EJN fens EUROPEAN JOURNAL OF NEUROSCIENCE

European Journal of Neuroscience, pp. 1–12, 2013 doi:10.1111/ejn.12238

REVIEW
Sleep: a synchrony of cell activity-driven small network states

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Keywords: ATP, brain imaging, cerebral blood flow, cytokine, receptor

Abstract

We posit a bottom-up sleep-regulatory paradigm in which state changes are initiated within small networks as a consequence of local cell activity. Bottom-up regulatory mechanisms are prevalent throughout nature, occurring in vastly different systems and levels of organization. Synchronization of state without top-down regulation is a fundamental property of large collections of small semi-autonomous entities. We posit that such synchronization mechanisms are sufficient and necessary for whole-organism sleep onset. Within the brain we posit that small networks of highly interconnected neurons and glia, for example cortical columns, are semi-autonomous units oscillating between sleep-like and wake-like states. We review evidence showing that cells, small networks and regional areas of the brain share sleep-like properties with whole-animal sleep. A testable hypothesis focused on how sleep is initiated within local networks is presented. We posit that the release of cell activity-dependent molecules, such as ATP and nitric oxide, into the extracellular space initiates state changes within the local networks where they are produced. We review mechanisms of ATP induction of sleep-regulatory substances and their actions on receptor trafficking. Finally, we provide an example of how such local metabolic and state changes provide mechanistic explanations for clinical conditions, such as insomnia.

Introduction

The minimum amount of nervous tissue necessary and sufficient for sleep to occur has yet to be identified. Regardless, despite millions of cases of lesioned brains, not a single case of a surviving individual or animal completely lacking sleep has been reported. This strongly suggests that sleep is a fundamental property of nervous tissue and that sleep is self-organizing. These observations led to theories of sleep initiation and regulation that require universal mechanisms widely applicable to damaged nervous systems or viable nervous tissue components whether *in vivo or in vitro* (Krueger & Obál, 1993; Kavanau, 1994; Tononi & Cirelli, 2003). The prevailing theories of sleep regulation are top-down regulatory mechanisms; they posit that sleep-regulatory circuits impose sleep on the brain. Top-down regulatory systems are characteristic of engineered systems, for example the air traffic control system, but are fragile if disturbed. However, the top-down theories persist despite the robust evidence that lesion of any one of the sleep-regulatory circuits fails to eliminate sleep, although after such lesions sleep is often abnormal in timing, behavior and electrophysiologically. Such sleep center theories have inadequately addressed many known sleep phenomena, including sleep-dependent optimum performance, recovery of sleep after lesions, sleep inertia and clinical conditions associated with state dissociations (Mahowald *et al.*, 2011). Further, the top-down theories have failed to provide insight into how brain activity is translated into sleep-regulatory signals or how the waking brain transitions into sleep states. Logically, if one posits top-down sleep regulation, for instance by a sleep-regulatory center, it leads to an infinite regress. Thus, if a sleep-regulatory center is posited to impose sleep on the entire brain, then one has to ask 'What is telling the center to impose sleep?' If an answer is provided, then one must ask; 'Who is telling the teller?' etc. Bottom-up mechanisms avoid this logic pitfall.

A new sleep bottom-up regulatory paradigm is developing. Bottom-up mechanisms are fundamentally different from top-down regulation, lacking a central command. Within biology, bird flocking is an example of a dynamic bottom-up mechanism regulating state changes (direction of flock flight). The individual birds are semi-autonomous entities loosely connected via sight. No individual bird is dictating flock direction. Instead, the responses of an individual bird to another bird's change in flight direction leads to the entire flock rapidly changing direction. Bottom-up mechanisms are prevalent in nature occurring in vastly different systems and levels of organization. Semi-autonomous units spontaneously synchronize without central control (Strogatz, 2004). We apply those ideas to sleep by positing that small highly interconnected networks of neurons and glia, such as cortical columns, are fundamental semi-autonomous units, loosely connected via electrical and chemical signaling, oscillating between states and synchronizing with each other. As such, sleep is viewed as a distributed process in the brain being initiated within local small circuits as a consequence of prior activity and the associated changes in metabolism and cerebral

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Received 4 February 2013, revised 27 March 2013, accepted 29 March 2013

blood flow (CBF) within those circuits (Krueger *et al.*, 2008; Rector *et al.*, 2009). In these views, state oscillations occur within any viable neuronal/glia network and organism sleep emerges as local circuits synchronize state. The known sleep-regulatory circuits may orchestrate the spatial and temporal coordination of state in multiple smaller networks. This organization in turn contributes to niche-appropriate predictive and preemptive behavior. Herein we address the issue of state changes occurring at different levels of tissue organization and weave a testable theory of sleep initiation and regulation.

Sleep-like phenotypes at different levels of tissue organization

Do neurons or glia sleep?

This question raises definitional problems. It is not a simple matter of an inactive neuron being asleep and an active neuron being awake. There are many brain phenomena where inactivity provides or fine-tunes information, for example inhibitory surround areas within sensory receptive fields. Further, the separation of glia and neuron involvement in sleep regulation is difficult because astrocytes are intimately involved in sleep (Halassa *et al.*, 2009). Other cell types in the brain may also be involved, for example capillary endothelial cells or arteriolar smooth muscle cells controlling CBF. Regardless, thalamic and cortical neurons display a burst-pause action potential firing pattern during non-rapid eye movement sleep (NREMS). Bursts of action potentials lasting about 500 ms are followed by roughly 500 ms of silence. These burst-pause patterns unfold as an animal is going to sleep, and when synchronized with each other lead to a slow 1 Hz component of the electroencephalogram (EEG). High-amplitude 0.5–4-Hz EEG waves characterize slow-wave sleep (SWS). Thus, one could use a burst-pause firing pattern as a definition for a neuron going to sleep as long as the caveats mentioned are attached to the definition, for example the unknown role of glia. Further, burst-pause activity can occur when an animal is awake (Pigarev *et al.*, 1997), although the synchronized pattern of populations of neurons exhibiting the burst-pause pattern is absent during waking (Vyazovskiy *et al.*, 2011a).

State oscillations in mixed neuronal/glia cultures

If we define a network state as a stereotypic output in response to a stable input, then a new state occurs when the same input leads to a different output. For instance, waking stimuli that induce explicit conscious perceptions often do not during sleep. Extending this logic to small networks, including cultured neurons and glia, the following are predicted. (a) Characteristics of state oscillations, frequency, amplitude and synchronization are activity dependent. In neuronal/glial cultures action potentials are most often used to characterize state, but other measures such as field potentials, gene expression and neurotransmitter/modulator release are also used. (b) State oscillations are regulated by activity-dependent genes. (c) Unlike whole animals, cultures lack dynamic changes in blood flow and afferent input to drive activity; thus, the nature of exogenously supplied input will dictate gene expression and state oscillation characteristics. (d) If small networks are connected either electrically or chemically, the respective state oscillations will synchronize and coalesce into states expressing emergent properties. Predictions (a)–(c) have already been tested as outlined below; the experimental investigation of prediction (d) will likely provide major insights into emergent properties of brain tissue including sleep.

Mature neuronal/glial tissue cultures form active networks that display periodic bursts of action potentials. Although the inter-burst intervals in culture are longer than the inter-burst intervals that characterize thalamic and cortical neurons during sleep, the firing patterns suggest a sleep-like default state (Corner, 2008; Hinard *et al.*, 2012). Slow-frequency (0.05–0.2 Hz) electrical stimulation of such cultures entrains the spontaneous network bursts and recruits more active channels to participate in network-wide bursts, suggesting a sleep-like state (Wagenaar *et al.*, 2005; Chiappalone *et al.*, 2007). In contrast, higher frequency stimulation (4–10 Hz) induces more random firing with fewer bursts than occur during baseline spontaneous conditions (Wagenaar *et al.*, 2005). Tafti and colleagues (Hinard *et al.*, 2012) showed that the default sleep-like state could be transformed to a tonic firing pattern similar to that observed in wakefulness by stimulating the cultures with a cocktail of excitatory neurotransmitters. In addition, the chemically stimulated cultures exhibited a transcriptome similar to the transcriptome of cortical cells harvested from sleep-deprived mice. Studies of neuronal culture state oscillations are not expected to provide a full understanding of sleep as a whole-animal global behavior state unfolding in time and space. However, they are just in their infancy and already they indicate that the fundamental electro-chemical and genetic mechanisms responsible for network state oscillations and the consequences of state oscillations can be studied under controlled conditions *in vitro*. These results also lead to the issue of whether small networks *in vivo* demonstrate state oscillations and, if so, whether there is any connection of those oscillations to sleep and performance.

Cortical column sleep

A seminal paper by Pigarev *et al.* (1997) connects cortical neuron firing pattern to local cortical network state. The investigators measured firing patterns of individual occipital cortex/visual cortex neurons of monkeys as they were falling asleep yet still performing a visual task. During the wake–sleep transition, some of the cells started to fail to fire in response to stimulation whereas other cells did not. Importantly, the topographic location of those neurons within their visual receptive field predicted when the neuron would stop responding. Neurons in the peripheral part of the receptive stop responding before those in the central part of the receptive field. This strongly suggests that the change in local state is a network phenomenon because the order of recruitment is topographic dependent. Pigarev concluded that sleep was a property of local networks.

Cortical columns are anatomically defined, experimentally accessible, examples of small neuronal/glial networks. The rat somatosensory cortex is organized into columns with afferent nerve fibers from facial whiskers mapping onto specific columns and individual columns primarily receiving input from a specific whisker. Repeated single-whisker stimulation and analysis of individual traces demonstrates evoked response potential (ERP) patterns that exhibit stereotypical temporal patterns. Electrical activity of single columns in response to evoked afferent input can be isolated then correlated with whole-animal sleep (Rector *et al.*, 2005). When the animal is awake, the ERP amplitude is smaller than when the rat is in NREMS if low sensory stimulus intensities are used (Phillips *et al.*, 2012). When the animal is asleep, about 80% of the ERPs are sleep-like in that they have a high amplitude. Conversely, when the animal is awake, most of the ERPs exhibit low amplitudes suggesting they are wake-like. Further, the longer a cortical column is in the wake-like state, i.e. has a low ERP magnitude, the higher the

probability over the next few minutes it would enter the sleep-like state. This property is similar to a whole-animal sleep in that the longer wakefulness persists, the higher the future probability of sleep. Further, because cortical neurons are more active during waking (Vyazovskiy *et al.*, 2009), these results suggest that the probability of sleep occurring is activity dependent. Most importantly, Rector and colleagues (Walker *et al.*, 2005; Topchiy *et al.*, 2009) showed that the cortical column state made a difference in the animal's performance. He trained rats to lick in response to the stimulation of a single whisker, and then measured the ERP to characterize the state of that whisker's column. When the ERP was of low amplitude, suggesting the column was in the wake-like state, the animal made the correct response (Fig. 1). In contrast, if the ERP was of high amplitude, suggesting a sleep-like state, errors of omission or co-mission occurred. Further, the local application of tumor necrosis factor (TNF) alpha, a sleep-regulatory substance (SRS), to cortical columns promotes the sleep-like state determined using ERPs (Churchill *et al.*, 2008). We conclude from these experiments that: (a) there is a behavioral manifestation of cortical column state that parallels whole-animal state-dependency of behavior; (b) sleep does not occur uniformly even within functionally coherent brain regions; and (c) the oscillations of columns between states is dependent upon prior cell activity within the column.

Our model posits that a local network oscillates between states whenever there is an activity-dependent build-up of SRS. If the animal/human happens to be doing a task at that moment, and as the input/output relationship of the network is altered, the result can be an error in data processing resulting in performance degradation. Thus, one could easily envision a requirement of multiple networks being engaged in a behavioral task; if one or more of the local networks oscillated into the sleep-like state the collective output of multiple networks would be changed – perhaps leading to an error. Further, it is parsimonious to posit that all subcortical networks, including known sleep-regulatory networks, also are subject to activity-dependent molecular and genetic mechanisms as are cortical columns. A logical extension of this hypothesis is that both NREMS and rapid eye movement sleep (REMS) are a consequence of these mechanisms but mechanistically involve different levels of the CNS (Krueger & Obál, 1993).

Sleep in larger parts of the brain

In animals, surgically prepared cortical islands, lacking thalamic input but with intact blood flow, exhibit oscillations between EEG-slow waves and wake-like states, independent of behavioral sleep–wake state (Kristiansen & Courtois, 1949). The SRSs, interleukin-1 (IL1) beta, TNF, growth hormone-releasing hormone and brain-derived neurotrophic factor (BDNF), act locally within the cortex to alter EEG δ power, a sleep phenotype. After unilateral application of these substances to the cortical surface, EEG δ power during NREMS on the ipsilateral side, but not on the contralateral side, is enhanced, suggesting a more intense sleep on the side receiving these SRSs (Yoshida *et al.*, 2004; Yasuda *et al.*, 2005, 2007; Faraguna *et al.*, 2008). Ipsilateral EEG δ power is not altered by these substances during waking or REMS. These SRS-induced unilateral EEG δ power changes correlate with enhanced cFos and IL1 immunoreactivity in the corresponding cortical areas and reticular thalamus (Hallett *et al.*, 2010). These results are consistent with and implicate the involvement of known biochemical sleep-regulatory pathways (Krueger, 2008) and known cortico-thalamic sleep-regulatory circuitry (Steriade, 2003) in these uni-hemispheric sleep phenotypes. Further, coupled with what is known about use-dependent production of IL1, TNF and BDNF, these data strongly support the idea that sleep is targeted to active circuits and is initiated at a local network level.

Local to global

The observation of state oscillations at various levels of tissue organization suggests that sleep and some sleep phenotypes emerge from the integration and synchronization of smaller local network states, and that sleep is dependent upon prior cell activity. Several sleep-regulatory circuits, such as the hypothalamic ventrolateral preoptic area, are well characterized and reviewed extensively elsewhere (Jones, 2003; Saper *et al.*, 2005; Datta & Maclean, 2007; Szymusiak & McGinty, 2008). Less well known are the observations that any coupled oscillators will spontaneously self-organize and synchronize oscillations. Oscillation frequency and amplitude are dependent upon system characteristics, such as the strength of coupling between the semi-autonomous units. Synchrony of such networks occurs spontaneously throughout nature even in the absence of top-down regulatory control (Strogatz, 1997, 2004). As described above, cortical columns are semi-autonomous networks that oscillate between states (Rector *et al.*, 2005), and are coupled electrically and biochemically to each other. Thus, we develop the idea that sleep results from the spontaneous local network state synchronization (Krueger *et al.*, 2008), and this hypothesis has been modeled mathematically (Roy *et al.*, 2008). Whole-organism sleep is viewed as an emergent property of synchronized states of smaller local networks. The idea that sleep-like states are a fundamental property of local networks and are dependent upon the activity of such networks developed from our knowledge of the biochemical mechanisms of sleep (Krueger & Obál, 1993). Such a view is not dissimilar to the modern view of the emergence of whole-animal circadian rhythms from multiple semi-autonomous cells, each expressing the genes that collectively make the molecular clock (Lowrey & Takahashi, 2011). We now turn to sleep biochemical mechanisms before further integrating the newer concepts of brain organization of sleep into sleep-related synaptic connectivity.

Indexing brain activity to track prior activity and conversion to a sleep-regulatory signal

A basic tenet of our local use-dependent sleep hypothesis is that CNS cell activity predicts sleep need (Krueger & Obál, 1993). This section addresses what is known of mechanisms and gene expressions involved in the initiation of state oscillations. Figure 2 outlines a cellular molecular mechanism that is posited to lead to state oscillations within small networks and whole animals.[1] ATP concentration in synaptic vesicles is 10–50 times higher than in the cytosol. ATP is released from γ-aminobutyric acid (GABA)ergic, cholinergic, noradrenergic and glutamatergic neurons and glia as a consequence of cell activity into the surrounding extracellular space (Burnstock, 2006, 2007). ATP is thus considered a neuro- and gliotransmitter. Some of the extracellular ATP is converted to adenosine via the ectonucleotidases CD39 and CD73. Extracellular adenosine from this source could contribute to sleep, although extracellular

[1]For ease of conception we limit our model to glial and neuronal release of ATP because ATP induces SRS and is catabolized to adenosine, a vasodilator that induces sleep. Other molecules and processes that are likely involved (Krueger *et al.*, 2008) include NO (Kapas *et al.*, 1994), cytokine production (Willenborg *et al.*, 2007) and cerebral blood flow.

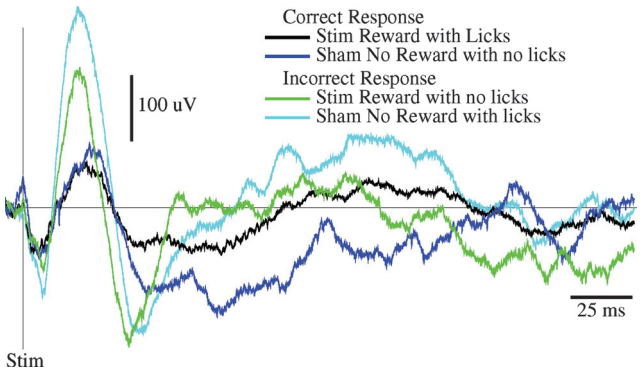

FIG. 1. Response of a rat trained to lick a sucrose solution after stimulation of a specific facial whisker. Animals were trained to lick for a sweetened water reward when a particular whisker was stimulated (Stim Reward), but not to lick when a different whisker was stimulated (Sham No Reward). Training occurred over a 3–6-month period. Before training, a 64-channel electrode array was also implanted over the surface of the somatosensory cortex, and individual whisker cortical columns (barrels) were mapped and associated with the particular whiskers being stimulated. Once animals achieved > 80% correct responses, the electrical evoked responses from each electrode corresponding to the Stim and Sham whisker were sorted into those trials that were correct (Stim Reward with Licks or Sham No Reward no Licks) and those that were incorrect (Stim Reward with no Licks or Sham No Reward with Licks), and averaged across trials. Evoked responses were over 200 μV larger before incorrect responses, suggesting that the cortical column for each whisker was in its sleep-like state during the trial that resulted in an incorrect response.

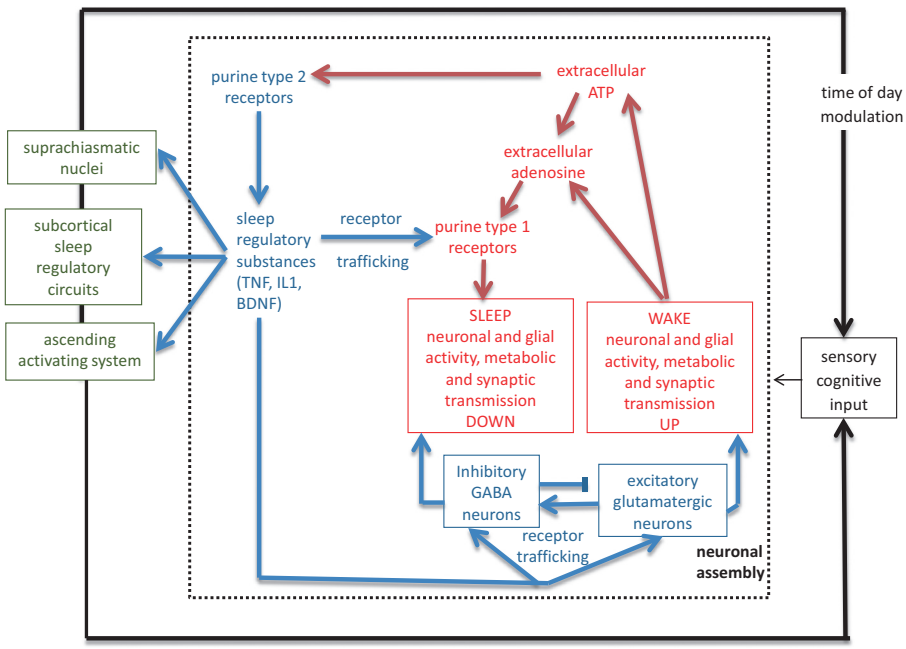

FIG. 2. A proposed mechanism for the indexing of prior brain activity and its translation into a sleep-regulatory mechanism. The steps within the broken line box are envisioned to occur within small networks, such as cortical columns (see text). Those steps result in a state shift within the local network and in the production of molecules that interact with known sleep-regulatory circuits (far left small boxes) that in turn coordinate state of larger areas of the brain for niche-adaptation purposes. For instance, local application of IL1 to the cortex induces local cortical delta waves (Yasuda *et al.*, 2005) and fos expression in the ventrolateral preoptic hypothalamic area (Yasuda *et al.*, 2007), a well-known sleep-regulatory circuit. Neuronal activity is greater during waking than sleep (Vyazovskiy *et al.*, 2009). Cell activity is associated with release of ATP into the extracellular (ex) space. ATPex either rapidly is catabolized to adenosine via ectonucleotidases or it binds to purine type 2 receptors. Ex-adenosine binds to purine type 1 receptors, and thereby rapidly and transiently hyperpolarizes neurons. In contrast, activation of the purine type 2 receptor P2X7 releases cytokines and neurotrophins from glia or neurons (see text); these molecules affect receptor trafficking including purine type 1, GABA and glutamate receptors (Krueger *et al.*, 2008; Imeri & Opp, 2009; Reyes-Vazquez *et al.*, 2012). Cytokines also interact with known sleep-regulatory circuits (far left) and thereby affect sleep (Nistico *et al.*, 1992; Santello *et al.*, 2011). For instance, IL1 inhibits serotonergic neurons and enhances GABAergic signaling in the dorsal raphe nucleus (Manfridi *et al.*, 2003; Brambilla *et al.*, 2007, 2010). IL1 also modulates locus coeruleus (De Sarro *et al.*, 1997), preoptic, basal forebrain and cholinergic laterodorsal tegmental neurons to affect sleep (Alam *et al.*, 2004), and the suprachiasmatic nucleus to affect clock genes (Cavadini *et al.*, 2007). → indicates stimulation; ⊥ indicates inhibition.

adenosine, like extracellular ATP, is rapidly metabolized and removed. Nevertheless, extracellular adenosine is a key signal for induction of cerebral blood vessel dilatation and consequent increases in blood flow. Further, extracellular adenosine increases K^+ permeability to hyperpolarize cells via purine type I receptors. This cellular hyperpolarization, called the down-state, leads to the action potential pauses that characterize thalamic and cortical cells in sleeping animals mentioned earlier. This is a low-energy demand

condition that, coupled with the adenosine-enhanced blood flow, provides an opportunity for energy restoration.

Conversion of extracellular ATP to adenosine is rapid and does not appear to be self-sustaining. As such, it could be involved in rapid state transitions but is unlikely to be involved in long-term sleep regulation. A slower process is also initiated by the transient changes in extracellular ATP. These changes are detected by membrane purine type 2 receptors and these receptors, for example the P2X7 receptor, in turn, cause the release of activity-dependent SRSs, such as TNF, IL1 and BDNF (Hide *et al.*, 2000; Solle *et al.*, 2001; Suzuki *et al.*, 2004; Bianco *et al.*, 2005; Ferrari *et al.*, 2006; Verderio *et al.*, 2006). ATP agonists enhance NREMS while ATP antagonists inhibit sleep in mice (Krueger *et al.*, 2010). Further, mice lacking the P2X7 receptor exhibit reduced duration of NREMS and EEG δ wave power during NREMS compared with control mice after sleep deprivation. ATP-modulated release of IL1, TNF and BDNF provides for the translation of the transient ATP signal into local longer-lived (minutes to hours) regulatory signals capable of indexing prior cell activity. IL1, TNF and BDNF are pleiotropic, having several activities via their respective receptors and signaling cascades, including promotion of sleep and acting on synaptic efficacy. For instance, they activate nuclear factor kappa B (NFkB). Expression of purine type 1 receptors (Khoa *et al.*, 2001; St Hilaire *et al.*, 2009) and the glutamate α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptor-gluR1 mRNAs (Furukawa & Mattson, 1998; Yu *et al.*, 2002; O'Mahony *et al.*, 2006) are affected by TNF and/or NFkB activation. Activation of NFkB in mammals promotes NREMS (Chen *et al.*, 1999; Kubota *et al.*, 2000) and in fruit flies relish, the homolog gene for mammalian NFkB, is involved in sleep (Williams *et al.*, 2007; Kuo *et al.*, 2010). The respective receptors and their subsequent cell membrane expression would change sensitivity of the postsynaptic neurons. Such receptor population change mechanisms take place over longer periods and they are proto-typical of synaptic scaling because the expression of postsynaptic receptors is modulated by presynaptic neuron activity as initiated by the release of ATP. Thus, postsynaptic neuron sensitivity is scaled to the prior use of the presynaptic synapse. TNF and BDNF are firmly linked to synaptic scaling (Beattie *et al.*, 2002; Stellwagen & Malenka, 2006; Turrigiano, 2008). These ATP/adenosine/cytokine events occur locally within active networks, and the collective electrochemical changes result in a shift in input–output relationships within the networks, i.e. a state shift.

The evidence implicating cytokines in sleep regulation was developed independently of the ATP literature; by way of example, the TNF-sleep literature is briefly summarized (Krueger, 2008). If TNF is injected almost all of the consequences associated with prolonged sleep loss are induced. These include sensitivity to pain stimuli; cognitive, memory and performance impairments; and symptoms of depression, sleepiness, fatigue and prolonged sleep. TNF injection also leads to symptoms associated with chronic sleep loss-associated pathologies, such as metabolic syndrome, chronic inflammation and cardiovascular disease. Further, a clinically available blocker of TNF (Enbrel) alleviates many of the sleep loss-associated symptoms, for example fatigue and sleepiness (Franklin, 1999; Vgontzas *et al.*, 2004). In animals, TNF injections promote sleep, and inhibition of TNF using antibodies or soluble receptors reduces sleep. Mice lacking TNF receptors have reduced NREMS and REMS. In humans and animals, sleep deprivation upregulates TNF levels in the blood or brain. Local application of TNF to cortical columns drives the columns into a sleep-like state (Churchill *et al.*, 2008), and application of TNF to one side of the cortex enhances EEG SWA on the ipsilateral side but not on the contralateral side during sleep, but not during wakefulness (Yoshida *et al.*, 2004). In contrast, inhibition of spontaneous cortical TNF expression using a TNF small interfering RNA has the opposite effects (Taishi *et al.*, 2007). TNF immunereactivity in neurons is enhanced after neuronal activity. An independent literature has characterized the involvement of TNF in synaptic scaling involving receptor trafficking as mentioned.

Sleep regulation and receptor trafficking: functional implications

By mobilizing neurotrophins, cytokines and synaptic receptors, which are the center-stage molecular substrates for neural plasticity, the sleep-regulatory mechanisms tap into the common paths that mediate experience-dependent plasticity, such as those that occur during learning and memory. Indeed, sleep-induced receptor trafficking has been directly compared with synaptic long-term potentiation or depression (LTP/LTD), which are best known as cellular substrates of learning and memory (Bredt & Nicoll, 2003). For example, in the rodent cerebral cortex and hippocampus, sleep is accompanied by a general downregulation of synaptic AMPA receptors (AMPARs) as well as LTD-like molecular signatures, including decreased phosphorylation of the AMPAR subunit GluR1 and CaMKII (Vyazovskiy *et al.*, 2008; Hagewoud *et al.*, 2010). Further, AMPAR responsiveness to unitary vesicular release of glutamate is decreased, suggesting decreased transmission efficacy (Liu *et al.*, 2010). Consequently, after sleep, there is an enhanced capacity to induce LTP of AMPAR transmission in the cortex (Vyazovskiy *et al.*, 2008), and after acute or prolonged sleep loss LTP is inhibited (Davis *et al.*, 2003; Vyazovskiy *et al.*, 2011b). In an extension of those findings, removal of AMPARs during sleep in layer V pyramidal neurons occurs in the somatosensory cortex, this involves specifically the removal of Ca^{2+}-permeable AMPARs (Lante *et al.*, 2011). In the hippocampus, sleep deprivation results in reduced surface expression of *N*-methyl-D-aspartate (NMDA) receptors (NMDARs) in CA1 pyramidal neurons, which leads to impaired induction of NMDAR-dependent AMPAR LTP, thus affecting AMPAR trafficking by regulating synaptic NMDARs (McDermott *et al.*, 2003, 2006; Kopp *et al.*, 2006). Interestingly, when sleep-regulated plasticity genes were examined independent of circadian time, a number of the key players, including phosphorylated CREB, BDNF and Arc, were regulated by the ebb and flow of noradrenergic innervations (NE) during the sleep–wake cycle (Cirelli & Tononi, 2000). An important link was then provided in the context of emotion-charged learning; NE facilitates synaptic delivery of AMPARs and LTP induction by driving GluR1 phosphorylation (Hu *et al.*, 2007). Thus, NE may represent one of the global regulators in setting the general tone of AMPAR downregulation during sleep.

The above observations lead to the impression that sleep is generally accompanied by an LTD-like process in the cortex and hippocampus, which facilitates LTP induction during wakefulness, and thus supports the hypothesis that sleep restores neural plasticity mechanisms and benefits subsequent learning and memory (Krueger & Obál, 1993; Tononi & Cirelli, 2003). However, this generalization may be premature. Within the cortex, there is good evidence for LTP-like processes occurring during sleep that mediate memory consolidation rather than erasure. In the cat primary visual cortex, LTP-like changes in protein phosphorylation occur during sleep following prior visual experience, including GluR1 of AMPARs, ERK1/2 187 and CaMKIIα/β. These changes are accompanied by synaptic strengthening that consolidates the waking visual experience (Aton *et al.*, 2009). In layer V/VI pyramidal cells of the medial prefrontal cortex, an enhanced miniature excitatory postsynaptic

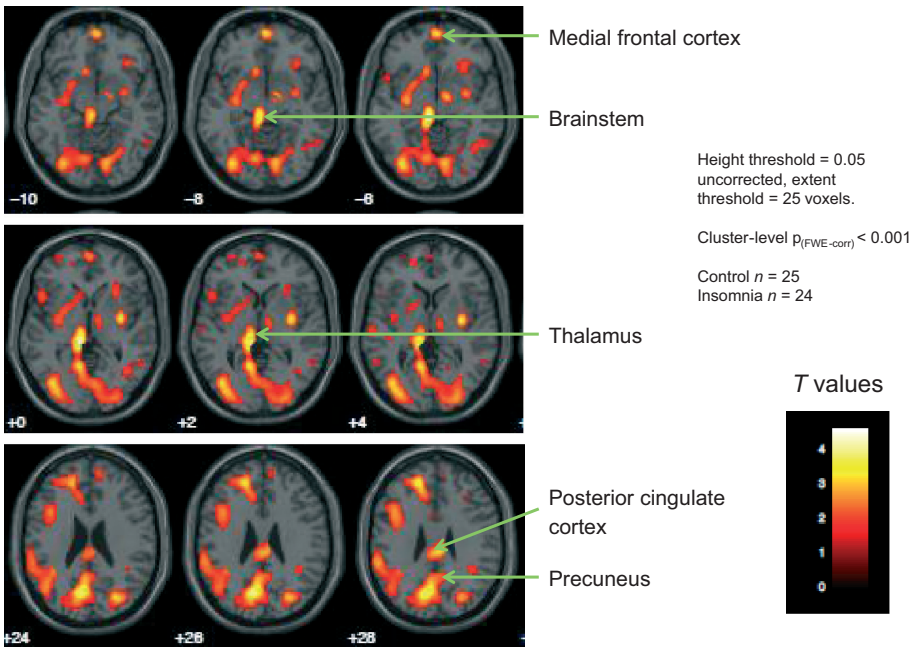

FIG. 3. Subtraction images of FDG PET scans conducted in participants with chronic insomnia and good sleepers. Participants in each group had FDG PET scans during morning wakefulness and the first NREMS period. Statistical Parametric Mapping (SPM) version 8 was used to examine the interaction of sleep–wake state with the participant group. The images above indicate areas in which the wake–NREMS differences were smaller for participants with chronic insomnia vs controls. Relatively smaller wake–sleep changes were observed for insomnia participants in regions related to introspective, self-focused mental activity (precuneus, posterior parietal cortex), emotion regulation (medial frontal cortex) and sleep–wake regulation (thalamus, brainstem). The color scale corresponds to *t*-values for individual voxels in the SPM comparison. Height extent = threshold value for considering voxels significantly different. Extent threshold = number of contiguous voxels required to consider a cluster of voxels significantly different.

current has been recorded after sleep, again suggesting strengthened AMPAR transmission during sleep (Winters *et al.*, 2011). Evidence along this line not only exemplifies the molecular and cellular substrates in support of the long-standing view that memory consolidation can occur during sleep (Frank *et al.*, 2001; Walker & Stickgold, 2004; Marshall *et al.*, 2006; Aton *et al.*, 2009; Mander *et al.*, 2011), but also underscores the importance of specifying brain regions and local neural ensembles in defining the mechanisms or functional consequences of sleep.

The seemingly opposing results showing both strengthening and weakening of AMPAR transmission during sleep suggest a degree of complexity governing the sleep-regulatory effects on synaptic transmission across brain regions. A key variable affecting the magnitude and direction of AMPAR transmission may be local network activity. For example, cortical pyramidal neurons fire action potentials either as semi-random individual spikes or as bursts of distinct frequencies. Both the timing of single action potentials firing and the frequency of action potential bursts within the range of sleep-related EEG oscillations can determine the direction (LTP or LTD) and extent of plasticity (Birtoli & Ulrich, 2004; Czarnecki *et al.*, 2007). Nonetheless, sleep slow oscillations during NREM sleep are posited to be responsible both for LTD-like synaptic depression (Tononi & Cirelli, 2003; Czarnecki *et al.*, 2007) and for LTP-like potentiation in the rodent somatosensory cortex (Chauvette *et al.*, 2012), suggesting yet another layer of unidentified local regulatory mechanisms. If regulation of sleep is dependent on prior wake activity, and if both wake activity and sleep regulation has a local component, there is good reason to predict that sleep – from the molecular regulatory machinery to the functional consequence – inevitably reflects local needs.

Long-term synaptic reorganization achieved during sleep is best characterized in the cerebral cortex and the hippocampus, though it may go far beyond. In studying the nucleus accumbens (NAc) in rodents, a critical forebrain region at the ventral striatum that mediates reward processing, we found that the GABA transmission onto NAc principle neurons was enhanced relative to glutamate transmission following acute sleep deprivation (Zheng, L., Wang, Y. & Huang, Y.H., unpublished data). This may have direct implications to the altered reward-seeking behaviors that result from sleep deprivation (Steiner & Ellman, 1972; Aalto & Kiianmaa, 1986; Everson *et al.*, 1989; Puhl *et al.*, 2009; Hanlon *et al.*, 2010), as GABA transmission in the NAc is shown to be critical for the regulation of both food reward (Hanlon *et al.*, 2004) and intracranial self-stimulation (Cheer *et al.*, 2005). In humans, although sleep is well-recognized for its involvement in regulating emotional and motivational behaviors (Drummond *et al.*, 1998; Crum *et al.*, 2004; Walker, 2010; Gujar *et al.*, 2011a,b; Hanlon & Van Cauter, 2011; Minkel *et al.*, 2011; Venkatraman *et al.*, 2011; Hasler *et al.*, 2012), the underlying cellular and molecular mechanisms remain poorly understood. Knowledge about sleep-induced synaptic reorganization in brain reward circuitry will not only provide mechanistic insights for reward behavioral research, but also benefit sleep research by offering a common ground for a mechanistic comparison of sleep across brain regions. Thus, although the molecular details may differ significantly across different brain regions, sleep-induced synaptic (and network) remodeling has direct and diverse functional implications for the subsequent wake period. How those changes are affected by or may contribute to local as well as global sleep regulation are only beginning to be understood.

Sleep mechanisms are inseparable from brain plasticity mechanisms

Within the brain the connectivity process is regulated in part by gene expression; changes in gene expression affect the functional

properties of the neuronal/glial networks. For instance, changes in receptor populations within a network will change that network's responsiveness to appropriate stimuli. Many of these connectivity genes are activity dependent in that their expression is directly altered by cell activity, for example action potentials. Further, activity-dependent brain expression of many of those genes, for example IL1, TNF and neurotrophins such as BDNF, is also characterized as being involved in neuronal connectivity including synaptic scaling and as SRS (Kushikata *et al.*, 1999; Krueger *et al.*, 2008; Turrigiano, 2008). Because these sleep-regulatory genes are activity dependent they provide a mechanism to target active networks/cells/synapses. Such mechanisms are thus bottom-up function-dependent regulatory events targeted to the networks and synapses used. Use-dependent connectivity changes are established epigenetic brain plasticity mechanisms. They also provide positive feedback leading to enhanced strength of connectivity thus to greater re-use of the active synapses/circuits whether they are excitatory or inhibitory. With time and greater use and re-use such a mechanism would be potentially destabilizing, leading, for example, to rigid non-plastic networks (Kavanau, 1994; Turrigiano, 2008). These observations suggest the presence of stabilizing mechanisms to preserve the brain's epigenetic use-dependent plasticity (Krueger & Obál, 1993). We propose that these mechanisms are activity dependent, involve the same molecules as regulate sleep, occur within the used local networks, provide a means for the brain to track prior activity, target network state changes to the active areas, and lead to emergent sleep within larger network collectives.

Human brain imaging studies; implications for regional sleep and application to a clinical condition

Human functional neuroimaging studies of NREMS and REMS have examined regional CBF using $H_2{}^{15}O$ positron emission tomography (PET), and relative regional glucose metabolism (RRGM) using [^{18}F] fluorodeoxyglucose (FDG) PET. NREMS, and SWS in particular, is characterized by widespread reductions in CBF and glucose metabolic rate. The reductions are particularly marked in subcortical structures including the thalamus, brainstem (including pontine and mesencephalic tegmentum), basal ganglia and basal forebrain; and in cortical regions including the orbital, medial and dorsolateral prefrontal cortex, medial parietal cortex (precuneus and posterior cingulate), mesiotemporal cortex, and anterior cingulate (Maquet, 2000; Dang-Vu *et al.*, 2010). Within SWS, phasic EEG features such as sleep spindles and slow waves are associated with more specific decreases in regional CBF: within the thalamus for sleep spindles, and within medial frontal and parietal cortex for slow waves (Hofle *et al.*, 1997; Dang-Vu *et al.*, 2005). Subcortical changes during SWS likely reflect deactivation of arousal and sleep modulatory structures, as well as disfacilitation of the thalamus. On the other hand, widespread reductions in cortical blood flow and metabolism during SWS correspond to structures and circuits involved in waking functions, such as cognitive control (frontal), emotion regulation (anterior cingulate, medial and orbitofrontal, mesial temporal) and self-awareness (precuneus, posterior cingulate, medial frontal).

Human functional neuroimaging studies of REMS show a very different pattern. Significant increases in CBF and RRGM (relative to SWS and wake) occur in subcortical structures, including the pontine tegmentum and thalamus, in limbic structures (amygdala, hippocampus and anterior cingulate cortex) and in the temporaloccipital cortex. In contrast, persistent deactivation occurs in cortical structures, including the dorsolateral prefrontal, and medial and lateral parietal cortices, including the precuneus/posterior cingulate (Maquet, 2000; Dang-Vu *et al.*, 2010). This pattern of activation and deactivation could be interpreted as indicating a state of arousal (brainstem, limbic system) accompanied by a relative lack of cognitive control (prefrontal cortex) or self-awareness (precuneus/posterior cingulate). This pattern could also be interpreted as being consistent with typical dream characteristics, such as prominent visual and auditory perception, emotionality, lack of insight and temporal organization, and poor recall (Maquet *et al.*, 1996).

In summary, NREMS and REMS in humans show dramatically different patterns of regional brain activation and deactivation. While both states are characterized by reduced activity in the frontoparietal cortex, NREMS is additionally characterized by reduced subcortical and limbic system activity, and REMS is characterized by increased activity in these structures.

The concept that regions of the brain semi-independently express state as demonstrated by imaging studies may also be clinically applicable. FDG PET studies suggest that individuals with insomnia have smaller wake–NREMS reductions of metabolism in arousal centers (brainstem, thalamus, amygdala, basal forebrain-hypothalamus, cingulate) compared with good sleepers (Nofzinger *et al.*, 2004). Thus, higher RRGM occurs in these structures during NREMS compared with controls. RRGM in these structures during NREMS correlates with self-reported wakefulness after sleep onset (Nofzinger *et al.*, 2006). More recent analyses also indicate that individuals with insomnia have higher RRGM in the precuneus, posterior cingulate and medial frontal cortex (Fig. 3; Buysse *et al.*, 2011). These are central structures in the brain's 'default mode network' (DMN). The DMN is most active during passive resting wakefulness, and de-activates during tasks requiring focused attention (Cavanna & Trimble, 2006; Fox & Raichle, 2007; Boly *et al.*, 2008; Buckner *et al.*, 2008; Broyd *et al.*, 2009; Raichle, 2010). DMN activity is increased during unfocused, exploratory monitoring of the environment, internal mentation drawing on personal memory, and self-referential thinking (Cavanna & Trimble, 2006; Buckner *et al.*, 2008). Increased DMN activity during NREMS is consistent with symptoms of enhanced awareness and 'mind-wandering' among individuals with insomnia, even during EEG-defined sleep, and with observations that mind-wandering is associated with both enhanced DMN activity (Mason *et al.*, 2007) and unhappiness (Killingsworth & Gilbert, 2010). Individuals with insomnia typically report more severe subjective symptoms (e.g. longer sleep latency and greater wakefulness after sleep onset) than is measured with concurrent polysomnography, a phenomenon sometimes known as sleep state misperception (Rosa & Bonnet, 2000; Krystal *et al.*, 2002; Edinger & Krystal, 2003). Persistent DMN activity during NREMS may be a functional correlate of this phenomenon. Conversely, reduced activity of the DMN during NREMS in good sleepers may be consistent with a lack of self-awareness that leads this group to underestimate sleep latency and wakefulness after sleep onset (Manconi *et al.*, 2010).

The hypothesis that sleep manifestations vary among brain regions is also relevant to a number of other common clinical sleep disorders and phenomena (Mahowald & Schenck, 2005). Patients with parasomnias arising from NREMS (e.g. sleepwalking, sleep terrors, confusional arousals) exhibit synchronized SWA characteristic of NREMS concurrent with wake-like behaviors, such as walking, talking and eating (Schenck *et al.*, 1998). Case studies demonstrate waking EEG patterns in motor and cingulate cortices concurrent with sleep-like delta EEG activity in association cortex (Terzaghi *et al.*, 2009), a pattern similar to that observed in a single case study with SPECT imaging (Bassetti *et al.*, 2000). An even more dramatic

example occurs in REM sleep behavior disorder (RBD), in which patients have vivid, often violent dreams associated with motor behaviors ranging from simple to complex; injury to the patient or bed partner is common (Schenck *et al.*, 1993; Boeve, 2010). The behavior is attributed to loss of the usual atonia during REMS, mediated by several brainstem regions, including the peri-locus coeruleus alpha. RBD often occurs in conjunction with dementia with Lewy bodies or other synucleinopathies, neurodegenerative disorders that lead to widely-distributed cortical and subcortical lesions (Boeve *et al.*, 2003; Ferrini-Strambi *et al.*, 2005). The human disorder of RBD was predicted by lesion studies in cats, in which the extent of behavioral disinhibition was proportional to the size and location of the brainstem lesion (Hendricks *et al.*, 1982). Narcolepsy, a neurological disorder characterized by neuron loss in the orexinergic cells of the lateral hypothalamus, offers another example of how clinical symptoms may arise from the simultaneous occurrence of multiple sleep–wake states. In addition to sleep episodes intruding into wakefulness, patients with narcolepsy experience cataplexy (episodes of muscle atonia during wakefulness), sleep-related hallucinations and sleep paralysis (muscle atonia during sleep–wake transitions). Each of these last three symptoms represent dissociated sleep–wake states characterized by simultaneous features of wakefulness (alertness, awareness of the environment) and REMS (atonia, dream-like imagery). Finally, some normal sleep-related phenomena can be seen as manifestations of local variations in sleep–wake states. The process of awakening from sleep is a gradual and regionally variable process (Balkin *et al.*, 2002). Regional blood flow first increases in the brainstem, thalamus and other centrencephalic structures, whereas the medial and dorsolateral cortex show increased blood flow over the first 20 min of awakening. This may relate to the phenomenon of sleep inertia, or sleep drunkenness, characterized by difficulty in achieving the sleep–wake transition. Lucid dreaming, in which the individual is aware that he is dreaming in real time, could also represent a manifestation of local sleep. During lucid dreaming compared with REMS in general, EEG gamma activity and EEG coherence are higher in frontal and frontolateral regions (Voss *et al.*, 2009).

Conclusion and implications for sleep function

After prolonged activation of glia/neurons within local networks, ATP, IL1, TNF, BDNF and possibly additional SRS release would change the network's responsiveness to inputs and cause a state shift (Fig. 2). If the original input–output relationships of the active network were environmentally relevant and adaptive, then the new output associated with the new state, because they are qualitatively and quantitatively different from the original output, could be maladaptive if the animal remained responsive to environmental input. Further, the state changes of multiple local networks would likely synchronize spontaneously. Thus, after the shift in input–output relationships, the outputs would lack the integrated network-activity patterns needed to induce environmentally adaptive cognitive or motor outputs. The classic sleep–wake regulatory circuits may coordinate the activity of multiple small networks, thereby ensuring the absence of whole-organism behavior at such times.

Local sleep mechanisms are inseparable from synaptic efficacy/connectivity regulatory functions of sleep. These local activity-dependent mechanisms also cause network output that characterizes the altered consciousness that pervades sleep. The environmentally disconnected outputs occurring during sleep, which are an alternative network pattern of synaptic use, could serve to preserve adaptive plasticity within the networks. Further, the mechanisms outlined herein would ensure an alternative pattern of neuronal activation occurring periodically as a consequence of cell activity. As a consequence of the synaptic efficacy and connectivity use rules and synaptic mechanisms, such as scaling, the ability of the brain to retain its capacity to change is maintained. This may be the critical primordial function of sleep. If so, then sleep function cannot be separated from sleep mechanisms.

Acknowledgements

This work was supported in part by grants from the National Institutes of Health (NS025378 and HD036520 to J.M.K., MH60263 to D.M.R., MH024657, RR024153 and AG020677 to D.J.B., and DA029565 to Y.H.) and by a grant from the W.M. Keck Foundation.

Abbreviations

AMPA, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid; AMPAR, AMPA receptor; BDNF, brain-derived neurotrophic factor; CBF, cerebral blood flow; DMN, default mode network; EEG, electroencephalogram; ERP, evoked response potential; FDG, [^{18}F] fluorodeoxyglucose; GABA, γ-aminobutyric acid; IL1, interleukin-1; LTD, long-term depression; LTP, long-term potentiation; NAc, nucleus accumbens; NE, noradrenergic innervations; NFkB, nuclear factor kappa B; NMDAR, *N*-methyl-D-aspartate receptor; NREMS, non-rapid eye movement sleep; PET, positron emission tomography; RBD, REM sleep behavior disorder; REMS, rapid eye movement sleep; RRGM, relative regional glucose metabolism; SRS, sleep-regulatory substances; SWA, slow wave activity; SWS, slow-wave sleep; TNF, tumor necrosis factor.

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