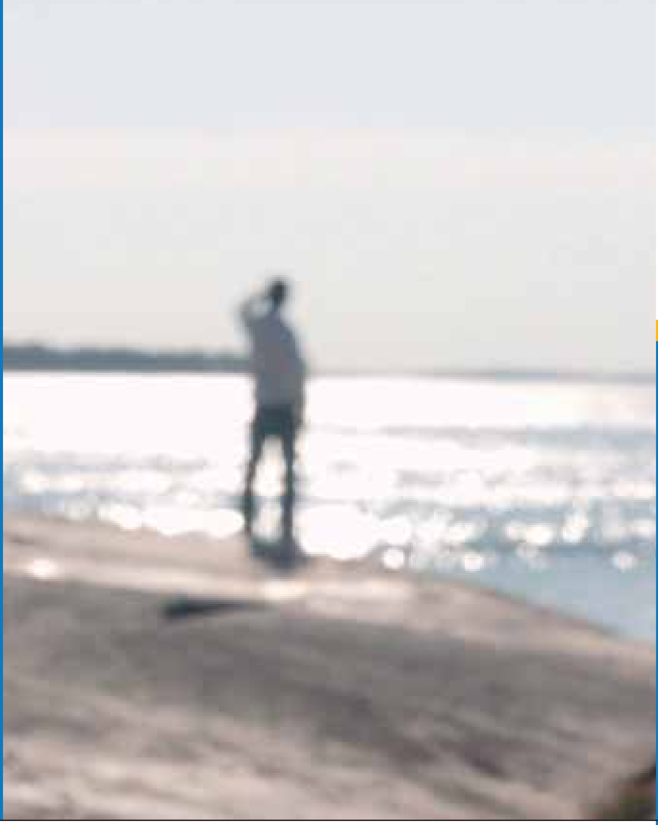

Tuuli Lahti

Circadian Rhythm Disruptions and Health

Publications of the National Public Health Institute A 21/2008

Department of Mental Health and Alcohol Research
National Public Health Institute, Helsinki
and
Faculty of Biosciences, Department of Physiology
University of Helsinki

Helsinki, Finland 2008

National Public Health Institute,
Department of Mental Health and Alcohol Research,
Helsinki, Finland
and
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Tuuli Lahti

Circadian Rhythm Disruptions and Health

ACADEMIC DISSERTATION

To be publicly discussed
with the permission of the Faculty of Biosciences, University of Helsinki,
at the auditorium 1041, Biocenter 2, Viikinkaari 5,
on October 3rd 2008, at 12 o'clock.

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For sweet dreams

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ABSTRACT

The doctoral thesis defined connections between circadian rhythm disruptions and health problems. Sleep debt, jet-lag, shift work, as well as transitions into and out of the daylight saving time may lead to circadian rhythm disruptions. Disturbed circadian rhythm causes sleep deprivation and decrease of mood and these effects may lead to higher accident rates and trigger mental illnesses. Circadian clock genes are involved in the regulation of the cell cycle and metabolism and thus unstable circadian rhythmicity may also lead to cancer development.

In publications I-III it was explored how transitions into and out of the daylight saving time impact the sleep efficiency and the rest-activity cycles of healthy individuals. Also it was explored whether the effect of transition is different in fall as compared to spring, and whether there are subgroup specific differences in the adjustment to transitions into and out of daylight saving time. The healthy participants of studies I-III used actigraphs before and after the transitions and filled in the morningness-eveningness and seasonal pattern assessment questionnaires.

In publication IV the incidence of hospital-treated accidents and manic episodes was explored two weeks before and two weeks after the transitions into and out of the daylight saving time in years 1987-2003.

In publication V the relationship between circadian rhythm disruption and the prevalence of Non-Hodgkin lymphoma was studied. The study V consisted of all working aged Finns who participated in the national population census in 1970. For our study, all the cancers diagnosed during the years 1971-1995 were extracted from the Finnish Cancer Register and linked with the 1970 census files.

In studies I-III it was noticed that transitions into and out of daylight saving time disturbs the sleep-wake cycle and the sleep efficiency of the healthy participants. We also noticed that short sleepers were more sensitive than long sleepers for sudden changes in the circadian rhythm. Our results also indicated that adaptation to changes in the circadian rhythm is potentially sex, age and chronotype-specific. In study IV no significant increase in the occurence of hospital treated accidents or manic episodes was noticed. However, interesting observations about the seasonal fluctuation of the occurrence rates of accidents and manic episodes were made.

Study V revealed that there might be close relationship between circadian rhythm disruption and cancer. The prevalence of Non-Hodgkin lymphoma was the highest among night workers.

The five publications included in this thesis together point out that disturbed circadian rhythms may have adverse effect on health. Disturbed circadian rhythms decrease the quality of sleep and weaken the sleep-wake cycle. A continuous circadian rhythm disruption may also predispose individuals to cancer development. Since circadian rhythm disruptions are common in modern society they might have a remarkable impact on the public health. Thus it is important to continue circadian rhythm research so that better prevention and treatment methods can be developed.

Keywords:
Circadian rhythm, daylight saving time, manic episodes, accidents, Non-Hodgkin lymphoma

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TIIVISTELMÄ

Väitöskirjatyössä kartoitettiin vuorokausirytmin häiriöiden terveysvaikutuksia. Vuorokausirytmin häiriintymistä aiheuttavat useat tekijät, joista yleisimpiä ovat unen puute, vuorotyö, aikaerorasitus sekä kesä- ja talviaikaan siirtyminen. Vuorokausirytmin häiriöit voivat aiheuttaa univaikeuksia, lisätä onnettomuuksien määrää ja laukaista mielenterveysongelmia. Koska vuorokausirytmiä säätelevät kellogeenit osallistuvat solusyklin säätelyyn ja aineenvaihduntaan, epävakaa vuorokausirytmi voi häiritä myös solunjakautumista ja johtaa syövän syntyyn. Viimeaikaisissa tutkimuksissa onkin saatu viitteitä siitä, että vuorokausirytmin häiriöt altistavat tietyille syöpäsairauksille.

Tutkimuksissa I-III kartoitettiin, miten kesä- ja talviaikaan siirtyminen vaikuttaa terveiden koehenkilöiden unen laatuun ja uni-valverytmiin, ovatko vuorokausirytmin häiriintymisen vaikutukset erilaisia keväisin ja syksyisin, ja onko muuttuneeseen vuorokausirytmiin sopeutumisessa alaryhmien välisiä eroja. Tutkimuksiin I-III osallistuneet koehenkilöt käyttivät tutkimuksen ajan aktigrafeja ja vastasivat aamuisuus-iltaisuus- ja vuodenaikaisuus-kyselylomakkeisiin.

Tutkimuksessa IV selvitettiin lisääko kesä- ja talviaikaan siirtyminen maniajaksojen ja tapaturmien määrää. Tutkimusta varten kartoitettiin sairaalassa hoidetut maniajaksot ja tapaturmat kaksi viikkoa ennen kesä- ja talviaikaan siirtymistä ja kaksi viikkoa siirtymien jälkeen vuosina 1987-2003.

Tutkimuksessa V kartoitettiin, onko vuorokausirytmin häiriintymisellä yhteyttä Non-Hodgkin-lymfooman esiintyvyyteen. Tutkimusta V varten käytiin läpi syöpärekisterin tiedot vuonna 1970 väestölaskentaan osallistuneiden työikäisten syöpäsairauksista vuosilta 1971-1995.

Tutkimuksissa I-III havaittiin kesä- ja talviaikaan siirtymisen häiritsevän sekä uni-valverytmiä että nukkumisen tehokkuutta. Lisäksi havaittiin, että lyhyt uniset ovat pitkä unisia herkempiä vuorokausirytmin muutoksille. Tutkimustulokset viittaavat myös siihen, että vuorokausirytmin muutoksiin sopeutuminen saattaa olla ikä-, sukupuoli- ja kronotyyppi sidonnaista.

Tutkimuksessa IV ei havaittu kesä- tai talviaikaan siirtymisen lisäävän merkittävästi sairaalahoitoa vaativien maniajaksojen tai tapaturmien esiintyvyyttä. Tutkimus IV kuitenkin paljasti mielenkiintoisia eroja tapaturmien ja maniajaksojen ilmaantuvuudessa eri vuodenaikojen välillä.

Tutkimuksessa V havaittiin, että vuorokausirytmin häiriintymisellä saattaa olla yhteyksiä syövän syntyyn. Non-Hodgkin-lymfooma oli yleisintä yötyötä tekevillä.

Väitöskirjatyön osajulkaisut yhdessä osoittavat, että vuorokausirytmin häiriöillä on haitallisia terveysvaikutuksia. Vuorokausirytmin häiriintyminen heikentää unen laatua ja uni-valverytmiä, ja pitkään jatkuessaan voi johtaa syöpäkasvainten kehitykseen. Vuorokausirytmin häiriöt ovat yleisiä ja täten häiriöiden terveysvaikutuksilla on kansanterveydellistä merkitystä. Täten vuorokausirytmin häiriöiden terveysvaikutusten tutkimusta tulee jatkaa parempien ennaltaehkäisy- ja hoitomenetelmien kehittämiseksi.

Asiasanat:
Vuorokausirytmi, kesäaika, mania-jaksot, tapaturmat, Non-Hodgkin lymfooma

ABBREVIATIONS

DST	Daylight saving time
FINJEM	Finnish job-exposure matrix
GSS	Global Seasonality Score
ICD	International Classification of Diseases
MEQ	Morningness-Eveningness Questionnaire
NHL	Non-Hodgkin lymphoma
SCN	Suprachiasmatic nucleus
SPAQ	Seasonal Pattern Assessment Questionnaire

LIST OF ORIGINAL PUBLICATIONS

This thesis is based on the following original articles referred to in the text by their Roman numerals:

I Lahti TA, Leppämäki S, Ojanen SM, Haukka J, Tuulio-Henriksson A, Lönnqvist J, Partonen T. Transition into daylight saving time influences the fragmentation of the rest-activity cycle.
J Circadian Rhythms. 2006 Jan 19;4(1):1.

II Lahti TA, Leppämäki S, Lönnqvist J, Partonen T. Transition to daylight saving time reduces sleep duration plus sleep efficiency of the deprived sleep.
Neurosci Lett. 2006 Oct 9;406(3):174-7.

III Lahti TA, Leppämäki S, Lönnqvist J, Partonen T. Transitions into and out of daylight saving time compromise sleep and the rest-activity cycles.
BMC Physiol. 2008 Feb 12;8(1):3.

IV Lahti TA, Haukka J, Lönnqvist J, Partonen T. Daylight saving time transitions and hospital treatments due to accidents or manic episodes.
BMC Public Health. 2008 Feb 26;8(1):7.

V Lahti TA, Partonen T, Kyyrönen P, Kauppinen T, Pukkala E. Night-time work predisposes to Non-Hodgkin Lymphoma.
Int J Cancer. 2008 Aug 11;123:2148-2151.

In addition to articles I-V, some earlier unpublished results are presented.

1 INTRODUCTION

The hasty urban life no longer follows the time signals of nature. Because of the constantly used artificial lights, the trees are dropping their leaves later in the fall and we are exposed to irregular sleep-wake cycles. In modern societies people work and socialize around the clock and thus it is not a surprise that the circadian rhythm disruptions are becoming more common (Rajaratnam and Arendt, 2001). Circadian rhythm disruptions lead to sleep deprivation and cause brain dysfunction and may decrease mood, motivation, attention and alertness. Lack of alertness and attention may predispose individuals to accidents such as car crashes. Decrease of mood and motivation may trigger mental illnesses such as depression and manic episodes.

Biological clocks have significance on all biological levels from a single cell to an ecosystem. The clocks synchronize the daily activity of an organism to coincide with its ecological role; to be active when food is available or when mating partners are active. This requires a synchronization of the related physiological processes which are ultimately caused by circadian processes in individual cells. Thus abnormalities in the circadian clockwork are likely to harm the normal functioning of an organism in multiple and unexpected ways. For example certain cancers are known to be more common among those whose circadian rhythm is constantly disturbed (Megdal et al. 2005, Harris et al. 1999, Sahar and Sassone-Corsi 2007, Zhu et al. 2008). The disruptions in circadian clockwork are also known to shorten the lifetimes of laboratory-animals (Hurd and Ralph, 1998).

Because of the significance of sleep and normal circadian rhythm to health, abnormalities in these factors may have a wide-range of deleterious effects to public health. To anticipate how and to what extent the circadian rhythm disruptions cause physiological and mental dysfunctions and to prevent and cure these conditions we must carefully study both the genetics and the physiology behind the circadian rhythms.

2 REVIEW OF THE LITERATURE

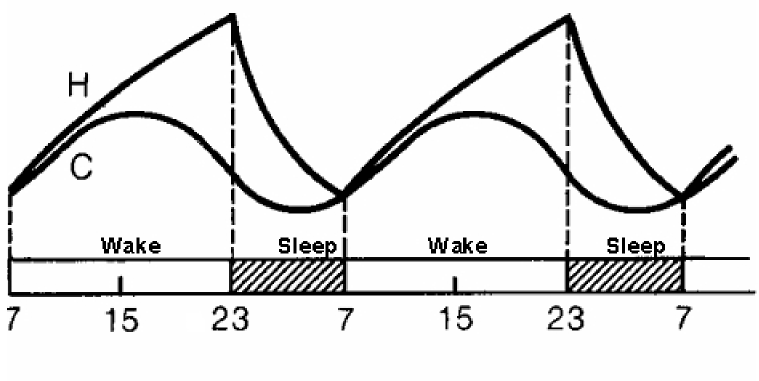
The earth rotates around its axis approximately in 24 hours. This rotation causes changes in the lighting conditions: when there is a day in western hemisphere the eastern hemisphere experiences a night and vice versa. Organisms have adaptated to the constantly changing lighting conditions of Earth by evolving biological clocks. In humans, the main regulator of circadian rhythms is the suprachiasmatic nucleus (SCN), which coordinates the circadian oscillation of the cells in the brain and also in the peripheral organs. The alternation of day and night is a natural time signal to the SCN. Daylight synchronizes this biological clock to 24-hour periods. The SCN regulates metabolism, the sleep-wake cycle and other cyclical biological events, and thus its normal functioning is essential to well-being.

Disturbed circadian clockwork leads to physiological dysfunctions such as sleep-disorders and metabolic syndrome (Sookoian et al. 2008, Froy 2007). It also seems that people whose circadian rhythm is constantly disrupted report higher morbidity and worser health conditions than those who do not have problems with circadian rhythmicity (Taillard et al. 2001). Thus there are evidences that the circadian clockwork impacts both the subjective experience of health and also the physical conditions. Hence it is important to study how SCN regulates our vital functions, what are its implications in diseases and what are the impacts of its disruption.

2.1 The Two Process Model of Sleep

The two process model describes how homeostatic and circadian factors regulate the amount and timing of sleep (Borbely 1982). The need for sleep increases during wakefulness because of the homeostatic processes in the brain. In recent years the mechanisms mediating alteration of sleep and wakefulness have been elucidated in closer detail (Allada 2008, Sakurai 2007). In the two process model [Figure 1], the circadian process C reflects the circadian alteration of alertness. The likelihood of wakefulness and sleep alternates in a circadian manner.

Figure 1. The two process model of sleep. During wakefulness the homeostatic process (H) constitutes a message which ultimately causes falling asleep. The circadian process (C) reflects the circadian alteration of alertness. Numbers at the bottom of the picture refer to the time of day.

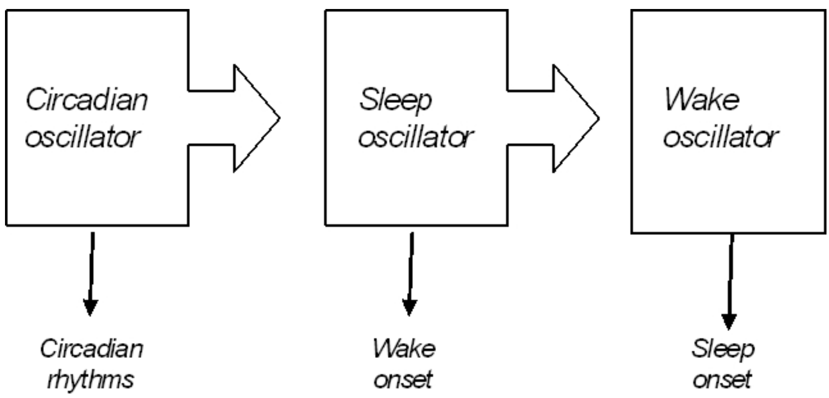


Our genotype defines, through our inherited clock genes, our individual sleep-wake rhythm. The amount of sleep needed and the timing of sleep is an innate characteristic. Circadian period differences exists between organisms and also between individuals, but for each individual the endogenous period shows a remarkable precision with a variability of only some minutes from day to day (Meijer et al. 2007). Some people are short sleepers who need at maximum 6 hours of sleep per night whereas others are long sleepers who need at least 9 hours of sleep per night. On average people need 7 to 8 hour of sleep per night. Sleep duration depends strongly on chronotype and the chronotype is both age- and sex-dependent. Chronotype describes the innate tedency of individuals to wake up and fall asleep at specific times. Some of us are morning types with the preference for morning activities and early bedtimes, whereas others are evening types with the preference for evening activities and late mornings. Most people are somewhere in the middle of early and late chorontypes and thus they are called as intermediate types.

2.2 The Three Oscillator Model of the Human Circadian System

The three oscillator model [Figure 2] of the human circadian system is derived from free-running experiments where subjects live isolated in caves or cellars and thus do not receive any timing signals from the external environment. Without light, metabolism synchronizes our circadian rhythm. Circadian rhythmicity of metabolism is a natural time signal for the organism and consequently regulates the sleep-wake cycle. The circadian oscillator controls the duration of sleep by influencing the sleep oscillator which, determines the timing of wake onset. The wake oscillator determines the timing of sleep onset and therefore mainly controls the duration of the waking state (Kawato et al. 1982). Because the circadian oscillator regulates the sleep-wake cycle, disruptions in this cycle indicate a dysfunction in the oscillator. Thus, by studying the sleep-wake cycle, we can gather information about how and when the oscillator is disrupted. This kind of study also provides us with knowledge about the mechanisms which can synchronize the circadian oscillator after disruption and how long the synchronization of the oscillator usually takes.

Figure 2. The three-oscillator model of circadian rhythms and the sleep-wake cycle.



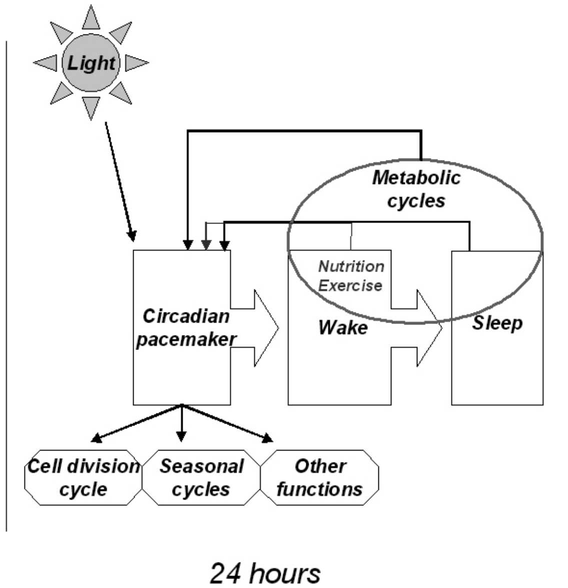
2.3 Studying circadian rhythm disruptions

The circadian oscillator can be studied under strict laboratory conditions but this is rarely possible. Usually circadian rhythm disruptions are studied under normal circumstances and among clinical patients, and thus there is a need to study the function of circadian oscillator indirectly by dissecting the sleep-wake cycle. The sleep-wake cycle can be studied using various methods. Among these are actigraphic measurements that provide us with knowledge about the rest-activity cycles of the subjects. Detrimental effects of circadian rhythm disruption can also be studied by following the dysfunctions caused by the disruption. For example, shift work and jet lag challenge circadian regulation and may cause failures in vital functions. Thus, circadian rhythm disruption may lead to disturbances in metabolism, mood, behavior and the sleep-wake cycle and cause diseases related to these dysfunctions.

This thesis was based on the assumption that circadian rhythm disruption destabilizes the sleep-wake cycle and also causes mental and physical dysfunctions. To explore the effects of circadian rhythm disruption we studied the sleep-wake cycle of healthy adults and the occurrence rates of accidents and manic episodes after transitions into and out of daylight saving time. To explore how circadian rhythm disruption impacts the cell division cycle, we also studied the prevalence of Non-Hodgkin lymphoma among night workers. Thus, in this thesis a wide range of phenomena that are connected to circadian regulation were tested. In Figure 3 these phenomena are shown in a diagram with connections to each other to clarify their relationships. Figure 3 describes how the circadian pacemaker regulates sleep, wakefulness and other functions and what the mechanisms that regulate the circadian pacemaker itself are.

Light synchronizes the circadian pacemaker every day and this synchronization regulates wakefulness. The wakefulness regulates sleep. Both wakefulness and sleep give feedback to the circadian pacemaker and thus participate in the regulation of the circadian clockwork. Without light, metabolism synchronizes the circadian clock. Except for sleep-wake cycle, the circadian pacemaker also regulates other vital rhythms such as cell division and seasonal cycles [Figure 3].

Figure 3. The circadian pacemaker regulates the sleep-wake cycle, cell division, seasonal and other biological cycles. We studied the effects of circadian rhythm disruption on the sleep-wake cycle in publications I-III, on the seasonal cycle in publications III and IV and on the cell division cycle in publication V.



2.4 Circadian rhythms

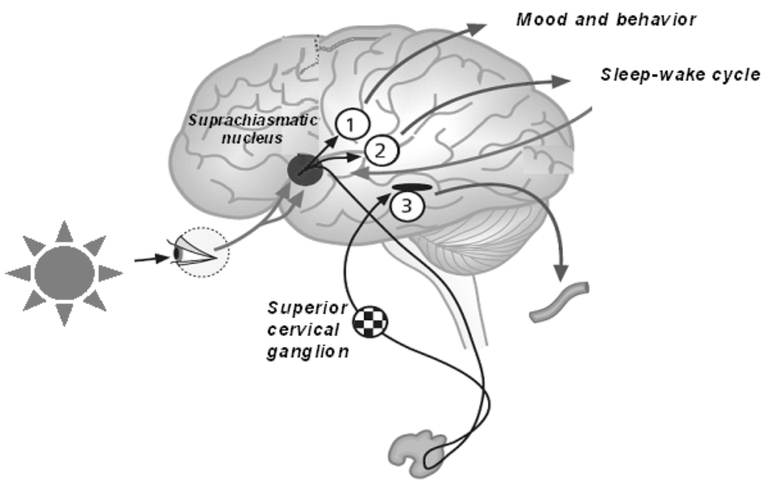
2.4.1 The physiology of circadian rhythms

Circadian rhythms regulate the endogenous rhythm of vital functions such as gene expression, metabolism, hormone secretion, cell proliferation and behavior. The main regulator of these rhythms, the biological clock, is situated at the SCN [Figure 4]. The SCN is a paired cluster of neurons located at the base of the hypothalamus, just above the optic chiasm (Ralph et al. 1990, Moore and Lenn 1972). Many SCN neurons are sensitive to light stimulation via the retina. The light causes molecular changes in the visual pigments of the retina. These molecular changes lead to nerve impulses which are mediated from the retina to the SCN along specific nerve pathway, the retino-hypothalamic tract (RHT) (Lucas et al. 2001). RHT therefore mediates the synchronizing information about the length of light to the SCN. When the light intensity diminishes SCN sends nerve impulses to the pineal gland. These impulses evoke the pineal gland to produce melatonin hormone.

The light information is first mediated from eyes to SCN and from SCN to pineal gland electrically but in pineal gland this electrical input is changed to chemical message. This chemical message is then mediated by blood from pineal gland to other parts of the body.

Light can shift the circadian phase of SCN depending on when the SCN is exposed to it (Quintero et al. 2003, Kuhlman et al. 2003, Morris et al. 1998). Light exposure in the evening delays the rhythm of the SCN and in the early morning the effect is opposite, advance of the rhythm. Hence the external environment influences our endogenous rhythms.

Figure 4. The SCN is a paired cluster of neurons located at the anterior hypothalamus. Several nerve connections come from the SCN such as those to paraventricular nucleus (1), subparaventricular zone (2) and pineal gland (3). Nerve cells located at these brain areas take part into the regulation of behavioral and physiological mechanisms. Picture is modified with the kind permission of Duodecim Medical Journal (Partonen 2004).



2.4.2 Suprachiasmatic nucleus

The SCN of humans consists of approximately 20 000 neurons (Aton and Herzog 2005) which vary in their ability to sense environmental timing cues (Antle and Silver 2005). The circadian oscillation of SCN neurons generates an endogenous rhythm in electrical activity with a period of approximately 24 hours. According to Czeisler and his colleagues, the average length of the intrinsic period of the human circadian pacemaker is 24 hours and 10 minutes (Czeisler et al. 1999).

Animal studies have shown that removal of the SCN makes laboratory hamster arrhythmic (Abrahamson and Moore 2006, Abrahamson and Moore 2001, Ralph et al. 1990). If the SCN of a hamster is transplanted to another hamster, the recipient expresses the circadian rhythmicity of the donor hamster (Ralph et al. 1990). These findings support the assumption that circadian rhythms are endogenous and individual.

Certain neurotransmitters seem to be involved in SCN synchronization. One of these is gamma-aminobutyric acid (GABA). GABA is expressed in most SCN neurons and GABA receptors are found throughout the SCN (Belenky et al. 2008). Thus it seems plausible that GABA is one of the neurotransmitters that regulate the oscillation of SCN neurons. Recent research has shown that exogenously applied GABA can phase-shift the firing rhythms of individual SCN neurons in vitro and that GABA synchronizes firing rhythms of neurons within a cell culture (Liu and Reppert 2000). Another neurotransmitter that seems to be involved in SCN regulation is vasoactive intestinal polypeptide (VIP). VIP is synthesized by the SCN neurons. About 15% of the SCN neurons are VIPergic (Abrahamson and Moore 2001). There is evidence that VIP release shifts both behavioral and SCN firing rhythms (Brown et al. 2007) and that the loss of VIP or its receptors weakens the regeneration and synchronization of circadian oscillation (Vosko et al. 2007). In addition to GABA and VIP, many other neurotransmitters may be involved in SCN regulation. For example, the roles of gastrin-releasing peptide (Romijn et al. 1998), neuropeptide Y (Liou and Albers 1991) and neurotensin in SCN regulation are currently being intensively investigated. Signals from SCN are mediated downstream by dopamine, serotonin and noradrenaline (Gonzalez and Aston-Jones 2008, Sakurai 2007).

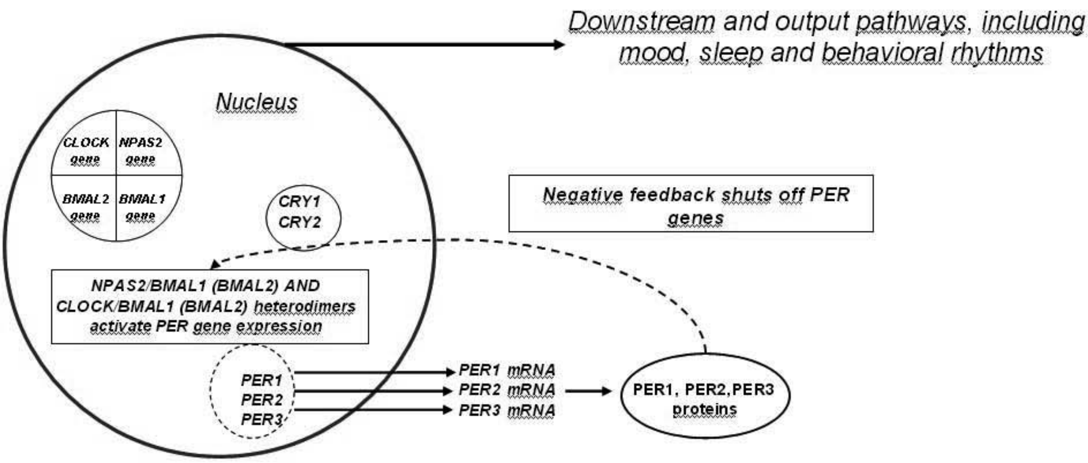
The internal clocks in the SCN and other parts of the brain are functionally connected (Schibler and Sassone-Corsi 2002). Besides the brain, internal clocks are found in peripheral organs such as liver, kidneys, bones and adipose tissue. The SCN regulates these slave oscillators which are mainly connected to the regulation of metabolism (Pando et al. 2001).

2.4.3 Circadian clock genes

The circadian clock genes are expressed in individual SCN neurons. These genes guide the organism to follow natural time signals and help vital functions to adapt to environmental demands. Circadian clock genes are essential regulators of the cell cycle and modify the metabolism and respiration of the cell. Ten to fifteen percent of all genes oscillate in a daily rhythm, and the SCN regulates this rhythm. Thus disturbed regulation of circadian clock genes may derail a cell, interfering with its normal function and leading to cancer development (Filipski et al. 2002). The most important clock genes are the Circadian locomoter output cycles kaput-gene (Clock) and Period 2-gene (Per2). The function of clock genes is necessary for brain to recognize circadian light-dark changes.

The circadian clock genes encode the expression of clock proteins. These proteins mediate the information of clock genes in the brain, as well as in other organs (Reppert and Weaver 2002). The expression of clock genes is regulated by transcriptional and post-transcriptional feedback-loops. The feedback loops arise from the interaction of the clock proteins [Figure 5].

Figure 5. The expression of clock genes is regulated by transcriptional and post-transcriptional feedback-loops.



Abbreviations: Neuronal PAS domain protein 2 (NPAS2), Period 1-3 (PER1, PER2, PER3), Cryptochrome 1-2 (CRY1, CRY2), Circadian Locomoter Output Cycles Kaput (CLOCK), and Brain and Muscle ARNT-Like 1-2 (BMAL1, BMAL 2).

Malfunction of the circadian clockwork is linked to cancer, to Non-Hodgkin lymphoma (NHL) in particular but also to breast cancer (Zhu et al. 2008, Zhu et al. 2007). Molecules of particular interest for the pathogenesis of NHL include circadian clock genes such as Per2 and Npas2 (Kaasik and Lee 2004). The function of the Per2 gene product in particular prevents tumor growth by regulating DNA damage-responsive pathways (Sun et al. 2006). For example a mutated Per2 gene causes malignant tumor growth in the lymhoid tissue of a mouse (Fu et al. 2002). This evidence underlines the major impact of circadian clockwork for physiological functions and health.

2.5 Circadian rhythm disruption

In a modern society there are several sources for circadian rhythm disturbance. The most intense disrupter of the circadian clock is jet-lag. The effects of jet-lag such as sleepiness, decreased alertness and gastrointestinal problems, occur rapidly after crossing a number of time zones. The duration and severity of jet-lag depends on the number of time zones crossed and the direction of the travel. Travelling westward tends to cause milder jet-lag symptoms than travelling eastward because the circadian rhythm is longer than 24 hours and thus there is a natural tendency for longer days. According to Finnair statistics, approximately 1,270,800 passengers travel on their regular long distance flights every year (leisure flights not included). Finnair's aircrew, approximately 2000 persons, is also repeatedly subjected to jet-lag. Thus, approximately 1,300,000 Finnish people are burdened by jet-lag on Finnair flights annually. Additional people are also subjected to jet-lag by other carriers.

Shift work is one of the most important disrupters of circadian rhythms, since approximately 24% of Finns of working age engage in shift work (according to the Finnish Institute of Occupational Health). Thus, approximately 624,480 Finnish people (according to Statistics Finland) may suffer from circadian disorders due to shift work. The most detrimental form of shift work is night work, which seriously disturbs circadian rhythmicity.

In addition to jet-lag and shift work, transitions into and out of daylight saving time disturbs circadian rhythms annually. Thus, all 5,300,484 Finns (according to the Finnish Population Register Center) are exposed to circadian rhythm disturbance twice a year after the transitions into and out of daylight saving time.

A major public health concern is minor but chronic sleep deprivation, which is usual among school aged children and youngsters as well as among working-aged adults. Sleep debt causes lack of attention, and problems with memory and mood, and thus its impacts may be very serious. Animal studies have shown that disruption of the circadian timing shortens the lifetime of laboratory animals (Davidson et al. 2006, Klarsfeld and Rouyer 1998, Penev et al. 1998, Hurd and Ralph 1998). Abnormalities in the circadian clockwork have also been implicated in mood disorders and in the metabolic syndrome (Rintamäki et al. 2008, Partonen et al. 2007).

Circadian rhythm research provides essential information about how circadian rhythm disruptions affect public health and safety. By recognizing those who have an increased risk to fall ill from diseases caused by circadian rhythm disruption, we can develop more accurate follow-up and prevention practices.

2.5.1 Daylight saving time

Since the circadian rhythm is endogenous, it does not adjust immediately to sudden changes in the light-dark cycle. One sudden change to the light-dark cycle is produced twice a year in many countries when the clocks are turned forward and backward during the transitions into and out of daylight saving time (DST). The rationale for DST is to coordinate the seasonal daylight exposure changes with the activity peaks of the population. In the European Union, DST currently begins on the last Sunday of March, when the clocks are turned forwards by one hour, and ends on the last Sunday of October, when the clocks are turned backwards by one hour. The fall transition out of DST thus increases the available daylight in the morning by one hour and the spring transition leads to an increase of the available daylight in the evening.

DST is commonly used worldwide and thus affects millions of people annually. Despite the fact that DST impacts a large number of people and the disruption of the light-dark cycle cause circadian rhythm disruptions (Kantermann et al. 2007), the consequences of DST are still widely unknown. Consequently it is important to gather more information about the effects of DST transitions to public health and safety. DST research can produce important knowledge of the types of people who will generally find it easy to adjust (Monk and Aplin 1980) and the types of people who are at increased risk of developing symptoms caused by circadian rhythm disturbance.

2.5.1.1 Accidents

The DST transitions disrupt the sleep-wake cycle and hence may impair cognitive functions such as attention, memory and mood. Loss of alertness may lead to higher accident rates (Mahowald 2000) and thus it is possible that the amount of accidents is higher after DST transitions. It seems that in the modern societies many of us are chronically sleep-deprived (Bonnet and Arand 1995) and due to this, even a small additional loss of sleep may have consequences for public and individual safety (Coren 1996a). So far, studies have yielded contradictory information about the effects of DST on the number of accidents (Coate and Markowitz 2004, Coren 1996b, Ferguson et al. 1995). Thus more studies on accidents around

DST transitions are needed to understand how circadian rhythm disruption impacts for instance ones ability to drive. Accidents are a burden to the national economy and safety, and therefore it is important to study them. Prevention is possible only if the risk factors are recognized.

2.5.1.2 Manic episodes

Manic episodes are characterized by unusual thought patterns and elevated self-respect and activity. The episodes can last from a few days to months and usually require hospital treatment. Manic episodes are usually associated with bipolar disorder, where depressive and manic episodes alternate.

The conflict between external time cues and internal biological rhythms may trigger the appearance of a mental illness (Katz et al. 2002). Although the shift for one hour in the sleep-wake cycle caused by the DST transition may seem like a minor alteration, it may have serious impacts. Patients suffering from mental problems are very vulnerable to sleep disruption (Roenneberg and Merrow 2005, Wehr et al. 1983, Frangos at al. 1980). Manic episodes are associated with dysfunction of the circadian timing system (Wehr et al. 1983) and patients may suffer from an inability to adjust to seasonal light changes (Suhail and Cochrane 1998, Jones et al. 1995, Frangos et al. 1980). Hence, the circadian rhythm disruption caused by the DST transition can trigger or worsen the condition of a manic patient. The influence of light and circadian rhythms on mental illnesses is currently being investigated.

2.5.2 Night work

From the physiological point of view, the night is the most unnatural time to work. Night work causes health problems such as sleep disorders, lipid intolerance and increased incidence of cardiovascular disease. Even so, a large number of people at working age are engaged with irregular shift work schedules and therefore to abnormalities in the circadian clockwork.

2.5.2.1 Non-Hodgkin lymphoma

Non-Hodgkin lymphoma (NHL) is a cancer caused by tumor growth in lymphoid tissue (Fisher and Fisher 2004). NHL is slightly more common among men than women and its incidence grows with age. Genetic, environmental, viral or other biological factors may influence tumor growth. Because the circadian clock shares common features with the cell-division cycle and there seem to be common regulatory elements shared by these systems (Gillette and Sejnowski 2005), one suggested factor for predisposing to NHL is the disruption of the circadian clockwork (Harris et al. 1997). Disturbed circadian rhythms may lead to failures in control of the cell-division cycle and thereby may cause not only sleep or mental disorders but also cancers. There are reports indicating that people doing shift-work have increased risk for cancer development (Sahar and Sassone-Corsi 2007, Zhu et al. 2007, Davis and Mirick 2006, Megdal et al. 2005, Harris et al. 1997). The assumption that there is a circadian effect on cancer is also supported by observations that the efficacy of chemotherapy appears to be better at particular times of the day (Hunt and Sassone-Corsi 2007) and the prognosis for cancer is poorer in patients having disrupted circadian rhythms (Sahar and Sassone-Corsi, 2007).

To understand the pathogenesis of cancer in more detail it will be important to identify the mechanisms which contribute to the loss of control of the cell-division cycle.

3 AIMS OF THE STUDY

Our studies were based on the following hypotheses:

I Daylight saving time transitions affect the quality of sleep and the rest-activity cycles of healthy adults

II The effect of the daylight saving time transitions are different in fall versus spring

III There are subgroup-specific differences in the adjustment to the daylight saving time transitions

IV Daylight saving time transitions influence the incidence rates of hospital-treated accidents and manic episodes

V There is a relationship between disruption of the circadian clockwork due to night work and the incidence of Non-Hodgkin lymphoma

These hypotheses were tested in Studies I-V.

4 SUBJECTS AND METHODS

4.1 Design of the study

4.1.1 Materials

4.1.1.1 Subjects

The volunteer participants in studies I-III were healthy adults free of any psychotropic medication. Before starting the study, the subjects gave written informed consent. All subjects lived in Helsinki, Finland and none was a shift-worker nor crossed time zones during the study. All subjects used an alarm clock regularly. Participants were asked to retain their normal or regular daily schedule during the study.

For study IV, information about hospital-treated accidents and manic episodes was gathered from the Finnish Hospital Discharge register. The years 1987 to 2003 were studied.

Study V consisted of all Finns born from 1906 to 1945 who participated in the National population census on 31 December 1970 (2 186 029 persons). For our cohort study, all the cancers diagnosed from 1971 to 1995 among persons born from 1906 to 1945 were extracted from the Finnish Cancer Register and sent to Statistics Finland for linkage with the 1970 census files.

4.1.1.2 The Finnish Hospital Discharge Register

The Finnish Hospital Discharge Register covers all mental and general hospitals, as well as in-patient wards of local health centers, military wards, prison hospitals and private hospitals in Finland. From this register we obtained the information about the hospital-treated accidents and manic episodes during two weeks before and two weeks after the transitions in 1987-2003.

4.1.1.3 Cancer registry

The Finnish Cancer Registry has collected data on all cancer cases diagnosed in Finland since 1953. All physicians, hospitals, and pathology, cytology and hematology laboratories in the country are obligated to send a notification to the registry of all cancer cases that come to their attention. In addition, Statistics Finland annually sends to the registry a computerized file of death certificates in which a malignant disease is mentioned. The coverage of the registry is virtually complete, and the data accuracy is high (Central Statistical Office of Finland, 1974).

4.1.2 Methods

4.1.2.1 Wrist-worn accelometers

Wrist-worn accelometers, actigraphs, are one of the best-known methods for sleep research. Actigraphs provide information about the quality and amount of sleep and the activity of the subject. Actigraph detects and records the intensity and duration of movements.

Actigraphs (Actiwatch-Plus®, Cambridge Neurotechnology Ltd., Cambridgeshire, UK), were used in studies I-III to measure the rest-activity cycles of the subjects before and after the transition into and out of DST. The subjects wore the actigraphs on their non-dominant arm all the time, except when bathing or swimming. The actigraphic variables used for the analysis in studies I-III are listed in Tables 1 and 2. The actigraphic data was analyzed with the software provided by the manufacturer (The Actiwatch Sleep Analysis Programme 2001, version 1.19).

Table 1. Actigraphic actogram analysis variables used in studies I and III.

Variable	Abbreviation	Description
The 10 hours of highest activity	M10	The most active 10-hour period of the 24-hour pattern. Average activity during M10 provides an indication of the peak of the rhythm
The 5 hours of lowest activity	L5	The least active 5-hour period of the 24-hour pattern. Lower values indicate more restful sleep
Intra-daily stability	IS	Quantifies the strength of coupling of the sleep-wake rhythm of the 24-hour regularity in the environment. Higher values indicate a more stable rhythm and lower values indicate a weak circadian rhythm
Intra-daily variability	IV	Quantifies the fragmentation of periods of rest and activity. Higher values indicate a more fragmented rhythm
Relative amplitude	RA	Quantifies the difference between daytime and night-time activity levels. Higher values indicate a stronger rhythm and lower values indicate a weak circadian rhythm
Circadian period	tau	Estimates the circadian period of the individual

Table 2. Actigraphic sleep analysis variables used in studies II and III. In addition to these, naps were scored using the Actiwatch Sleep Analysis software.

Variable	Abbreviation	Description
Time in bed	TIB	The total time spent in bed
Assumed sleep	AS	The difference between sleep end and sleep start
Actual sleep time	AST	Assumed sleep minus time awake in bed
Bed time	BT	The time when subject went to bed
Get up time	GUT	The time when the subject rises in the morning
Actual wake time	AWT	The actual time spent awake in bed
Sleep efficiency	SE	The percentage of time spent asleep whilst in bed
Sleep latency	SL	The time delay between going to bed and falling asleep
Number of minutes immobile	IM	The total number of minutes immobile during sleep
Number of minutes moving	MO	The total number of minutes moving during sleep
Total activity score	TAS	The total number of activity counts between sleep start and sleep end
Mean activity score	MAS	The average value of the activity counts per epoch over the assumed sleep period
Mean score in active periods	MAP	The average activity score in those epochs where scores of greater than zero were recorded during the assumed sleep period
Movement and fragmentation index	FI	Indicates the rate of restlessness of the sleep

4.1.2.2 International Classification of Diseases

Accidents and manic episodes were classified according to the International Classification of Diseases (ICD). Before 1995, the diagnoses were coded according to ICD-9, and for 1996-2003 they were coded according to ICD-10. All periods of hospital treatment due to accidents or manic episodes occurring within the two weeks preceding or following spring and fall transitions were mapped out, and from this data, the following information was gathered: the start and end days of treatment, diagnosis, the year of birth, sex and personal identity number.

4.1.2.3 Job-exposure matrix

The occupational exposure estimates used in study V were based on the Finnish job-exposure matrix FINJEM (Kauppinen et al. 1998). The basic dimensions of exposure assessment in FINJEM include occupation and calendar time or period. FINJEM provides estimates of the proportion (P) of exposed persons, the mean level (L) of exposure among the exposed in each occupation, and the cumulative index (P x L) as a function of time for each occupational exposure. In study V a cumulative index of night work was calculated. The prevalence of night work in all occupations was assessed on the basis of responses to the question "How is your working time arranged". Only in few occupations did all workers do regular daytime work without any irregular working hours. Concerning the cumulative index of night work, P (proportion) is the probability (no unit) of night work for a given occupation, L (level) is 1 (no unit) for all occupations, since the number of hours per week or of days per year of night work was not scored in the survey, and t is time (in years) spent in a given occupation. For example, an index of 10 means that a person was estimated to have worked in an occupation whose probability of night work is 1 for 10 years, or in an occupation whose probability of night work is 0.5 for 20 years, etc. Low, moderate and high exposures to night work refer to 1 to 10, 11 to 20 and 21 or more years of night work, respectively. It was not possible to use regular daytime workers as the unexposed reference group, because the exposure assessment was not based on individual data but on the prevalence of night work in occupational groups.

4.1.2.4 Self-reports

4.1.2.4.1 Morningness-Eveningness Questionnaire

To assess preference with respect to daily activity patterns, the participants completed the Morningness-Eveningness Questionnaire (MEQ) before starting studies I-III. MEQ is a self-reporting instrument that includes 19 items estimating preference for the timing of different activities and behaviors, whose sum yields the Morningn type-Evening type Score (MES), ranging from 16 to 86 (Horne and Östberg 1976). The highest score (59-86 points) indicates preference for activities in the morning (Morning type), whereas the lowest score (16-41 points) indicates preference for activities in the evening (Evening type). Most of people are intermediate types whose activity is highest in the daytime (42-58 points).

In contact with MEQ we also asked the participants to indicate how many hours of sleep they would need in order to feel refreshed and what is their usual daily schedule. The amount of sleep debt was calculated as the difference between the preferred and actual length of sleep per night.

4.1.2.4.2 Seasonal Pattern Assessment Questionnaire

Seasonal Pattern Assessment Questionnaire (SPAQ) is a self-report instrument for the assessment of the seasonal changes in the length of sleep, social activity, mood, weight, appetite, and energy whose sum yields the Global Seasonality Score (GSS), ranging from 0 to 24. The higher the score is the more the seasonal changes impact the subject. Over 10 points or more indicates high seasonality. Participants filled in the Seasonal Pattern Assessment Questionnaire (Rosenthal et al. 1984) before starting the study III.

4.1.2.4.3 Sleep diaries

Sleep diaries are a commonly used method for evaluating sleep schedules. Sleep diaries provide subjective information about the quality and quantity of sleep. During studies I-III, participants wrote down the times when they woke up and went to sleep. Participants also estimated the time when they fell asleep and reported if they had any naps during the daytime. The sleep diaries were used as a supplement to the actigraphic analysis.

4.2 Ethics

All subjects were adults (over 18 years of age) at the time of the enrollment and signed an informed consent form prior to participation in the study. The ethics committee of the Helsinki and Uusimaa Hospital District approved the study protocol of studies I-III. For studies IV and V no ethical clearance was needed because the dataholders, the National Research and Development Centre for Welfare and Health (The Finnish Hospital Disharge Registry) and Finnish Cancer registry, gave their permission for the information to be used.

4.3 Statistics

The statistical analyses were calculated using SPSS for Windows (Versions 11.5.1 to 15.0, SPSS Inc., Chicago, Illinois, USA), R (Version 1.8.1, R Development Core Team, 2005) and SAS (Eight Revision 1999-2001, SAS Institute, Cary, North Carolina, USA) programs. Study protocols, aims and parameters of interest provided the rationale for the variables for the statistical analysis in each study.

In study I, our aim was to analyze the impact of DST transition on the daily rest-activity cycles as a function of time. Relevant variables were explored, and they included: the 10 hours of highest activity (M10), the 5 hours of lowest activity (L5), intra-daily stability (IS), intra-daily variability (IV), relative amplitude (RA) and circadian period (tau). The subgroups used in the analysis were based on the morningness-eveningness typology and on the preferred length of sleep.

In study II, we assessed the impact of DST transition on the night-time sleep. Assumed sleep (AS), actual wake time (AWT), sleep efficiency (SE), and movement and fragmentation index (FI) were included in the analysis. As in study I, also in study II the subgroups used in the analysis were based on the morningness-eveningness typology and on the preferred length of sleep.

In study III, we wanted to elucidate the impact of DST on the daily rest-activity cycles and the night-time sleep. Movement and fragmentation index (FI), sleep efficiency (SE), relative amplitude (RA), intra-daily variability (IV) and intra-daily stability were relevant to the analysis. As in studies I and II, in study III the subgroups used in the analysis were based on the morningness-eveningness typology, and in addition on the seasonal changes on mood and behavior.

In study IV, the number of hospital treatments due to accidents or manic episodes was studied in respect to the year, season (spring or fall), study period (before or after DST transition), geographical location, sex and age.

In study V, we aimed at analyzing the exposure to night work in relation to the occurrence of Non-Hodgkin lymphoma.

The outcome-variables of studies I-V were analyzed with appropriate statistical methods as described in the original publications.

5 RESULTS

5.1 Studies I and II

In 2003, DST started on the 30th of March at 3 a.m. Rest-activity cycles were measured for the period from the 23rd of March to the 3rd of April, thus yielding data for a period of ten days around the transition. In 2004, DST started on the 28th of March at 3 a.m. and the rest-activity cycles were measured as for the previous year for a period of ten days around the transition from the 22nd of March to the 1st of April. Complete data was obtained from 10 participants, 6 females and 4 males, with a mean age of 45.2 years (ranging from 32 to 70 years) during a period of two years. Altogether over 2200 hours of actigraphic data was analyzed for studies I and II.

The participants were assigned to subgroups by the preferred pattern for daily activity (morning, intermediate or evening type) and by the preferred length of sleep (more than 8 hours per night as long sleepers, 8 hours or less per night as short sleepers). Four participants had a preference for morning activities, with a mean MES of 61.0, and six were intermediate, with a mean MES of 50.8. Five reported the preferred length of sleep to be 8 hours or less, and five needed more than 8 hours of sleep per night.

5.1.1 Rest-activity cycles

In study I, the transition night (Saturday to Sunday) was excluded from the analysis. The main finding of study I was that there are subgroup-specific differences in the adjustment into DST.

Among the short sleepers, the intra-daily variability was increased after transition into daylight saving time. Increased intra-daily variability indicates a more fragmented rhythm. This finding was significant (P=0.04). Another, however not a significant finding, was the decreased relative amplitude among the short sleepers after the transition. Decreased relative amplitude indicates a weakening of the circadian rhythm. Among the long sleepers the changes were opposite to those seen among the short sleepers. Among the long sleepers the intra-daily variability was decreased significantly (P=0.05) and the relative amplitude increased. The increase of the relative amplitude was not significant but still apparent.

Another finding of the subgroup analysis was the difference between the morning and intermediate types. Among the morning types the circadian period shortened and the intra-daily variability was reduced. Among the intermediate types the changes were opposite to those seen among the morning types since the circadian period of the intermediate types extended and intra-daily variability increased. These findings were not significant but interesting since the changes were opposite inside the subgroups. It is also remarkable that among the morning types the average level of rest-activity cycles increased significantly after the transition into DST (P=0.01).

There were no significant differences in the adjustment between men and women. However, the intra-daily variability decreased among men but increased among women. The relative amplitude increased among men and decreased among women, respectively. It was also noticed that the intra-daily variability decreased among older and increased among younger participants.

5.1.2 Sleep-variables

In study II we analyzed the results for all the measured days and also for only weekdays (weekends from Friday night to Sunday morning were excluded from the analysis) to see whether there is a significant weekend effect which might cause changes in the results. According to our results, the effect of weekends on sleep variables was mild since our participants followed a regular daily schedule.

Transition into DST reduced both the assumed sleep and the sleep efficiency. The assumed sleep time was reduced by approximately one hour (P<0.01) and the sleep efficiency by approximately 10% (P<0.01) after the transitions. The reduction in assumed sleep and sleep efficiency was seen in both years after transition into DST and the results were similar among short sleepers and long sleepers and among the morning and intermediate types.

Subgroup analysis revealed that the sleep debt was a significant variable since the persons with more sleep debt experienced greater decrease in sleep efficiency after the transition (P=0.04). Also gender and the preferred length of sleep impacted the ability to adjust to the disruption but this impact was not significant.

Our analysis also revealed that sleep becomes more restless after the transition. Actual wake time, number of minutes moving and mean activity score were increased after the transitions and the number of minutes immobile was decreased. All these variables describe the restlessness of the sleep.

5.2 Study III

In fall 2005, DST started on the 30th of October at 3 a.m. Rest-activity cycles were measured for the period from the 24th of October to the 3rd or the 10th of November, thus yielding data for one week before and one (6 participants) or two (3 participants) weeks after the transition. The analysis was made for the data gathered one week before and one week after the transitions. In spring 2006, DST started on the 26th of March at 3 a.m.

Rest-activity cycles were measured for a period from the 20th of March to the 3rd of April, thus yielding data for one week before and one week after the transition. The rest-activity cycles were measured around the transitions out of and into DST in fall 2005 and spring 2006 respectively. Complete data was obtained for both years from 9 participants, 8 females and 1 male, with a mean age of 27.9 years (range from 20 to 40). In study III, we excluded all weekends (Friday night to Sunday morning) from the analysis. Altogether over 2000 hours of actigraphic data was analyzed for study III.

The participants were assigned into subgroups by the preferred pattern for daily activity (morning, intermediate or evening type) and by the GSS score. Four participants had a preference for morning activities, with a mean MES of 59.0, and five were intermediate, with a mean MES of 48.2. For the participants, the mean GSS (SD and 95% CI) was 9.11. We compared the activity scores before the spring and fall transitions to see whether there were any differences in the baseline conditions, and there were none.

5.2.1 Subgroups

Adjustments to transitions into and out of DST were not accurate or complete four days afterwards. According to the results the spring transition was more harmful for more the evening type persons, as their intra-daily stability was reduced significantly after the transition (P=0.02). After the fall transition this effect was not seen. Transitions into and out of DST were both more harmful for those persons who had greater seasonal changes in mood and behavior. After the fall transition, the movement and fragmentation index increased more (P<0.05) among those with a higher GSS.

5.2.2 Sleep and rest-activity cycles

The movement and fragmentation index, which indicates the restlessness of the sleep, increased in all the participants after both transitions (P=0.01). In fall, sleep efficiency (P=0.02) and relative amplitude (P=0.02) were significantly reduced in all except one participant after the transition. Also in spring a reduction in sleep efficiency and relative amplitude was seen, but in spring the reduction was not significant.

5.3 Study IV

The material for study IV was derived from the Finnish Hospital Discharge Register. From the register we obtained information about hospital-treated accidents and manic episodes during the two weeks before and two weeks after the transitions during years 1987 to 2003. The into-transitions took place on the last Sunday of March during the study period. Prior to 1996, the out-of-transitions took place on the last Sunday of September. Since 1996, Finland as a member of the European Union adopted the last Sunday of October as the out-of-transition date.

Transitions into or out of DST did not have a significant impact on the incidence of hospital treated accidents or manic episodes during the study period. We also analyzed whether there were any significant effects of the different timing of fall transitions on the incidence of accidents or manic episodes, but there was none. However a mild change was seen in the incidence rates of accidents and manic episodes for a week after the spring and fall transitions.

The changes were not similar on all the years studied, but overall the changes were parallel from year to year (tables 3 and 4). During the years 1987-2003 altogether 310 accidents more were recorded into the Finnish Hospital Discharge Register on the week after the transition than on the week before. In fall the change was opposite to that seen in spring. In fall there were altogether 231 accidents less after the transition. The occurrence of manic episodes was higher in fall than in spring. After the fall transition there were altogether 55 cases less recorded into the statistics whereas after the spring transition the occurrence rates of manic episodes increased slightly since 27 cases more were recorded into the statistics.

Table 3. The total number of accidents occurred before and after transitions into and out of daylight saving time on years 1987-2002 in Finland.

	FALL		SPRING	
Year	1 week before	1 week after	1 week before	1 week after
1987	1288	1386	1277	1267
1988	1341	1291	1318	1114
1989	1500	1353	1162	1430
1990	1400	1434	1464	1436
1991	1353	1405	1272	1493
1992	1492	1370	1443	1538
1993	1486	1456	1693	1513
1994	1602	1625	1660	1501
1995	1728	1734	1360	1905
1996	1754	1697	1886	1738
1997	1955	1907	1784	1870
1998	1751	1730	1917	1923
1999	1752	1792	1831	1589
2000	1837	1800	2052	1996
2001	1761	1849	1829	1969
2002	1851	1791	1888	1864
Total	25851	25620	25836	26146

Table 4. The total number of manic episodes occurred before and after transitions into and out of daylight saving time on years 1987-2002 in Finland.

	FALL		SPRING	
Year	1 week before	1 week after	1 week before	1 week after
1987	33	23	28	38
1988	30	22	28	37
1989	39	29	25	30
1990	47	37	35	28
1991	33	34	34	23
1992	40	34	33	35
1993	35	40	44	41
1994	51	50	42	41
1995	58	45	37	49
1996	41	40	47	44
1997	50	49	44	57
1998	51	55	49	49
1999	51	57	58	58
2000	59	61	56	46
2001	61	67	65	83
2002	94	75	86	79
Total	773	718	711	738

5.4 Study V

The cohort of economically active persons from ages 25 to 64 during the 1970 population census consisted of 1 669 272 persons; 6307 of them (3813 men and 2494 women) had a NHL during the follow-up period. Economically inactive persons, children and pensionaires, were excluded from the analysis. Work between 23:00-06:00 was defined as night work.

5.4.1 Lag times of 2 and 5 years

With a lag time of 2 years, the risk ratio was significant among those men who had a low exposure to night work and among those women who had had a moderate exposure to night work. For the former the risk ratio was 8% (P=0.05) and for the latter 23% (P=0.04).

With a lag time of 5 years the risk ratios were significant for the men with high and low exposures to night work, 22% (P=0.05) for the former and 10% (P=0.02) for the latter. For women with a moderate exposure to night work the risk ratio was 26% (P=0.02).

5.4.2 Lag time of 10 years

Night work and NHL were most consistently associated with a lag time of 10 years. Night work significantly increased the risk of NHL in men, the overall relative risk being 10% (P=0.01), but not in women, whose overall relative risk was 2%. The risk ratios of males with low and high exposures to night work were 10% (P=0.01) and 28% (P=0.03), respectively, when compared to those who had been working during daytime only. Among women, the risk ratio was significantly increased only among those who had a moderate exposure to night work, the relative risk being 10% (P=0.03).

5.4.3 Lag times of 15 and 20 years

Using lag times of 20 and 15 years there were significant associations among men only. Lag time of 15 years revealed that the risk ratio was significant among those men who had a low exposure to night work, the risk ratio being 10% (P=0.01).

When using lag time 20 years, the risk ratio was significant among those men who had low and moderate exposures to night work. The risk ratios were 10% (P=0.02) for the former and 25% (P=0.03) for the latter.

6 DISCUSSION

6.1 Transitions into and out of the daylight saving time

According to our results the transitions into and out of DST may disrupt the rest-activity cycles of healthy adults and cause significant changes in sleep variables. Several changes were noticed in actigraphic variables after the transitions. Our results suggest that the transitions may compromise the process of sleep, both by depriving sleep and by reducing the efficiency of the sleep. Our findings also indicated that the effects of transitions might be sex, age and chronotype specific. Also the preferred length of sleep and the seasonality affects the ability to rebalance the circadian rhythm after disruptions.

6.1.1 Methods

There are some limitations while using actigraphy. First of all without documenting the sleep- and wake times with sleep diaries, actigraphy may overestimate the sleep time. It seems that the method does not always accurately differentiate the periods of quiet wakefulness and sleep (Hyde et al. 2007). Thus it is important to always use sleep diaries in conjunction with actigraphy. We used sleep diaries in studies I-III and all the subjects returned their diaries. Thus this limitation does not concern our studies here but the limitation of the method should be noticed. Actigraphy seems to be useful for measuring rest-activity cycles of healthy individuals, as we used it in studies I-III, but it has to be pointed out that it is not clear whether the accuracy of the method is lower when used in clinical studies (Acebo and LeBourgeois 2006, Morgenthaler et al. 2007). However, several studies have confirmed that actigraphy is very accurate method for estimating sleep when compared to the gold standard of sleep research, the polysomnography (PSG) (Acebo and LeBourgeois 2006, Morgenthaler et al. 2007, Hyde et al. 2007). Actigraphy is a very useful method for investigating group differences and sleep pattern variation over time. When compared to PSG, actigraphy has many benefits. The wrist-worn accelometer is a small device and thus less disturbing than the classical PSG equipment. Wrist-worn accelometers can be used over long periods of time and during every-day activities unlike the PSG which is usually recorded in hospital over one or two nights. Results from actigraphical recordings also correlate well with measurements of melatonin and core body temperature rhythms (Sack et al. 2007). With actigraphs the sleep-wake cycle can be followed very accurately.

The seasonal changes in mood and behavior were analyzed by using a self-report questionnaire (SPAQ). SPAQ is retrospective to the routine seasonal changes during lifetime and has been evaluated to have a high internal consistency (Magnusson et al.

1997) and two-month test-retest reliability (Young et al. 2003). We assessed the circadian preference of daily activities using a self-report questionnaire as well. This questionnaire (MEQ) has been evaluated to be a fair predictor of the circadian period and phase, and established laboratory protocols have demonstrated that the phases of melatonin and core body temperature rhythms are closely related to the self-reported circadian preference (Griefahn 2002, Duffy et al. 2001, Duffy et al. 1999). Recent analyses have confirmed good psychometric properties for both SPAQ and MEQ (Rintamäki et al. 2008, Hätönen et al. 2008). In a Finnish population, 67% of people are intermediate types, 22% are morning-types and 11% are evening types (E.Kronholm, 2007, unpublished data of FINRISK 2007 survey). This may explain why there were no evening types in our samples in studies I-III. However, the samples represent the two major chronotypes of Finnish population and thus give some understanding about the changes seen in the major population after the transitions into and out of DST.

6.1.2 Changes in actigraphic variables

The results of studies I-III support the hypothesis that a disrupted circadian process is a major cause of disrupted sleep. Sleep disruption after transition into and out of DST seems to be mediated by an unbalanced circadian rhythm.

6.1.2.1 Sleep efficiency

Our studies in years 2003-2005 pointed out that the sleep efficiency is reduced after transitions into and out of DST. These effects were similar to long sleepers and short sleepers and also to morning and intermediate types.

In study II we noticed that the sleep efficiency was reduced 10% after the spring transition. Originally we thought that since the clocks are turned forwards after the spring transition and the sleeper is losing one hour, the shortage of the sleep time would make sleep more compact and efficient. Usually shorter sleep is more coherent whereas longer sleep tends to be lighter. However the transition into DST reduced the sleep efficiency and this effect was similar in all the participants of study II. Same effect was also seen in study III after the spring transition but there the reduction was not significant. The difference between studies II and III may derive from the statistical uncertainty inherent in small sample size, and the finding must be confirmed in further studies before generalizing the results to the whole population.

Our results also pointed out that the sleep efficiency is reduced after the fall transition. This was assumable since turning the clocks backwards during the fall transition extends the night and gives the sleeper one more hour. Longer sleep is usually more fragmented and thus also less efficient. According to recent research (Lehnkering and Siegmund 2007) the duration of actual sleep-time is significantly longer in fall than in spring. Thus the additional one hour gained after the fall transition extends the sleep time even more. It is more difficult to keep the longer sleep time unfragmented. Since the sleep efficiency was reduced after both transitions it seems that swinging of the rhythm is always detrimental.

In study II we also noticed that persons with more sleep debt experienced a greater decrease in sleep efficiency after the spring transition. A mechanism of action explaining this effect needs further exploration.

6.1.2.2 Assumed sleep

Our studies in years 2003 and 2004 pointed out that the amount of assumed sleep was reduced after the spring transitions. These effects were similar for long sleepers and short sleepers as also for morning and intermediate types. The assumed sleep was reduced by approximately one hour after spring transition. This is probably derived from the inability to adjust to the new time caused by the spring transition. It seems that we continue living in the old time for some time and go to bed as we used to do before the transition even when the time has changed. However working hours force us to wake up at a certain time and thus we acquire a sleep debt after the transition. The sleep debt causes daytime sleepiness and thus decreases attention and motivation. Our findings suggest that it takes at least four days to adjust to the new time, as has also been confirmed by other researchers (Monk and Aplin, 1980; Monk and Folkard, 1976).

6.1.2.3 Activity

Study II revealed that three variables: actual wake time, number of minutes moving and mean activity score increased after the spring transition. Oppositely, the number of minutes immobile decreased. These changes indicate that the sleep became more restless. In study III we detected an increase in the movement and fragmentation index after both transitions. This supports the findings of study II by also suggesting that the restlessness is increased after the transitions. The findings about the restlessness are parallel to the changes seen in sleep efficiency and assumed sleep which were also impaired after the transitions. The transitions disrupt our circadian timekeeping system and seem to weaken the efficiency of the sleep.

In study III we noticed that the relative amplitude of daily rest-activity cycles decreased after the transitions. The relative amplitude quantifies the difference between daytime and night time activity levels. Decreased values of relative amplitude indicate weakening of the rhythm. In study III we did not divide our subjects to short sleepers and long sleepers as we did in study I. In study III the relative amplitude was calculated for the whole study population. In study I we noticed that the changes in the relative amplitude are different among the short sleepers and long sleepers. The observation made in study III points out that at least to some extent the relative amplitude is decreased after transitions into and out of DST even though this effect seems to exhibit variation between individuals.

6.1.2.4 Short sleepers and long sleepers

In study I the rest-activity cycles of the healthy participants were measured. The data gathered after the spring transitions in 2003 and 2004 pointed out that the short sleepers are more vulnerable to sudden changes in the sleep-wake cycle. The intra-daily variability and relative amplitude were compromised after the transition into DST among those healthy adults who were short sleepers. For the long sleepers, the impacts of the transition were on the contrary positive since their intra-daily variability decreased and relative amplitude increased. Our results indicate that the long sleepers gain from the transitions into DST whereas the short sleepers tend to lose. It might be that the circadian time-keeping system of the short sleepers is not as flexible as that of the long sleepers. It seems that the long sleepers are more able to stand reductions in sleep duration whereas for the short sleepers it is difficult to reduce the sleep time any more since they already sleep very short periods. This may explain why it is harder for the short sleepers to adjust to the new rhythm after the spring transition.

6.1.2.5 Morningness-Eveningness typology

According to the morningness-eveningess typology, our results in studies I and III indicated that the impacts of the transitions into DST were positive among the morning type of people, since the transition into DST shortened their circadian period and reduced the intra-daily variability. The reduction in intra-daily variability refers to a more solid rest-activity rhythm, which is a positive change. Among the morning types the average level of the rest-activity cycles was significantly increased after the transition into DST. The increase in the average level of the rest-activity cycles indicates a better adaptation to the new rhythm.

Among the intermediate types the transition into DST caused harmful effects since their circadian period was extended. The extension of the circadian period is harmful since it leads to a phase advance. The circadian period of humans advance approximately 10 minutes per day (Czeisler et al. 1999) and thus the additional extension of the rhythm lead to even greater daily advance. The greater the advance the harder it is to attain the normal rhythm. Also the intra-daily variability and intra-daily stability were compromised after the spring transition among the intermediate types. The intra-daily variability was increased and the intra-daily stability decreased indicating an instability of the rhythm after the transition. These negative changes seen among the intermediate types in our studies are similar to those found by Kantermann et al. (Kantermann et al. 2007). They suggest that the evening type of people never adjust to the new time caused by the spring transition and assumably the adjustment is very difficult for intermediate types as well.

6.1.2.6 Global seasonality score

According to our results individuals having higher global seasonality scores had more disruptions in their rest-activity cycles after the transitions. They may thus be more vulnerable to sudden changes in the sleep-wake cycle. Interestingly Øyane et al. found recently that the higher seasonality is associated with a higher amount of sleep-related problems (Øyane et al. 2008). This finding supports our results in study III. Assumably the circadian timing system of the individuals experiencing the seasonality is more sensitive to changes in external environment.

6.1.2.7 Sex and age specific differences

Our findings showed that both women and younger people are likely to react more strongly to abrupt changes in the light-dark cycle or bedtime schedules. However this finding must be interpreted carefully because of the limitations of statistical methods in small sample sizes.

6.2 Accidents and manic episodes

There were no significant changes in the occurrences of hospital treated accidents or manic episodes after the transitions into and out of DST during years 1987-2003. During this 17-year study period, the date for fall transition was changed from September to October in 1996 because Finland joined the European Union. However, the timing of the fall transition date did not make a difference concerning the occurrence of hospital treated accidents and manic episodes. During the study period, a new revision of the International Classification of Diseases was established. Before 1995, the diagnoses were coded according to ICD-9. From year 1996, ICD-10 was used for coding. However, this change did not influence the contents of the diagnostic criteria for the conditions under study. As always in life, there is a small possibility of misdiagnosis. However, in Finland, the clinical diagnoses of bipolar disorder as assessed in hospitals have been documented to be very reliable (Pakaslahti 1987), possibly because manic episodes are easily recognized. We assumed that the effect of transitions into and out of DST can be observed fully within two weeks after the transition. This assumption was based on the fact that it usually takes a week or less for manic episodes to emerge and hospitalization often takes place shortly. Moreover, the accidents which require hospital treatment are severe enough to necessitate immediate hospitalization. Our assumption hence was that longer lag times were not relevant because all hospitalizations due to DST transitions take place within two weeks.

According to our results, transitions into and out of DST have no significant effect on the occurrence of accidents or manic episodes. This finding was surprising since the background evidence suggested that the circadian disruption may trigger mental disorders (Katz et al. 2002). It seems that the one-hour shift is not disturbing enough to trigger conditions for which hospitalization is needed. Interestingly, we noticed that there were more manic episodes in the fall than in the spring (table 4). This finding however was not consistent in all years of the study period, possibly due to weather conditions changing year to year or other external factors. The first depressive episode of bipolar disorder also takes place most often in fall (Partonen and Lönnqvist, 1996). Another interesting finding was that the occurrence of manic episodes was reduced after the fall transition and increased after the spring transition in most of the years. In the spring, the loss of sleep may provoke insomnia thereby triggering manic episodes and ending in hospitalization. Originally, we hypothesized that the increased exposure to morning light after the fall transition might cause phase advance on top of the phase advanced position in bipolar patients and thereby worsen their condition. However, now it seems that at least some patients may benefit from the fall transitions. The fall transition may in fact have a beneficial effect on bipolar patients, as far as their manic rather than depressive episodes are concerned, whereas the effect of the spring transition is a negative one. Overall it seems that the factors related to the fall season have a negative effect on bipolar patients regarding both their depressive and manic episodes. A mechanism of the underlying action remains to be elucidated. Studies of manic episodes of bipolar disorders among the Finns are challenging because the prevalence is low as compared with other Western-type populations (Kieseppä et al. 2004).

According to our results there were more accidents in spring than in fall (table 3), having however fluctuation from year to year. The slight although not significant increase in accidents rates after the spring transitions may be for instance due to the loss of sleep or weather conditions which makes the streets slippery. Sleep deprivation tends to compromise reaction times and alertness levels and is therefore an important predisposing factor for accidents. Opposite to spring, in fall the accident rates were slightly reduced after the transition out of DST. In fall the clocks are turned backwards and thus the sleeper gains one more hour. This additional hour of sleep, if used for sleeping, may explain to some extent why there was a reduction in accident rates after the fall transition.

6.3 Night work and cancer

There seems to be an association between night work and increased risk of NHL. This was presumable due to the fact that the circadian rhythms are tightly connected to the regulation of the cell cycle (Zhu et al. 2008, Filipiski et al. 2002, Fu et al. 2002). From a physiological point of view, night is the most unnatural time to work, and therefore abnormalities in the circadian clockwork are most frequent and potentially most severe after night work in particular. Our findings support this assumption since our results indicated that NHL was especially associated with night work, not with shift work in general. Our main finding was that night work elevated the risk of NHL significantly among men. This finding was consistent with different lag-times and with different amounts of exposure to night work. Among women the prevalence of NHL was significantly increased only with lag times of 2, 5 and 10 years and only among those who had been exposed to moderate degree of night work. These sex-specific differences found may result from a small sample size and a limited power to detect the association among women, or alternatively due to biological differences, for example, in some hormonal factors. It is also possible that the differences in prevalence rates are caused by different tumor types since NHL is a heterogenous group of diseases caused by malignant growth in lymphoid tissue. Because the different malignant types causing NHL are not registered to the Cancer Registry, we can only speculate about this impact. However it might be that different tumor types appear with different lag times and with different rates of exposure.

Previous research has revealed that some clock genes participate in the regulation of immune-response. For example laboratory animals with mutations in Per2 gene lack the physiological daily rhythm of interferon-gamma protein expression in spleen and serum (Arjona and Sarkar 2006). Moreover the Arntl gene has been implied as critical in the development of B cells, specifically in the differentiation of pre-B cells to mature B cells. This evidence indicates that the dysfunction of circadian clockwork may disturb the function of immune system and ultimately lead to cancer development in lymphatic tissue.

One interesting factor that might also be involved in cancers caused by night work is melatonin secretion. It is presumable that night work reduces melatonin secretion since the worker is exposed to light during day and night. Melatonin has antioxidative properties which protect from cell damage and prevent malignant growth (Bartsch et al. 2002). The reduction in melatonin production may thus be harmful and one of the factors behind the high prevalence of cancers among night workers (Srinivasan et al. 2007, Dopfel et al. 2007). Since individuals who work at night may also have a lower exposure to sunlight, confounding by this mechanism is a possibility that needs to be explored as the current evidence is contradictory. There is evidence that the high exposure to UV-light reduces the risk of NHL (Kricker et al. 2008, Smedby et al. 2005). However other researchers report that UV-radiation increases the risk of NHL (Zhang et al. 2007). It might be that the UV-radiation has different kinds of effects varying by the NHL subtypes.

To which extent the abnormalities in the circadian clockwork impact the cell division cycle is still unclear. Since abnormalities in the circadian clockwork may predispose individuals to cancer development, further studies about the connections between circadian rhythm disruptions and malignant growth are needed.

6.4 Limitations of the studies

6.4.1 Studies I-III

The statistical differences observed before versus after the transitions into and out of DST were modest. This was probably due to a relatively small sample size being consisting of healthy subjects in whom substantial changes in the rest-activity cycles are not expected to occur frequently. The results of studies I-III need to be confirmed in further studies before any generalization to the general population or to clinical populations with circadian rhythm-related sleep or mood disorders is made.

Another limitation in studies I-III is the age of the subjects. In studies I and II the mean age was 45.2 years (ranging from 32 to 70), whereas in study III the mean age was 27.6 years (ranging from 20 to 40 years). Thus the study population in study III was younger than the study population in studies I and II. The age difference may have influenced the results, but if this effect exists it is presumably rather small (Czeisler et al. 1999).

6.4.2 Study IV

It is probable that the transition into and out of DST increases the number of accidents such as pedestrian casualties and fender benders that do not require hospitalization. This might in part explain why there was no change in the occurrence of accidents after the transitions into and out of DST. Another limitation of study IV was the low prevalence of manic episodes among the Finnish population (Kieseppä et al. 2004) which may explain why the impact of DST transitions cannot be seen in our statistics. It might also be that turning clocks one hour backwards or forwards has such an effect on the biological clock that it can be kept under control with medication among those who have current treatment because of mental illness.

6.4.3 Study V

Several possibilities for confounding effects exist as a limitation of study V. Both genetics and environmental factors can predispose individuals to cancer development and it is impossible to map all the possible factors out. Thus we have to hypothesize and try to figure out which effects most likely are behind the disruption of the cell division cycle leading to malignant growth.

As a limitation of study V, the exposure assessment was not based on individual data but on the prevalence of night work in occupational groups. Another limitation is that the subtypes of NHL are advised to not to be separated in the Finnish Cancer Registry coding system in order to avoid misclassification.

6.5 Implications and future research

For further exploration, we propose a trial analyzing the effects of transitions into and out of DST in a clinical population, e.g. among the depressed who tend to have clear abnormalities in the circadian clockwork (Bunney and Bunney 2000). As DST affects everyone in a society, it is likely that on a population level many are affected more than the average in our study population. Transitions into and out of DST may have no long-term effect on the circadian rhythms or rest-activity cycles in healthy individuals, but in clinical populations the effects might be stronger.

The one-hour disruption of the circadian rhytm did not trigger significantly more manic episodes than usual, but other studies suggest that the circadian disruption may trigger episodes of mental disorders (Katz et al. 2002). It is important to sort out which mental health conditions particularly are triggered by the circadian rhythm disruption so that people with an increased risk can protect themselves from such triggering events and anticipate the occurrence of symptoms better. This information could also be useful for the assessment, treatment and follow-up of patients. Thus, the connections between circadian rhythm disruptions and mental health deserve further elucidation.

Mental health conditions and accidents that do not require hospitalization may emerge after DST transitions. This information may be derived from statistics other than the hospital discharge register available. In spring 2008, we established a new research project to explore the occurrence of work-related accidents after transitions into and out of DST in Finland. This project is now focused on all accidents having a health-related outcome. We hope that this project will clarify whether there is any change in the number of accidents after the transition.

Since abnormalities in the circadian clockwork have a potentially great and growing impact on public health, their mechanisms of action on malignant growth are worth further research. We are planning to start a new research project aiming at connections between circadian rhythm disruptions and the prevalence rates of a range of cancers.

7 CONCLUSIONS

7.1 Transitions into and out of daylight saving time

According to our results, transitions into and out of DST have a negative effect on the quality and amount of sleep of healthy adults, as we hypothesized. Both the sleep efficiency and the assumed sleep were reduced after the transitions and sleeping became more restless. Also as hypothesized, there were differences between the impacts of spring and fall transitions even though these differences were small. We noticed that changes after the transitions were subgroup-specific. Short sleepers, intermediate types and people with a higher global seasonality score seems to be more vulnerable to sudden changes in the sleep-wake cycle, since their rest-activity cycles and sleep parameters were compromised after transitions. Our results herein are preliminary and further studies having bigger samples as well as clinical samples are needed.

7.2 Accidents and manic episodes

There was no significant change in the occurrence of accidents or manic episodes around the transitions into and out of DST. Herein our hypothesis was incorrect, apparently because the one hour shift backwards or forwards is not disturbing enough to cause accidents or to trigger manic episodes. However, in study IV, a difference in the total numbers of accidents and manic episodes between spring and fall transitions was observed.

Study IV was the first study to explore the rates of manic episodes after the transitions into and out of DST. The results of this big-scale study provide a useful addition to the literature concerning the connections between circadian rhythms and manic episodes.

7.3 Non-Hodgkin lymphoma

As we hypothesized, there seems to be a relationship between the disruption of the circadian clockwork and the incidence of Non-Hodgkin lymphoma. Our latest study revealed that night work may predispose individuals to NHL. This finding suggests that the pathogenesis of NHL involves abnormalities in the circadian clockwork. Night work challenges the circadian clockwork to the limit and may thereby cause failures in the control of the cell-division cycle, consequently leading to malignant growth.

One important challenge is to identify all cancers that are related to disrupted circadian rhythms and to try to prevent these cancers by making living circumstances more compatible with the innate human physiology.

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