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Review Paper

# The times they're a-changing: Effects of circadian desynchronization on physiology and disease

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ABSTRACT

Circadian rhythms are endogenous and need to be continuously entrained (synchronized) with the environment. Entrainment includes both coupling internal oscillators to external periodic changes as well as synchrony between the central clock and peripheral oscillators, which have been shown to exhibit different phases and resynchronization speed. Temporal desynchronization induces diverse physiological alterations that ultimately decrease quality of life and induces pathological situations. Indeed, there is a considerable amount of evidence regarding the deleterious effect of circadian dysfunction on overall health or on disease onset and progression, both in human studies and in animal models. In this review we discuss the general features of circadian entrainment and introduce diverse experimental models of desynchronization. In addition, we focus on metabolic, immune and cognitive alterations under situations of acute or chronic circadian desynchronization, as exemplified by jet-lag and shiftwork schedules. Moreover, such situations might lead to an enhanced susceptibility to diverse cancer types. Possible interventions (including light exposure, scheduled timing for meals and use of chronobiotics) are also discussed.



**Contents**



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## 1. Introduction

As a species, we have evolved on a planet that imposes specific periodicities in our physiology and behavior: the day and the year. Most (if not all) organisms have developed the ability to keep track of daily time by means of an endogenous circadian timing system originating in internal oscillators or biological clocks. Such clocks are autonomous and generate an about-24 h rhythm (i.e., "circadian", about a day) that needs to be entrained to the environment in order to cope with periodic changes in food availability, light exposure or predatorial risks. The best known mechanism for circadian entrainment is involving light, which in mammals stimulates specific retinal cells whose axons form a retinohypothalamic tract ending in the suprachiasmatic nuclei (SCN), the site of the central circadian clock (Golombek and Rosenstein, 2010). Besides the SCN, a number of independent peripheral oscillators have been described that maintain their period and phase when assessed in isolation, although the central clock is probably needed to synchronize temporal physiology in the whole organism (Dibner et al., 2010).

Humans are diurnal species that orchestrate their internal variables throughout the day; in general, cognitive and physical variables demanding a high metabolic rate and high energy requirements tend to peak in the diurnal hours, whereas repair, consolidation and growth mechanisms tend to peak in the night. However, social constraints conspire against the pure diurnality of our species. Indeed, work, services and even school schedules have turned most of the population into a so-called 24-h society which is forced to perform outside its natural temporal scope. There are estimates that claim that about half of the population in industrialized societies exhibit circadian rhythms that are out of phase with their imposed daily schedule (Lee Philips, 2009). The new term of "social jet-lag" has arised to describe this phenomenon (Wittmann et al., 2006), taking into account the interindividual variability in temporal preferences of the population (i.e., chronotypes) which might vary from the extreme morning ("lark") type to the extreme nocturnal ("owl") type. When forced into social jet-lag, the appearance of disrupted circadian rhythms might lead into different pathological situations. In addition, internal desynchronization between the SCN and peripheral clocks will also result in health disorders, including sleep, metabolic and even psychiatric conditions.

Another important consideration is that chronotypes are not fixed throughout development. For example, adolescents are extreme owls who definitely suffer from social jet-lag when forced into the very early schedule of high school. As a result, their alertness rate is usually low in the early morning, and slightly changing such schedule (by delaying the start of classes by 30–60 min) results in increases in academic and sports performance, better mood and a decrease in medical visits (Carskadon, 2011; Wahlstrom, 2010; Wolfson and Carskadon, 2003).

However, the best known examples of desynchronization with environmental conditions inducing social jet-lag refer to two situations in which internal time (as dictated by the endogenous clock) is out of synchrony with the outside clock time: transmeridian flights (jet-lag) and shiftwork (Sack et al., 2007; Waterhouse, 1999). The transmeridian traveler experiments abrupt changes in geophysical cues (such as the timing of the light-dark cycle) as well as in social cues and mealtimes, inducing a progressive realignment of the circadian system (Sack, 2010; Waterhouse et al., 2007). This situation is chronical for the shiftworker, who experiments such changes periodically and needs to cope with their changing days and nights (Driscoll et al., 2007). Both situations induce a decrease in the quality of life and might induce disease; indeed, a report from the World Health Organization concluded that "shift-work that involves circadian disruption is probably carcinogenic to humans" (Straif et al., 2007). A rough estimation indicated that about 20% of the workforce (at least in the United States of America) are subjected to shiftwork – while in some types of industrial organizations the percentage rises to about 50% of the working population. These workers share with frequent travelers (in particular, airline pilots and crew) an increased susceptibility to gastrointestinal and cardiovascular disorders, in addition to the more common sleep disruptions (Sack et al., 2007). In addition, as we shall discuss later, circadian disruptions are associated with severe metabolic changes, since the circadian system synchronizes energy use and expenditure (Maury et al., 2010). Indeed, when the system is not properly regulated, there is a clear disbalance in the autonomic nervous system leading to metabolic disease. Since the two main output channels for the circadian clock are through humoral release or sympathetic/parasympathetic relay stations, alterations in entrainment and/or rhythm generation will result in alterations of integratory mechanisms in the body (Golombek, 2012), including metabolic syndrome and even immune disease. Different kinds of interventions have been suggested for desynchronization-related situations, including phototherapy, scheduled sleep (including naps), alertness-enhancing drugs (such as modafinil) and chronobiotics, i.e., drugs that are able to change the hands of the circadian clock, such as melatonin (Arendt and Skene, 2005; Czeisler et al., 2005; Waterhouse et al., 2007).

The general effects of desynchronization (in particular, when it occurs chronically) can be observed in different dimensions of physiology. In this review we shall focus on the different models to study desynchronization processes, as well as their general effects in health, cognition and the immune system.

## 2. Synchronization to light/dark (LD) cycles

Temporal synchrony between the organism and the environment is achieved by entrainment of the circadian clock, setting physiological and behavioral rhythms fine-tuned with environmental resources to optimize metabolic processes (Menaker, 2006). Since the circadian period ($\tau$) is slightly deviated from 24 h, systematic changes induced by the light-dark (LD) cycle in the circadian period and/or in the circadian phase of the clock are needed for correct synchronization with the LD *zeitgeber* ("time giver", $T$). This is achieved through both chronic effects on the endogenous period by the LD cycle and the acute effects of light on circadian phase (i.e., a light-pulse induced phase shift). The magnitude and direction of these phase-shifts depend on the timing of the stimulus; briefly, phase-delays are generated when a light-pulse is received during the early night, while phase advances are elicited during the late night; this time-dependent effects configure a phase response curve (PRC) (for a review, see Johnson et al., 2003). Thus, synchronization depends on the establishment of a specific phase-relationship between the LD cycle and the circadian clock, with a steady-state elicited phase-shift which accounts for the $\tau - T$ difference (for a review, see Roenneberg et al., 2003).

When abrupt changes in the phase-relationship between the zeitgeber and the clock are imposed, as occurs during advancing or delaying LD cycles (e.g., jet-lag), a transient resynchronization mechanism of the clock is generated until steady-state is reestablished. In addition, LD cycles with a $T$ period different from 24 h (i.e., $T$ cycles) can induce an abnormal phase relationship between environmental and endogenous timing (Plano et al., 2010; Schwartz et al., 2011).

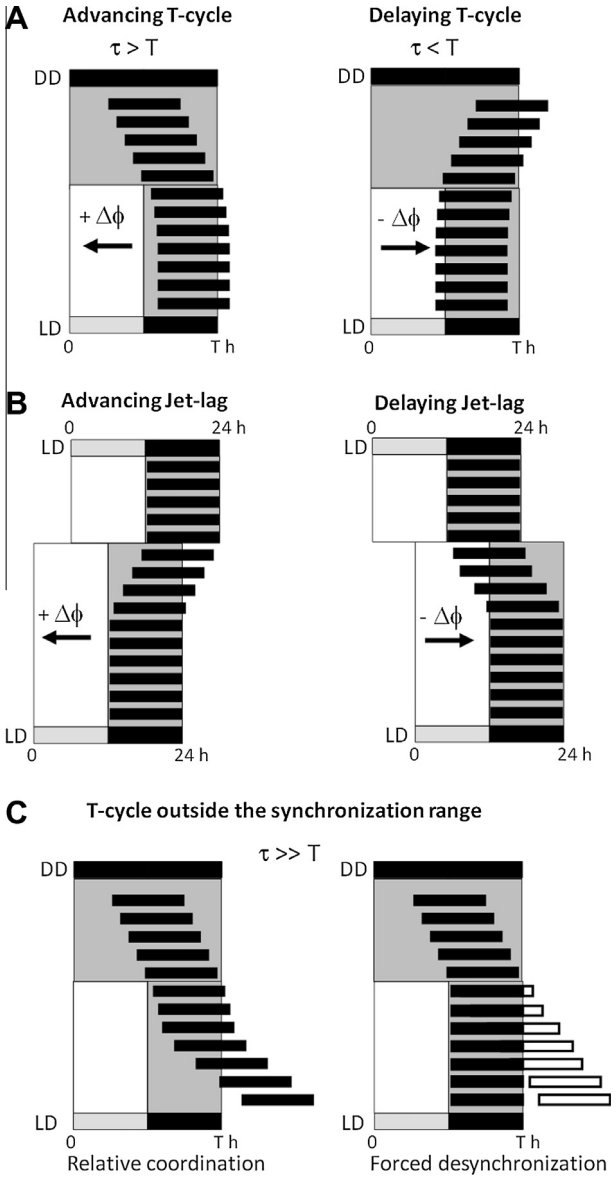


**Fig. 1.** Entrainment process of a behavioral rhythm (e.g., locomotor activity) in a nocturnal rodent with different examples of desynchronization. Schematic actograms are presented, where the black blocks represent the daily activity bouts in a vertical progression through the successive days under the different conditions. The clear and shaded areas represent the light and dark conditions, respectively. (A) Actograms representing an initial condition under constant dark (DD), where circadian rhythms assume the endogenous circadian period of the organism. After DD the animals are synchronized to an LD cycle with a period different to 24 h (i.e., a *T*-cycle) within the synchronization range. The panel on the left shows the expected phase-relationship for an advancing *T*-cycle (i.e., when $\tau < T$), when steady-state advances of the phase of the rhythm ($+\Delta\phi$) are imposed. For a delaying *T*-cycle (panel on the right), rhythm is synchronized by steady-state delays ($-\Delta\phi$). In both cases there is a phase difference (delay or advance) between activity onset and the time of lights off. (B) After entrainment to a normal 24-h LD cycle, an abrupt change in the phase of the LD cycle (i.e., an experimental jet-lag) leads to the transient desynchronization of the circadian system before steady-state entrainment is regained. Advancing lights-OFF and ON times induces the resynchronization by advances to the new LD phase (panel on the left), while a delaying jet-lag protocol (right) induces resynchronization by delays. (C) A *T*-cycle outside the synchronization range (in this example, $\tau \gg T$), when the $\tau - T$ difference cannot be compensated by phase advances, leads to systematic desynchronization. A relative coordination of the rhythm (i.e., a modulation of circadian period, as shown in the left panel) is normally observed under this condition. Both under a *T*-cycle of 22 h (de la Iglesia et al., 2004), or an advancing chronic jet-lag schedule (Casiraghi et al., 2012), a dissociation of behavioral rhythm into two components can be observed (as in the right panel), one that is synchronized to the LD schedule (black bars), and a second one (clear bars) that runs in relative coordination.

### 2.1. Abnormal synchronization to LD cycles

In general, alterations in normal synchronization must involve: (1) the inability to process LD cycle information, as in blindness (for a review, see Skene and Arendt, 2007) or senescence (for a review, see Gibson et al., 2009), or (2) conflicts between the circadian phase and the LD cycle. This conflict can be originated by endogenous alterations of the normal phase-relationship, as in genetic disorders of the circadian clock, or by exogenous alterations, both by shifting LD cycles (i.e., in jet-lag), or by shifting the activity/rest cycle (i.e., in shiftwork). Fig. 1 summarizes some typical situations of abnormal entrainment to LD cycles.

#### 2.1.1. Endogenous alterations of entrainment

Some genetic sleep disorders are related to an abnormal synchronization of the clock. In advanced sleep-phase syndrome, patients report daytime somnolence and difficulties to sleep at night (Dauvilliers and Tafti, 2008). This syndrome is associated with a specific mutation in the human clock genes Per2 and Casein kinase Iε (CKI epsilon) (Toh et al., 2001; Xu et al., 2005). The alteration of CKIε and/or CKIδ activity induces changes in the circadian period in mammals (Lowrey et al., 2000; Meng et al., 2008; Xu et al., 2005) by the accumulation of PER-CRY dimers (Akashi et al., 2002; Eide et al., 2002, 2005; Lee et al., 2001). Current treatment for this syndrome includes phototherapy and the use of chronobiotics such as melatonin (or its analogs ramelteon and tasimelteon) or armodafinil (Hirai et al., 2005; Revell and Eastman, 2005; Zisapel, 2001). The *tau* hamster can be considered an animal model for this circadian alteration, where a single autosomal mutation in the enzyme CKIε correlates with a significant decrease in the period of free running activity rhythms (from ca. 24 to ca. 20 h) (Ralph and Menaker, 1988) and endocrine rhythms (Lucas et al., 1999). Delayed sleep phase syndrome is associated with a polymorphism in the PER3 gene (Archer et al., 2003; Ebisawa et al., 2001; Pereira et al., 2005). This syndrome is associated with a misalignment between the phase of the biological clock and the environment causing an abnormal entrainment and altered sleep homeostasis (Okawa and Uchiyama, 2007). Current treatments for this disorder include melatonin administration and bright light exposure during the morning.

#### 2.1.2. Exogenous alterations of entrainment

Classical studies in humans by Jürgen Aschoff show that temperature and activity/rest rhythms can desynchronize under constant conditions or unstable LD synchronization (Aschoff and Wever, 1976). Indeed, changes in the phase relationship between the LD cycle and the circadian system, as those experienced during jet-lag due to rapid travel across multiple time zones, will generate conflictive light information appearing during the subjective night, forcing the circadian clock to be resynchronized to the new schedule. Since the clock is slow to adjust its phase, this exogenous desynchrony may persist for several days, and is frequently accompanied with health alterations, from which the most reported are insomnia, fatigue and sleepiness during the day, as well as gastrointestinal symptoms (for a review, see Sack, 2009). This is thought to arise from the internal desynchronization between circadian oscillators, with different resetting dynamics responding to environmental inputs (for a review, see Harrington, 2010), which was evidenced for instance in airline pilots experiencing jet-lag (Arizanavarreta et al., 2002). The severity of the symptoms depends on multiple factors including the number of time zones crossed and the direction of the travel: eastward travel induces stronger symptoms and a longer duration of jet-lag (Medicine, 2005; Waterhouse et al., 2007). Since the human PRC exhibits larger phase advances than delays (Khalsa et al., 2003), resynchronization to a

shortened day after eastward flights is usually more difficult to achieve; however, since the human circadian period is distributed in a range of 23.8–24.4 h (Wright et al., 2005), the mechanistic base for this asymmetry is still controversial.

As jet-lag experienced after a single abrupt LD shift generates a transient desynchronization between circadian oscillators, chronic jet-lag schedules consisting of frequent and recurrent LD-advances can generate a stable desynchronization of two activity components in animal models (Casiraghi et al., 2012). This phenomenon of forced desynchronization was described previously by imposing a *T* cycle of 22 h outside the limits of synchronization, and seems to be based on uncoupled oscillators at the proper circadian clock in the SCN (de la Iglesia et al., 2004).

## 3. The physiology of desynchronization

Entrainment involves SCN processing of photic information by activation of intracellular transduction pathways leading to the phase-locking of clock gene expression, extracellular communication mechanisms and synchronization of the whole SCN tissue network (Golombek and Rosenstein, 2010). Indeed, the SCN is composed of two functional subregions that differ in their cytoarchitecture, connectivity, topography and histochemistry (Antle and Silver, 2005; Moore et al., 2002) with different patterns of clock gene expression and electrical activity (Aton and Herzog, 2005). Typically, the retinorecipient ventrolateral (VL) cells respond to a photic stimulus during the subjective night with an increase in the expression of clock genes from the Period (Per) family and immediate early genes such as cFos, whereas the dorsomedial (DM) cells shows a circadian oscillation in the expression of these genes. SCN synchronization to an LD cycle depends on gating light information from the VL-SCN to the DM-SCN (Schwartz et al., 2010). Although under steady-state LD synchronization the VL- and DM-SCN oscillations have a constant phase relationship, this coupling can be challenged by different experimental manipulations. Abrupt phase shifts in the LD cycle, which mimic jet-lag changes in time zones, produce quick changes in the phase of the rhythms of electrical activity and clock gene expression in the VL-SCN but not in the phase of the DM-SCN, which takes several cycles to shift (Aton and Herzog, 2005; Nagano et al., 2003; Nakamura et al., 2005). This transient desynchrony between SCN subregions generates desynchrony of its respective physiological outputs with respect to the LD cycle. For instance, when exposed to a forced desynchronization protocol based on LD cycles of 22 h, temperature, rapid-eye movement sleep and melatonin rhythms, coupled to the DM-SCN, are virtually desynchronized from the LD cycle (Cambras et al., 2007; Schwartz et al., 2009). Melatonin, a hormone related with biological timing which is normally secreted during the night under the control of the DM-SCN, is suppressed by light gated at the VL-SCN (Schwartz et al., 2009), and it is associated with low core body temperature and the induction of sleep processes. This nocturnal melatonin pattern is uncoupled from the sleep/wake rhythm in airline pilots suffering jet-lag (Tresguerres et al., 2001), and also in night workers (Dumont et al., 2012). A night shiftworker whose circadian clock is in "day mode", or unadapted, will secrete melatonin during work hours. Similarly, workers who have adapted their clock to the night shift will secrete melatonin during the day and on return to day shift or rest days will secrete melatonin during the hours of natural daylight. In general, the inability to achieve a stable nocturnal activity rhythm will generate a permanent desynchrony. These alterations could explain sleep pattern disruptions and fatigue observed in humans under conflicting LD synchronization such as those occurring during shiftwork, due to the lack of a complete circadian resynchronization, together with an elevated homeostatic sleep pressure during the day (Ohayon et al., 2010).

### 3.1. Desynchrony between central and peripheral clocks

The SCN, as a master circadian clock, synchronizes the peripheral oscillators (such as the retina, liver and kidney, among others) through neuronal and hormonal pathways (Perreau-Lenz et al., 2004; Schibler et al., 2003). During jet-lag, desynchrony occurs between the master circadian clock and the peripheral output clocks, probably underlying many associated disorders (Arendt, 2009). For example, experiments with tissue explants from transgenic mice shows that Per expression rhythms resynchronize faster in the SCN than in any of the other tissues examined (Davidson et al., 2009; Yamazaki et al., 2000). Interestingly, each tissue has a specific dynamics for the resynchronizaton of circadian genes during jet-lag, perhaps due to their precise input pathway (Dibner et al., 2010). One of the most important peripheral oscillators is the adrenal gland, which controls glucocorticoid (GCs) rhythms in the blood (Oster et al., 2006). Adrenal GCs can both reset the peripheral clocks and influence photic synchronization of the activity/rest rhythm (Balsalobre et al., 2000; Sage et al., 2004). Manipulation of the GCs rhythm regulates the speed of behavioral resynchronization to an experimental jet-lag (Kiessling et al., 2010), suggesting a key role for these hormones in the communication of circadian phase.

## 4. Strategies to cope with desynchronization

In general, strategies for a better adaptation to conflictive LD synchronization depend on minimizing the number of days to achieve complete reentrainment (for a review, see Arendt, 2009). Theoretically, a chronic nightwork schedule should be designed aiming at stabilizing the activity/rest rhythm in order to avoid permanent resynchronization, or in more realistic terms, to achieve a compromise phase not incompatible with late nighttime sleep on days off (Lee et al., 2006). For instance, adapting the circadian clock following a transmeridional flight with short stopovers (1–2 days) is not advised, while acceleration of reentrainment rate to the new LD schedule is desired if an extended permanence at the destination is planned. Clock phase can be modified by manipulations of the light input, indirectly by pharmacological manipulations of photic second messengers and melatonin, and by behavioral–social arousing stimuli (for a review, see Mistlberger and Skene, 2004). Timed light exposure (or avoidance) needs to be delivered based on the circadian clock phase in order to achieve the desired phase-change (Paul et al., 2009). In general, avoidance of early morning light and exposure to late-morning and afternoon light alone or in conjunction with bedtime melatonin, can accelerate re-entrainment following eastward travel. For westward travel, a circadian delay can be achieved after arrival with afternoon and early-evening light exposure, together with bedtime melatonin administration (for a review, see Kolla and Auger, 2011 or Zee and Goldstein, 2010). In addition, a combination of afternoon melatonin administration, morning bright light, and a gradually advancing sleep schedule proved to be effective in the advance of circadian phase by about 1 h/d (Revell et al., 2006). However, light treatment was ineffective to accelerate resynchronization and reduce jet-lag symptoms after a westward flight (Boulos et al., 2002). In some field studies with humans simulating nightwork, light applied with a diurnal pattern improved the synchronization of the melatonin rhythm to the diurnal rest (Dumont et al., 2009).

Using an experimental jet-lag protocol in hamsters, changes in the cGMP-related signal transduction achieved by inhibiting cGMP enzimatic degradation accelerated resynchronization after an abrupt advance in the LD cycle (Agostino et al., 2007). Another

possible target is the serotonergic pathway from the raphe nucleus to the SCN. NAN-190 (which activates autoreceptors and functionally antagonize post-synaptic receptors) potentiates the response to light (Kessler et al., 2008; Lall and Harrington, 2006) and accelerates re-entrainment to a 6 h advance of the light dark cycle (Kessler et al., 2008). Melatonin is used in totally blind people to favor the acquisition of a stable 24 h period (for a review, see Skene and Arendt, 2007). Social stimuli were also effective in totally blind people under laboratory conditions, but there is no effect of social synchronization in bilaterally enucleated blind subjects (Mistlberger and Skene, 2004).

## 5. Temporal disruption and human health

Non-stop 24/7 schemes of production and services are widely present in contemporary society, including factories, hospitals, public and private transport, security, and many others. This operation requires the application of schedules of nocturnal work as well as rotating shiftwork schedules. Airline workers who perform frequent transmeridian flights are subjected to a similar situation when daily cues are continuously changing. A vast amount of bibliography accounts for the great number of health challenges observed in people working under these circadian-stressing routines (Costa et al., 2010; Folkard, 2008). Health problems associated to work-related temporal disruption include cardiovascular and gastrointestinal diseases, metabolic alterations, sleep disorders, and notably, elevated cancer rates.

The incidence of electrocardiographic left ventricular hypertrophy and increased systolic blood pressure is significantly higher in pilots compared to general population (Ekstrand et al., 1996). More specifically, shiftworkers have been reported to show increased cardiovascular disease risk (Peter et al., 1999), obesity, high triglycerides, and low HDL cholesterol concentrations among other indicators of potential metabolic syndrome (Al-Naimi et al., 2004; Karlsson et al., 2001, 2003). Workers on rotating night-shifts exhibit desynchrony between melatonin levels, which normally rise in the night, and diurnal sleep time (Dumont et al., 2009). Indeed, the onset of melatonin secretion changes across the week of both day and night shifts, without circadian adaptation to this lifestyle and with sleep disorders (Ferguson et al., 2011).

The health sector is one of the most studied work environment in relation to shift- and night-working. Not only the workers' health may be at stake due to extreme working schedules, but potential risks for inpatients may also arise due to poor sleep and attention levels. The results from two large, well-established, long-term cohorts in a Nurses' Health Study suggest a positive association between extended rotating night shiftwork and type 2 diabetes risk (Pan et al., 2011). Physicians observed a high incidence of sleep disturbances (including sleep latency, total sleep time, total activity score), which may last for days after a shiftwork episode (Ok et al., 2011). Cortisol rhythms were altered in night-working emergency physicians (Machi et al., 2012) and shift-working nurses (Korompeli et al., 2009). Decrease in cortisol values was observed in police officers working night or afternoon shifts, especially after 5 days of shift-work (Wirth et al., 2011). Shift-working nurses showed altered circadian patterns of blood pressure and heart rate during night as well as day shifts (Anjum et al., 2011).

Unconventional meal timing due to abnormal working schedules represents a supplementary problem as feeding is a strong circadian zeitgeber per se (Stephan, 2002). Atypically or irregularly timed meals in conflict with the natural time of food intake can disrupt rhythmic functions and lead to a variety of gastrointestinal symptoms including gastric and duodenal ulcers in shiftworkers (Segawa et al., 1987).

### 5.1. Circadian rhythms, the immune system and cancer

The connection between circadian rhythms and cancer mechanisms is set at different levels. The core genes of the molecular circadian clock are tightly related to cell-cycle and cell proliferation components, to tumor suppression and DNA repair function, topics which have been vastly reviewed (Borgs et al., 2009; Hrushesky et al., 2009; Khapre et al., 2010; Rana and Mahmood, 2010; Sancar et al., 2010; Yang et al., 2009). A second level can be found at the tight circadian control of immune functions, important in preventing and fighting cancer (Leone et al., 2007).

Circadian rhythms have been observed in immune system components, including cytokine levels and NK or *T* cells number, which are essential mediators of the antitumoral response (Arjona and Sarkar, 2006). As described above, rhythms in cortisol, the main regulator of the immune system, are disrupted in shift or night workers. Chronodisruption may result in disordered immune responses such as aberrant immune cell trafficking and abnormal cell proliferation cycles (Mormont and Levi, 1997). A study conducted on female nurses working in a three-shift rotating system shows a progressive decrease in NK cell activity and CD16(+)CD56(+) cells number, from day shifts to the end of night shifts (Nagai et al., 2011). Sleep deprivation leads to (a) suppression of immune defense that may permit the establishment and/or growth of malignant clones, and (b) alterations in the HPA axis, a major neuroendocrine component regulating the immune system. This change in HPA activity consequently affects the expression of pro-inflammatory cytokines, such as IL-6 or TNF-alpha (Vgontzas and Chrousos, 2002). In line with this concept, IL-6 and other cytokines have been shown to correlate with several cancer types (Sansone et al., 2007). Per3 clock gene polymorphisms have also been associated with circadian disruption and increased cancer risk together with elevated IL-6 concentrations (Guess et al., 2009).

Prognosis of cancer is worse in patients with altered circadian rhythms as compared to patients with normal rhythms (Innominato et al., 2009; Mormont et al., 2000; Sephton et al., 2000). A comparative study in colon cancer patients with pronounced or dampened circadian rhythms, showed that increased IL-6 and TGF-alpha levels in the dampened group are associated with poorer performance status, impaired emotional and social functioning, worsened appetite loss, increased fatigue and disrupted circadian motor activity (Rich et al., 2005). This finding is of particular interest in light of the recent reports in rodents showing that TGF-alpha is highly expressed in SCN and mediates hypothalamic signaling for the circadian regulation of motor activity, sleep, and body temperature (Kramer et al., 2001). Conversely, environmental or behavioral manipulations designed to increase the amplitude of circadian rhythms, may improve the quality of life of patients, a possibility successfully tested in animal models (discussed later).

A growing number of studies suggest that circadian variation is particularly relevant to endocrine malignances. Incidence of hormone-related breast and prostate cancer increases significantly in women and men, respectively, working night shifts (Hansen, 2001a; Megdal et al., 2005). This association between disrupted circadian cycles and the increased rates of cancer may be due to circadian sex hormonal disturbances (Sahar and Sassone-Corsi, 2007). Elevated levels of FSH and LH were also reported in night-shift-working nurses women during both night work and daytime sleep compared to dayshift-working women during nighttime sleep (Davis et al., 2012).

Decreased melatonin production, due to acute suppression of pineal melatonin secretion by light exposure during night-work, has been suggested to have a role in the higher cancer risk associated with prolonged experience of night-work (Sahar and Sassone-Corsi, 2007). Furthermore, melatonin may exhibit antioncogenic potential through direct interaction with estrogen receptors and

**Table 1**
Chronic jet-lag (CJL) effects on health and disease in rodents. Protocols are indicated as: phase-shift size/days between shifts. ± Indicates intercalated advance and delay shifts.

| Protocol | Model | Observed issues | References |
|---|---|---|---|
| 8/2 | Rats | • Accelerated growth of Glasgow-osteosarcoma and DEN-induced hepatocarcinoma tumors<br>• Disrupted rhythms of locomotor activity, temperature, corticosterone and clock gene expression | Filipski et al. (2004) and Filipski et al. (2009) |
| | Mice | • Accelerated Lewis lung tumor growth and higher number of lung metastasis | Wu et al. (2012) |
| 4/1 | Mice | • Increased weight gain<br>• Deregulated plasma leptin and insulin<br>• Decreased medium prefrontal cortex neurons complexity<br>• Impaired cognitive flexibility | Karatsoreos et al. (2011) |
| 6/2 | Rats | • Accelerated growth of MADB106 lung tumors<br>• Disrupted NK cell functions rhythms | Logan et al. (2012) |
| | Mice | • Accelerated growth of B16 and 3LL tumors<br>• Increased weight gain | Casiraghi et al. (unpublished) |
| ±8/3 | wt, cry1/2−/−, per1/2−/− mice | • Increased spontaneous and γ-radiation-induced tumor development<br>• Hyperplasia in the salivary gland, preputial gland, liver and uterus<br>• Spontaneous lymphoma, liver and ovarian tumor | Lee et al. (2010) |
| | p53−/− mice | • Increased liver and salivary gland hyperplasia<br>• Kidney failure<br>• Accelerated lymphoma and osteosarcoma development | Lee et al. (2010) |
| 6/3 | Hamsters | • Reduced hippocampal neurogenesis<br>• Decreased memory and learning | Gibson et al. (2010) |
| | HIP rats | • Increased beta cell apoposis followed by accelerated diabetes development | Gale et al. (2011) |
| 6/7 | Mice | • Increased LPS-induced mortality, hypothermia and cytokines expression | Castanon-Cervantes et al. (2010) |
| 6/7; 6/4 | Aged mice | • Shortened lifespan | Davidson et al. (2006) |

**Table 2**
Protocols of circadian disruption and their effects on health and disease in rodents.

| Protocol | Model | Observed issues | References |
|---|---|---|---|
| Chronic LD cycle inversions | Mice | • Accelerated growth of Ehrlich-carcinoma and sarcoma-180 tumors | Li and Xu (1997) |
| | Mice | • Dramatic worsening of dextran sulfate-induced colitis | Preuss et al. (2008) |
| Constant light | Rats | • Increased DEN-induced hepatocarcinoma | van den Heiligenberg et al. (1999) |
| Chronic light at night | Young rats | • Accelerated aging<br>• Increased spontaneous tumorigenesis | Vinogradova et al. (2010) |
| | Mice | • Increased weight gain<br>• Reduced glucose tolerance | Fonken et al. (2010) |
| | Rats | • Faster xenograft tumor growth | Blask et al. (2009) |
| Forced day activity | Rats | • Disrupted circadian rhythms of locomotor activity, plasma glucose, TAG and corticosterone<br>• Disrupted Per expression in the SCN<br>• Desynchronization within hypothalamic areas<br>• Increased weight gain | Salgado-Delgado et al. (2008, 2010a,b) |
| SCN lesion | Mice | • Accelerated growth of Glasgow-osteosarcoma and P03-adenocarcinoma tumors | Filipski et al. (2003) |

modulation of the cell cycle progression (Costa et al., 2010) and immune variables (Hardeland et al., 2011).

Epidemiologic research has led to the discovery that cancer rates are higher among pilots and flight attendants involved in frequent traveling through time zones or people who work rotating shifts (Costa et al., 2010; Hansen, 2001b; Lahti et al., 2008; Megdal et al., 2005; Schernhammer et al., 2003; Stevens, 2005). Women who worked for more than 20 years under rotating night shifts had a significantly increased risk of endometrial cancer (Viswanathan et al., 2007). Moreover, a higher incidence of colorectal cancer has been reported after prolonged exposure to shiftwork in women participating in the Nurses' Health Study (Machi et al., 2012; Schernhammer et al., 2003).

Based on this epidemiological evidence, the WHO's International Agency for Research on Cancer (IARC) declared shift-working as a relevant risk factor for cancer (Straif et al., 2007). The current definition of 'shiftwork' identifies several major domains that should be considered: (1) shift system (start time of shift, number of hours per day, rotating or permanent, speed and direction of a rotating system, regular or irregular); (2) years on a particular non-day shift schedule; and (3) shift intensity given as the time off between successive work days on the shift schedule (Stevens et al., 2011).

### 5.2. Circadian disruption and health in animal models

Animal models under chronic jet-lag (CJL) schedules, constant light conditions and reverse-phase forced activity – which may be considered model paradigms for shift- and night-work conditions in humans – as well as rodent circadian mutants, have been employed to study the role of circadian disruption on disease development. Tables 1 and 2 summarize the diverse physiological alterations described under such experimental paradigms.

Clock genes mutations which alter circadian function account for several health issues in rodents (see Table 3), in particular when

**Table 3**
Circadian mutations and their effects on health and disease in rodents.

| Genotype | Observed issues | References |
|---|---|---|
| *tau* hamster | • Cardiopathy and renal disease | Martino et al. (2008) |
| per1 (Brd) mice | • Disrupted glucocorticoid rhythms | Dallmann et al. (2006) |
| bmal−/−, clock mutant mice | • Altered glucose homeostasis | Rudic et al. (2004) |
| mper2 mutant mice | • Accelerated ApcMin/+ tumorigenesis<br>• Increased tumor development after γ-irradiation | Wood et al. (2008)<br>Fu et al. (2002) |
| clock mutant mice mper1/2/3 triple deficient mice | • Diverse symptoms of metabolic syndrome | Turek et al. (2005) and Dallmann and Weaver (2010) |
| cry1/2−/−, per1/2−/− mice | • Increased spontaneous and radiation induced tumor development | Lee et al. (2010) |

these animals are subjected to an environmental cycle that does not match their endogenous circadian period.

The hamster short-period mutant *tau* suffers from pathological complications which include cardiomyopathy, fibrosis, impaired contractility and renal disease (Martino et al., 2008). This phenotype is reversed when *tau* hamsters are housed under a 22 h LD cycle. Glucose homeostasis is altered in *bmal* and *clock* mutant mice (Rudic et al., 2004) and glucocorticoid rhythmicity is impaired in *per1* (Brd) mice (Dallmann et al., 2006). Obesity and metabolic syndrome symptoms have been described in the *clock* (Turek et al., 2005) and in the *mper1/2/3* (Dallmann and Weaver, 2010) mutant mice. Per2 mutant mice have been shown to present enhanced susceptibility to cancer and related pathologies (Fu et al., 2002; Wood et al., 2008).

Several recent reports have linked disruption of the circadian system with higher rates of cancer development under different paradigms in rats and mice. As early as 1997, Li and Xu reported that mice injected with Ehrlich-carcinoma or sarcoma-180 and subjected to chronic LD cycle inversions every 3 days showed a reduction in survival and faster tumor growth (Li and Xu, 1997). Levi and collaborators have shown that SCN lesions in mice accelerate Glasgow osteosarcoma and P03 pancreatic adenocarcinoma growth (Filipski et al., 2003). In the last decade, this group has consistently reported that a CJL schedule consisting in 8 h advances of the light phase every 2 days which severely disrupts circadian rhythms of locomotor activity, temperature, corticosterone and clock gene expression, results in high growth rates of transplanted Glasgow osteosarcoma (Filipski et al., 2004), and diethylnitrosamine (DEN)-induced liver carcinoma (Filipski and Levi, 2009) in rats. DEN induced hepatocarcinogenesis has been also reported to increase under constant light conditions in rats (van den Heiligenberg et al., 1999). Interestingly, circadian timing of meals under the above 8 h CJL schedule prevents chronodisruption and decelerates tumor growth (Filipski et al., 2005). Wu et al. (2012) used this same CJL schedule in mice and found faster Lewis lung tumors and higher numbers of lung metastasis. Lee et al. (2010) have shown that a CJL schedule based on intercalated 8 h advances and delays of the light phase every 3 days increases spontaneous and gamma-radiation-induced tumor development as ulcerative dermatitis and hyperplasia in the salivary gland, preputial gland, liver and uterus as well as spontaneous lymphoma, liver and ovarian tumor development in wild type and in already cancer-prone *cry*-, *per*- and *bmal1*-mutant mice. Repeatedly phase shifted *p53*−/− mice show increased liver and salivary gland hyperplasia, kidney failure, and accelerated lymphoma and osteosarcoma development as compared to unchallenged *p53*−/−. Recently, Logan et al. (2012) studied rats under a CJL schedule (6 h shifts every 2 days), and found accelerated lung tumorigenesis after MADB106 tumor cells injection, along with disrupted circadian rhythms of NK cell gene expression and function. Chronically administered light during the night has also been shown to accelerate aging and increase spontaneous tumorigenesis in young rats (Vinogradova et al., 2010), and to increase xenograft breast tumor growth rate in rats (Blask et al., 2009). Preliminary results from our laboratory indicate that mice under a CJL schedule consisting in 6 h advances every 2 days display higher rates of B16 breast and 3LL lung cancer tumors, and increased weight gain as compared to controls (Casiraghi et al., unpublished).

The above findings on cancer development support the hypothesis that not only cancer onset but also its progression may be favored by circadian disruption. Other disease models present similar features. Preuss et al. (2008) challenged mice with dextran sulfate to produce experimental colitis and subjected them to chronic inversions of the LD cycle every 5 days. This led to a dramatic worsening of the colitis as indicated by reduced body mass, abnormal intestinal histopathology, and potentiated inflammatory response.

CJL severely disrupts innate immune function in response to a septic challenge. Castanon-Cervantes et al. (2010) studied the inflammatory response of mice under weekly 6 h phase-advances to LPS administration. After 4 consecutive shifts, jet-lagged mice displayed a 5-fold increase in mortality and severe hypothermia due to LPS as compared to unshifted controls. In chronically shifted mice, the expression of IL-1β, IL-10, IL-12, IL-13, GM-CSF and TNF-α was significantly increased 24 h after LPS injection, and in vitro macrophage stimulation with LPS produced higher levels of IL-6.

Another CJL schedule consisting in 6 h advances every 3 days severely reduced hippocampal neurogenesis in the dentate gyrus of hamsters, and impairment of hippocampal-depending task learning and memory (Gibson et al., 2010). Decreased neurogenesis has been shown to rise from REM sleep deprivation independently of circadian disruption (Mueller et al., 2011). Thus, sleep architecture disruption under chronic jet-lag should be also studied as a potential hazard on its own (see below for cognitive alterations of circadian disruption).

Mice housed under a 20 h LD cycle (which can be understood as a daily 4 h advancing CJL schedule) showed metabolic alterations, as compared to control animals, ranging from accelerated weight gain to abnormally increased plasma leptin, insulin, and insulin:glucose ratio. The complexity of neurons in the medial prefrontal cortex as measured from morphological analysis of dendrites was reduced in the experimental group under disruption of circadian clocks, which showed also decreased cognitive flexibility (Karatsoreos et al., 2011).

Diverse metabolic alterations have been described under different circadian disruption protocols. The diverse symptoms of metabolic syndrome as a consequence of altered clock function offer an important field of study, taking into account the high occurrence of such syndrome in shift- and night-workers.

An animal model for human night-work was developed by Escobar and collaborators by forcing rats, which are normally nocturnal, to be awake and active (i.e. to "work") for 8 h during the light phase (Salgado-Delgado et al., 2008). Internal desynchronization at several levels arose as a consequence of this counter-phase

forced activity, which may help to understand the myriad of health issues associated with night-work and light-at-night in humans. Along the weeks under this scheme, rats progressively decreased their nocturnal levels of activity, and hence the amplitude of normal LD locomotor rhythms was dampened. Plasma glucose, TAG and corticosterone rhythms became disrupted, and Per proteins rhythms in the SCN were altered as well. Moreover, a dysregulation of orexin expression in the PeF, with abnormal high levels during work hours, was detected (Salgado-Delgado et al., 2010a). Metabolic alterations are indeed also present as rats working during the day gain significantly more weight than controls (Salgado-Delgado et al., 2010b). Interestingly, while working and control rats consume equal amounts of food, workers feed mainly during the day as opposed to control and other nocturnal animals, and restricting feeding time to night hours was able to prevent abnormal weight gain and rhythmic and metabolic disturbances.

Chronic jet-lag has also negative effects on metabolism. Ten weeks of chronic 6-h advances of the LD cycle every 3 days, and also constant light, led to accelerated development of diabetes attributed to an increase in beta-cell apoptosis in diabetes-prone HIP transgenic rats (Gale et al., 2011). Preliminary results from our laboratory indicate that body weight gain is accelerated in mice under the previously described CJL protocol (Casiraghi et al., unpublished).

Light at night also alters metabolism in mice. Fonken et al. (2010) housed mice under schedules involving bright or dim light during the dark phase; these mice switched their food intake time to the day and gained more weight and fat than animals under control LD conditions. They also showed reduced glucose tolerance, another indicator of possible metabolic syndrome. Body mass gain was prevented by restricting food to the night. The light-induced melatonin decrease also affects the metabolic variables. In high fat-fed rats, melatonin attenuated body weight increase, hyperglycemia and hyperinsulinemia, as well as the increase in mean plasma adiponectin, leptin, triglycerides and cholesterol levels (Rios-Lugo et al., 2010).

Overall life expectancy is affected by circadian disruption. Lifespan of mice is shortened by CJL environments. Davidson et al. (2006) showed that aged C57BL/6 mice subjected to 6 h advances of the LD cycle every 7 or 4 days displayed higher rates of nonspecific mortality than control and chronic phase-delayed mice. These findings, along with the fact that aging is correlated with alterations in circadian rhythms (Yamazaki et al., 2002), suggest that shift-working health challenge is increased in older adults.

In summary, there is a considerable amount of evidence regarding the deleterious effect of circadian system dysfunction on overall health and on disease onset or progression. The vast and diverse research work in the field has also provided convenient animal models of circadian disruption on which to evaluate these hazards, elucidate the mechanisms on which these relay and, very importantly, design and test potential therapeutic treatments to alleviate and prevent pathologies and improve quality of life in humans. The results described previously (Filipski and Levi, 2009; Fonken et al., 2010; Salgado-Delgado et al., 2010a) have shown that scheduling feeding to normal times significantly improve the negative symptoms associated to their respective disruptive protocols. These findings add support to the hypothesis that the design of routines involving meal times, activity and light may be of therapeutic importance for the alleviation of health problems associated to circadian-disturbing environments (and maybe also to counter cancer related circadian disturbances).

A present problem in the development of animal models of jet-lag, shift-working and related conditions is the lack of standardized criteria for the design of protocols. This fact is evident, to take a clear example, in the diversity of CJL schedules employed in the findings reported above (see Table 1). Tackling this problem should result in a better understanding of the results.

## 6. Lack of temporality affects cognitive processes

Temporal control of cognitive performance is dependent on the combined action of three processes: the circadian process, the homeostatic process, and sleep inertia. Under normal nocturnal sleep conditions, these processes are aligned in order to provide optimal daytime performance and consolidated nighttime sleep. However, under conditions of sleep deprivation, shiftwork or transmeridian travel, misalignment occurs, resulting in fatigue and cognitive deficits (Raslear et al., 2011).

Several lines of investigation using human and animal models suggest a pronounced influence of circadian timekeeping on learning and memory (Cho, 2001; Cho et al., 2000; Ralph et al., 2002; Tapp and Holloway, 1981). In this sense, desynchrony between internal and environmental time has been associated with impaired cognitive function (Maywood et al., 2006). For example, there is clear evidence that chronic phase shifts of the light/dark cycle interfere with memory in rats (Devan et al., 2001; Fekete et al., 1985) and mice (Loh et al., 2010). As already mentioned, it has also been reported that circadian disruptions in female hamsters suppress hippocampal neurogenesis via a glucocorticoid-independent mechanism, imposing pronounced and persistent impairments on learning and memory (Gibson et al., 2010). In humans, learning and memory deficits and reduced temporal lobe volume are observed in chronically jet-lagged female flight attendants relative to controls (Cho, 2001; Cho et al., 2000). These cognitive deficits are associated with elevated circulating cortisol concentrations during transmeridian flights (Cho et al., 2000). After an abrupt change of the light/dark cycle, circadian rhythms gradually adapt to the new environmental conditions. Thus, resynchronization to a 6-h advance of the light/dark cycle takes 8–10 days usually in rodents (Agostino et al., 2007; Kiessling et al., 2010). It was recently reported that the process of jet-lag is characterized by marked heterogeneity in phase resetting of specific genes that operate in the positive and negative branches of the circadian clock (Kiessling et al., 2010). In this sense, misalignment of the transcriptional feedback loops driving the circadian molecular clock may be involved in the transient perturbation of cognitive function. Moreover, specific processes which require neural plasticity, such as a variety of learning and memory procedures, are also affected by circadian manipulations that include changes in the light/dark cycle (Cain et al., 2004), suggesting that circadian desynchronization transiently impairs several cognitive mechanisms, although the exact mechanism through which this occurs is currently not understood.

Circadian effects on cognitive performance have also been studied under conditions of constant routine and forced desynchrony (for a review, see Blatter and Cajochen, 2007). Spontaneous internal desynchronization occurs usually after 2 weeks under time isolation and low light levels (Zulley et al., 1981). In addition, it can be forced by scheduling subjects on extreme sleep–wake schedules, which deviate considerably from the 24-h rhythm (for instance, 20 h or 28 h days have been used), to such an extent that the subject's biological clock is unable to synchronize to this schedule (Dijk et al., 1992). Under a constant routine protocol subjective alertness and cognitive performance remain at a practically stable level throughout a 16-h period that coincides with the subject's normal waking day. In the same study, analysis of the forced desynchrony data indicates that prior wakefulness within this range results in a significant deterioration of both performance and alertness. This suggests that the interaction between circadian phase and prior wakefulness codetermines subjective alertness

and cognitive performance (Dijk et al., 1992). Furthermore, other forced desynchrony studies have shown that the interaction of homeostatic and circadian processes on neurobehavioral functions – such as alertness and performance – is complex and non-linear (Babkoff et al., 1992).

In addition, changes of alertness and cognitive efficiency have been documented in people whose circadian rhythms are disrupted as a consequence of night or shift-work (Folkard, 1996). Cognitive impairments include slowed reaction times, increased error rates, reduced vigilance, memory decrements, poor motivation, increased variability in performance, as well as reduced subjective alertness, and subjective well-being (Dijk et al., 1992; Horowitz et al., 2001; Santhi et al., 2008, 2007). Moreover, long-term exposure to shift-work impairs cognitive functioning, including verbal memory and speed performances. In this sense, shift-workers exhibit lower cognitive performance than control workers and memory performance tended to decrease with increasing shift-work duration. Among former shift-workers, cognitive performance of subjects having stopped shift-work for more than 4 years seemed to be increased, suggesting a possible reversibility of effects (Rouch et al., 2005).

A fundamental component of cognition is the perception of the passage of time. Timing and time perception are fundamental to survival and goal reaching in humans and other animals. Organisms have developed diverse mechanisms for timing across different scales, the most important being circadian timing, interval timing and millisecond timing (Buhusi and Meck, 2005). The perception of short durations in the seconds-to-minutes range, known as interval timing, is crucial to learning, memory, decision making and other cognitive tasks. Several studies have shown that time judgments in humans covary with normal circadian rhythms. (Kuriyama et al., 2005; Lustig and Meck, 2001). In line with this finding, a circadian rhythm in time estimates was documented in control subjects, but was found to be disrupted in shiftworkers (Pati and Gupta, 1994). Furthermore, it was reported that sleep deprivation influences diurnal variation of time estimation in humans (Soshi et al., 2010).

Rats exhibit circadian variations in time perception similar to those that have been demonstrated in humans (Shurtleff et al., 1990). We have recently reported significant differences in the estimation of 24-s intervals at different times of day in mice (Agostino et al., 2011). These differences were maintained under constant dark (DD) conditions. Interval timing was impaired in mice under constant light (LL) conditions, which abolish circadian rhythmicity. Moreover, short time estimation in animals subjected to a 6-h advance of the light/dark cycle was transiently affected. Taken together, these results suggest that short-time estimation is modulated by the circadian clock. Importantly, the transient desynchronization of the circadian system during a jet-lag simulation negatively affects time estimation.

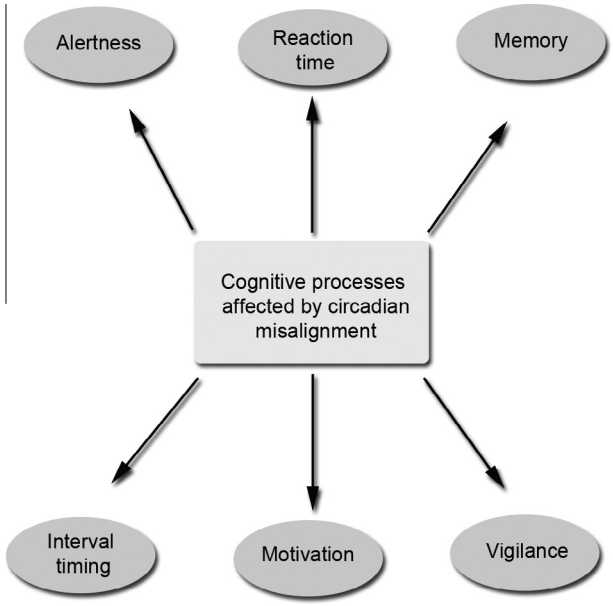


**Fig. 2.** Cognitive impairments as a consequence of the lack of circadian synchronization.

Fig. 2 summarizes the main cognitive impairments as a consequence of the lack of circadian synchronization. These detrimental effects on performance have important social implications including, but not limited to, compromised public safety, diminished health and well-being, and lower productivity of the affected population. Several treatments have been tested to minimize or avoid the decrements in performance that are related to sleepiness caused by prolonged wakefulness and working at adverse circadian phases. These include behavioral (naps, exercise, work breaks), environmental (light), and pharmacological interventions. On the last group, amphetamines, caffeine, melatonin and modafinil have been extensively studied (Crowley et al., 2003; Grady et al., 2010; Pigeau et al., 1995; Wyatt et al., 2004). Development of effective treatments for circadian disorders may be an important strategy for improving public safety, health, well being and productivity of the affected population.

## 7. Conclusion

Circadian desynchronization with the environment results in diverse physiological alterations that ultimately decrease quality of life and induce pathological situations in both humans and animal models. Entrainment includes both coupling internal oscillators to external periodic changes as well as synchrony between the central clock and peripheral oscillators, which have been shown to exhibit different phases and resynchronization speed. Indeed, a proper internal temporal order guarantees an ideal use of resources and the ability to predict homeostatic variations.

In particular, we have focused on metabolic, immune and cognitive alterations under situations of acute or chronic circadian desynchronization, as exemplified by jet-lag and shiftwork schedules. Moreover, such situations might lead to an enhanced susceptibility to diverse cancer types. The good news is that properly scheduled light exposure, meal timing and chronobiotics administration seem to represent a valid therapeutic tool to prevent these reported physiological challenges, by reinforcing the temporal alignment of endogenous clocks to a changing environment.

Contemporary societies depend on forcing our internal timing mechanisms outside their natural range, which in turn results in poor cognitive and physical performance (with a higher accident rate and a decrease in productivity) as well as increased susceptibility to illness. *The times are changing*, but it is only by listening to our biological clocks we will be able to reverse the effects of desynchronization on our daily lives.

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