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Research report

Brain organization and sleep function

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Abstract

A view of brain organization and sleep function is presented. Sleep is hypothesized to begin at the neuronal group level. Sleep results in the use and thus maintenance, of synapses that are insufficiently stimulated during wakefulness thereby serving to preserve a constancy of a synaptic superstructure. It is further hypothesized that sleep at the neuronal group level is regulated by the production of substances whose rate of production or catabolism is synaptic use-dependent. If sufficient number of neuronal groups are in a sleep state (also called disjunctive state) then the perception of sleepiness occurs. Coordination of neuronal group sleep results from humoral and neuronal projection systems previously linked to sleep regulation. The theory presented is unique in that it: (a) hypothesizes an organizational level at which sleep occurs; (b) hypothesizes that sleep is neuronal – use-dependent, not wakefulness-dependent; (c) hypothesizes that sleep first occurs in evolution when complex ganglia evolved; and (d) hypothesizes the both non-rapid eye movement sleep (NREMS) and REMS serve the same function of synaptic reorganization. The theory is consistent with past theories of sleep function, yet provides a fundamentally new paradigm for sleep research.

Key words: Sleep; Rapid eye movement sleep; Sleep function; Sleep evolution; Sleepiness; Sleep theory

1. Introduction

An understanding of sleep function and brain organization as it applies to sleep is likely to be a necessary step in any solution to the problems of perception, memory and consciousness. Many theories of sleep function exist though none have been convincingly experimentally verified. These theories fall into two general categories; those positing that sleep serves to maintain, repair or consolidate synapses and/or neuronal circuits and those focusing on bodily functions of sleep. A problem associated with bodily function theories, is that they fail to explain why the loss of vigilance associated with sleep is necessary. In contrast, if sleep serves to stimulate, thus preserve synapses necessary for survival but insufficiently stimulated during wakefulness then an uncoupling from waking effector mechanisms, be they cognitive or motor, is necessary. In this essay, we will develop the argument that sleep serves a synaptic maintenance function that is a CNS manifestation of a wider growth function for sleep.

It is our opinion that sleep function should be discussed within a theoretical framework of how the brain is functionally organized. By doing so, one is led to predictions as to: the level of brain organization that sleep occurs, when in evolution sleep first occurs, manifestations of sleep pathology (altered states) and finally the function of sleep itself. In this essay our arguments concerning brain organization as applied to sleep and sleep function are developed within the neuronal group selection theory presented by Edelman [8]. This is done for ease of conception; the main arguments presented here are also applicable within the context of other views of brain organization [36]. Elements of Edelman's theory important to this discussion include: (1) macroscopic connectivity within the brain is genetically coded; (2) microscopic connectivity develops epigenetically; (3) specific connectivity between neurons is dynamic and use-dependent even in adults; and (4) the use-dependent connectivity leads to a coalescing of neurons into functional neuronal groups which form the fundamental units of brain organization [12]. Thus, Edelman argues that a functional manifestation of synaptic plasticity is the formation of neuronal groups. The specifics of the plasticity are driven by use-dependent mechanisms; one consequence of use (e.g., action potentials) is an induction of synthesis of growth factors/substrate molecules critical to synaptic formation and efficacy. Such a mechanism

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allows for the 'imprinting' of the real world via sensory projections onto the brain in a functionally meaningful manner. This allows the brain to name things and events without the necessity of an a priori genetic encoding (reviewed in [8]). Nevertheless, included in this scheme there is a need for genetically determined neuronal connections and the use rules for synaptic dynamics are likely to apply to all synapses whether genetically specified or not. We will argue that: (1) normal wakefulness activity leads to the disproportionate stimulation of some synapses while failing to stimulate sufficiently other populations of synapses critical to survival; (2) sleep serves to provide a pattern of stimulation to preserve the critical populations of synapses insufficiently stimulated during wakefulness; (3) sleep itself, like synaptic efficacy, is driven by use-dependent synthesis of substances that serve to induce oscillations of neuronal activity as well as synaptic maintenance/growth functions; (4) that these use-dependent events occur within and aid in the formation of neuronal groups while simultaneously preserving reentrant signaling; and (5) the neuronal group is the organizational level at which sleep has a fundamental function.

The sleep literature contains evidence suggesting that sleep indeed occurs at some level between single neurons and the whole brain. A discussion of that evidence will be followed by a discussion of the interactions of humoral agents and neuronal circuits. The question, 'what does sleep?', is seldom addressed. This is likely due to the fact that sleep is usually defined at the organism level using a combination of measures of physiological parameters, e.g., EEG, EMG, EOG, behavior, none of which is specific or necessary for sleep but collectively define the state. Nevertheless, it is useful to ask whether the entire brain or single neurons or some level of organization in between, sleep. Previously, we summarized the evidence supporting the hypothesis that a sleep-like state occurs at the neuronal group level [23]. Briefly, the following points were emphasized. (1) Some animals sleep on only one side of the brain [dolphins [30]] and if only one side of the dolphin brain is deprived of sleep only that side recovers as manifest by unilateral sleep rebound [33]. These data provide strong evidence that sleep is not a whole brain phenomena. (2) After lesions of the brain, regardless of their location, if the animal survives the lesion, non-rapid eye movement sleep (NREMS) always occurs (reviewed in [25,27]). Such data suggest that there is no common necessary pathway for sleep and EEG synchronization and that the high amplitude EEG slow-waves of NREMS are indicative of a fundamental mode of brain function operating independently of global coordinating mechanisms. (3) Slow electrical stimulation of many areas of the brain or rhythmic sensory stimulation induces EEG synchronization (reviewed in [18]). These data suggest that much of the encephalon has hypnogenic properties. (4) There are also clinical data suggesting that different parts of the brain can simultaneously be in different states (reviewed in [26]). Collectively, these data suggest that sleep is a local neuronal group phenomenon.

Sleep is regulated by both humoral and neuronal mechanisms; these mechanisms act in concert with each other (reviewed in [24]). One of our major hypotheses is that the accumulation of molecules whose production during wakefulness leads to the local induction at the neuronal group level of an alternative firing pattern herein called the disjunctive state which promotes the maintenance of critical but under used synapses. The concept of a humoral modulation of circuits for the generation of rhythmic outputs has been developed for other brain functions (reviewed in [11]). Humoral inputs affect almost every aspect of those circuits, including their neuronal composition, synaptic connectivity, responsiveness to stimuli and the intrinsic properties of the cells. It is likely that humoral-induced circuit dynamics are a fundamental mechanism of sleep.

An implicit hypothesis derived from the above view of brain organization is that one would not expect to find either humoral agents nor neuronal groups that are specific for sleep. All the putative sleep-promoting substances thus far identified have multiple biological activities and some of their activities are not normally observed during sleep. We have constructed a model (reviewed in [25] and see Fig. 1) to illustrate how specific sleep responses may be elicited from multiple substances each having multiple biological activities. Such models are also applicable to similar problems of specificity confronting the humoral regulation of all physiological functions. Similar issues are also relevant to neuronal regulation of physiological functions; e.g., single hypothalamic neurons respond to changes in osmotic pressure, temperature and glucose concentration [38]. Moreover, neuronal sensitivity to such stimuli is dynamic; e.g., some cells that are insensitive to temperature become more sensitive to heat after exposure to interleukin-1 (IL-1) [9]. Similarly, a single neuron can be part of more than one sensory network [13]. Nevertheless, it is currently clear that sleep results from the dynamic interplay between neurons and humoral modulators. Further, the literature and theoretical considerations support the hypothesis that sleep occurs at the neuronal group level (the disjunctive state if referring to a single neuronal group).

2. Humoral agent induction of the disjunctive state

At the neuronal group level, it is likely that neural activity leads to an enhanced production of substances

which, in turn, lead to a modulation of the neural activity that induced their production. We hypothesize that this leads at the local level to a temporary disjunction between input and output of the neuronal group or to the disjunctive state. At the cellular level the effects of a substance, produced as a result of neural use, could be in the form, for example, of induction of synthesis of specific ion channels and/or of molecules critical for synaptic efficacy. Regardless of specifics, the substance is envisioned to act locally, altering membrane events resulting in the amplified strength of synapses infrequently used during wakefulness.

In its simplest form, the current hypothesis for sleep function is that sleep serves to reinforce certain synapses relative to others. To show that this is mechanistically plausible, previously we presented a model to illustrate that with even one set of molecules it is easy to envision neuronal-activity-driven synthesis of molecules that leads to oscillatory excitation-inhibition within a very simple network [23]. However, sleep involves multiple neuronal groups and substances; the model presented in Fig. 1 is meant to help envision these more complex events. We treat sleepiness as a perception resulting from populations of neuronal groups in the disjunctive state. Sleepiness induces behavioral changes which end in the consumptive point of a niche-adapted sleep state. In this sense sleep at the organism level is adaptive, since it partially removes the animal from environmental challenge at a time when the animal is less able to cope with the environment.

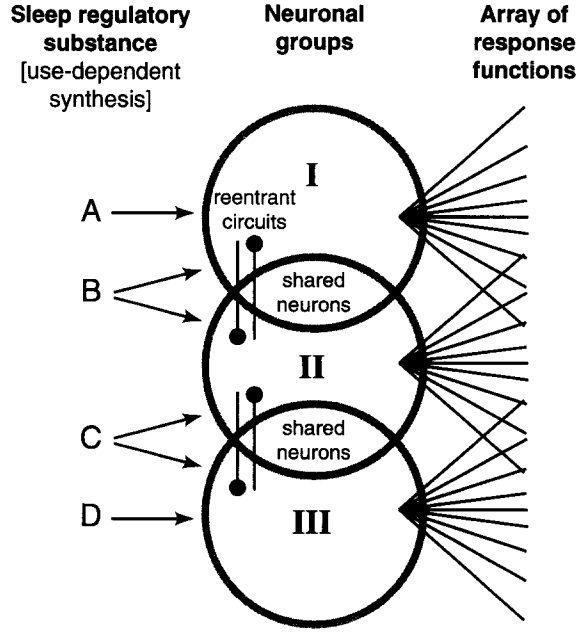

Fig. 1. Hypothetical interactions of several sleep-promoting substances with neuronal groups. The current theory emphasizes that multiple sleep regulatory substances and neuronal groups are involved in the generation of sleep at the organism level. No single substance or group is necessary for sleep. One of the response functions that results as an emergent property from a population of neuronal groups in the disjunctive state is sleepiness. Collaterals from the reentrant circuits form higher order neuronal groups which in themselves may have a disjunctive state and which coordinate the disjunctive state of many neuronal groups into niche-adapted sleep. A function of the disjunctive state is to preserve the shared use of neurons between groups [12] which helps to preserve brain complexity with evolutionary efficiency [20].

We envision that a single neuronal group will interact with more than one sleep regulatory substance (2 in the case of Fig. 1) and that the degree to which a neuronal group is stimulated depends upon the concentrations of the substances interacting with it and as mentioned above, the production of these substances is use-dependent. A single substance may interact with more than one neuronal group, and the actions of a substance on one neuronal group may differ from its actions on another neuronal group. Thus, a substance may be excitatory in one neuronal group while inhibitory in another (e.g., IL-1 generally depresses hypothalamic warm-sensitive neurons while exciting cold-sensitive neurons [37]). This type of effect on different neuronal groups may contribute to the inhibitory effects observed after injection of combinations of sleep-promoting substances reported by Kimura et al. [21].

At any one time some neuronal groups are likely to be in the disjunctive state. If a sufficient population of neuronal groups is in the disjunctive state the perception of sleepiness occurs. If the entry of neuronal groups into the disjunctive state is coordinated then sleep at the organism level occurs. This coordination is brought about by the global projection systems already tied to sleep regulation (reviewed in [16,40]). By way of a concrete example one could envision the basal forebrain cholinergic projections to the cortex influencing the thalamo-cortical-GABAergic mechanism described by Steriade et al. [41]; such an influence could help time the biochemical events leading to the disjunctive state. More than one global coordinating mechanism is needed to niche-adapt sleep. For example, the suprachiasmatic nucleus is involved in the circadian distribution of sleep [42], but sometimes it is disadvantageous to sleep at 'normal' times, e.g., staying late at the office. Thus, in this case one might imagine an activation of the mesencephalic reticular activating system and/or the basal forebrain cholinergic mechanisms mentioned above.

Substances A–D of Fig. 1 are labeled sleep regulatory substances, since these humoral agents influence circuits as described above. These same substances are the growth factors/substrate molecules involved in synaptic efficacy. These substances are responsible for the shifting of borders of neuronal groups; they will determine, in part, which neuronal groups a neuron is most likely to be associated with. The neurons labeled as shared neurons in Fig. 1 would be most susceptible to this type of influence.

Each neuronal group is viewed as contributing to an array of functions (right side of Fig. 1). Specificity of response for any one function would come from the con-

vergence of outputs from a large variety of neuronal groups [8]. For specific physiological functions, e.g., muscle contraction or glandular secretion, the convergence is also anatomical and the system is hierarchical. For example, in the motor system cerebral cortical, cerebellar and basal ganglia outputs eventually converge on spinal motor neurons (the final common pathway). In contrast, for higher order CNS function such as memory, perception (including sleepiness) or thought, convergence is virtual, but not anatomical. There is no final common pathway or center. Each neuronal group contributes only part of a thought or perception (like sleepiness) though specific functions may be regional, e.g., specific memories can be localized (reviewed in [15,36,39]. Thus there can be fragments of thoughts or partial memories; as the outputs of more neuronal groups are coordinated, details are filled in. The same coordinating systems that are used for the niche-adapted coordination of neuronal groups in the disjunctive state are used to coordinate neuronal group output for other perceptions and memory. In this sense, memory and perception, including sleepiness, can be viewed as being emergent properties of populations of neuronal groups (reviewed in [36]).

Thus, viewed in this light, sleepiness is just another perception. It is a useful perception, since it is telling us that wakefulness activity has disproportionately stimulated, hence reinforced certain synapses. Like other perceptions, it can trigger behavior, e.g., seeking a safe place and involves coordination systems which allow niche-adapted sleep. The consumptive end of other perceptions and cognitions are far more varied (e.g., clear memories, hallucinations, motor acts, fainting, etc.) even though they involve some of the same coordinating mechanisms. Further, that variation would be greatly affected by neuronal groups in the disjunctive state; this probably provided a selection factor for the evolution of sleepiness ending in sleep. In other words, as one becomes progressively more sleepy (more neuronal groups in the disjunctive state) memories and other cognitions become more impaired; since this would be maladaptive, sleep evolved.

3. Special considerations

3.1. The need for the disjunctive state: evolution of the regulation of sleep-wake cycles and sleep

Rest-activity cycles likely occurred early in evolution. For example, in response to daily fluctuations of temperature and light, single cell organisms probably began to time their production of specific enzymes to availability of nutrients, because such timing would be metabolically more efficient. Thus, the earliest function of rest-activity cycles could be viewed as metabolic (Fig. 2). Such coordination requires chemical signals; some of which were probably eventually used to signal other cells. As multiple cell organisms evolved, such humoral signals became important for whole animal coordination and the signals themselves began to be influenced directly by the rest-activity cycles as well as by environmental stimuli. Because some of these humoral signals were charged, there also was a current associated with the signaling event. Though these electrical events were undoubtedly present (as they are today) in single cell organisms, their use in higher order information processing only truly became of age with the development of neurons and nerve nets of simple multicellular organisms. At this level, again the complexity of regulation was amplified, since rest/activity cycles, humoral signals, electrical events and environmental stimuli all interacted with each other (Fig. 2).

It is envisioned that sleep developed as nerve nets gave way to far more complex ganglia and eventually brains. The evolutionary advantage of complex sensory/motor information processing is obvious. It is reasonable to propose that the evolution of complex ganglia could occur by either greatly increasing the total number of neurons with precise predesignated connections (much like the current evolution of computers) or alternatively and more efficiently by the shared use of neurons with multiple connections by two or more neuronal groups. In either case, the complexity of connections would rapidly outgrow the informational content of the available genetic material. If the strategy of increasing the total number of neurons was chosen, limits were soon reached. It is likely that from an evolutionary point of view, the shared use of neurons was a more advantageous design, since fewer neurons needed to be produced and fed and hence total weight, size and metabolic demands of the ganglionic load could be minimized. However, the price to be paid was the development of epigenetic plasticity and rules of connectivity between neurons that were use-dependent [8]. For reasons outlined above, such developments required a functional mode ensuring the maintenance of infrequently used synaptic connections. It is likely that sleep developed from the rest portion of rest-activity cycles, since during rest, niche-appropriate inactivity already was developed. Further, the regulatory events for sleep were probably adapted from the regulatory events already regulating rest. Sleep itself added to the regulatory complexity by directly affecting rest-activity cycles, humoral signals, electrical events and responses to environmental stimuli (Fig. 2). Finally, in terms of function, since sleep is a modified rest period, the metabolic function associated with rest remained a function of sleep, perhaps even amplified. Thus, sleep has an energy-saving, anabolic function in both the central nervous system and the body. However, the first function of sleep per

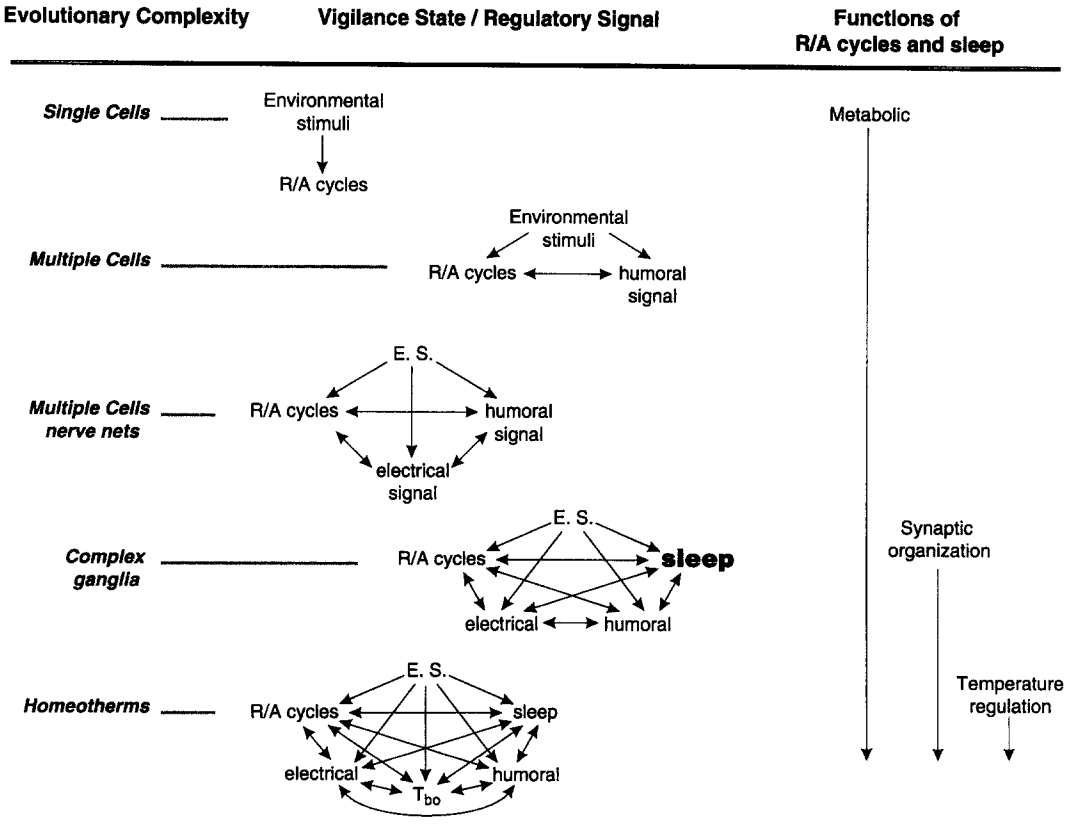

Fig. 2. The evolution of sleep and sleep functions. With greater complexity of cellular organization, the regulation of rest-activity cycles (R-A) and sleep becomes progressively more complex. Also illustrated is the concept that sleep serves metabolic and thermoregulatory functions in addition to its primary function of maintenance of synapses, thereby enhancing neuronal complexity.

se was the maintenance of ganglia plasticity, complexity and synaptic connectivity of shared neurons.

The success of homeotherms is attributed, in part, to the regularity of brain function resulting from carefully regulated brain temperature independent from changes of environmental temperatures. Since sleep was already associated with metabolic function and brain complexity, it is reasonable to suggest that the evolution of homeotherms was tightly coupled to sleep. Indeed, the regulation of sleep and temperature are tightly coupled to each other (reviewed in [31]). Further, sleep in modern day homeotherms is also likely to serve directly a temperature regulatory function as previously proposed [28,31].

3.2. Ontogeny

During early development connections between neurons are very dynamic. Neuronal groups compete with each other for individual neurons (neural Darwinism [8]). Thus, initially, informational processing events use a wide array of synapses; later as the result of neuronal group competition, learning, reinforcement, development of skill, the most suitable synapses are selected for specific tasks. Neither wakefulness or NREMS (as defined from physiological parameters) is well-developed in neonates; the waking EEG contains slow-waves, whereas EEG slow-wave activity is underdeveloped during NREMS (called quiet sleep in neonates for this reason). This suggests that the separation of the waking and sleep mode functioning of neuronal groups develops gradually. Interestingly, Koukkou and Lehmann [22] list arguments that waking and sleeping mentation in children are similar.

It seems, therefore, that the ontogeny of NREMS and wakefulness parallels the establishment of selective use of synapses during wakefulness. This notion strongly supports the proposed model of sleep function/regulation. The assumption that the organization of information processing in the neuronal groups is different during sleep than during wakefulness provides a basis for the differences between waking and sleep (NREMS) mentation as suggested by Koukkou and Lehmann. Since different neural connections are used, the mechanism of processing and the memory contents against which the information is evaluated, will also be different between sleep and wakefulness.

3.3. Rapid eye movement sleep

It is likely that REMS is functionally the same as NREMS at the neuronal group level, but mechanistically

involves different levels of the central nervous system. Jouvet [17] reported that, after transection between the mesencephalon and diencephalon in the preparation below the transection there is no more NREMS, whereas REMS continues (the isolated forebrain, of course, has periods of NREMS). Thus, REMS could be considered to serve the same function for the brainstem as NREMS for the diencephalon/telecephalon. That is, REMS enhances synaptic efficacy in the brainstem (possibly even the spinal cord) and is regulated by a local growth factor releasing mechanism in the brainstem. That there are neuronal groups especially important for REMS ('REMS-centers', reviewed in [40]) does not interfere with this proposal, since NREMS also seems to have neuronal groups of special importance, although not necessary (see above). The serious autonomic disturbances (e.g., thermoregulation, loss of baroreceptor sensitivity) characteristic of REMS also indicate that REMS is accompanied by a neuronal reorganization at a lower level than NREMS. This suggests that the important difference between NREMS and REMS is in the level of neuronal reorganization. It is further emphasized that, since some of the brainstem neuronal groups have influence on the forebrain there will be functional manifestations of REMS in the forebrain. These changes, like the autonomic disturbances mentioned above, should be viewed as evidence for brainstem neuronal group reorganization during REMS. Furthermore, changes in the forebrain induced by brainstem neuronal group reorganization during REMS very likely also possess a function of their own, developed over the course of evolution (e.g., memory consolidation). Such forebrain functions of REMS are appended to the primordial function of REMS which is brainstem neuronal group reorganization.

Crick and Mitchinson [5] suggested that the neuronal network of the cerebral cortex might produce 'parasitic modes of behavior' as a result of waking activity or growth. This behavior is attributed to the associations strengthened by waking mentation. Although there are obvious differences in details, the basic idea of the Crick-Mitchinson's hypothesis is similar to the one proposed herein: the neuronal activity during wakefulness may cause fundamental alterations in cortical neuronal connectivity. In both hypotheses, sleep is the solution to this problem. Crick and Mitchinson, however, suggest that REMS is the state of sleep where 'forgetting' occurs: it is a reverse learning mechanism which protects the cerebral cortex by providing a random stimulation.

In our theory, the mechanism which protects forebrain neuronal networks is attributed to NREMS. REMS is sometimes implicated in memory consolidation processes (a possible secondary function) in part because alterations in REMS were observed after learning trials [44]. Learning, however, affects both REMS and NREMS [1]. The most important argument against the idea that REMS serves a primordial function associated with the cerebral cortex or forebrain is that the need for REMS does not arise from the forebrain. As mentioned above after transection between the mesencephalon and diencephalon, REMS continues in the preparation below the transection whereas NREMS occurs in the isolated forebrain. Indeed, when there is a great need for sleep, e.g., after modest sleep deprivation, the forebrain gives priority to NREMS and suppresses REMS [3,10].

4. The central hypothesis

Within the context of the above considerations, sleep is viewed as follows: (a) it begins as a local neuronal group event involving oscillations of neuronal excitation/inhibition; (b) it results in the use and thus maintenance, of synapses insufficiently stimulated during wakefulness thereby *serving to preserve a constancy of a synaptic superstructure important to brain organization and physiological regulation*; (c) it is regulated by the local production of substances whose rate of production/catabolism is synaptic use-dependent; (d) at the local level, reentrant circuitry (e.g., thalamo-cortical, cortico-thalamic projections) serves to time and amplify signaling events responsible for the disjunctive state of individual neuronal groups; (e) at a higher level, collateral projections from the local reentrant circuitry form higher order neuronal groups serving to globally coordinate sleep among groups. These might be strategically located neuronal groups that are capable of influencing large areas of the brain either through their extensive projections or via humoral agents. The altered functioning of neuronal groups directly controlling these strategically located units results in more or less synchronized functional changes throughout the brain. It is likely that these strategic neuronal groups have a dominant role in determining sleep onset and duration under normal conditions. Their destruction leads to temporary sleep loss as defined at the macroscopic level, but not to microscopic sleep loss; the disjunctive state of individual neuronal groups persist but they are transiently desynchronized. With recovery from lesions, new higher order neuronal groups are formed leading to the reappearance of sleep, as inferred from changes in physiological events, but this sleep is unlikely to be niche-adapted, since the genetically defined component of anatomy was destroyed by the lesion. For example, after recovery from suprachiasmatic nucleus lesions, duration of sleep is close to prelesion values but the occurrence of sleep lacks a circadian rhythm.

Thus the brain's capacity to adapt to challenge is dependent, in part, on the maintenance of synapses infre-

quently used during wakefulness. The interaction with the environment results in the selection of the most adaptive neuronal group responses [8], resulting in the disproportionate use of some synapses during wakefulness. Because synaptic connectivity is use-dependent, this wakefulness activity would tend to eliminate some synaptic connections and individual neurons would tend to lock into a particular neuronal group. This is, indeed, likely to be a major facet of epigenetic brain development [8], but if taken to its logical end, the brain would develop into a collection of rigid networks resulting in a superstructure loss unless there was a mechanism to ensure connectivity within and between neuronal groups. We hypothesize that sleep occupies such a large fraction of time because the repeated stimulation of synapses, insufficiently driven by the dominant sensory/motor stimuli during wakefulness, is needed to maintain necessary connections between neuronal networks.

This theory is derived, in part, from and is consistent with previous proposals on the function of sleep. Moruzzi [29] suggested "... that sleep concerns primarily not the whole cerebrum, nor even the entire neocortex, but only those neurons or synapses and possibly glia cells, which during wakefulness are responsible for or related to, the brain functions concerned with conscious behavior." Moruzzi thus identified the level at which sleep served a function. He presented it within the context of a 'local homeostasis' concept postulating that during wakefulness there is an accumulation of 'wear and tear' in used neurons and sleep serves to reverse these effects. The current theory hypothesizes the opposite; that sleep serves to stimulate the use of structures insufficiently activated during wakefulness thereby saving them from atrophy. Oswald's [34] suggestions on the importance of sleep for body regeneration, Horne's [14] and Moruzzi's [29] ideas on the importance of sleep for brain homeostasis; Berger's suggestions on the energy conservation function of sleep [2]; and previous ideas on the thermoregulation [28,31] and memory [6,44] all are consistent with the current theory. For example, interleukin-1, the growth factors, e.g., the growth hormone releasing hormone/growth hormone/insulin-like growth factor axis [32], are likely involved in the initiation of sleep and in the sleep-associated neuronal group synaptic superstructure-maintenance mechanism. Thus, intracerebral growth factors are indicative not only of the function of sleep but can also be viewed as causative agents for sleep at the neuronal group level and, in combination with global coordinating mechanisms, as a major input for sleep regulation. Furthermore, it is likely that in case of increased need for tissue growth/repair/anabolism outside the central nervous system, e.g., infectious disease, strenuous exercise, starvation and high blood concentrations of nutrients after food intake, stimuli from the body can also act as an input for sleep. In this case the input could be either directly from the growth factors crossing the blood brain barrier or indirectly, e.g., via peripheral nerve stimulation. Thus, what sleep does for the brain and for the body are likely to be manifestations of the same functions in different targets.

5. Conclusions

5.1. Experimental support

Some of the experimental support for the ideas presented here was previously outlined [23]. Some recent findings also support the neuronal group theory of sleep function. Kattler et al. [19], tested whether excessive local activation of brain regions during wakefulness in fact affects sleep as estimated from the EEG. After vibratory stimuli applied to the right hand during wakefulenss, increased delta power was observed over the left somatosensory cortex in the first hour of sleep. In another abstract Pigarev [35] reports a change in the responsiveness of cortical neurons to sensory stimuli. Visual neurons identified in the cat's primary visual cortex during wakefulness become increasingly sensitive to visceral stimuli during sleep. This finding clearly indicates that the neural groups are fundamentally reorganized during sleep.

5.2. Philosophical consideration

Within the context of the present theory it is a valid and useful pursuit to seek and identify the neuronal group coordinating mechanisms necessary for niche-adapted sleep. In fact, as mentioned above, many of these mechanisms are already identified [40]. Further, the present theory amplifies upon their importance, since a corollary hypothesis is that these coordinating mechanisms are also involved in other cognitive functions. However, the current theory is inconsistent with notions of either a single necessary sleep-specific sleep-promoting substance or neurotransmitter system. Indeed, the literature supports multiple humoral agents and neurotransmitters involved in sleep regulation (reviewed in [4,25]).

Dennett [7], Edelman [8] and the proponents of parallel distribution processing theory [36] and complexity theory (e.g., [20]) have argued either implicitly or explicitly that memories/thoughts/states result as an emergent property of a population of interacting neurons thereby avoiding the Cartesian proposition that: a specific circuit stimulation pattern equals a specific perception/memory/state. The current theory also posits that the perception of sleepiness is an emergent property. Nevertheless, the focus of modern science is reductionistic. We have found cells,

neurons, molecules, elements, subatomic particles, strings and even multiple universes. Yet we cannot predict atomic behavior from subatomic particles nor molecular behavior from the component atoms, any more than we can explain behavior of populations of neurons from the properties of single neurons. The emergent property explanation is needed in all cases. However, populations of neurons differ in a very important way from populations of molecules, particles or computer chips. The form and function of neurons are derived from biological history and their activity is not random but directed by sensory input. As a consequence, it is reasonable and even necessary to propose an evolutionary rationale for the design of the nervous system and for any emergent property that ensues from it. Nevertheless, since the anatomical, physiological and molecular processes responsible for emergent properties are shaped by evolution, we can only be conscious of what those historic events allow.

"Individual events. Events beyond law. Events so numerous and so uncoordinated that, flaunting their freedom from formula, they yet fabricate firm form."

John Wheeler: *Frontiers of Time* [43].

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