Chapter

Introductory Chapter: The Promise of Sleep Pharmacotherapy - Healing Systems Level Dysfunction

Denis Larrivee

1. Introduction

Perhaps no behavioral feature is more evident and more widely distributed, nor more sought after than sleep. Yet, it is for its distinctiveness that sleep has often seemed at odds with daily needs, where attention and responsivity are critical to survival. Its presence, therefore, reveals the existence of some undetermined physical need, which no other mechanism can physically respond to.

Given the prominence and regularity of sleep, this physical need, and the physiological mechanisms used to satisfy it, can be expected to exert an influence on many bodily processes. Indeed, the events of sleep are now known to affect a broad number of fundamental bodily systems that may be enhanced or diminished in parallel with sleep phases. Sleep or circadian-related influences, for example, have been documented for autonomic function [1], hormone secretion/core-body temperature rhythm [2], energy production such as glucose metabolism [3], and coordinated motor and immune functions. By extension, disruption of sleep mechanisms can be expected to negatively impact the many processes that are subject to their influence [4].

A growing body of evidence indicates that the events of sleep have their origin in properties of the brain and nervous system circuitry. During NREM sleep, for instance, down states have been shown to be associated with a slowly traveling, oscillation wave that is synchronized throughout the cortex and substantial portions of the subcortex [5]. Transitioning between sleep stages, additionally, involves the modulation of an arousal system that is distributed throughout the brain and that choreographs the shape of sleep architecture. These and many other details imply that the systemic processes affected by sleep are initially affected by a global impact exerted at the level of the brain, which potentially affects such events as developmental regimes of synaptogenesis [6], psychiatric dysfunctions [7], addiction [8], hormonal rhythms [1], and cognitive processes like memory and learning [9].

Those dysfunctional sleep mechanisms that can be linked to secondary systemic dysfunctions offer the intriguing possibility of medically managing and even of therapeutically alleviating such dysfunctions through treatment modalities developed chiefly for sleep disturbances. Drugs that enhance states of sleep, for instance, are also known to alter autonomic physiology, behavior, cognition, and affect [10]. While the complexities of the brain's neurochemistry and circuits mediating

wakefulness and sleep make the control of the precise physiological mechanisms uncertain, there has been considerable progress in developing medications that are narrowly tailored to various features of sleep, such as rapid sleep onset, minimal hangover, and low abuse potential, among other properties [11]. That is, the current evolution in sleep pharmacotherapy has generated an armamentarium of sufficient precision that it may be redirected to other neural systems. An improving database, moreover, can be expected to further the ability to tailor sleep modulation so as to selectively modulate events directly affected by sleep mechanisms.

An important component of rational therapeutic intervention, nonetheless, clearly also requires a continually improving understanding of the sleep mechanisms themselves [12]. This is to say that only from a knowledge of sleep can the understanding of how it affects other systems be discerned. Accordingly, this chapter will review several leading hypotheses regarding the physical properties that govern sleep mechanisms, the prospects for modulating these properties pharmacologically, and the systemic effects such therapy may have.

2. The universal need for sleep

Each time sleep occurs the ability to appraise the events around us is lost. This interruption of sensorial content represents a definitional and unique feature of sleep, one that distinguishes it from other behavioral states, all of which otherwise retain the ability to promptly respond to stimuli. Although it is unknown why it should be necessary to prevent the brain from receiving input for prolonged intervals, the fact that humans and all other animal species require sleep indicates the existence of a fundamental physical and neural reason for it to occur; that is, sleep serves at least one essential function that cannot be carried out while awake.

One widely acknowledged proposal links this essential function to neuronal properties evoked by centrally directed communication, which involves changes in interneuronal exchange at the level of the synapse. This hypothesis, termed the synaptic homeostasis hypothesis (SHY), privileges the unique ability of the brain to learn from external events of the world that become inscribed through neuroplastic changes in synaptic connections [12]. The SHY hypothesis proposes that these neuroplastic changes entail sensorium-induced increases in synaptic potentiation, which can be visualized electrophysiologically in miniature endplate potentials; that is, there is a *sensorium-induced* increase in synaptic potentiation. Because the extent of potentiation necessarily possesses an upper limit, there is a need to regularly reduce the level of potentiation so that the brain can continue to learn. This readjustment is proposed to occur during sleep.

Hence, sleep is the mechanism that has evolved to account for the cost of the physical events of neuroplasticity, which enable the organism to adapt and survive in a constantly changing environment [13]. When this cost is not accounted for cognitive function is poor. Acute and chronic sleep loss, for example, have pervasive negative effects on performance and many brain functions, including the ability to learn, remember, speak clearly, judge risk, and understand complex information needed for decision making [14]. Post-training "fatigue," for example, the impaired capacity for new learning that follows intense training in a motor or visual task, is restored only by sleep. Physically, therefore, sleep assists in maintaining an overall balance of synaptic strength across brain circuits, which may be conceived as a synaptic renormalization. The hypothesis thus predicts that overall synaptic strength in the brain should not be balanced at all times, but instead should be biased toward a net potentiation during the major wake period and toward a net depression during sleep.

Similar to the SHY hypothesis, the free energy principle of Friston and colleagues hypothesizes that ongoing informational input from the sensorium leads to a rise in the information-related, state variable, entropy [15]. Like potentiation, entropy is a saturable quantity driven by sensorial input that progressively approaches an upper bound. Unlike the potentiation hypothesis, the free energy principle does not postulate a specific period devoted to recovery from synaptic changes. Instead, the brain is proposed to counter the ensuing information accumulation by optimizing behavioral patterns that minimize the need for future change. For instance, inputs that occur together more frequently than would be expected by chance are registered because they suggest regularities in the environment that are predictable. Once these "coincidences" are detected, a neuron communicates them to its target neuron, typically through synaptic strengthening. The effect of registering these "coincidences" thus enables the brain to structure its behavior so as to minimize surprisal and guide the selection of behavioral responses. By such active inferencing [16], the brain comes to reflect the regularities observed in the external world, an organizational arrangement that serves to maximize free energy efficiency.

The free energy principle governing cognition resembles aspects of the SHY hypothesis in providing an explanation for changes in synaptic events that are due to sensorial input and that build on the brain's ability to enable the organism to better confront a continually changing, environmental landscape. Moreover, by staging causal optimization in terms of an entropic cost function, the model accounts for some physical constraints that place an upper bound on synaptic change.

Nonetheless, the free energy principle only indirectly addresses the issue of saturability due to ongoing sensorial novelty, which is inherent in the interactive circumstances of the external world and presumably greatly amplified by the presence of living organisms [17]. This means that the persistence of novel input from the sensorium will continue to generate synaptic reorganization, despite causal inferencing that may diminish the overall level of reorganization. Faced with ongoing novelty, organizational resources of brain synapses can be expected to operate within physical ranges that regularly encounter upper limits under the assumptions of both proposals. Indeed, the observation that all known animal species need to "regularly disconnect" constitutes a strong argument that sensorial novelty is persistent and that its input repeatedly saturates a physical condition that must subsequently be replenished; that is, the brain is "awash" in new experiences for which physical compensation is required. *Hence, while the free energy principle is agnostic with regard to underlying mechanisms that result in saturability, both it and the SHY hypothesis link sleep to ongoing afferent input that modifies the brain's synaptic organization in such a manner as to regularly require renormalization.*

3. Theoretical implications of current sleep models

This conclusion, drawn from two leading proposals that describe sleep mechanisms, has several implications. First – though tautological, existing evidence strongly supports it – observable replenishment mechanisms should entail a sensorial disconnection from the external world and so renormalization should occur during unconsciousness. It has been argued for instance [12] that if the nervous system must acquire information about the environment to survive, such acquisition should be confined to periods of waking rather than during sleep, when neural activity is at least partly disconnected from the external world" [18]. Second, such mechanisms should occur globally; that is, at a minimum, they should be found in all brain domains having sensorial input. Additionally, neuroplastic changes

should also affect downstream targeted destinations; that is, rather than modifying only brain regions receiving direct sensorial input, connectivity changes should be distributed across most domains of the brain. Thirdly, renormalization should occur cyclically, a conclusion that is implicit in the first two consequences of these hypotheses.

3.1 Disconnecting from the sensorium

For excitatory synapses, which account for the majority of the synapses in the mammalian brain, the first prediction has received support from molecular, ultrastructural, and electrophysiological measures of synaptic strength [19]. At the molecular level, changes in the strength of excitatory synapses have been shown to involve changes in the surface expression and subunit composition of the glutamatergic AMPA receptors, as well as phosphorylation and other post-translational changes that alter the open probability of these receptors and their ability to remain anchored to the membrane. Surface insertion of GluA1-containing receptors, and the phosphorylation of GluA1 at Ser831 and Ser845 by CaMKII and PKA, particularly, have been correlated with synaptic potentiation.

RNA-seq analysis in the adult mouse frontal cortex, moreover, has revealed a significant overlap of transcripts differentially expressed between acute sleep deprivation and sleep, and transcripts affected by the loss of the transcription factor myocyte enhancer factor 2C (MEF2C) [20]. This study also found a relative dephosphorylation of MEF2C after 6 h of sleep deprivation as compared to sleep, consistent with a wake-related increase in MEF2C transcriptional activity. Additionally, the study observed an increase in the frequency and amplitude of mEPSCs. Altogether, these findings point to a key role for MEF2C in mediating the response to sleep deprivation and the sleep-dependent decline in excitatory synaptic strength. Consistent with this, MEF2 transcriptional activity is activated in response to glutamate release and membrane depolarization, with the main effect of MEF2 activity in postmitotic neurons that of constraining of dendritic spines and excitatory synapses [21]. Many targets of MEF2, additionally, have been shown to be involved in synaptic weakening, including the genes *Arc* and *Homer1a*.

Electrophysiologically, experimental evidence supports distinct physical changes during the wake or sleep periods that are reflected in spontaneous miniature excitatory postsynaptic currents (mEPSCs) in the rodent cortex. By the end of the wakeful period, the amplitude and frequency of mEPSCs increase in the superficial layers of the rat and mouse frontal cortices whereas following recovery sleep they decrease. Ultrastructurally, the increase of the former has been correlated with the synaptic insertion of calcium-permeable AMPA receptors [22]. During sleep, this GluA1 synaptic expression decreases with a corresponding shrinkage of the axon-spine interface.

3.2 The global distribution of sleep mechanisms

The second implication of these proposals is that renormalization should occur globally; that is, if sleep is a consequence of enhanced synaptic strengthening, renormalization should occur in all brain regions where sensorial input causes neuroplastic change.

Current evidence indicates that for this to occur neuronal activity is crucial, especially during NREM sleep, which comprises roughly 80% of all sleep time. New studies show that down selection is, surprisingly, a consequence of spiking activity involving several distinct electrophysiological signatures, including hippocampal sharp waves, ripples, and slow oscillations [23]. Despite a broad consensus that

SWRs are likely candidates for inducing synaptic potentiation, recent studies have shown that SWRs promote synaptic weakening instead [24]. Consistent with these results, closed-loop optogenetic inhibition of SWRs prevents the decline in the slope of hippocampal fEPSPs that normally occurs in sleeping mice. Furthermore, such experimental inhibition reduces firing during the ON/UP states of the slow oscillation and prevents post-sleep improvement in neuroprosthetic learning. The same optogenetic manipulation during the DOWN/OFF periods has no effect, showing that the UP state of the slow oscillation – that is, the activity phase -– is the critical period required for down-selection to occur.

Significantly, sleep-dependent renormalization seems to spare those neurons and/or synapses that are most active during sleep. It is well established, for example, that neurons activated during exploration and learning are preferentially reactivated with a similar sequential pattern of firing during SWRs, while disruption of SWRs impairs memory [25], suggesting that they play an important role in its consolidation.

Organization of sharp waves and ripples appears to be mediated by a distinctive, slow oscillation that features prominently during NREM sleep. The slow oscillation wave originates from the thalamus and cortex and oscillates roughly every second between an UP period of depolarization with spiking and a DOWN/OFF period of hyperpolarization with neuronal silence [26]. During non-REM (NREM) sleep, for instance, neural activity is observed in the EEG as a succession of K-complexes, sleep spindles, and slow waves. This defining feature of NREM sleep occurs more or less in synchrony across all neurons, allowing their pooled activity to be detected at the cortical surface as slow waves. This means that the slow oscillation is a global, synchronized network phenomenon, involving neurons throughout the cortex and, to a lesser degree, neurons in subcortical areas, including the thalamus, striatum, and cerebellum. Within the local cortical network (within a few tens of millimeters), cortical neurons synchronously depolarize and hyperpolarize during the slow oscillations.

3.3 The slow oscillation is a traveling wave

Studies monitoring the distribution of selected slow oscillation phases reveal that the timing of the negative peak exhibits a continuous shift that can be traced spatially throughout the cortex. On average, the maximum delay across the cortex, calculated by determining the difference between the negative peak of the initial slow-wave trace to the negative peak of the terminal trace is about 120 msec. Additionally, slow oscillations originate more frequently in anterior regions and propagate posteriorly. Streamline maps that condense the spatio-temporal dynamics of the slow oscillation display an origin density that coincides with the positioning of anterior electrodes, while the average delay map assumes a predominant fronto-occipital direction of propagation. Importantly, the pattern of origin and propagation of slow oscillations is reproducible across time and across subjects.

Taken together, these studies show that post-learning sleep occurs across the cortex leading to a slight increase in firing in a small set of neurons whose activity is causally linked to neuroplasticity learning, with an activity synchronized and much greater decrease in firing of a larger set of neurons not involved in neuroplastic modulation, consistent with the renormalization hypothesis.

3.4 The cyclical nature of sleep

A third implication of the current sleep hypotheses is the cyclical character of renormalization events, which are dictated by the ongoing twin needs of

neuroplastic learning during wakeful periods and of replenishment during sleep. The temporal organization of these cycles follows nature's light/dark rhythms, where the overall balance in total synaptic strength is maintained across the circadian 24-hour sleep/wake cycle with its temporally regulated, reoccurrence of similar events.

3.5 Circadian rhythms

Based on the presence of this pattern, the fields of circadian biology and sleep–wake regulation have been closely linked for decades, with studies exploring how the circadian clock regulates daily rhythms in sleep and wakefulness, and in turn, how arousal levels in animals affect their circadian clocks. Despite their close relationship, the two, nonetheless, are physiologically independent. Collectively, they may be understood as a homeostatic process – the plastic, organizational events of wakefulness and the dissociative, restorative events of sleep – and the circadian clock-like mechanisms that temporally govern the distribution of wakefulness and sleep periods in synchrony with the external environment [27]. While the two systems have been shown to share elements of their mechanisms, in other aspects the two display many distinct features, evident in their anatomical, molecular, and electrophysiological details.

The preeminent circadian clock in mammals is located in the suprachiasmatic nucleus (SCN), immediately above the optic chiasm and juxtaposed with the third ventricle. Lesions of the SCN eliminate daily rhythms such as the sleep–wake rhythm [28]. The SCN circadian oscillator consists of a transcriptional-translational negative feedback loop (TTFL), involving a group of clock genes that includes Period (Per) 1 and 2; Cryptochrome (Cry) 1 and 2, Brain and muscle Arnt-like-1 (Bmal1), and Clock. While the SCN clock phase is modulated by many inputs the primary environmental synchronizer is light stimulation via the retina, which is then relayed to the SCN. Circadian mechanisms regulating sleep include SCN efferents to the subparaventricular zone, which sends excitatory projections to the medial preoptic and dorsomedial hypothalamus, the latter of which sends additional excitatory projections to LH orexin neurons and to the LC [27]. SCN neuronal activity is higher in the day, with initial output from the SCN excitatory in diurnal animals. Distinct from the circadian signals emanating from the SCN, there are also distributed circadian influences on sleep. For example, the circadian clock gene Bmal1 regulates the rhythmic production of histamine in wake-promoting tuberomammillary neurons. Selective Bmal1 deletion in these neurons, renders them arrhythmic. Another circadian clock gene, Reverbα, regulates circadian dopamine production in the VTA.

Unlike the SCN circadian clock, the sleep–wake system is distributed across many brain regions, including the brainstem, midbrain, hypothalamus, thalamus, and cortex. Moreover, sleep is composed of a complex mixture of different brain states, having their unique electrical recording features. Broadly these include slow-wave sleep, i.e., non rapid eye movement sleep (NREM), characterized by high amplitude, low-frequency brain waves, and rapid eye movement sleep (REMS), defined by low amplitude, higher frequency EEG activity, with mixtures of these occurring during transitional phases [29]. The nature of the homeostatic "process" is less clear than that of circadian rhythms, and likely encompasses multiple factors. Examples of postulated molecules include extracellular adenosine, which has been shown to increase during the wake in parallel with higher metabolic activity and to decrease during sleep as metabolism wanes [30]; prostaglandin D2, which also accumulates during wake, activates DP1 receptors and increases extracellular adenosine levels; and cytokines such as interleukin (IL)-1β and tumor

necrosis factor (TNF)α. Central to the concept of "process" is that sleep serves a restorative function that allows the brain to consolidate synaptic changes generated by previous events, replenish energy stores, and eliminate accumulated metabolic byproducts [12]. Although the circadian and sleep–wake systems are quite distinct, it is noteworthy that they share many cellular processes. Accumulating evidence supports both systems utilizing extracellular processes that overlap the synaptic mechanisms associated with learning, memory, and drug addiction, including changes in enzymatic activity, morphological changes associated with the extracellular matrix (ECM) and ECM-associated proteins, and astrocyte-associated processes [31].

4. The arousal system and the modulation of global up and down states

4.1 The arousal system

The universality of sleep implies the need for precise mechanisms that enable renormalization as well as the transitioning therefrom to wakeful periods of interactive learning. Insight into these mechanisms has emerged from studies of trauma lesions in humans, pharmacological experimentation in mammalian species, and in situ preparations. Together, they have revealed a critical dependence of sleep-like states on the modulation of arousal systems, with the inhibition of neurotransmitters like GABA leading to sleep and their stimulation to wakefulness. While these have to date been the primary mechanisms identified for transitioning between sleep stages, other work has also revealed physiological mechanisms that act directly to induce sleep.

Characteristic of the trauma observations is the case of a 39-year-old man [32] who suffered head trauma resulting from a car collision. Immediately after the head trauma incident, the patient complained of excessive sleepiness and sudden muscle weakness of all four extremities. At three months after onset, his Epworth Sleepiness Scale score was 19, which has a normal range of 10. Diffusion tensor imaging data of the *ascending reticular activating system* (ARAS) showed that the tract volume of the right ventral lower ARAS was substantially decreased compared with control subjects indicating neural trauma to the structure at the site between the pontine RF and the hypothalamus, thus revealing the involvement of the ARAS in sleep modulation.

Consistent with such trauma observations, data from many laboratories has demonstrated that GABAergic transmission in the PnO promotes wakefulness [33]. Inhibiting GABAergic transmission in the PnO by microinjection of the GABA synthesis inhibitor (3-MPA), for instance, decreases anesthesia induction time with isoflurane and/or propofol. Elevating GABA levels with the uptake inhibitor (NPA) into the PnO reverses this effect. On the other hand, modulation of GABA levels in the PnO does not alter the time to recovery of anesthesia. These data provide support for the conclusion that modulation of arousal is a primary mechanism for transitioning between sleep stages, while the lack of effect on the emergence from anesthesia implicates a more complex process for this aspect of arousal than GABA modulation alone.

In addition to GABA the peptides hypocretin-1 and -2, termed orexin A and B, also modulate sleep stage transitioning via the arousal system [34]. Similar to the case of GABA receptors, receptors for the hypocretins are site-specific and widely dispersed. Cell bodies of hypocretin-producing neurons have been localized to the dorsolateral hypothalamus but send projections to all the major brain regions that regulate arousal. Hypocretin-1 delivered to rat dorsal raphé nucleus increases serotonin release in the dorsal raphé and to the pontine nucleus increases acetylcholine

and GABA levels, suggesting that the peptide may broadly activate neurotransmitter release as a function of brain location.

Few studies have revealed a direct induction of sleep via neurotransmitter upregulation. Of these, REM sleep was induced in rats using vasoactive intestinal polypeptide (VIP). A closely related peptide, the pituitary adenylyl cyclase-activating polypeptide (PACAP), was even more effective [35]. The IC_{50} for PACAP was 2.4 and 3.2 nM, for example, as compared with VIP $IC_{50} > 1$ mM, suggesting the peptide has a highly specific and effective role in the induction of REM sleep regulation. In an interesting observation, injection of PACAP into the PnO generated REM sleep lasting 11 consecutive days.

4.2 Targeting the arousal system

Due to an improving understanding of the regulatory mechanisms for sleep transitions, pharmacotherapy has chiefly emphasized the evolution of drugs targeting receptors for neurotransmitters of the arousal system. These are briefly discussed with regard to the selectivity of their effects and the specificity of their interactions with sleep phases.

4.2.1 GABA, regional influences, and NREM sleep

Because of their powerful inhibitory effects, $GABA_A$ receptors have been the targets of most sedative/hypnotic and general anesthetic drugs. $GABA_A$ receptors exist as multiple subtypes and these subtypes are differentially located throughout the brain. The differences in clinical effects caused by various benzodiazepine (e.g., diazepam) and non-benzodiazepine (e.g., eszopiclone) sedative/hypnotics are attributed to the relative selectivity for different $GABA_A$ receptor subtypes. For example, administering the benzodiazepine site agonists zolpidem, diazepam, and eszopiclone directly into the PnO caused drug-specific changes in cortical electroencephalographic activity and increased acetylcholine release in the PnO [11]. Systemic administration of eszopiclone to awake rats significantly decreased acetylcholine release in the PnO and increased electroencephalographic power in the delta frequency. These data suggest that different classes of clinically used sedative-hypnotics can exert their arousal-modulating effects by actions at different GABAA receptors in the PnO.

On the other hand, the development of sedative/hypnotic pharmaceuticals has largely been empiric, leading to the present consecutive evolution from the benzodiazepines, the initial drugs of choice, which were limited by their addiction potential. The empiric approach has produced clinically useful drugs but has not generated drugs with a comprehensive range of desirable properties. Nonetheless, the identification and characterization of receptor subtypes, the regional distribution of their siting within the brain, a growing ability to modify and simulate sleep architecture, improved knowledge of the physiological features that distinguish sleep phases, and technological advances in drug delivery hold promise for more selective therapeutic intervention. As mentioned, for example, systemic administration of GABA mimetic drugs is known to promote sleep, sedation, or general anesthesia. In brain regions containing neurons that promote wakefulness, GABAergic inhibition has been shown to cause an increase in sleep. These brain regions include the dorsal raphé nucleus and the tuberomamillary nucleus of the posterior hypothalamus, for example. Yet, direct administration into the pontine reticular formation of drugs that increase GABAergic transmission increases wakefulness and inhibits sleep.

4.2.2 Acetylcholine and REM sleep

Although acetylcholine plays a primary role in generating the brain-activated states of wakefulness and REM sleep, cholinergic drugs are not part of the standard pharmacological armamentarium of sleep disorders medicine. Nonetheless, understanding the mechanisms by which cholinergic neurotransmission generates and maintains REM sleep is crucial, because of its selective influence on this phase of sleep architecture as well as its interaction with other transmitter systems that are targets of sleep pharmacotherapy [11].

Much of the research on the regulation of sleep by acetylcholine has focused on transmission mediated by muscarinic cholinergic receptors. Of the five subtypes (M_1–M_5) of muscarinic receptors that have been identified, the M2 subtype plays a key role in the generation of REM sleep. Cholinergic signaling originating from the laterodorsal tegmental and pedunculopontine tegmental nuclei (LDT/PPT) and the basal forebrain promotes the cortically activated states of wakefulness and REM sleep. The distinction between sleep phases has been shown to be due to the presence of two cortical populations of neurons that induce either wakefulness and REM sleep (referred to as Wake-On/REM-On) or wakefulness alone (Wake-On/REM-Off).

In vivo data obtained from normal rats demonstrate that the sedative/hypnotics zolpidem, diazepam, and eszopiclone differentially alter acetylcholine release in the pontine nucleus, increase EEG delta power, and decrease acetylcholine release in rat pontine reticular formation. Intravenous administration of eszopiclone, for instance, prevents the REM phase of sleep, increases EEG delta power, and decreases acetylcholine release in rat pontine reticular formation.

5. Sleep dysfunction and dysfunctional system states

5.1 Global dysfunction

5.1.1 Psychiatric diseases

Psychiatric diseases are often conceptualized as broadly linked to global brain states, and so subject to the influences of global sleep disturbances. Several examples indicate that sleep disturbances comprise etiological factors resulting in psychiatric dysfunctions [36].

In adolescents at high-risk (UHR) for psychosis, for example, the study of the relationships between sleep disturbances and psychosis symptoms, the volume of an integral sleep structure (thalamus), and associations between thalamic abnormalities and sleep impairment in UHR youth an increased latency to sleep onset and greater sleep disturbances/disrupted continuity compared to normal youth, over and above concurrent mood symptoms. Among UHR youth, increased sleep dysfunction was associated with greater negative symptom severity. Compared to HC adolescents, UHR participants displayed decreased bilateral thalamus volume, which appeared to be correlated with increased sleep dysfunction.

Slow waves and sleep spindles are the two main oscillations occurring during NREM sleep. While slow oscillations are primarily generated and modulated by the cortex, sleep spindles are initiated by the thalamic reticular nucleus (TRN) and regulated by thalamo-reticular and thalamo-cortical circuits. Monitoring these distinct electrical signatures in 18 medicated schizophrenics revealed reduced sleep spindles compared to healthy and depressed subjects during the first NREM episode. Whole night hd-EEG recordings from a larger patient cohort revealed whole-night deficits

in spindle power (12–16 Hz) and in slow (12–14 Hz) and fast (14–16 Hz) spindle amplitude, duration, number, and integrated spindle activity (ISA) in prefrontal, centroparietal and temporal regions. By contrast, no slow wave deficits were found in schizophrenics. These results indicate that spindle deficits can be reliably established in schizophrenics and are stable across the night, suggesting deficits in TRN and thalamo- reticular circuits *unrelated* to antipsychotic medications.

It is widely known that children and adolescents with autism spectrum disorders (ASD) suffer from sleep disorders. These include increased bedtime resistance, insomnia, awakening, parasomnia, sleep-breathing disorders, and waking difficulties. Frequently, the sleep disorder appears first, suggesting that sleep is a causal factor in ASD development [7]. Abnormal behaviors from future ASD patients have been recognized in the newborn period. These display sleep disorders preceding the onset of ASD.

5.2 Impaired regulation of sensorial input

5.2.1 Learning impairments due to disturbances that affect slow oscillations in NREM sleep

A key postulate of current sleep models is the restorative effect of sleep on learning in brain areas that have experienced heavy neuroplastic changes during wakeful periods. This postulate was tested in experiments that focally perturbed deep sleep in the motor cortex and investigated the consequences on behavioral and neurophysiological markers of neuroplasticity related to motor practice. The restoration in the ability to learn was markedly attenuated in these experiments when slow waves were selectively perturbed in the motor cortex. This demonstrated that deep sleep – specifically its electrical signature – was needed to maintain the ability to learn efficiently after recovery from sleep and that disturbances of sleep like insomnia would therefore be likely to impede learning.

5.2.2 Cyclical irregularities affect autonomic balance and addiction

Disorders in sleep rhythms are increasingly commonly encountered in pediatric and adolescent populations. Characteristic clinical features include familial advanced sleep phase syndrome (ASPS) and delayed sleep phase syndrome (DSPS), non-24-h sleep–wake syndrome (non-24), and morningness-eveningness recognition. Accompanying these rhythm irregularities are severe fatigue and gastrointestinal discomfort [2] that appear to be due to autonomic imbalances.

Cyclical irregularities appear to also impact dopaminergic brain regions that are substantially associated with addiction. In investigations of the midbrain ventral tegmental area (VTA) neural activity recordings exhibited a strong vigilance state with increased activity during wakefulness and rapid eye movement sleep relative to non-rapid eye movement sleep. Six hours of sleep deprivation induced a significant depression of neuronal activity in both areas. Surprisingly, these alterations lasted for up to 48 hours and persisted even after the normalization of cortical EEG waves. These results show that sleep disturbances significantly affect neuronal activity in midbrain DA structures and so are likely to reflect the frequently observed relationship between sleep alterations and dysfunction of the DA circuitry observed in addiction [37].

6. Conclusion

The clear implication from the current theoretical picture of sleep is that its influence is fundamental to many neuronal systems. As such its properties are key

to understanding how sleep broadly affects brain function and systemic well-being. To date, however, the ability to assess this influence has lacked experimental tools having sufficient precision to characterize these systems. This circumstance is gradually in the process of resolution as the ongoing expansion in the pharmacopeia of sleep medications continues.

While the data describing these medications offer a sobering reminder of the complexity that must be logically integrated if we are to derive a coherent model of the processes regulating sleep, it is simultaneously a cogent argument that the manipulation of these mechanisms now has the potential for refined control. Indeed, today's pharmacopeia presents a spectrum of drugs tailored to various sleep features.

The focus on the use of these medications is likely to demonstrate the cross-cutting relevance of sleep for the practice of medicine in numerous neurological issues. The pressing clinical problem of sleep disorders medicine will thus continue to stimulate advances in understanding not merely the neurochemical regulation of sleep but also the health of the brain's broader neurological functioning.

Author details

Denis Larrivee[1,2]

1 Mind and Brain Institute, University of Navarra Medical School, Spain

2 Loyola University Chicago, USA

*Address all correspondence to: sallar1@aol.com

References

[1] Noda A, Yasuma F, Okada T, et al. Circadian rhythm of autonomic activity in patients with obstructive sleep apnea syndrome. Clinical Cardiology. 1998;**21**:271-276

[2] Tomoda A, Miike T, Yonamine K, et al. Disturbed circadian core body temperature rhythm and sleep disturbance in school refusal children and adolescents. Biological Psychiatry. 1997;**41**:810-813

[3] Toyoura M, Miike T, Tajima S, et al. Inadequate sleep as a contributor to impaired glucose tolerance: A cross-sectional study in children, adolescents, and young adults with circadian rhythm sleep-wake disorder. Pediatric Diabetes. 2020 Jun;**21**(4):557-564

[4] Lunsford-Avery JR, Mittal VA. Sleep dysfunction prior to the onset of schizophrenia: A review and neurodevelopmental diathesis–stress conceptualization Clinical Psychology: Science and Practice. 2013;**20**:291-320

[5] Massimini M, Huber R, Ferrarelli F, Hill S, Tononi G. The sleep slow oscillation as a traveling wave. The Journal of Neuroscience. 2004;**24**(31):6862-6870

[6] Ismail FY, Fatemi A, Johnston MV. Cerebral plasticity: Windows of opportunity in the developing brain. European Journal of Paediatric Neurology. 2017;**21**:23-48

[7] Peiper NC, Ridenour TA, Fishbein DH. Characterizing psychiatric symptoms and neurocognitive functioning among substance-naïve early adolescents: Associations with sleep problems. Early Intervention in Psychiatry. 2020;**14**:439-449

[8] Brower KJ, Perron BE. Sleep disturbance as a universal risk factor for relapse in addictions to psychoactive substances. Medical Hypotheses. 2010;**74**:928-933

[9] Feld GB, Born BJ. Neurochemical mechanisms for memory processing during sleep: Basic findings in humans and neuropsychiatric implications. Neuropsychopharmacology. 2020;**45**: 31-44. DOI: 10.1038/s41386-019-0490-9

[10] Vadnie CA, McClung CA. Circadian rhythm disturbances in mood disorders: Insights into the role of the suprachiasmatic nucleus. Hindawi Neuroplasticity. 2017;**11**(5):28. DOI: 10.1155/2017/1504507

[11] Watson CJ, Baghdoyan HA, Lydic R. Neuropharmacology of sleep and wakefulness: 2012 update. Sleep Medicine Clinics. 2012;7(3):469-486. DOI: 10.1016/j.jsmc.2012.06.010

[12] Tononi G, Cirelli C. Sleep and synaptic down-selection. The European Journal of Neuroscience. 2020;**51**:413-421

[13] Aton SJ, Broussard C, Dumoulin M, Seibt J, Watson A, Coleman T, et al. Visual experience and subsequent sleep induce sequential plastic changes in putative inhibitory and excitatory cortical neurons. Proceedings of the National Academy of Sciences of the United States of America. 2013;**110**:3101-3106

[14] Goel N, Rao H, Durmer JS, Dinges DF. Neurocognitive consequences of sleep deprivation. Seminars in Neurology. 2009;**29**: 320-339

[15] Kirchhoff M, Parr T, Palacios E, Friston K, Kiverstein J. The Markov blankets of life: autonomy, Active inference and the free energy principle. Journal of the Royal Society Interface. 2018;**15**:20170792. DOI: 10.1098/rsif.2017.0792

[16] Friston K, Sengupta B, Auletta G. Cognitive dynamics: From attractors to active inference. Proceedings of the IEEE. 2014;**102**(4):427-446

[17] Bedau M. The nature of life. In: Boden M, editor. The Philosophy of Artificial Life. Vol. c1966. Oxford: Oxford University Press; 1996. pp. 332-360

[18] Tononi G, Cirelli C. Some considerations on sleep and neural plasticity. Archives Italiennes de Biologie. 2001;**139**:221-241

[19] Cirelli C, Tononi G. Effects of sleep and waking on the synaptic ultrastructure. Philosophical Transactions of the Royal Society B. 2020;**375**:20190235

[20] Bjorness TE, Kulkarni A, Rybalchenko V, Suzuki A, Bridges C, Harrington AJ, et al. An essential role for MEF2C in the cortical response to loss of sleep in mice. eLife. 2020;**9**:1

[21] Flavell SW, Cowan CW, Kim TK, Greer PL, Lin Y, Paradis S, et al. Activity-dependent regulation of MEF2 transcription factors suppresses excitatory synapse number. Science. 2006;**31**:11008-11012

[22] Lante F, Toledo-Salas JC, Ondrejcak T, Rowan MJ, Ulrich D. Removal of synaptic Ca(2)+−permeable AMPA receptors during sleep. The Journal of Neuroscience. 2011;**31**:3953-3961

[23] Gulati T, Guo L, Ramanathan DS, Bodepudi A, Ganguly K. Neural reactivations during sleep determine network credit assignment. Nature Neuroscience. 2017;**20**:1277-1284. DOI: doi. org/10.1038/nn.4601

[24] Norimoto H, Makino K, Gao M, Shikano Y, Okamoto K, Ishikawa T, et al. Hippocampal ripples down-regulate synapses. Science. 2018;**359**:1524-1527

[25] Girardeau G, Benchenane K, Wiener SI, Buzsaki G, Zugaro MB. Selective suppression of hippocampal ripples impairs spatial memory. Nature Neuroscience. 2009;**12**:1222-1223. DOI: doi. org/10.1038/nn.2384

[26] Steriade M, Timofeev I, Grenier F. Natural waking and sleep states: A view from inside neocortical neurons. Journal of Neurophysiology. 2001;**85**:1969-1985. DOI: doi.org/10.1152/jn.2001.85.5.1969

[27] Borbely AA, Daan S, Wirz-Justice A, Deboer T. The two-process model of sleep regulation: A reappraisal. Journal of Sleep Research. 2016;**25**:131-143

[28] Moore RY. Organization of the mammalian circadian system. Ciba Foundation Symposium. 1995; **1995**(183):88-106

[29] Scammell TE, Arrigoni E, Lipton JO. Neural circuitry of wakefulness and sleep. Neuron. 2017;**93**:747-765

[30] Holst SC, Landolt HP. Sleep homeostasis, metabolism, and adenosine. Current Sleep Medicine Reports. 2015;**1**:27-37

[31] Panja D, Bramham CR. BDNF mechanisms in late LTP formation: A synthesis and breakdown. Neuropharmacology. 2014;**2014**(76): 664-676

[32] Jang SH, Seo WS, Hyeok KG. Post-traumatic narcolepsy and injury of the ascending reticular activating system. Sleep Medicine. 2016;**17**:124-125

[33] Vanini G, Watson CJ, Soto-Calderon H, Lydic R, Baghdoyan HA. GABA levels in cat pontine reticular formation (PRF) and pedunculopontine tegmental nucleus (PPT) vary with arousal state. In: Neuroscience Meeting Planner 458.15. Atlanta, GA Soc Neurosci. 2006

[34] Wang C, Wang Q, Ji B, Pan Y, Xu C, Cheng B, et al. The orexin receptor system: Molecular mechanism and

therapeutic potential for neurological diseases. Frontiers in Molecular Neuroscience. 2018;**11**:220. DOI: 10.3389/fnmol.2018.00220

[35] Ahnaou A, Basille M, Gonzalez B, Vaudry H, Hamon M, Adrienand J, et al. Long-term enhancement of REM sleep by the pituitary adenylyl cyclase-activating polypeptide (PACAP) in the pontine reticular formation of the rat. The European Journal of Neuroscience. 1999;**11**:4051-4058

[36] Lunsford-Avery JR, Orr JM, Gupta T, Pelletier-Baldelli A, Dean DJ, Smith Watts AK, et al. Sleep dysfunction and thalamic abnormalities in adolescents at ultra high-risk for psychosis. Schizophrenia Research. 2013;**151**(151):148-153

[37] Fifel K, Johanna H, Meijer JH, Deboer T. Circadian and homeostatic modulation of multi-unit activity in midbrain dopaminergic structures. Scientific Reports. 2018;**8**:7765. DOI: 10.1038/s41598-018-25770-5