

A hypothesis regarding how sleep can calibrate neuronal excitability in the central nervous system and thereby offer stability, sensitivity and the best possible cognitive function

J.H. Sture Hansson¹

Department of Clinical Neurophysiology, Farsta, Stockholm, Sweden

ARTICLE INFO

Keywords:

Sleep function
Excitability
Stability
Sensitivity
Central nervous system
Calibration

ABSTRACT

The function of sleep in mammal and other vertebrates is one of the great mysteries of biology. Many hypotheses have been proposed, but few of these have made even the slightest attempt to explain the essence of sleep – the uncompromising need for reversible unconsciousness. During sleep, epiphenomena – often of a somatic character – occur, but these cannot explain the core function of sleep. One answer could be hidden in the observations made for long periods of time of the function of the central nervous system (CNS). The CNS is faced with conflicting requirements on stability and excitability. A high level of excitability is desirable, and is also a prerequisite for sensitivity and quick reaction times; however, it can also lead to instability and the risk of feedback, with life-threatening epileptic seizures. Activity-dependent negative feedback in neuronal excitability improves stability in the short term, but not to the degree that is required. A hypothesis is presented here demonstrating how calibration of individual neurons – an activity which occurs only during sleep – can establish the balanced and highest possible excitability while also preserving stability in the CNS. One example of a possible mechanism is the observation of slow oscillations in EEGs made on birds and mammals during slow wave sleep. Calibration to a genetically determined level of excitability could take place in individual neurons during the slow oscillation. This is only possible offline, which explains the need for sleep. The hypothesis can explain phenomena such as the need for unconsciousness during sleep, with the disconnection of sensory stimuli, slow EEG oscillations, the relationship of sleep and epilepsy, age, the effects of sleep on neuronal firing rate and the effects of sleep deprivation and sleep homeostasis. This is with regard primarily to mammals, including humans, but also all other vertebrates.

Sleep: A general background

In mammals, sleep is a state of reversible unconsciousness from which the individual is easily awakened, with reduced reactive ability, disconnection of sensory input to the thalamus and cortex and reduction of motor functions. All vertebrates engage in some form of sleep. In mammals and birds, sleep is dominated by non-rapid eye movement sleep (NREM sleep), which includes slow wave sleep (SWS – characterized by an EEG diagram with slow wave activity (SWA) [1] – as well as rapid eye movement sleep (REM sleep) [2,3]. Birds and cetaceans have the ability to sleep unihemispherically [4]. Insects such as bees [5] and *Drosophila melanogaster* [6,7], mollusks such as cuttlefish and octopus [8,9], the pond snail [10] and the *Cassiopeia* jellyfish [11] engage in sleep-like behavior. This shows that sleep has an important, indispensable and fundamental function not only in humans and other

mammals but throughout the animal kingdom.

During sleep, the brain's interaction with the external environment is at a low level, and it can be assumed that the individual must pay a price for this state. The absence of consciousness leads to vulnerability to predators and other dangers [12]. However, evolution has not been able to eliminate the need for sleep, and even if sleep is expressed in different ways by different species, its core function can be the same. This does not rule out that NREM sleep and REM sleep could have developed independently at various points during the evolutionary process [4].

Other physiological functions outside the nervous system are also affected. Because these functions are not dependent on reversible unconsciousness, they are hardly associated directly with the true reason for sleep, and can thus be considered epiphenomena. Circadian rhythms control not only sleep and rest but also metabolic, immunological and

E-mail address: jh.sture@outlook.com.

¹ ORCID ID 0000-0003-3383-1217.

hormonal functions, without these being involved with the true function of sleep.

Consciousness, unconsciousness and sleep are the terms for distinct functional states of brain function, whose outer boundaries are fixed. The human brain has been estimated to contain 86 billion neurons and 85 billion non-neurons [13]. Within a limited volume, perception, cognition, memory, motor functions, emotional functions, sensitivity, precision and reaction times should be spurred to perform at the highest possible level and balance. Despite general requirements on the conservation of metabolic resources, the human brain is characterized by high metabolism, with up to 20% of the body's total energy consumption taking place in only 2% of the volume. Metabolic activity decreases only marginally during sleep [14]. Thus the brain remains active and does not rest during sleep. This has been seen in EEGs registered on the scalp surface. The electrical activity dominated during wakefulness by rhythms of high frequency and low amplitude is transformed during sleep to an activity with low frequency and high amplitude, i.e. SWA within the frequency band of 0.5–5 Hz. In humans, sleep can be divided into approximately three to six cycles, where each cycle lasts 60–90 min. Each cycle undergoes a transition period of sleep stages 1–2 and is then dominated by SWA during sleep stage 3, and this is followed by a shorter period of REM sleep. During REM sleep, the surface EEG returns to a pattern similar to that observed during wakefulness.

Prerequisites and concepts of significance for the hypothesis

Evolution has demonstrated an ability to find solutions to complex problems. This is why it makes sense to study evolution as a powerful problem-solver. The following presents problems encountered with stability in the neurons in networks as well as with stability within neurons. Examples will be given of how stability can be established with reasonable and existing physiological mechanisms and that solutions are possible.

The following review refers primarily to mammals, including humans, but can refer as well to all high-level organisms in the animal kingdom. The pertinent parts of the CNS in mammals are primarily the thalamus and the cortex, which dominate the gray matter.

The nervous system as an alarm system

In very simplified terms, the nervous system – from low-level to high-level organisms such as mammals – can be perceived as an alarm system with the capability to adapt simultaneously to temporary or permanent changes in the external environment. In an extreme situation, the correct and immediate response to stimuli can be the difference between life and death for an individual or offspring. The nervous system must choose – friend or foe, predator or prey, fight or flight – in highly stressful situations. Thus, evolution has driven the nervous system to enable the best performance. Sleep plays an important role here.

Plasticity

Plasticity is the general term for the adaptation of the brain or ganglia to the external environment, and the foundation for experience, learning, memory and development. One important form of plasticity is Hebbian plasticity, a reinforcement of the synapses which are most active during impulse generation from one neuron to another [15,16]. This form of plasticity is associated with certain forms of memory, such as declarative and procedural memory [17,18].

Excitability

Excitability is a term for both the networks in the nervous system and individual neurons, and can be explored using technical electrophysiological methods such as sensory evoked potentials and magnetic

stimulation. A common factor for both these in vivo and non-invasive tests of excitability is that they are more or less dependent on complete networks with excitatory and inhibitory functions. Transcranial magnetic stimulation activates for example both excitatory and inhibitory neurons. Even though excitability in networks has been studied during sleep, less is known about the excitability of individual, isolated neurons during and after sleep compared with excitability during consciousness (with the exception of some research efforts [19–23]). Contributors to excitability in individual neurons include components such as synaptic strength, which is influenced by synapses, structural conditions, receptors for signaling substances, ion channels etc. Another area can be described as non-synaptic excitability with ion channels and structures in dendrites and soma, where the travel of impulses takes place with cumulative graded potentials. A decisive, subsequent component in non-synaptic excitability is intrinsic excitability, which can be determined by the threshold for the electrical excitement of an action potential in axonal initial segments (AIS) [24,25], consisting largely of voltage-dependent Na, Ca and K channels. This threshold is relevant for stimuli with action potentials from synapses or gap junctions, or through electrical fields, for example in the case of epileptic discharges.

Synaptic scaling and negative feedback in non-synaptic excitability and intrinsic excitability

One mechanism that compensates for the neurons' changing requirements and plasticity's destabilizing influence is synaptic scaling [26,27], which is most easily described as negative feedback in synaptic strength. Regulation of synaptic strength and non-synaptic excitability can be mediated via the firing rate (FR), even if other mechanisms cannot be ruled out. Variations of FR must be placed in relation to the individual neuron's state of equilibrium FR_{fb} during consciousness, with a characteristic value for each neuron, with a wide range from 0.01 Hz to 10 Hz [26]. High levels of impulse traffic in the neuron reduces synaptic strength in all synapses in the neuron and thus suppresses the impulse traffic through a homeostatic regulation that is mediated by FR [19,27]. Homeostatic regulation or negative feedback requires a set point, a reference value that the regulation attempts to return to after a perturbation. How stable and when and how set points are regulated is seldom discussed, with few exceptions [28]. Thus a neuromuscular synapse in *Drosophila* is regulated homeostatically with a set point that changes at the 42 day age of the animals and this is otherwise stable. This mechanism is unknown, but might be genetic. Synaptic scaling depends on activity, and locally in the short term, it acts as a stabilizer. The neuron's intrinsic excitability can be regulated in a similar, activity-dependent way with negative feedback [24,29]. Because synaptic scaling can be perceived as having an unclear definition, the more specific terms negative feedback in synaptic strength (including all the synapses of the neuron) and negative feedback in non-synaptic excitability or intrinsic excitability are sometimes used.

A mechanism for shared bidirectional homeostatic regulation via FR of excitatory synaptic scaling and intrinsic excitability, which is thus not limited only to synaptic scaling, has been shown [30].

One unanswered question is whether regulation of synaptic scaling without connection to non-synaptic excitability exists in vivo. Earlier findings on synaptic scaling considered only the synaptic contributions to excitability, and the relationship between synaptic scaling and non-synaptic excitability has only recently been noted.

One risk with negative feedback in synaptic strength and non-synaptic excitability is that neurons which seldom need to be active would risk being regulated upward, though it is not clear that the rare activation of a particular neuron depends on excessively low excitability. The following simplified thought experiments demonstrate a need for stability that can resist activity-dependent synaptic scaling and feedback in non-synaptic excitability. Assume that red is the signal for danger. The signal is unusual but is expected to initiate activity in a

hypothetical neuron or local network, and it requires a specific response. In the absence of a red signal, the impulse traffic increases as a result of negative feedback in synaptic strength and non-synaptic excitability. The frequency of false red signals – with the possibly undesirable reaction this could cause – would thus increase. Over a longer period of time, a fixed level of excitability would guarantee stable and balanced function, even in the case of these potentially important, but perhaps seldom active neurons [12]. The opposite can also be possible for very active neurons. Below, a solution for this is shown: the resetting of the neuron to its genetically predetermined, stable excitability through calibration.

The balance between excitability and stability

Instability is built into the function of a collection of neurons in a network [26]. An impulse from a neuron can generate impulses in other neurons through synapses, gap junctions and ephaptic transfer. In this system, an uncontrollable chain reaction or feedback can easily occur. Neural networks need homeostatic regulation of individual neurons to maintain stability. Hyperexcitability results in the risk of epileptic seizures in motoneurons in *Drosophila* [31]. If excitability in the neuron or network is too high, the worst-case scenario is that this will spark an epileptic discharge.

Electroconvulsive therapy (ECT) is used as a treatment for psychoses and mood disorders [32]. Electrodes placed on the surface of the skull induce reactions similar to epileptic seizures. Remarkably, it seems that seizures can always be induced [32]. The potentials for epileptic discharges induced through ECT are not limited to humans; a model for ECT exists in rats [33,34]. The level of excitability in individual neurons and the cortex is always sufficiently high for spreading of epileptic seizures. Nevertheless, epileptic seizures rarely occur spontaneously in a healthy brain. Exceptions exist and in these cases, it is plausible that the general level of excitability in the neurons and networks is elevated.

Prior to initiation of epileptic discharges, inhibitory neurons exert a suppressive effect through synapses. However, a subsequent spreading can be non-synaptic, where the mechanism can also be mediated via electrical field effects, as shown in the hippocampus [35,36]; paradoxically, this would possibly mean that inhibitory neurons with high excitability could also contribute. Theoretically, therefore, it is not certain that high excitability in inhibitory neurons can prevent the spreading of epileptic impulses. This could mean that a regulation of network excitability solely through the balancing of inhibitory neurons against excitatory neurons would only succeed to certain degree before seizures spread. This regulation would thus be unreliable.

For this reason, evolution has developed an acceptably reliable level of excitability in individual neurons. This level is as high as possible but still below the level at which unprovoked adverse reactions and epileptic seizures can occur (Fig. 1A). This means that neuronal excitability maintains a high, evenly distributed level, and in the absence of provocation, excitability will not induce potentially life-threatening, general epileptic seizures (Fig. 1B). However, despite this, seizures can occur in the case of illness or other causes such as ECT (Fig. 1C). This presumes a well-considered regulation of excitability in all neurons within all regions of the cortex.

If stability is to be maintained, the excitability of all individual neurons must have an upper limit which is determined by the requirement that

- unprovoked seizures must be avoided
- saturation of the neuron, which even at moderate levels of stimulation would react with maximum effect [24], needs to be avoided
- excessively high sensitivity can result in false-positive reactions

Excessively low levels of excitability must also be avoided, because they can result in

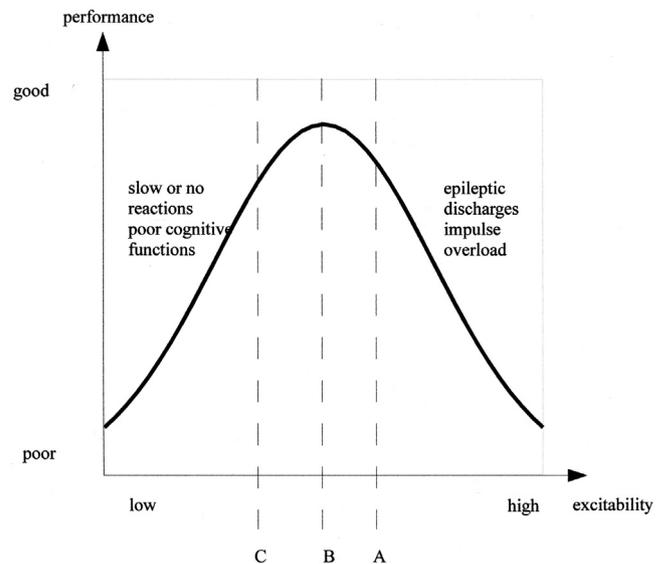


Fig. 1. Schematic drawing showing some levels of neuronal excitability A–C with possible consequences. A. Lower limit when generalized epileptic seizure can occur without provocation, all neurons calibrated to optimal level. B. Optimal level for calibration. C. Lower level when generalized seizure can occur with provocation such as electroconvulsive treatment, all neurons calibrated to optimal level.

- slow reaction times
- false negative reactions
- general sluggishness and reduced cognitive function

The level of excitability that incurs risk for seizures and false-positive reactions cannot be directly identified in a simple way, for example as body temperature can be homeostatically regulated. Excessively high temperatures are detected by sensors and are lowered, just as excessively low temperatures are raised. Seizures and false-positive reactions, on the other hand, occur without any prior warning signs, just as excessively low excitability with accompanying lack of performance does not offer detectable signals. Only the species' experiences over time, inherited via evolution, can determine the optimal level of excitability – and this level can differ for the various parts of the neuronal networks.

At the same time that excitability is to remain within these stringent limits, the conditions for stability are continually challenged by changes taking place in the brain [37]:

- growth and pruning of neurons and changes in neuron geometry
- turnover of ion channels
- neuromodulatory changes
- changes related to aging
- activity-dependent influences such as Hebbian plasticity and negative feedback in excitability

High excitability in a neuron in a chain that is part of a network cannot be compensated by low excitability in another neuron. This kind of regulation would lead to suboptimal function in both neurons.

The hypothesis

Highly developed species in the animal kingdom - mammals and others – can be described by the argument below. All neurons in the CNS, regardless of whether they are excitatory (with for example transmitter substances such as glutamate or acetylcholine), and thus stimulating the postsynaptic neuron, or inhibitory (such as GABA-erga), and thus suppressing the postsynaptic neuron, must contribute to the

best possible functions with respect to impulse creation.

“Calibration” is a technical term referring to checking and adjustment against a set standard; in this hypothesis, the standard is a genetically predetermined and fixed level of excitability, regardless of the activity. The guarantor of stable, predetermined and well-defined excitability in individual neurons is calibration. Activity-dependent negative feedback maintains temporary stability during periods of wakefulness between calibrating sleep periods. In addition to the mandatory requirement of sleep, it can be assumed that calibration has many physiological mechanisms.

The following describes a proposal regarding the physiological mechanisms for calibration, to show that calibration is possible. Every credible sleep hypothesis must explain why reversible unconsciousness is a necessary and central condition [12]. It is not sufficient to say that unconsciousness is one of many equivalent factors that merely facilitate the function of sleep. In that case, evolution would have been able to eliminate sleep for one or more species or individuals.

A calibration of neuronal non-synaptic excitability requires a predictable, stable environment without external influences in the form of uncontrollable impulses with origins in the sensory organs. The condition can be fulfilled through a disconnection of the brain when the afferent impulse traffic is reduced on one or more levels and cognitive and other functions (including the synaptic function) are suppressed in the brain - and finally unconsciousness. The impulse traffic generated during calibration would not only prevent meaningful function but would also lead to chaotic, damaging function; therefore, motor functions must be reduced.

SWA

SWA is most intensive at the beginning of SWS [38]. Electrodes placed deep in the brain or intracellularly in thalamic or cortical pyramidal cells have shown that the polarization of the cell membrane during SWA switches between an up and a down state. “Up” is a depolarized, excitable state close to the cell membrane’s resting potential and “down” is a hyperpolarized, non-excitable state that is synchronous across groups of neurons [39]. Despite thorough and detailed knowledge of the membrane characteristics of neurons and networks in vitro and in vivo during SWS, and in trials using anesthetized animals, consensus is lacking regarding the slow oscillations [33]. Their function has been called a mystery; however, the notion that they play a role in the creation of memory has been proposed [40], as has their participation in a normalization of synapse strength [41]. How these oscillations are generated is unclear [42]. The oscillations are characterized by a square wave with an up- and down-phase with a frequency of < 1 Hz. The up- and down-phases have a stable plateau shape [42,43]. The down-phase has a shorter duration [19,44]. During the up-phase, discharges of action potentials occur [39]. The slow oscillation could be part of a mechanism for calibration.

The calibration mechanism for non-synaptic excitability and SWA

The following mechanism for the generation of action potentials and calibration during SWA should be understood as a theoretical proposal. During the down-phase with hyperpolarization, synchronously within larger regions, significant stoppage of circulating impulse traffic takes place in the region. The inactivation of Na channels – and during the up-phase this involves a significant number of Na channels [45] – is halted. All Na channels in relevant neurons in the AIS thus become available for activation, and non-synaptic excitability increases. As a result, during the transition to the up-phase, trains of action potentials are created. The down-phase can also contribute, based on hyperpolarization, to the stabilization of the membrane potentials of the up-phase.

If the oscillation’s up-phase close to the resting phase of the membrane potential encounters a high threshold and the accompanying

excessively low non-synaptic excitability does not lead to action potentials or action potentials with low FR, this will lead – via negative feedback in non-synaptic excitability – to a slight decrease of the threshold for each period of the up-phase. Non-synaptic excitability will increase until action potentials are generated with increasingly higher FR until the FR_{cal} (which can but is not required to be identical with FR_{fb}) is reached. If in a corresponding manner the oscillation’s up-phase encounters a low threshold, there will be a downward regulation of excitability via negative feedback. Gradually the threshold level will be calibrated to a level adapted to the polarization of the up-phase, with the neuron’s FR_{cal} as the set point for regulation. The entire neuron participates in impulse generation, but the decisive factor for this feedback with regulation of excitability (in addition to dendrites and soma) is found in the AIS [46,47]. Growth and regeneration of voltage-sensitive Na channels, K channels and Ca channels can offer such mechanisms [48,49]. On a cellular and molecular level, there are many examples of mechanisms that enable regulation of both synapses and intrinsic excitability. For summary reviews of possible mechanisms see Krueger/Obal [12], Meier/Semtner/Wolfart or Nelson/Turrigiano [50]. Therefore, with calibration during slow oscillations, a genetically predetermined, stable threshold is created for impulse generation in the neuron. Inhibitory neurons can also require calibration to maintain a balance with respect to excitatory neurons [51,52].

Neuronal excitability is determined by non-synaptic excitability as well as synaptic strength. It is possible that in this first step, calibration with slow oscillations does not affect synaptic functions and concerns primarily non-synaptic excitability.

The fact that SWA can play a role in calibration does not rule out another type of calibration in limited neuron populations or regions of the brain during NREM or REM sleep. Also other sleep rhythms (such as sleep spindles) could have a calibrating function. The lack of SWA in animals such as reptiles and *Drosophila melanogaster* indicates that they are equipped with other mechanisms for sleep calibration.

REM sleep is also characterized by reversible unconsciousness. As in the case of SWS, it is difficult to find another credible cause than function control and calibration. REM sleep can also be part of the secondary regulation of synaptic strength, as discussed below.

A proposed mechanism for secondary regulation of synaptic strength based on non-synaptic excitability

The calibration of non-synaptic excitability could have a secondary purpose of stabilizing synaptic strength, which is included in the neuron’s total excitability, with a stepwise, iterative process and a solution is possible. Feedback in synaptic strength, in common with non-synaptic excitability, can lead to a specific synaptic strength via resetting of FR, whose desired state of equilibrium FR_{fb} has been altered during the calibration of non-synaptic excitability. As a result, both synaptic strength and non-synaptic excitability will be able to reach a single, unique, stable equilibrium, and be bound to each other.

This secondary feedback regulation of synaptic strength and non-synaptic excitability can take place during non-SWS, i.e. during REM sleep or light sleep. In the absence of sensory signal input, spontaneous, post-synaptic excitatory and inhibitory miniature potentials have noise-like characteristics, quite stationary and unchanged from calibration to calibration [43,51]. In the first step after calibration, the secondary feedback regulation will once again shift non-synaptic excitability from the level of FR_{cal} , which was the target during calibration, to the level of FR_{fb} . The calibration with SWA can then return with additional steps toward ever smaller deviations of FR from the desired levels of FR_{fb} and FR_{cal} in an iterative process that switches between SWS and non-SWS. A calibration of the neuron’s total excitability will thus be facilitated, for example by human sleep architecture, by a cyclical process where SWS is followed by REM sleep and light sleep. The sleep architecture of dogs [53], cats [54] and rats [23,55] with its rapid and frequent transitions between SWS and non-SWS can also facilitate the calibration of

neuronal excitability.

Observations that can support the hypothesis

Effects of sleep deprivation

Sleep deprivation leads to increased cortical excitability, measured through median-nerve stimulation and transcranial magnetic stimulation [56,57]. It also increases intrinsic excitability in rat prefrontal neurons [21]. This mechanism may be due to a reduced after-hyperpolarization. Sleep calibration restores excitability in individual excitatory and perhaps inhibitory neurons and thus returns networks to their original levels. In addition, sleep deprivation has been shown to diminish cognitive function in humans [58]. Sleep deprivation can be expected to lead to reduced balance, with increased and/or decreased excitability in excitatory or inhibitory neurons. This is why sleep improves cognitive function.

Partial or total sleep deprivation results in general increased reaction times [59,60]. This is contradictory according to the observations above regarding increased excitability that has been observed in cortical networks, but it would be consistent with reduced excitability in certain neurons after sleep deprivation, in analogy with the notion that reduced excitability is associated with increased latency from stimulus to action potentials in neurons in tissue cultures [61]. Sleep with calibration restores reaction times. However, increased reaction times after sleep deprivation are difficult to combine with generally increased excitability, which is one of the prerequisites for Synaptic Homeostasis Hypothesis (SHY, see below).

Sleep deprivation results in unstable and unpredictable behavior patterns [59], not just the lack of response to stimulation (false-negative response) and response without stimuli (false-positive response). This could be consistent with the presence of uncalibrated neurons with randomly increased or decreased excitability.

Sleep deprivation can induce clinical seizures or epileptiform interictal activity in EEGs [62]. Possible causes could be uncalibrated excitatory neurons with high excitability or inhibitory neurons with low (or high) excitability [52,63,64]. Calibration reduces this risk.

Sleep homeostasis

Long periods of wakefulness can be expected to lead to greater deviations from the optimal level of excitability [38]. The duration of SWS has been shown to increase after sleep deprivation, which could be explained by larger deviations prior to calibration [65,66]. The time for resetting this excitability and the duration of sleep therefore increases.

Age-related variations in sleep

During growth and development, the neuronal environment changes quickly, and this places greater requirements on calibration. Young individuals sleep longer and with more SWA, while older individual sleep less and with less SWA.

Memory consolidation

Under certain circumstances, NREM sleep can affect plasticity. During the critical period for visual development in cats, sleep strengthens the synaptic remodeling that takes place after monocular deprivation (MD) [67]. This finding can be considered a typical example of memory consolidation during sleep.

The following arguments could be applied to MD, but also to other events that lead to plasticity. Excitability reduced by plasticity in the synapses in question and the resulting decrease in the neuron's impulse traffic would lead to negative feedback in the conscious state, which counteracts the effect in these neurons with some lessening of the decrease in excitability as a result. According to this hypothesis, a

subsequent calibration during sleep with resetting of excitability – which would decrease – would thus counteract the effect of feedback in excitability and partially restore the effect of plasticity. The corresponding argument can be made for events with increased excitability, which with increased impulse traffic in the neuron in question is counteracted by feedback in excitability. Calibration restores excitability, and thus appears to have strengthened the effect of plasticity. Both of these variants of calibration partially restore the effect of plasticity and could contribute to a result that resembles consolidation during sleep.

FR homeostasis inhibited during sleep

Visual deprivation disturbance affects the FR of rats, first with a decrease in FR, which later returns to the neuron characteristic value [23]. During epochs of sleep with a median of 18 min, this later phase of return stops up to a plateau-like level. This may seem to contradict the hypothesis, which at first sight would be expected to restore FR during these epochs. A possible interpretation of the finding in line with this hypothesis could be based on that synaptic strength increases during the return phase of Hebbian plasticity from the low level. Intrinsic excitability compensates homeostatically with high excitability. In the following calibration, intrinsic excitability is successively restored to a lower set point, which more or less interacts with rising synaptic strength to create a plateau-like condition in the FR.

Reduced spreading of FR during sleep

The spreading of FR in pyramid cells in rats decreases during sleep [19]. Fast-rate firing pyramid cells reduce their FR during sleep, while slow-rate firing cells increase their FR. This is interpreted as a general reduction or increase of FR, based on the pyramid cells' designation as fast- or slow-firing. Another interpretation based on this hypothesis is that wakefulness results in spreading of FR in individual pyramid cells from the original FR_b .

It can be shown that

$$FR_a^2 = FR_b^2 + FR_w^2$$

where

FR_a^2 is the variance in FR in the entire population of pyramid cells after a period of wakefulness

FR_b^2 is the variance in FR in the entire population of pyramid cells before a period of wakefulness

and FR_w^2 is the variance in the additional spreading in individual pyramid cells that takes place during the wakeful period.

This results in the observation of generally increased spreading of FR during wakefulness with a shifting of the distribution graph tails with fast-rate firing toward an even faster rate and slow-rate firing toward a slower rate. During sleep, the spreading decreases once again.

Comparisons with some earlier hypotheses

- The Null Hypothesis – sleep occurs because there is no other meaningful activity [68 70].
- During sleep, metabolic products are released from nerve cells [70].

Neither of these hypotheses or similar ones can explain the absolute need for reversible unconsciousness.

- Memory retention and consolidation have been observed to benefit from sleep, and this has been considered the best explanation for the need for sleep [71].

There are no fundamental or sufficiently strong reasons that consolidation would require unconsciousness, and that this process could not take place during consciousness. Therefore, memory consolidation should be understood as an epiphenomenon.

- A hypothesis for the function of sleep, SHY, is particularly interesting because it is based on the need for stability in the brain, and builds on the mechanisms that resemble synaptic scaling and the requirement on the reversible unconsciousness offered by sleep [69,72,73]. The hypothesis is based on the notion that as a result of Hebbian plasticity and accumulated experiences, synaptic strength generally increases during consciousness. Maintaining stability would require downward regulation of synaptic strength with synaptic downscaling during sleep, which would lead to the normalization of synaptic strength at a lower level. This hypothesis has met with criticism [74,75]. Like the hypothesis presented here, SHY is based on the demand for stability in neuronal networks. The difference is that this hypothesis assumes that negative feedback in neuronal excitability takes place during consciousness, and that a subsequent calibration to genetically predetermined levels can both increase and decrease excitability in individual neurons. Calibration is also needed to counteract other changes in the nervous system.

Both hypotheses include slow oscillations as part of a possible mechanism for regulation, with downward adjustment of synaptic strength in SHY and up- or downscaling of neuronal excitability in this hypothesis. In connection with SHY, computer simulation has shown that under certain circumstances, downscaling can result in a bistable function with SWA-like up- and down-states, and that this could actively contribute to “renormalization” [41]. In this hypothesis, SWA is assigned as active role in the regulation of non-synaptic excitability.

The foundational principle of SHY – a general downscaling during sleep – is an activity that should be able to take place simultaneously with Hebbian plasticity, which operates during consciousness. It is difficult to find counterarguments to this cited reference [74]. If so, the need for downscaling during sleep would have been able to be eliminated with the help of evolution. Nevertheless, sleep is still around, and it clearly has another important function that cannot be sufficiently explained by SHY and downscaling. In addition, it has recently been demonstrated that sleep achieves both upward and downward regulation of FR, and thus excitability [19].

Conclusions

Hypothetically, a nervous system could also function without sleep and calibration, but at the cost of diminished and less reliable function and/or greater risk for uncontrolled feedback, i.e., epileptic discharges; however, evolution has clearly abandoned this alternative.

A basic dilemma for a complex central nervous system is that stability is counter to excitability and flexibility. Instability resulting from sleep deprivation creates a risk of uncontrolled feedback as in the case of epileptic seizures, but can also manifest itself as an unpredictable function. Positive feedback such as Hebbian plasticity contributes to instability. Negative feedback provides only a short-term solution to the stability problem, and can create other problems, for example in the case of unusual events.

The primary hypothesis – that the function of sleep is to enable calibration of individual neurons in a central nervous system – is founded on the circumstances that can be observed in a close examination of ECT results; excitability in the cortex is higher than would be possible without fine, precision adjustment of excitability in individual neurons, and that sleep lacks a plausible explanation. The hypothesis finds more or less support in the previously published observation cited here:

The existence of a notable phenomenon such as SWA has not been clearly explained, but it could have a part to play in calibration. The risk of epileptic seizures and unforeseen reactions support the notion of increased instability resulting from sleep deprivation, but these effects are counteracted by sleep with calibration, which also stabilizes.

A longer period of wakefulness entails greater deviations from stable excitability, which results in the need for longer calibration times (sleep homeostasis).

Neurons or networks that are seldom active but important cannot be stabilized with negative feedback, but calibration can solve this problem.

Calibration can only take place offline, and this requires reversible unconsciousness with disconnection from muscular activity.

Sleep architecture with cyclical processes can be consistent with an iterative process that extends stability in the neuron to synaptic strength.

Rapid changes in neurons and the environment of young individuals threaten stability. In young individuals, calibration and sleep require more time.

Under certain circumstances, calibration during sleep could offer results that (at least superficially) resemble memory consolidation. Calibration of excitability in individual neurons could explain how the spreading of FR during consciousness in rats is restored during sleep.

Sleep resets evolution’s genetic memory tracks that have developed of long periods of time, after the less permanent experiences gained during consciousness. During consciousness, flexibility with plasticity is the order of the day, modified by negative feedback in excitability. During sleep, stability is ensured with calibration of excitability.

Knowledge about the function of sleep is essential in human medicine. Sleep is an important factor in Alzheimer’s disease [76]. In *Drosophila*, β -amyloid (a peptide with a key role in the development of Alzheimer’s disease) gives a reduced sleep, which in turn leads to increased intrinsic excitability. In a vicious circle this then leads to increase in β -amyloid burden [22]. Even in conditions such as schizophrenia [77], depression [78,79], fibromyalgia [80], headache [81] and pain from rheumatoid arthritis [82], sleep is an important factor. The understanding of the brain cannot be complete without an understanding of the function of sleep.

Funding

No funding.

Declaration of Competing Interest

None.

References

- [1] Steriade M, McCormick DA, Sejnowski TJ. Thalamocortical oscillations in the sleeping and aroused brain. *Science* 1993;262:679–85.
- [2] Mignot E. Why we sleep: the temporal organization of recovery. *PLoS Biol* 2008;6(4):e106.
- [3] Rattenborg NC. Evolution of slow-wave sleep and palliopalial connectivity in mammals and birds: a hypothesis. *Brain Res Bull* 2006;69(1):20–9.
- [4] Rattenborg NC, Amlaner CJ, Lima SL. Behavioral, neurophysiological and evolutionary perspectives on unihemispheric sleep. *Neurosci Biobehav Rev* 2000;24(8):817–42.
- [5] Kaiser W, Steiner-Kaiser J. Neuronal correlates of sleep, wakefulness and arousal in a diurnal insect. *Nature* 1983;1983:707–9.
- [6] Nitz DA, van Swinderen B, Tononi G, Greenspan RJ. Electrophysiological correlates of rest and activity in *Drosophila melanogaster*. *Curr Biol* 2002;12(22):1934–40.
- [7] Hendricks JC, Finn SM, Panckeri KA, Chavkin J, Williams JA, Sehgal A, et al. Rest in *Drosophila* is a sleep-like state. *Neuron* 2000;25(1):129–38.
- [8] Frank MG, Waldrop RH, Dumoulin M, Aton S, Boal JG. A preliminary analysis of sleep-like states in the cuttlefish *sepia officinalis*. Balaban E, editor. *PLoS One* 2012;7(6):e38125.
- [9] Harliwicz DD. Behavioural aspects of the New Zealand octopus *Pinnocotopus cordiformis*: acclimation, sleep deprivation and responses to video stimuli [thesis]. University of Canterbury; 2011.
- [10] Stephenson R, Lewis V. Behavioural evidence for a sleep-like quiescent state in a pulmonate mollusc, *Lymnaea stagnalis* (Linnaeus). *J Exp Biol* 2011;214:747–56.
- [11] Nath RD, Bedbrook CN, Abrams MJ, Basinger T, Bois JS, Prober DA, et al. The jellyfish *cassiopea* exhibits a sleep-like state. *Curr Biol* 2017

- Oct;27(19):2984–2990.e3.
- [12] Krueger JM, Obal Jr F. Sleep function. *Front Biosci* 2003;1(8):d511–9.
- [13] Herculano-Houzel S. The human brain in numbers: a linearly scaled-up primate brain. *Front Hum Neurosci* 2009;3.
- [14] DiNuzzo M, Nedergaard M. Brain energetics during the sleep–wake cycle. *Curr Opin Neurobiol* 2017;47:65–72.
- [15] Markram H, Lübke J, Frotscher M, Sakmann B. Regulation of synaptic efficacy by coincidence of postsynaptic APs and EPSPs. *Science* 1997;275(5297):213–5.
- [16] Magee JC, Johnston D. A synaptically controlled, associative signal for hebbian plasticity in hippocampal neurons. *Science* 1997;1997(275):209–13.
- [17] Diekelmann S, Born J. The memory function of sleep. *Nat Rev Neurosci* 2010;11:114–26.
- [18] Ellenbogen JM, Hulbert JC, Stickgold R, Dinges DF, Thompson-Schill SL. Interfering with theories of sleep and memory: sleep, declarative memory, and associative interference. *Curr Biol* 2006;16(13):1290–4.
- [19] Watson BO, Levenstein D, Greene JP, Gelinas JN, Buzsáki G. Network homeostasis and state dynamics of neocortical sleep. *Neuron* 2016;90(4):839–52.
- [20] Miyawaki H, Diba K. Regulation of hippocampal firing by network oscillations during sleep. *Curr Biol* 2016;26(7):893–902.
- [21] Yan J, Li J-C, Xie M-L, Zhang D, Qi A-P, Hu B, et al. Short-term sleep deprivation increases intrinsic excitability of prefrontal cortical neurons. *Brain Res* 2011;1401:52–8.
- [22] Tabuchi M, Lone SR, Liu S, Liu Q, Zhang J, Spira AP, et al. Sleep interacts with A β to modulate intrinsic neuronal excitability. *Curr Biol*. 2015;25(6):702–12.
- [23] Hengen KB, Torrado Pacheco A, McGregor JN, Van Hooser SD, Turrigiano GG. Neuronal firing rate homeostasis is inhibited by sleep and promoted by wake. *Cell* 2016;165(1):180–91.
- [24] Schulz DJ. Plasticity and stability in neuronal output via changes in intrinsic excitability: it's what's inside that counts. *J Exp Biol* 2006;209(24):4821–7.
- [25] D'Angelo E. Homeostasis of intrinsic excitability: making the point. *J Physiol* 2010;588(6):901–2.
- [26] Turrigiano GG. Homeostatic plasticity in neuronal networks: the more things change, the more they stay the same. *Trends Neurosci* 1999;22(5):221–7.
- [27] Turrigiano GG. The self-tuning neuron: synaptic scaling of excitatory synapses. *Cell* 2008 Oct;135(3):422–35.
- [28] Mahoney RE, Rawson JM, Eaton BA. An age-dependent change in the set point of synaptic homeostasis. *J Neurosci*. 2014;34(6):2111–9.
- [29] Desai NS. Homeostatic plasticity in the CNS: synaptic and intrinsic forms. *J Physiol-Paris* 2003;97(4–6):391–402.
- [30] Joseph A, Turrigiano GG. All for one but not one for all: excitatory synaptic scaling and intrinsic excitability are coregulated by CaMKIV, Whereas inhibitory synaptic scaling is under independent control. *J Neurosci* 2017;37(28):6778–85.
- [31] Giachello CN, Baines RA. Regulation of motoneuron excitability and the setting of homeostatic limits. *Curr Opin Neurobiol* 2017;43:1–6.
- [32] van Waarde JA, Verwey B, van der Mast RC. Meta-analysis of initial seizure thresholds in electroconvulsive therapy. *Eur Arch Psychiatry Clin Neurosci* 2009;259(8):467–74.
- [33] Porsolt RD, Le Pichon M, Jalfre M. Depression: a new animal model sensitive to antidepressant treatments. *Nature* 1977;266:730–2.
- [34] Li B, Suemaru K, Cui R, Kitamura Y, Gomita Y, Araki H. Repeated electroconvulsive stimuli increase brain-derived neurotrophic factor in ACTH-treated rats. *Eur J Pharmacol* 2006;529(1–3):114–21.
- [35] Zhang M, Ladas TP, Qiu C, Shivacharan RS, Gonzalez-Reyes LE, Durand DM. Propagation of epileptiform activity can be independent of synaptic transmission, gap junctions, or diffusion and is consistent with electrical field transmission. *J Neurosci* 2014;34(4):1409–19.
- [36] Qiu C, Shivacharan RS, Zhang M, Durand DM. Can neural activity propagate by endogenous electrical field? *J Neurosci* 2015;35(48):15800–11.
- [37] Marder E, Prinz AA. Current compensation in neuronal homeostasis. *Neuron* 2003;37(1):2–3.
- [38] Dijk D-J. EEG slow waves and sleep spindles: windows on the sleeping brain. *Behav Brain Res* 1995;1995(69):109–16.
- [39] Neske GT. The slow oscillation in cortical and thalamic networks: mechanisms and functions. *Front Neural Circuits* 2016;9.
- [40] Timofeev I, Bazhenov M. Mechanisms and biological role of thalamocortical oscillations. In: Columbus FH, editor. *Trends in Chronobiology Research*. New York: Nova Science Publishers; 2006. p. 1–47.
- [41] Olcese U, Esser SK, Tononi G. Sleep and synaptic renormalization: a computational study. *J Neurophysiol* 2010;104(6):3476–93.
- [42] Wilson MT, Barry M, Reynolds JNJ, Crump WP, Steyn-Ross DA, Steyn-Ross ML, et al. An analysis of the transitions between down and up states of the cortical slow oscillation under urethane anaesthesia. *J Biol Phys* 2010;36(3):245–59.
- [43] Haider B. Neocortical network activity in vivo is generated through a dynamic balance of excitation and inhibition. *J Neurosci* 2006;26(17):4535–45.
- [44] Chauvette S, Crochet S, Volgushev M, Timofeev I. Properties of slow oscillation during slow-wave sleep and anesthesia in cats. *J Neurosci* 2011;31(42):14998–5008.
- [45] Kuo C-C, Bean BP. Na⁺ channels must deactivate to recover from inactivation. *Neuron* 1994;12(4):819–29.
- [46] Buffington SA, Rasband MN. The axon initial segment in nervous system disease and injury: the AIS in nervous system disease. *Eur J Neurosci* 2011 Nov;34(10):1609–19.
- [47] Clark BD, Goldberg EM, Rudy B. Electrotonic tuning of the axon initial segment. *Neuroscientist* 2009;15(6):651–68.
- [48] Kuba H, Oichi Y, Ohmori H. Presynaptic activity regulates Na⁺ channel distribution at the axon initial segment. *Nature* 2010;465(7301):1075–8.
- [49] Bender KJ, Uebele VN, Renger JJ, Trussell LO. Control of firing patterns through modulation of axon initial segment T-type calcium channels: axon initial segment control of firing patterns. *J Physiol* 2012;590(1):109–18.
- [50] Nelson SB, Turrigiano GG. Strength through diversity. *Neuron* 2008;60(3):477–82.
- [51] van Vreeswijk C, Sompolinsky H. Chaos in neuronal networks with balanced excitatory and inhibitory activity. *Science* 1996;274(5293):1724.
- [52] Isaacson JS, Scanziani M. How inhibition shapes cortical activity. *Neuron* 2011 Oct;72(2):231–43.
- [53] Kaitin KI, Kilduff TS, Dement WC. Sleep fragmentation in canine narcolepsy. *Sleep* 1986;1:116–9.
- [54] Prospero-Garcia O, Herold N, Phillips TR, Elder JH, Bloom FE, Henriksen SJ. Sleep patterns are disturbed in cats infected with feline immunodeficiency virus. *Proceedings of the National Academy of Sciences*; 1994. p. 12947–51.
- [55] Leemburg S, Vyazovskiy VV, Olcese U, Bassetti CL, Tononi G, Cirelli C. Sleep homeostasis in the rat is preserved during chronic sleep restriction. *PNAS* 2010;36:15939–44.
- [56] Gorgoni M, Ferlazzo F, Moroni F, D'Atri A, Donarelli S, Fanelli S, et al. Sleep deprivation affects somatosensory cortex excitability as tested through median nerve stimulation. *Brain Stimulat* 2014;7(5):732–9.
- [57] Huber R, Maki H, Rosanova M, Casarotto S, Canali P, Casali AG, et al. Human cortical excitability increases with time awake. *Cereb Cortex* 2013;23(2):1–7.
- [58] Jackson ML, Croft RJ, Owens K, Pierce RJ, Kennedy GA, Crewther D, et al. The effect of acute sleep deprivation on visual evoked potentials in professional drivers. *Sleep* 2008;31(9):1261–9.
- [59] Lim J, Dinges DF. Sleep deprivation and vigilant attention. *Ann N Y Acad Sci* 2008;1129(1):305–22.
- [60] Taheri M, Arabameri E. The effect of sleep deprivation on choice reaction time and anaerobic power of college student athletes. *Asian J Sports Med* 2012;3(1):15.
- [61] Gal A, Eytan D, Wallach A, Sandler M, Schiller J, Marom S. Dynamics of excitability over extended timescales in cultured cortical neurons. *J Neurosci* 2010;30(48):16332–42.
- [62] Ellingson RJ, Wilken K, Bennett DR. Efficacy of sleep deprivation as an activation procedure in epilepsy patients. *J Clin Neurophysiol* 1984;1(1):83–101.
- [63] Meisel C, Schulze-Bonhage A, Freestone D, Cook MJ, Achermann P, Plenz D. Intrinsic excitability measures track antiepileptic drug action and uncover increasing/decreasing excitability over the wake/sleep cycle. *Proc Natl Acad Sci* 2015;112(47):14694–9.
- [64] Scalise A, Desiato MT, Gigli GL, Romigi A, Tombini M, Marciani MG, et al. Increasing cortical excitability: a possible explanation for the proconvulsant role of sleep deprivation. *Sleep* 2006;29(12):1595–8.
- [65] Greene RW, Frank MG. Slow wave activity during sleep: functional and therapeutic implications. *Neuroscientist* 2010;16(6):618–33.
- [66] Davis CJ, Clinton JM, Jewett KA, Zielinski MR, Krueger MJ. Delta wave power: an independent sleep phenotype or epiphenomenon? *J Clin Sleep Med* 2011;7(5):S16–8.
- [67] Frank MG, Issa NP, Stryker MP. Sleep enhances plasticity in the developing visual cortex. *Neuron* 2001;30(1):275–87.
- [68] Rial RV, Nicolau MC, Gamundi A, Akaärir M, Aparicio S, Garau C, et al. The trivial function of sleep. *Sleep Med Rev* 2007;11(4):311–25.
- [69] Cirelli C, Tononi G. Is sleep essential? *PLoS Biol* 2008;6(8):e216.
- [70] Xie L, Kang H, Xu Q, Chen MJ, Liao Y, Thiyyagarajan M, et al. Sleep drives metabolite clearance from the adult brain. *Science* 2013;342(6156):373–7.
- [71] Wang G, Grone B, Colas D, Appelbaum L, Mourrain P. Synaptic plasticity in sleep: learning, homeostasis and disease. *Trends Neurosci* 2011;34(9):452–63.
- [72] Tononi G, Cirelli C. Sleep and the price of plasticity: from synaptic and cellular homeostasis to memory consolidation and integration. *Neuron* 2014;81(1):12–34.
- [73] Tononi G, Cirelli C. Sleep and synaptic homeostasis: a hypothesis. *Brain Res Bull* 2003 Dec;62(2):143–50.
- [74] Frank MG. Erasing synapses in sleep: is it time to be SHY? *Neural Plast* 2012;2012:1–15.
- [75] Frank MG. Why I am not SHY: A reply to Tononi and Cirelli. *Neural Plast* 2013;2013:1–3.
- [76] Peter-Derex L, Yammine P, Bastuji H, Croisile B. Sleep and Alzheimer's disease. *Sleep Med Rev* 2015;19:29–38.
- [77] Ferrarelli F, Huber R, Peterson MJ, Massimini M, Murphy M, Riedner BA, et al. Reduced sleep spindle activity in schizophrenia patients. *Am J Psychiatry* 2007;164(3):483–92.
- [78] Kundermann B, Hemminger-Spernal J, Huber MT, Krieg J-C, Lautenbacher S. Effects of total sleep deprivation in major depression: overnight improvement of mood is accompanied by increased pain sensitivity and augmented pain complaints. *Psychosom Med* 2008;70(1):92–101.
- [79] Hemminger U-M, Hemminger-Spernal J, Krieg J-C. Sleep deprivation in depression. *Expert Rev Neurother* 2010;10(7):1101–15.
- [80] Roizenblatt S, Neto NSR, Tufik S. Sleep disorders and fibromyalgia. *Curr Pain Headache Rep* 2011;15(5):347–57.
- [81] Alberti A. Headache and sleep. *Sleep Med Rev* 2006;10(6):431–7.
- [82] Irwin MR, Olmstead R, Carrillo C, Sadeghi N, FitzGerald JD, Ranganath VK, et al. Sleep loss exacerbates fatigue, depression, and pain in rheumatoid arthritis. *Sleep* 2012 Apr 1;35(4):537–43.