. Sleep Res.*, **13**, Supplement 1, 575 (2004).
35. I. N. Pigarev, G. O. Fedorov, E. V. Levichkina, et al., "Visually triggered K-complexes. A study in New Zealand rabbits," *Exp. Brain Res.*, **210**, 131–142 (2011).
36. I. N. Pigarev, H.-C. Nothdurft, and S. Kastner, "Evidence for asynchronous development of sleep in cortical areas," *Neuroreport*, **8**, No. 11, 2557–2560 (1997).
37. I. N. Pigarev and E. I. Rodionova, "Neuronal activity in caudate nucleus in the sleep–waking cycle," *J. Sleep Res.*, **24A**, 54 (1995).
38. I. N. Pigarev, M. L. Pigareva, L. P. Filaretova, and E. M. Rutzkova, "Disturbances of normal sleep pattern as a possible reason of stress-induced visceral dysfunction," *J. Sleep Res.*, **17**, S1, 262 (2008).
39. S. Ranjbaran, L. Keefer, E. Stepanski, et al., "The relevance of sleep abnormalities to chronic inflammatory conditions," *Inflamm. Res.*, **56**, 51–57(2007).
40. A. Rechtshaffen and B. M. Bergmann, "Sleep deprivation in the rat: An update of the 1989 paper," *Sleep*, **25**, No. 1, 18–24 (2002).
41. W. Singer, "Control of thalamic transmission by corticofugal and ascending reticular pathways in the visual system," *Physiol. Rev.*, **57**, No. 3, 386–416(1977).
42. A. Stocco, C. Lebiere, and J. R. Anderson, "Conditional routing of information to the cortex: A model of the basal ganglia's role in cognitive coordination," *Psychol. Rev.*, **117**, No. 2, 541–574 (2010).
43. C. Sturzenegger and C. L. Bassetti, "The clinical spectrum of narcolepsy with cataplexy: a reappraisal," *J. Sleep Res.*, **13**, 395–406 (2004).
44. H. Suzuki, M. Uchiyama, H. Tagaya, et al., "Dreaming during non-rapid eye movement sleep in the absence of prior rapid eye movement sleep," *Sleep*, **27**, No. 8, 1486–1490 (2004).
45. Y. Tang, F. Preuss, F. W. Turek, et al., "Sleep deprivation worsens inflammation and delays recovery in a mouse model of colitis," *Sleep Med.*, **10**, No. 6, 597–603 (2009).