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REVIEWS

Cerebral Information Processing during Sleep: Evolutionary and Ecological Approaches

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Abstract—Based on the analysis of extensive clinical, psychophysiological and experimental data, the author comes to the conclusion that the widespread idea of the cerebral information processing during sleep related to previous wakefulness and necessary for the formation of long-term memory and other cognitive resources of the brain is inapplicable. This hypothesis is poorly consistent with a range of data regarding both slow wave (non-REM) and paradoxical (REM) sleep. The state of the cerebral cortex in non-REM sleep is more adequately described by the classical term "diffuse cortical inhibition." As for REM sleep, here, too, the very intensive work of the brain does not play any adaptive role (at least for an adult organism)—information is processed, figuratively speaking, "idle." All the vast experimental and clinical material accumulated in recent decades speaks in favor of the "ecological" hypothesis, which considers sleep as periods of "adaptive inactivity" of the body, increasing its survival in a hostile environment. The function of sleep consists in a radical restructuring of all waking reflexes for the normal course of such periods.

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At present, it is generally accepted to compare the brain with an information machine—analog or analog–digital [1]. It is clear what kind of information the central nervous tissue processes in a wakeful state; these are afferent signals coming from the sense organs in real time (on-line), called sensory inflow. These signals are studied by the physiology of sensory systems, and much is known about their processing. The formation of the so-called "acquired" behavior is also well studied: new skills are formed during training due to associative links and other characteristics of sensory systems. The analysis of sensory input occurs in close interaction with "endogenous" signals associated with innate behavioral programs. However, how this hereditary encoding of behavior occurs and how it is transferred to neural memory is still unknown. Anyway, it is clear that all this information is processed by the brain of humans and other mammals in wakefulness both on-line and off-line.

However, a natural question arises: how does the brain process information during sleep, which occupies a significant part of the time of the day (in humans—33%, in most mammals and birds—50% or more), and what is the meaning of this processing for the body and behavior? Three options are logically possible: information in sleep is processed either off-line, or on-line, or not processed at all. It is known that the sleep of mammals and birds consists of two different states, non-REM and REM sleep, which are as different

from each other as they are from wakefulness [2]. Therefore, we will consider all possible answers to the question posed, separately for non-REM and REM sleep.

CEREBRAL INFORMATION PROCESSING DURING NON-REM SLEEP OFF LINE

In the course of sleep there is some kind of processing of the information acquired in the previous wakefulness; this idea arose with the advent of the first computing devices. Until now, this idea is universally accepted; it is expressed in all books and textbooks on neuro- and psychophysiology, without exception, and in most review articles on the problem of sleep It is believed that the brain is also capable of processing incoming sensory signals during sleep, since "complete isolation from the external environment would represent a huge evolutionary risk." A number of studies, especially those that have appeared in the last decade, specify the limited possibility of some forms of learning, in particular, the development of classical conditioning in sleep in certain cases [3]. It is assumed that this is the main (or one of the main), vital function of sleep, responsible for its restorative properties in relation to the body as a whole.

However, already in the first studies of the neuronal activity of experimental animals in the natural sleep–wake cycle, this hypothesis was called into question. As is well known, during the transition from wakeful state to non-REM sleep, the "individual" character of neocortical pyramidal neuron discharges is replaced by a "choral" burst–pause pattern [4, 5]. In this case, there is a sharp change in lengthy extreme hyperpolarization/ deep inhibition (down state) of cells (up to –75 mV, in some cases –90 mV) and extreme depolarization (upstate, –61 mV); the latter accompanied by exaltation, powerful bursts of action potentials. Such pattern of neuronal activity generating rhythms of sleep spindles and delta waves in the total EEG is unfavorable for the reception, processing and transmission of information by neurons. Based on his work with Giacomo Rizzolatti at the University of Parma and other studies by Italian authors carried out in the late 1960s and early 1970s by extracellular recording of the activity of single neurons in non-anesthetized cats, Lev Mukhametov[1] wrote in 1977: "...against the background of the 'burst–pause' pattern, a barrier appears at the thalamic level for the normal flow of information into the thalamus-cortex system. For the same reasons, the dissemination of information through the thalamus between its various nuclei and through various fields of the cerebral cortex should be difficult. Consequently, during non-REM sleep at the cortico-thalamic level, information processing is significantly hampered. On this basis, it can be assumed that during non-REM sleep (unlike REM sleep), the coordinated implementation of complex mental functions is impossible" [7].

Later the results of the studies of the Italian school were fully confirmed and developed by Igor Timofeev and other researchers of the laboratory of Mircea Steriade (Laval, Quebec, Canada) [4, 5], as well as in laboratories in the USA and other countries [8]. However, not a single researcher "dared" to draw such a radical conclusion as the one above. All of them remained within the framework of the traditional paradigm regarding "cerebral processing in non-REM sleep of information received in the previous wakefulness, necessary for the formation of long-term memory", etc. This function of deep slow-wave sleep (stage 3 in humans, or "delta sleep") has been considered and is considered to be vitally important, since this stage is the first to recover after a more or less long period of sleep deprivation or limitation of the sleep duration, both in humans and in experimental animals.

Such behavior of the neurons of the thalamocortical complex, the substratum of the higher mental functions in humans, is, in fact, the very "diffused cortical inhibition", predicted by Ivan P. Pavlov with ingenious intuition a hundred years ago. It would seem that modern ideas about the "activity of the sleeping brain" forever "buried" this Pavlovian hypothesis. However, the thing is that earlier such a state was misunderstood as the "turning off" of neurons from their active work. This also takes place, but only in cold-blooded vertebrates at rest, when the animal's body cools down [9]. In mammals, these

[1] About the life of L.M. Mukhametov and his contribution to science, see [6].

neurons never "go silent", but only restructure their work, radically changing the pattern of discharges in non-REM sleep. At the same time, inhibitory processes rapidly spread throughout the cortex, mediated by the activity of long-axonal neurons of the "sleep centers" in the ventrolateral and median preoptic areas, the basal forebrain and the reticular thalamic nucleus, as well as by the activity of short-axonal interneurons of the cortex itself. All these cells secrete GABA, the main inhibitory mediator of the brain, as well as inhibitory neuropeptides—galanin, melanin-concentrating hormone, etc. In addition, in the areas where inhibitory neurons accumulate, the concentration of adenosine increases, the main modulator of the transition of the body from wake to a sleepy state, mediated by receptors A2A [10]. The state of the neocortex (more precisely, the thalamo-cortical complex) arising in non-REM (but, of course, not REM) sleep is quite adequately described by the term "diffuse cortical inhibition."

In addition to the results of direct neuronal activity studies, over time, more and more indirect data accumulate—clinical, psychophysiological and experimental, which does not fit into the framework of traditional ideas about "cerebral information processing" as a vital, indispensable function of sleep. Yuri Panchin called such hypothesis the modern somnology based upon, as "Indispensable Sleep Scenario (ISS)" [11]. Thus, a unique case of many months of agripnia (complete lack of sleep), reported by Michel Jouvet, entered the history of medicine. A patient with a rare disease called Morvan's chorea was under round-the-clock continuous polysomnographic monitoring for four months in 1974, until his death (which followed, despite the best efforts of doctors to treat him). This patient retained the capacity for normal mental activity including completely intact the short-term and long-term memories, as well as the ability to learn and concentrate. "Our patient's wakefulness system showed [...] exceptional lack of mental fatigue for several months in the absence of an active sleep system designed to inhibit it [...]. A person deprived of sleep and dreams for four months (only a few minutes of nocturnal hallucinations remain), is able to read newspapers during the day, make plans, play cards and win, and at the same time lie in the dark on the bed all night without sleep!.. It turns out that slow-wave and paradoxical sleep is not necessary for life..." [12].

Subsequently, several more similar clinical cases of complete loss of total sleep were described [13, 14]. In addition, there are polysomnographically confirmed data (including those cited by Jouvet himself in the aforementioned book) about "short sleep" people who do not experience either increased daytime sleepiness or any special psychological or physiological difficulties [15, 16]. It has been shown that some genome variations (within the framework of population polymorphism) greatly reduce human sleep without any side effects. Several human mutations strongly affecting this phenotype have been recently identified by direct genetic screening in families with so-called natural short sleep (FNSS). Members of such families sleep 4–6 hours per night (ie, 3–4 cycles instead of normal 5–6), feel well rested and do not show obvious disturbances that usually occur with chronic sleep deprivation. One of these mutations is associated with the clock genes [17], another with the β1-adrenergic receptor [18], and the third with the type 1 neuropeptide S receptor [19]. All of these genes code for different families of proteins with no apparent functional overlap or participation in common known signaling pathways. The experimental introduction of such mutations into the genome of mice also led to a reduction in the daily percentage of non-REM sleep. The "short-sleeping" strains of laboratory mice obtained as a result of such genetic engineering manipulations also exist without visible behavioral disorders and a life span reduction.

Although "sleepless" animals have not been found in the wild, the enormous variation in the average daily duration of natural sleep (from two hours in elephants [20] to 20 hours in some bat species [21]) is also poorly compatible with the "cerebral information processing" hypothesis. As noted in numerous review and theoretical works on this topic, all mammals with the ecological advantage of "safe sleep" always use it to the fullest; they have a high total daily sleep duration (12 hours and more). And those mammals that, due to their ecology, are victims of predators, or

eat low-calorie plant food and are forced to spend most of the day time searching for it, feeding and chewing, are content with the minimum duration of daily sleep (2–4 hours) [22]. Thus, a high correlation of sleep duration with the lifestyle, ecology of a given species, and not at all with its "cognitive level" (which would be expected based on the "cerebral information processing" hypothesis) is found: humans and some of the most "intelligent" mammals, for example, elephants are among the least sleeping species.

Less than 7% (40 minutes) of the duration of daily sleep that is noted on land (7 hours) was registered by EEG in a great frigatebird during a many-day "non-stop" flight. However, upon coming back to the nest, no pronounced rebound of sleep was observed [23]. In other words, the need for sleep practically disappeared during the flight and returned again upon landing. Some birds significantly reduce the daily duration of sleep during the mating season. As a result, males who sleep less are mating with more females. Judging by the frequency of occurrence of birds and their survival, the reduction in sleep duration during the breeding season does not have negative consequences for their physiological state [24]. All these facts are also poorly consistent with the above hypothesis of "cerebral information processing" in sleep.

The last years, the idea of the presence of mental activity in non-REM sleep, supposedly "indistinguishable" from REM dreams, has become more and more widespread [25]. Such views are associated, in our opinion, with too confiding, uncritical attitude of researchers and doctors to the so-called "reports" of subjects and patients, and in fact to their irresponsible reasoning. Supporters of such idea somehow lose sight of the simple consideration that, if this were true, it would mean a complete break between the EEG and mental processes: not only can various mental processes occur on the same EEG background (which is well known), but also the same mental processes—on a completely different EEG background! In fact, mental activity in non-REM sleep, if it does not disappear completely, is of a different nature, and its main difference from REM dreams is the absence of pronounced emotionality. The state of consciousness in non-REM sleep should be referred to by other terms: hypnagogic hallucinations (in stage 1), "thought-like" activity (in stages 2 and 3). In general, the most "reliable" psychological studies—interviews of patients and healthy subjects directly upon awakening from different stages of sleep—undoubtedly testify in favor of the above assumption by Lev Mukhametov (half a century ago!), that during non-REM sleep (in contrast to REM sleep) it is impossible (or at least significantly difficult) the coordinated implementation of complex mental functions.

CEREBRAL INFORMATION PROCESSING DURING NON-REM SLEEP ON LINE

A few years ago, Ivan Nikolaevich Pigarev[2] published an original hypothesis on the function of non-REM sleep based on his own experiments using extracellular recording of single neurons in non-anesthetized cats. In according to his hypothesis, during non-REM sleep the brain cortex continues to process information in real time, not extero-, but interoceptive. This "visceral hypothesis of sleep", which he called a theory, suggests that during sleep (obviously, non-REM sleep), the central nervous system, in particular the cerebral cortex, switches from the analysis of exteroceptive information to the analysis of signals coming from interoreceptors distributed in all systems of living organism [27]. When cortical afferentation changes during sleep, the directions of efferent flows from the cerebral cortex also change, switching from structures that ensure behavior in the environment to structures that ensure the effective operation of all visceral systems. Ivan Nikolaevich believed that many pathological conditions associated with the sleep–wake cycle can be explained by violations of the synchronism of switching information flows to and from the cerebral cortex during the transition from wakefulness to sleep and vice versa.

It should be said that Pigarev's hypothesis has become widely known, subjected to serious criticism more than once (it was pointed out, in particular, that a response to a stimulus does not

[2] About the life of I.N. Pigarev and his contribution to science, see [26].

necessarily mean that the cell analyzes "information"), but over the past years has not received either independent confirmation or refutation. It fundamentally contradicts the "encephalocentric" idea of the famous Harvard somnologist Allen Hobson, who once proclaimed: "Sleep is of the brain, by the brain and for the brain" [28], but also poorly consistent with the idea of Lev Mukhametov, and with all the other counterarguments above regarding the hypothesis of "cerebral information processing" during sleep (it does not matter which one: extero- or interoceptive). It has been suggested that low-threshold calcium channels localized on the neuronal soma could be regarded as the cellular basis of Pigarev's hypothesis. Indeed, the hyperpolarization changes in the membrane potential which predominate in non-REM sleep are the optimal conditions for their opening [5]. However, such processes should be equally suitable for processing exteroceptive signals. However, no experimental confirmations, either for the former or the latter ones, have yet been received.

Let us summarize all these disparate arguments for information processing by the brain in non-REM sleep, namely:

A. Neurophysiological Argument

(1) the transition of the pyramidal neurons of the thalamo-cortical complex during non-REM sleep into the pattern of "choral" burst–pause activity hardly using for cerebral information processing;

B. Clinical Argument

(2) case report—a description of a Morvan's disease patient, who did not sleep a minute for 4 months (under continuous EEG control) without any need for sleep and any cognitive impairment;

B. Genetic arguments

(3) discovery of gene population polymorphisms leading to a significant shortening of human nighttime sleep without any signs of daytime sleepiness or any cognitive impairment;

(4) creation of genetically modified mouse strains with significantly shortened 24-hour sleep, showing neither behavioral disturbances nor reduced lifespan;

B. Ecological arguments

(5) discovery of a daily sleep duration connection with the ecology of a given species, and not with its "intelligence";

(6) temporary disappearance of the need for sleep due to ecology in some bird species.

Basing upon these arguments, one can draw a preliminary conclusion that no cerebral information processing occurs in non-REM sleep. Rather, the thalamo-cortical system is in a mode of functional isolation, a kind of "idling" activity in this state. This conclusion can be regarded in favor of the classical hypothesis of "diffuse cortical inhibition" that occurs during non-REM sleep.

CEREBRAL INFORMATION PROCESSING IN REM SLEEP OFF LINE

REM sleep is a special state of the body of warm-blooded animals, characterized by extremely high activation of the brain against the background of "turning off" sensory systems and deep inhibition of the spinal cord [2]. There is no doubt that the brain processes information very intensively during REM sleep; numerous evidences have been obtained both at the neuronal and metabolic levels [29]. Subjects' reports of emotionally rich, vivid dreams also support cerebral information processing at the psychological level. Radical differences between the two sleep states are well known. Nevertheless, there is important characteristic common to both of them: the functional isolation of the forebrain from both afferent and efferent streams. The latter is studied quite well in REM sleep; that is associated with such pathologies as narcolepsy with cataplexy [30], REM sleep behavior disorders (RBD) [31] and restless legs syndrome (RLS) [32]. At the same time the blockade of sensory inputs in REM sleep remains almost unexplored. However, it is not a big mistake to assume that information in REM sleep is processed primarily (if not exclusively) off-line. This information, images retrieved from memory by a sleeping, but highly active brain, are bizarrely deformed and combined, being realized at the mental level in the form of a special kind of altered consciousness, brightly emotionally colored dreams, which, apparently, are poorly remembered. The neuroscanning show a significant decrease in blood flow

and metabolism in the dorsolateral prefrontal cortex, which in neuropsychology is considered to be an area involved in the process of working memory formation [33].

As is known, REM sleep predominates in early ontogeny; thus, in a newborn, half of the total sleep time (8 hours out of 16) is occupied by the so-called activated sleep, which is considered the precursor of adult REM sleep. As the brain tissue matures, the daily duration of REM sleep decreases and, upon the cessation of neurogenesis, at the age of 5–9 years, reaches adult values (1.5–2 h per night) [34]. As Francis Crick and Graeme Mitchison [35] wrote, if one tries to explain the function of REM sleep from the developmental biology point of view (as a necessary element of cell proliferation, the process of maturation and formation of the nervous system), it remains unclear why this sleep state is preserved in adult humans and animals (in some species, rather significant percentage), when the mitoses of nerve cells have long been completed? If one explains the function of REM sleep from a psychological point of view (for the realization of dreams, search activity, emotional balance, the formation of long-term memory, the translation of genetic information into neurological memory, etc), then it is not clear why this state dominates precisely in early ontogeny (when there is no explicit consciousness, behavior, or memory yet) and sharply decreases with the maturation of "higher mental functions"?

Unexpected for the authors of all these hypotheses were reports that among us, it turns out, there are people with a complete (or almost complete) lack of REM sleep, living perfectly and successfully working for many years. And they don't have any memory impairment or cognitive deficits. First of all, we are talking about a well-known patient of the Israeli somnologist Peretz Lavie [36]. This man, aged 20, received severe shrapnel wound to the head, metal fragments were lodged in his brainstem, thalamus and cerebellum. After the injury, he was in coma for 10 days, remained in critical condition for another two weeks, but then gradually recovered, completed his education, became a professional lawyer, an amateur artist, and even earned money by compiling crossword puzzles in the city newspaper. When he was 33, his relatives took him to the sleep laboratory at the Technion University in Haifa. The reason was his nightly cries in sleep, similar to those sometimes made by children (pavor nocturnus). Polysomnographic recordings in this patient were performed in the laboratory for 8 nights. He slept little, an average of 4.5 hours (i.e. 3 normal cycles), but the cyclicity itself was broken and, to the surprise of the doctors, he did not have REM episodes at all in the first 3 nights. Then such episodes began to appear at the end of the entire sleep period, in the morning, but they were very short: on average, one episode per night lasting 6 minutes (instead of the usual 4–6 episodes with a total duration of 1.5–2 hours). This patient did not show any deterioration in intelligence and memory. Despite his disability, he worked and led a normal life.

After 35 years, this man was found and again subjected to a thorough polysomnographic examination in combination with psychological testing [37]. Now he was 68 years old. In the lab, he averaged 6 hours of sleep per night (i.e. 4 cycles), and REM sleep averaged 16 minutes (0 to 3 short episodes at the end of sleep). Testing revealed completely normal scores on all scales (from intermediate to higher level), including memory, intelligence and cognitive abilities. Thus, a person who lived his entire adult life (almost) without REM sleep showed no impairment that could be attributed to its absence. Peretz Lavie stated that "he is probably the most normal person I know and one of the most successful" [38].

Of course, such cases are extremely rare—usually destructions in the rostral part of the brain stem are incompatible with life. However, a couple of other case reports have been published that occasionally, people with limited lesions in this area and complete (or almost complete) loss of REM sleep can gradually recover and lead a normal life, and in no case was there any cognitive impairment [39]. Another piece of evidence for the possibility of "living without REM sleep" comes from psychopharmacology. It is well known that most antidepressant drugs (tricyclic drugs and selective serotonin reuptake inhibitors—SSRIs) profoundly suppress REM sleep. MAO inhibitors are especially effective in this regard, which can almost completely suppress

REM sleep for months and years. And SSRIs have the ability to suppress REM sleep without subsequent impact, that is, to eliminate the very need for REM sleep. Millions of patients around the world have taken and are taking these drugs. No cases of cognitive impairment have been reported; instead, there is some evidence that MAO inhibitors and SSRIs even improve memory! In contrast, the latest generation of benzodiazepines, which are used as hypnotics and do not significantly affect the duration and distribution of REM sleep, have a pronounced detrimental effect on memory due to the effect of these drugs on the GABA signaling system [40].

Recently, a special role of certain muscarinic receptors in the regulation of REM sleep has been discovered by Japanese authors. The authors of the articles [41, 42] found two out of five existing muscarinic receptors, gene knockout of each of which significantly disrupts the normal course of REM sleep in mice: knockout of the Chrm3 gene causes fragmentation of REM sleep, and of the Chrm1 gene, a reduction in its duration. But the most surprising result awaited the authors when they produced a double-knockout for both genes. In these mice, REM sleep disappeared altogether. Unfortunately, nothing on the phenotyping of these mice is reported, except for the structure of the sleep–wake cycle, but noted their "unexpected vitality despite almost absent REM sleep". Yamada et al. wonder if REM sleep really plays such an important role in the body, including learning and memory processes that is attributed to it?—and refer to the above-mentioned well-known hypotheses.

The animal world demonstrates great variability in the daily percentage of REM sleep in adults, even greater than that of non-REM sleep. As already mentioned, many representatives of evolutionarily ancient mammalian species exhibit a high percentage of REM sleep (>20%). In addition, adult mammals with "safe" sleeping conditions (e.g., deep burrows) show a high percentage of REM sleep, usually having relatively short gestation periods and giving birth to altricial cubs with a high percentage of activated sleep (e.g., carnivores and many rodents). On the contrary, mammals that sleep in the wild without much shelter, directly on the surface of the earth (ungulates, guinea pigs, etc.), have a long gestation period and give birth to mature (precocial) cubs with an initially low percentage of REM sleep, demonstrate a low percentage of this sleep in adulthood too (<10% of total sleep) [43].

Similar regularities were noted in birds [24]. Although, in general, their percentage of REM sleep is much lower than that of mammals, and its episodes are shorter, nevertheless, evolutionary older species of birds (Palaeognathae), for example, ostriches, show a higher percentage of REM sleep and longer its episodes than more evolutionarily young species (Neognathae) [44]. There are species of birds that hatch from eggs immature, and there are those that are more mature. The former, like mammals, have a higher initial level of REM sleep and, accordingly, its higher level in the adult state than the latter [45].

Finally, researchers have always been struck by the fact that in many species of birds and small mammals, episodes of REM sleep are so short (no more than a few seconds) that no biochemical reaction can be completed in such a period, and it is very difficult to imagine "cerebral information processing" and "memory formation" by the brain in such short portions.

A strong blow to the supporters of the hypothesis of "cerebral processing of meaningful information and memory consolidation in REM sleep" was caused by the discovery of animals that do not have this sleep state at all. First, we are talking about echidna, a special species of monotreme mammals that separated from the main evolutionary branch at its very inception. Despite a special study by three different groups of researchers, the presence of REM sleep in this animal remains questionable [45]. Secondly, of course, we are talking about such a widely known fact as the lack of REM sleep in dolphins [46, 47]. Under the leadership of Lev Mukhametov and Oleg Lyamin, two generations of researchers at the Utrish marine station of the Severtsov Institute studied sleep–wakefulness in four different species of toothed whales, including the Amazonian river dolphin. Significant efforts have been made to identify any, even fragmentary, episodes of REM sleep in these animals. These efforts included long-term video recordings combined with cable-free polysomnographic recording using implanted

intracranial electrodes and miniature autonomic recorders attached to the body of animals in free-swimming conditions in the experimental pool. However, during this entire 40-year period, not a single such episode could be detected [48, 49].

Even more surprising results were obtained by the same group of researchers in a polysomnographic study of the sleep–wake cycle of eared seals (fur seals and sea lions) [49, 50]. These animals spend the breeding season on rookeries, and most of the year, chasing schools of fish, they spend in the ocean, where they are forced to sleep in the water. Scientists simulated this situation by building a platform in the pool, which can be above or below the water surface, depending on its level. And it turned out that when a fur seal sleeps in water, its sleep structure is similar to that of a dolphin: non-REM sleep is unihemispheric, and REM sleep disappears almost completely (by 99%). And when a fur seal sleeps on a platform, the structure of his sleep is the same as that of terrestrial mammals: non-REM sleep is of the usual bihemispheric nature, REM sleep is well expressed and its percentage is high. When, after a long period of stay in the water, the fur seal goes to the platform, REM sleep is restored, but in a normal proportion, the phenomenon of REM sleep rebound does not occur. In other words, when a fur seal sleeps in the water, the very need for REM sleep disappears, which reappears when he goes to land. All these facts cannot be reconciled with the hypothesis of "cerebral processing of vital information" in REM sleep, but they are very well combined with environmental factors and the animal's lifestyle.

Let's summarize all these disparate data on information processing by the brain in REM sleep off line:

A. Psychological argument

(1) poor dream memory retention, as evidenced by a decrease in the BOLD signal in the dorsolateral prefrontal cortex during REM sleep;

B. Clinical argument

(2) case report: a description of a quite professionally successful person who has lived his entire adult life (almost) without REM sleep, without the slightest impairment of cognitive abilities;

B. The genetic argument

(3) the creation of a genetically modified mouse strain without REM sleep that do not show any obvious disturbances in behavior or physiological processes;

D. The ontogenetic argument

(4) the maximum percentage of activated/REM sleep in the late prenatal/early postnatal stages of individual development;

E. Pharmacological Argument

(5) the presence in the world of millions of patients who are constantly taking antidepressants that suppress REM sleep to varying degrees, up to its complete disappearance, and their memory not only safe, but, in some cases, even improves;

E. Environmental arguments

(6) correlation of the REM sleep percentage with evolutionary and ecological, rather than some other (for example, "cognitive") characteristics of a given species of mammals and birds;

(7) lack of REM sleep in dolphins and possibly also in echidnas;

(8) the disappearance of the need for REM sleep in eared seals when sleeping in the water and its restoration when returning to land without demonstrating the rebound phenomenon.

It is possible to come to the "paradoxical" conclusion that intensive cerebral processing of information in REM sleep does not play any adaptive role (at least for an adult organism); information is processed, figuratively speaking, "idle".

SLEEP GENERATION AND REALIZATION

However, the question arises: how to combine all of the above data with the well-known facts of everyday life, confirmed thousands of times by clinical material, regarding the importance of sleep, quantitatively sufficient and qualitatively complete, for maintaining health, cognitive abilities and longevity? And vice versa, with a violation of health and mental activity with chronic sleep deficit and/or a decrease in its quality?

Michel Jouvet, speaking about his patient [12], answers these questions in the following way: "The agripnia demonstrated by this patient is interesting to compare with examples of experimental sleep deprivation in humans [here Jouvet refers to two earlier works; later such experiments on humans were prohibited]. In both cases, polygraphic and behavioral controls, as well as

psychomotor testing, were carried out. Let us immediately note the difference between our patient lying in bed all night and sometimes even taking sleeping pills—and healthy volunteer subjects who are paid to be sleepless, avoid even lying down, and constantly stimulate themselves to stay awake. In the first case, the patient would like to sleep and constantly tried to sleep, but [without experiencing drowsiness] could not sleep even after four months of insomnia. In the second case, on the contrary, the subjects constantly struggled with sleepiness and after 120, 200 and 264 sleepless hours fell from fatigue, demonstrating a long sleep rebound." In our patient, Jouvet points out, "the very *sleep generation system* was disturbed" [italics mine, KV]. It is clear that at the end of his life Jouvet came close to the idea of sleep generation mechanisms separate from the mechanisms of its realization. What might these "sleep-generating" mechanisms be?

Morvan's chorea has long seemed a mysterious disease, but now there is irrefutable evidence of its autoimmune etiology associated with the formation of autoantibodies to the complex of voltage-gated potassium channels (VGKC). It is known that antibodies to VGKC affect the peripheral nervous system, causing neuromyotonia, and can cross the blood–brain barrier and act centrally by binding to hippocampal neurons [51]. It has been shown that some VGKCs are indeed involved in the regulation of the rest-activity rhythm in fruit flies and the sleep–wake cycle in mice [52]. If these channels are destroyed, K^+ ions lose the ability to leave the cell and accumulate inside it; therefore the membrane potential jumps up to –55 mV, the neurons are constantly excited and incapable of hyperpolarization and transition to the burst-pause pattern. As for the REM sleep generation system, it can be mediated by the above-mentioned muscarinic receptor types 1 and 3, knockout of which causes the disappearance of this sleep phase in mice without noticeable consequences.

It can be assumed that numerous examples of a significant and prolonged (lifelong) reduction in the daily duration of sleep (total sleep or only REM sleep) without consequences in humans and animals, discussed above, are associated with the weakening (and cessation) of the activity of namely the hypothetical systems for generating non-REM and REM sleep, respectively. For certain reasons, which will be discussed below, this does not entail noticeable disturbances in the activity of the brain and the body as a whole. At the same time, long-term suppression of the system of realization of both non-REM and REM sleep, including instrumental, which also leads to a sharp reduction in the duration and destruction of the structure of sleep, can lead to very serious and even catastrophic consequences for patients and experimental animals. Physicians and researchers usually deal with the effects of damage to sleep realization systems, and they are well studied.

All these facts revealed the unsatisfactoriness of the traditional hypothesis of "cerebral information processing in sleep" (some researchers even started talking about sleep in general or REM sleep particularly as a "phenomenon without function" or "evolutionary error") and drew the attention to the development of an alternative paradigm. Yuri Panchin called it "Adaptive Inactivity Scenario" (AIS) [11]. It is based on the very simple idea that circadian periods of rest and sleep, or "adaptive inactivity" [53], in themselves have an evolutionary advantage, because the extra wake time makes animals more vulnerable in the wild surrounding. Assuming that such a strategy of "life without fuss" is adaptive, sleep-like behavior could arise independently and repeatedly in the evolution of different groups of organisms.

But why is it necessary to turn off sensory inflow and stop the cerebral information processing during sleep? Why is it necessary to sleep deeply, why can't a quite wakefulness replace sleep? The fact is that behavior in the waking state is controlled by various sensory stimuli and is realized by the completion of certain motor reactions. Afferent impulses that enter the brain in a state of quite wakefulness from extero- and interoreceptors (especially from proprioreceptors) will interfere with this process, preventing it from proceeding. Indeed, every person knows how hard it is to spend several hours in bed without sleep! Evolutionarily adaptive periodic inactivity requires a radical restructuring of existing wakefulness reflexes. Sleep is perhaps the simplest evolutionary innovation to achieve this adaptation.

Therefore, periodic inactivity is supported by natural selection. That is why it depends on behavioral and environmental factors and can vary widely, from absence to significant level. If sleep is an adaptive factor, but does not perform some unknown ("mysterious, secret") function associated with the cerebral processing of vital information, then, from an evolutionary point of view, non-sleeping animals will be eliminated by natural selection, not because they die from lack of sleep, but because additional waking time makes them more vulnerable in the wild.

It can be assumed that the biological role of sleep has evolved due to the synchronization and connection of some physiological functions (primarily those that are not associated with the mandatory involvement of the central nervous system: metabolic, endocrine, immune, etc.) with periods of sleep and wakefulness. An analogy with the circadian rhythm is appropriate here: all processes in the human and animal body are controlled by this rhythm; its violation causes desynchronosis with all its well-studied consequences and sharply reduces the survival rate of an individual in the wild. At the same time, under vivarium conditions, for example, hamsters with experimentally destroyed suprachiasmatic nuclei survive, feed, and reproduce perfectly. All physiological functions in them proceed normally, but are randomly distributed in time.

Since the internal life of a warm-blooded organism continues during periods of rest, certain functions, for one reason or another (sometimes, perhaps accidental), began to be "drawn" into periods of non-REM and REM sleep. That is, between sleep and the life processes that occur during it, there is a rigid temporal, but not a causal relationship.

Perhaps there is really "no mystery to sleep" [54] and the "trivial function of sleep" [55, 56] is not "cerebral information processing", rather a radical restructuring of all waking reflexes for the normal course of "adaptive inactivity" periods [53, 57]?

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CONFLICT OF INTEREST

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REFERENCES

1. Brette R (2022) Brains as computers: metaphor, analogy, theory or fact? Front Ecol Evol 10: 878729. https://doi.org/10.3389/fevo.2022.878729
2. Kovalzon VM (2011) Basics of somnology. Physiology and neurochemistry of the sleep–wakefulness cycle. BINOM. Laboratory of knowledge, Moscow. (In Russ).
3. Puchkova AN (2020) Studies of learning during sleep: problems, progress, and perspectives. Neurosci Behav Physiol 50(3): 257–263. https://doi.org/10.1007/s11055-020-00895-1
4. Steriade M, McCarley RW (2005) Brain Control of Wakefulness and Sleep, 2nd ed. Springer/Kluwer/Plenum, NY.
5. Timofeev I, Chauvette S (2019) Neuronal activity during the sleep–wake cycle. Handbook Sleep Res 30: 3–17. https://doi.org/10.1016/b978-0-12-813743-7.00001-3
6. Kovalzon VM, Lyamin OI (2022) In memory of Lev Mukhametov. J Sleep Res 31: e13470. https://doi.org/10.1111/jsr.13470
7. Mukhametov LM (1977) Activity of cerebral cells during sleep. Priroda 8: 37–41. (In Russ).
8. Singer W (1977) Control of thalamic transmission by corticofugal and ascending reticular pathways in the visual system. Physiol Rev 57(3): 386–420.
9. Eiland MM, Lyamin OI, Siegel JM (2001) State-related discharge of neurons in the brainstem of

freely moving box turtles, *Terrapene carolina major*. Archives Italiennes de Biologie 139(1–2): 23–36.
10. Lazarus M, Oishi Y, Bjorness TE and Greene RW (2019) Gating and the need for sleep: dissociable effects of adenosine A1 and A2a receptors. Front Neurosci 13: 740. https://doi.org/10.3389/fnins.2019.00740
11. Panchin Y, Kovalzon VM (2021) Total wake: natural, pathological, and experimental limits to sleep reduction. Front Neurosci 15: 643496. https://doi.org/10.3389/fnins.2021.643496
12. Jouvet M (2016) Le sommeil, la conscience et l'éveil. Odile Jacob, Paris.
13. Touzet C (2016) Morvan's syndrome and the sustained absence of all sleep rhythms for months or years: An hypothesis. Med Hypoth 94: 51–54. https://doi.org/10.1016/j.mehy.2016.06.011
14. Irani SR, Pettingill P, Kleopa KA, Schiza N, Waters P, Mazia C, Zuliani L, Watanabe O, Lang B, Buckley C, Vincent A (2012) Morvan syndrome: clinical and serological observations in 29 cases. Ann Neuro 72(2): 241–255. https://doi.org/10.1002/ana.23577
15. Jones HS, Oswald I (1968) Two cases of healthy insomnia. Electroenceph clin Neurophysiol 24: 378–380.
16. Meddis R, Pearson AJD, Langford G (1973) An extreme case of healthy insomnia. Electroenceph clin Neurophysiol 35: 213–214.
17. He Y, Jones CR, Fujiki N, Xu Y, Guo B, Holder JL Jr, Rossner MJ, Nishino S, Fuet Y-H (2009) The transcriptional repressor DEC2 regulates sleep length in mammals. Science 325: 866–870. https://doi.org/10.1126/science.1174443
18. Shi G, Yin C, Fan Z, Xing L, Mostovoy Y, Kwok P-Y, Ashbrook LH, Krystal AD, Ptáček LJ, Fu Y-H (2021) Mutations in metabotropic glutamate receptor 1 contribute to natural short sleep trait. Curr Biol 31: 13–24. https://doi.org/10.1016/j.cub.2020.09.071
19. Xing L, Shi G, Mostovoy Y, Gentry NW, Fan Z, McMahon TB, Kwok P-Y, Jones CR, Ptáček LJ, Fu Y-H (2019) Mutant neuropeptide S receptor reduces sleep duration with preserved memory consolidation. Sci Transl Med 11: eaax2014. https://doi.org/10.1126/scitranslmed.aax2014
20. Gravett N, Bhagwandin A, Sutcliffe R, Landen K, Chase MJ, Lyamin OI, Siegel JM, Manger PR (2017) Inactivity/sleep in two wild free-roaming African elephant matriarchs—Does large body size make elephants the shortest mammalian sleepers? PLoS ONE 12(3): e0171903. https://doi.org/10.1371/journal. pone.0171903
21. Harding CD, Yovel Y, Peirson SN, Hackett TD, Vyazovskiy VV (2022) Re-examining extreme sleep duration in bats: implications for sleep phylogeny, ecology, and function. Sleep 45(8): zsac064. https://doi.org/10.1093/sleep/zsac064
22. Siegel JM (2022) Sleep function: an evolutionary perspective. Lancet Neurol 21: 937–946.
23. Rattenborg NC, Voirin B, Cruz SM, Tisdale R, Dell'Omo G, Lipp H-P, Wikelski M, Vyssotski AL (2016) Evidence that birds sleep in mid-flight. Nat Communicat 7: 12468. https://doi.org/10.1038/ncomms12468
24. Lesku J A, Rattenborg NC (2014) Avian sleep. Current Biology 24(1): R12–R14.
25. Siclari F, Baird B, Perogamvros L, Bernardi G, LaRocque JJ, Riedner B, Boly M, Postle BR, Tononi G (2017) The neural correlates of dreaming. Nat Neurosci 20(6): 872–878. https://doi.org/10.1038/nn.4545
26. Rodionova EI, Kastner S, Krueger JM, Saalmann YB, Lüthi A, Nobili L, Kovalzon VM, Vyazovskiy VV (2022) In memoriam: Professor Ivan Pigarev (1941–2021). J Sleep Res 31: e13492. https://doi.org/10.1111/jsr.13492
27. Pigarev IN (2013) Visceral theory of sleep. J High Nerv Activ 63(1): 86–104. (In Russ). https://doi.org/10.7868/S0044467713010115
28. Hobson JA (2005) Sleep is of the brain, by the brain and for the brain. Nature 437(7063): 1254–1256. https://doi.org/10.1038/nature04283
29. Dewan EM (1970) The programing (P) hypothesis for REM sleep. Internat Psychiatry Clin 7(2): 295–307.
30. Mahoney CE, Cogswell A, Koralnik IJ, Scammell TE (2019) The neurobiological basis of narcolepsy. Nat Rev Neurosci 20(2): 83–93. https://doi.org/10.1038/s41583-018-0097-x
31. Peever J, Luppi PH, Montplaisir J (2014) Breakdown in REM sleep circuitry underlies REM sleep behavior disorder. Trends Neurosci 37(5): 279–288. https://doi.org/10.1016/j.tins.2014.02.009
32. Antelmi E, Rocchi L, Latorre A, Belvisi D, Magrinelli F, Bhatia KP, Tinazzi M (2022) Restless legs syndrome: known knowns and known unknowns. Brain Sci 12: 118. https://doi.org/10.3390/brainsci12010118
33. Bassetti CL, Bischof M, Valko P (2006) Dreaming: a neurological view. In: Mancia M (ed) Psychoanalysis and Neuroscience. Springer, Milan, pp. 351–387.
34. Roffwarg HP, Muzio JN, Dement WC (1966)

Ontogenetic development of the human sleep–dream cycle. Sci New Series 152(3722): 604–619.
35. Crick F, Mitchison G (1983) The function of dream sleep. Nature 304(5922): 111–114.
36. Lavie P, Pratt H, Scharf B, Peled R, Brown J (1984) Localized pontine lesion: nearly total absence of REM sleep. Neurology 34: 118–120.
37. Magidov E, Hayat H, Sharon O, Andelman F, Katzav S, Lavie P, Tauman R, Nir Y (2018) Near-total absence of REM sleep co-occurring with normal cognition: an update of the 1984 paper. Sleep Med 52: 134–137. https://doi.org/10.1016/j.sleep.2018.09.003
38. Vertes RP, Siegel JM (2005) Time for the sleep community to take a critical look at the purported role of sleep in memory processing. Sleep 28(10): 1228–1229.
39. Vertes RP (2004) Memory consolidation in sleep: Dream or reality. Neuron 44: 135–148.
40. Siegel JM (2001) The REM sleep–memory consolidation hypothesis. Science 294: 1058-1063.
41. Niwa Y, Kanda GN, Yamada RG, Shi S, Sunagawa GA, Ukai-Tadenuma M, Fujishima H, Matsumoto N, Masumoto K-h, Nagano M, Kasukawa T, Galloway J, Perrin D, Shigeyoshi Y, Ukai H, Kiyonari H, Sumiyama K, Ueda HR (2018) Muscarinic acetylcholine receptors Chrm1 and Chrm3 are essential for REM sleep. Cell Rep 24: 2231–2247. https://doi.org/10.1016/j.celrep.2018.07.082
42. Yamada RG, Ueda H (2020) Molecular mechanisms of REM sleep. Front Neurosci 13 1402. https://doi.org/10.3389/fnins.2019.01402
43. Capellini I, Barton RA, McNamara P, Preston BT, Nunn CL (2008) Phylogenetic analysis of the ecology and evolution of mammalian sleep. Evolution 62(7): 1764–1776. https://doi.org/10.1111/j.1558-5646.2008.00392.x
44. Lyamin OI, Kibalnikov AS, Siegel JM (2021) Sleep in ostrich chicks (*Struthio camelus*). Sleep 44(5): zsaa259. https://doi.org/10.1093/sleep/zsaa259
45. Lyamin OI (2018) Evolution of Sleep from Simple Organisms to Mammals. Effectivnaya farmakoterapiya. Nevrologiya i psihiatriya. Spetsvypusk: "Son i ego rasstroistva-6" 35: 8–16. (In Russ). https://umedp.ru/upload/iblock/3eb/Lyamin.pdf
46. Mukhametov LM (1988) The absence of paradoxical sleep in dolphins. In: Koella WP, Obal F, Schulz H, Visser P (eds) Sleep'86. Gustav Fischer Verlag, Stuttgart, pp 154–156.
47. Lyamin OI, Manger PR, Ridgway SH, Mukhametov LM, Siegel JM (2008) Cetacean sleep: An unusual form of mammalian sleep. Neuroscience and Biobehavioral Reviews 32:1451–1484. https://doi.org/10.1016/j.neubiorev.2008.05.023
48. Lyamin OI, Lapierre JL, Mukhametov LM (2013) Sleep in aquatic species. In: Kushida C (ed) The Encyclopedia of Sleep, vol. 1. Academic Press, Waltham; MA, pp. 57–62. https://doi.org/10.1016/B978-0-12-378610-4.00013-9
49. Mukhametov LM (2017) Research Start of Marine Mammals' Hemisphere Sleep. Effectivnaya farmakoterapiya. Nevrologiya i psihiatriya. Spetsvypusk: "Son I ego rasstroistva-5" 35: 132–136. (In Russ). https://umedp.ru/upload/iblock/565/Muhametov.pdf
50. Lyamin OI, Mukhametov LM, Siegel JM (2017) Sleep in the northern fur seal. Current Opin Neurobiol 44: 144–151. https://doi.org/10.1016/j.conb.2017.04.009
51. Liguori R, Vincent A, Clover L, Avoni P, Plazzi G, Cortelli P, Baruzzi A, Carey T, Gambetti P, Lugaresi E, Montagna P (2001) Morvan's syndrome: peripheral and central nervous system and cardiac involvement with antibodies to voltage-gated potassium channels. Brain 124(12): 2417–2426.
52. Cirelli C (2009) The genetic and molecular regulation of sleep: from fruit flies to humans. Nat Rev Neurosci 10(8): 549–560. https://doi.org/10.1038/nrn2683
53. Siegel JM (2009) Sleep viewed as a state of adaptive inactivity. Nat Rev Neurosci 10: 747–753. https://doi.org/10.1038/nrn2697
54. Foster RG (2018) There is no mystery to sleep. PsyCh Journal 7: 206–208. https://doi.org/10.1002/pchj.247
55. Rial RV, Nicolau MC, Gamundí A, Akaârir M, Aparicio S, Garau C, Tejada S, Roca C, Gené L, Moranta D, Esteban S (2007) The trivial function of sleep. Sleep Medicine Reviews 11(4): 311–325. https://doi.org/10.1016/j.smrv.2007.03.001
56. Rial RV, Canellas F, Akaârir M, Rubico JA, Barcely P, Martín A, Gamundí A, Nicolau MC (2022) The birth of the mammalian sleep. Biology 11: 734. https://doi.org/10.3390/biology11050734
57. Frank MG (2021) Challenging sleep homeostasis. Neurobiol Sleep Circad Rhythm 10: 100060. https://doi.org/10.1016/j.nbscr.2021.100060

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