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Review

The energy allocation function of sleep: A unifying theory of sleep, torpor, and continuous wakefulness

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ABSTRACT

The energy allocation (EA) model defines behavioral strategies that optimize the temporal utilization of energy to maximize reproductive success. This model proposes that all species of the animal kingdom share a universal sleep function that shunts waking energy utilization toward sleep-dependent biological investment. For endotherms, REM sleep evolved to enhance energy appropriation for somatic and CNS-related processes by eliminating thermoregulatory defenses and skeletal muscle tone. Alternating REM with NREM sleep conserves energy by decreasing the need for core body temperature defense. Three EA phenotypes are proposed: sleep–wake cycling, torpor, and continuous (or predominant) wakefulness. Each phenotype carries inherent costs and benefits. Sleep–wake cycling downregulates specific biological processes in waking and upregulates them in sleep, thereby decreasing energy demands imposed by wakefulness, reducing cellular infrastructure requirements, and resulting in overall energy conservation. Torpor achieves the greatest energy savings, but critical biological operations are compromised. Continuous wakefulness maximizes niche exploitation, but endures the greatest energy demands. The EA model advances a new construct for understanding sleep–wake organization in ontogenetic and phylogenetic domains.

Contents

Abbreviations: BAT, brown adipose tissue; BI, biological investment; BMR, basal metabolic rate; CNS, central nervous system; EA, Energy Allocation; EE, energy expenditure; EEG, electroencephalogram; G, growth; M, maintenance; MCH, melanin concentrating hormone; NREM, non-rapid eye movement; REM, rapid eye movement; R, reproduction; SCN, suprachiasmatic nucleus; T_a, ambient temperature; T_c, core body temperature; T_{set}, set point for core body temperature; TE, thermoregulatory effort; WE, waking effort.

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"The optimal animal, born with some amount of energy, proceeds through life gaining and expending energy according to some schedule that maximizes its total reproductive success."
-Schoener (1971), p. 375

1. Introduction

Sleep remains the only universal behavior known to biology with no clear consensus regarding a fundamental underlying function. The recognition of sleep behavior across multiple phyla of the animal kingdom strongly suggests the presence of a shared or universal function. These diverse phyla include: insects (Hendricks et al., 2000; Huber et al., 2004b; Kaiser, 1985; Kaiser and Steiner-Kaiser, 1983; Shaw et al., 2000; Tobler and Neuner-Jehle, 1992), nematodes (Raizen et al., 2008), mammals (Zepelin et al., 2005), birds (Amlaner and Ball, 1989; Campbell and Tobler, 1984; Dewasmes et al., 1985), reptiles (Flanigan, 1973, 1974; Flanigan et al., 1973, 1974; Hartse, 1989), amphibians (Hartse, 1989; Lazarev, 1978; Segura, 1966), and fishes (Peyrethon and Dusan-Peyrethon, 1967; Shapiro and Hepburn, 1976; Zhdanova et al., 2001).

A universal need for sleep, however, has been questioned (Siegel, 2008). For example, although some species may exhibit prolonged periods of wakefulness with little or no sleep during seasonal mating (Lesku et al., 2012), migration (Rattenborg et al., 2004), or birthing (Lyamin et al., 2007; Lyamin et al., 2005), they show no apparent functional deficits during these times (Lesku et al., 2012; Rattenborg et al., 2004). Moreover, other species may forgo sleep for extended periods, such as during torpor or hibernation, when challenged by increased energy demands or limited energy supply. In light of these observations, the specific aim of this manuscript is to introduce a unifying theory of sleep function, including NREM and REM sleep, based on energy utilization or allocation, a theory that also integrates two additional behavioral phenotypes apart from sleep: torpor and continuous wakefulness.

1.1. Prior theories on the functions of sleep

Phylogenetic analyses of sleep and wakefulness across many orders of mammals (Allada and Siegel, 2008; Capellini et al., 2008a; Lesku et al., 2006; Lesku et al., 2008, 2009) and birds (Lima et al., 2005; Roth et al., 2006), as well as the great diversity in sleep expression in species with extreme specializations (Tobler, 1995), have led to a number of perceived contradictions with respect to identifying sleep's function. Complicating the search for a unifying function of sleep has been the historical recognition that endothermic birds and mammals exhibit two distinct stages of sleep, i.e., NREM and REM sleep (see Box 1 on Defining Sleep). Moreover, the characteristics of REM sleep are so diverse, ranging from muscle atonia to rapid eye movements and penile erections, that its "descriptive features obviously fail to converge on a common function" (Rechtschaffen, 1998), let alone on an obvious function that may be similar to NREM sleep.

Box 1: Defining sleep.
Sleep in most species can be defined by behavioral criteria (Flanigan et al., 1973), including (1) species-specific posture, (2) behavioral quiescence, (3) elevated arousal threshold, and (4) rapid state reversibility. There is also a homeostatic regulatory capacity that includes compensation with increased sleep intensity or duration after loss (Tobler, 1995). The vast majority of species exhibit only one identifiable type of sleep, whereas endothermic birds and mammals exhibit two distinct sleep states with the appearance of rapid eye movement (REM) sleep. Non-REM (NREM) sleep or its equivalent is characterized by generalized immobility, regular respiration and heart rate, and, in species with a neocortex, a state of cortical electroencephalographic (EEG) slowing, often with high amplitude EEG slow waves. REM sleep, on the other hand, only occurs after bouts of NREM sleep and is characterized by a loss of thermoregulatory defense and the appearance of rapid eye movements, a generalized skeletal muscle atonia with intermittent muscle twitches of the distal extremities, penile or clitoral erections, cortical EEG activation resembling wakefulness, reports of vivid dreaming in humans and increased respiratory and heart rate variability. REM sleep is also referred to as paradoxical sleep or active sleep.

One of the most commonly cited theories on sleep function is that it conserves energy beyond what is attainable from quiet wakefulness (Berger and Phillips, 1993, 1995). This model has been viewed as a relatively passive process in which all biological functions are equally reduced during sleep, similar in concept to torpor or hibernation (Berger, 1984; Berger and Phillips, 1993, 1995; Siegel, 2009). Given, however, that REM sleep is a state of increased brain energy metabolism, REM sleep would appear to contradict this model. Moreover, because the amount of energy saved during sleep compared to wake is relatively small, some argue that it is inconsequential for energy conservation to be considered sleep's *primary* function (Horne, 1988; Rechtschaffen, 1998; Zepelin and Rechtschaffen, 1974).

Another longstanding theory is that sleep is a time for recovery or provides some recuperative process (Adam, 1980; Mignot, 2008; Oswald, 1980), but what is actually being recovered has remained elusive (Rechtschaffen, 1998). The findings that whole-body protein synthesis is actually greater during wakefulness than sleep and that protein synthesis is influenced by feeding (Clugston and Garlick, 1982a,b; Golden and Waterlow, 1977), have led to a refutation of the restorative hypothesis of sleep (Horne, 1980, 1988). Moreover, even though species with the largest bodies and brain sizes presumably require the greatest cellular or tissue recovery

needs, large herbivores as a group have the least amount of sleep, whereas those with the smallest bodies and brain sizes tend to experience the greatest amounts of sleep (Siegel, 2005; Zepelin et al., 2005). It has been proposed instead that restitution is not specific to sleep and may equally occur during quiet wakefulness (Horne, 1980, 1988).

Sleep has also been suggested as a time of neural network reorganization (Aton et al., 2009; Kavanau, 1996, 1997a,b; Krueger et al., 1999; Tononi and Cirelli, 2003, 2006, 2014; Vyazovskiy et al., 2008), with NREM and REM sleep both potentially playing specific roles in memory processing (Stickgold, 2005; Stickgold and Walker, 2005; Walker and Stickgold, 2004). Nonetheless, even as species demonstrate marked reductions in total sleep time for weeks at a time during the migration or mating seasons, they show neither deficits in learning operant tasks (Rattenborg et al., 2004) nor reductions in mating success (Lesku et al., 2012) during these times. Further, although REM sleep is believed to play an important role in memory consolidation, the cetaceans, considered to include some of the most intelligent non-human mammals with respect to learning capacity, demonstrate no identifiable REM sleep (Lyamin et al., 2008). On the other hand, REM sleep quotas correlate with the degree of maturity at birth. Altricial mammals, born immature with the lowest percentage of adult brain weight, show the highest REM sleep quotas at birth compared to precocial animals (Lesku et al., 2009; Zepelin et al., 2005). This finding is consistent with the long-held view that REM sleep plays a vital role in brain maturation (Roffwarg et al., 1966).

Finally, others have proposed that sleep provides an immobilization strategy (Meddis, 1975; Rial et al., 2007; Siegel, 2009; Webb, 1974). According to this view, such "adaptive nonresponding" may conserve energy (Siegel, 2009), but sleep is seen primarily as an adaptive mechanism that keeps an animal out of "harm's way" when it is not efficient to forage or when foraging involves increased predatory danger. In other words, sleep merely fills time that is otherwise not beneficial for the animal. However, the fact that sleep is persistently observed in even the most exposed and unsafe of sleeping sites, suggests that the underlying importance of sleep is even greater than the relative safety otherwise provided by quiet wakefulness. Moreover, given the augmented sleep pressure and neurocognitive deficits following sleep deprivation, the physiological drive for sleep may be considered behaviorally maladaptive in this model since it may actually increase waking predation risk (Rechtschaffen, 1998).

The paradoxes and short-comings of the many previously proposed sleep functions have been reviewed elsewhere (Rechtschaffen, 1998), highlighting the commonly held view that a unifying function of sleep remains elusive. Some theorists have thus suggested that, even if no single universal function is identifiable, sleep may actually serve many different functions depending on the species in question (Cirelli and Tononi, 2008; Siegel, 2005). However, despite the great diversity of life and the diversity of ecological constraints, the expression of sleep behavior throughout the animal kingdom suggests that sleep has evolved to serve one underlying function in all species.

1.2. A unifying theory

In this paper, a unifying theory of sleep is proposed based on the most universal need of all species on Earth; namely, the need to optimally allocate limited energy resources to essential biological processes. This theory, here titled the Energy Allocation (EA) Model of Sleep, is based on the well-defined evolutionary principles advanced by life history theory; specifically, that all organisms have evolved to temporally allocate energy to basic functions such as growth, maintenance and reproduction throughout their life histories from birth to death in a manner that maximizes reproductive output while meeting the energy constraints of the ecological niche.

The evidence for an energy allocation function of sleep will be presented in detail. The following four postulates summarize key elements of the model:

(1) Three energy allocation strategies or phenotypes are proposed: sleep–wake cycling; torpor; and continuous or predominant wakefulness. Each phenotype is associated with trade-offs regarding benefits and costs in an energy allocation economy, outlining the evolutionary selective pressures that influence expression of one or more phenotypes for a given species during its life history.
(2) Species employing the sleep–wake cycling phenotype have evolved to perform unique and essential biological processes during sleep so as to decrease the cumulative or peak energy requirements of wakefulness, dedicate more energy reserves to the needs of waking niche exploitation, and reduce total daily energy expenditure (EE) through a repartitioning of energy resources across behavioral states. Species employing torpor, by contrast, experience the greatest energy savings, but many critical biological processes normally performed during sleep are sacrificed in torpor. Although continuous wakefulness may maximize niche exploitation, it harbors the greatest burden on daily EE.
(3) NREM and REM sleep perform the same core function in endotherms. Both sleep states reallocate energy utilization away from the high demands of wakefulness into other essential biological operations when the organism is outside of its temporal niche of waking specialization and/or when it is no longer profitable to expend energy on waking-related activities. REM sleep, by eliminating both thermoregulatory defense and skeletal muscle tone, enhances energy allocation for somatic and CNS-related functions, thereby allowing even greater energy resources to be dedicated for REM sleep-specific biological activities.
(4) Thermoregulatory control is suspended in REM sleep in the service of an energy allocation function. To increase total REM sleep time without expending excess energy for core body temperature (T_c) defense, REM sleep cycles with NREM sleep in a predictable manner governed by thermal inertia. This theory posits thermal inertia (largely defined by the animal's body mass and surface area-to-volume ratio) as a significant variable influencing both mean REM sleep bout length and the NREM–REM sleep cycle length for a given species.

In the EA model, species have evolved to downregulate specific categories of energy consuming biological activities in waking, and instead direct these processes to occur while "offline" in sleep as a means of conserving or reducing overall daily energy requirements. The coupling of specific biological processes, such as gene expression, with either circadian time or behavioral state is thus viewed, in this model, as a mechanism to optimize energy utilization across the circadian cycle, while also anticipating habitual metabolic or energy demands associated with the waking state. If the activation of sleep-specific biological operations are restricted through sleep deprivation or restriction, several predictions can be advanced: First, functional deficits should ensue that reflect the biological functions that remain unfulfilled due to insufficient sleep; second, total daily energy requirements should increase in order to maintain the habitual energy demands of the waking state while simultaneously upregulating biological operations that are normally allocated to sleep; third, adaptation to sustained sleep restriction should include not only mechanisms to replenish functional deficits, but also additional systems to adjust to the higher daily energy requirements and resultant cellular stress; and fourth,

homeostatic responses are expected to increase either sleep intensity or duration as a means of reallocating energy resources to the restoration of remaining deficits.

The EA model not only provides a construct for understanding fundamental observations of sleep–wake organization that apply to all species of the animal kingdom, but it also addresses salient questions generated from the model. For example, how does REM sleep provide energy savings and an evolutionary advantage for endotherms despite potential increased costs of defending T_c due to loss of thermoregulatory control during REM sleep? How should ecological constraints and natural selection govern the amount of energy invested into biological processes during sleep? And how does the EA model relate sleep–wake cycling to torpor and continuous wakefulness?

The first section of this paper introduces basic concepts regarding life history theory and the function of sleep as an energy allocation strategy (including NREM and REM sleep). The second section discusses significant implications of the EA model with respect to sleep deprivation. The third section places sleep in a broader context and proposes three major energy allocation phenotypes: sleep–wake cycling, torpor, and continuous or predominant wakefulness. Finally, the fourth section presents phylogenetic aspects of the EA model, including the influence of body size, ecological energy constraints, and altriciality at birth on daily NREM and REM sleep quotas across species.

2. Energy allocation, sleep, and life history theory

Life history theory explains the design of organisms and their phenotypic traits, such as body size, age of maturity, and number of offspring in a given mating season, and the allocation of energy to these traits throughout the animal's life history in a manner that maximizes lifetime reproductive success (Roff, 2002; Stearns, 2004). Although proximate physiological mechanisms have evolved to govern the life cycles of living species, life history theory provides an ultimate or evolutionary perspective upon phenotypic variation in life cycles found within or across given populations. Life history theory reveals "the underlying simplicities that unite and explain the diversity of living things and the complexities of their life cycles" (Stearns, 2004). Why does an albatross lay only one egg in any given mating year, whereas many species of fish lay clouds of eggs over days or weeks during a reproductive season? Life history theory explains the actions of natural selection on such traits by addressing trade-offs related to genetic and phenotypic differences found within and between populations.

The application of life history theory to traits such as sleep and wakefulness has yet to be explored. The EA model, as here proposed, borrows key concepts from life history theory which, I believe, reveals unforeseen clues regarding the function of sleep, particularly with respect to the temporal allocation of energy across behavioral states of sleep and wakefulness. Given the importance of life history theory in the EA model, some fundamental aspects of life history theory are now reviewed.

2.1. Background on life history theory

The energy requirements of a hypothetical animal at a given point in its life history may be partitioned into several categories, such as energy allocated to growth (G), maintenance (M), or reproduction (R) (Stearns, 2004). Reproductive effort, for example, may be further partitioned into mating effort, parental effort (parental care, such as egg fanning in fish, defense of progeny against predators, nest building, etc.), and gametic effort (gamete production). Growth and maintenance may be partitioned in a similar manner. Let us focus at present on the three main general categories: G, M, and R.

If "1" is the sum of all energy presently available to an animal, then:

$$1 = G + M + R \quad (1)$$

Therefore, as energy allocated to R increases, energy available to G and M must proportionately decrease. Life history theory addresses many different trade-offs, including the trade-off between current investment into R at the cost of investment into current G and M. Accordingly, an animal that disproportionately allocates present investment in R will reduce its potential investment into G, possibly diminishing its future reproductive success. Species have thus evolved ways to differentially allocate energy during their life histories to maximize lifetime reproductive success for the niches they occupy. The following example illustrates these concepts.

Pacific salmon leave their native fresh water streams shortly after birth and spend several years in the ocean where they grow and mature (Quinn, 2005). During this period, energy is allocated almost exclusively to G and M at the expense of R. An implication of equation (1) is that allocation of energy to R at this stage reduces the energy available to G and M, potentially delaying the age of maturity. At the end of their final ocean year, energy is allocated almost entirely to R as salmon return to the fresh water streams from which they hatched. These fish expend tremendous energy traveling upstream where they will later spawn. Hooknose males shed their feeding teeth and grow large fighting teeth called kypes during the transition back to fresh water. These kypes are used to fight other males to gain access to females (Gross, 1984). Females, on the other hand, fight for superior nest sites to lay their eggs. At the end of this reproductive phase, a cascade of physiological consequences triggered by a depletion of energy reserves leads to death (Cooke et al., 2006; Hruska et al., 2010; Jeffries et al., 2011; Jeffries et al., 2012), a destiny shared by all Pacific salmon irrespective of their success at spawning. This behavior and its associated physiological processes are under genetic control (Evans et al., 2011; Makino et al., 2007; Onuma et al., 2003) so as to allocate virtually all available energy resources into R (at the expense of G and M) to the degree that they perish following completion of the reproductive phase. This life history contrasts with related species such as the steelhead trout which have lower costs of migration and breeding competition, species that have evolved an optimized life history with continuous investment into G and M during R and thus repeated years of breeding (Quinn, 2005).

2.2. Wakefulness and energy allocation

Wakefulness is a time to gather energy resources and to expend energy reserves in a manner that maximizes reproductive output. The daily energy budget for a hypothetical animal may be partitioned into two broad categories, categories derived by reorganizing those typically employed in life history theory. The first category encompasses waking activities directed toward the external environment for niche exploitation. This category includes the energy requirements for vigilance (V) and motor activity or mobility (Mob) and is here referred to as waking effort (WE), so that WE = V + Mob. As such, WE includes foraging to capture energy, vigilance to avoid predation and mortality, and reproduction to produce offspring and replicate DNA. A second broad category includes biological operations directed toward the internal environment or body. This category is here referred to as biological investment (BI) and is defined as the energy needed for all other biological activities not requiring either vigilance or motor activity. These waking-independent operations encompass energy-consuming functions related to repair, neural plasticity or neural network reorganization,

cellular housekeeping, immune function, and growth or maintenance of reproductive organs and supporting neurophysiology, among others. If the organism is viewed as a "machine", WE defines the energy needed to run the machine, whereas BI as the energy required to maintain the machine. If "1" is the sum of all energy available to the organism, the following Eq. (2) may be written:

$$1 = \mathbf{WE} + \mathrm{BI} \quad (2)$$

During wakefulness, energy deployed for WE is increased and therefore bolded in the equation.

An implication of Eq. (2) is that "running the machine" (WE) and "maintaining the machine" (BI) involve biological functions that are in potential conflict for energy resources. This conflict presents a trade-off in that energy deployed for WE at any given moment in time is energy not available to BI. Eq. (2) elucidates two important concepts relevant to daily energy allocation, particularly with respect to management of the waking energy budget. First, an ability to decrease BI during waking allows for proportionately more energy to be directed toward WE for niche exploitation. Second, if WE is to be maintained, increasing BI during wakefulness requires an increase in total energy demands during the waking state. The solution, per life history theory, is to optimize the repartitioning of energy over time with the goal of maximizing lifetime reproductive success (fitness). The EA model predicts that BI, although downregulated in wakefulness, will be maintained to varying degrees during waking for most species based on the fitness return on the energy investment. These points have particular significance in the energy allocation function of sleep–wake cycling, which will be reviewed below.

Animals must avoid predation and compete for resources, and such competition is generally greatest during a portion of the circadian day for which the species is adapted. Being adapted to a specialized temporal and ecological niche, however, is not, in and of itself, necessarily sufficient as an optimal strategy. The example of Pacific Salmon is illustrative of the extreme case. The EA model predicts an evolutionary selective pressure to disproportionately allocate energy toward gaining access to resources and reproductive effort (mating effort, parental care, etc.) during waking at the expense of BI for other somatic processes. An alternative strategy is allocation of more energy into BI during wakefulness while simultaneously utilizing limited energy resources for obligate waking functions (WE). This alternative strategy potentially limits energy resources available for niche exploitation and, consequently, may harbor a greater selective disadvantage.

The EA model borrows principles from life history theory regarding energy optimization that may be applied to the shorter time scale of the circadian rest-activity cycle. An animal's likelihood to maximize reproductive success is increased when it: (a) is adapted to an ecological and circadian temporal niche, and (b) is able to decrease non-essential investments into BI during the waking state. As will be examined, the degree to which biological operations are downregulated in waking predictably occurs in a manner governed by cost–benefit trade-offs related to energy supply and demand. Optimization of rates of return on energy investments is the singular design principle for the organization of sleep and wakefulness.

2.3. Energy allocation and the function of sleep

The EA model proposes that sleep evolved to optimize the allocation of energy for biological investment (BI). The evolutionary drive to deploy energy for exploiting a specialized ecological and temporal niche in waking is undertaken at significant cost with respect to BI (e.g., cellular repair, immune function, and neural network reorganization). Accordingly, sleep is viewed as a behavioral state during which energy reserves are reallocated or shunted to

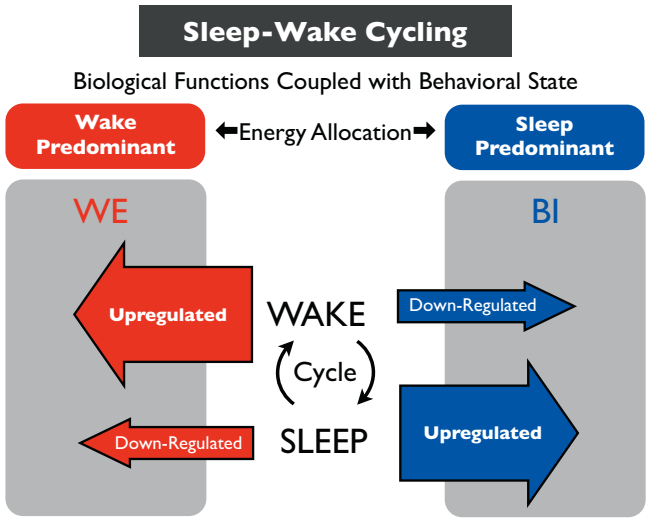

Fig. 1. A schematic of the sleep–wake cycling energy allocation model. During wakefulness, energy utilization is preferentially allocated to waking effort (WE): i.e., vigilance, foraging, and reproduction. The supporting physiology of these wake-predominant processes, however, is downregulated during sleep. In contrast, biological activities not immediately required for niche exploitation are downregulated during wakefulness, and, instead, upregulated during sleep. These upregulated biological operations in sleep are related to growth, cellular housekeeping, repair, immune function, and neural network reorganization, and, as a group, are referred to as biological investment (BI). The size of the arrows represents the relative allocation of energy dedicated to these operations during wake and sleep, respectively, whereas the color of the arrows depicts biological functions coupled with behavioral state as either primarily wake-predominant (red) or sleep-predominant (blue). See text for details.

BI as a means of replenishing deficits accumulated in the waking state and to prepare for the next bout of wakefulness. It is the expected cycling of wakefulness and sleep, resulting from the predictability of Earth's rotation and daily cycling of its ecology, that allows for investments into biological operations to be differentially allocated or shared among behavioral states (see Fig. 1). In the EA model, sleep–wake cycling evolved to optimize energy utilization and reduce internal conflict by means of repartitioning energy demands to competing biological processes over circadian time. Sleep–wake cycling, in this manner, not only reduces peak, or cumulative, energy demands and cellular stress associated with the waking state, but also conserves energy through more efficient allocation of daily energy utilization. Although this subsection is devoted to a role of sleep in energy allocation that applies to all species of the animal kingdom, a parallel function of REM sleep is addressed in the following subsection.

Restricting investments into specific biological functions during wakefulness to optimize the immediate needs of waking niche exploitation is feasible only if deferred, but less immediate, investments are upregulated in a predictable manner during the rest phase, i.e., sleep. Moreover, this orchestrated, differential allocation of biological operations determines that the categories of activities to be activated in waking may be very different from those upregulated in sleep, a proposition supported by recent data.

A growing body of literature demonstrates that maximal activation of many genes within the brain are specific to either sleep or wakefulness and relatively independent of circadian time of day (Cirelli et al., 2004, 2005b; Mackiewicz et al., 2007; Terao et al., 2006). One limitation of this genetic research is the current difficulty in differentiating which genes are activated during specific stages of sleep such as NREM versus REM sleep. Therefore, in this paper, the activation of genes is referred to as sleep-related gene expression without reference to sleep stage.

Of the genes that modulate their expression depending on the behavioral state of the animal, approximately half increase

expression during wakefulness while half do so during sleep (Cirelli, 2005; Cirelli et al., 2004). More importantly, the activation of wakefulness-related and sleep-related transcripts belong to different functional categories or classes of physiological processes, a finding consistent with a division of labor regarding state-dependent allocation of energy resources. As noted by Cirelli (2005), "Waking-related transcripts are involved in energy metabolism, excitatory neurotransmission, transcriptional activation, synaptic potentiation and memory acquisition, and the response to cellular stress. Sleep-related transcripts are involved in brain protein synthesis, synaptic consolidation/depression, and membrane trafficking and maintenance, including cholesterol metabolism, myelin formation, and synaptic vesicle turnover."

A subsequent microarray study of gene expression in mouse cerebral cortex and hypothalamus found similar results (Mackiewicz et al., 2007). The categories of genes increasing their expression during sleep are those involved in protein biosynthesis and intracellular transport, including the synthesis of cholesterol and proteins for lipid transport (Mackiewicz et al., 2007). Genes encoding proteins localized in the cellular compartments of the cytoplasm, mitochondria, structural constituents of ribosomes, lysosomes, and vacuoles, comprise the most overrepresented categories of genes that increase expression during sleep (Mackiewicz et al., 2007). Marked upregulation also is noted for genes encoding proteins needed for energy regulating pathways (Mackiewicz et al., 2007).

Microarray-based gene expression studies also demonstrate consistency across rodent species with respect to the categories of genes specifically activated during sleep and wakefulness (Terao et al., 2006). It is noteworthy that the fruit fly, Drosophila (Cirelli et al., 2005b; Zimmerman et al., 2006), as well as the avian white-crowned sparrow (Jones et al., 2008a) and humans (as demonstrated through blood transcriptome analyses (Moller-Levet et al., 2013)) also exhibit similar categories of genes activated during wakefulness, categories that are functionally different from those activated during sleep. These data suggest that the partitioning of metabolic processes across sleep and wakefulness, and, consequently, the differential allocation of energy demands during these behavioral states, may be a fundamental basis of sleep–wake organization across the animal kingdom.

Notwithstanding current technical limitations in determining whether changes in gene expression during sleep directly translate into alterations in protein level (Andretic et al., 2008), findings from the microarray-based gene technology are consistent with prior data demonstrating that brain protein synthesis appears to increase during slow wave sleep in both the rat (Ramm and Smith, 1990; Richardson and Rose, 1971) and rhesus monkey (Nakanishi et al., 1997). Given that local cerebral metabolism is overall reduced during sleep relative to wakefulness (Ramm and Frost, 1986), Ramm and Smith (1990) speculated that decreasing the metabolic demands of wakefulness "may actually favor biosynthetic processes during slow wave sleep" (p. 753). The EA model is able to extend this statement further. Specifically, when an animal is outside of its waking temporal niche, many energy consuming operations, such as unique categories of macromolecule biosynthesis, are genetically engineered to optimally occur "offline" during the behavioral state we call sleep, a state that reallocates energy utilization away from the demands of wakefulness and into these essential biological activities in a manner that maximizes reproductive success.

Although the function of sleep has been argued by some "to be of the brain, by the brain, and for the brain" (Hobson, 2005), the EA model makes no prediction that the differential allocation of energy resources, i.e., sleep, is only for the brain. On the contrary, all central and peripheral energy consuming biological operations should be subjected to evolutionary selective pressures to differentially allocate energy resources toward optimizing daily energy utilization. In support of this view, one of the few studies designed to evaluate gene expression in both brain and periphery in relation to sleep and wakefulness found three times as many sleep-dependent transcriptional changes in the liver compared to whole brain (Maret et al., 2007). In short, the temporal allocation of resources may be governed by either behavioral state or circadian time to anticipate the needs of the rest-activity cycle.

The concept that sleep may be a time of growth and repair for peripheral tissues was proposed over three decades ago (Adam, 1980; Oswald, 1980). A key argument of these investigators for a restorative function of sleep is the observation that hormones released during sleep, such as growth hormone, prolactin, luteinizing hormone and testosterone, exhibit predominantly anabolic functions, unlike the catabolic effects of cortisol release associated with wakefulness. Growth hormone, for example, is primarily released during NREM sleep in humans (Sassin et al., 1969; Van Cauter, 2005) and has wide ranging effects on peripheral tissues, including the promotion of protein and RNA synthesis, activation of lipid metabolism (leading to increased circulating levels of free fatty acids while also reducing glucose utilization), and increasing resting energy expenditure (Moller and Jorgensen, 2009; Moller et al., 2009). Sleep plays a major role in stimulating prolactin secretion (Van Cauter, 2005). In addition to its effects on lactation, prolactin exhibits more actions on central and peripheral tissues than all other pituitary hormones combined (Bole-Feysot et al., 1998). Prolactin's effects include, among others, a role in immune function, as well as cell growth or mitosis in many peripheral tissues such as skin, liver, intestine, vascular smooth muscle and proliferation of β-cells in the pancreas (Bole-Feysot et al., 1998; Goffin et al., 1998). Finally, testosterone release increases during sleep in males (Luboshitzky et al., 1999; Roffwarg et al., 1982) and its anabolic effects, such as regulation of skeletal muscle protein synthesis (Kadi, 2008; Sheffield-Moore, 2000; Sinha-Hikim et al., 2006) and the remodeling of bone (Brown, 2008; Oury et al., 2011), have been well documented.

An early criticism of the original restorative hypothesis was its inability to adequately explain why sleep is required for restoration. For example, total whole body protein synthesis is actually greater during wakefulness than sleep (Clugston and Garlick, 1982a) and more dependent on feeding than on behavioral state (Clugston and Garlick, 1982b; Golden and Waterlow, 1977), findings that led Horne (1980, 1988) to refute the restorative function of sleep. However, the microarray-based data reviewed above may offer more clarity as to a potential restorative property of sleep. Indeed, it is the functional specificity of gene expression during sleep versus wakefulness that is critical to understanding how the EA model differs from the original restorative hypothesis.

Sleep may be viewed as "restorative" in the EA model primarily in the sense that specific biological activities, including categories of gene expression, are downregulated in waking and require the cyclical expression of sleep for their eventual upregulation or "restoration" (see Fig. 1), without which, deficits in biological processes will occur (see section: Energy Allocation and Sleep Deprivation). Total daily, whole body, protein synthesis, including the processing and folding of proteins within the endoplasmic reticulum, has an energy cost (Braakman et al., 1992; Dorner et al., 1990), and protein synthesis is one of the first ATP-consuming cellular operations to be downregulated or sacrificed when energy reserves are limited (Buttgereit and Brand, 1995; Wieser and Krumschnabel, 2001). The types of biological activities to be upregulated during sleep, however, may not be limited to gene expression or protein synthesis, but, rather, include diverse functions ranging from cell membrane repair or intracellular transport (Mackiewicz et al., 2009) to clearance of metabolic waste

(Varshavsky, 2012; Xie et al., 2013), among others. Biologically coupling key categories of energy-consuming processes to occur during sleep would therefore: (a) decrease the peak or cumulative energy demands (and cellular stress) during wakefulness by repartitioning competing biological operations over circadian time; (b) allow proportionately more energy reserves to be dedicated to the immediate needs of niche exploitation; (c) maintain relative stability in energy utilization across circadian time; and (d) more efficiently utilize energy resources throughout a 24-h period so as to decrease overall daily energy requirements.

2.4. Energy allocation and the function of REM sleep

Endothermic mammals and birds experience an additional somatic cost related to thermoregulation, a cost not imposed on lower vertebrates. To maintain a high, constant body temperature, for example, mammals encounter a five- to ten-fold increase in energy requirements relative to ectothermic vertebrates of similar body size (Else and Hulbert, 1981; Hulbert and Else, 1989; Kortner and Geiser, 2000). Although mitochondrial activity in mammals and reptiles is similar in some organs such as liver, kidney and brain, basal mitochondrial activity in mammalian heart, lung and skeletal muscle is twice as active as observed in reptilian mitochondria (Hulbert and Else, 1989). The heat generated from this basal cellular functioning is called obligatory thermogenesis, giving rise to the higher basal metabolic expenditures in endothermic compared to poikilothermic species (Silva, 2005). In addition, small mammals with large surface area-to-volume ratios must, due to their increased thermal conductance, expend a disproportionate amount of energy, relative to larger animals, to maintain an elevated metabolic rate (Snyder and Nestler, 1990), even without invoking shivering or other forms of facultative thermogenesis (Silva, 2005). Indeed, small birds and mammals, because of their high thermoregulatory energy demands, may consume more food per day than their own body mass (Kortner and Geiser, 2000). Although endothermy is an expensive adaptation, the associated benefits of maintaining a constant body temperature independent of the environment are great. Any mechanism that reduces the costs of thermoregulation or reallocates energy utilization away from thermoregulatory defense into other somatic processes, would be highly advantageous.

I advance the concept that REM sleep has evolved as a functional component of endothermy, insofar as REM sleep *specifically* reduces thermoregulatory effort for the purpose of reallocating energy resources into other competing biological benefits. Robust inhibition of thermoregulation and whole body heat production occurs during REM sleep (Parmeggiani, 2003; Schmidek et al., 1983). Although, on the one hand, metabolic heat production drops in mammals during NREM sleep relative to wakefulness, thermoregulatory responses such as shivering, panting, or sweating still occur. In REM sleep, on the other hand, these thermoregulatory responses cease entirely, even in abnormally high or low ambient temperatures (Hendricks, 1982; Parmeggiani, 2003). Brown adipose tissue (BAT) plays an important role in non-shivering thermogenesis (Silva, 2011), and BAT function is reduced during REM sleep in adult mammals, even when challenged at low ambient temperatures (Calasso et al., 1993). Although BAT activity increases in cold-challenged infants and has been hypothesized to occur during REM sleep (Blumberg and Stolba, 1996; Sokoloff and Blumberg, 1998), there is no direct experimental evidence for REM-specific BAT activity. Experimental conditions that challenge thermoregulatory responses, such as cooling or warming the hypothalamus directly, provoke differing metabolic responses depending on the vigilant state of the animal (Alam et al., 1995a,b; Glotzbach and Heller, 1976). The increase in metabolic rate induced during NREM sleep is somewhat lower than in wakefulness, but cooling the hypothalamus has no effect on metabolic rate when applied during REM sleep (Glotzbach and Heller, 1976).

Although one might expect a significant decrease in metabolic rate during REM sleep, given the reduction in thermoregulatory responses to ambient temperature challenges, such a decrease does not occur. Instead, whole-body metabolic rate during REM sleep remains unchanged relative to the NREM state (Fontvieille et al., 1994; Haskell et al., 1981b; Jung et al., 2011; Katayose et al., 2009; White et al., 1985; Zhang et al., 2007). This finding is consistent with the hypothesis that energy normally allocated to core body temperature defense is being utilized for other biological processes.

The potential targets of increased metabolic utilization during REM sleep have been the basis of extensive research over the past several decades, research that has focused on the physiological phenomena most apparent during this sleep state. These phenomena include the prominent rapid eye movements and increased cortical activation that typify REM sleep, giving rise to theories that this stage of sleep plays a role in the development and maintenance of visual systems or cortical reorganization (Berger, 1969; Frank et al., 2001; Marks et al., 1995; Roffwarg et al., 1966). The muscle atonia and frequent brief muscle twitches in REM sleep (as well as the appearance of REM sleep behavior disorder when the atonia is disrupted (Arnulf, 2012; Luppi et al., 2011; Mahowald and Schenck, 2005)) are consistent with a function for REM sleep in the development or maintenance of motor systems (Blumberg, 2010; Jouvet, 1998). Penile and clitoral erections are characteristic of REM sleep (Hirshkowitz and Schmidt, 2005; Schmidt et al., 1994), and the production of REM-related erections requires neural connections from the forebrain (Schmidt et al., 2000) to spinal cord (Schmidt et al., 1999) and erectile tissue at the end-organ level (Schmidt, 2005), suggesting that the reproductive system is a beneficiary of such an energy allocation strategy in some mammals. The vivid dreaming and activation of the limbic system during REM sleep is suggested to play an important role in emotional memory and development (Brown et al., 2012; Wagner et al., 2001) and the learning of programed behavior (Jouvet, 1975, 1998). Finally, neuroimaging (Maquet et al., 2000) and unit recording studies (Louie and Wilson, 2001; Poe et al., 2000) have identified specific brain regions that become reactivated during REM sleep, either replaying sequences or altering characteristics of neuronal firing that were associated with learned behavior during the previous day. These data support the long-held hypothesis that REM sleep plays a role in memory consolidation. Similar neuronal activation associated with learning has been observed during NREM sleep (Euston et al., 2007; Nadasdy et al., 1999). All of these proposed functions of REM sleep require energy, energy that, per the EA model, is actively shunted or diverted away from other biological processes.

Although certain metabolic operations are increased during REM sleep, others, as noted above, are diminished or inhibited, as would be expected in an energy allocation economy. The most obvious reduction in energy utilization and heat production results from the generalized muscle atonia that characterizes the REM sleep state (Chase and Morales, 2005). The skeletal muscle atonia during REM sleep is extensive. It is maintained by an active hyperpolarization of alpha motoneurons throughout the ventral horn of the spinal cord from lumbosacral to brainstem levels, and this hyperpolarization eliminates skeletal muscle tone by preventing acetylcholine release at the neuromuscular endplate (Brown et al., 2012; Chase and Morales, 2005; Sakai and Neuzeret, 2011). The muscle atonia of REM sleep has been viewed as an adaptive mechanism that prevents dream-enacting behavior during a time of central motor activation. Nevertheless, maintenance of skeletal muscle tone also has a significant energy cost, and muscle tone is a means of heat production central to thermoregulatory control, be it obligatory thermogenesis or shivering, facultative thermogenesis (Parmeggiani, 2003; Silva, 2011). The general muscle paralysis

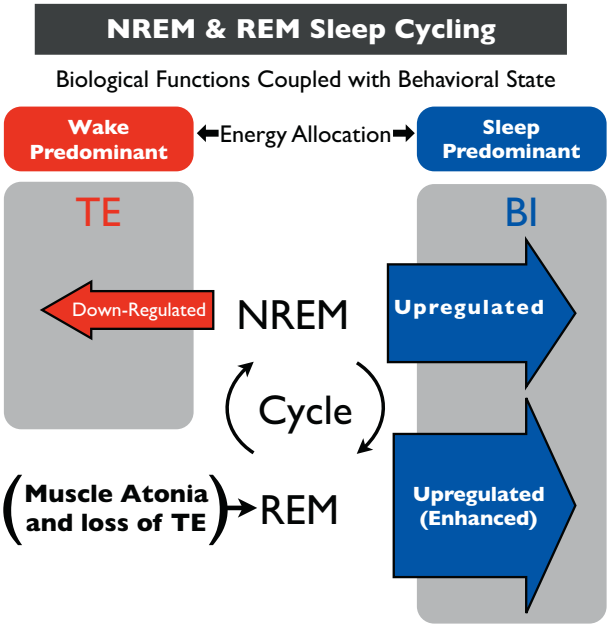

Fig. 2. The parallel energy allocation function of NREM and REM sleep. NREM sleep reallocates energy utilization away from wakefulness into specific categories of biological activities that are upregulated during sleep. REM sleep augments this energy allocation process by suspending the high-energy demands related to thermoregulatory effort (TE) and eliminating skeletal muscle tone. The sizes of the arrows represent the relative allocation of energy dedicated to these operations, whereas the color of the arrows depicts biological functions that are either wake-predominant (red) or sleep-predominant (blue). WE: waking effort (vigilance, foraging, and reproduction); TE: thermoregulatory effort; BI: biological investment (growth, maintenance, repair, and neural network reorganization).

during REM sleep involves not only antigravity musculature, as might be expected to prevent dream-enacting behavior, but also the entire intercostal musculature and most accessory muscles of breathing including the tongue. If the purpose of generalized muscle atonia were only to prevent dream-enacting behavior, it would seem that paralysis of accessory muscles of breathing would be maladaptive. The EA model views a function of this muscle paralysis, however, as serving a specific energy saving strategy during REM sleep (see Fig. 2).

Investments into biological activities during REM sleep are proposed to occur at a cost with respect to thermoregulatory effort (TE); specifically, energy normally utilized for thermoregulatory defenses and the associated muscle tone is diverted, as shown in Fig. 2, to CNS-related processes or BI as a means of decreasing total energy requirements. As a result of this energy allocation mechanism, the organism is faced with a potential dilemma: increase total REM sleep time without expending energy to defend its core body temperature (T_c), which is challenged as a result of suspending thermoregulatory responses and the elimination of muscle tone. The longer any single bout of REM sleep, the more likely T_c may deviate toward the ambient temperature (T_a) (Sichieri and Schmidek, 1984; Walker et al., 1983) and more energy may ultimately be required by the organism to defend or maintain T_c. Expending energy to defend T_c potentially defeats the overall energy savings conferred by the REM sleep energy allocation strategy. Moreover, if, as proposed, a primary function of REM sleep is to divert energy utilization away from thermoregulatory defense toward other biological processes, REM sleep duration should be increased in a thermoneutral T_a. However, REM sleep should be reduced in a T_a below thermoneutrality where T_c is preferentially more vulnerable to T_a challenges than in NREM sleep. In other words, the benefits of energy allocation, when thermally challenged, are particularly compromised during REM sleep compared to the NREM sleep state where thermoregulatory defenses are maintained.

Two observations are well established: REM sleep is maximally expressed when sleep occurs at the high end of the thermoneutral zone, and T_a challenges deviating from thermoneutrality preferentially decrease REM sleep expression in favor of NREM sleep (Heller, 2005; Muzet et al., 1984; Szymusiak and Satinoff, 1981). For example, Szymusiak and Satinoff (1981) demonstrated that, although oxygen consumption and NREM sleep time in rats remains relatively constant at a T_a between 25 and 31 °C, total REM sleep time more than doubles over this temperature range. Indeed, the highest REM sleep quantities occur at the thermoneutral T_a of 29 °C and significantly decrease as the T_a deviates from this value. Similar decreases in REM sleep secondary to thermal challenges have been well described in other species including humans (Haskell et al., 1981a; Muzet et al., 1983; Valatx et al., 1973), although partial re-emergence of REM sleep may occur in some species following acclimation to cold ambient temperatures (Sichieri and Schmidek, 1984).

When viewed through the lens of the energy allocation model, the lineage-specific absence of REM sleep in cetaceans (Lyamin et al., 2008) might be conceptualized as resulting from the high thermal conductance of water; that is, the proposed energy savings provided by the energy allocation function of REM sleep may not outweigh the necessary costs of defending T_c in a cold-water environment. Dolphins, for example, are faced with the particular challenge of maintaining a constant body temperature. They regularly employ intermittent tail beating as a method of heat generation, and the rate of tail beating significantly correlates with an animal's surface area-to-volume ratio: smaller dolphins with lower thermal inertia demonstrate the highest rates of tail movements (Pillay and Manger, 2004). Cetaceans also have the unique complication of maintaining respiration in water. With respect to the proposed energy allocation benefits of REM sleep, the need to maintain thermoregulatory body movements during a REM-like state may have defeated the evolutionary advantage of REM sleep for this phylogenetic lineage, particularly when also weighing other immobility-related costs of REM sleep, such as the need for respiration or predator defense in an open water environment. The EA model predicts that functions normally fulfilled by REM sleep in terrestrial mammals are likely not surrendered in cetaceans, but, rather, accomplished through alternative strategies in either NREM sleep or wakefulness.

For terrestrial mammals, I propose that REM sleep predictably cycles with NREM sleep in a manner such that thermal inertia (largely defined by an animal's surface area-to-volume ratio) is a significant variable governing mean REM sleep bout length and even influencing NREM–REM sleep cycle length in given species. The cycling of the two sleep states allows endotherms to optimize energy utilization during sleep by increasing total REM sleep time while decreasing the energy costs for T_c defense. Larger animals are predicted to maintain longer bouts of REM sleep without T_c deviations because of their smaller surface area-to-volume ratios and the greater thermal inertia provided by their larger body masses. Given the proposed limitation of REM sleep bout length based on body mass or thermal inertia, smaller animals are predicted to cycle more frequently between NREM and REM sleep as a means of increasing total REM sleep time, while reducing the energy demands of T_c defense.

As shown in Fig. 3, this prediction is consistent with a significant correlation that is observed in phylogenetic analyses across mammalian species (Capellini et al., 2008b; Elgar et al., 1988; Savage and West, 2007; Zepelin et al., 2005). The correlation has been well described but has remained without explanation since the 1960s (Hartmann, 1968). The smallest mammals, e.g., mice, exhibit the shortest bouts of REM sleep and the shortest NREM–REM

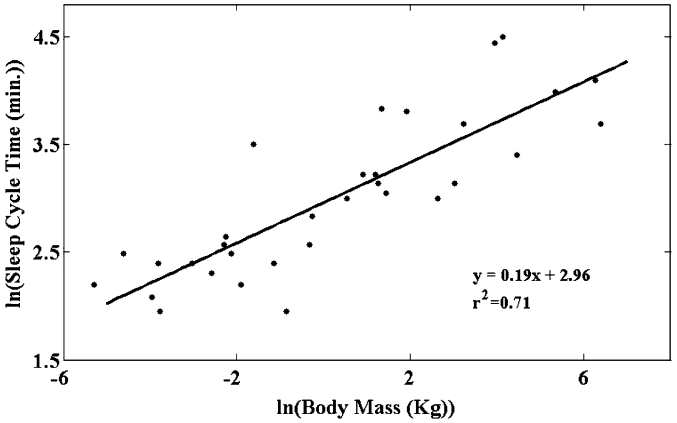

Fig. 3. Correlation between body mass and NREM–REM sleep cycle length. REM sleep is proposed to cycle with NREM sleep in a manner that increases total or cumulative REM sleep time while limiting energy expense for core body temperature (T_c) defense (see text). In support of this proposition, a significant positive correlation is observed between body mass and NREM–REM sleep cycle length across species. It should be noted that the slope of this correlation is less than the typical 2/3 or 3/4 scaling between body mass and metabolic rate, consistent with the premise that correlation between body mass and sleep cycle length is based on factors other than simply metabolic rate. According to the EA model, other variables are also predicted to influence the scaling of sleep cycle length, including surface area to volume ratio, fat stores, thickness of fur, and mean ambient temperatures of the species' environment. The correlation in this figure derived by using the sleep data base made publically available from Savage and West (2007). Similar correlations between cycle length and body mass have been observed by other investigators (see text).

cycle lengths, whereas larger animals, e.g., elephants, have much longer bouts of REM sleep and longer NREM–REM cycle lengths (Hartmann et al., 1968; Tobler, 1992). It has long been recognized that NREM–REM sleep cycle length is most strongly correlated with brain weight (Zepelin et al., 2005), a correlation that will also be addressed below.

Although mean NREM–REM sleep cycle length may be largely species-specific, data suggest that this cycle length predictably changes at the individual level in response to T_a challenges. The NREM–REM cycle for individual mammals, including humans, lengthens as T_a falls below thermoneutrality, and is shortest when the individual is sleeping in a thermoneutral T_a (Heller, 2005; Muzet et al., 1983). In a study of human subjects, mean NREM–REM cycle length varied from 108.6 min at a T_a of 13 °C to 85.2 min at 25 °C (Muzet et al., 1983), suggesting that NREM–REM sleep-cycle length may be adjusted opportunistically so as to optimize the competing energy demands between T_c defense and the biological benefits gained through REM sleep. In addition to body or brain mass, other variables, such as surface area-to-volume ratio, fat stores, thickness of fur, and ambient temperature of a species' environment, are all predicted to influence the scaling of NREM–REM sleep cycle length.

How may the suspension of thermoregulatory defense during REM sleep provide overall energy savings when the animal sleeps in ambient conditions below thermoneutrality (a time when defense of T_c is increased)? The following four points summarize the concepts and provide several additional elements in the model with respect to REM sleep:

(1) REM sleep expression is more sensitive to ambient temperature challenges than NREM sleep, such that REM sleep will be reduced or sacrificed before NREM sleep when sleeping below thermoneutrality (Heller, 2005; Muzet et al., 1984; Szymusiak and Satinoff, 1981). This would be expected if energy allocation is a primary function of REM sleep. In other words, REM sleep is suppressed if the benefits of an energy allocation strategy do not outweigh the costs of defending the T_c.
(2) As a result, each REM sleep bout is short enough in duration, so that T_c minimally deviates from baseline, even at ambient temperatures well below thermoneutrality (Muzet et al., 1984; Sichieri and Schmidek, 1984). This limitation in REM sleep expression decreases the need for T_c defense.
(3) Although thermoregulation is suspended during REM sleep, heat production is not. Indeed, heat production within the inner core, i.e., brain, is increased during REM sleep, a finding that has led to the hypothesis of a brain warming function for REM sleep (Wehr, 1992). According to the EA model, CNS heat production during REM sleep simply reflects increased brain metabolism associated with activation of REM sleep-specific biological processes.
(4) The increase in peripheral vasodilatation during sleep (Krauchi and Deboer, 2010) may help distribute heat from the inner core to the periphery to decrease the need to defend peripheral temperatures, even when REM sleep occurs in conditions below thermoneutrality. If CNS heat production plays a role in maintaining peripheral temperatures during REM sleep in this manner, it may explain why NREM–REM sleep cycle length has the closest correlation with brain mass when controlling for body weight (Zepelin et al., 2005). Because of the potential for increased heat loss, however, such a heat distribution strategy from brain to periphery also limits REM sleep bout duration.

In summary, so long as mechanisms are in place to appropriately limit or control REM sleep expression, REM sleep is hypothesized to provide overall energy savings, even when an animal sleeps in ambient temperatures below thermoneutrality. Through an elegant energy allocation mechanism, endotherms may obtain the benefits of diverting energy utilization away from thermoregulatory defense and general skeletal muscle tone into REM sleep-specific biological functions while maintaining stability in whole-body energy utilization during sleep. The alternative strategy of maintaining the high CNS neuronal activation of REM sleep, while simultaneously maintaining thermoregulatory defenses and muscle tone, would otherwise increase total daily EE. Although each REM sleep bout is relatively short in duration, as is required to minimize T_c deviation, cumulative REM sleep time is significant across endotherms. Through this energy allocation strategy, the overall energy savings achieved may, instead, be invested into biological functions that enhance survival and reproductive success. Moreover, the EA model of REM sleep relies on the same general principles outlined for NREM sleep in the previous section and, thereby, suggests a parallel core function for the two states of sleep.

2.5. Additional perspectives on the energy allocation model

The EA model of sleep–wake cycling provides an evolutionary explanation across species for the temporal organization of biological operations, such as gene expression and energy utilization. As different as the states of NREM and REM sleep may appear, the energy allocation theory is the first model to explain a parallel function of these two states of sleep. Both states can be viewed as alternative energy allocation strategies. Through redistribution of energy utilization, NREM and REM sleep benefit central as well as peripheral biological processes, whereas REM sleep may augment investments in CNS-related functions. The coexistence of the two sleep states in endotherms allows consideration of additional benefits of cycling NREM with REM sleep. Accordingly, several authors had earlier proposed that the macromolecules synthesized during NREM sleep are utilized during REM sleep for REM-specific functions such as neural network reorganization, memory consolidation, or tissue repair (Adam, 1980; Hartmann, 1973).

The EA model of sleep also proposes that total energy is conserved beyond what it attainable alone through quiet wakefulness

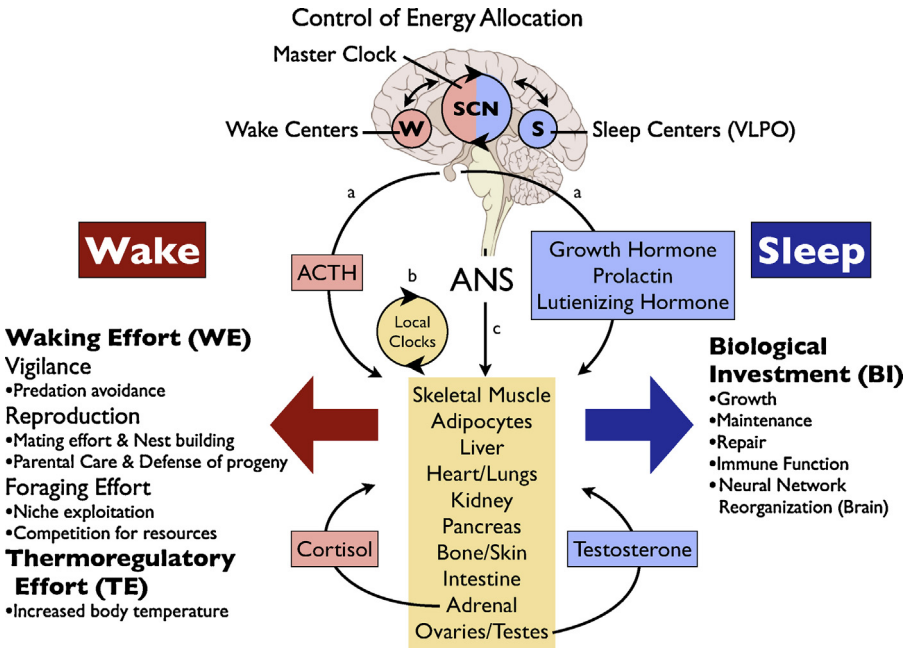

Fig. 4. The control of energy allocation, as here proposed, is an active and orchestrated process involving both brain and periphery. Within the brain, the expression of sleep or wakefulness involves the interplay between sleep (S) and wake (W) promoting centers, the timing of which is gated by the circadian clock in the suprachiasmatic nucleus (SCN). With respect to the periphery, wake-predominant (red) or sleep-predominant (blue) metabolic processes may be synchronized with the behavioral expression of wakefulness or sleep through (a) hormonal control, (b) local autonomous circadian clocks in peripheral tissues, and (c) direct descending influence from brain to periphery via the autonomic nervous system (ANS). The majority of all cells in the periphery contain semi-autonomous circadian clocks that modulate metabolic pathways (see text). These peripheral clocks are synchronized with the "master" SCN through a number of mechanisms, including the circadian body temperature rhythm (Buhr et al., 2010; Edery, 2010).

(see Section 4, Phenotypes of Energy Allocation), but the EA model is based on a set of principles different from the energy conservation model originally advanced as a function of sleep (Berger and Phillips, 1993, 1995). The original conservation model postulated a mechanism comparable in principle to shallow torpor or hibernation as the means by which sleep conserves energy (Berger, 1984, 1993; Walker and Berger, 1980). This earlier model, by definition, depicts a passive process whereby all energy requirements of the body and brain are equally reduced during sleep, "analogous to turning out the lights when you leave a room" (Siegel, 2009) or turning down the dimmer on a light switch.

The EA model of sleep–wake cycling, in contrast, is a highly active and dynamic process (see Fig. 4) in which certain biological processes, such as thermoregulatory effort and much of the cellular machinery needed for vigilance, are *reduced*, while energy for other functions, such as macromolecule biosynthesis and memory consolidation, are *increased*. Although the net energy savings of sleep appears modest when superficially compared to wakefulness, it is the optimization of energy distribution over the 24-h period that allows for relative stability of energy utilization across behavioral states. The EA model, therefore, conserves energy via two principle mechanisms: First, the metabolic rate of sleep is 5–15% lower than that of quiet waking (Jung et al., 2011; Markwald et al., 2013; White et al., 1985; Zepelin, 1989), allowing sleep-related biological operations to be completed at a lower overall energy cost compared to waking. Second, through a more efficient use of energy across circadian time, energy-consuming cellular infrastructure requirements can be reduced. In the EA model, this latter mechanism is hypothesized to conserve energy beyond the simple calculated difference between sleeping and waking metabolic rates.

The EA model is consistent with an emerging view integrating energy metabolism with circadian chronobiology and sleep–wake neurophysiology. For example, in addition to a central "master clock" in the suprachiasmatic nucleus (SCN) that modulates the timing of sleep and wakefulness, the majority of all cells in the body contain partially autonomous circadian clocks that are intimately involved in metabolic pathways and play fundamental roles in regulating metabolism at the local or cellular level (Bass and Takahashi, 2010; Froy, 2011; Kohsaka and Bass, 2007; Mohawk et al., 2012) (see Fig. 4). The timing of the peripheral clocks is influenced by the "master" SCN pacemaker's output rhythms (Buhr et al., 2010; Mohawk et al., 2012).

An additional illustration reflects the integration of sleep–wake neurophysiology with energy metabolism. For example, while hypocretin (orexin) neurons in the hypothalamus play a major role in promoting wakefulness (Brown et al., 2012), these neurons are also sensitive to metabolic hormones such as leptin and ghrelin, and, as such, are sensors of energy balance and modulators of feeding behavior (Adamantidis and de Lecea, 2009; Sakurai, 2005; Saper, 2006; Tsujino et al., 2005). More recent data have identified adjacent hypothalamic neurons, expressing melanin-concentrating hormone (MCH), that regulate expression of REM sleep (Hassani et al., 2009; Jego et al., 2013; Jego et al., 2012; Monti et al., 2013; Peyron et al., 2009), at least in part through their direct descending connections with brainstem REM sleep-generating structures (Clement et al., 2012; Jego et al., 2012; Luppi et al., 2013; Verret et al., 2003). These MCH neurons maximally discharge during REM sleep and fire reciprocally in relation to adjacent, wake-active hypocretin neurons (Hassani et al., 2009). The MCH neurons co-express Nesfatin-1 and also play a role in appetite, satiety, and energy homeostasis (Fort et al., 2008; Macneil, 2013; Oh et al., 2006), consistent with the role of the hypothalamus in orchestrating energy allocation through behavioral state modification. More research is required to elucidate whether these MCH neurons interact with other hypothalamic thermosensitive neurons to control or limit REM sleep expression when sleep takes place in ambient temperatures below thermoneutrality. Accepting that proximate or physiological mechanisms vary from one species

to another, the EA model integrates sleep–wake organization with energy metabolism in a unifying theory that may be applied to all species.

3. Energy allocation and sleep deprivation

The coupling of unique biological processes with behavioral state is viewed as a means of reducing metabolically expensive cellular infrastructure requirements by regulating energy utilization across the sleep–wake cycle. Energy is conserved (and moment-to-moment demands on cellular organelles are reduced) when the up- or down-regulation of biological operations in sleep and waking predictably cycle "in phase" with external environmental demands, thereby allowing for relative stability in energy utilization across circadian time. However, well-defined consequences are anticipated during sleep restriction when habitual waking bout durations are abnormally extended, particularly when protracted over several days or longer. These include: (1) physiological deficits; (2) increased energy requirements; (3) adaptive mechanisms; and (4) homeostatic responses. These outcomes, as viewed through the EA model, are explored in this section.

3.1. Sleep deprivation and physiological deficits

According to the EA theory, functional deficits reflect sleep-dependent, biological processes that remain unfulfilled secondary to sleep loss. Microarray-based gene expression studies consistently find that sleep deprivation or extended wakefulness, be it in the mouse (Mackiewicz et al., 2007) or in Drosophila (Zimmerman et al., 2006), is associated with a downregulation of genes that encode key components of protein synthesis normally upregulated in sleep. In general, genes that are upregulated during sleep remain downregulated during short-term sleep deprivation. This section highlights a broad array of central and peripheral biological functions that are adversely affected by sleep loss for species that cycle between sleep and wakefulness and also raises several issues that must be addressed by the EA model.

3.1.1. Sleep deprivation and central deficits

The detrimental effects of sleep restriction on cognitive functioning are extensive (Balkin, 2011; Dinges et al., 2005; Durmer and Dinges, 2005; Jackson et al., 2013; Ratcliff and Van Dongen, 2009), ranging from increased reaction times (Doran et al., 2001; Ratcliff and Van Dongen, 2011) and decreased signal detection associated with lapses in attention (Van Dongen et al., 2012) to disruption of higher executive functioning or decision making (Harrison and Horne, 2000; Tucker et al., 2010). A number of hypotheses implicate sleep loss as a cause of cognitive deficits. The state-instability hypothesis (Doran et al., 2001) postulates progressive inability to maintain wakefulness following prolonged sleep loss that results in moment-to-moment fluctuations in level of alertness, which are particularly manifested in tasks requiring sustained attention. A second hypothesis is specific or preferential disruption in the prefrontal cortex following sleep deprivation, leading to degradation of higher-order cognitive processes (Harrison et al., 2000; Horne, 1993). Yet another concept describes the over-taxing of neuronal populations at the local level, whether in the prefrontal cortex (Harrison et al., 2000) or other brain regions (Tucker et al., 2010), as a consequence of repetitive use during extended wakefulness (Krueger and Obal, 1993; Van Dongen et al., 2011), resulting in a "locally diminished capacity for information throughput" (Van Dongen, 2012). This latter perspective is consistent with the premise that "over-taxing" of neuronal assemblies during sleep loss is, at least in part, functionally related to the local depletion of substrate normally replenished through sleep-dependent macromolecule biosynthesis. This perspective requires further investigation.

Although state instability, prefrontal cortex malfunction, and over-taxing of neuronal assemblies may all play important roles in cognitive impairment during sleep loss, it is increasingly clear that waking cognitive performance is enhanced by neural network reorganization that is normally performed during sleep. This energy-consuming activity is impaired by sleep restriction. To illustrate, learning is improved following a night of sleep beyond what is achieved during an equivalent period of wakefulness, a finding consistent with data showing that sleep plays a role in memory consolidation (Smith, 1996, 2001; Stickgold, 2005; Stickgold and Walker, 2005; Walker and Stickgold, 2004). Further, growth of new neurons within the dentate gyrus of the hippocampus is suppressed or reduced following varying lengths of sleep deprivation (Guzman-Marin et al., 2005; Guzman-Marin et al., 2003; Hairston et al., 2005; Roman et al., 2005; Tung et al., 2005), suggesting that such growth occurs primarily during sleep (Meerlo et al., 2009). Pre-existing (post-mitotic) neurons in almost all brain regions, however, survive in spite of the marked cellular stress characteristic of prolonged sleep loss (Cirelli, 2006; Cirelli et al., 1999).

The mechanisms of cognitive impairment owing to sleep deprivation remain to be elucidated. Two principle research findings that are particularly relevant to the EA theory will be considered throughout the remaining sections: One is that cognitive performance deficits arising from sustained sleep restriction appear to be cumulative or build up over time in a dose-response fashion (Belenky et al., 2003; Rupp et al., 2009; Van Dongen et al., 2003); the second is that marked, trait-like, individual differences in susceptibility to cognitive impairment are observed in response to acute total sleep loss, even when prior sleep history is controlled for (Rupp et al., 2012; Van Dongen, 2012; Van Dongen et al., 2004; Van Dongen et al., 2012). These data reveal that some individuals are more affected by sleep loss than others. This phenotypic variation within the population suggests that genetic or developmental history may contribute to the homeostatic and circadian control of sleep need (Goel et al., 2010; Retey et al., 2006; Van Dongen et al., 2012; Viola et al., 2007).

These findings raise additional questions regarding the fundamental organization of sleep and wakefulness. How, for example, are the optimal wake and sleep bout durations in a given species determined? How much wake time or throughput should neuronal assemblies be designed to tolerate (or be taxed) during wakefulness? Energy demand is a major constraint on neuronal signaling (Jolivet et al., 2009). In the EA model, the high-energy requirements of waking neurotransmission impose competing energy demands that limit energy resources for other biological activities such as intracellular transport, membrane repair or myelin formation, processes that are upregulated during sleep (Cirelli, 2005; Mackiewicz et al., 2007). To what extent these downregulated operations in waking free up mitochondrial energy support for cortical signaling and non-signaling components to be conserved across a wide range of activity levels (Hyder et al., 2013) remains to be determined. Moreover, further research is required to elucidate the contribution of cellular infrastructure in permitting longer wake-bout durations, particularly given the role for glia in supporting neuronal energy demands through such mechanisms as the astrocyte-neuron lactate shuttle (Petit et al., 2013).

Although physiological mechanisms exist to increase sleep pressure as wakefulness is extended (leading to state instability), what is the mechanism by which some species can sustain almost continuous wakefulness for weeks at a time without manifesting apparent deficits? These questions require an evolutionary perspective as to why and to what extent specific biological processes have evolved to occur during sleep or when such operations may be upregulated in waking. Further, how do phenotypic variations within and across

populations provide varying but selective advantages in meeting the energy constraints of a given ecological niche. These issues will be taken up again in Sections 3.4.2 and 4.

3.1.2. Sleep deprivation and peripheral deficits

The observation that many peripheral tissues also are adversely affected by sleep deprivation (Everson et al., 2005; Everson and Szabo, 2011) conflicts with the hypothesis that sleep is only for the brain (Hobson, 2005). Indeed, peripheral tissues are perhaps even less protected against the effects of sleep loss than brain tissue, which possesses additional adaptive responses (see below) to protect against such effects (Cirelli, 2006). Following sleep deprivation, markers of generalized cell injury and uncompensated oxidative stress are found in vital organs, such as liver, intestine, lung and heart (Everson et al., 2005; Everson et al., 2008). Further, recovery sleep is not a quiescent time, as indicated by the induction of recuperative processes, such as heme oxygenase-1 (a sign of cell stress) in the lung and a twofold increase in myeloperoxidase in the intestine (Everson et al., 2008). Profound skin lesions develop on the tails and plantar surfaces of the paws of sleep-deprived rats (Kushida et al., 1989b). Moreover, changes in the fur of animals subjected to sleep restriction are common—e.g., hair loss, lackluster appearance, and oiliness—all of which appear to normalize following recovery sleep (Everson and Szabo, 2011).

Chronic sleep loss additionally leads to alterations in bone metabolism in rats, e.g., decreased bone formation, as indicated by reduction in osteoblast activity, a shift to bone resorption, and signs of osteoporosis (Everson et al., 2012). In humans, circulating levels of growth hormone, normally released during slow-wave sleep (Sassin et al., 1969; Van Cauter, 2005), are significantly decreased during sleep deprivation (Radomski et al., 1992; Seifritz et al., 1995). Large human epidemiological studies have identified chronic sleep loss as a significant risk factor for numerous chronic diseases, including cardiovascular disease, diabetes, osteoporosis, stroke and cancer (see for example: Altman et al., 2012; Lima et al., 2012; Magee et al., 2012; von Ruesten et al., 2012). Finally, sleep deprivation studies that do not allow for recovery of sleep systematically demonstrated that sleep loss is fatal in rats (Rechtschaffen et al., 1989b) and Drosophila (Shaw et al., 2002).

A common cause of death following prolonged sleep deprivation in rodents is systemic bacterial invasion (Everson and Toth, 2000). These and other data have contributed to an understanding that normal sleep physiology is integrated with immune function (Bryant et al., 2004; Imeri and Opp, 2009; Krueger et al., 1994; Toth, 1995; Toth et al., 1995). A number of immune reactions, such as tumor necrosis factor alpha (TNF-α) increasing during infection, are known to augment total sleep time (Imeri and Opp, 2009). Whereas sleep deprivation adversely affects host defense (Everson, 1993), lengthened sleep duration confers survival benefit during microbial infection (Toth et al., 1993). Recent data reveal that antibody response to hepatitis B vaccination in humans significantly diminishes when inoculation occurs during sleep restriction (Prather et al., 2012).

Taken together, these and other findings have documented that sleep deprivation causes diverse functional deficits in peripheral biological processes. Moreover, the adverse effects of sleep loss upon peripheral tissues appear to be cumulative over time (Everson and Szabo, 2011; Rechtschaffen et al., 1989b), occurring in a dose-dependent manner, similar in scope but more gradual in progression and parallel to the cognitive performance deficits observed during prolonged sleep deprivation.

All biological processes carry an energy cost. From an evolutionary perspective, spending energy to maximize lifetime reproductive success involves trade-offs in energy investment between competing biological demands and, therefore, requires optimization as a solution. For example, the energy costs of an immune response are high, leading Demas and colleagues (1997) to state that "mounting an immune response requires significant energy and therefore requires using resources that could otherwise be allocated to other physiological processes." Immunological responses involve the production of fever and increased protein synthesis, among others. Indeed, the competing energy demands of thermoregulation or reproduction (gamete production, lactation, or parental care) lead to well-described trade-offs that limit energy availability for other biological activities such as immune function. (Buehler et al., 2009; Burness et al., 2010; Lennie, 1998; Lennie et al., 1995; Sheldon and Verhulst, 1996). These data show that such trade-offs may compromise immune function when energy reserves are limited.

In the EA model, the increase in sleep triggered by infection, such as via TNF-α, is viewed as an adaptive response, a means of decreasing the energy demands of wakefulness while moving energy resources toward mounting an immune response during sleep. This premise is consistent with a recent mammalian phylogenetic analysis demonstrating that species with increased sleep durations show enhanced immune defenses as measured by the number of immune cells in peripheral blood and reduced levels of parasitic infection (Preston et al., 2009). During severe sleep deprivation, however, the EA model predicts that competing energy requirements to replenish compounding deficits from sleep loss diverts limited energy resources away from immune function, thereby compromising immunological status and increasing the likelihood for opportunistic infection, including systemic bacterial invasion.

3.2. Sleep deprivation and increased energy requirements

Often, prior investigations of energy utilization during sleep have either assumed that biological processes in waking are essentially the same as (or similar to) those occurring during sleep, or, alternatively, not taken into consideration the coupling of specific biological operations with behavioral state or circadian time. Commonly cited, for instance, are that the metabolic rate in sleep is only marginally lower than the resting metabolic rate in waking (Rechtschaffen, 1998; Zepelin, 1989; Zepelin and Rechtschaffen, 1974), and that sleep reduces total daily energy expenditure (EE) by 5–15% in most species examined (Jung et al., 2011; Markwald et al., 2013; White et al., 1985; Zepelin, 1989). Taking an alternative view regarding the relative stability in metabolic rate during sleep compared to quiet waking in a human study, Wright and colleagues (Jung et al., 2011) hypothesized that sleep may redistribute energy "to support other critical *sleep-dependent* physiological processes" (italics added). Poikilothermic species, which utilize the nocturnal decrease in ambient temperatures to lower metabolic rate, may achieve relatively greater reduction in EE during sleep compared to wakefulness (Revell and Dunbar, 2007).

Most studies on gene expression have focused only on short-term sleep loss (see, for example, Cirelli et al., 2004, 2005b; Mackiewicz et al., 2009; Zimmerman et al., 2006). In contrast, a recent study of blood transcriptome in human subjects undergoing ~40 h of total sleep deprivation identified a seven-fold rise in the number of "prevalent time-awake-dependent genes" in subjects who experienced seven nights of sleep restriction (before the total sleep deprivation condition), compared to control subjects who were saturated with sleep prior to deprivation (Moller-Levet et al., 2013). These data signal that gene expression during extended wakefulness is qualitatively different following long-term sleep loss.

The EA theory postulates that the measured difference between sleeping and waking (resting) metabolic rates under normal (sleep saturated) conditions underestimates the energy savings conferred by cycling sleep with wakefulness, particularly in organisms that

couple unique biological processes with behavioral state. This idea is based, in part, on the premise that the accumulation of biological deficits resulting from sleep restriction compounds energy requirements, given the expected need to eventually replenish such deficits.

In the EA model, the increase in energy requirements secondary to sleep deprivation is conceptualized as a two-phase process governed by the extent of sleep loss. In the first phase, the increase in energy requirements resulting from short-term sleep deprivation, or "extended wakefulness", reflects merely the difference between wake and sleep metabolic needs, i.e., a 5–15% increase in EE associated with the higher energy requirements of the waking state. The second phase, however, develops when prolonged sleep deprivation begins to restrict the biological functions that normally require sleep for completion. This results in a progression of biological deficits outlined in the previous section and depicted in Fig. 5A. In addition, extending wake bouts beyond their habitual duration not only means increasing overall substrate demands in an effort to maintain the waking state, but also amplifies the overall deficit burden. As sleep deprivation during this second phase is prolonged, the organism, in this model, becomes obligated during waking to expend energy on the usual metabolic demands of this state while simultaneously up-regulating essential biological operations in the waking state that normally occur in sleep (see Fig. 5B). Energy requirements are predicted to accelerate during the second, potentially lethal, phase of chronic sleep deprivation. If sleep restriction lasts for several days or weeks, the anticipated opportunity to replenish sleep-related processes is compromised. Prolonged sleep loss without recovery ushers in a vicious cycle, or "death spiral", of compounding energy requirements to meet the growing homeostatic demand to replenish compounded deficits, ultimately resulting in cellular stress, dysfunction and death. The model predicts that death will occur if: (a) sufficient sleep loss can be obtained from the protocol design, and (b) the organism (species) is unable to adequately upregulate sleep- and wake-related biological operations concurrently during the prolonged waking state.

The classic disk-over-water sleep-deprivation studies in rats conducted by Rechtschaffen and colleagues are consistent with the energy requirement predictions just elaborated. This array of experiments achieved either total sleep deprivation (NREM + REM sleep) or selective REM sleep deprivation (Bergmann et al., 1989a,b; Everson et al., 1989a,b; Gilliland et al., 1989; Kushida et al., 1989a,b; Rechtschaffen et al., 1989a,b). All studies from this group found the same general effects in the experimental animals (Rechtschaffen et al., 1989b). First, serious skin lesions developed on the tails and plantar surfaces of the animal's paws, as noted earlier (Kushida et al., 1989b). Second, food intake dramatically increased as a function of sleep loss to as much as 100% above baseline, whereas body weight progressively declined, excrement weights remained relatively stable, and bomb calorimetry studies of wastes showed no loss in efficiency of gut absorption. Third, total EE dramatically accelerated, as calculated from caloric value of food, CO2 production, and the double-labeled water method (Bergmann et al., 1989a). Fourth, core body temperature declined in the latter part of the experiment. Finally, all sleep-deprived rats eventually died (or were killed when death was imminent). In sum, these data demonstrated that total daily EE in sleep-deprived rats progressively increases far beyond the level expected based on traditional models of waking metabolic needs.

Recent data using the same disk-over-water method to examine chronic sleep restriction instead of total sleep deprivation have replicated and extended these results (Everson and Szabo, 2009, 2011). The experimental protocol employed six cycles of 10-day sleep restriction (35% reduction in total sleep time relative to controls) with 2 days of recovery between each sleep deprivation

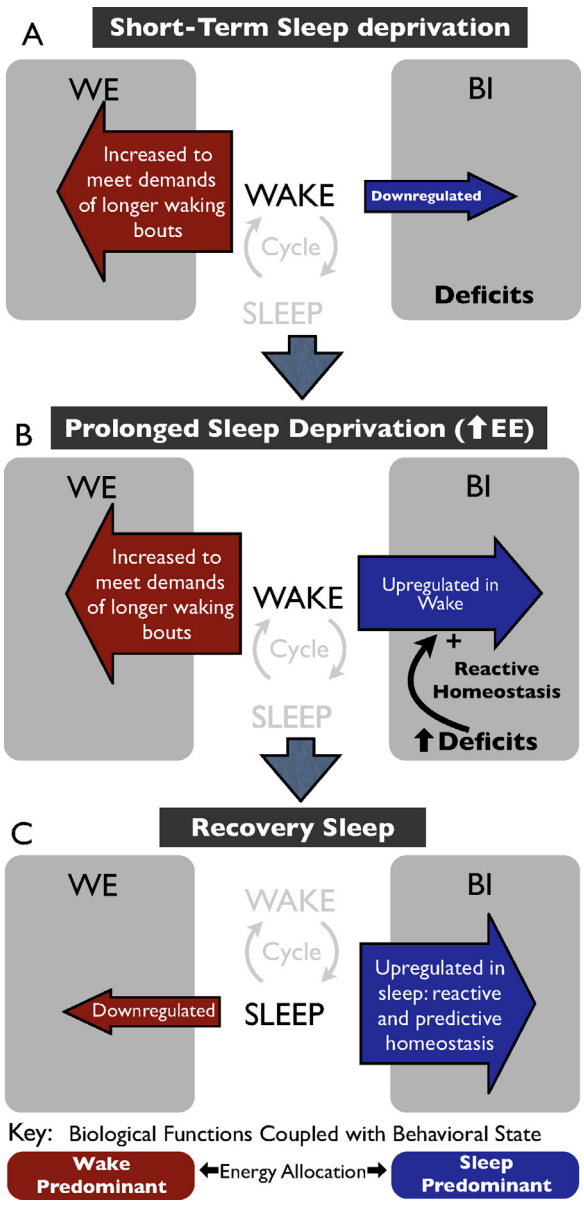

Fig. 5. Energy allocation, sleep deprivation, and homeostasis. (A) During short-term sleep deprivation, sleep-predominant biological functions (blue) are prevented, resulting in deficits related to biological investment (BI) normally completed during sleep. Waking effort (WE) is increased in the service of maintaining longer waking bouts (red). (B) During prolonged sleep deprivation, deficits related to BI accumulate and are, by necessity, upregulated via reactive homeostasis during the waking state to enhance survival. Total daily energy expenditure (EE) accelerates during this prolonged, second phase of sleep deprivation as a result of maintaining the energy demands of continuous wakefulness while also upregulating biological processes during waking that normally occur in sleep. (C) During recovery sleep, energy utilization is reallocated away from waking functions (WE) and into the upregulation of somatic processes (BI) during sleep, to replenish deficits (reactive homeostasis) and to prepare for the following bout of wakefulness (predictive homeostasis).

cycle. As illustrated in Fig. 6, weights progressively decreased while hyperphagia and calculated EE increased after approximately 20 days into the experimental protocol. These changes accelerated by the fourth 10-day cycle of sleep restriction and showed doubling or tripling of baseline, peak food intake by the fifth and sixth cycles (Everson and Szabo, 2009, 2011). Changes in the viscera were observed in the aftermath of sleep restriction and were consistent with high-energy production and demand. The alterations included 30% lengthening of the small intestine in sleep-restricted rats compared to matched controls (a finding thought to reflect the increase

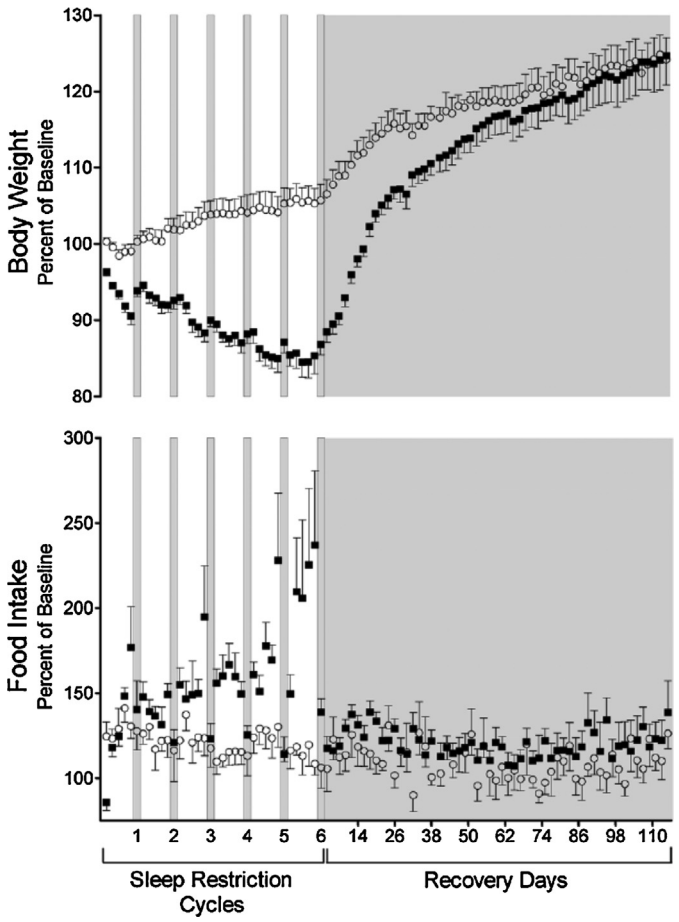

Fig. 6. The effects on body weight and food intake from 6 cycles of sleep restriction or ambulation control in rats using the disk-over-water method, following by an extended recovery period. The data are expressed as a percentage change from baseline in sleep-restricted (■) and ambulation control (○) rats. The large increase in food intake begins to accelerate during the third to sixth cycle of 10-day sleep restriction while body weight continues to decrease. Only marginal effects on food intake and physical appearance were observed during the first two cycles of 10-day sleep restriction. Each sleep restriction cycle was followed by a 2-day period of ad libitum sleep (shaded bars). All rats were given 114 days of ad libitum sleep conditions for recovery (shaded area) at the end of the sleep-restriction period.
Figure adapted with permission from Everson and Szabo (2011).

in absorption of nutrients required during sleep deprivation); additional findings included a loss of fattiness in connective tissue and remodeling of adipose tissue, two observations that are consistent with increased energy demand and utilization (Everson and Szabo, 2009, 2011). Similar increases in EE triggered by sleep deprivation have been documented in rodents by other investigators (Barf et al., 2012; Caron and Stephenson, 2010; Hipolide et al., 2006; Koban and Swinson, 2005). These results are consistent with the EA model in so far as chronic sleep restriction, or total sleep deprivation, induces a rise in energy requirements that attempts to keep pace with the compounding biological deficits.

The effects of sleep restriction on EE in humans are less well understood. Several studies have uncovered no changes in EE (Bosy-Westphal et al., 2008; Hursel et al., 2011), and most studies have demonstrated weight gain instead of weight loss (Klingenberg et al., 2012). Several investigators have suggested that the metabolic effects of sleep deprivation in humans may be less pronounced than (or unrelated to) the findings in rodents (Klingenberg et al., 2012). Species differences based on body size are predicted in the EA model, and the effects of sleep loss may be more gradual in large animals (see Section 5).

Claims that rodents and humans respond differently to sleep deprivation regarding EE are made with insufficient experimental evidence at this time. The duration of sleep restriction and degree of sleep loss in human study protocols is considerably less severe than the demands typically employed in rodent experiments. For example, in the chronic sleep restriction studies of rodents reviewed above, Everson and colleagues chronically reduced daily total sleep time in the sleep-restricted rats by 35% compared to controls, but only marginal changes regarding EE, food intake, and other effects were observed during the first 10–20 days. Significant and progressive increases in food intake and EE, as well as pathological changes in physical appearance, became apparent only between days 24–72 in the sleep restricted group, indicating chronic effects that were not visible during the acute condition (see Fig. 6). Moreover, Rechtschaffen and colleagues demonstrated that, although total sleep deprivation in rats results in death on average after 15 days (when EE more than doubled during the last quarter of the experiment), only marginal increases in EE were found in the first 3–4 days of the protocol compared to controls (Everson et al., 1989a). Most studies examining EE in humans, in contrast, employ protocols with comparatively small reductions in total sleep time, generally no longer than 1–4 days in duration (Benedict et al., 2011; Bonnet et al., 1991; Bosy-Westphal et al., 2008; Hursel et al., 2011; Jung et al., 2011). Only a few studies extended partial sleep restriction up to 14 days (Klingenberg et al., 2012; Nedeltcheva et al., 2009; Nedeltcheva et al., 2010). These milder forms of sleep restriction likely diminish the impact on EE in humans, making direct comparisons about the effects of sleep loss in humans and rodents difficult at the present time.

Adding to the perceived discrepancy with rodent data, findings in humans demonstrate a positive energy balance, i.e., weight gain, when sleep restricted subjects are allowed ad libitum access to high caloric food during the protocol (Spaeth et al., 2013). In contrast to the common protocol design, however, a recent study in humans employed moderate caloric restriction while total sleep time was curtailed to 5.5 h/day for 14 days (Nedeltcheva et al., 2010). Significantly increased hunger and greater loss in fat-free body mass occurred in the sleep-restricted group compared to controls, demonstrating a modified negative energy balance in humans during sleep loss when caloric intake is restricted (Nedeltcheva et al., 2010).

One of the most uniform findings in the human sleep deprivation literature is the marked increase in hunger, appetite, and food intake triggered by sleep restriction (Hanlon and Van Cauter, 2011; Knutson et al., 2007; Spiegel et al., 2004). A recent elegant study monitored 24-h EE, using whole-room calorimetry, in a protocol that monitored changes in food intake in subjects with ad libitum access to food who were restricted to 5-h of sleep per night for 5 days (Markwald et al., 2013). Daily EE increased in the sleep-restricted group by ~5–9% over control conditions, but the greater food intake triggered by sleep loss more than compensated for the increased energy requirements, leading to a positive energy balance in the group with modest sleep restriction.

In aggregate, these data are consistent with the premise that sleep deprivation increases the energy requirements placed on an organism, suggesting that escalation of appetite or food intake is, at least in part, an adaptive response. Indeed, providing sleep-deprived animals food sources with high caloric content significantly increases both their survival time and the general ability to withstand a sleep deprivation challenge compared to animals fed a lower caloric food source (Everson and Wehr, 1993). From an evolutionary perspective, heightened appetite during periods of extended wakefulness in some species, such as humans, raises the possibility of another potential behavioral adaptation; namely, the ability to exploit seasonal increases in food availability normally associated with longer days, as a means of storing increased energy

reserves. The findings of increased appetite and hunger in both humans and rodents suggest a similar behavioral response to sleep debt across species. As hypothesized by the EA model, this is one of several adaptive responses to increased brain- or whole-body energy demands triggered by sleep deprivation (see below).

3.3. Adaptive responses related to cellular stress and thermoregulation

Organisms that have evolved to upregulate specific metabolic processes during sleep, such as gene expression as shown by the microarray data, face a potential two-fold dilemma as a consequence of their genetic engineering when sleep is prevented. First, presuming that macromolecule biosynthesis in sleep is essential for the biological functioning of the animal, some of the processes primarily carried out in sleep may be forced to upregulate during prolonged wakefulness, particularly if deficits must be replenished for survival (see Fig. 5B). Adding to the transcriptional, translational, and protein-processing demands typically associated with the waking state, even small to modest increases in gene expression during wakefulness (to simultaneously meet wake-related as well as sleep-related substrate demands) should increase cellular energy requirements and cellular stress. On the contrary, if these presumably essential biological processes of sleep are incapable of upregulating during waking in the face of sleep restriction, potential uncoupling of metabolic processes may occur, further aggravating cellular stress and inefficient use of energy resources.

3.3.1. Cellular stress and adaptive responses

At the cellular level, well-described adaptations indicate that not only is the cellular stress of wakefulness high, but also the cellular stress of prolonged waking, i.e., sleep deprivation, is even greater. Microarray gene expression studies consistently identify upregulation during wakefulness and down-regulation during sleep of genes within the cerebral cortex that respond to cellular stress, such as heat shock proteins and molecular chaperones (Cirelli, 2006). Cellular stress that leads to damage of DNA, RNA, lipids, and proteins, among others, typically results from perturbations in cellular homeostasis. Numerous stress-response proteins have been discovered, encompassing DNA repair proteins, proteasome regulators, and molecular chaperones in the endoplasmic reticulum. Conditions that disrupt the endoplasmic reticulum and the process of protein-folding are associated with higher levels of molecular chaperones, BiP and Grp94 (Cirelli et al., 2004; Terao et al., 2006).

Within the brain of rodents, birds and Drosophila, prolonged wakefulness or short-term sleep deprivation is associated with an increase in BiP expression (Mackiewicz et al., 2008), indicating an adaptive response to prolonged wakefulness that is evolutionarily conserved (Cirelli, 2006, 2009; Mackiewicz et al., 2008; Mackiewicz et al., 2009). BiP, one of several stress-response proteins known as heat shock proteins, plays an important role in the folding and assembly of newly synthesized glycoproteins and secretory polypeptides. BiP expression is particularly important when proteins accumulate within the endoplasmic reticulum, such as after heat shock or ischemia. BiP is induced by short-term sleep deprivation (Naidoo, 2009), whereas other heat shock proteins, such as HSP27 and alpha-crystallin, are induced only during longer-term sleep restriction (Cirelli, 2006). Homer1a is markedly upregulated during sleep deprivation and plays an important role in reducing or buffering glutamate-induced intracellular calcium release (Maret et al., 2007). Homer1a also appears to promote longer wake bout durations in normal, non-sleep-deprived, conditions (Naidoo et al., 2012). Sleep deprivation has recently been demonstrated to upregulate gene expression related to cellular stress in humans, as identified through blood transcriptome analyses (Moller-Levet et al., 2013). This finding is consistent with previous data demonstrating cellular stress as a conserved response to sleep deprivation across species. To what extent this cellular stress is triggered by the simultaneous induction of wake-and sleep-related biological processes during prolongation of the waking state, an event that overtaxes organelles and cellular infrastructure in the EA model, requires further investigation.

3.3.2. Thermoregulatory control and adaptive responses

The EA model contributes two predictions regarding thermoregulatory effort and sleep deprivation. First, the model posits that, as energy demands become elevated from *prolonged* sleep loss, energy allocated to thermoregulatory defense is reduced in waking when the organism is thermally challenged, so that remaining energy reserves may be redirected to other critical needs as a means of increasing survivability during sustained wakefulness. This hypothesis is in accord with experimental data described earlier. Indeed, one of the most reproducible findings in chronic sleep deprivation research, using the disk-over-water method, is the significant decline in T_c of rats subjected either to selective REM sleep deprivation (Bergmann et al., 1989a; Kushida et al., 1989a) or to total (NREM + REM) sleep deprivation (Bergmann et al., 1989a; Everson et al., 1989a). These conditions provoke accelerated increases in food intake and total daily EE (Landis et al., 1992; Prete et al., 1991; Rechtschaffen and Bergmann, 2002).

The decrease in T_c had been interpreted as secondary to a pathologic increase in heat loss (Rechtschaffen et al., 1989b; Zenko et al., 2000). Interpreting these data from an energy allocation perspective, however, opens up a different possibility; namely, the decrease in T_c associated with sleep deprivation is an expected adaptive response triggered by the increased energy demands needed to reverse compounding biological deficits. Progressive decreases in mean T_c over successive days of total sleep deprivation also have been well described in humans, though circadian rhythmicity of body temperature is maintained (Bach et al., 1994; Fiorica et al., 1968; Murray et al., 1958; Vaara et al., 2009). This finding was first reported by Patrick and Gilbert (1896), and is so robust across species that Kleitman's only figure in his chapter on *Deprivation of Sleep* (Kleitman, 1963) is devoted to this effect (see reprint in Fig. 7A).

When faced with energy constraints, birds also commonly demonstrate significant declines of 4–5 °C in T_c during sleep (Berger and Phillips, 1993; MacMillen and Trost, 1967; Rashotte et al., 1998) in a remarkably similar descent over successive days (Fig. 7B). Likewise, many mammals initiate daily torpor (Berger and Phillips, 1995; Kortner and Geiser, 2000) (see Section 4). Such opportunistic manipulations of T_c in response to a negative energy balance are known to occur in many endotherms.

Second, as a means of decreasing thermoregulatory defense while accelerating the reallocation of energy to essential, sleep-related, biological functions that are needed for survival during recovery sleep, sleep-deprived animals predictably seek warm ambient temperatures at least within, but potentially exceeding, the thermoneutral zone for their sleeping environments. When sleep-deprived animals are permitted to select an ambient temperature gradient, they initially choose a T_a exceeding baseline thermoneutrality, even potentially higher than their T_c (Landis et al., 1992; Prete et al., 1991; Rechtschaffen et al., 1989b; Shaw et al., 1998). Once a temperature within the gradient is chosen, the animal promptly initiates sleep. Because study animals were systematically removed one minute after onset of sleep to limit recovery during the sleep deprivation protocol, the design of the original experiments prevented habituation to a preferred T_a (see Prete et al. (1991)). It is unclear, however, if this protocol design adequately assesses the true set point for core body temperature

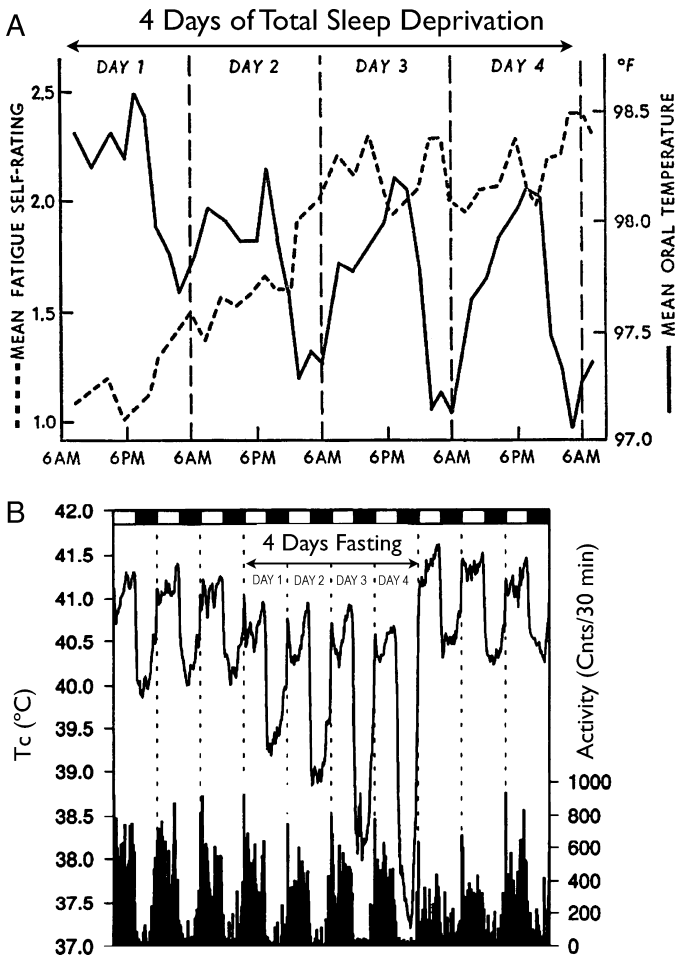

Fig. 7. Opportunistic manipulations of the T_c are well described in endotherms in response to challenges in energy balance. (A) Progressive decreases in mean oral temperature (F) and increased fatigue self-ratings over four days of total sleep deprivation in human subjects ($n = 15$). Reprinted from figure 22.1 in Kleitman (1963), originally based on the work of Murray et al. (1958) and adapted with permission. (B) Progressive decreases in T_c (°C) during the night (sleep) in birds subjected to four days of fasting. Data include 3 days before and after the fasting period, along with daily activity counts. Not shown is the decrease in body weight during the fasting period. Reprinted with permission from Berger and Phillips (1993).

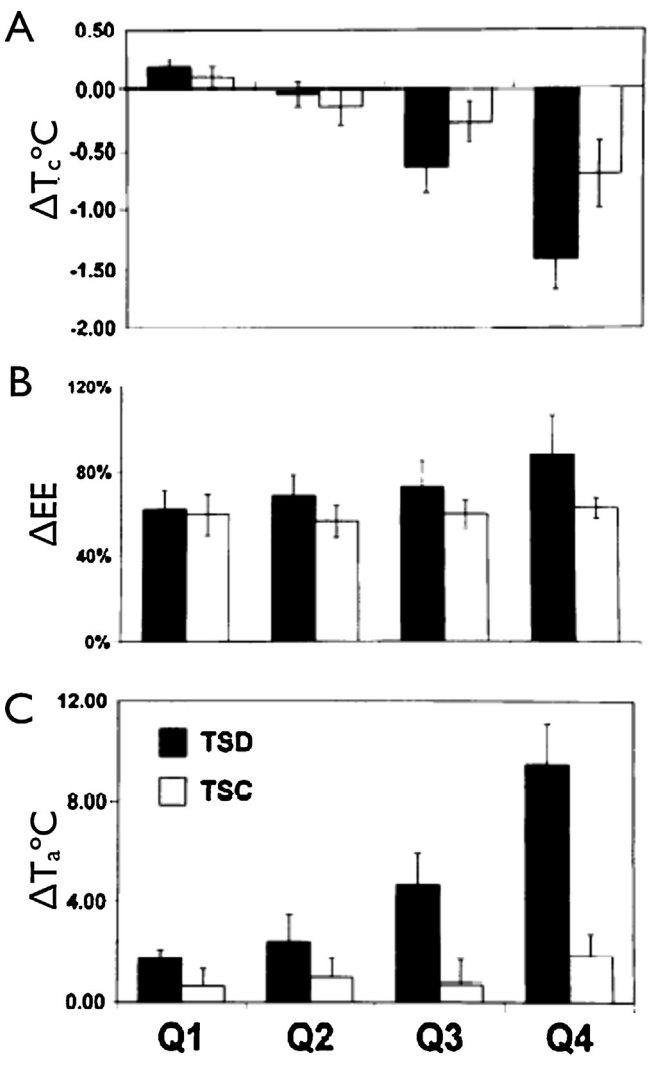

Fig. 8. Mean change in (A) core body temperature (ΔT_c, °C), (B) energy expenditure (ΔEE), and (C) ambient temperature selection (ΔT_a, °C) during the four quartiles (Q1–Q4) of the sleep deprivation protocol in total sleep deprived (TSD) and yoked-control (TSC) rats. Shaw et al. (1997) utilized the disk-over-water method in a protocol design that allowed both the sleep-deprived and yoked-control animals to operantly manipulate the T_a by poking their noses through a small hole in their individual Plexiglas cages. This action activated a heater placed above the cage. In the figure, note the inverse relationship between the decline in T_c and the increase in ΔEE from Q1 to Q4, as well as the increase in ambient temperature operantly selected by rats during sleep deprivation. Prolonged, total sleep deprivation resulted in rats maintaining the T_a of their cages at an abnormally high mean of 37 °C. Although the increase in ambient temperature selection was greatest in the TSD group, a trend was also noted for the TSC group with T_a selections of the yoked-controls increasing by a mean of 3.6 °C over baseline during the last 10% of the sleep deprivation protocol (data not shown).
Figure adapted by permission from Shaw et al. (1997).

(T_{set}). When animals were given extra time within the gradient, they moved to a T_a approaching thermoneutrality (Prete et al., 1991).

The prevailing explanation for why animals choose a T_a above thermoneutrality is that T_{set} increases with sleep deprivation, and the animal may lose its ability to maintain its T_{set} in the face of pathologic heat loss (Rechtschaffen et al., 1989b). As illustrated in Fig. 8, the heat loss hypothesis is largely based on the observation of an inverse relationship between decreasing T_c and increasing EE in addition to the elevated T_a selection of sleep-deprived animals (Rechtschaffen and Bergmann, 2002). However, the decrease in T_c observed during sleep deprivation occurs despite largely intact control of vasomotor responses (Zenko et al., 2000) and absence of signs of systemic infection (Bergmann et al., 1996). Perhaps underlying the interpretation that T_{set} is increased during sleep deprivation is the presumption that the T_a behaviorally chosen by an animal reflects the T_{set} in non-pathological conditions. It is not clear, however, whether this assumption applies to sleep deprivation or, even, normal sleepiness. Humans, like other endotherms tend to seek warmth (a thermoneutral environment) when sleepy, despite the circadian decrease of T_c when habitual bedtime approaches. It may be that our circadian clock actively decreases T_{set} even as we behaviorally seek a relatively warmer T_a. This finding is consistent with rodent sleep deprivation data.

A reinterpretation of the classic, rodent sleep deprivation experiments that were just summarized suggests that the divergence between lowered T_{set} and behavioral preference for a warmer T_a may be little more than an accentuation under sleep-deprived conditions. The combination of actively reducing the T_{set} as a means of lowering T_c during wakefulness, while simultaneously seeking out a T_a either within or higher than the baseline thermoneutral zone with the increased physiological drive to sleep, would maximally reduce energy demands for thermoregulatory defense. This behavioral strategy during sleep deprivation seems to allow for the greatest reallocation of energy toward biological compensation

during recovery sleep (see Fig. 5C). The observation that the T_c rapidly increases during recovery sleep and even exceeds the waking, pre-sleep T_c (Feng et al., 1995), is in harmony with the physiology of homeostatic upregulation of sleep-related biological processes activated in response to severe sleep deprivation. This view also suggests that rats choosing a T_a that exceeds baseline thermoneutrality following sleep loss are enlisting an adaptive behavioral maneuver that both activates and accelerates essential, energy-consuming, metabolic pathways during recovery sleep, particularly while the T_c rises back to baseline after protracted sleep deprivation.

3.4. Sleep deprivation, energy allocation and homeostasis

Sleep deprivation is well known to increase sleep pressure; prolonged waking becomes increasingly difficult to sustain as wake periods exceed their typical bout lengths (Benington, 2000; Borbely, 1982). Following sleep deprivation and an opportunity for recovery, a rebound phenomenon takes place, characterized by an increase in intensity and duration of sleep. Recovery sleep incorporates an increase in EEG delta power, which is a known indicator of homeostatic sleep pressure in mammals (Borbely and Achermann, 1999; Franken et al., 2001) and some species of birds (Jones et al., 2008c; Rattenborg et al., 2009). The likelihood of manifesting sleep in the face of sleep deprivation is also gated or influenced by circadian time (Borbely, 1982; Daan et al., 1984).

A number of theories have attempted to explain this rebound phenomenon in EEG delta power. Tononi and Cirelli (2003, 2006, 2014) proposed a well-developed theory that waking is associated with synaptic potentiation of cortical circuits that accrue energy demands secondary to increased synaptic load. In this model, slow-wave sleep allows synaptic downscaling, which reduces total energy requirements and also optimizes neural function and performance.

The role of REM sleep, however, in this and other models is generally not addressed, and any theory of sleep homeostasis must account for the homeostatic regulation of both NREM and REM sleep. Indeed, it should be noted that sleep homeostasis also galvanizes a rise in REM sleep pressure after sleep deprivation. What is more, extreme (long-term) sleep deprivation promotes enhancement of REM sleep over slow-wave sleep in the initial recovery phase (Everson et al., 1989b; Rechtschaffen et al., 1989b). As these latter findings demonstrate, a theory of sleep function not including a model for REM sleep homeostasis remains incomplete.

3.4.1. Energy balance and prior theories of sleep homeostasis

With respect to energy balance, Benington and Heller (1995) proposed that the high energy demands of waking reduce brain glycogen, so that "replenishment of cerebral glycogen stores is the restorative process taking place in sleep" (p. 357). This view put cerebral glycogen in the position of the ultimate regulator in the homeostatic control of sleep. In the Benington–Heller model, the primary cellular energy molecule, adenosine triphosphate (ATP), is reduced during waking as cerebral glycogen stores are depleted, in turn leading to a higher ratio of adenosine monophosphate (AMP) and increased extracellular adenosine. Extracellular adenosine is also hypothesized in this view to facilitate sleepiness as well as augment EEG delta power during sleep. As glycogen stores are replenished during sleep, extracellular adenosine levels decline, and the ATP/AMP ratio increases. As a result, maximal wakefulness is again restored.

Although the Benington–Heller model did not address the function of REM sleep, it nevertheless stimulated almost two decades of research into cellular energy charge and sleep–wake control. Over that time period, however, it has become increasingly apparent that regulation of cerebral glycogen and cellular energy charge is considerably more complicated than outlined in the Benington–Heller model (see Scharf et al. (2008) for a review). For example, although cerebral glycogen initially decreases following the transition from sleep to waking, it is restored to baseline levels again during the waking state (Scharf et al., 2008). Moreover, the findings during sleep deprivation are inconsistent: cerebral glycogen levels are reported variously to decrease, remain stable, and even increase during short-term sleep deprivation (Everson et al., 1994; Franken et al., 2003, 2006; Gip et al., 2002; Gip et al., 2004; Kong et al., 2002). The latter findings are contrary to the Benington–Heller prediction (Franken et al., 2003).

Given that extracellular adenosine level in certain brain regions increases in waking and decreases in sleep (Bjorness and Greene, 2009; Bjorness et al., 2009; Porkka-Heiskanen et al., 1997), and that adenosine is sleep-promoting (Gallopin et al., 2005; Porkka-Heiskanen et al., 1997), cellular energy charge continues to be viewed as a homeostatic regulator of sleep. Scharf et al. (2008), for example, proposed a revision of the Benington–Heller model, on the basis of evidence that it is the ATP energy requirement needed to restore and maintain cerebral glycogen during waking which brings about the increased extracellular adenosine. The latter is a putative somnogenic factor that, in turn, acts to terminate wakefulness and facilitate onset of sleep. More recently, Dworak et al. (2010) demonstrated a "surge" in ATP levels in the initial hours of spontaneous sleep in normally wake-active brain regions of the rat. These investigators believe that this ATP surge promotes anabolic processes during sleep, though others question this interpretation. For example, might the increase in brain ATP, which is restricted to the initial hours of sleep, simply reflect a decrease in ATP degradation as sleep supervenes (Wong-Riley, 2011)? Also, if restoration of brain energy is the primary function of sleep, why are brain ATP levels not reduced during waking (Haddad, 2011)? These and other data highlight a persisting controversy surrounding cellular energy charge or brain energy metabolism and raise serious questions as to whether they represent an ultimate function of sleep or sleep homeostasis.

3.4.2. The energy allocation model and sleep homeostasis

In the EA model, the homeostatic drive to sleep is governed by an accumulation of biological deficits, or unfulfilled biological functions, favored by natural selection to utilize the state of sleep to complete such processes. The model advances the idea that at least some biological functions that preferentially occur during sleep are required to upregulate to a certain degree during extended waking to enhance survival (as shown in Fig. 5B). Indeed, the ability to upregulate many sleep-related biological operations in waking during periods of prolonged sleep loss, could explain the historical difficulty in identifying specific deficits resulting from sleep deprivation. Nevertheless, the simultaneous activation of both sleep-related and wake-related activities during sleep deprivation results in physiological consequences tied to the increased demands in gene expression and other energy requirements induced by extended waking. These include, among others: increased extracellular adenosine; metabolic cascades associated with cellular stress; and accumulation of unfolded proteins in the endoplasmic reticulum (triggering expression of molecular chaperones). Although these physiological events, such as rising extracellular adenosine, may also promote sleep, the completion of sleep-related biological functions, in this view, constitutes the ultimate regulator of both NREM and REM sleep homeostasis. Cellular energy charge and glycogen level may operate as signaling mechanisms when energy stores are challenged that facilitate reallocation of energy utilization away from the high-energy demands and gene expression of waking toward, instead, biological processes favoring sleep for optimal completion (see Fig. 5C).

The EA model is also in synchrony with the premise that the drive for sleep and intensity of sleep are homeostatically regulated at the local tissue level (Krueger et al., 2008). The EA theory complements this view: any behavior or biological event that increases local metabolic demands during a prior bout of wakefulness, or leads to depletion of biological substrate normally coupled with sleep for restoration, should increase sleep drive, even in the absence of sleep deprivation. The latter stipulation means that local tissue deficits, through classic, reactive homeostatic mechanisms, will increase either the intensity or duration of sleep-related processes at local levels.

In support of this hypothesis, localized increases in EEG delta power during sleep appear to reflect use-dependent activity in specific brain regions, such as in the cerebral cortex of mammals (Huber et al., 2004a; Vyazovskiy and Tobler, 2008) and primary visual processing region, hyperpallium, of birds (Lesku et al., 2011). These are brain areas that show local homeostatic responses when challenged during the previous waking state. It is still unclear, however, to what extent sleep-dependent macromolecule biosynthesis coincides with increased EEG delta power in comparison to other sleep stage phenomena. Consistent with the concept of local homeostatic regulation of sleep, recent data demonstrate that, after prolonged waking, certain regional cortical neurons briefly go "offline" and display slow-wave activity, even when other areas of cortex and physical behavior indicate wake activity (Vyazovskiy et al., 2011). These data support the idea that biological processes coupled with sleep are homeostatically regulated at the local level. A corollary hypothesis is that such local mechanisms may not be limited to brain, and, instead, may underlie a fundamental property of all energy-consuming peripheral tissues. However, local, sleep-predominant, homeostatic responses in the periphery following sleep loss remain to be investigated.

A final homeostatic concept concordant with the EA model pertains to "predictive homeostasis", a homeostatic mechanism that governs how much energy the organism should invest into biological functions during sleep. In addition to the reactive homeostasis that responds to deficits, as outlined above, predictive homeostasis anticipates the biological investments required during sleep to prepare for the usual biological demands for subsequent waking bouts. The concept of predictive homeostasis has previously been attributed to circadian/circannual timing systems as well as sleep–wake behavior (Jouvet, 1994; Moore-Ede, 1986). Predictive homeostasis is seen by the EA model as not only ensuring that sufficient biological processes will be completed in sleep to exploit the subsequent waking niche, but also conserving energy by limiting investments during sleep in a manner that only anticipates the usual biological demands required for finite waking bouts. Limiting investments into sleep-dependent operations to anticipate habitual waking needs may offer some explanation of the compounding of biological deficits during sleep deprivation when waking episodes become chronically extended.

To illustrate this point, biological deficits become most apparent as wakefulness extends beyond habitual waking-bout length, giving rise to the "wake extension hypothesis" of homeostatic control (Dinges et al., 2005; Van Dongen et al., 2003), a model historically applied to cognitive performance. Wakefulness that exceeds the initial 16 h in humans is referred to as "extended wakefulness". Measures, such as the psychomotor vigilance task (PVT), document that signs of neurocognitive impairment in humans become apparent as the wake period exceeds 16 h. In a sleep deprivation protocol (Van Dongen et al., 2003), 4 days of complete sleep deprivation is considered equivalent to approximately 72 h of extended wakefulness and a loss of 25 h of sleep. Although subjects restricted to 4 h of sleep per night for 14 nights have greater cumulative sleep loss (55 h), they develop fewer neurocognitive deficits than those undergoing four days of total sleep deprivation (25 h of sleep loss). Total "extended wakefulness" is greater in the total sleep deprivation group than in the group restricted to 4 h of sleep per night. The strongest correlation with neurocognitive deficits is with cumulative extended wakefulness rather than cumulative sleep loss (Dinges et al., 2005; Van Dongen et al., 2003).

These and other findings buttress the EA model's powerful construct of the homeostatic regulation of sleep. In summary, when durations of wake and sleep bouts in a given species are highly predictable from one day to another, the cycling of sleep and waking conserves energy. It does so not only because of the differential allocation of biological operations between states, but also through limitation of investment into such processes during sleep to only anticipate what the organism will require during subsequent waking bouts. However, the inherent design of this energy allocation strategy, i.e., to only prepare for immediate waking biological needs, also exposes its greatest weakness: namely, the accumulation of biological and neurocognitive deficits over successive days of sleep restriction when daily, waking bout durations are habitually longer than what the organism has been genetically engineered through natural selection and development to anticipate.

4. Phenotypes of energy allocation

There has been recent controversy as to whether the widely shared and commonly held assumption that all animals sleep is correct (see Cirelli and Tononi (2008); Siegel (2008) for discussion). Often cited is the finding that killer-whale and bottlenose-dolphin neonates and their mothers persist in a highly active swimming pattern for the first three months after the calf's birth and show no identifiable sleep behavior (Lyamin et al., 2007; Lyamin et al., 2005). Some investigators suggest (without direct EEG evidence) that microsleeps, or unihemishperic slow-wave sleep, are possible during these unremittingly active periods in cetaceans (Gnone et al., 2006; Sekiguchi et al., 2006). Current evidence, however, weighs on the side that sleep, if present at all during the neonatal period, is markedly reduced. Direct EEG recordings in birds during periods of migration (Rattenborg et al., 2004) or during the mating season (Lesku et al., 2012) reveal dramatic reductions in sleep time and periods of prolonged wakefulness lasting days or weeks at a time. Reptiles may also demonstrate prolonged bouts of apparently continuous wakefulness during adaptation to experimental conditions (Hartse, 1989).

Although sleep behavior has been documented among an extraordinarily diverse group of living beings, the EA model does not predict that all animals sleep. Alternative evolutionary strategies, such as allocating energy resources for all transcriptional, translational, and other biological needs, during long bouts of continuous or predominant wakefulness, may exist so long as the energy reserves of the organism or the energy resources of the niche are supportive. Marine mammals and birds conceivably engage in this strategy when maintaining long bouts of wakefulness without apparent detrimental effects on cognition and mating success, and without showing signs of homeostatic sleep rebound (Lesku et al., 2012; Lyamin et al., 2005; Rattenborg et al., 2004). Weight loss during migration remains one of the few consequences identified (Gerson and Guglielmo, 2011; Schwilch et al., 2002). Moreover, some species have evolved alternative strategies of energy utilization such as daily torpor or long bouts of hibernation (Geiser, 1998, 2004; Heller and Ruby, 2004; Kortner and Geiser, 2000). Finally, many species are able to enlist multiple behavioral strategies, alternating between traditional sleep–wake cycling in some periods during their life history with torpor, hibernation, or predominant wakefulness in other periods. These observations suggest that the ecological niche of specialization exercises a dramatic influence over the optimal energy allocation strategy employed by an animal at a given time in its life history.

The EA model defines behavioral strategies that optimize the temporal utilization of energy. Multiple behavioral phenotypes across and within species in the animal kingdom are to be expected. Moreover, each phenotype should carry its own inherent set of trade-offs between benefits and costs, upon which natural selection may act as organisms evolve to meet the selective pressures that are unique to their ecological niche. The EA model proposes three major phenotypic categories that are differentiated on the basis of energy utilization and allocation: (1) sleep–wake cycling; (2) daily torpor or hibernation; and, (3) predominant wakefulness. The defining features, as well as the associated costs and benefits, of each phenotype will be outlined below.

4.1. Phenotype of sleep–wake cycling

Of the three principal phenotypes, sleep–wake cycling is the most commonly expressed energy allocation strategy in the animal kingdom. Species that have evolved to exploit a discrete temporal or circadian niche are those predicted to benefit most from this energy allocation phenotype, which decreases waking investments in biological processes not immediately essential for the niche. The categories of essential biological operations selected for upregulation during either sleep or wakefulness are probably similar across species but are expected to vary somewhat depending on the ecological needs or constraints affecting the species.

A number of genetic polymorphisms or variations have been identified for species that manifest the sleep–wake cycling phenotype. These include well-described genetic mutants of short sleepers in Drosophila and mice (Bushey et al., 2007; Cirelli et al., 2005a; Espinosa et al., 2004; Koh et al., 2008) and implies a strong genetic contribution to regulation of sleep bout-lengths within populations. Other species, such as cetaceans (Lyamin et al., 2008; Mukhametov et al., 1977) and many varieties of birds (Rattenborg et al., 2000), demonstrate unihemispheric sleep; typically, an alternating cycle of sleep in one hemisphere and simultaneous waking in the other. This adaptation is hypothesized to play an important role in control of breathing in cetaceans and also predation avoidance in birds. The quantity of sleep, as well as the presence of unihemispheric sleep, varies considerably across species, but the sleep–wake cycling phenotype is characterized by well-defined and predictable bouts of sleep alternating with waking. Although more data are required to confirm the presence of a rebound phenomenon when sleep deprivation is isolated to one hemisphere in cetaceans (Oleksenko et al., 1992), an intact homeostatic regulation of sleep is viewed as a unifying feature for organisms expressing the sleep–wake cycling phenotype.

Predator–prey relationships result in well-described ecological constraints that influence wake and sleep bout-lengths. For example, species of birds that have exposed nesting sites on the ground, as a group, sleep significantly less than species that maintain more protected sites, e.g., in trees (Roth et al., 2006). On the contrary, birds exposed to high predation at foraging sites demonstrate shorter wake bouts and have significantly more sleep time (Zimmer et al., 2011). It remains to be determined whether high waking predation at foraging sites drives nest-building toward safer sites, such as in trees or burrows, to accommodate or promote the longer sleeping bouts.

The diversity of ecological and temporal niches inhabited by species, either when awake or asleep, raises two questions: How much energy should be reserved for somatic effort during wakefulness?; alternatively, how much energy should be reallocated to biological operations during sleep while outside the specialized waking niche? Species-specific ecological constraints, such as predator–prey relationships, are expected to exert selective pressures on the categories of biological activities performed during sleep and waking, and the extent to which processes can be shared or interchanged between the states.

Trade-offs based on the temporal utilization of energy in this model are suggested to govern the optimization of wake and sleep bout-lengths for a given species. As an example, though longer sleep durations in a safe environment (one that avoids predation at a foraging site) decrease the energy demands of waking and consequently conserve energy, longer sleep durations also decrease potential mating and foraging opportunities. In contrast, high predation at a sleep site would seem to favor longer waking bouts and allow for more of such opportunities, but an increased cost in total daily energy requirements is expected.

4.2. Phenotype of torpor

Two basic subcategories of torpor are described: shallow torpor and deep torpor or hibernation (Geiser, 2004). Shallow torpor is manifested in many species of birds and mammals in a circadian pattern during the habitual sleep period and, for that reason, is referred to as daily torpor. The T_c during daily torpor decreases from approximately 37 °C in wakefulness to ~17 °C in the daily torpor periods, although this decrease varies among species (Geiser, 1998). Energy savings resulting from daily torpor is documented to reduce metabolic rate to approximately 30% of the basal metabolic rate (BMR) of waking. Deep torpor (hibernation), in contrast, occurs in significantly longer bouts lasting 1–3 weeks in duration and with the average minimum T_c decreasing to approximately 6 °C (Geiser, 1998; Kortner and Geiser, 2000). The energy savings of hibernation is therefore much greater than daily torpor, and metabolic rate may descend to only 5% of the BMR. Daily torpor is associated with only modest rewarming requirements; hibernation requires considerably more time and energy to return to the euthermic state, potentially exposing the animal to increased risk of predation and missed foraging or mating opportunities during a the longer rewarming phase.

During daily torpor and hibernation, energy is allocated only to life's most essential biological functions, the ultimate goal being conservation of energy (Heldmaier et al., 2004). Initiation of daily torpor in animals that use it opportunistically is often seasonal and triggered by decreases in food availability, ambient temperature, or body energy reserves (Kortner and Geiser, 2000). Although ambient temperature plays some role, availability of energy supplies is the most significant factor in expression of torpor (Kortner and Geiser, 2000). Daily torpor in the blossom-bat (Bartels et al., 1998) and hibernation in the lemur, *C. medius* (Dausmann et al., 2004), illustrate this point; both occur in warm, tropical environments during periods when available food sources are scarce.

Expression of daily torpor is most common in small animals (median weight 19 g) that have large surface area-to-volume ratios, relatively poor insulation, and the highest energy demands for maintenance of euthermic body temperature (Kortner and Geiser, 2000). A greater proportion of their daily energy budget is dedicated to thermoregulatory defense (Kortner and Geiser, 2000). In contrast, hibernators are generally larger (median weight 85 g) than animals employing daily torpor (Kortner and Geiser, 2000). Shallow and deep torpor are well described adaptive responses to seasonal bottlenecks in energy supply (Kelm and von Helversen, 2007). When energy supplies are abundant, some species may forgo torpor even in harsh climates (Kortner and Geiser, 2000) and, instead, employ the sleep–wake cycling phenotype.

As a means of decreasing metabolic rate during torpor, essential biological operations, such as transcription, translation, protein synthesis, and cell proliferation (such as in normally highly proliferating sites as intestinal epithelia) are either reduced or suspended (Heldmaier et al., 2004; Morin and Storey, 2009; Storey and Storey, 2010; van Breukelen and Martin, 2001, 2002). As an example,

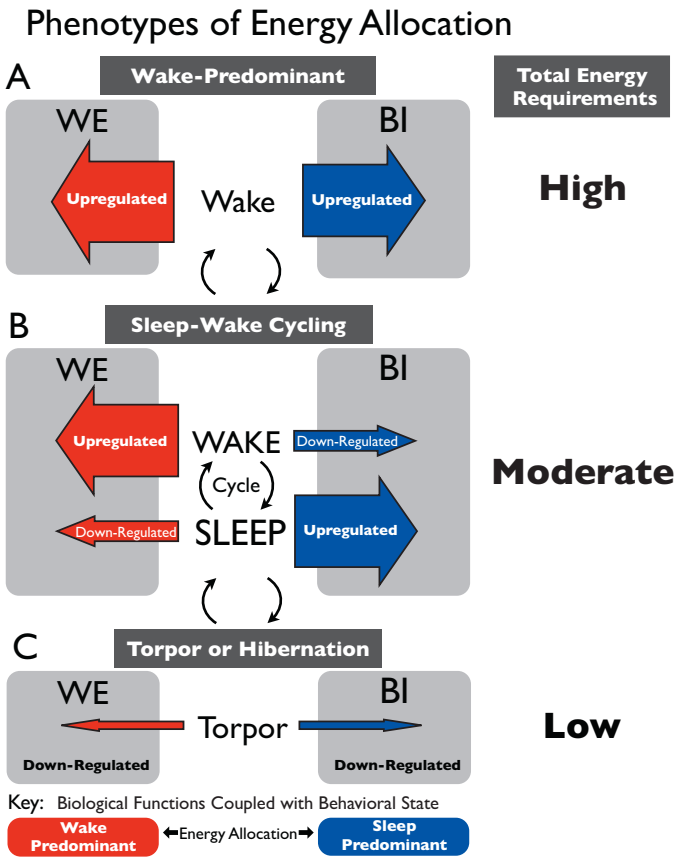

Fig. 9. Three phenotypes of energy allocation are proposed in the energy allocation model, including (A) wake-predominant, (B) sleep–wake cycling, and (C) torpor or hibernation. These phenotypes are differentiated, at least in part, by the types of biological activities that are up or downregulated during predominant wakefulness, sleep, or torpor (see text for details). The total energy requirements for these phenotypes vary, being highest for the wake-predominant phenotype and lowest for the torpor or hibernation phenotype. WE: waking effort; BI: biological investment.

initiation of torpor in golden-mantled ground squirrels is associated with cessation of protein synthesis when the T_c falls below 18 °C, even though elongation of pre-initiated polypeptides continues at a reduced rate at this T_c (van Breukelen and Martin, 2001). During prolonged hibernation with T_c approaching 5 °C, an arrest of transcription ensues secondary to moderately lowered depression in initiation of RNA synthesis and severe inhibition of elongation of transcripts (van Breukelen and Martin, 2002). Fig. 9 demonstrates a schematic of the decrease in appropriation of energy toward both thermoregulatory effort (TE) and biological investment (BI) in torpor relative to sleep–wake cycling. Interestingly, hibernators demonstrate well-defined bouts of rewarming in the course of hibernation. These occur at 5–12 day intervals and are associated with high amplitude, cortical slow-wave activity (Daan et al., 1991; Heller and Ruby, 2004; Trachsel et al., 1991). The brief rewarming periods during hibernation are associated with marked reversal of the depression in gene expression and, instead, active resumption of transcription of gene products that may exceed the level observed in the active waking period, suggesting a "hyperactivation of gene expression at the level of mRNA synthesis during these brief euthermic periods" (van Breukelen and Martin, 2002).

Cyclical emergence of NREM sleep with high amplitude slow-wave activity during the rewarming bouts of hibernation has led to the suggestion that hibernation is a time of sleep deprivation (Daan et al., 1991; Deboer and Tobler, 2000; Heller and Ruby, 2004; Palchykova et al., 2002; Trachsel et al., 1991). Perhaps the need for sleep slowly builds during periods of deep torpor. Similar to the gradual decline in cortical slow-wave amplitude seen during recovery sleep from sleep deprivation, the high amplitude EEG slow-waves observed in the rewarming periods are characteristically highest at the onset and then decline as the next bout of deep torpor begins. The longer the bout of hibernation, the greater the intensity of slow-wave activity at the emergence of sleep (Trachsel et al., 1991). Whether the increase in slow-wave activity following hibernation is secondary to sleep deprivation or to loss of neuronal connectivity associated with deep torpor is not yet clear (see Strijkstra and Daan (1998)).

Some workers have cautioned that it is not the loss of sleep during hibernation per se that increases sleep pressure, but rather the need for sleep's "restorative properties" to aid recovery or maintenance of brain function after long bouts of central nervous system hypometabolism (Larkin and Heller, 1999). It needs to be emphasized that the low body temperatures associated with hibernation are incompatible with many functions normally completed during sleep and waking. Indeed, manipulations that prevent euthermic arousal episodes during hibernation may be fatal (Satinoff, 1967). Recent findings demonstrate that NREM sleep may not be the only stage of sleep to contribute a biological benefit during hibernation. The periodic rewarming episodes seen in the tropical, primate hibernator, fat-tailed dwarf lemur (*C. medius*), preferentially involve REM sleep instead of NREM sleep when ambient temperature rises above 25–30 °C during daytime (Krystal et al., 2013). The REM sleep-related rewarming episodes during hibernation in this tropical lemur include an increase in metabolic rate (Krystal et al., 2013).

Given increased energy demands associated with sleep during the rewarming periods of hibernation, the data support the fundamental premise that sleep has an energy cost. Accordingly, the function of sleep is not simply conservation of energy. If daily torpor is more efficient than sleep at conserving energy, then why is daily torpor not the most commonly employed energy allocation strategy in the animal kingdom? And why do not other species, including humans, employ daily or nightly torpor? The answer, if torpor is exploited, may be the need to suspend critical biological operations that normally occur in sleep. In other words, although torpor presents a major benefit in terms of energy savings, it also carries potential costs when compared to sleep.

Trade-offs between sleep's role in memory consolidation and the energy conservation gained in torpor were recently examined in detail (Roth et al., 2010). The investigators reviewed the selective costs of hypometabolic states on brain and memory function. For example, ground squirrels after hibernating demonstrate reduced operant and spatial memory function (Millesi et al., 2001) and fail to recognize previously familiar conspecifics (Mateo and Johnston, 2000). Hamsters show deficits in familiar object-retrieval in a complex spatial scene after reentering euthermia (Palchykova et al., 2006). As Roth et al. (2010) state regarding trade-offs between sleep and torpor, "This creates an interesting conflict between sleeping to form memories about where food is located and reducing sleep to save energy when food is in short supply". In addition to memory function being adversely affected by torpor, investment into other, non-brain, functions are also reduced. To illustrate, REM sleep is a time of increased testosterone release and erectile function for mammals, whereas daily torpor in the Djungarian hamster is associated with testicular regression (Kortner and Geiser, 2000).

4.3. Phenotype of predominant wakefulness

Several features characterize what is here termed the *predominant wakefulness phenotype*. First, this phenotype is generally expressed only during predictable periods in the life cycle, such as mating, migration, birthing, periods of increased foraging

opportunities, and periods of perceived predation in species that generally exhibit the sleep–wake cycling phenotype. Second, a homeostatic response appears reduced (Lesku et al., 2012) or non-existent (Lyamin et al., 2005) during either the period of sleep loss or during the return to baseline sleep–wake cycling, such that sleep rebound or sleep pressure is significantly decreased in predominant wakefulness. Finally, cognitive deficits or adverse somatic effects are either blunted or not apparent during prolonged reduction in sleep lasting weeks or months at a time (Lesku et al., 2012; Rattenborg et al., 2004; Siegel, 2008).

With respect to the apparent absence of adverse effects during expression of the predominant wakefulness phenotype, birds demonstrate striking differences in learning in operant-testing chambers during the nonmigratory and migratory seasons; accuracy and performance significantly decline when birds are experimentally sleep-deprived during the nonmigratory season, but no such declines are found with sleep loss during the migratory season (Rattenborg et al., 2004). Moreover, in the nonmigratory season, birds demonstrate reduced responses when learning an operant task after sleep deprivation, yet they exhibit increased responses during predominant wakefulness in the migratory season (Rattenborg et al., 2004). Dolphins display an ability to maintain accuracy on a detection task during a period of almost continuous vigilance for five days, while showing no evidence of a sleep rebound effect (Ridgway et al., 2006). Further, some male pectoral sandpipers demonstrate marked reductions in sleep during their three-week mating season, a time of intense male-male competition for access to fertile females (Lesku et al., 2012). In this elegant study, males that slept the least sired the most offspring and were also more likely to return to the same breeding site in later years.

These results urge the conclusion that species exhibiting the predominant wakefulness phenotype upregulate in waking many of the essential biological processes normally allocated to sleep. Such upregulation is presumed necessary by the EA model to sustain the waking state without appreciable behavioral deficits or homeostatic reversal resulting from prolonged sleep loss (see Fig. 9A). Although speculative at this time, such an upregulation of BI during waking is hypothesized to be a controlled process that prevents aggregation of biological deficits or reactive homeostasis, i.e., increased sleep pressure. Only one study has examined gene expression during a period when a species expresses what is here defined as the predominant wakefulness phenotype. This study investigated gene expression in the brain during the migratory phase of the white-crowned sparrow and found only 29 transcripts differentially expressed during migration relative to sleep restriction and waking (Jones et al., 2008b). Accordingly, additional data are required to evaluate the hypothesized upregulation of sleep-predominant biological processes during the wake state in migration.

Expression of the continuous or predominant wakefulness phenotype allows a remarkable adaptive advantage for maximizing reproductive success in certain species. There may also be an associated cost of virtually continuous wakefulness, however, for it not to serve as the primary phenotype in any known population. The amount of metabolic substrate and cellular infrastructure required to meet the increased demands of transcription, translation, and protein processing during indefinite durations of continuous wakefulness is theoretically great, even if anticipated by changes in gene expression so that deficits do not proliferate. Some species may be capable of meeting these increased energy demands during relatively short periods of their life histories. The increased energy requirements in a predominant wakefulness phenotype would also be its primary limiting factor, consequently contributing the required selective pressure necessary to limit expression of this phenotype in the animal kingdom.

5. Phylogenetic considerations of the energy allocation model

With the aim of identifying phylogenetic clues to the function of sleep, a number of phylogenetic or comparative analyses across species have examined sleep parameters, such as total sleep time and NREM and REM sleep times, in relation to constitutive variables, including body and brain mass, basal metabolic rate (BMR), maximum life span, and gestational period, among others. Early comparative analyses treated each species as an independent statistical unit (Allison and Cicchetti, 1976; Elgar et al., 1988; Zepelin and Rechtschaffen, 1974), but these analyses have been criticized as over-representing certain orders or types of animals, such as rodents, in the correlational data (Lesku et al., 2006, 2008). Recent analyses have attempted to address the non-independence of data resulting from the shared evolutionary history of related species (Capellini et al., 2008a,b; Capellini et al., 2010; Lesku et al., 2006, 2008, 2009). The latter approach (Lesku et al., 2009) has contradicted some of the earlier findings, including the hypothesis that species with high metabolic rates sleep more (Zepelin and Rechtschaffen, 1974).

Investigators of the phylogeny of sleep have recognized the limitations inherent in such analyses, particularly in regard to the limited number of species for which sleep data are available and lack of adequate field data (with over-reliance on laboratory recordings of sleep and wake durations in controlled conditions) (Lesku et al., 2009). Comprehensive reviews of the most current phylogenetic data have been published (see Allada and Siegel, 2008; Capellini et al., 2008a,b; Lesku et al., 2006, 2008, 2009; Lima et al., 2005; Roth et al., 2006). There is consensus that a single, underlying function of sleep has not been uncovered from this work.

Despite the limitations, comparative phylogenetic analyses continue to provide important avenues to understanding the ecological constraints that affect expression of sleep and wake in many species, such as the influence of predation risks on sleep quotas. As an example, the trophic position of a species (herbivore versus carnivore) affects the likelihood of being preyed upon. Herbivores sleep less than carnivores when variables such as body size are controlled (Capellini et al., 2008a; Lesku et al., 2006, 2008, 2009). Large herbivores may also need to forage longer (and sleep less) to acquire adequate food supplies, given the lower energy content of their food sources (Allison and Cicchetti, 1976; Capellini et al., 2008a; Elgar et al., 1988). Perhaps related to the elevated arousal thresholds in REM sleep for most species (which may increase sleep-related predation risk), species exposed to greater predation show disproportionately lower ratios of REM sleep relative to NREM sleep (Lima et al., 2005). Carnivores, by contrast, have the highest ratios of REM sleep (Lima et al., 2005). The importance of ecological factors on sleep quotas will likely grow as more field data become available.

Phylogenetic analyses can be used to test a proposed function of sleep by comparing specific predictions of the model against observed trends in NREM and REM sleep quotas across species. A new theory of sleep function, such as presented by the EA model, needs to be analyzed in a similar manner, using sophisticated phylogenetic approaches. Although these data cannot be presented in detail here, several phylogenetic findings that potentially play an important role in the EA model are briefly discussed in Sections 5.1 and 5.2.

5.1. Contributions of body size and energy constraints on sleep quotas

The relationship between body size and sleep quota across species is still debated. A number of studies report a significant negative correlation between body weight and sleep duration (Allison and Cicchetti, 1976; Capellini et al., 2008b; Elgar et al., 1988; Lesku

et al., 2008; Zepelin and Rechtschaffen, 1974). Alternatively, this relationship can be interpreted as mediated through variables that are influenced by body mass, such as BMR, brain mass, sleep exposure and gestation period (Lesku et al., 2006, 2009). With respect to sleep exposure, smaller animals often sleep in protected burrows and may sleep more since they secure safer sleeping sites, whereas larger animals tend to sleep in the open (Lesku et al., 2006). Moreover, since "no hypothesis for the function of sleep has a mechanistic relationship between sleep parameters and body size" (Lesku et al., 2009), some recent phylogenetic studies have, instead, focused upon statistical analyses of other competing mediator variables, such as brain weight. In contrast, the EA model strongly configures body mass and ecological energy constraints among several variables influencing sleep quotas across species.

In terms of body size, mammals with smaller body masses are predicted to express more sleep than larger mammals, at least in part because of the body size-dependent energy demands of thermoregulation. Small mammals expend a disproportionate percentage of their daily energy budget on thermoregulatory defense so as to maintain a high, constant body temperature. These species put 75–90% of their energy resources into thermoregulation because of greater heat loss from their large surface area-to-volume ratios and smaller quantities of fur and fat stores. Smaller mammals, therefore, experience the most selective pressure to minimize investment into BI in waking to allow relatively greater deployment of finite energy resources to WE; i.e., waking functions such as vigilance, reproduction, and foraging, as shown in Eq. (2).

The EA model accounts for a trade-off regarding energy distribution due to body mass between thermoregulatory defense and competing metabolic requirements related to BI. This, in turn, affects total sleep quotas. The longer total sleep time of small mammals has a three-fold basis: First, decreasing BI during waking (because of greater thermoregulatory demands) requires that a higher proportion of BI be made during sleep, thereby exerting pressure for proportionately greater sleep time or sleep intensity. Second, although core body temperature decreases 1–3 °C during sleep, the energy demands of thermoregulation during sleep remain relatively high for smaller animals compared to larger animals. On theoretical grounds (based on competing energy requirements imposed by thermoregulation), longer total sleep times may have evolved in small endotherms to allow completion of needed biological operations during sleep. Third, smaller animals, including many species of small birds and mammals, have evolved the added ability to express the phenotype of torpor in response to energy constraints (Geiser, 1998). Many of these species alternate on a daily basis between wake, sleep and torpor (Heller and Ruby, 2004). The addition of daily torpor further reduces wake time if critical, sleep-dependent, biological processes are to be maintained during the sleep state. Small mammals in the face of energy constraints, therefore, experience shorter waking bouts in part because of the competing benefits gained from both torpor (energy conservation) and sleep (biological investment).

This model considers that large animals tend to dedicate a relatively smaller portion of their waking energy budget to thermoregulatory defense, allowing for proportionately larger allocations of energy into BI during the waking state. For larger species, the types of biological investments that may be upregulated during waking (instead of during sleep as in smaller species) are currently speculative, but may include immune function, growth, and repair, among others. Also, larger animals require a smaller percentage of their energy reserves to maintain thermoregulation during sleep. This allows a greater percentage of their energy budget to be put into BI during sleep. In theory, increased outlay into BI during both waking and sleep (rather than toward thermoregulatory defense) operate to permit lower total sleep quotas for larger endotherms.

According to the EA model, energy constraints also are predicted to play a role in modulating sleep quotas. Species exploiting a broad temporal and ecological niche high in energy resources are expected to experience selective pressures to sustain longer bouts of waking and shorter bouts of sleep. This prediction is consistent with data demonstrating that species with small body sizes and increased energy constraints tend to have polyphasic sleep with shorter, intermittent waking bouts, in contrast to large species which tend to have monophasic sleep and more consolidated, continuous wake bouts (Capellini et al., 2008b). When energy supplies within the niche permit, selective pressures are expected to drive greater allocation of energy into BI during waking (which amplifies the capacity to exploit an environmental niche rich in energy reserves). Increased investment into BI during waking stands to decrease the need to make such investments during sleep, and, thereby, reduces sleep need.

The energy constraints of a niche, and a diminishing rate of return on energy investment, are predicted to maintain *sleep–wake cycling* as the predominant energy allocation strategy in a particular population. Under extreme circumstances, however, some species express the *predominant wakefulness phenotype* at critical phases in their life cycles, such as when mating or migrating (as described in the previous section and shown in Fig. 9A). Consistent with the EA model, predominant wakefulness is expressed if the return on energy investment supports a transition to this phenotype. Although Fig. 9 implies that the two phenotypes, sleep–wake cycling and predominant wakefulness, are discrete entities (see Fig. 9A vs B), the EA model allows for a wide range of possible sleep quotas based on energy availability. Variations in energy availability might, at least partially, explain variations in sleep quotas across species possessing a similar body mass.

In summary, a strength of the EA model is that it allows for multiple variables that contribute competing selective pressures influencing the expression of sleep quotas. Body mass, for example, is only one such variable. Trophic position (herbivore vs carnivore), energy source (diet), and predation risks at either foraging or sleeping sites, may all ultimately influence sleep quotas. A lion, for example, is a large animal with a high sleep quota (Siegel, 2005), but its trophic position and diet may have influenced the evolution of greater sleep durations for this species. When phylogenetic analyses of sleep quotas are restricted to a more homogeneous population, e.g., herbivores, these other variables (trophic position and diet) are to a large extent controlled for within the subgroup. As a result, the correlation of body mass with sleep quotas is more apparent in herbivores (Siegel, 2005), a correlation that may be missed when all species of mammals are included in the analysis.

5.2. Altricial versus precocial species and REM sleep quotas

Comparative phylogenetic analyses demonstrate that high REM sleep percentage at birth relative to adulthood is most pronounced in altricial young born immature with the lowest percentage of adult brain weight, whereas low REM sleep percentage at birth is characteristic of precocial young born relatively mature with a proportionately larger brain (Lesku et al., 2009; Zepelin et al., 2005). The rat and cat, for example, are born immature and, as newborns, exhibit approximately 90% of their total sleep time in REM sleep. Elevated percentages of REM sleep time persist during the first 20 days after birth in these altricial young, unlike the precocial guinea pig, which exhibits a much smaller and relatively constant quantity of REM sleep from birth to adulthood (Jouvet-Mounier et al., 1970). Interestingly, the guinea pig has a markedly elevated REM sleep time in utero 20 days prior to birth, a time when the brain is at a similar level of development as the rat at birth (Astic and Jouvet-Mounier, 1970). Such a phenomenon is found in humans as well. A normal human adult typically exhibits two hours of REM sleep

per day, or 25% of total sleep time, representing a marked decrease from the infant who spends as much as eight hours in REM sleep per day, or approximately 50% of total sleep time (Roffwarg et al., 1966). Although REM sleep quotas decrease gradually throughout development, they remain highest during a human's first few years of life, the period during which it is most dependent on parental care.

The large quantities of REM sleep in human infants relative to adults led Roffwarg et al. (1966) to propose the ontogenetic hypothesis. This theory proposes that activation of the forebrain from REM sleep-generating brainstem structures during sleep plays an important role in early CNS development when waking life experience is limited. Subsequent work from this group and others focused on the visual system, particularly in regard to the role of ascending, REM sleep-specific, ponto-geniculo-occipital (PGO) waves originating in the pons. This activation of higher centers during REM sleep has been shown to be essential for the activity-dependent, neuronal differentiation and development of the lateral geniculate nucleus in the thalamus (Davenne and Adrien, 1984, 1987; Davenne et al., 1989; Marks et al., 1999; Shaffery et al., 1998; Shaffery et al., 1999), and also for the age-dependent ability to elicit long-term potentiation (LTP), a measure of plasticity in the visual cortex (Shaffery and Roffwarg, 2003; Shaffery et al., 2002). These data elegantly demonstrate how internally generated neuronal activation during REM sleep in early life promotes activity-dependent brain maturation during the developmental period when there is a relative paucity of input from the external world.

It has also been suggested that the role of REM sleep in brain development is not restricted to the visual system (Blumberg, 2010; Roffwarg et al., 1966). In the setting of generalized skeletal muscle atonia during *active sleep* in neonates (a term often used to describe REM sleep in infants before eye movements are present in some species), myoclonic twitching of the head, whiskers, extremities, and trunk are particularly prevalent (Blumberg and Seelke, 2010; Jouvet-Mounier et al., 1970). Blumberg (2010) has proposed a developmental role for the primary descending brainstem activation of myoclonic twitching during REM sleep; namely, the local twitching in the periphery triggers a volley of proprioceptive sensory feedback to the forebrain from the affected muscles, joints, or whiskers (Tiriac et al., 2012) which modifies brain activity during sleep. This sensory feedback activation during REM sleep further elaborates the ontogenetic hypothesis, suggesting that REM sleep plays a role in sensorimotor integration during development.

Although the specific roles of REM versus NREM sleep in the development of other brain systems is less well understood, recent data reveal that juvenile songbirds preferentially learn an adult "tutor" song during sleep (Margoliash and Schmidt, 2010; Shank and Margoliash, 2009), and sleep improves conditioned responses (Fifer et al., 2010) as well as the learning of language (Hupbach et al., 2009) in human infants. Relative to the EA model, the data reviewed in this section robustly demonstrate that energy-consuming biological processes targeting neuronal development, maintenance, and function are performed during sleep throughout life across species.

In altricial mammals, the young rely on parental care for nourishment and safety, as well as some forms of behavioral thermoregulation like swaddling in human infants or direct transfer of body heat from parent to infant (Blumberg, 2002). The large surface area-to-volume ratios of small neonates and their relatively modest fat stores and insulating fur make thermoregulation particularly challenging for altricial infants who often utilize brown adipose tissue (BAT) for non-shivering thermogenesis (Blumberg, 2001). In addition, altricial mammals tend to be born into large litters that allow for group huddling. This is a common strategy employed to facilitate thermoregulation for individual neonates within the huddle so as to retain heat owing of the smaller surface area-to-volume ratio of the huddle (Alberts, 1978a,b; Hull and Hull, 1982; Schank and Alberts, 1997; Schmidt et al., 1986; Sokoloff et al., 2000). Individual rat pups, for example, save metabolic energy by huddling with their littermates, even when challenged across a broad range of ambient temperatures (Alberts, 1978a). Indeed, individual pups will move to the middle of the huddle when cold or to the surface when warm, demonstrating their ability to behaviorally thermoregulate within a huddle (Alberts, 1978a; Blumberg, 2002).

As viewed through the EA model, I propose that high REM sleep percentage at birth has evolved in altricial endotherms as a means of reducing the energy costs of thermoregulatory defense so that limited energy resources may be deployed, instead, for rapid growth and CNS development. The EA model posits REM sleep as an energy allocation strategy that shunts energy utilization away from the demands of thermoregulation and maintenance of generalized skeletal muscle tone. By using the heat generated by, or retained from, littermates within the huddle or from parental intervention, altricial neonates can defer the costs of individual thermoregulation during REM sleep and direct their available energy resources into other biological operations that promote rapid growth. Based on the EA model, an alternative evolutionary strategy that allocates more energy for greater thermoregulatory independence (such as by increasing BAT quantity or activity as a source of thermoregulation) would delay maturation by decreasing the energy available for BI (e.g., growth and neural network reorganization).

If energy allocation is a function of REM sleep that promotes rapid CNS development in altricial infants in a manner that optimizes energy utilization, then the model would also predict that altricial neonates opportunistically express REM sleep when defense of T_c can be minimized; that is, for example, when the infant is placed in the high end of its thermoneutral zone (~35 °C for rat pups). On the contrary, if the benefits of an energy allocation strategy do not outweigh the costs of suspending thermoregulatory control, REM sleep expression in neonates should be suppressed or sacrificed.

These tenets of the EA model pertaining to neonates are supported by experimental data. The findings suggest that REM sleep may be opportunistically expressed when neonates are placed at the high end of the thermoneutral zone as a means of harnessing external sources of heat to increase the allocation of energy to CNS development. To illustrate, warming of neonates will precipitate or trigger REM sleep expression (Kleitman and Satinoff, 1982; Sokoloff and Blumberg, 1998). And whereas myoclonic twitching (REM or active sleep) in neonatal rat pups is maximally expressed as the T_a approaches ~35 °C, REM sleep significantly decreases as the T_a falls below 27 °C, and may even be suspended when the T_a decreases below 23 °C (Blumberg and Stolba, 1996; Seelke and Blumberg, 2005; Sokoloff and Blumberg, 1998).

Altricial neonates, in comparison to precocial mammals, have a greater urgency for rapid growth to provide safety from predation and self-defense of body temperature regulation. The ontogenetic hypothesis provides a mechanism through which REM sleep-related activation promotes internally stimulated development for the maturing infant brain, and the EA model provides an evolutionary perspective that supports this proposition. By employing thermoregulatory strategies that harness external sources of heat to minimize the need for defense of T_c, altricial endotherms are able to increase REM sleep quotas and preferentially expend more energy on CNS growth and development. The proposed selective advantage afforded by this energy allocation function of REM sleep is consistent with the high REM sleep percentages observed in altricial neonates across endothermic species. Finally, the EA model may ultimately help explain the role of development and epigenetic influences in the eventual segregation or coupling of gene expression with behavioral state, as well as the optimal allocation of energy to different biological processes across circadian time, to optimize daily energy expenditure. It remains to be

determined whether such epigenetic influences potentially explain the persistently higher levels of REM sleep seen in altricial relative to precocial mammals as they develop into adulthood.

6. Summary

The EA model of sleep function is a new theory based on the temporal organization of energy acquisition and utilization. Through the lens of this model, the underlying function of sleep is inextricably linked to waking, in that investments into biological processes are differentially shared between the states in a manner that optimizes energy utilization to maximize lifetime reproductive success. It is the predictable cycling of sleep and wakefulness that allows for completion of biological activities to be coordinated between these behavioral states. Well-developed evolutionary principles of life history theory were utilized to uncover the selective pressures driving reductions in contributions to biological investment (BI) during wakefulness. These reductions are related to biological functions not immediately required to exploit the waking niche, such as specific categories of gene expression. The apportionment of energy to these downregulated activities of waking and other essential mechanisms occurs when it no longer profits an organism to expend energy on waking effort (WE), such as foraging or reproduction. Sleep is viewed in this schema as a mechanism that not only allows for a downregulation of expensive biological operations of waking, but also ensures that utilization of energy for sleep-related activities is harnessed in rapid and efficient ways.

The EA model is the first sleep theory to delineate a parallel core function for NREM and REM sleep, highlighting their role in energy appropriation. Absence of thermoregulatory control in REM sleep has often been viewed as one of this state's most peculiar physiological features. However, it is central to the EA model of sleep function. Decreasing thermoregulatory defenses during REM sleep, together with loss of skeletal muscle tone, enhances energy availability for other somatic and CNS-related biological functions. The cycling of NREM and REM sleep to optimize energy utilization during sleep by decreasing the need for T_c defense is also a novel hypothesis. The finding that *whole-body* metabolic rate during REM sleep is lower than that of quiet waking (Jung et al., 2011) supports the proposition that essential biological activities can be performed during REM sleep at a lower energy cost per unit of time relative to the waking state.

Sleep is thought to serve many functions, with most theories in the past century divided into three main categories: energy conservation, body or brain restoration, and neural network reorganization. Several theorists have suggested that a single, universal function of sleep, though desirable, may not be found given the many varied, and often disparate sleep functions identified (Cirelli and Tononi, 2008; Siegel, 2005). The EA model, nevertheless, does unify or integrate many earlier theories into one model. Specifically, wakefulness and sleep are viewed as energy allocation states during which many biological functions optimally occur. The types of biological operations to be performed during sleep, or the extent to which these "functions" are shared between sleep and wake, are predicted to vary somewhat across species according to cost–benefit trade-offs related to energy supply and demand. REM sleep may be the behavioral state during which memory consolidation optimally occurs for some species at a lower energy cost by diverting energy utilization away from thermoregulation and the maintenance of muscle tone, but memory function is not evolutionarily "locked" to REM sleep in this model. Indeed, observations that memory processing remains intact following REM sleep-suppression with antidepressants in humans (Rasch et al., 2009), and that cetaceans include some of the most intelligent non-human mammals despite the absence of REM sleep, are consistent with this perspective.

The EA model also predicts that the brain is not alone in benefiting from the energy distribution strategy afforded by sleep. Additional energy-consuming physiological requirements, such as growth and maintenance of peripheral tissues and immune functioning, among others, also appear to utilize sleep as a platform for the execution of important biological operations that may be actively downregulated during waking. The coupling of metabolic processes in the periphery with the behavioral expression of either wakefulness or sleep is achieved through multiple mechanisms, including those depicted in Fig. 4. These include hormonal control; local, autonomous circadian clocks in peripheral tissues that regulate metabolic pathways; and, a direct descending influence from brain to periphery via the autonomic nervous system.

The EA model addresses several controversies in regard to prior sleep theories. One debate has centered on whether sleep saves sufficient energy for energy conservation to be considered the primary function of sleep. The finding that metabolic rate during sleep is only marginally lower than that of quiet waking has presented a challenge to the earlier energy conservation model (Horne, 1988; Rechtschaffen, 1998; Zepelin and Rechtschaffen, 1974). Moreover, the emphasis on energy reduction during sleep in this prior theory has hindered the integration of REM sleep into the model, a state of high brain energy metabolism. Alternatively, the EA model emphasizes the relative stability of energy utilization across circadian time by means of sleep–wake cycling and the repartitioning of energy into unique biological operations performed during each state. This division of labor for biological functions, achieved through their coupling with behavioral state, may also reduce moment-to-moment demands placed on cellular infrastructure, e.g., organelles, mitochondria, and protein processing pathways. In this manner, sleep permits the reduction of energy-consuming infrastructure through a state-dependent division of labor of metabolic activity at the cellular level. In this model, the advantage of sleep–wake cycling is daily energy savings *in addition to* uninterrupted implementation of biological operations across circadian time. This combination of benefits affords an aggregate energy savings that outweighs a simple, metabolic cost difference calculated for sleep relative to waking.

Another unsettled question of sleep function is whether sleep affords restoration. In opposition to the restorative hypothesis of sleep, it has been argued that protein synthesis and restitution are at least as likely to occur in quiet waking after feeding (Horne, 1980, 1988). In the EA model, sleep is viewed as "restorative", but primarily in the sense that the unique categories of biological processes that are downregulated during waking require sleep for eventual upregulation or "restitution". The EA model also helps to explain the biological consequences of sleep deprivation, which include the accumulation of biological deficits; the eventual need in waking to upregulate a number of essential biological steps (usually occurring in sleep) that are prevented by sleep restriction; and, the increase in energy demands and cellular stress associated with the simultaneous activation of sleep-related and wake-related biological operations imposed by prolongation of the waking state.

The EA model is also able to account for the adaptive responses to sleep loss, such as increase in appetite and the decreased defense of T_c (both of which constitute responses to the increased energy demands of indefinite maintenance of the waking state), as well as the behavioral drive in endotherms to seek a warm environment for recovery sleep. This latter behavior promotes activation or acceleration of metabolic processes that remain unfulfilled during sleep loss and that are genetically engineered for optimal completion during recovery sleep. The model addresses, both, reactive and predictive homeostatic regulation of sleep. Whereas reactive homeostatic mechanisms restore sleep-dependent biological deficits through an increase in sleep duration or intensity, predictive homeostasis limits energy investment during sleep to only

anticipate the biological substrate needs that are usually required in the next episode of waking.

From an evolutionary perspective, the EA model puts forward a robust construct to differentiate sleep–wake cycling from torpor. It also introduces a third energy allocation phenotype that accounts for prolonged periods of continuous or predominant wakefulness observed during the life history of certain species. The sleep–wake cycling phenotype appears to offer a cost–benefit advantage for most species over both the torpor and continuous wakefulness phenotypes in terms of optimal energy utilization. Specifically, sleep–wake cycling provides energy savings compared to continuous wakefulness, and, unlike torpor, sleep–wake cycling promotes energy utilization for biological processes in the "offline" state of sleep to maximize reproductive success (see Fig. 9).

In an energy allocation economy, the currency is energy. Natural selection is presumed to be the driving force that ultimately determines which of the three phenotypes is the most advantageous during particular periods in the life history of a given species. Several phylogenetic considerations encompassed by the EA model may optimize energy utilization through manipulation of sleep quotas as a way to respond, in part, to the thermoregulatory demands imposed by body mass, as well as to the ecological energy constraints found within the niche. Finally, the model accounts for the high expression of REM sleep in altricial endotherms, in that REM sleep promotes rapid growth and development by decreasing the energy requirements of thermoregulation.

The great diversity of organisms expressing sleep, in combination with the wide range of environments in which cycling of sleep and wakefulness are observed, suggest that sleep carries an essential benefit beyond what is achievable in quiet, immobilized waking. In the EA model, the energy demands imposed by the biological activities of wakefulness are incompatible with the energy allocation requirements of sleep. For example, maintenance of muscle tone and thermoregulatory defense are essential for endotherms in waking, but these same biological functions would diminish or eliminate the energy allocation benefits realized through REM sleep. Similar arguments may be made for brain function. The high neuronal activation of wakefulness imposes demands for energy that would compete with the energy needed for myelin formation, growth of new neurons, and many other brain functions, potentially explaining why these processes are normally coupled with sleep.

Most all species, from their origin, are faced with energy constraints, either on a daily basis or at certain times in their evolutionary history. Natural selection favors behavioral and physiological strategies that optimize energy utilization to maximize lifetime reproductive success. In the EA model, the "schedule" of energy investments providing the greatest fitness return is regulated through sleep–wake cycling and the coupling of biological operations with behavioral state, illuminating why sleep evolved to become one of the most universal behaviors shared by species on Earth.

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