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Sleep homeostasis and the circadian clock: Do the circadian pacemaker and the sleep homeostat influence each other's functioning?☆

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ABSTRACT

Sleep is regulated by a homeostatic and a circadian process. Together these two processes determine most aspects of sleep and related variables like sleepiness and alertness. The two processes are known to be able to work independently, but also to both influence sleep and sleep related variables in an additive or more complex manner. The question remains whether the two processes are directly influencing each other.

The present review summarizes evidence from behavioural and electroencephalographic determined sleep, electrophysiology, gene knock out mouse models, and mathematical modelling to explore whether sleep homeostasis can influence circadian clock functioning and *vice versa*.

There is a multitude of data available showing parallel action or influence of sleep homeostatic mechanisms and the circadian clock on several objective and subjective variables related to sleep and alertness. However, the evidence of a direct influence of the circadian clock on sleep homeostatic mechanisms is sparse and more research is needed, particularly applying longer sleep deprivations that include a second night.

The strongest evidence of an influence of sleep homeostatic mechanisms on clock functioning comes from sleep deprivation experiments, demonstrating an attenuation of phase shifts of the circadian rhythm to light pulses when sleep homeostatic pressure is increased. The data suggest that the circadian clock is less susceptible to light when sleep pressure is high.

The available data indicate that a strong central clock will induce periods of deep sleep, which in turn will strengthen clock function. Both are therefore important for health and wellbeing. Weakening of one will also hamper functioning of the other. Shift work and jet lag are situations where one tries to adapt to zeitgebers in a condition where sleep is compromised. Adaptation to zeitgebers may be improved by introducing nap schedules to reduce sleep pressure, and through that increasing clock susceptibility to light.

1. Introduction

Since the origin of life on earth, behaviour and physiology have been shaped by the rotation of our planet around its axis. As a result a biological circadian timing system evolved that enabled organisms to anticipate daily environmental changes rather than just reacting to them. These timing systems involve endogenous pacemakers that run independently from environmental cycles, but can be entrained to the 24 hour geophysical cycle. Accordingly, circadian timing systems enabled organisms to anticipate daily changes in temperature, radiation, and food availability resulting from the movement of our planet, have an (evolutionary) advantage over organisms in which the circadian clock was removed and cannot predict these changes (Ouyang et al., 1998; Woelfe et al., 2004). In more complex organisms this clock optimizes internal physiology to reduce energy expenditure and the use of internal recourses. During the active phase ingestion and reproduction are prominent, during rest maintenance and growth. The evolution of a central nervous system did not basically change rest-activity behaviour, but it added a further dimension as it seems the brain needs to go offline during rest, since compromising this offline period has serious consequences for several brain and bodily functions. This offline period is generally called sleep and the vulnerability of the organism during this offline period emphasizes the importance of sleep. If it was not important natural selection would have limited its occurrence as much as possible. Moreover, loss of sleep is followed by increased sleep indicating some kind of homeostatic regulation of sleep.

This review summarizes the evidence of a reciprocal interaction between sleep homeostatic mechanisms and the circadian clock. As will be discussed below, it is clear that both, independent of each other have an influence on the amount and timing of sleep, and that they together are probably the most important players in explaining the timing and depth of sleep. Both are also affecting other objective and subjective variables related

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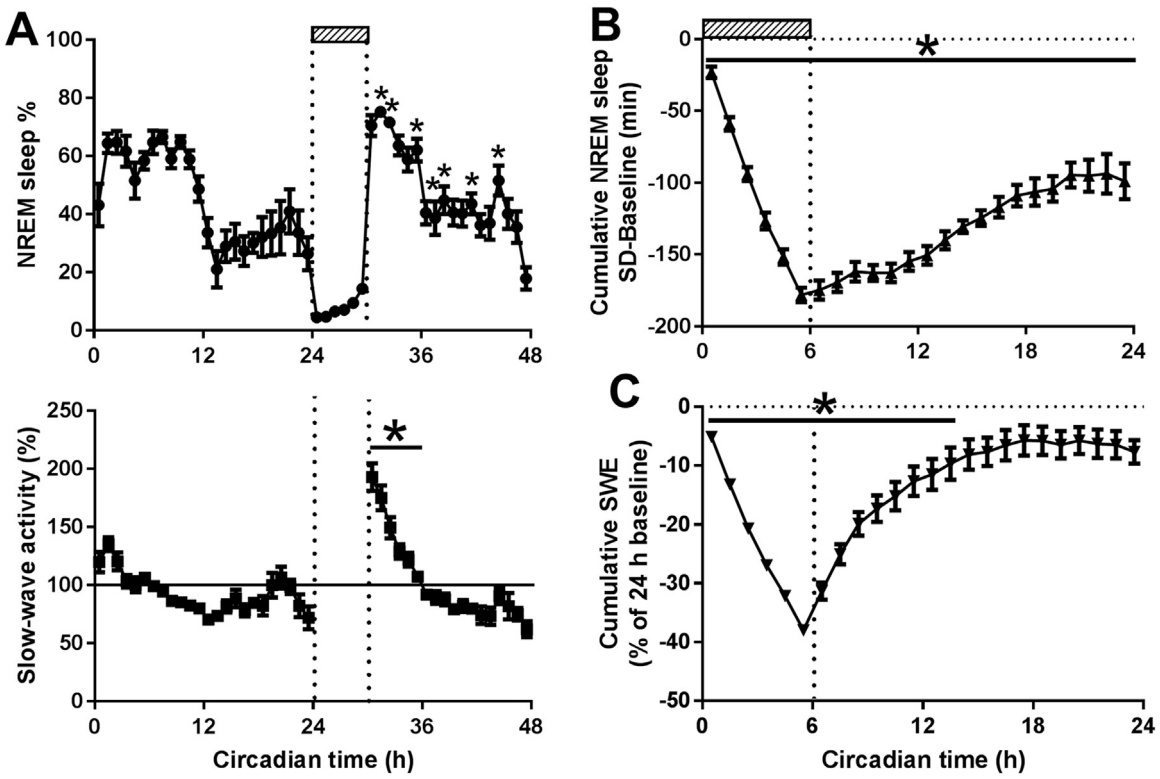

Fig. 1. Demonstrating sleep homeostasis. Panels A: Time course of 48 h of non-rapid eye movement (NREM) sleep and slow-wave activity (SWA, electroencephalogram power density between 1 and 4 Hz) in NREM sleep across a baseline day, during a sleep deprivation performed during the first 6 h of the rest period (hatched bar at the top), and 18-h recovery in 1-h mean values (± SEM, n = 11 Wistar rats). The recordings were obtained after 7 days adaptation to constant darkness. The amount of NREM sleep is expressed as a percentage of total recording time (= 100%). SWA is expressed as the average over 24-h baseline (= 100%). Asterisks and solid lines indicate where recovery significantly differed from the in time corresponding baseline values ($p < 0.05$, two-tailed paired t-test after significant ANOVA factor *day*). **Panel B:** Cumulative NREM sleep lost and gained in 1-h mean values (± SEM, n = 11), calculated by subtracting the minutes of NREM sleep during deprivation (hatched bar at the top) and recovery from the corresponding baseline value and summing the difference with the preceding hour. Asterisks and solid lines indicate where sleep deprivation and recovery significantly differed from baseline ($p < 0.05$, two-tailed paired t-test after significant ANOVA factor *day*). Note that a significant part of NREM sleep is lost and not recovered. **Panel C:** Slow-wave energy (SWE, accumulated SWA), in 1-h mean values (± SEM, n = 11) lost and gained, calculated by subtracting the accumulated SWA over the recovery day from the accumulated SWA during the same period in the baseline day. Asterisks and solid lines indicate where sleep deprivation and recovery significantly differed from baseline ($p < 0.05$, two-tailed paired t-test after significant ANOVA factor *day*). Note that SWE lost during the sleep deprivation is virtually totally recovered in the course of the recovery period.

to sleep and waking. The question addressed in this review is whether there is a direct influence of sleep homeostatic mechanisms on circadian clock functioning, and *vice versa*. To be able to understand the putative reciprocal interaction, first an overview will be given on the present status of the knowledge of homeostatic and circadian regulation of sleep. Subsequently both directions of influence will be discussed.

2. Clocks and homeostats

In most complex organisms two mechanisms regulate most physiological processes. There is the concept of homeostasis where physiological variables are regulated to remain near a defined value, to remain nearly constant over time (Cannon, 1929). On the other hand there is the concept of circadian regulation (Halberg et al., 1959); to change the level of each variable for optimal functioning at the proper time of the day. To join the two, the term “Rheostasis” was coined by Mrosovsky (1990). With this one can, for instance, understand that body temperature in endotherms is precisely regulated, and yet is allowed to fluctuate with a period of approximately 24 h. A similar idea has been developed for sleep.

2.1. The circadian clock

In mammals the master circadian pacemaker is located in the suprachiasmatic nucleus (SCN) of the hypothalamus (Leak and Moore, 2001; Vansteensel et al., 2007). It consists of two nuclei above the optic chiasm at the base of the third ventricle. A large variety of experimental approaches have been applied in search for the anatomical location of the endogenous circadian clock in mammals. SCN lesion studies provided first evidence of this location. Rhythms in drinking, locomotor activity, and corticosterone disappeared after lesioning of the SCN area (Moore and Eichler, 1972; Stephan and Zucker, 1972). Also the diurnal or nocturnal distribution in sleep-wake rhythms disappear after SCN lesioning (Edgar et al., 1993a; Mistlberger et al., 1983; Tobler et al., 1983; Trachsel et al., 1992). Transplanting the SCN of tau mutant hamsters, which carry a mutation that induces a shorter endogenous period (Ralph and Menaker, 1988), into the third ventricle of wildtype host hamsters showed that the period of the donor was transplanted into the host (Ralph et al., 1990). Together the data clearly demonstrate that the endogenous rest-activity behaviour and circadian period are determined by the SCN.

Individual SCN neurons show a circadian rhythm but these rhythms show a large variability in period length (Welsh et al., 1995). Inside each neuron, the rhythm is generated and maintained with a transcription-translational feedback loop that is regulated by 5–7 core clock genes (Albrecht, 2002). When these neurons are connected in a network in a prepared SCN brain slice the period distribution is narrower (Herzog et al., 1998; Honma et al., 2004) and most neurons show activity during the subjective day (Schaap et al., 2003; Quintero et al., 2003), suggesting that intercellular communication synchronizes the SCN neurons and increases the precision in its output.

Although each rodent SCN consists of approximately 10,000 neurons, the output under normal healthy conditions, is usually considered to come from a single source having one single circadian period. There are however exceptions to this rule. Under specific circumstances it seems that part of the SCN rhythm can be light driven whereas another part remains endogenous

(De la Iglesia et al., 2004; Stenvers et al., 2016) and two behavioural rhythms with different periods can be observed. Under constant bright light conditions the activity bout can split in two components in antiphase, so called splitting (Vansteensel et al., 2007). This behaviour is induced by the independent functioning of the left and right SCN 180° out of phase with each other (De la Iglesia et al., 2000). In the latter condition, both components have the same period. With its output, the circadian clock in the SCN regulates the daily modulation of many physiological functions, including sleep. The most reliable, and easy to measure output markers are used in circadian rhythm research to monitor clock functioning. In animals the rest-activity rhythm or core body temperature rhythm is often used as a marker for the endogenous phase of the circadian clock. In humans the most used markers are body temperature or the melatonin excretion rhythm.

2.2. The sleep homeostat

Next to its circadian modulation, sleep shows a certain level of homeostatic regulatory capacity. When sleep is lost, this loss is compensated by extending subsequent sleep. This homeostatic aspect is thought to be one of the main regulatory processes in sleep and seems to be universal, as it is found in many different *phyla* of the animal kingdom (Deboer, 2015). Behavioural sleep homeostasis in mammals is illustrated in Fig. 1A. It shows the average hourly values of electroencephalogram (EEG) confirmed sleep in a group of rats during a baseline day and during and after they have been subjected to a 6 h sleep deprivation. In the first hours after the sleep deprivation sleep is enhanced above the corresponding baseline levels of the previous day, a response seen in many species. In humans, a monophasic sleeping species, the amount of sleep per hour is usually not much increased after sleep deprivation, but sleep can be significantly extended. However, the latter is not often observed in experiments as too few protocols in human laboratory studies allow more than 8 h of sleep. Another similarity between many species is that the recovery of the amount of behavioural sleep is not complete. The amount of sleep lost, be it non-rapid eye movement (NREM) or REM sleep, is not regained in the following hours or days (Fig. 1B). The sleep homeostatic response does not involve complete recovery of the amount of sleep lost and there is an additional way to recover sleep.

Another aspect of sleep is its depth, which changes depending on the previous waking duration. Sleep depth or intensity remained a relatively abstract notion until the introduction of EEG recordings. It was soon clear that a positive correlation exists between the difficulty to awaken a subject or animal and the prominence of slow-waves (< 5 Hz) in the NREM sleep EEG (Blake and Gerard, 1937; Ferrara et al., 1999; Neckelmann and Ursin, 1993; Rosa and Bonnet, 1985; Williams et al., 1964). Nowadays, by applying spectral analysis on the EEG, slow-wave activity (SWA, EEG power density between ~ 0.5 and 4.0 Hz) can be calculated and quantified. In all diurnal and nocturnal mammals with a clearly distinct main rest and active period, slow-waves and SWA in the NREM sleep EEG are more prominent at the beginning of the main rest period and this subsides as sleep progresses (Fig. 1A). In addition, in most mammals and some birds investigated, SWA in NREM sleep increases after sleep deprivation (Deboer, 2015; Rattenborg et al., 2009). As an alternative, it was shown that theta/alpha activity in the waking EEG shows similar wake dependent changes (Cajochen et al., 1995).

The data suggest that mammals can compensate sleep loss with two different strategies. The amount of sleep can be increased, but in addition by increasing SWA, NREM sleep can be deepened or intensified. When calculating a combined measure of cumulative SWA over time, incorporating both the increase in NREM sleep amount and the increase in SWA, it shows that the resulting slow-wave energy (SWE) gained can fully cover the SWE lost during the preceding sleep deprivation (Fig. 1C). At least this is true for short lasting sleep deprivations, within a normal physiological range. With long, or complex sleep deprivation protocols which last many days, sleep homeostatic mechanisms seem to become less predictable (Kim et al., 2007; Leemburg et al., 2010; Stephenson et al., 2015), but the cause of this decrease and whether this is really the case is still subject of debate (Beersma and Daan, 2015).

The sleep homeostatic response was further investigated with nap studies and applying different sleep deprivation durations. In humans it was shown that a nap during the day decreases subsequent SWA in NREM sleep during the following night in a predictable way (Borbely et al., 2016; Werth et al., 1996). In addition, in most mammalian species investigated, a dose response relationship between waking duration and subsequent SWA in NREM sleep was established (Deboer, 2015).

From these results one can conclude that there is some kind of process which keeps track of the prior duration of sleep and waking, and the level of this process is reflected in the activity of the slow-waves in the NREM sleep EEG. It increases with prior waking duration, it decreases in the course of sleep and it shows a predictable change from baseline when naps are introduced during the day. Mathematical modelling of the homeostatic sleep response has been applied successfully in human (Achermann et al., 1993) rat (Deboer, 2009; Franken et al., 1991) and mouse (Franken et al., 2001; Huber et al., 2000).

2.3. Brain areas involved in sleep regulation

Many functions in sleep-wake regulation come together in the hypothalamus and the pons (reviewed by Saper et al., 2005). There are two ascending pathways that stimulate wake maintenance. The first is a pathway from the pons to the thalamus that activates thalamic relay neurons crucial for transmission of information to the cortex. It consists of acetylcholine producing neurons in the pedunculopontine nucleus (PPT) and the laterodorsal tegmental nuclei (LDT) (Hallanger et al., 1987). These cells are active during waking and REM sleep and much less active during NREM sleep (McCormick 1989). The second branch originates from monoaminergic neurons, like the noradrenergic locus coeruleus (LC), serotonergic dorsal and medial raphe, dopaminergic ventral periaqueductal grey matter and histaminergic tuberomammillary neurons. They project to the lateral hypothalamus, the basal for brain and throughout the cerebral cortex (Jones, 2003). These neurons are most active during waking, reduce activity during NREM sleep and are silent during REM sleep (Aston-Jones et al., 1981; Fornal et al., 1985; Steininger et al., 1999).

On the opposite side, stimulating sleep, stands the ventrolateral preoptic (VLPO) area. It has outputs to all the major cell groups mentioned above to be involved in waking and arousal. Its neurons are mainly active during sleep and release the inhibitory neurotransmitters galanin and GABA (Gaus et al., 2002; Sherin et al., 1998; Szymusiak et al., 1998). In addition, the VLPO receives afferents from all the major monoaminergic neuronal areas it is inhibiting.

As such, the sleep-wake regulatory circuit resembles a self-reinforcing loop, where activity on one side shuts down input from the other side and therefore disinhibits its own action. In electrical engineering this is called a 'flip-flop switch' and this term has therefore been coined to describe the sleep-wake regulator network (Saper et al. 2005). A flip-flop switch is a self-reinforcing loop that avoids transitional states. This explains why sleep-wake transitions are experienced as abrupt, instead of slow. However, a flip-flop switch is not stable. Without stabilisation uncontrolled switching back and forth between states is likely to occur.

Specific neurons in the lateral hypothalamus (LH), releasing orexin (also called hypocretin) are suggested to be the stabilizing component of the network. Their function was discovered at the end of the 1990s when it was shown that narcoleptic dogs, mice and humans show mutations in orexin receptors or completely lack orexin (Chemelli et al., 1999; Lin et al., 1999; Thannickal et al., 2000; Peyron et al., 2000; Ripley et al., 2001). Orexin neurons are mainly active during waking (Estabrooke et al., 2001; Lee et al., 2005; Mileykovskiy et al., 2005) and orexin levels in the brain increase in the course of the main waking period and after SD (Deboer et al., 2004; Zeitzer et al., 2003; Zhang et al., 2004). It is thought that orexin neurons reinforce arousal without inhibiting the VLPO (Saper et al., 2005).

For circadian timing of sleep and waking, the central circadian

pacemaker in the SCN should be able to influence the activity of these sleep and wake active centres in the brain. However, the SCN has limited direct output to these centres, but does have indirect connections to LH and VLPO. The main output of the SCN is to the dorsal and ventral subparaventricular zone, which in turn have strong input to the dorsomedial hypothalamus. From there GABA containing neurons project to the VLPO and glutamatergic neurons project to LH (Chou et al., 2003). The SCN therefore seems to be able to influence the main centres that maintain sleep or waking via this indirect pathway.

How then does the brain fall asleep? Adenosine, a breakdown product of the depletion of ATP in the brain, has been proposed as a homeostatic accumulator of the need to sleep (Landolt, 2008). Adenosine is known to increase in extracellular space in the course of prolonged waking (Porkka-Heiskanen et al., 1997). In several regions of the brain stimulation of A1 adenosine receptors depresses glutamate release reducing the amplitude of postsynaptic currents (Barrie and Nicholls, 1993; Dolphin and Prestwich, 1985; Oliet and Poulain, 1999). The accumulation of adenosine, but also other sleep promoting substances, may reduce the activity of wake promoting areas and disinhibit sleep promoting areas in this way.

3. Two processes working together

Particularly in humans, it is clear that the timing of sleep is strongly regulated by the circadian clock. In addition, sleep homeostatic mechanisms have a strong influence on the depth and maintenance of sleep. The two-process model of sleep regulation was proposed to incorporate the two regulatory processes (Borbely, 1982; Borbely et al., 2016; Daan et al., 1984). It posits that the interaction of a homeostatic process (process S), depending on the prior amount of sleep and waking, with a process controlled by the circadian pacemaker (process C), determines the main aspects of sleep regulation (Fig. 2). The model was probably the most dominant model in the sleep field in the past 30 years, and initiated a large amount of new research, as the concepts of the model are easy to apply to a broad range of questions in the sleep research field. This is the main reason why it also here is used as a basis to discuss the evidence of a putative reciprocal interaction between the two processes.

In the two process model, Process S represents sleep homeostasis or sleep debt, which increases during waking and decreases during sleep, within a range that oscillates with a periodicity that is entrained to day and night by the circadian pacemaker (Fig. 2). When S approaches the lower threshold it triggers waking, when it reaches the upper threshold it initiates sleep. NREM sleep EEG SWA is thought to reflect the level of S during sleep. Between then and now, other models have been proposed (Achermann and Borbely, 2017), but most of them have a circadian clock and a sleep homeostatic process incorporated and the concept of two processes influencing sleep physiology and behaviour is generally accepted.

The most important interactions between the two processes occur at the moments where S reaches the upper threshold, transferring from waking to sleep or the lower threshold, changing from sleep to waking. One can question whether these are the only moments during the day that the two interact and work together. It is known that the two processes can function independently of each other. In rats it was shown that sleep homeostasis still functions without the endogenous circadian clock, as NREM sleep and SWA still increase after a sleep deprivation in SCN lesioned animals (Tobler et al., 1983; Trachsel et al., 1992), or when the SCN is not functioning because of genetic manipulation (Wisor et al., 2002), or manipulations with light pulses (Larkin et al., 2004). On the other hand, it was shown in humans that shifting the circadian clock by bright light in the morning can change the phase of the clock, but does not change the depth of sleep (Dijk et al., 1987). This indicates that the two processes are regulated separately and independently and do not seem to influence each other. However, from the beginning of the conception of the model it was suggested that a continuous interaction between the two processes may occur. When the model was proposed one example of its predictive value was the rating

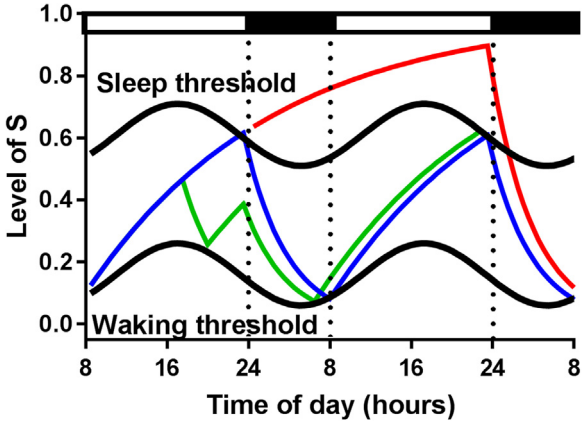

Fig. 2. The two process model of sleep regulation. A simplified representation of the two process model of sleep regulation, similar to the version of the model in the initial publication (Borbely, 1982). Simulation of the homeostatic process S according to different experimental conditions within a two day period. The normal sleep wake timing is indicated by black and white bars, respectively. The blue line indicates the baseline condition with 8 hours of sleep and 16 hours of waking. During the time period that the blue line increases the model is awake. When it reaches the upper threshold (the upper sinusoidal black line) the model goes to sleep and the line decreases. This process continues until it reaches the lower threshold and the model awakens again. The green line indicates the effects of a 2-h nap starting around 18:00 followed by a normal night of sleep. The red line indicates sleep deprivation (40 h of continuous waking by skipping a night) and recovery sleep during the following night. Note that the model assumes that naps and sleep deprivations have no effect on circadian regulation on the next day.

of fatigue over a sleep deprivation experiment lasting 3 days (Daan et al., 1984). Fatigue showed a clear circadian rhythm rising in the night and decreasing during the day, but it also showed a general increasing trend over the three days (Akerstedt Froberg, 1981; Froberg et al., 1975). Assuming that fatigue in the model is the distance between the lower threshold of process C and the level of process S, this time course of a circadian modulation mixed with a gradual increase over days could be modelled quite well.

Knowledge on this mutual influence on output parameters was greatly expanded in the 1990 with help of the forced desynchrony protocol where in human subjects sleep and waking were systematically shifted over the circadian phase. It was shown that many objective and subjective measures were influenced by sleep homeostatic and circadian components as it was shown that they were changing with the phase of the endogenous clock, but also with the duration of prior sleep and waking. This was not only true for the amount and quality of sleep (Dijk and Czeisler, 1995), but also for sleep spindles (Dijk et al., 1997), EEG activity during waking (Cajochen et al., 2002), and different objective and subjective performance measures, like subjective alertness, sleepiness, sustained vigilance, memory, and visual search tests (Dijk et al., 1992; Horowitz et al., 2003, Monk et al. 1997; Wyatt et al., 1999).

More recently, by combining total sleep deprivation protocols with protocols that allow regular naps, it was confirmed that the circadian modulation of several objective and subjective measures is influenced by the level of the sleep homeostatic process. Psychomotor vigilance (Blatter et al., 2006), sequence learning (Cajochen et al., 2004), sustained vigilance (Graw et al., 2004), subjective wellbeing (Birchler-Pedross et al., 2009), skin temperature and sleepiness (Krauchi et al., 2006) and certain features in the EEG, like spindle frequency activity (Knoblauch et al., 2002), showed a circadian modulation that was influenced by the previous amount of sleep and waking. In general circadian amplitude was reduced when sleep pressure was increased. Data obtained with fMRI confirms that activity in cortical regions is influenced by a combination of sleep pressure changes and circadian phase, whereas subcortical region seem to mainly follow the endogenous circadian clock and are less influenced by sleep pressure changes (Muto et al., 2016).

From the data available there is little doubt that homeostatic changes in sleep pressure exist. This homeostatic sleep pressure is reflected in EEG SWA during NREM sleep. One can question whether, within all the data collected in the past, there are clues of a circadian modulation of sleep pressure. From forced desynchrony data and from the nap protocols it is clear that there is a systematic modulation of sleep latency over circadian phase, with longer sleep latencies in the endogenous evening phase (Lavie 1986; Dijk and Czeisler, 1995; Knoblauch et al., 2002; Krauchi et al. 2006; Birchler-Pedross et al. 2009). The inverse time course of this circadian modulation of sleep latency can be taken as a marker for sleep pressure at that circadian phase (Fig. 3). The time course of the changes in homeostatic and circadian sleep pressure may give a combined time course of sleep pressure which is thought to maintain a low level of sleep pressure throughout the active daytime period, subsequently shows an acute peak at sleep onset, and gradually decreases during the main sleep period (Edgar 1996; Dijk and Edgar 1999). However, the model is quite crude and quantification is lacking. To bring this further, more data, investigating the influence of the circadian clock on sleep timing and sleep pressure, needs to be collected.

The available data show that the circadian clock and sleep homeostat both influence the same processes in humans. Whether this is a linear addition or whether this combined influence is non-linear has been a matter of debate for fatigue and other variables related to sleep and alertness, and this has not been completely resolved (see for instance Achermann, 1999 and Dijk et al., 1999). Also in this aspect most models agree: The two processes can influence the same output marker and together they explain a significant part of the patterns observed. There is also the possibility that disruption of sleep or circadian rhythms results in peripheral disturbances that could in turn impact sleep homeostasis or circadian clock functioning. However, this does not automatically mean that the two processes influence each other. It is likely that these variables show an interaction between clock and sleep homeostat because both influence these processes down-stream. Core body temperature and melatonin release are considered to be two strong and reliable markers for functioning and timing of the circadian clock in humans. Both did not show any changes related to changes in sleep pressure (Birchler-Pedross et al., 2009; Krauchi et al., 2006) and either of the two is used as a circadian marker in virtually all studies reported here. The question remains whether longer sleep deprivations, including a second night period, will change this image, but until then these data cannot be considered as evidence of a direct interaction between sleep homeostasis and the circadian clock. Therefore, the question remains whether the homeostatic process is influenced by the time of day or endogenous phase of the circadian clock? *Vice versa*, does the functioning of the circadian clock change under influence of changes in the level of the presumed sleep homeostat?

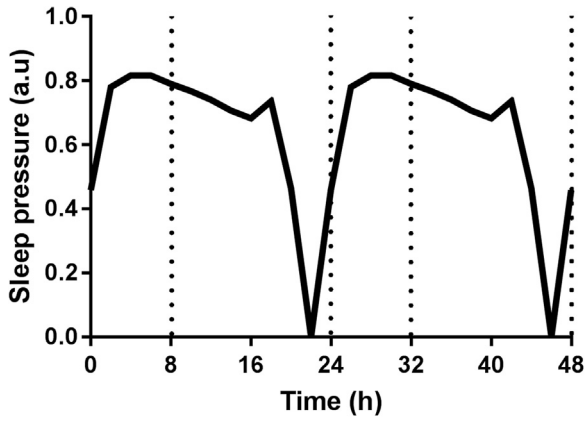

Fig. 3. Circadian modulation of sleep pressure The panel shows the inverse of sleep latency (in artificial units) over circadian time as recorded in the forced desynchrony protocol by Dijk and Czeisler (1995, redrawn from Fig. 2) which can be used as a marker for circadian sleepiness. The combined modulation of circadian sleepiness together with sleep homeostatic changes in sleep pressure is thought to enable maintenance of a low level of sleep pressure throughout the day with an acute drop in the evening (the peak in wake maintenance) shortly before the main sleep period starts.

4. The influence of the clock

For the first question the data available are rather limited as this question is not addressed directly very often. However, three types of approaches provide data that may give us an idea whether there is an influence of the clock on sleep homeostatic mechanisms. There are data available in clock gene mutant or knock out mice showing changes in sleep. There are data gathered under constant routines or forced desynchrony protocols that show a circadian modulation in SWA, and there are some modelling studies showing discrepancies with the available data when subjects sleep outside of the normal circadian sleep period.

4.1. Clock genes and sleep

There is evidence for a role of clock genes in sleep homeostasis (Deboer, 2007; Franken, 2013). Knocking out one or more of the main clock genes (Period: *Per1-3*, *Clock*, *Bmal1*, Cryptochrome: *Cry1* and *Cry2*, *Npas2*) (Albrecht, 2002) changes or disables the circadian clock, but it also modifies sleep homeostatic markers, which seems to suggest that sleep homeostasis and circadian regulation may interact on the molecular and genetic level. *Cry1-Cry2* double knockout mice lack a functional circadian clock and are behaviourally arrhythmic under constant dark conditions (Van der Horst et al., 1999; Vitaterna et al., 1999), but they also show increased NREM sleep, increased sleep consolidation and increased EEG SWA, as if homeostatic sleep pressure is increased in these mice (Wisor et al., 2002). In contrast, *Clock* mutant mice, which also lose rhythmicity in constant darkness (Vitaterna et al., 1994), sleep less than wild type mice (Naylor et al., 2000), and *Bmal1* and *Npas2* knockout mice show altered EEG SWA and altered responses to sleep deprivation (Franken et al., 2006; Laposky et al., 2005). Single *Per*-knockout mice did not show a sleep homeostasis phenotype (Kopp et al., 2002), however *Per1,2* double knockout mice seemed to show an increase in EEG SWA (Shiromani et al., 2004), suggesting increased sleep pressure in these mice. The latter would mean that *Per* signalling is also involved in sleep homeostasis.

In invertebrates this type of information is less easy to assess. Recently a brain circuitry has been identified which seems to control sleep homeostasis (Donlea et al., 2018), but an intensity dimension of sleep is harder to determine in this group of animals. However, there is evidence from research in *Drosophila* that supports the notion that clock genes are implicated in the homeostatic regulation of sleep. Fruit flies lacking the *cycle* gene, a homolog of *Bmal1,* display an overshoot of compensatory sleep after sleep deprivation (Shaw et al., 2002) and the animals die when the deprivation lasts longer than 10 h.

In humans the role of clock genes has been assessed by investigating the consequences of naturally occurring polymorphisms of these genes. The human PER3 gene has been shown to occur in two variants with a tandem repeat of 4 or 5. 50% of the population is homozygous for the 4-repeat ($PER3^{4/4}$) and 10% for the 5-repeat ($PER3^{5/5}$) (Nadkami et al., 2005), and the occurrence of $PER3^{5/5}$ is associated with morning types. It turned out that the PER3 polymorphisms affected EEG and behavioural markers of sleep homeostasis, whereas no effect on circadian rhythm parameters were found (reviewed in Dijk and Archer, 2010). The data imply that PER3 in humans, although a member of the PER clock gene family, affects homeostatic aspects of sleep.

Some of the results in mice are quite remarkable. *Cry* double knockout mice and *Clock* mutant mice are arrhythmic and are therefore considered to be almost equivalent to SCN lesioned mice. However, removal of the SCN never resulted in an overall change in sleep amount in rodents (Ibuka et al., 1980; Mistlberger et al., 1983; Tobler et al., 1983; Trachsel et al., 1992), indicating that arhythmicity caused by loss of the SCN may not be the same

as arhythmicity caused by deletion of clock genes. Nevertheless, the data obtained in these animal models suggest that clock genes are also involved in sleep homeostatic mechanisms.

The involvement of clock genes in sleep homeostatic mechanisms is likely to occur in brain areas outside of the SCN as it was shown that clock gene levels outside of the SCN (for instance in the cortex) are changed in clock mutant mice and also change in response to sleep deprivation. *Per1* and *Per2* are increased in *Cry* double knockouts (Rutter et al., 2002; Wisor et al., 2002; Yamaguchi et al., 2000) and decreased in *Clock*-mutant mice, suggesting that *Per1* and *Per2* expression and sleep pressure have a positive relationship. This notion is corroborated by the finding that Per expression increases as a function of prior sleep deprivation duration (Franken et al., 2007). In addition, it was shown that the changes vary with time of day (Curie et al., 2013), suggesting that the expression of *Per2* depends on the interaction between sleep-wake driven factors and the circadian clock. *Per2* levels came back to baseline levels within 2 hours after start of recovery sleep (Franken et al., 2007; Wisor et al., 2008) confirming its close relationship with sleep homeostatic mechanisms. Remarkably, clock gene levels in the SCN do not seem to be influenced by sleep deprivation (Curie et al., 2015), but the latter was determined on only one circadian time point and these experiments need to be expanded to cover the entire circadian day. How sleep-wake state or sleep deprivation influences clock-gene expression is unclear, but it was proposed that these are, at least in part, mediated by changes in the level of Clock and Npas2-Bmal1 protein and that it enables the animals to respond to restrictions in the environment, like for instance food availability, in a behaviourally flexible way (reviewed by Franken, 2013). New data on how sleep deprivation changes clock gene expression acutely and over the next few circadian cycles, in the SCN and elsewhere in the body, will reveal if and where in the body sleep deprivation might interact with circadian timekeeping mechanisms.

4.2. Electroencephalographic evidence

The assumption that the circadian clock influences sleep timing is strongly supported by experimental results demonstrating that spontaneous awakenings after initiating sleep at different times of the day show a distribution that fits within the concepts of the two process model (Borbely, 1982; Daan et al., 1984). Also the forced desynchrony experiments (Dijk and Czeisler, 1995) and the nap protocols (Carskadon and Dement, 1975; Carskadon and Dement, 1980; Munch et al., 2007) in humans demonstrate clearly that the circadian clock supports waking, and maybe also sleep, at the appropriate time of the day. In particular it was shown that subjects found it difficult to maintain sleep around the maximum of the endogenous core body temperature rhythm (Dijk and Czeisler, 1995). In the previous section it was shown that SWA in undisturbed NREM sleep is a function of the time awake and that this relationship is very predictable. However, there is some evidence suggesting that there may be an influence of the phase of the endogenous clock on the level of SWA as well.

From data obtained in the forced desynchrony protocol and nap protocols it is clear that SWA in NREM sleep shows a modest, but significant, modulation over circadian time (Dijk and Czeisler, 1995; Munch et al., 2007). It is not completely clear whether this represents an endogenous circadian modulation of SWA, independent of the sleep homeostatic process, or whether it can be explained by the uneven distribution of sleep and waking over circadian phase due to sleep deficiencies around the maximum of core body temperature and the circadian peak in REM sleep just after the minimum of core body temperature (Dijk and Czeisler, 1995).

A 2 h/2 h nap protocol experiment in the rat showed no significant modulation of SWA when sleep was more or less equally distributed across the day (Yasenkov and Deboer, 2010, 2011), suggesting that the circadian modulation of SWA in humans is caused by the remaining unequal distribution of sleep and waking due to the stronger influence of the circadian clock on sleep wake distribution in humans compared to the rat.

4.3. Modelling sleep homeostasis

Additional clues come from the modelling field. Modelling the changes in SWA or process S based on the assumption that a homeostatic process keeps track of the duration of prior waking and sleep has been highly successful. However, there are conditions where the modelling is more successful than in others. There seems to be a consistency in these hits and misses as it is clear from the literature that modelling works best when applied to data from subjects sleeping at the normal phase of the circadian cycle. When sleep was timed differently (Achermann et al., 1993), or when afternoon naps were introduced (Werth et al., 1996), the goodness of fit decreased. Simulations in animal models were mainly performed in rats and mice. In the mouse no additional modifications of the model were applied (Huber et al., 2000). However, in the rat differences in modelling success and model time constants were obtained between sleep deprivations performed in the light or dark period (Vyazovskiy et al., 2007). Also different time constants for the rest and active phase were introduced to optimize the fit of the model both under light-dark conditions (Franken et al., 1991) and in constant darkness (Deboer, 2009). It shows that the success of modelling sleep homeostasis in humans and rats depends on the circadian phase. There have been some attempts to incorporate a circadian modulation in the homeostatic process (Dijk and Archer, 2010; Putilov, 1995), and it was suggested that these models were more successful than the original “pure” homeostatic models. However, these attempts have been rare and the data collected to test these models usually show too much variation to appreciate their additional value.

Together the EEG data and modelling results suggest that there may be a difference in the speed of the homeostatic processes depending on internal circadian phase. This could be caused by an endogenous circadian modulation of EEG slow-wave production or the homeostatic processes, which basically means an unknown cause. However, it could also be caused by differences in the quality of sleep, due to circadian induced interruptions with waking and REM sleep, or a difference in the quality of previous waking due to, for instance, a circadian modulation of alertness. Clearly not enough is known about the possible influences of the circadian clock on sleep homeostatic mechanism and more data, and simulations, are needed to be able to tackle this question.

5. The influence of the homeostat

In the opposite direction, on the question: *Does the functioning of the circadian clock change under influence of the level of the sleep homeostat?* much more research has been performed. These are mainly findings obtained with sleep deprivation, which not only changes subsequent depth of sleep, but was also shown to change light responsiveness and phase shifting capacity of the circadian clock.

5.1. Behavioural studies

Properly timed light pulses will phase shift the circadian clock (Meijer and Rietveld, 1989). In mice and hamsters, sleep deprivation attenuates these phase shifts induced by light (Challet et al., 2001; Mistlberger et al., 1997; Van Diepen et al., 2014), suggesting that increased sleep pressure reduces circadian clock responses to this zeitgeber. Similarly, in humans attenuated phase advances to light were found after sleep restriction (Burgess, 2010). These data suggest that sleep deprivation reduces light responsiveness or phase shifting capacity of the clock in diurnal and nocturnal animals.

More recently it was found in the grass rat (*Arvicanthis ansorgei*), a day active rodent, that sleep deprivation enhances light induced phase shifts (Jha et al., 2017). In contrast to previous findings, it was suggested that diurnal animals will show increased phase shifting after

sleep deprivation, whereas nocturnal animals will show a decrease. This result is surprising considering the previous results obtained in rodents and humans and more data in different diurnal and nocturnal species are needed to resolve this issue.

5.2. Suprachiasmatic nucleus neuronal activity

Neuronal activity in the SCN can be recorded with electrophysiological techniques. It shows that the electrical spiking activity of the SCN neurons is high during the subjective day and low during the subjective night, both in diurnal and nocturnal animals (Sato and Kawamura, 1984; Vansteensel et al., 2007). When this activity is recorded simultaneously with EEG and EMG it was shown in rats that SCN neuronal activity increases during waking and REM sleep and decreases during NREM sleep (Deboer et al., 2003). These increases and decreases were visible on top of the circadian modulation. Slow-wave deprivation during NREM sleep, reducing SWA but still allowing the animals to sleep, resulted in an increase in SCN neuronal activity (Deboer et al., 2003). Increasing SWA by sleep deprivation led to a decrease in SCN neuronal activity, which gradually returned to baseline values, parallel to the decrease in SWA, in the course of recovery sleep (Deboer et al., 2007).

There is a negative relationship between SCN electrical neuronal activity and depth of sleep or sleep pressure. This negative relationship may also exist in humans. The SCN is small and difficult to investigate, however the fMRI BOLD signal in human subjects, recorded during a psychomotor vigilance task, declined in the area around the SCN when sleep pressure was increased (Schmidt et al., 2009). This change in BOLD signal in the evening correlated with SWA in the first nocturnal NREM sleep episode. Thus, the circadian pacemaker in the SCN seems to obtain feedback on the status of the sleep homeostat, in a way that increased sleep pressure reduces SCN neuronal activity and the circadian amplitude of the output of the SCN.

5.3. Serotonin or adenosine release as a possible mechanism

Together the data show that sleep deprivation reduces activity of SCN neurons and diminishes the phase shifting capacity of the circadian clock in response to light. Can there be inhibition of SCN neuronal activity coming from sleep regulatory centres? The PPT and LDT provide cholinergic input to the SCN (Bina et al., 1993) and also serotonergic projections from the raphe to the SCN have been described (Moore et al., 1978). It is unlikely that a short lasting sleep deprivation affects the cholinergic system of te PPT/LDT as chronic sleep deprivation of 10 days resulted in only small changes in acetylcholine receptor binding (Tsai et al., 1994).

Interestingly, brain serotonin turnover is increased after short (4–6 h) sleep deprivation (Asikainen et al., 1995, 1997). Serotonin levels increase in the SCN during sleep deprivation (Grossman et al., 2000), and serotonin is known to reduce SCN neuronal activity in vitro (Yu et al., 2001). Moreover, impairment of serotonin transmission could partially restore the phase shifting capacity of light (Challet et al., 2001). Serotonin and its agonists has a phase shifting capacity of its own (Prosser et al. 1990). However, in vivo application of the latter mainly results in time of day dependent advances but no delays (Edgar et al., 1993b). Therefore changes in serotonergic activity may underlie the observed changes in SCN neuronal activity after sleep deprivation and may be the basis for spontaneous phase shifts after sleep deprivation.

Alternatively, the reduction in neuronal activity may also be caused by an unspecific increase in adenosine levels, which are known to increase due to prolonged waking (Porkka-Heiskanen et al., 1997) and generally induce a suppression of neuronal activity. Light shifts the clock in the SCN via retinal ganglion cells and the retino-hypothalamic tract (RHT, Vansteensel et al., 2007). Following activation by light, glutamate is released at the nerve terminals of the RHT (Ding et al., 1994; Johnson et al., 1988), leading to increased neuronal activity in the SCN (Meijer et al., 1998; Van Diepen et al., 2013). Application of glutamate to the SCN mimics this effect of light (Ding et al., 1994). Sleep deprivation may reduce the phase shifting capacity by diminishing the strength of the photic signal from the RHT, possibly through blocking of glutamate release. One of the possible inhibiting signals may be an increase in adenosine, which is thought to be involved in sleep regulation (Landolt, 2008). This may, therefore, be the mechanism by which sleep deprivation reduces the light responsiveness of the circadian clock. The conclusion would be that the sleep homeostat reduces light responsiveness of the circadian clock in mammals on the input side of the SCN by excess adenosine reducing the release of glutamate when light information is transmitted from the retina to the SCN. This is supported by data showing that application of an adenosine agonist attenuates light-induced phase delays in behaviour, which subsequently can be restored by an adenosine receptor antagonist (Elliot et al., 2001; Sigworth and Rea, 2003). In accordance with that, a 6-h sleep deprivation in mice reduces the electrophysiologically recorded responses of SCN neurons to light compared to control, and caffeine, a general antagonist of adenosine, restores this response (Van Diepen et al., 2014). Caffeine also strengthens phase shifting effect of light in the day active grass rat and in humans (Burke et al., 2015; Jha et al., 2017). These data support the notion of an interactive role of adenosine and glutamate on SCN clock functioning. As adenosine is considered to be an important endogenous substance involved in sleep regulation, it may be the linking pin between sleep homeostatic mechanisms and its influence on the circadian clock.

Although there seems to be a clear influence of changes in sleep pressure on the phase shifting capacity of the circadian clock, until now it was not shown that expression of clock genes in the SCN changes under influence of sleep deprivation (Curie et al., 2015). This is corroborated by the finding that sleep deprivation *per se* does not change the phase of the circadian clock in hamsters (Mistlberger et al., 2003) and no (Challet et al., 2001) or only minor shifts (Van Diepen et al., 2014) were found in mice. Also the amplitude of circadian clock output markers in humans, like melatonin release or core body temperature, does not change under influence of increased sleep pressure (Krauchi et al., 2006; Birchler-Pedross et al., 2009). Therefore, the influence of homeostatic sleep pressure on the central circadian pacemaker may be on clock input or output, possibly changing the response to phase shifting zeitgebers, but not directly on clock gene expression and the phase or period of the clock.

6. Conclusion

Fig. 4 summarizes the findings collected in this review. The circadian clock and sleep homeostatic mechanisms together regulate the occurrence of sleep and waking. From the evidence, it can be concluded that more research is needed on the question whether the endogenous circadian clock is influencing sleep homeostatic mechanisms. There is evidence from clock gene mutant and knockout animals, which show changes in amount and depth of sleep, that these genes may also be involved in sleep homeostasis. The other findings, based on recording of EEG SWA at different circadian phases and modelling of sleep homeostatic mechanisms, particularly of sleep timed outside of the normal circadian sleep phase, also suggest that there may be an influence of the circadian clock on sleep homeostasis. However, also here a mechanism is lacking. It is not clear whether this effect is due to an influence of the clock on the distribution or quality of sleep and waking, or has another circadian origin. In general a clear mechanism is lacking and the evidence of an influence of the circadian clock on sleep homeostatic mechanisms.

On the other hand, it can be concluded that it is very likely that there is an influence of sleep homeostasis on the functioning of the circadian clock (Fig. 4). There is no evidence that this results directly in changes in the endogenous period of the clock, but longer sleep

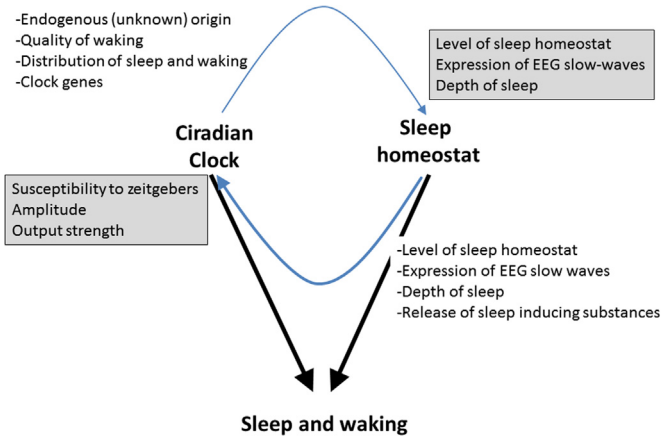

Fig. 4. Effects of circadian clock and sleep homeostat A summary of the putative effects of the circadian clock on sleep homeostatic mechanism and *vice versa*. In the old situation, the circadian clock and the sleep homeostat both are acting on sleep and waking shaping sleep-wake behaviour, which is represented by the black arrows. Putative mechanistic influences of the circadian clock (Top left) and the sleep homeostat and of the sleep homeostat (Bottom right) on the circadian clock are listed. In grey boxes the consequences of these influences are listed on the side of the affected process. In this new situation the clock and sleep homeostat influence each other's functioning, which is represented by the blue arrows. The thickness of the arrows represents the strength of this putative influence in which the present data suggest that the influence of the sleep homeostat on the circadian clock is larger than the reciprocal influence.

deprivation experiments, including a second circadian cycle may shed more light on this issue. There does seem to be an influence of sleep homeostatic pressure on the amplitude of the circadian clock and on circadian clock functioning. This could meant that there is a reciprocal relationship which, under normal conditions, would be beneficial for the organisms, as a strong rhythm will benefit sleep, and good healthy sleep will strengthen clock functioning. When disturbed, however, this reciprocal relationship may also strengthen in a vicious circle and disturbed sleep may result in a less functional circadian clock, which in its turn reduces the quality of sleep.

Most clear are the effects of sleep deprivation on light induced phase shifts, which are significantly reduced in most cases. The light information seems to reach the clock less well when an animal is sleep deprived. The opposing effect of caffeine and serotonin antagonists suggests that adenosinergic and serotonergic inhibition of neuronal activity is involved in this reduced response. The latter knowledge may have practical relevance. In modern society humans get exposed to conditions that induce sleep deprivation or sleep restriction, in combination with adjustments to changed zeitgebers. The most common situations are shift work and jet lag. Both require that rest-activity behaviour is adjusted to a new external time, whereas at the same time sleep is compromised. The insight that sleep deprivation induced mechanisms may influence responsiveness of the circadian clock to zeitgebers can help alleviate the adverse effects of these circumstances, for instance by introducing nap protocols or timed consumption of caffeinated beverages.

Conflict of interest

I wish to confirm that there are no known conflicts of interest associated with this publication and there has been no significant financial support for this work that could have influenced its outcome. I confirm that the manuscript has been read and approved by all named authors and that there are no other persons who satisfied the criteria for authorship but are not listed. We further confirm that the order of authors listed in the manuscript has been approved by all of us. I confirm that we have given due consideration to the protection of intellectual property associated with this work and that there are no impediments to publication, including the timing of publication, with respect to intellectual property. In so doing we confirm that we have followed the regulations of our institutions concerning intellectual property. I further confirm that any aspect of the work covered in this manuscript that has involved either experimental animals or human patients has been conducted with the ethical approval of all relevant bodies and that such approvals are acknowledged within the manuscript.

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