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The two-process model of sleep regulation: a reappraisal

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Abstract

In the last three decades the two-process model of sleep regulation has served as a major conceptual framework in sleep research. It has been widely applied in studies on fatigue and performance and to dissect individual differences in sleep regulation. The model posits that a homeostatic process (Process S) interacts with a process controlled by the circadian pacemaker (Process C), with time courses derived from physiological and behavioural variables. The model successfully simulates the timing and intensity of sleep in diverse experimental protocols. Electrophysiological recordings from the suprachiasmatic nuclei (SCN) suggest that S and C interact continuously. Oscillators outside the SCN that are linked to energy metabolism are evident in SCN-lesioned arrhythmic animals subjected to restricted feeding or methamphetamine administration, as well as in human subjects during internal desynchronisation. In intact animals these peripheral oscillators may dissociate from the central pacemaker rhythm. A sleep/fast and wake/feed phase segregate antagonistic anabolic and catabolic metabolic processes in peripheral tissues.

A deficiency of Process S was proposed to account for both depressive sleep disturbances and the antidepressant effect of sleep deprivation. The model supported development of novel non-pharmacologic treatment paradigms in psychiatry, based on manipulating circadian phase, sleep and light exposure.

In conclusion, the model remains conceptually useful for promoting the integration of sleep and circadian rhythm research. Sleep appears to have not only a short-term, use dependent function, but it also serves to enforce rest and fasting, thereby supporting the optimization of metabolic processes at the appropriate phase of the 24-h cycle.

1. Introductory remarks

The two-process model of sleep regulation was proposed more than three decades ago. It had a large impact on sleep research and is still a prevalent conceptual model. This is reflected by the persistently high number of citations per year of the original papers. AAB and SD published the original papers of the two process model (Borbély, 1982, Daan et al., 1984), whereas AAB and AWJ related the model to sleep in depression and the antidepressant effect of sleep deprivation (Borbély and Wirz-Justice, 1982). The present review was triggered by a symposium at the ESRS Congress in Tallinn in September 2014, in which the authors highlighted important developments and assessed merits and limitations of the model.[1] The review focuses on conceptual issues and does not cover other important aspects such as applications of the model to work

[1] Historical note: AAB, SD and AWJ had established in the 1980s a Zürich-Groningen-Basel (ZGB) research triangle that gave rise to a continuous exchange of students and ideas related to sleep regulation as well as experiments testing the model. TD was a student in Groningen and Zürich, and now focuses his research on the interaction of the two processes. A further key person in the investigation of sleep and depression was the late Rutger van den Hoofdakker in Groningen. Many of the students and postdocs who were trained in the ZGB research triangle have continued their research into the two-process model. They include Irene Tobler, Domien Beersma, Peter Achermann, Derk-Jan Dijk, Kurt Kräuchi, Christian Cajochen, Paul Franken, Hanspeter Landolt, Daniel Brunner, Daniel Aeschbach, Esther Werth, Reto Huber and Vladislav Vyazovskiy. Their enthusiasm and creativity were instrumental in the further development and validation of the model.

schedules or performance measures, its mathematical refinements, age-related changes, and new insights on the molecular mechanisms underlying the two processes.

2. The original two-process model of sleep regulation and its predictive power

2.1. A brief restatement of the model

The two-process model posits that the interaction of a homeostatic process depending on sleep and wake (Process S) with a process controlled by the circadian pacemaker (Process C) determines salient aspects of sleep regulation. Process S, representing sleep debt, increases during wakefulness and declines during sleep, within a value-range that oscillates with a periodicity that is normally entrained to day and night by the circadian pacemaker. When S approaches the range's lower boundary it triggers awakening, near the upper boundary it triggers sleep. NonREM sleep EEG slow-wave activity (SWA) represents the principal marker of S during sleep, theta activity in waking is a marker of the rising limb of S (reviewed by Borbély and Achermann, 1999). Core body temperature and melatonin rhythms are markers of C. In animals rendered arrhythmic by lesioning the SCN, sleep homeostasis is not disrupted (Tobler et al., 1983, Trachsel et al., 1992). This indicates that the two processes are separately regulated. In humans, the forced desynchrony protocol, an imposed sleep-wake periodicity that is outside the range of entrainment of the circadian pacemaker, results in sleep occurring at different circadian phases. This disentangles the sleep-wake cycle from the circadian rhythm, allowing assessment of their separate influence on sleep and performance variables (Dijk and Czeisler, 1995, Wyatt et al., 1999).

2.2 Tests of the model

In humans, the model was initially found to be consistent with the phenomenon of internal desynchronisation between sleep-wake and circadian body temperature cycles in the absence of time cues, with circadian oscillations in fatigue during prolonged (3-day) sleep deprivation, with sleep fragmentation during continuous bedrest, with SWA in

sleep after different durations of sleep deprivation, and with sleep duration in shift-workers (Daan et al., 1984).

Predictions derived from the model were then tested. NonREM sleep SWA during brief daytime naps increased with duration of prior wakefulness (Dijk et al., 1987a). After such naps, SWA in normal night sleep was reduced in quantitative agreement with model predictions (Daan et al., 1988, Werth et al., 1996b). Both tests are summarized in Figure 1. Prolonged sleep after sleep deprivation was characterised by a monotonic decrease in SWA (Dijk et al., 1990). Suppression of SWA during the initial part of time asleep without disturbing sleep caused a rebound in SWA during subsequent sleep (Dijk et al., 1987b), albeit without affecting spontaneous sleep duration (Dijk and Beersma, 1989). This finding indicates that EEG SWA reflects the rate of decay of the regulating variable S, rather than S itself, as was originally postulated. In a further elaborated version of the model addressing changes within nonREM sleep episodes, a close fit between simulated and empirical data was obtained (Achermann et al., 1993).

Fewer studies have focused on the role of C in sleep timing in humans. Exposure to bright light in the morning, advancing the circadian oscillation, also advances awakening on the next day without affecting nonREM sleep SWA (Dijk et al., 1989). Readiness for nocturnal sleep is initiated by the circadian signal of melatonin release in the evening, which induces distal vasodilatation, enhancing the probability of sleep onset (Kräuchi and Wirz-Justice, 2001).

In animals, the rest-activity rhythm is a traditional marker of the circadian pacemaker (C). In the two-process model it is implicitly a marker of both C and S. The relationship of behaviour to S has proved important for studying sleep-like phenomena in species in which conventional electrophysiological markers are not available (e.g., invertebrates). Monitoring motor activity in the cockroach and scorpion after keeping these animals awake enhanced subsequent periods of immobility (Tobler, 1983, Tobler and Stalder, 1988). Also in the rat, brief arousals as a behavioural variable showed a negative correlation with EEG SWA (Franken et al., 1991a). The use of behavioural markers of "sleep homeostasis" has opened up the field of sleep research to invertebrates and in particular to Drosophila and its mutants (reviewed in (Huber et al., 2004, Faville et al.,

2015)). Such markers however preclude the assessment of an intensity dimension to sleep as in the mammalian SWA (in contrast to Faville et al., 2015).

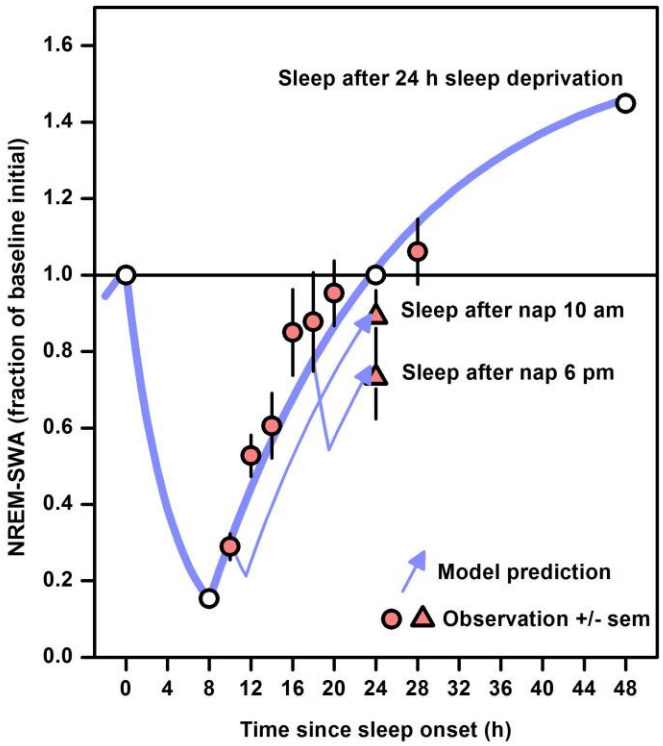

Figure 1. Quantitative tests of model predictions (blue solid lines, open circles) of prior sleep and wake effects on initial nonREM slow-wave activity (SWA). Red circles: mean normalized SWA (± s.e.m.) in first half hour of naps at different times of day (modified after Dijk et al 1987a). Red triangles: mean normalized SWA (± s.e.m.) in first half hour of sleep at 24 h subsequent to a ca 2-h nap at 10 a.m. and at 6 p.m. (modified after Daan et al 1988).

3. New complexities not incorporated in the original model

3.1. Brain differentiation

An important development in the last two decades has been the recognition that sleep homeostasis is not only a global brain phenomenon, but also shows regional, use-

dependent aspects (Krueger and Obal, 1993). Prolonged selective unihemispheric activation of the cortex during wake increased slow-waves over the activated area during subsequent sleep (Kattler et al., 1994). This finding was confirmed and extended using high-density EEG recordings (Huber et al., 2004, Krueger and Tononi, 2011).

Regional differences in the sleep EEG have implications for the two-process model. There is a distinct antero-posterior power gradient in the nonREM sleep EEG with a predominance of low-frequency power in frontal derivations (Werth et al., 1996a). Analysis of the parameters of Process S have confirmed topographic differences (Rusterholz and Achermann, 2011, Zavada et al., 2009). Both the increase and decrease of S are slowest in the fronto-central area. This finding may reflect the functional specialization of cortical areas (e.g., involvement of the frontal cortex in cognitive functions; reviewed in (Ferrara and De Gennaro, 2011)). In the context of the two-process model, such regional differences imply that quantitative SWA-based predictions are dependent on which brain area is chosen to estimate the time course of S. There is currently no scientific basis for this choice.

The two-process model has strong functional implications, but it was formulated without specifying the function of sleep, except that sleep must subserve long-term maintenance of cerebral integrity. Tononi and Cirelli have proposed the synaptic homeostasis hypothesis of sleep regulation (Tononi and Cirelli, 2006, Tononi and Cirelli, 2014). The main tenet is that synaptic and cellular processes that had been challenged during waking are reestablished during sleep. Sleep is viewed as a price the brain pays for plasticity. Addressing the same issue, Frank and Cantera argue that not only sleep homeostasis but also the output of the biological clock influences brain plasticity (Frank and Cantera, 2014). Their state-clock model has received recent support from a human forced desynchrony study showing that SWA, the major index of sleep homeostasis, undergoes marked circadian variation in central and posterior cortical regions (Lazar et al., 2015). Homeostatic and circadian factors seem to make synergistic contributions to synaptic plasticity.

3.2. Continuous interaction of S and C

In the classical two-process model the sleep homeostat and the circadian process interact only at discrete events. When the homeostatic Process S approaches the upper threshold of C, sleep occurs, and when Process S reaches the lower threshold, waking is triggered. This happens twice per circadian cycle under standard (monophasic) conditions, but more often with polyphasic sleep as occurs in humans under continuous bedrest. A continuous interaction between the two processes was envisioned from the first outline of the model. The propensity for sleep or wake was assumed to depend on the distance of S to the upper or lower thresholds of C (Borbély, 1982). Sleep propensity corresponds therefore to the difference between S and C. However, Process S in the model did not influence functioning of the circadian clock and sleep homeostatic processes did not change with circadian phase.

Growing evidence suggests such mutual influence, and several additive and interactive models have been proposed (Achermann, 1999, Achermann and Borbély, 2003, Dijk and Archer, 2010, Dijk and Edgar, 1999, Folkard et al., 1999, Jewett and Kronauer, 1999). In particular, human data obtained in the forced desynchrony protocol have been interpreted as a non-additive interaction between sleep homeostatic mechanisms and the circadian clock (Boivin et al., 1997, Dijk and Czeisler, 1995, Dijk et al., 1992, Wyatt et al., 1999). In this protocol, the circadian amplitude of many neurobehavioural functions was modulated by homeostatic sleep pressure. In general, a lower circadian amplitude was found when sleep pressure was high, and amplitude increased when sleep pressure was reduced. Together, the data indicate that sleep pressure affects the influence of the clock on behaviour and physiology.

In the opposite direction, the circadian clock may also influence the rise and fall of Process S. The circadian phase where prolonged waking occurs (either spontaneous or induced) modifies the level of subsequent slow-wave activity in the nonREM sleep EEG (Werth et al., 1996b, Vyazovskiy et al., 2007). The success of predicting the level of S in a model of homeostatic sleep regulation depends on time of day (Franken et al., 1991b, Werth et al., 1996b, Vyazovskiy et al., 2007, Deboer, 2009). The level of S or EEG SWA may therefore not be simply a function of previous wake duration, but may also depend on the time of day the waking occurs. Whether this is caused by an influence of time of day on the expression of slow waves, dissociating process S from

slow-wave expression, or by a circadian modulation in the quality of sleep and waking, is still unclear (Deboer, 2015, Lazar et al., 2015).

The evidence for a role of clock genes in sleep homeostasis, reviewed elsewhere (Deboer, 2007, Franken, 2013), indicates that sleep homeostasis and circadian regulation also interact on the molecular/genetic level. Knocking out one or more of the 5-7 main clock genes (Period *Per1-3*, *Clock, Bmal1*, Cryptochrome *Cry1* and *Cry2*, *Npas2*) not only changed or disabled the circadian clock, but also modified sleep homeostatic markers in these animal models. *Cry1-Cry2* double knockout mice show increased nonREM sleep time, sleep consolidation, and EEG SWA, all signs of high nonREM sleep pressure. *Clock* mutants, in contrast, sleep less than wild type control animals. *Bmal1* and *Npas2* knockout mice show altered EEG SWA and altered responses to sleep deprivation. Clock gene expression in the brain, particularly in the cerebral cortex, depends significantly on prior sleep-wake history. Sleep deprivation during the light phase induces a duration-dependent increase in *Per2* mRNA in the mouse brain, which returns to baseline levels within 2 hours of recovery sleep. These changes vary with time of day, so both factors are involved. In contrast, within the SCN, *Per2* RNA and PER2 protein expression (Curie et al., 2015) remains unaffected by preceding sleep wake history. There is no evidence that core molecular clock mechanisms in the SCN are influenced by modulations in sleep and waking.

3.3. Interactions of SCN activity and sleep pressure

To gain more direct insight into the interaction of the circadian pacemaker and sleep, the EEG and electromyogram (EMG) have been recorded simultaneously with SCN electrical neuronal activity *in vivo* in freely moving rats. SCN neuronal activity is high during the subjective day and low during the subjective night, irrespective whether an animal is diurnal or nocturnal (Sato and Kawamura, 1984, Vansteensel et al., 2008). In such simultaneous recordings it was shown that SCN neuronal activity increases during waking and REM sleep and decreases during nonREM sleep, in addition to the well-known circadian changes. These ultradian modulations correlate with the level of SWA

in the different sleep states. In addition, careful slow-wave deprivation during nonREM sleep, reducing SWA but still allowing the animals to sleep, results in increased SCN neuronal activity (Deboer et al., 2003). Increasing SWA by sleep deprivation leads to a decrease in SCN neuronal activity in nonREM sleep and REM sleep (Deboer et al., 2007).

This relationship between SCN neuronal activity and sleep pressure in rats has also been found in humans. The fMRI BOLD signal, recorded during a psychomotor vigilance task, declined in the suprachiasmatic area when sleep pressure was increased (Schmidt et al., 2009). The change in BOLD signal correlated with SWA in the first nonREM sleep episode. Thus, the circadian pacemaker appears to obtain feedback from the status of the sleep homeostat, such that increased sleep pressure reduces circadian amplitude.

3.4. Sleep pressure changes and clock functioning

Interactions between sleep pressure changes and circadian clock functioning have been observed in rodents. In mice and hamsters sleep deprivation attenuates phase shifts induced by light (Mistlberger et al., 1997, Challet et al., 2001, van Diepen et al., 2014), suggesting that increased sleep pressure reduces circadian clock response to the zeitgeber. Similarly, in humans, attenuated phase advances were found after sleep restriction (Burgess, 2010).

Light shifts the clock in the SCN via retinal ganglion cells and a monosynaptic pathway, the retinohypothalamic tract. Following activation by light, glutamate is released at the nerve terminals (Johnson et al., 1988, Ding et al., 1994), leading to an increase in SCN neuronal activity (Meijer et al., 1998, van Diepen et al., 2013). Application of glutamate to the SCN mimics the effect of light (Ding et al., 1994). Sleep deprivation may reduce the phase shifting capacity of light by diminishing the strength of the photic signal reaching the SCN, possibly through blocking glutamate release.

Adenosine is thought to be involved in the homeostatic regulation of sleep (Landolt, 2008) and its extracellular level in the brain increases in the course of prolonged waking

(Porkka-Heiskanen et al., 1997). In various brain regions, stimulation of presynaptic A1 adenosine receptors depresses glutamate release and reduces the amplitude of excitatory postsynaptic currents (Dolphin and Prestwich, 1985, Barrie and Nicholls, 1993, Oliet and Poulain, 1999). This may be the mechanism whereby increased adenosine levels after sleep deprivation influence the light responsiveness of the circadian clock. Indeed, after a 6 h sleep deprivation ending at CT14, the light response in the SCN was reduced compared to control; systemic injection of caffeine restored this attenuation of the SCN light response almost completely (van Diepen et al., 2014), supporting the interactive role of adenosine and glutamate. The reduced response to light of SCN neuronal activity after sleep deprivation provides evidence that clock functioning may be modified by sleep homeostatic pressure.

Figure 2 summarizes some changes in clock output and functioning under the influence of increased sleep pressure. Thus, it can be concluded that a continuous exchange of information between the two processes takes place. The homeostatic and circadian processes are not simply independent or additive, but probably subject to more complex interactions. Future modeling efforts should consider the strength of clock output as a function of sleep homeostatic pressure.

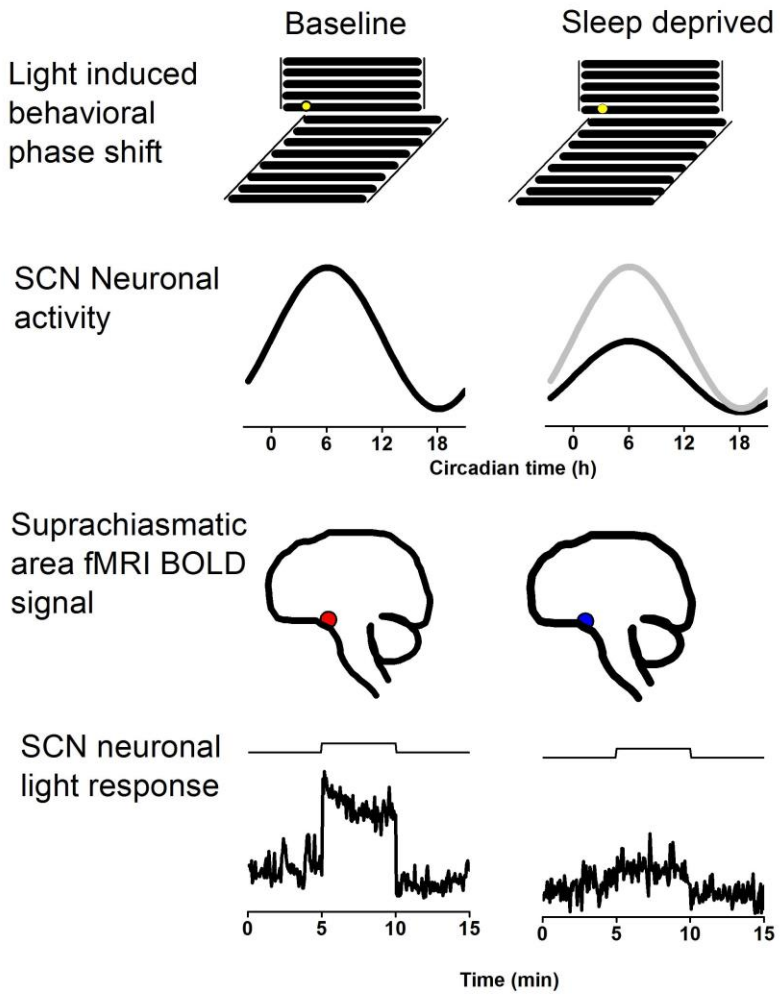

Figure 2. Selected effects of sleep deprivation on circadian clock modulated brain and behavioural functions. Sleep deprivation reduces light induced behavioural phase shifts (Mistlberger et al 1997; Challet et al 2001; Van Diepen et al 2014) and the amplitude of the circadian modulation of SCN neuronal activity (Deboer et al 2007). In humans it reduces the fMRI BOLD response during a psychomotor vigilance task (Schmidt et al 2009). In rodents it reduces the light induced increase in firing rate in SCN neurons (Van Diepen et al 2014).

3.5. Sleep-wake timing controlled by a circadian oscillator outside the SCN

The original view of Process S as a global cortical process has been modified to include regional and use-dependent facets. Similarly, the traditional view of Process C as a hierarchical circadian system under the strict control of the SCN has been expanded by the recognition of peripheral circadian oscillators that exhibit a high degree of independence and flexibility and may respond to physiological and behavioural concomitants of sleep and waking. Thus, as had been shown for sleep homeostasis, a global (systemic) and a local regulation can be distinguished also for circadian rhythms (Asher and Schibler, 2011). These new insights have been obtained in the domain of chronobiology and their repercussions with respect to sleep have not yet been closely examined.

There is accumulating evidence that circadian rest-activity cycles generated outside the SCN can emerge in different organisms under non-standard (laboratory) conditions. In several field studies, rodents that are typically nocturnal in the lab may become diurnal under naturalistic conditions: spiny mice (Levy et al., 2007), Syrian hamster (Gattermann et al., 2008), house mouse (Daan et al., 2011), and Tuco-tuco (Tomotani et al., 2012). The degu, a species considered diurnal, becomes nocturnal when given a running wheel in the lab, while the circadian pacemaker, as judged from its light response curve, remains at the original phase (Kas and Edgar, 2000). Circadian rhythmicity in rest-activity can even be expressed in the absence of the SCN, as found in SCN-lesioned rats under temporal food restriction, apparently driven by a separate oscillator (Stephan et al., 1979). Rats and mice given methamphetamine in their drinking water show pronounced circadian rest-activity rhythms, that typically run with longer periods no longer entrained to about 24 hours by the SCN and even persist in absence of the SCN (Honma and Honma, 2009). This methamphetamine-sensitive rhythm was shown to be independent of the canonical SCN clock genes *cry1* and *cry2* (Honma et al., 2008) or *per1, per2, bmal1, npas2, clock* and *Ck1*ε (Mohawk et al., 2009). The nature of this circadian oscillator outside the SCN is still enigmatic, but it may well be identical with the food entrainable oscillator, since the rhythm of methamphetamine-treated, SCN-lesioned rats entrains to restricted daily feeding

(Honma et al., 1989). Thus, it has become likely that the overt rest-activity rhythm is generated by a circadian oscillator outside the SCN that, under standard conditions, maintains a rather fixed phase relationship with the SCN and thereby with the light-dark cycle. Recently, a dopaminergic ultradian oscillator has been identified in the mouse which normally cycles in harmony with the circadian clock, but can desynchronise when dopaminergic tone is elevated (Blum et al., 2014). This can give rise to aberrant behavioural oscillations and may account for the methamphetamine-induced cyclicity. In this view, the role of the SCN is not so much the generation of activity rhythms, but rather the maintenance of temporal integrity of circadian physiology and behaviour with external day and night. The loss of control over sleep-wake oscillations in human internal desynchronisation has been explained by reduced amplitude of Process C in the absence of resonance with any zeitgeber (Daan et al., 1984), but this does not disprove that sleep and wake could themselves be generated by an as yet unknown oscillator outside the SCN.

3.6. A role for metabolism in the control of rest-activity timing

As reviewed above, the circadian rhythm of activity and rest can adopt different phase relationships with the pacemaker. Animals that are diurnal in the field can become nocturnal in the lab. Mice that are nocturnal in the lab become diurnal when they do not receive their food *ad libitum* as is standard in the lab, but have to work to obtain it, as is usual in nature (Hut et al., 2011). The gradual shift of activity from night to day is eventually followed by the occurrence of torpor (body temperature around 23^{o}C) in the late night. Both low temperature and the working-for-food protocol shift mouse activity from night into day, even though the SCN retains its original phase relationship to the light-dark cycle: a rigid clock driving flexible rhythms (van der Vinne et al., 2014). These findings strongly support a role for energy metabolism in determining the phase of the rest-activity rhythm relative to the SCN. The emergence of activity rhythms in SCN-lesioned rodents under restricted feeding (Stephan et al., 1979) indicates that the amplitude of the underlying oscillator is also affected by energy metabolism.

A further potential link between human rest-activity cycles and energy metabolism is present in the data obtained by Aschoff and coworkers in subjects under isolation from time cues. During internal desynchronisation, the time between meals varied in proportion to the duration of wakefulness (varying from 12 to 42 h) (Aschoff et al., 1986). Indeed, caloric intake per cycle (Green et al., 1987) and activity per cycle (Aschoff, 1993) remained the same despite very large changes in cycle duration. Aschoff deduced early on that the length of the rest-activity cycle may be negatively associated with basal metabolic rate (Aschoff, 1993). While energy metabolism was not assessed in these studies, subsequent analyses demonstrated a negative association between cycle length and core body temperature (Daan et al., 2013). To the extent that the variation in body temperature reflects the variation in heat production (metabolic rate), the results are consistent with the proposition that the spontaneous frequency of the human sleep-wake oscillator is associated with metabolic rate, as suggested on the basis of the proportionality of meal frequency and sleep-wake frequency. The original S-C model may still provide a framework for the much needed analysis of the role of metabolism in the temporal organization of sleep and wake, and its integration with sleep homeostasis. Yet, this should account for the role of an oscillator outside the SCN, and outside the realm of the canonical transcriptional oscillator in the SCN. The big unanswered experimental question here is how the rise of S and the spontaneous timing of sleep and wake depend on metabolic rate.

3.7. Temporal segregation of metabolic processes

The field of circadian rhythms also evolved in another aspect. Gene transcription is not a prerequisite for circadian rhythms, and non-transcriptional events are sufficient to sustain circadian rhythms in human red blood cells (O'Neill and Reddy, 2011). Cellular circadian rhythms may share a common molecular origin. The oxidation–reduction cycles of peroxiredoxin proteins has been proposed to constitute a universal marker for circadian rhythms in all domains of life (Edgar et al., 2012). Metabolic cycles and circadian oscillators may be so inextricably linked that little meaningful distinction can be

made between them. One of the central functional aspects is the temporal segregation of mutually antagonistic metabolic processes.

In the framework of chronobiology, sleep is increasingly viewed in the context of metabolism. Metabolic processes are modulated by time of day, and via synchronization of the circadian pacemaker to the light-dark cycle; thereby predominantly anabolic and predominantly catabolic processes in peripheral tissues are segregated. Thus, in the wake-feeding episode glycogen and cholesterol synthesis are promoted, whereas in the sleep-fasting episode gluconeogenesis and glycogenolysis prevail (Bass and Takahashi, 2010). In terms of hormone secretion, release of glucocorticoids and insulin dominates in the former, with release of melatonin, growth hormone and leptin in the latter. It is noteworthy that the gut microbiome is highly dynamic, exhibiting daily cyclic fluctuations which have repercussions on host metabolism and provide evidence for a cross-regulation of prokaryotic and eukaryotic circadian rhythms (Thaiss et al., 2014, Zarrinpar et al., 2014). We could view the microbiome as forming part of our internal environment.

Contemporary chronobiology appears to revive concepts advanced more than 80 years ago. Walter Rudolf Hess (Hess, 1932) advocated two functional phases of the autonomic nervous system: The ergotropic phase is characterized by the predominance of the sympathetic nervous system, enabling interaction with the external environment such as in foraging, social interaction and predator avoidance. The trophotropic phase with the predominance of the parasympathetic system is the opposite – with an energy preserving, stress preventing and restorative function (Fig. 3). According to Hess, sleep is a vegetative process by which the autonomic nervous system regulates activity of higher cerebral functions.

"The special mechanisms which bring about repair during sleep are hidden in the tissues. They have not yet been fully explained; their existence is only deduced from their effects; yet they lie at the heart of the problem of sleep, and the resting of the sense-organs, muscles, and psychic functions are only accessory factors facilitating restoration within the tissues." (Hess, 1932).

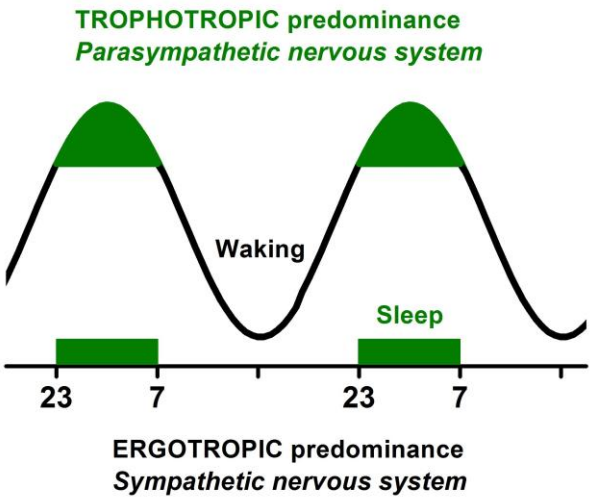

Figure 3. Functional antagonism within the circadian cycle. Hess distinguished within the 24-h cycle a trophotropic phase with parasympathetic predominance characterized by resting, fasting and anabolism, and an ergotropic phase with sympathetic predominance characterized by motor activity, feeding, drinking and catabolism. Hess's concept has been revived in contemporary rhythm research by the circadian clock's partitioning of behavioral and metabolic processes according to the time of day.

In other words, by enforcing quiescence and fasting, sleep ensures optimal physiological and behavioural conditions for restorative peripheral metabolic processes to occur. In this respect, sleep is an adjunct of the 24-hour cycle of metabolism. If sleep does not occur within the appropriate phase of the cycle, by being either too short or too long, the risk of type 2 diabetes increases (Cappuccio et al., 2010). Delaying the habitual sleep phase reduces insulin sensitivity and enhances a marker for

inflammation, presumably by exposing peripheral organs to nutrients during the habitual overnight fast period (Leproult et al., 2014).

Sleep has been shown to be an important factor for maintaining rhythmicity of circadian transcripts in the periphery. When sleep is phase-shifted with respect to the clock, the majority of circadian transcripts become arrhythmic (Archer et al., 2014). Thus, sleep occurring at its habitual circadian phase engenders "resonance" between central and peripheral cues.

4. Impact of the two-process model on clinical research

4.1. Sleep deprivation

Formulation of the two-process model provided an immediate tool for depression research. In the seventies, Pflug and Tölle had systematically investigated the remarkably rapid antidepressant effect of one night's sleep deprivation in affective disorders (Pflug and Tölle, 1971). As documented in thousands of patients, the depression usually lifts towards the morning after a complete night awake, and often returns following the recovery night sleep. This clinical observation lent itself to the question as to whether such a rapid improvement and rapid relapse could be related to and modelled by abnormalities in Process S (Borbély and Wirz-Justice, 1982) (Fig. 4).

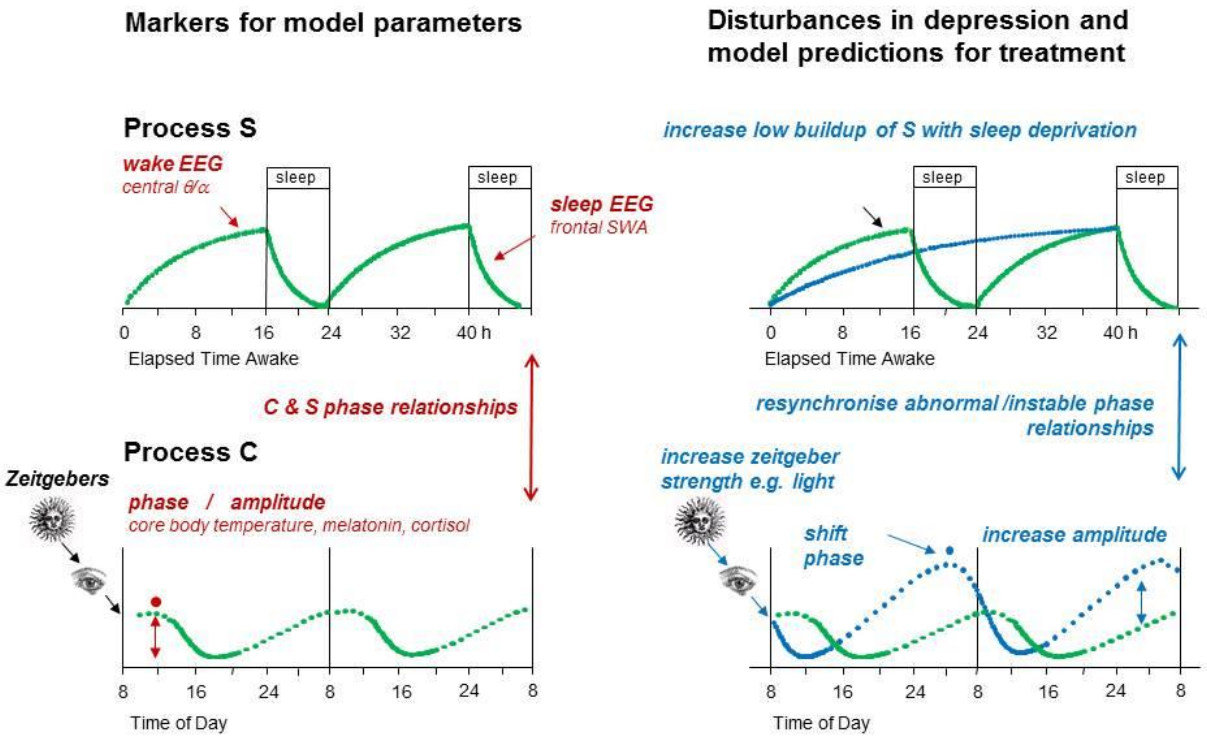

Figure 4. Schematic of the two-process model and its application to depression. Normal situation with markers for model parameters (left) and putative pathological changes and their remedies (right). The skewed sinusoidal function of C corresponds to the quantitative version of the model (Daan et al., 1984) and does not represent the time course of the markers.

The S-deficiency hypothesis of depression did not specify a neurochemical / molecular mechanism; its merit lays in the simple proposal that a deficient S-process is normalised after sleep deprivation. A second „internal coincidence“ model additionally incorporated Process C: appropriate timing of sleep with respect to the internal clock was crucial for stable mood (Wehr and Wirz-Justice, 1981) (Fig.5). This latter model developed out of clinical manipulations of sleep length and timing in depressive patients - partial sleep deprivation in the second half of the night was as efficacious as total sleep deprivation. Even phase-advancing the sleep-wake cycle (without deprivation of sleep) was

antidepressant and, though it took longer for the effect to develop, it also lasted longer (Wirz-Justice and Van den Hoofdakker, 1999) (Fig.5). There was an initial flurry of sleep EEG studies after publication of the hypothesis, but only recently has there been a rekindling of interest in the mechanisms underlying clinical sleep deprivation using new imaging technologies, more stringent protocols, and carefully diagnosed patient groups, following markers of both processes S and C. A very concise, extensive new review of sleep deprivation in depression covers all aspects of putative mechanisms from imaging to synaptic plasticity (Dallaspezia and Benedetti, 2015).

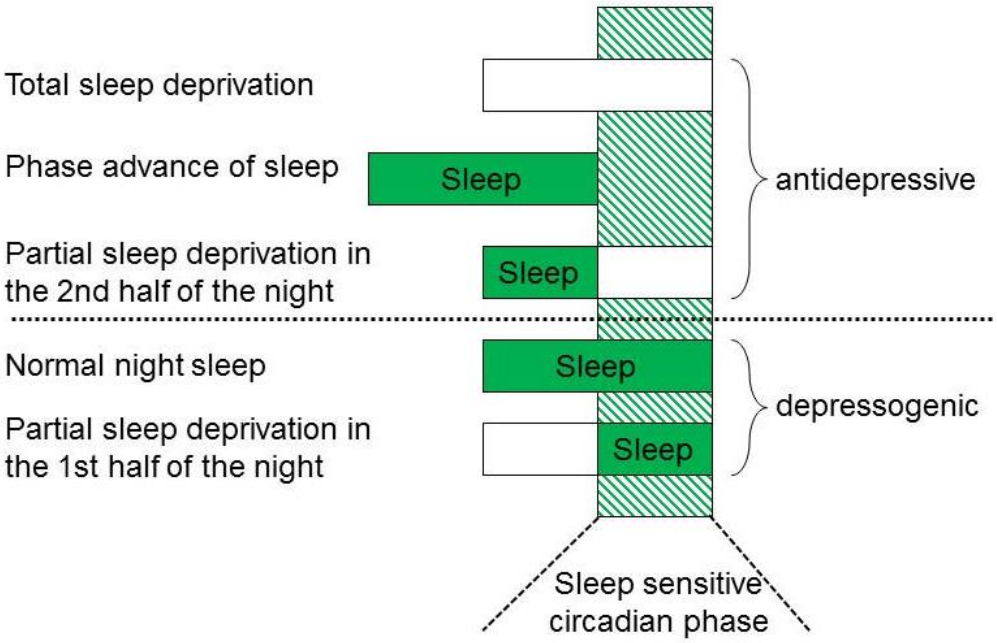

Figure 5. Timing of sleep and mood - the internal coincidence model of sleep deprivation (Wehr and Wirz-Justice, 1981).

4.2. Seasonal Affective Disorder

The most consistent and careful studies based on the model, using both forced desynchrony and constant routine protocols, have been carried out in patients with winter Seasonal Affective Disorder (SAD). Remarkably few differences between SAD and controls in terms of circadian period, phase, or sleep SWA were observed (Wirz-Justice et al., 1995, Brunner et al., 1996, Koorengevel et al., 2002a, Koorengevel et al., 2002b). Studies of classical photoreceptor function (ERG, EOG, dark adaptation) predominantly show normal retinal parameters in SAD in summer and sub-sensitivity to environmental light in winter, however the data are not quite consistent (Danilenko and Levitan, 2012). More specifically, SAD patients may have a decreased retinal sensitivity related to melanopsin gene variations in the non-image forming light-input pathway as measured by the post-illumination pupil response (Roecklein et al., 2013). fMRI imaging has revealed abnormal hypothalamic responses to light in SAD (Vandewalle et al., 2011).

We still do not know why SAD patients are vulnerable to diminishing photoperiod in winter (Danilenko and Levitan, 2012). However, the model provided a conceptual framework to rigorously test hypotheses of SAD pathophysiology, and, most importantly, to investigate the clinical effects of the zeitgeber light.

4.3. Light as therapy

Light for SAD was the first treatment in psychiatry based on neurobiological research – the simulation of a spring photoperiod to counteract the long winter night (Rosenthal et al., 1984). Later, it was found that an early dawn signal was sufficient for clinical response in SAD (Terman and Terman, 2006): part of this improvement is related to the phase advance induced by morning light, but also to direct effects of light on mood, probably via the same serotonergic systems as found responding to classical SSRIs (Spindelegger et al., 2012). Light does not modify sleep EEG spectra in SAD (Brunner et al., 1996). According to the model (Fig 4), light acts on Process C to shift phase and

increase amplitude, and by increasing zeitgeber strength it stabilises entrainment. The direct neurochemical effects of light may explain why it is effective at different times of day, the circadian modulation being relevant for better morning response.

There is an impressive literature on light's multiple actions on the brain, in particular, the non-visual effects of light transduced by wavelength-dependent novel melanopsin-containing photoreceptors (ipRGCs) (Gaggioni et al., 2014). For example, an aberrant light cycle that neither changed the amount and architecture of sleep nor caused changes in the circadian timing system, directly regulated mood-related behaviours and cognitive functions in mice via the ipRGCs (LeGates et al., 2012).

4.4. Major depression

Even though the two-process model was initially applied to major depression, there have been few studies in these patients, with results ranging from the early finding of low nonREM EEG delta power (Borbély et al., 1984) to higher SWA in young depressed women (Frey et al., 2012), who show a stronger response to sleep deprivation than controls, particularly in frontal brain regions. High-density EEG demonstrated higher SWA primarily in prefrontal channels only in depressed women (Plante et al., 2012). In contrast, another study found lower SWA in outpatients with depression, particularly men aged 20-30 (Brower et al., 2011). We are not aware of any stringent investigations of sleep and circadian rhythms in major non-seasonal depression or bipolar disorder under constant routine or forced desynchrony protocols.

Evidence for the tenets of the two-process model has been found in the antidepressant effects of selective slow wave sleep deprivation (Landsness et al., 2011). The reduction in depressive symptoms correlated with the overnight dissipation of fronto-central SWA during baseline sleep, and the rebound in right frontal all-night SWA during recovery sleep.

Measures of cortical responses evoked by transcranial magnetic stimulation (TMS) have been correlated with synaptic strength in rodents, and change with sleep homeostatic pressure in humans. TMS/EEG in prefrontal cortex in bipolar depression

reveal that cortical excitability, putatively a direct measure of Process S, increases as a function of time awake, more in clinical responders than in non-responders (Canali et al., 2014). Dallaspezia and Benedetti (2015) conclude in their review: "Moreover, considering that cortical excitability has been proposed as a correlate of process S, these findings then confirm hypotheses of process S increase as a core mechanism of action of antidepressant SD."

A striking development in the clinical domain has been a new generation of treatments combining manipulations of Processes S and C: sleep deprivation with light therapy – yielding a fast and long-lasting response (e.g., Wu et al., 2009, Martiny et al., 2012, Benedetti et al., 2014), some even including a sleep phase advance (Echizenya et al., 2013, Sahlem et al., 2014). Thus, the two components of the model may not be clearly understood, but the treatments arising therefrom are already established (Wirz-Justice et al., 2013).

4.5. Beyond depression

Many abnormal sleep patterns in psychiatry and other medical disciplines can be better understood when considering the contributions of S and C in order to specify the disturbance. An example: arrhythmic rest-activity cycles in a schizophrenic patient treated with the sedating antipsychotic haloperidol led to measurement of melatonin rhythms as a circadian marker (Wirz-Justice et al., 1997). Surprisingly, the melatonin rhythm persisted, indicating a functioning clock. In the two-process model, the frequency of sleep-wake alternations depends on the distance between the circadian thresholds defining sleep and wake. In simulations, reducing this interval induces polyphasic sleep (Daan et al., 1984), leading to the question as to whether the drug-induced sedation could have been the reason for the poor rest-activity pattern. This led to a change in medication followed by re-emergence of a circadian pattern.

A broad field of application has been in alertness management (fatigue and performance), development (adolescence) and ageing, dissecting out reasons for individual differences (long/short sleepers, early/late chronotype, genotype). It has led in new directions, to investigations of trait-like individual responses to sleep loss or

circadian misalignment, time-on-task effects, cumulative effects of sleep restriction, executive function, and local vs. global sleep. Though not initially developed for clinical application, the model has unraveled the two processes contributing to many physiological, behavioural and cognitive functions. This research has yielded novel, non-pharmacological antidepressant treatments such as light therapy, sleep deprivation and sleep phase advance.

5. Concluding remarks

The two process model continues to be conceptually useful for organizing the thinking about sleep regulation along two axes. It is still helpful for bringing the disciplines of sleep and rhythm research closer together. It also remains influential in the design of experiments and data evaluation. In medicine, disease may induce non-specific impairment of homeostatic mechanisms. Illness may affect light-oriented behaviour that has consequences for stable entrainment. Even in its classical form, the two-process model provides a simple construct to differentiate sleep disturbances appropriately and thereby initiate specific treatments.

The detection of local, use-dependent changes of the sleep EEG has provided regional and functional specificity of the effect of waking on sleep. Recent neurophysiological and morphological studies have focused on local sleep-related changes at the synaptic level and their functional implications. It is important to be aware that plasticity in the brain is modified by both homeostatic and circadian factors. Some of the detrimental effects of sleep deprivation are due to the disruption of the synergy of S and C.

Our view of the circadian system has undergone profound changes. The SCN is now viewed as orchestrating and integrating rhythms rather than just generating and driving them. Homeostasis of (still imprecisely defined aspects of) brain function may be achieved through periodic sleep-wake alternation, which itself is generated by either an underlying neuronal oscillator outside the SCN or by a behavioural relaxation oscillator as conceived in Process S. The verdict on this issue is still pending. Slow advancing or delaying transients of experimentally shifted human sleep-wake cycles towards the unshifted circadian melatonin rhythm in temporal isolation (Hashimoto et al., 2004) are

consistent with an underlying sleep-wake oscillator. Other researchers have conceptualised a relaxation type sleep-wake switch involving both orexinergic wake-promoting and homeostatic sleep-promoting drives (Phillips et al., 2011). When the orexinergic wake promotion is under circadian control and reflects the daily rise in Process C, this is fully compatible with the two-process model.

Sleep has a large effect on peripheral circadian oscillators due to such factors as the absence of locomotion, reduced body temperature, increased growth hormone and reduced glucocorticoid secretion. If sleep occurs at the optimal circadian phase, it reinforces the temporal segregation of "sleep/fast-type" metabolism from "wake/feed-type" metabolism. In addition to a need-related facet that depends on previous history, sleep ensures an optimal internal environment for processes occurring during the circadian resting phase. In an early paper, the terms "recovery sleep" and "inactivity sleep" were used to refer to the two facets of sleep (Borbély, 1980). It was argued that the latter type of sleep ensures the immobility of the animal during specific parts of the 24-h cycle thereby minimizing energy expenditure and possibly reducing the risk of predation. Three decades later, we emphasize the metabolic benefits of inactivity. The possibility of modulating sleep intensity in addition to duration functionally contributes to optimal flexibility in the circadian timing of sleep.

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