Challenging the human circadian clock by Daylight Saving Time and Shift-Work

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Written by

Thomas Kantermann

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1. Gutachter / Prüfer:	**Prof. Gisela Grupe**
2. Gutachter / Prüfer:	**Prof. Benedikt Grothe**
3. Prüfer:	**Prof. Susanne Foitzik**
4. Prüfer:	**Prof. Gerhard Haszprunar**
Sondergutachter:	**Prof. Till Roenneberg**
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Für meine Schwester
Stefanie

„Probleme kann man niemals mit derselben Denkweise lösen, durch die sie entstanden sind.“

Albert Einstein
dt.-amerikan. Physiker, 1921 Nobelpreis für Physik
1879 – 1955

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1. Introduction

Good timing is a crucial attribute in nature. Being at the right time at the right place increases fitness and the chance to survive. Crucial and general as this statement may be, its principals can be found manifold in nature. These principles are reflected in complex interactions from human individuals as also from molecules in a cell. Bees and butterflies, for example, increase their fitness and chance to survive when they are aware of the time of their favoured flowers opening their blossoms to provide access to their nectar. Gazelles in the African steppe in turn do so when they can predict the time of day when not to visit a preferred oasis that might be shared by their predators at the same time. Therefore, to keep the principles of life arranged according to time is a common challenge for all organisms. For humans today, the importance of a good timing is furthermore expressed in terms of social virtues. These are, for instance, punctuality and obligations representing the maintenance of reliability, like the accuracy of flight and work plans or the monthly transfer of the salary. These last examples show that the aspects of increased fitness and survival are not necessarily immediately obvious in behaviours. What it does show, however, is that everything in nature has its time. The common denominator in the mentioned examples is the ability of an inherent time-system to track environmental temporal processes. This system owns the purpose to structure the existence of an organism by the ability to anticipate (predict) individually important environmental alterations. Comparable to organisms which have specialized to certain biotopes (Greek *bios* = life and *topos* = place) as, for example, to an aquatic or terrestric living, some organisms have further specialized to certain chronotopes (Greek *chrónos* = time; Roenneberg, 1992a). The latter means, that these are active during the night- or during the daytime hours. The ability to track time and thereby to specialize to individual chronotopes has been found in organisms of all phyla and described as so-called internal clocks. In analogy to wristwatches humans use to meet social deadlines, the internal clocks manage bodily processes to function in a well concerted action in alignment with the external 24-hour day, to meet biological deadlines.

Internal clocks are characterized by self-sustained inherent rhythms. This property makes the organization of the processes regulated by these internal clocks principally independent from external (eventually disturbing) signals. Those temporal biological rhythms that show a period of approximately 24 hours are called circadian rhythms (Latin, circa = about, dies = day). To maintain synchrony with the environmental 24-hour day the internal, circadian clocks must to be reset each day by so-called entraining signals. Various external factors have been identified as entraining signals whereas for mammals, and therefore also for humans, the most potent signal is light. Chronobiology investigates these biological internal rhythms and the mechanisms behind the temporal organization of living systems. This thesis is about those influences from everyday life on the human circadian clock that interfere with the temporal organization of meeting biological and social deadlines. These influences are (i) the biannual transitions to and from Daylight Saving Time and (ii) shift-work. The subsequent paragraphs will introduce into the field of biological clocks and the challenges on these from real life.

1.1. Biological (circa-) Rhythms

Biological rhythms can either appear dependent or independent from external stimuli (Klerman, 2005). Dependent rhythms are triggered by a given stimulus and only occur in direct relation to an environmental factor. These rhythms vanish with the vanishing stimulus. Independent rhythms continue even in the absence of such external stimuli. External signals that are capable to synchronize (entrain) such rhythms are called zeitgebers, from the German word for ´time giver´. Most common zeitgebers in nature are light and temperature (Roenneberg and Foster, 1997 ; Sweeney and Hastings, 1960). Furthermore remarkable and unique for the independent rhythms is not only their persistence in zeitgeber absence, but additionally their persistence with an inherited period which equals the period of the stimulus. In general, biological rhythms are described by their phenomenology, depending on period length in relation to the earth’s rotation either around its own axis or around the sun.

Those rhythms with a period length (much) longer than 24-hours are called infradian, rhythms (much) shorter are called ultradian and those rhythms with a period length of about 24-hours are called circadian rhythms (Latin, *circa* = about, *dies* = day). The latter are major subject to chronobiological research. Halberg (1959) was first to describe such terminology of rhythms, showing periodicities of circa those of the corresponding stimulus. From this terminology, four circa-rhythms can be described in nature. First, these are the rhythms with period lengths of about one year and the expression of phenomena of seasonality (e.g. breeding rates) corresponding to the turn of the earth around the sun are called circannual rhythms. Second and third in relation to the turn of the moon, earth and the sun there are the circalunar and the circatidal rhythms. Concerning the circalunar rhythms, the female cycles in menstruation are often interpreted to be synchronized with moon phases, whereas this recently has been doubted and ascribed to rather display a synchronization to social or olfactory stimuli instead of having an endogenous circalunar clock as a basis (Roenneberg, 1998 ; Foster and Roenneberg, 2008 (in press)). Circatidal rhythms as the interplay of ebb and flood are mainly stimuli for marine organisms and those living in the shoreline. Last but not least, the fourth rhythm to mention in this context is the circadian rhythm that is characterized by a period close to 24-hours, orientating on stimuli in the relation to the earth's rotation around its own axis. The evolutionary clou of the circadian clock is giving an organism the opportunity to anticipate its "the needs of life" (Moser et al., 2006). These "needs" encompass both being active during the daylight hours (ergotrophic function of "fight and flight") and to rest in terms of regeneration during the dark period within 24-hours (Moser et al., 2006). As already mentioned in the previous section many of these aspects finally increase survival. Therefore, circadian rhythms are found to regulate many physiological processes in a body, from, for example, basal rhythms in heart rate, hormone and electrolyte levels up to complex behaviours like the alternation of sleep and wakefulness (see chapter 1.2 below). Figure 1 provides an overview of the spectrum of internal, spontaneous rhythms found in human bodies, which are major topic of this thesis.

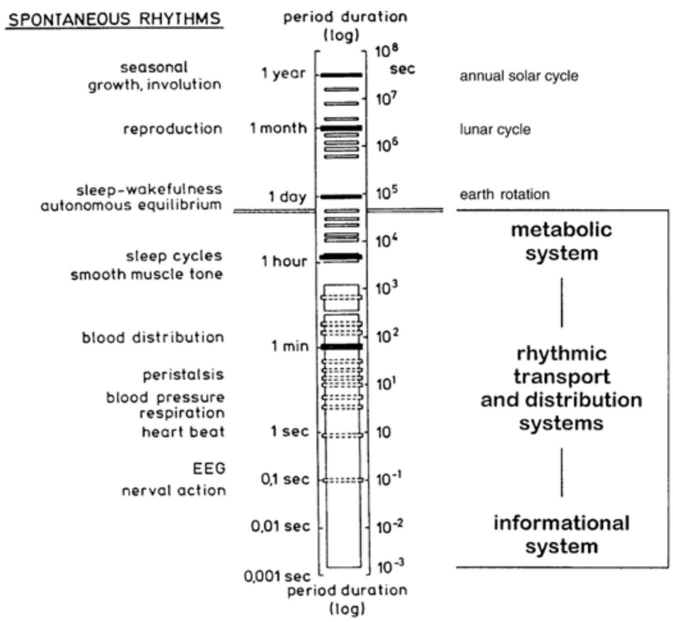


Figure 1 Spectrum of biological rhythms in a human body. The spectrum of circadian rhythms is presented in this figure at the level of period duration of 1 day (log 105), indicated by rhythms of 'sleep-wakefulness' (left side) and 'earth rotation (right side) (Figure taken from Moser et al., 2006).

As circadian rhythms are defined on a 24-hour scale and as humans (normally) take a resting period within a 24-hour day in which they sleep, chronobiological research combines investigations on both behaviours of wakefulness and sleep, and the interaction of these two. This is especially the case for the studies in this thesis. Therefore, before going into detail on the principles of the internal clock (which will be explained in chapter 1.3), the following section gives a brief overview of sleep basics and associated problems.

1.2. Sleep

The alteration between rest (sleep) and activity (wakefulness) is an evolutionary conserved behaviour found in invertebrates, vertebrates and mammals (Campbell and Tobler, 1984 ; Tobler, 2005) and further represents the most obvious states in physiology and behaviour. Historically, body and brain have for a long time been regarded to be inactive during sleep. This has been disproved by displaying the electric activity of a human brain during sleep with means of an electroencephalogram (EEG; first by Caton in 1894). Additionally, this has helped to distinguish between the different neuronal states of rest and activity (Berger, 1929 ; Loomis et al., 1935 and 1937). Dement and Kleitman in 1957 distinguished different sleep stages from different neuronal firing rates in the ablated cortical potentials, summated in the EEG. Based on these findings, Rechtschaffen and Kales (1968) established a standardised scale for a sleep-EEG, which is still in use today.

Due to this standard scale, sleep is separated into REM sleep stages (REM = rapid-eye-movement) and non-REM sleep stages (NREM; aka slow-wave-sleep). REM sleep has been first described by Aserinsky and Kleitman (1953) and is also described as paradoxical sleep, because it is characterized by high activity in the electro-occulogram (hence rapid-eye-movement), a loss of muscle tone in the electromyogram and a low voltage (1-7 Hz), mixed pattern in EEG frequency. Ablations of non-REM sleep further display four different sleep stages (NREM stages I-IV) which the brain runs through during the night (from stage I to stage IV and back to stage I). Stage I represents a stage of transition between wakefulness and sleep and stage IV finally represents a stage of deep sleep (Figure 2). The non-REM stages I to IV and the REM-sleep stages constitute sleep cycles of 90 to 110 minutes duration each. Figure 2 shows that REM-sleep stages become longer in duration over the course of the sleep period and the sleep depth in turn decreases, with the latter facilitating the awakening in the morning.

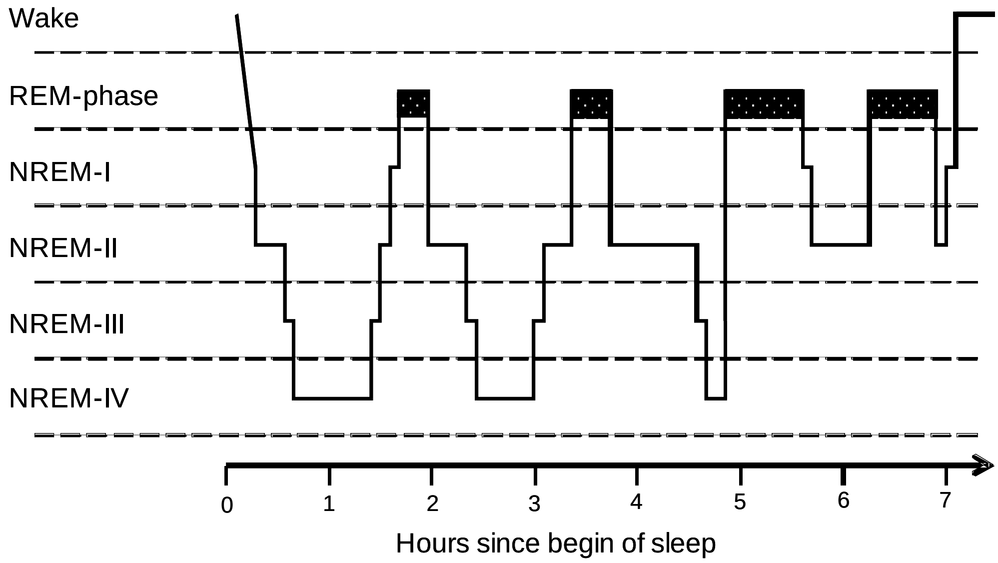


Figure 2 The structure of sleep with the 5 different stages, REM-stage and NREM-stages I to IV. These 5 stages constitute one sleep cycle that takes between 90 and 110 minutes. The duration of the REM-sleep stages increases over the course of the sleep period (adapted from Roenneberg, 2006).

During the past century, sleep has been studied intensively, but its function still remains largely uncertain. Common interpretations range from sleep being necessary for restorative processes, for energy conservation and to recreate or to manifest neurologically what has been learned during the day. Recently, Tononi and Cirelli (2006) have put forward the idea that during sleep the brain is running through a process of reconsolidation and downscaling of neuronal activity and to rearrange synaptic connections, with the purpose to (i) structure activity pattern of the past day and (ii) to prepare the brain for the upcoming wake period. Sleep therefore constitutes a “concerted cerebral cleanup process” that verifies what is important and what is not, in terms that only the important synaptic connections “survive the night”. The logic of the Tononi and Cirelli concept (2006) is underscored by the plausible idea that beings sleep because they were awake and not vice versa, that wakefulness results from having slept. Therefore, science prefers to speak of a ‘need to sleep’ (or sleep pressure), and not of a ‘need to be awake’ (or wake-pressure). Furthermore, this assumption helps to explain the observation of why we as humans can only catch up missed sleep instead of being able to accumulate a forehanded “sleep-reservoir”. The sleep after a certain period of sleep deprivation is characterized by an increased amount of so-called *d*-waves (characteristic wave form in the EEG) that decrease during the recovery sleep. Sleep deprivation therefore has a measurable influence on the normal sleep-EEG-structure. The REM-phases occur later during the recovery nights, first after the sleep pressure has mainly been decreased.

Although, as mentioned above, the definite function of sleep has not been revealed, all prevalent hypotheses finally underscore that sleep is important, and likely an important counterpart to wakefulness. For example, humans cannot help (at least without external substitutes like caffeine or other drugs) from falling asleep after a prolonged period of being awake (e.g. after not having slept for one, two or more days). Furthermore, the fact that sleep in the animal kingdom has not been eliminated during the course of evolution and that it further can be observed in seemingly all species (of course in manifold expressions), does show that sleep obviously is important for our existence, health and well being. The next section is about the regulation of sleep initiation and termination.

1.2.1. Two Process Model of Sleep

Humans cannot end their sleep period on purpose at self selected times without external help from an alarm clock, for instance. Further, they cannot prevent from falling asleep beyond a certain threshold of tiredness. These two facts show that sleep is regulated by a flexible, but autonomous internal system. Borbély (1982) and Daan (1984) have introduced a model to explain the regulation of sleep timing and wakefulness, that combines these two aspects. This model has been introduced as the two-process model of sleep (see additionally a good explanation in Foster and Wulff, 2005). The model describes, that the longer the time one is awake, the higher becomes the sleep pressure that finally leads to sleep initiation. This increase in sleep pressure is measurable from the amount of slow d-waves (these constitute a characteristic wave form) in the sleep-EEG (homeostatic process S; see black curves in Figure 3). The slow-wave power in turn decreases during the subsequent sleep period. As the second component the internal clock regulates the timing of sleep (circadian process C; grey Curves in Figure 3). The internal clock thereby opens a “sleep-window” at a certain point of time and gives a threshold that depending on the amount of accumulated sleep pressure makes us fall asleep or waking up in a respective circadian fashion.

Disturbances on the interplay of these two sleep regulating processes described above, can lead to circadian rhythm sleep disorders, sleepiness and fatigue which will be described in the next chapter and also in the chapter on sleep problems from shift-work (chapter 4.5.1).

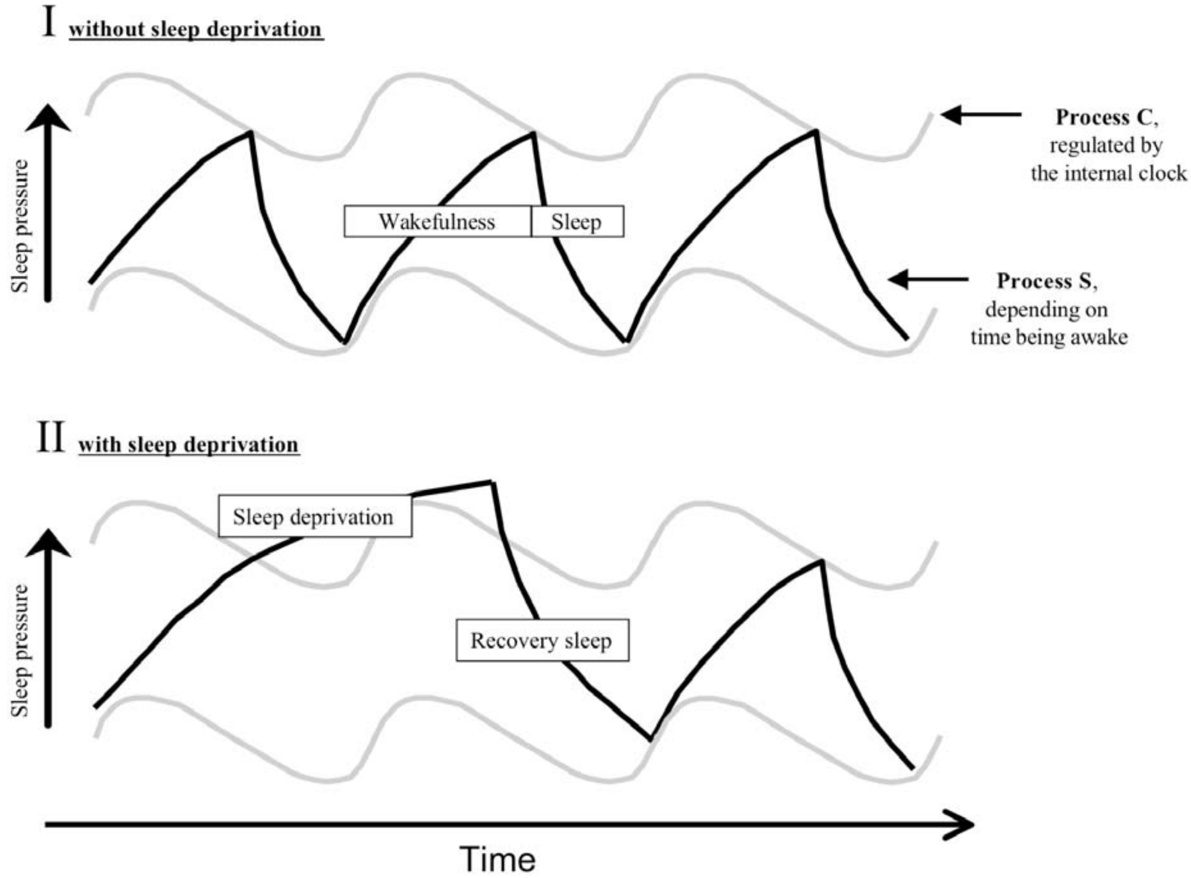


Figure 3 Two-process model of sleep regulation by Serge Daan und Alex Borbély (Borbély (1982) and Daan (1984)). The interplay between these two processes regulates both timing and duration of the sleep period (I, without sleep deprivation). After sleep depression the "slow wave power" at the beginning of sleep period increases and the duration of the recreation sleep is prolonged (II, with sleep deprivation) (adapted from Roenneberg, 2006).

1.2.2. Circadian Rhythm Sleep Disorders, Sleepiness and Fatigue

The importance of the internal clock for a proper sleep initiation and termination has been shown in the previous section, as interferences with the function of the internal clock can lead to sleep disturbances. These will also be subject in the chapter on sleep problems from shift-work (chapter 4.5.1). As a clinical form of such disturbances, the term of "Circadian Rhythm Sleep Disorders" (CRSD) has been introduced into the manual of the International Classification of Sleep Disorders (ICSD codes 780.55-9). The ICSD discusses CRSD being influenced by one or more of the following issues: shift-work; time zone travel (e.g. transmeridianal flights); irregular sleep/wake behaviour, advanced sleep-phase syndrome, or other (so far unspecified) chronobiological and pathophysiological reasons.

CRSD can lead to (daytime) sleepiness and even fatigue. The latter is a more physically pronounced variant of sleepiness, which does not immediately decrease after a sufficiently long sleep period (as sleepiness in most cases does). Fatigue has been characterized by several authors to be marked by (i) drowsiness and dullness, (ii) inability to concentrate and (iii) awareness of physical discomfort (Yoshitake, 1978) . Chalder (1993) categorised fatigue into a mental and a physical component. Smets et al. (1995 and 1996) have extended these models and created a five dimension system with (i) general fatigue, (ii) physical fatigue, (iii) mental fatigue, (iv) reduced motivation and (v) reduced activity. These definitions have in common that sleep deficits affect physical and psychological functions in people. These influences are discussed as risk factors especially in terms of accidents and injuries. The importance of the internal clock in sleep regulation has been pointed out above. In the following chapter I will come back the basics and characteristics of the internal clocks and how these are challenged in real life.

1.3. The Internal Clock

The first description of a process that today is classified as a circadian rhythm dates back to the early 18th century. The French astronomer Jean Jacques d'Ortous de Mairan (De Mairan 1729) described circadian rhythmicity (without being aware of their existence) in the mimosa (*Mimosa pudica*). He observed an alteration in the folding and unfolding of the leaves of the mimosa that pertained in complete darkness. Interestingly, the mimosa belongs to the group of *heliotrope* plants, and *heliotrope* is Latin for "turning toward the sun". This observation has made him conclude that the mimosa owns an inherent mechanism independent from the diurnal changes in light and darkness. In 1905, Simpson and Galbraith were the first to describe such phenomena in animals, in experiments on squirrel monkeys and their rhythm in body temperature.

The mechanism firstly described by de Mairan in 1729 has later been identified to be regulated by the ´internal clock´, which orchestrates all daily functions in organisms of all phyla. Every single cell in an organism has its own clock, which are all built up in tissue clocks, further organ clocks and finally in *the* internal clock (-work), which is observable as an organisms´ entity. All these clocks coordinate processes from gene expression, tissue metabolism, body temperature and complex behaviour (as the rhythm of rest (sleep) and activity (wakefulness)), which all in combination regulate an organisms´ existence (Moser et al., 2006).

In humans the centre (pacemaker) of this internal clock (-work) resides in the suprachiasmatic nucleus (SCN) located in the hypothalamus (Figure 4). Richter (1967) was the first to describe the hypothalamus as the locus of the internal clock, from lesion studies on blinded rats. He noticed that the drinking and eating behaviour was abolished when the hypothalamus was lesioned. The SCN in humans is build of two nuclei of about 10.000 neurons each (ca. 0.23 mm3), and is located on both sides at the basis of the lateral ventricles, approximately two centimetres behind the bridge adjacent to the crossing of the optic nerves (gr. Chiasma opticum; therefore suprachiasmatic nucleus; Figure 4). The cells of the SCN produce self-sustained, spontaneous excitations, which trigger pulsated releases of hormones and neuronal transmitters. These rhythms result from endogenous translation-transcription feedback cycles within each cell, regulated by clock genes (with the most prominent being period 1, 2 and 3 / chryptochrome 1 and 2; clock and bmal1) and their corresponding products, the clock-proteins. Via its rhythmic neuronal outputs, the SCN coordinates all the cellular clocks to adjust their physiology to the Earth's rotation.

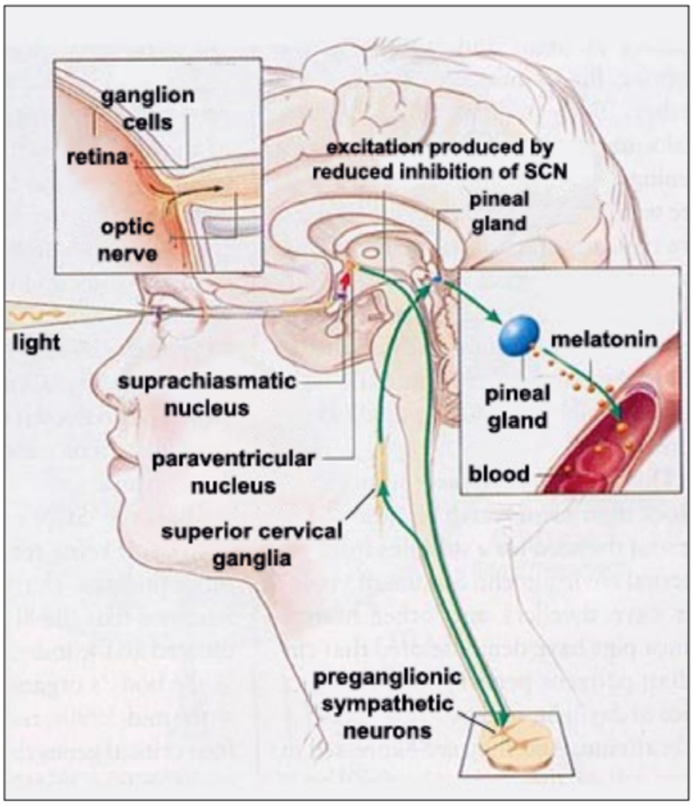


Figure 4 Image of the anatomical connections between the eye (light reception at the retina) and the neuronal pathway via the optic nerves to the suprachiasmatic nucleus (SCN). The figure additionally shows that Melatonin (synthesised in the pineal gland) is secreted into the blood system (source **http://thebrain.mcgill.ca**).

The periods of human internal clocks have been found to vary between 23.5 and 25 hours. The length depends on the individuality of the respective (clock) genes, which equals the distribution of other genetic traits, like hair-colour or body height. As the human internal clock has a period of approximately 24 hours (Latin circa = about and dies = day) it needs to be reset, by the neuronal integration of so-called zeitgeber information each day. Zeitgebers are environmental signals that are capable to entrain (synchronize) the circadian clock. For humans the most potent zeitgeber is (sun-) light (Roenneberg et al., 2007a,b ; Kantermann et al., 2007 ; Danilenko et al., 2000 ; Boivin et al., 1996). It therefore seems to be no coincidence that the SCN is located adjacent to the optic nerves. As in many other animals too light is detected exclusively by the eyes in humans. More precisely, light is received by a combination of rods, cones, and a recently discovered additional retinal photopigment, Melanopsin. This pigment is dispersed in the ganglion cell layer of the retina (Freedman et al., 1999 ; Panda et al., 2002). Melanopsin containing retinal ganglion cells (rGCs) receive photic information which is then transmitted via the glutamatergic retinohypthalamic tract (which are collaterals of the optic nerve) to the SCN (suprachiasmatic nucleus, Figure 4) (Provencio et al., 1998a,b and 2000 ; Hattar et al., 2002).

The internal biological clock starts to “run free” when it is shielded from the solar and social time cues. Remarkably, it does so keeping its inherited and endogenous period close to 24 hours. This was first shown in the pioneering works done by Jürgen Aschoff together with Rütger Wever and their team in the mid-1960ies. Starting with studies in an isolated cellar room in a Munich hospital, they later did famous experiments in a bunker, which has originally been built for exactly their studies in Andechs (Germany). In this bunker subjects have been kept and studied in constant dim-light conditions for several weeks, without any access to the external world. These bunker studies gave important insights into the behaviour of the human internal clock in zeitgeber absence (Aschoff, 1965, 1967, 1981; Wever, 1979; see also the comprehensive review from Mistlberger and Skene, 2004). These experiments have revealed, that the human clock in some people runs with a period length lightly longer than 24 hours and in some slightly shorter. Sleep times or the peak in core body temperature, for instance, of those subjects with a period length longer than 24 hours became later every day, whereas in those with a period length shorter than 24 hours the respective parameters became earlier. Depending on the amount of the deviation from 24 hours (ranges between 23.5 and 25 hours have been observed) it takes up to several weeks until the internal clock reaches the “starting phase point” again.

The function of the internal clock is not caused by the zeitgeber itself. The clou of the internal clock is, as already mentioned, the regulation of daily body processes even in the absence of zeitgebers. Otherwise, such laboratory experiments without zeitgebers would have had an unwanted or even fatal outcome. The mentioned independency allows the internal system to react flexible to environmental changes on the one hand and on the other to adjust these external deviations. One of the most important functions of the internal clock is anticipation. To anticipate the rhythmic changes in the environment makes predictions possible and can therefore be suggested to increase the fitness of an organism. Limits of this adjustability in case of the transition to and from Daylight Saving Time (DST) and shift-work will be explained in the chapters 3 and 4. In the next section, the process that ensures a stable synchronization of the internal clock to its environment will be introduced.

1.3.1. Phase of Entrainment – Chronotype

As introduced in the previous section, zeitgebers are environmental signals that are capable to entrain (synchronize) behaviours via influence on the circadian clock. These zeitgebers can be different among species. For example, light but also temperature have been found to be potent zeitgebers for the fungus *Neurospora crassa* (Merrow et al., 2001, 2006 ; Roenneberg et al., 2001, 2005 , Jacobson et al., 2006 ; Madeti (academic dissertation; in preparation)). Nutrients are potent zeitgebers for the clock in the unicellular alga *Gonyaulax polyedra* (Roenneberg et al., 1992b, 1995). Food is also capable to entrain mammalian behaviour (Honma, 1983; Aschoff, 1986 and 1987), and recent results have lead to the suggestion that food intake activates the dorsomedial hypothalamic nucleus (DMH) (Mieda et al., 2006 ; Gooley et al., 2006 ; Fuller et al., 2008). However, the latter has been shown only in the absence of light stimuli as a zeitgeber and whenever light is present, it turns out to be the most potent zeitgeber for the human internal clock. The effectiveness of entrainment depends on various aspects of the zeitgeber and the clock. These aspects are (i) the zeitgeber strength, (ii) the spectral composition of light (if used as a stimulus), (iii) the duration of exposure to the zeitgeber, (iv) the susceptibility of the light perceiving system and (v) the actual phase position of the clock (Hätönen, 2000; Pauley, 2004). This actual phase position plays a role for the resulting phase position, as zeitgeber exposure before a rhythms´ nadir will advance the rhythm, whereas exposure after the nadir will delay the clock. This property can be compared with the behaviour of a swing (Roenneberg et al., 2003a). Depending on the actual position of the swing, the resultant position after giving a push differs. This means, the swing can stop to swing, can be advanced in position or can be delayed in swinging. Individuals adopt a specific temporal relationship to their external zeitgebers (e.g., the time difference between dawn and wake-up, the core body temperature minimum, or the melatonin onset). This relationship between external and internal time is called phase of entrainment and people that differ in this trait are referred to as different Chronotypes (Roenneberg et al., 2003b). The Munich ChronoType Questionnaire (MCTQ, Figure 7 in chapter 3), developed by our work group, is a simple tool to assess Chronotype in a highly quantitative manner. The MCTQ asks for the individually preferred time of sleep on work and free days separately, from which the mid point of these sleep periods can be calculated as (i) the Mid-Sleep on Free Days (MSF) and (ii) the Mid-Sleep on Work Days (MSW). If, for example, the core sleep period (meaning the time from falling asleep until the time of waking up) is from 00:00 h to 09:00 h, the mid-sleep time point would be at 04:30 h. Sleep times differ between work and free days as many people sleep longer on free days when they do not have to go to work in the morning. In addition, longer sleep on free days can also result from an accumulated sleep deficit over the workweek. A sleep deficit in turn results when the wake up times on work days are earlier than the desired wake up times given from the internal clock (see also chapter 1.2.1, The Two Process Model of Sleep). Therefore, the mid-sleep time point has to be corrected for the weekly sleep deficit to yield the MSF 'sleep corrected' (MSFsc). The distribution of (uncorrected) MSF and the corresponding different Chronotypes (meaning early to intermediate to late Types) in a given population follows a near Gaussian distribution (Figure 5). This distribution can be, for example, compared with the distribution of body height with few very tall and very small people at both ends.

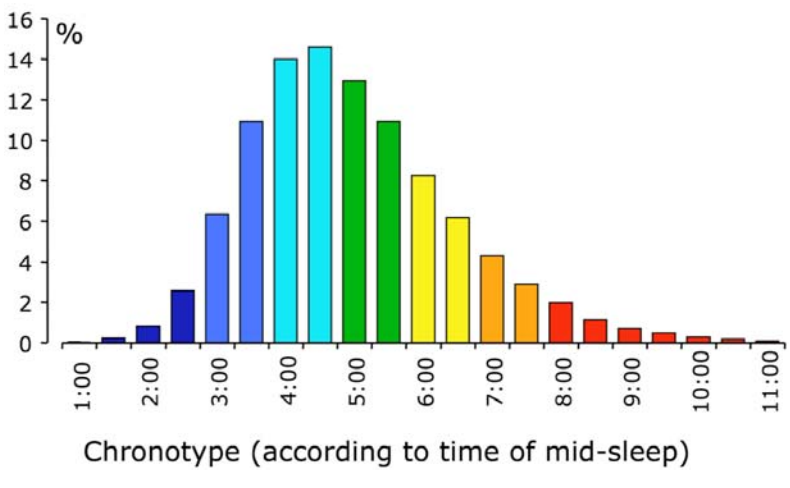


Figure 5 Distribution of Chronotypes calculated by mid-sleep on free days (MSF) from our MCTQ Database with entries from 60.000 people mainly dwelling in Germany, Switzerland, Austria and The Netherlands.

People having their MSF at “04:30 a.m.” would find themselves in the middle of this distribution. These therefore would be intermediate Chronotypes with a MSF of 4.5. Further adjustments for the sleep deficit can be made for **a**ge and **s**ex (MSFsasc; Roenneberg et al., 2007a). Figure 6 presents the distributions for MSF, MSFsc and MSFsasc, which can be narrowed down and get therefore more reliable (for a certain population) with each step of correction (Roenneberg et al., 2007a). As with other genetic traits, circadian properties depend on specific genotypes. Different variants of ‘clock’ genes (Young and Kay, 2001 ; Roenneberg and Merrow, 2003) are associated, for example, with the period length of the circadian rhythm in constant conditions. The free-running periods in a given population are distributed around a mean. Both animal experimentation (Pittendrigh and Daan, 1976a,b) and human studies (Wever, 1979 ; Klerman, 2001 ; Dijk and Lockley, 2002) have shown this distribution to be species-specific. Furthermore, genetic variations partly explain individual differences of the circadian clock function under entrained conditions (Jones et al., 1999 ; Ebisawa et al., 2001 ; Toh et al., 2001 ; Katzenberg et al., 1998 ; Hamet and Tremblay, 2006).

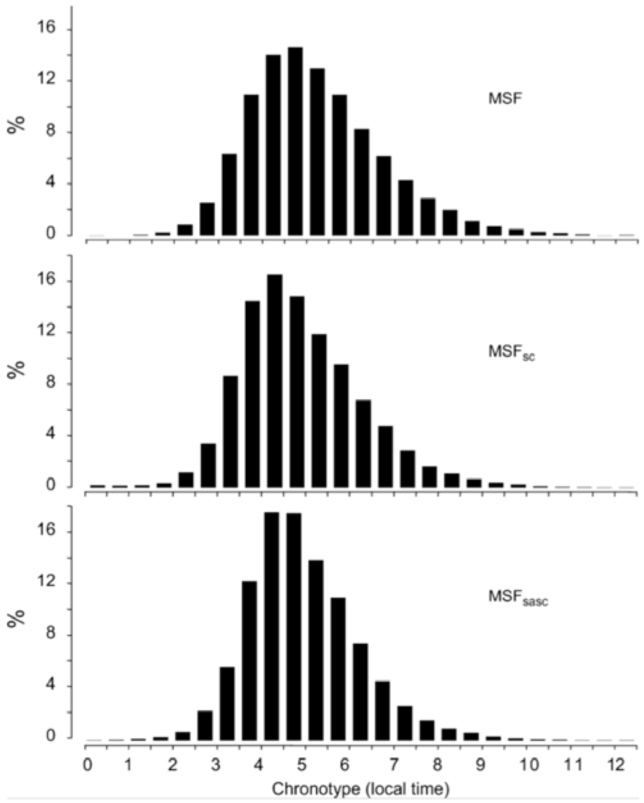


Figure 6 Distributions of Chronotypes judged by different calculations of mid-sleep. The figure on top shows the simple mid-sleep on free days (MSF). The figure in the middle shows the MSF corrected for the sleep debt accumulated during the workweek (MSFsc, see text for details). The figure at the bottom shows the MSFsc further corrected for age- and sex-dependent changes (MSFsasc, see text for details). (Taken from Roenneberg et al., 2007a)

One difficulty in studying circadian rhythms is to elucidate variations, with the aim to understand the behaviour of the internal clock in different situations. The next paragraph will therefore focus on those external factors that challenge the internal clock and thereby offering the opportunity to learn more about the principles of clock functioning.

1.3.2. Challenges to the circadian clock from real life

In the previous chapters it has been pointed out that the internal circadian clock regulates many physiological functions ranging from cellular events (e.g. cycles of DNA-transcription/translation, cell metabolism, etc.) to complex behaviours like the alternations between sleep and wake. As internal clocks are part of processes aiming at keeping the body in a "healthy status", it seems reasonable to investigate the role of internal clock (mal-) functioning leading to certain diseases. Disturbances of circadian rhythms are suggested to be part of the causal chain in the development of certain diseases, which will be presented in chapter 4.

Most of the knowledge about the human circadian clock is based on results from laboratory studies under controlled, artificial conditions. Very little is known about the impact of everyday life on the human circadian clock. Therefore, to yield more knowledge about processes of adjustment and adaptation of the human internal clock in everyday life might help us to develop strategies for disease management and prevention.

In 1979, Karvonen wrote that – generally spoken – the process of adaptation between two given extremes can either result in complete physical, psychological and social well-being or lead to death. The major function of the internal clock is – as pointed out earlier – to increase fitness and the chance of survival, by providing an organism with the ability to anticipate environmental changes. The human body is constantly influenced by external stimuli and is therefore challenged to maintain a state of homeostasis (Greek *homeo* = same and *stasis* = stable). If homeostasis is not maintained, the body runs into and through a process called allostasis (Greek *allo* = different, another). Allostasis is not a steady state but an active adaptation process to maintain stability (homeostasis) through change, which is strongly context dependent (Korte et al., 2005). The concept of allostasis will be adopted in chapter 4.7.2 for the discussion on the results from the literature shift-work survey. In analogy to a state of intermediate inconsistency like allostasis, the next paragraph will introduce a phenomenon from chronobiological research, the so-called internal desynchronisation.

1.3.2.1. Internal Desynchronisation

One important feature of the internal clock is that it is slow in phase adjustment to changes in timing of an individuals´ habits or environment. Especially this feature of slow adjustment prevents the internal clock from changes in the timing of the body clock in case of, for example, a brief nap at noon or awakenings during night, thereby providing a security interval in reactivity. For more permanent changes in the alignment of external and internal time, a lack of synchrony between the body clock and the environment is regarded to be responsible for feelings of sleepiness, discomfort and malaise. An example of an internal/external time mismatch is what time zone travellers experience when their internal clocks adjust step-by-step to the destinations´ environmental cues. This phenomenon known as Jetlag is the result of a rapid change in environmental cues (literarily from flying with a *jet*), which is much too fast for the internal clock to follow immediately with adjustment. Therefore, the internal clock *lags* behind the rapid change in time (hence this phenomenon is called Jetlag).

Studies on Jetlag after time zone travel have yielded insight into the susceptibilities of the internal clock in humans. The results show that the internal clock needs about one day for adjustment to each hour travelled westward and about 1.5 days after corresponding eastward travel (Waterhouse et al., 2002 ; Burgess et al., 2003 , Rüdiger, 2004 , Cajochen, 2005). Therefore, travelling westwards facilitates the adjustment of the internal clock compared to eastward travel. This observation shows that it is easier for humans to delay their sleep times than to advance these. It is easier for humans to get to bed later that to initiate sleep earlier. Concerning Jetlag after transmeridianal flights, one important aspect needs to be kept in mind, namely that Jetlag is experienced only transiently as after sufficient time at the destination, synchronization to the new environment is possible. If this synchronisation is not possible, the body gets into a condition called internal desynchronisation, which is currently discussed in the context of many health deteriorations (Waterhouse, 1999 ; Rüdiger, 2004 ; Cajochen, 2005 ; Haus and Smolensky, 2006).

The concept of internal desynchronisation was introduced first by Jürgen Aschoff (Aschoff, 1965 and Aschoff et al., 1967), from results of the early bunker experiments. Later, Rutenfranz et al. (1976) have adapted this concept to the field of shift-work research on human health. Internal desynchronisation is suggested leading to physiological stress, further to sleep problems and other stress related illnesses (e.g. digestive disturbances or even cardiovascular problems). The theory behind internal desynchronisation is a mismatch in entrainment. This mismatch is discussed to result from a discrepancy between internal, biological and external, environmental (social) time. Several authors have put forward the question if the severity in health problems depends if it is a repeated or a constant misalignment. As will be reported in the chapter on health problems in shift-workers (chapter 4), most health deteriorations are reported for shift-workers employed in a rotational shift schedule, compared to those following constant, not changing work schedules. Therefore, in case of constant shifts (e.g. offshore workers that stay two weeks offshore and two weeks onshore); the internal circadian rhythm has been expected to adjust better.

Up to today, the principles of internal desynchronisation have mainly been studied in laboratory experimentations with animals (Davidson et al., 2006 ; Filipski et al., 2004 ; Stokkan et al., 2001). Studies in this respect on human health are virtually nonexistent and the impact of internal desynchronisation in the aetiology of health problems still remains to be elucidated (Brown et al., 2008 ; Martino et al., 2008). Steven Brown in this context stated that between single cells even from the same tissue "divergent circadian phases of several minutes are normal" (personal conversation). This has been found after isolation of both human and murine fibroblasts. We can learn form this observation that even single cells from the same tissue can be circadian phase divergent. Therefore, a certain divergence in circadian phase might be an inherent phenomenon of these cells, which is not caused by external influences. This might be an additional factor that has to be taken into account to play a role in the individual susceptibility towards mismatches between internal and external time. Future research has to reveal the thresholds of internal desynchronisation that lead to disease when they are exceeded. The concept of internal desynchronisation will also be discussed further in chapter 4.7.2. To elucidate the causalities of internal desynchronisation, adequate parameters are needed to quantify the impact from everyday life onto the human internal clock. This will be discussed in the following chapter on Social Jetlag.

1.3.2.2. Social Jetlag

As described in the previous chapter, Jetlag after transmeridianal travel is associated with a number of health problems. The underlying mechanism that leads to Jetlag is the discrepancy between the internal, biological time and the external, social time at destination. The latter is set immediately with arrival, but the former takes several days to be set to the new time regime.

In analogy to this, a societal phenomenon arranging from modern life ("24/7-society"), which is independent from geographical translocations, has been described recently as ´Social Jetlag´ (Wittmann et al., 2006). For this thesis, the calculation of Social Jetlag has been modified, as proposed by Roenneberg et al. (in preparation). The amount of Social Jetlag will be calculated as the difference (in hours) between the individual internal and external mid-activity time points ($|\text{Mid-Act}_{int}$ - $\text{Mid-Act}_{ext}|$). Internal time (Mid-Act_{int}) is based on the mid-sleep on free days (MSF), calculated from the Munich Chronotype Questionnaire (MCTQ, see chapters 1.3.1 and 3). The corresponding mid-activity time point is then 12 hours phase apart and results from adding 12 hours to the MSF (e.g. with a MSF of 4.5 the Mid-Act_{int} .is 4.5+12 = 16.5; which is 16:30 h.). External time (Mid-Act_{ext}) is calculated as the external mid activity time point, given by mid point of the hours of wakefulness.

The larger the discrepancy between internal and external time, defined by $|\text{Mid-Act}_{int}$ - $\text{Mid-Act}_{ext}|$, the higher the level of Social Jetlag. In everyday life Social Jetlag can be observed, for example, as result from a sleep deficit due to early work or school beginnings that curtail sleep. When sleep is terminated before the desired time from the internal clock (see chapter 1.2.1) the sleep duration is decreased. This in turn is often compensated by prolonged sleep on free days and weekends. The larger the amount of prolonged sleep, the larger is the Social Jetlag.

The concept of Social Jetlag is central in this thesis to explain and discuss the impact of internal desynchronisation to large groups of populations. It will also be used to calculate the specific influence from shift-work on the human internal clock (chapter 5). Although Social Jetlag does not reflect the impact on single cells and organs (which are assumed to be concerned by internal desynchronisation, as pointed out in chapter 1.3.2.1), it will be introduced as a promising and easy measurable parameter in real-life studies at an initial step. In the next chapter, the aims of this work are presented.

2. Aims of this Work

The common approach in science to study the principles and functions of circadian clocks follows examinations in laboratories under controlled, artificial conditions. Real-life studies on the human internal clock are rare and often argued to be of minor use and questionable due to the many uncontrollable influences. Anyhow, with increasing awareness that the human internal clock is involved in almost all facets of health and disease, science cannot ignore the importance of studies in the field. Therefore, to increase the applicability of study results from the laboratory, it is necessary to validate these with data from real life investigations, because science relies on results being reconfirmed. Therefore, the focus of this thesis is put on real life studies. This methodological challenge directly leads to the question of how to gather valid results about the behaviour of the human internal clock under real life conditions, which lead to useful conclusions. The answer to this question of how to study the human clock both in real life and on a population wide level is found in (i) the biannual transitions to and from Daylight Saving Time (DST; affecting about 25% of the world's population; see chapter 3) and (ii) in Shift-work populations (constituting up to 20% of a workforce; see chapter 4). Based on these two major topics, this thesis is separated into three main chapters, which will be briefly introduced in the following sections.

2.1. Daylight Saving Time (DST) and the Human Clock (Chapter 3)

The rational to study the effect of DST has arisen from the facts that:

(i) DST has merely been studied in respect to the human physiology.

(ii) DST has to a lesser extent been studied for effects on the internal clock.

(iii) DST confronts about one quarter of the Worlds´ population that
   - (a) Underlines the importance for this study and additionally
   - (b) Facilitates the recruitment of subjects as these can be studied directly in their real environment.

(iv) DST is, compared to laboratory or bunker experiments, less expensive in terms of study costs for materials (see point iii) and analyses.

The approach to study the influence of DST on the human circadian clock was further propelled by previous results also from our own work group, on the differential behaviour of different Chronotypes in real life settings (Roenneberg et al., 2007a,b, 2003b, 2004, 1989, 1990a,b). Therefore, DST is an ideal topic for implementing chronobiological approaches to real life studies to elucidate the thresholds in adjustment capacities of circadian internal clocks. Results of this study have been already published as Kantermann et al. (2007) .

2.2. **Shift-Work and the Human Clock** (Chapter 4)

Shift-workers are forced by their schedules to work at times that most people use for recreation or sleep. These circumstances make this part of the workforce an excellent sample to study the influence of modern industrialised life on the human clock. The need to evaluate the health of shift-workers and to elucidate possible shift-work related health risks should be of major concern for the following reasons:

- There are distinct and consistent associations between shift-work and adverse health effects, stated by many authors from various different research areas, and
- Despite the awareness of these associations, the number of shift-workers increases worldwide, and
- Concepts to adequately quantify the impact of shift-work on health are missing.

As shift-workers already have been studies all over the world by many investigators, we aimed to elaborate the state of knowledge from the respective literature, before starting new, cost-intensive studies. The literature survey exclusively focused on field studies in real life, for the aforementioned arguments, with special considerations from chronobiology.

2.2.1. **Potential Health Costs from Shift-Work** (Chapter 4.7.3)

As the health situation of shift-workers is of major concern, the costs arising from any shift-work related health outcome is also of strong concern for the health insurance system. Therefore, after evaluating the impact(s) of shift-work on human health from the literature, a potential cost analysis will be performed.

2.3. **Shift-Work/Social-Jetlag-Model** (Chapter 5)

As there are virtually no tools for the quantification of the impact of shift-work on the human internal clock, a program has been development (the “Shift-Work/Social-Jetlag-Model”) that calculates the amount of Social Jetlag, as quantitative measure of the accumulative discrepancy between internal and external time in shift-workers, as has been proposed by Roenneberg et al. (in preparation). The idea to this model bases on the main result of the findings from the shift-work literature survey (chapter 4). These findings indicate that the direction in shift rotation likely lead(s) to different (long- and short term) health outcomes. Social Jetlag has been chosen as the output variable of the Shift-Work/Social-Jetlag-Model that additionally allows calculating chronotype-specific effects. The Shift-Work/Social-Jetlag-Model thereby introduces the concepts of chronobiological research into the field of epidemiological shift-work research, offering excellent opportunities for the design of chronotype-friendly work schedules.

3. Daylight Saving Time (DST) and the Human Clock – A Field Survey

3.1. Introduction

3.1.1. Brief History of Daylight Saving Time

Historically, Benjamin Franklin is said to be the initiator of Daylight Saving Time (DST). At the end of the 18th century he wrote a satirical letter (Franklin, 1784) in which he proposed the Parisians to get up earlier to more properly seize the day (-light). He developed the sparkling idea of saving wax for candles, as fewer candles would need to be burned during the evenings. He further proposed to tax people for burning candles at night or for closing shades during the day. However, Benjamin Franklin never really spoke of changing the clock time. It was William Willet, a famous builder of Great Britain, who in 1907 first came up with the idea of really changing clock time (Willet, 1907). With his pamphlet "The Waste of Daylight", Willet advertised his mainly profit orientated interest of his workers coming earlier to work in the morning. Like perfect salesman do, to sell their products, he additionally put emphasise on the benefit of gaining more time in the evenings for outdoor activities. He finally did not succeed in convincing the British parliament to really change clock time.

The introduction of DST as we know it today is also predominantly propelled by the idea of saving energy and costs on the one hand and to increase productivity by extending the daily working hours by a better use of the natural daylight on the other hand. Anyhow, the results on savings in energy are not consistent and most often not convincing. The statement that under DST less energy is spent is not really proven. Furthermore, an elevated electricity consumption in the mornings has been found by Kellogg and Wolff (2007) . The need to get up earlier during DST is "rewarded" by having more free time in the evenings that can be spent in daylight. The introduction and use of DST is further justified by an unproven statement, of a better fit of daily activities to the daylight hours. Many people complain about to commute to work or school in the dark hours of early morning after the time change in spring. Also, increase of tiredness and lack of awareness are often mentioned by the people.

Finally, it was Germany being the first nation that introduced DST on April 30th, 1916. Monetary and energy savings motivated the German government. To save electricity, oil and therefore money for the 1st World War preparation, the German population was forced to go on a short “eastward flight”, when the clocks changed from 23:00 h to 00:00 h on that day in April. Great Britain introduced DST the same year and the United States followed in 1918.

In the meanwhile, DST is most commonly used in temperate regions, due to the considerable variation in the amount of daylight versus darkness across the seasons in those regions. The word "summer" in this context includes most of spring after the spring equinox and nearly all of autumn (April through October). Likewise, the word "winter" here includes part of autumn and a few weeks in spring (November through March). This varies by time zone, of course, and can change over time as well.

All countries in Europe except Iceland observe DST and change on the same date and time, starting on the last Sunday in March and ending on the last Sunday in October. Europeans commonly refer to the system as summer time: Irish Summer Time, British Summer Time, and European Summer Time. This is reflected in the time zones names as well, e.g., Central European Time (CET) becomes Central European Summer Time (CEST). Today, more than 70 countries worldwide use DST and in 1994, the dates of changing the clocks have been standardised among the European Union. Spring change into summertime is on the last Sunday in March (0200 → 0300 h) and autumn change is on the last Sunday in October (0300 → 0200). In the West European (UTC), Central European (CET, UTC+1), and East European (UTC+2) time zones the change is simultaneous: on both dates the clocks are changed everywhere at 01:00 UTC, i.e. from local times of 01:00/02:00/03:00 to 02:00/03:00/04:00 in March, and vice versa in October. For further information on the history of Daylight Saving Time, I refer to the book “Spring Forward: The Annual Madness of Daylight Saving Time” by Michael Downing , which gives a good overview on this subject. In the next chapter, I will continue giving a brief overview of the previous studies on the impact of DST.

3.1.2. Brief History of Studies on Daylight Saving Time

Despite the fact that ≈1.6 billion people experience DST, few studies have investigated the impact of DST-transitions on physiology and behaviour. One found no effect on psychiatric disorders (Shapiro et al., 1990) . Others studied the effect on traffic accidents with inconsistent results (Varughese and Allen, 2001 ; Ferguson et al., 1995 ; Lambe and

Cummings, 2000 ; Pfaff and Weber, 1982). Behavioural studies accompanying subjects across DST-transitions are rare.

3.2. The Study on Daylight Saving Time

A quarter of the world's population is subjected to a one-hour-time-change twice a year due to daylight saving time (DST). Obviously, this reflects a change in social clocks but not environmental ones (e.g., dawn). The impact of this artificial time change is poorly understood. As in other organisms, the human circadian clock uses daylight to synchronize (entrain) to its environment. Entrainment is so exact that human behaviour adjusts to the east-west progression of dawn within a given time zone (Roenneberg et al., 2007b) . In a large survey (n=55,000), we show that the timing of sleep on free days follows the seasonal progression of dawn under standard time, but not under DST.

Contrary to studies on energy savings or traffic accident risks in times around the transitions, and despite increasing public complaints about the disadvantages of DST (e.g. commuting to work while still dark outside), health effects by these biannual time transitions have merely been studied. As DST is introduced in over 70 countries around the globe and with suspicion of DST affecting the seasonal adjustment in humans, the aim of this study was to gain more insight into the effects of DST on the human circadian clock. We, therefore, analysed the timing of sleep and activity for eight weeks around each of the two DST-transitions in 50 subjects who were chronotyped (analysed for their individual phase of entrainment Roenneberg et al., 2007a). We find that both parameters readily adjust to the release from DST in autumn but that the timing of activity does not adjust to the DST imposition in spring, especially in late Chronotypes. Our data indicate that the human circadian system does not adjust to DST and that its seasonal adaptation to the changing photoperiods is disrupted by the introduction of summer time. This disruption may extend to other aspects of seasonal biology in humans. Studying the effects of DST-transitions essentially investigates the potential re-entrainment of individuals to a new social schedule and should, therefore, consider Chronotype (an individual's phase of entrainment), which differs substantially within a given population (Roenneberg et al., 2007a) . Depending on genotype (Toh et al., 2001) , gender, age (Roenneberg et al., 2004) and light exposure, our clocks will adopt a different phase relationship to dawn.

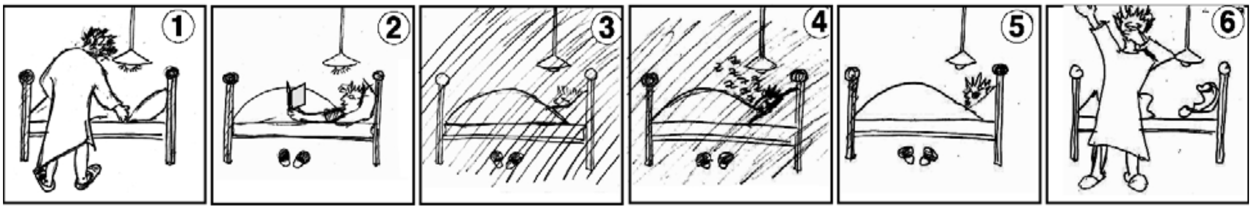
We have developed a simple tool, the Munich ChronoType Questionnaire (MCTQ, Figure 7) to assess Chronotype in a highly quantitative manner. Assessment of how the human clock adjusts to DST-transitions at non-equatorial latitudes is confounded by the fact that the times of dawn and dusk also change. Dawn times (see grey area in Figure 10) change rapidly around the spring DST-transition (which often occurs close to the March equinox) and change to a lesser extent around the autumn transition (which often occurs more than a month after the September equinox). Given that daylight (including the low light levels at dawn) is the predominant zeitgeber for our circadian system (Roenneberg et al., 2007b) it is unlikely that it readily adjusts to the abrupt and purely social DST-transitions.

3.3. Methods

Subjects, study design and instruments: The study included the autumn DST-transition (night of Oct 28/29 2006; study period: Oct 3 - Dec 3) and the spring DST-transition (night of Mar 24/25 2007; study period: Feb 19 - Apr 29). Volunteers (autumn: n= 51, 34 F/29 M; spring: n= 49, 32 F/17 M; age: 18-59 y, mean 34.5 y) were recruited by word of mouth from Germany, Italy, Switzerland, Scotland, Slovakia, The Netherlands, and Luxembourg. 43 subjects participated in both transitions and 6 new subjects were recruited for the spring study. Prerequisites were: informed consent; regular daytime employment; no diagnosed psychiatric diseases or sleep disorders; no travelling during the study periods. Delivery of questionnaires (the MCTQ, Figure 7), logs (Figure 8) and actimeters (Figure 9) were scheduled one week prior to the actual start of each study period, so that all participants were able to complete the full eight weeks in autumn and spring. As a reward, subjects participated in a lottery, whereby any subject could win 250 EUR in each study period. At the onset, participants completed an abbreviated version of the Munich ChronoType Questionnaire (Roenneberg et al., 2003b) (MCTQ; Figure 7), which we developed to assess Chronotype in a highly quantitative manner. The questionnaire contains questions about sleep times on both work and free days. Chronotype is then expressed as the time of mid-sleep on free days (MSF) because free-day-schedules are less confounded by social obligations such as regimented work. The MSF is corrected for sleep-debt accumulated over the work-week (MSFsc). MSFsc is a reliable marker for Chronotype and correlates significantly with the daily rhythms of activity and physiology (e.g., melatonin, cortisol or body temperature, recorded in constant routines) .

Munich Chronotype Questionnaire (MCTQ)

Please complete <u>all</u> sections, regardless of whether you are working on a regular basis or not. Use the 24 hour scale, 23:00 instead of 11:00 !!!!



On work days (includes the night before a work day)

... I go to bed at _________ o'clock **(see image 1)**

... at _________ o'clock, I decide to fall asleep **(see image 3)**

... I need _________ minutes to fall asleep **(see image 4)**

... I wake up at _________ o'clock **(see image 5)**

without alarm clock ☐ with alarm clock ☐

... after _________ minutes I get up **(see image 6)**

On average, how long per day,
do you spend outside exposed to daylight (without a roof above head)? ____h ____min

On free days (includes the night before a free day)

... I go to bed at _________ o'clock **(see image 1)**

... at _________ o'clock, I decide to fall asleep **(see image 3)**

... I need _________ minutes to fall asleep **(see image 4)**

... I wake up at _________ o'clock **(see image 5)**

without alarm clock ☐ with alarm clock ☐

... after _________ minutes I get up **(see image 6)**

On average, how long per day,
do you spend outside exposed to daylight (without a roof above head)? ____h ____min

Figure 7 Analysis of the original version of the Munich ChronoType Questionnaire (MCTQ) identified the rudimentary questions, necessary for quantitative Chronotype assessment. To avoid any confusion concerning the individual questions (e.g., when do you go to bed, get ready to fall asleep, etc.), cartoons exemplify the sequence of events from the time people go to bed and get up. Subjects filled out the MCTQ at the onset of each study period.

Sleep Log - Page 1 - Please send us pages 1 + 2 when completed!

Week	Date	sunlight		Time: "to bed"	Time: "decide sleep"	time to fall asleep	alertness "to bed"	Time: "woke up"	Time: "out of bed"	"alarm clock"		sleep quality	alertness "out of bed"	work day	free day	Comments (e.g. illness ...)
		Hours	Minutes							Yes	No					
1	EXAMPLE	1	30	23:30	23:45	10	4	06:45	06:50	x		7	6	x		
	Tue 20. / Wed 21. Feb.															
	Wed 21. / Thu 22. Feb.															
	Thu 22. / Fri 23. Feb.															
	Fri 23. / Sat 24. Feb.															
	Sat 24. / Sun 25. Feb.															
	Sun 25. / Mon 26. Feb.															
2	Mon 26. / Tue 27. Feb.															
	Tue 27. / Wed 28. Feb.															
	Wed 28. / Thu 1. March															
	Thu 1. / Fri 2. March															
	Fri 2. / Sat 3. March															
	Sat 3. / Sun 4. March															
	Sun 4. / Mon 5. March															
3	Mon 5. / Tue 6. March															
	Tue 6. / Wed 7. March															
	Wed 7. / Thu 8. March															
	Thu 8. / Fri 9. March															
	Fri 9. / Sat 10. March															
	Sat 10. / Sun 11. March															
	Sun 11. / Mon 12. March															

Number ......

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Figure 8 Sleep Log: Subjects filled out a sleep-log every morning after wake-up. Its questions relate to those in the MCTQ (Figure 7).

Every morning, directly after awakening, the following items were estimated and entered into the supplied sleep logs (Figure 8): time spent outside during the prior day, bed-time, time of preparing for sleep, sleep latency, subjective alertness at bed-time (0 to 10), time of wake-up, time of getting up, use of an alarm clock, subjective sleep quality (0 to 10), subjective alertness at wake-up (0 to 10), and whether it was the morning of a work or a free day. Time-spent-outside did not significantly contribute to DST-adjustment, possibly because no significant differences were found in time-spent-outside among the subjects. All subjects continually wore waterproof actimeters (Daqtometer Version 2.3 by Daqtix GbR, Oetzen Germany; Figure 9) around their wrists storing movement accelerations every minute. Subjects kept a protocol indicating when not wearing the actimeter.

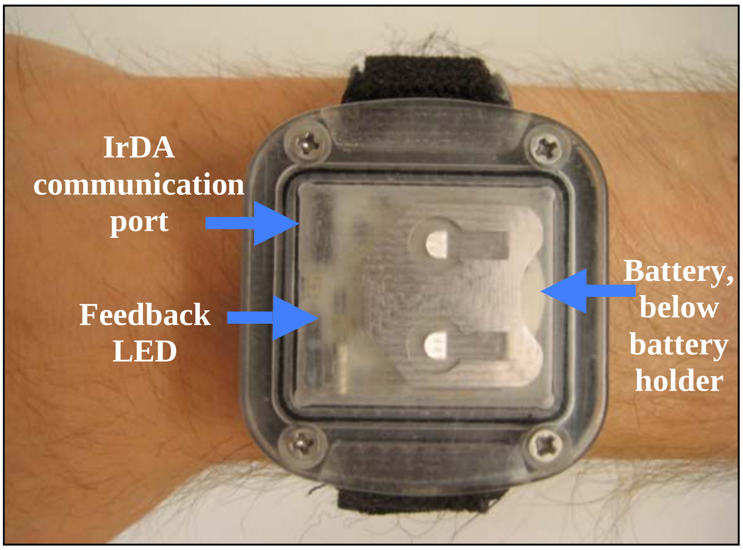


Figure 9 Image of a wrist worn actimetry device (Daqtometer Version 2.3). An integrated dual axis accelerometer (not shown) records both dynamic (motion) and static (gravity, i.e. change in position) acceleration. The energy source is a standard 3 Volt watch battery (CR2032).

Data Analysis

Sleep and activity data were analysed separately for work and free days (in many subjects, free days were not restricted to weekends, and some subjects also worked on Saturday or Sunday). Data were also analysed separately for three Chronotype groups based on Mid-Sleep-on-Free-days corrected for sleep debt (MSF_{sc}) as determined by the MCTQ (Early: $MSF_{sc} < 3.5$, $N_{autumn}/N_{spring} = 11/12$; Intermediate: n= 20/16; Late: $MSF_{sc} > 4.5$, n= 19/15) .

As a single reference point for sleep, daily mid-sleep times were calculated from the sleep-logs and were averaged for each week. Activity data, from wake-up to sleep onset (as determined by the activity profiles), were consolidated to 10-minute bins and also averaged for each week (the Sunday after the actual time change was excluded). For the determination of the activity's phase, we chose the Centre of Gravity method (CoAct; Kenagy, 1980) which is independent of the individual shape of the activity profile (see grey areas and squares in Figure 11). For further analysis, the weekly phases of both mid-sleep and CoAct for each subject were expressed as deviation from their average over the 4 weeks preceding each of the transitions (baseline). An additional average was calculated for weeks 7 and 8 in each study period (final relative phase). Figure 12A shows the averaged deviations from baseline of the entire cohort and Figure 12B shows those for the three groups of Chronotypes.

3.4. Results

We investigated the adaptation of the human circadian clock to both season and DST using two approaches. First, we mined the MCTQ database (containing ≈55,000 subjects from Central Europe, including the date of entry) for seasonal changes in sleep timing at the population level. Secondly, we conducted a longitudinal study to describe the adaptation to DST transitions at the individual level (50 subjects investigated for 4 weeks before and 4 weeks after both the autumn and the spring transition in 2006 and 2007, respectively). Mining the MCTQ database shows that mid-sleep on free days, MSF correlates with dawn under standard time while it is scattered around 3:30 under DST (Figure 10A). Notably, the onset of DST elicits no significant change in sleep timing whereas a large delay follows the offset of DST. Self-reported sleep duration changed significantly across seasons (by ≈20 min; Figure 10B).

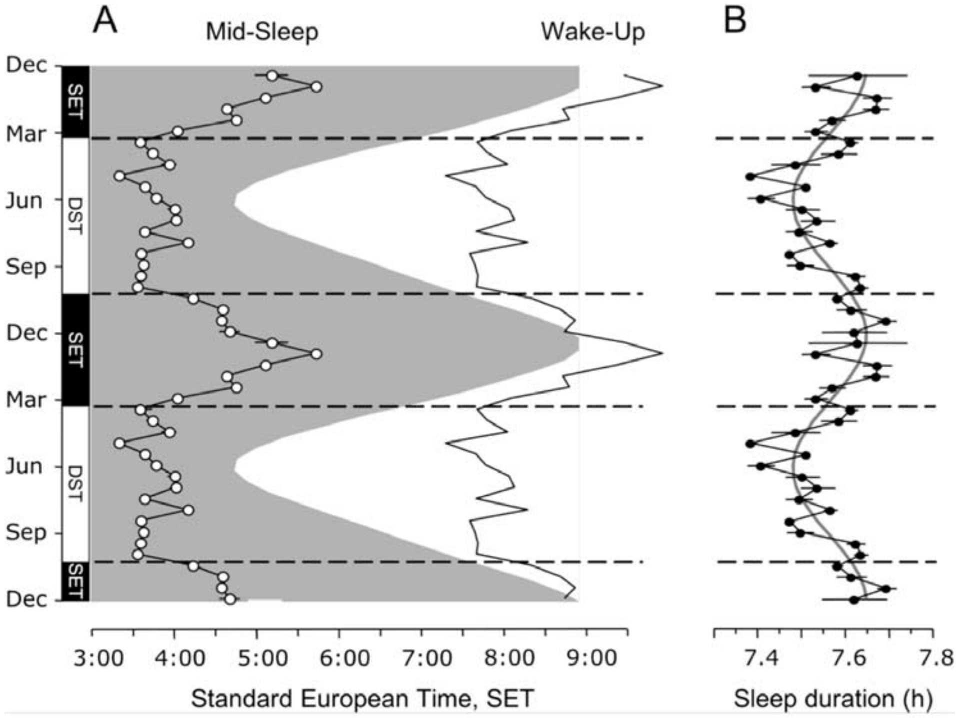


Figure 10 Seasonality in sleep timing taken from the MCTQ database (n≈ 55,000) Annual time courses are double plotted (the same data is shown sequentially to more easily visualize systematic trends). **A.** Half-monthly averages of Mid-Sleep times on Free days , MSF (open circles ± SEM) and of wake-up times (line). DST-periods are indicated by the open boxes and their transitions by stippled horizontal lines; dawn times are shown as a grey to white border. Whereas sleep times track dawn under standard time, mid-sleep is scattered around 3:30 (wake-up times around 7:40) under DST. Age and sex ratio were not significantly different in the 24 averages and showed no interactions. **B.** Seasonal changes in sleep duration (averaged over both free and work days) result in about 20 min more sleep in winter than in summer (cosine fit: r = 0.75; p<0.0001).

To understand the dynamics of how individuals respond to DST-transitions, we evaluated both the phase of sleep (as mid-sleep, calculated from sleep-logs) and the phase of activity (as Centre of Activity, CoAct, calculated from wrist actimetry; see Methods). Figure 11 shows how an individual's activity profile reflects early or late Chronotype. The individual weekly phase deviations from baseline are averaged for both markers (separately for free and work days) either for the entire cohort (Figure 12A) or for the different Chronotype groups (Figure 12B; see legend for statistical analysis). The timing of mid-sleep and CoAct for all subjects on free days fully adjusted to the release from DST in autumn within one week (top left panels in Figure 12A). On workdays, this acute response of CoAct was less pronounced, followed by a gradual change over the 4 post-transition weeks (top right panels in Figure 12A). While both mid-sleep and CoAct on workdays showed a constant (social) phase before the release from DST, they paralleled dawn thereafter, similar to the results shown in Figure 10A.

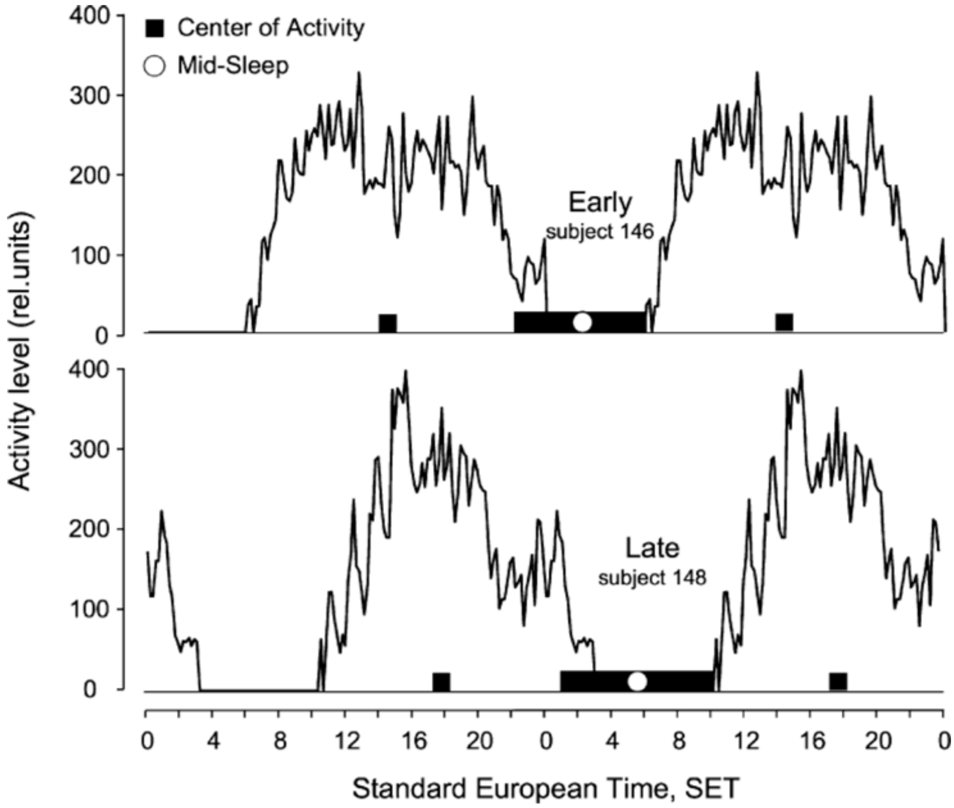


Figure 11 Comparison of sleep times and activity profiles between different Chronotypes. Sleep times (black bars) and activity (black lines) – recorded during the two longitudinal studies around the autumn and the spring DST-transition – averaged for the free days within the four weeks before the autumn change in an early (top) and a late (bottom) Chronotype. Sleep-onset and -offset times are taken from the sleep-logs; activity levels were measured by wrist actimetry. The phase of mid-sleep is indicated by an open circle within the sleep bar and the phase of the Centre of Activity (CoAct, see Methods) as a black square. Chronotype correlated highly with the CoAct at baseline (see Methods; $r = 0.56$, $p<0.0001$). Sleep log entries also correlated with the sleep-times extracted from the activity records similarly for both transitions (for the autumn: sleep-onset$_{before}$: $r = 0.38$, $p<0.001$; sleep-end$_{before}$: $r = 0.7$, $p<0.001$; sleep-onset$_{after}$: $r = 0.22$, $p<0.005$; sleep-end$_{after}$: $r = 0.55$, $p<0.001$).

The spring transition was anticipated by mid-sleep (hence, a reduced acute post-transition phase jump; Figure 12A). This was even more pronounced for the timing of activity (CoAct gradually advanced for 5 consecutive weeks), and indicates that the human clock tracks dawn as photoperiod increases. However, 2 weeks into DST, CoAct delayed again and settled at an advance of less than 30 min (final relative phase; see Methods). Both mid-sleep and CoAct on workdays tracked the social clock before the spring change as they did in autumn. While mid-sleep fully adjusted on workdays (60 % of the subjects indicated using an alarm clock on workdays), the incomplete advance of CoAct on free days was similar for workdays.

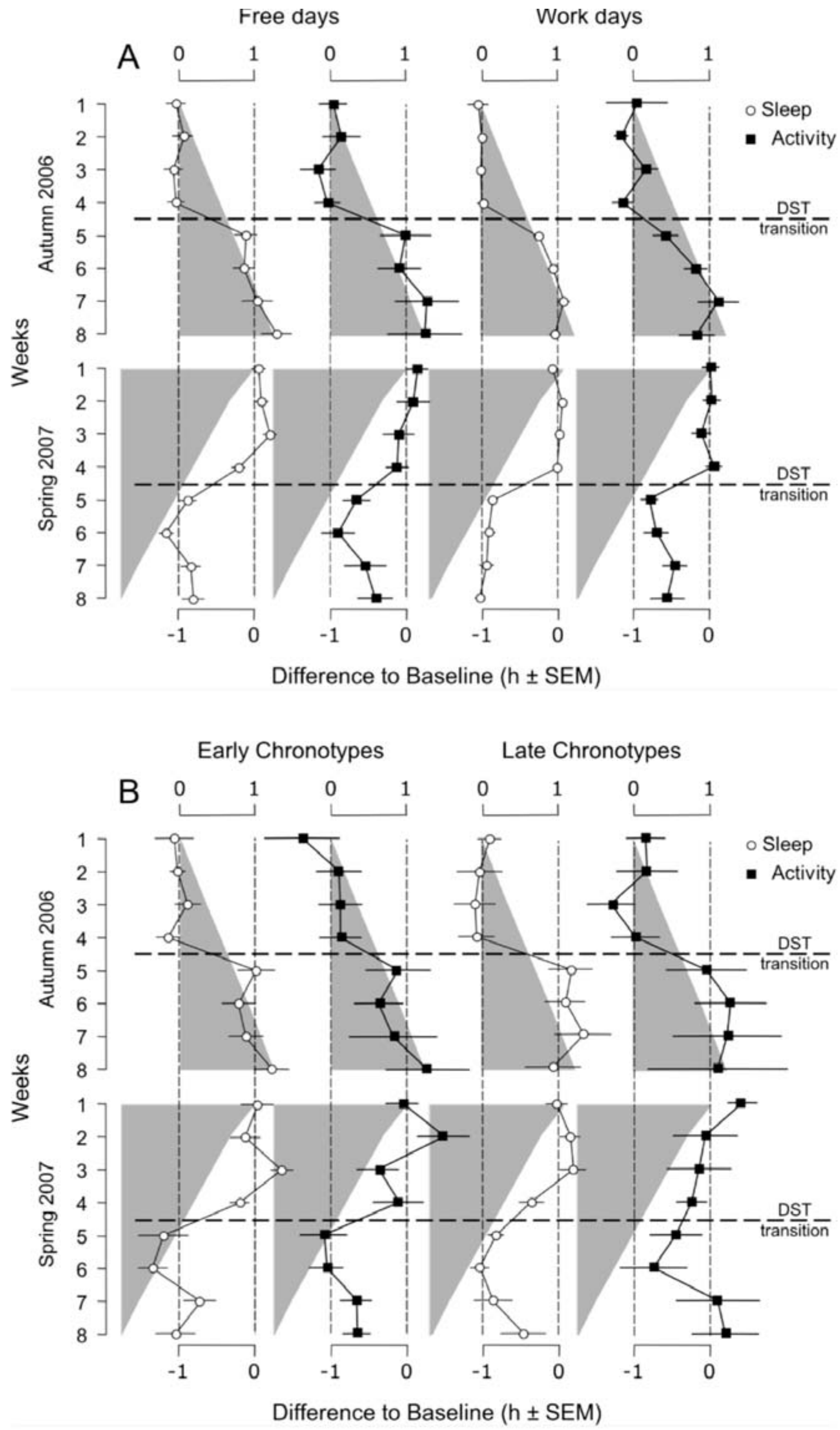


Figure 12 Adjustments to DST-transitions of sleep and activity times resulting from the longitudinal study (n=50) A. Phase adjustments of mid-sleep (circles) and activity (CoAct, black squares) around the DST-transitions expressed as weekly averages relative to each individual's baseline (average phase during the four pre-transition weeks, see Methods). Results are shown for the entire cohort both on free (left panels) and on work days (right panels). The autumn transition is shown in the top panels, the spring transition in the bottom panels. Horizontal bars connected to the respective symbols represent SEM which were in most cases smaller than the size of the symbols. B. The comparison between early (left panels) and late Chronotypes (left panels) is shown for free days only (otherwise as in A). For the changes of mid-sleep on free days in autumn, a mixed ANOVA (within-subject design with Chronotype,

early, intermediate and late, as a between-subject factor) shows a significant difference between all weeks (F (4.33; 117) =10.00, p<0.001). For both transitions, post-hoc tests show that neither the 4 pre- nor the four post-transition weeks differ among each other, while they differ significantly across the transitions. In autumn, the CoAct times show no difference between the 8 weeks (F (3.5; 94) =1.89, p=.13). The changes for CoAct of early Chronotypes correlates better with dawn than with social time (r: 0.938 vs. 0.896). In spring, the phase changes of both mid-sleep and CoAct differ significantly before versus after the transition (mixed design ANOVA; mid-sleep: F (4.57; 128) =20.26, p≤.001; CoAct: F (4.84; 170) =4.36, p≤.001) while they are statistically indifferent among the pre- and post-transition weeks. The changes for CoAct of late types between week 1 and 6 correlate better with dawn than with social time (r: 0.974 vs. 0.774). Whereas post-hoc tests show that the final phases reached in the last two weeks show no significant difference relative to any of the 4 weeks prior to transition for both Chronotypes, they differ significantly between early and late types (t(49)=2.13, p≤0.05).

3.5. Discussion

Different Chronotypes respond differently to time changes. Most people (except for early Chronotypes) adjust more readily to delays than to advances, i.e., they suffer less from jet-lag after westward than after eastward flights (Waterhouse et al., 2002) . A similar pattern is suggested for DST-transitions (Lathi et al., 2006a,b) . Our results show that adjustment to DST-transitions is Chronotype-specific (Figure 12B). We only present results for early and late Chronotypes here (‘larks’ and ‘owls’; those for intermediate Chronotypes lie predictably in between the two extremes) and concentrate on the less socially influenced free days. Mid-sleep in both larks and owls showed a large phase jump in response to the autumn delay (compare with Figure 10A); the response of the CoAct suggests that owls delay more readily than larks (at a level below significance). The Chronotype-specific differences are more marked after the spring change. Again both mid-sleep and CoAct moved with dawn before the transition to DST (compare with Figure 10A), most prominently in the late Chronotypes who gradually advanced their CoAct for 5 consecutive weeks (compare with Figure 12A). Mid-sleep of larks readily adjusted while an apparent full adjustment in owls was transient. Whereas larks advanced their CoAct only by 40 min, owls failed to adjust their CoAct to the advance of the social clock. The similarity between the longitudinal study (50 individuals followed across the DST-transitions) and those found in the database is remarkable (compare Figure 12A&B with Figure 10A). In both cases, the human circadian clock tracks dawn under standard time but not under DST. While the human clock (as measured by the CoAct) predictably advances from autumn to spring (15:54 SET, averaged between Nov 19 and Dec 3, compared to 15:14 SET, averaged between Mar 24 and Apr 21), it remains locked to the same time between spring and autumn (14:36 SET for both, averaged between Apr 15-29 and Oct 3-28, respectively).

These results, in combination with those from the database, suggest that the incomplete adjustment of activity in larks and the non-adjustment in owls continues beyond the 4 recorded post-transition weeks and throughout the months of DST. Our results also suggest that the circadian clock does not adjust to the DST-transition in spring – especially in late types. Notably, the strongest reduction of average sleep duration (for 8 consecutive weeks; Figure 10B) follows the spring transition.

What could trigger the severe effect of DST on seasonal adaptation of the human clock? It is unlikely that mid-sleep tracks dawn throughout the summer, especially at higher latitudes. It is, however, equally unlikely that the abrupt cessation of dawn-tracking, shown here, reflects a threshold beyond which the clock cannot advance (corresponding to a wake-up time around 7:30 SET, 8:30 DST). We have previously shown that the human clock is predominantly entrained to the natural light-dark cycle (zeitgeber$_N$) and that social time affects this entrainment (Roenneberg et al., 2007b) . Behaviourally induced light-dark cycles (e.g., by sleeping in a dark room with our eyes closed; zeitgeber$_B$) may compete with zeitgeber$_N$, especially in large cities where people efficiently shield themselves from environmental signals. We show here that zeitgeber$_B$ (sleep time, represented by mid-sleep) adjusts to DST, thus the “small” 1-h-time-change induced by DST, may have a much larger effect on our biological timing system (Figure 13).

The seasonal progression in phase relationship between the two zeitgebers is pushed back by the equivalent of 4 and 6 weeks in spring and autumn, respectively. The large autumn setback is reflected in the sudden, strong delay (Figure 10, Figure 12A&B). Assuming that the clock tracks dawn similarly in spring and autumn, the current transition from DST to standard time in late October is scheduled one month too late. In addition, DST reduces the seasonal amplitude of the relationship between the two zeitgebers (Figure 13B&C). DST-induced changes are theoretically equivalent to geographical translocations. The amplitude of the relationships as well as the degree of their perturbations by DST increase with latitude. The examples shown in Figure 13 are based on the location of Frankfurt. The 1-hour DST-advance in spring corresponds to travelling 15° westward and the reduction of amplitude corresponds to travelling 17° latitude southward. Thus, DST translocates the inhabitants of Central Germany to Morocco in spring and back in autumn, without changing time zone or climate. In some animals, the circadian clock adopts a fixed phase in long photoperiods under laboratory conditions while they track dawn in short photoperiods (Pittendrigh and Daan, 1976a,b). The interruption of seasonal adjustment in summer shown here, however, exactly coincides with the DST transitions and, therefore, suggests an additional effect of DST rather than a purely natural phenomenon. This would mean that DST severely affects our seasonal timing. Like other animals, humans are seasonal (Roenneberg and Aschoff, 1990a,b) (in birth-rates, mortality, suicide-rates, etc.). However, seasonality in humans has drastically declined in industrialized countries over the last 60 years (Roenneberg, 2004) . The main reason for this is probably increased shielding from natural zeitgebers but DST might constitute an additional factor for the dissociation of human biology from the seasons.

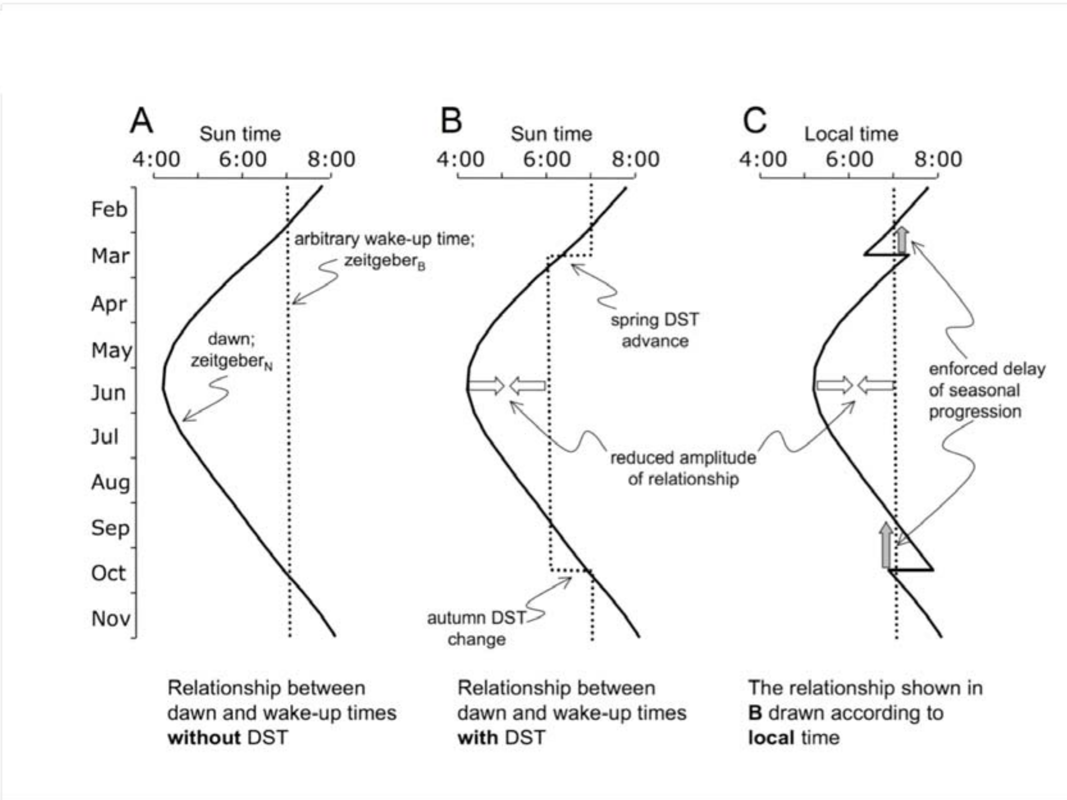


Figure 13 Relationship between natural and behavioural light: dark cycles (with and without DST). The relationship between the natural light-dark cycle (dawn, zeitgeber$_N$; solid curve) and the behavioural light-dark cycle (created by using artificial light and sleeping in dark rooms with closed eyes, zeitgeber$_B$, exemplified by an arbitrary wake-up time at 7 a.m.; dotted line) changes systematically with season (**A**). DST only affects zeitgeber$_B$ by advancing the social clock by one hour in spring and delaying it in autumn (**B**). The 1-hour advance corresponds to travelling 15° westward within the same time zone. DST-transitions have large effects on the seasonal relationship between the two zeitgebers. This phenomenon becomes more apparent if natural dawn is drawn with respect to local time (consistent with social wake-up times) (**C**). The seasonal progression of the phase relationship between the two zeitgebers is delayed by 4 weeks in the spring and by 6 weeks in the autumn (vertical grey arrows). Hence, we repeat almost 20% of the seasonal progression of the two zeitgebers every year. In addition, DST artificially changes the amplitude of the phase relationship in summer (horizontal white arrows in **B** and **C**), which mimics a translocation of 17° latitude. The diagrams are drawn for the dawn times in Frankfurt/Main (50°7'N/8°41'E) which roughly corresponds to the average coordinates of the 50 subjects' places of residence. In this case, the longitudinal and latitudinal translocations would mean moving from Frankfurt to Morocco in spring and back in autumn. The amplitude of the relationships as well as the degree of their perturbations by DST increases with latitude.

This study on the effects of DST on the human internal clock have shown that there is a measurable effect, detectable by simple approaches as use of sleep-logs combined with actimetry. The next chapter is about the effects from shift-work on human health and the internal clock.

4. Shift-Work and the Human Clock – A Literature Survey

4.1. Introduction

Due to the development of a 24-hour-active-world, traditional "9-to-5-jobs" (meaning jobs with work hours from 09:00 to 17:00 o'clock) become a rarity. Medical and security services are prominent examples of non-standard work hours and especially economic constraints as well as expanding global demands force plants and industries to be as productive as possible around the clock, seven days per week. In case of physicians, policemen, fire fighters and pilots, to name just a few, it becomes obvious that each of us depends on shift-workers and relies on them being healthy to do their job. This fact makes the research on shift-workers´ health highly important not only for the workers themselves, but on top for the whole society. The worldwide increase in the use of shift-work schedules to expand the productive period to the full 24-hours each day represents a modern phenomenon that underscores the well-known saying of "time is money". A recent survey by the European Foundation for the Improvement of Living and Working Conditions, (2007) showed the percentage of shift-work within the 27 EU and two EFTA (European Free Trade Association, CH, NO) countries to range between about 8 and up to more than 20 percent, depending on classification of the work hours (Figure 14). The differences in the number of shift-workers in the several countries and work sectors can be attributed to different definitions used to declare the status of a shift-worker.

The respective country codes used in Figure 14 are **AT** Austria, **BE** Belgium, **BG** Bulgaria, **CY** Cyprus, **CZ** Czech Republic, **DK** Denmark, **EE** Estonia, **FI** Finland, **FR** France, **DE** Germany, **EL** Greece, **HU** Hungary, **IE** Ireland, **IT** Italy, **LV** Latvia, **LT** Lithuania, **LU** Luxembourg, **MT** Malta, **NL** Netherlands, **PL** Poland, **PT** Portugal, **RO** Romania, **SK** Slovakia, **SI** Slovenia, **ES** Spain, **SE** Sweden, **UK** United Kingdom, **HR** Croatia, Non-EU: **NO** Norway, **CH** Switzerland, **TR** Turkey, **AC2** Two countries that joined the European Union in 2007: Bulgaria and Romania, CC2 Two candidate countries for membership of the EU: Croatia and Turkey, EU27 = 25 EU Member States, plus the AC2.

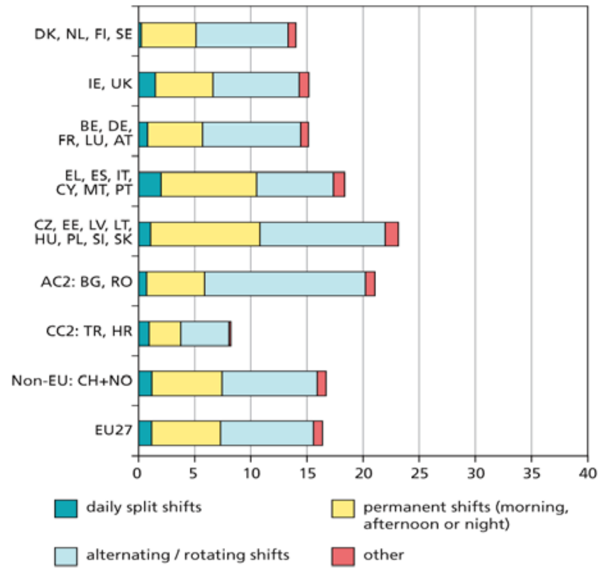


Figure 14 Distribution (in percent) of shift-workers within the 27 EU and two EFTA (European Free Trade Association, CH, NO) countries (taken from the Fourth European Working Conditions Survey, European Foundation for the Improvement of Living and Working Conditions, 2007).

Figure 15 displays the percentage of shift-work within the 27 EU and two EFTA (European Free Trade Association, CH, NO) countries due to working sector.

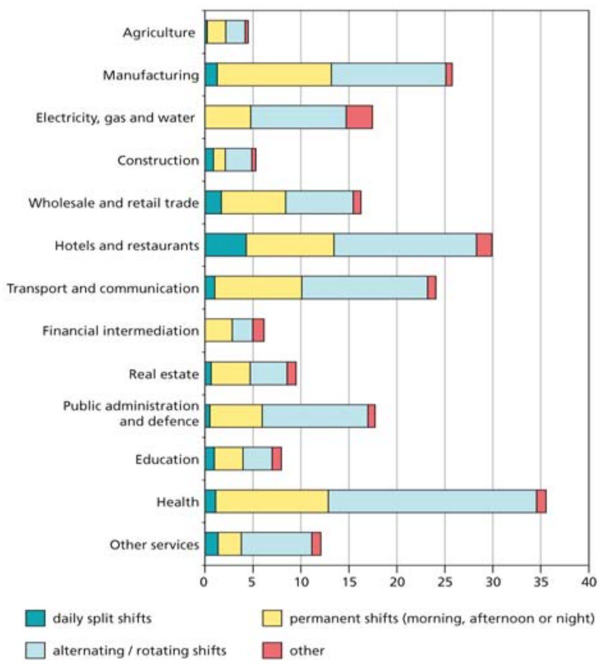


Figure 15 Distribution (in percent) of shift-workers by work sector within the 27 EU and two EFTA (European Free Trade Association, CH, NO) countries (taken from the Fourth European Working Conditions Survey, European Foundation for the Improvement of Living and Working Conditions, 2007).

The following section focuses on the already mentioned variability in shift-work definitions.

4.1.1. Definition of Shift-Work

The term "shift-work" is a synonym that is used for multiple different work schedules. Common descriptions of shift-work are, for example, (i) "work outside the normal working hours" (normal working hours are classified as starting between 08:00/09:00 h and ending between 16:00/17:00 h), (ii) "a work arrangement, in which one worker replaces another within a given work process, in order to maintain continuity in work and productivity over 24-hours" or (iii) "Working at changing or rotating hours". These descriptions show that shift-work is generally regarded due to external time. It has never been described on internal time. In many studies (which are excluded for this study) the authors did even not distinguish between permanent and rotating shift-workers for their analysis. Such mixed results must be interpreted with caution.

Information on the shift-work status is mostly obtained once at study entry (for the baseline evaluation), from either self-administered questionnaires or it has been defined by occupational code from respective file from the workplace. Shift-work has never been evaluated by the actual number of hours that have been worked. The lack of adequate update of the shift-work status might, especially in longitudinal studies, lead to misinterpretations, for example, in case of shift-changes (either due to flexible shift changes in case of colleagues falling sick or due to long-term reorganisations of the shift-work schedules) throughout a workers´ career. Further, work-flexibility, a keyword nowadays to keep up with global demands and needs, makes retrospective evaluations very difficult when such irregularities (e.g. from work-on-demand or overtime) in the work schedules are disregarded. Therefore, calculations on the dose-dependency of only total years in shift-work have to be interpreted with caution.

Definitions of shift-work schedules most often lack the following aspects:

- Shift type (morning, late, night shift)
- Change-over times (e.g. to reflect (very) early starting hours for the morning shift)
- Direction of rotation (e.g. rotating clockwise, counterclockwise, or fixed night work)
- Speed in rotation (e.g. shift changes every 2 days or on a weekly basis)
- Length of the shifts (e.g. 6-hour, 8-hour, 12-hour shifts)

These missing aspects are not to neglect for the evaluations concerning time and health in shift-workers, but are neglected by many researchers. It should further be regarded, that shift schedules differ from plant to plant and also work tasks differ in many occupations between the different shifts (e.g. due to different production processes between day and night shift or because of differing sizes in staff). As heterogeneous the field of shift-work appears, as heterogeneous are the reasons of taking a shift-work job. This is subject to the next paragraph, followed by a section on the social strata of the shift-work populations, common terms from epidemiological research used in this study. Chapter 4.2 finally will tell the rational for the shift-work literature survey.

4.1.2. Reasons for doing Shift-Work

An open question in the field of shift-work research is, if a shift-worker is “born or made”? The answer to this question depends on the individual reasons for people to do shift-work. These reasons are multiple and encompass both occupational and personal aspects. Especially the personal attitude towards shift-work might influence the perception of concomitant burdens. The self-perception and the individual feeling of being committed or not, might influence psychosocial stability and acceptance of certain discomforts. For example, nurses and night watchmen are seemingly aware right from the start of employment that their duty incorporates work hours during the night. In the following, examples will be presented for both occupational and personal reasons for people to be employed in shift-work. Especially the personal reasons have never been investigated in shift-work populations.

Occupational reasons for doing shift-work

- Shift-work is a “usual part of the job” (e.g. for pilots, night watchmen, nurses)
- Shift-work is necessary to guarantee social security (e.g. for the police or fire brigade)
- Shift-work is necessary to guarantee medical aid (e.g. for physicians or nurses)
- Shift-work is used to increase productivity (e.g. in the steel or automobile industry)
- Shift-work is used by an employer to bridge times of a labour bottleneck
- Shift-work is chosen by the worker to not depend on welfare (in case of unemployment, for instance)

Personal reasons for doing shift-work

- Shift-work offers the chance to earn extra money and to have more spare time to follow hobbies ("24-hour society")
- Shift-work allows for arrangements with the Partners´ work schedule
- Shift-work is used to reach a certain status (e.g. it pushes the career or entails a "coolness factor" in terms of being "important" because working during the night)
- Shift-work might suit people with sleep disorders that cannot sleep during the night
- Shift-work might arrange from "Moonlighting"

4.1.3. Shift-Work and Social Strata

Often shift-workers are said to belong to a lower social class. This conclusion results from a bias in the studies, as occupations from "upper social classes" have virtually not been studied that conclusively as, for example, nurses and steel workers. Due to the definition of shift-work as work outside the normal working hours, than also physicians, lawyers, bank or university directors need to be included. These occupations are no classical shift-work jobs and therefore never been in focus. Anyhow, it appears very questionable if such superficial argumentation on the social class is fruitful, as, needless to say, also well-paid physicians or lawyers would be found to smoke or to have low levels of physical leisure time activity. Finally, clarifying studies on this subject (upper vs. lower class jobs in terms of shift-work health outcomes) have not been performed.

4.1.4. Epidemiological terms

This section gives an overview of the most common epidemiological terms used in the studies that will be presented in the next chapters (taken from the Glossary of Terms in The Cochrane Collaboration Vs. 4.2.5 Updated May 2005).

Association / Correlation

A relationship between two characteristics, such that as one changes, the other changes in a predictable way. For example, statistics demonstrate that there is an association between smoking and lung cancer. In a positive association, one quantity increases as the other one increases (as with smoking and lung cancer). In a negative association, an increase in one quantity corresponds to a decrease in the other. Association does not necessarily imply a causal effect.

Bias

A systematic error or deviation in results or inferences from the truth. In studies of the effects of health care, the main types of bias arise from systematic differences in the groups that are compared (selection bias), the care that is provided, exposure to other factors apart from the intervention of interest (performance bias), withdrawals or exclusions of people entered into a study (attrition bias) or how outcomes are assessed (detection bias). Reviews of studies may also be particularly affected by reporting bias, where a biased subset of all the relevant data is available.

Confidence interval (CI)

A measure of the uncertainty around the main finding of a statistical analysis. Estimates of unknown quantities, such as the odds ratio comparing an experimental intervention with a control, are usually presented as a point estimate and a 95% confidence interval. This means that if someone were to keep repeating a study in other samples from the same population, 95% of the confidence intervals from those studies would contain the true value of the unknown quantity. Alternatives to 95%, such as 90% and 99% confidence intervals, are sometimes used. Wider intervals indicate lower precision; narrow intervals, greater precision.

Confounder

A factor that is associated with both an intervention (and exposure) and the outcome of interest. For example, if people in the experimental group of a controlled trial are younger than those in the control group, it will be difficult to decide whether a lower risk of death in one group is due to the intervention or the difference in ages. Age is then said to be a confounder, or a confounding variable. Randomisation is used to minimize imbalances in confounding variables between experimental and control groups. Confounding is a major concern in non-randomised studies.

Odds

A way of expressing the chance of an event, calculated by dividing the number of individuals in a sample who experienced the event by the number for whom it did not occur. For example, if in a sample of 100, 20 people died and 80 people survived the odds of death are 20/80 = ¼, 0.25 or 1:4.

Odds Ratio (OR)

The ratio of the odds of an event in one group to the odds of an event in another group. In studies of treatment effect, the odds in the treatment group are usually divided by the odds in the control group. An odds ratio of one indicates no difference between comparison groups. For undesirable outcomes an OR that is less than one indicates that the intervention was effective in reducing the risk of that outcome.

Risk Ratio / Relative Risk (RR)

The ratio of risks in two groups. In intervention studies, it is the ratio of the risk in the intervention group to the risk in the control group. A risk ratio of one indicates no difference between comparison groups. For undesirable outcomes, a risk ratio that is less than one indicates that the intervention was effective in reducing the risk of that outcome.

4.2. Rationale for the Study on Shift-Work

Research of the past decades has revealed associations between shift-work and adverse health effects. Certain factors are under discussion to modulate the coping ability of shift-workers with related burdens. These factors cover (i) sleep, (ii) social, psychosocial and domestic life and (iii) circadian functions, which in turn all three are interconnected to each other (Harma et al., 1998 ; Nachreiner, 1998 ; Furnham and Hughes, 1999 ; Boggild et al., 2001 ; Costa, 2003). According to the literature, shift-workers show higher prevalences of sleep, metabolic, cardiovascular and cancer problems compared to non-shift-workers (Knutsson, 2003 ; Akerstedt, 2003 ; Costa, 1997 and 2003 ; Haus and Smolensky, 2006 ; van Mark et al., 2006). These four major categories of health issues, as (i) sleep problems, (ii) cardiovascular problems, (iii) metabolic and digestive problems, and (iv) cancer, will also be used in this thesis.

Shift-work directly causes temporal variations in the daily routines of people. Thereby it represents a perfect example for chronobiological research of real life influences. Shifted work schedules interfere with the daily synchronization with environmental cues and leads thereby to exposure to altered (and/or weaker) zeitgeber strengths. This forces workers especially during the night hours to be active at times of their physiological trough. In contrast to time zone travels with its simultaneous changes in both social and natural zeitgebers (e.g. meal times and the hours of dusk and dawn), shift-workers are confronted with only shifts in social, external time, challenging the internal clock. The health outcomes ascribed to shift-workers equal in part those that time-zone travellers also experience (Aschoff, 1978a,b; Aschoff and Pohl, 1978; Cho et al., 2000 ; Rafnsson et al., 2001 ; Waterhouse et al., 2002). Although many aspects in the aetiology of shift-workers´ health problems still need to be elucidated, one thing becomes strikingly evident from the actual situation depicted above, namely that time not only is plain money, but time is health.

The aim of this study is to figure out the knowledge about shift-work and health, under special considerations from a chronobiological point of view.

4.3. Methods

The internet-databases *Pubmed / Medline, Scopus, Psychinfo, Web-of-Science und Biosis previews* have been used for the literature search, as these give access to the largest number of publications on humans and health. Broadly defined search terms have been chosen to scan these databases for all entries through December 2007, with the aim to get as much hits on original (primary) publications as possible. The respective search terms were: *shift-work / night work / night shift / shift schedule / alternating shift / alternating night shift / rotating shift / rotating night shift.* In addition, a hand search in the catalogue of the Bavarian State Library and the Library of the Ludwig-Maximilians University has been performed. In case of ambiguities, the primary author or the denoted contact person has been contacted. The internet database search resulted in a number of *Scopus: 2530, Pubmed/Medline: 2071, Biosis previews: 1812, Psychinfo (Embase):1763, Web-of-Science: 1799* hits (Figure 16). In addition, 2 articles have been found by traditional hand search (not included in Figure 16). Simple minimal exclusion criteria (Table 1) have been used to filter explicitly real life studies, concerning health aspects in shift-workers. Furthermore, the most important difference to previous reviews is that exclusively those studies with a control group of non-shift-workers and that have named the investigated shift-systems have been selected.

	Exclusion criteria for the literature survey
1	Reviews, Letters, Editorials, Comments
2	Animal experimentations
3	Shift-work simulations and laboratory studies
4	Sample size N < 10
5	Use of medication (e.g. melatonin or alcohol as sleep substitute)
6	Sex/gender differences
7	Impact on family life / social life of other than the shift-worker
8	Accident / injury estimations
9	Economy / productivity evaluations
10	Missing non-shift-work control group

Table 1 List of exclusion criteria that have been used to filter those articles that concerned shift-work health issues in human workers under real-life conditions.

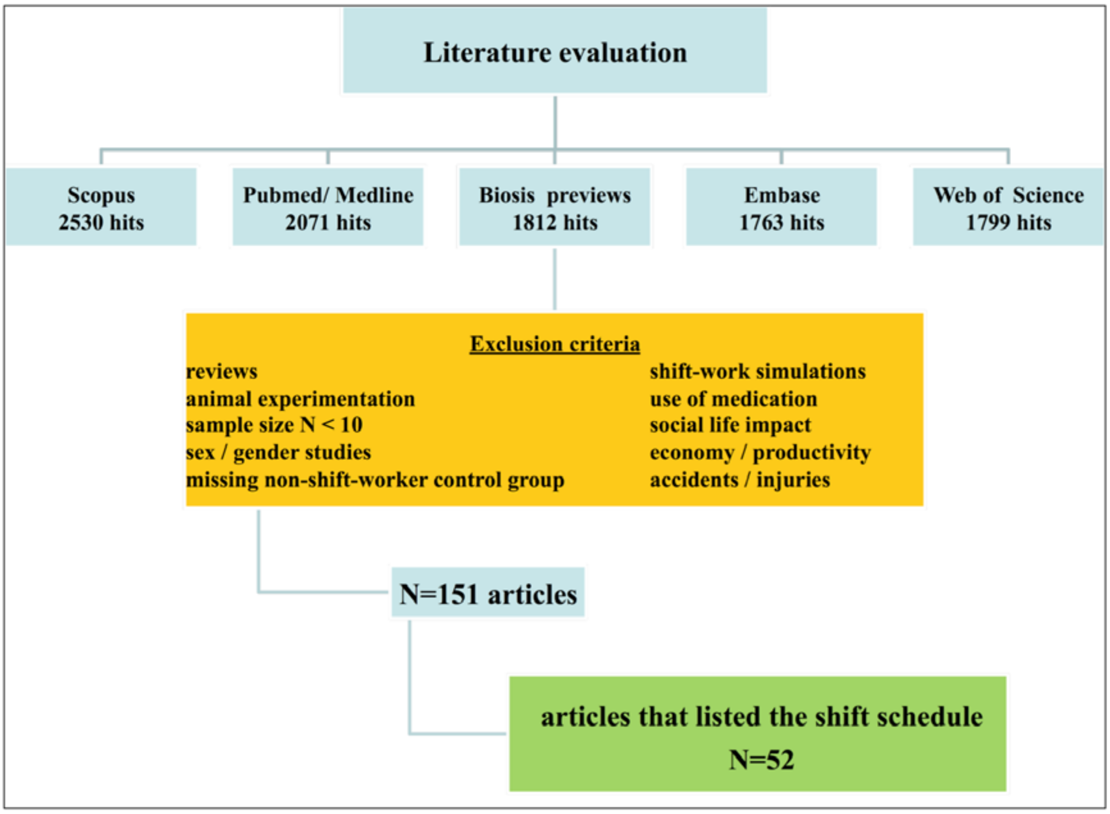


Figure 16 Flow chart of the internet literature search. On average 1995 hits have been identified from the search on the terms 'shift-work / night work / night shift / shift schedule / alternating shift / alternating night shift / rotating shift / rotating night shift'. A final number of 52 articles remained for further analyses.

4.4. Results

Of total 9975 hits from the initial search, a number of 1817 hits remained after exclusion of duplicates. Use of the exclusion criteria (Table 1) decreased this number to a final number of 52 publications (Figure 16). The factors that decreased the number of articles most were (i) non-presence of a non-shift-worker control group and (ii) that the respective shift-schedule was uncertain or even not mentioned. The earliest study dated from 1980 (*Costa et al., 1980). The selected articles are shown in Table 2 (sorted by shift rotation that has been examined in these studies).

	Author	Year	Shift Schedule	Rotation
1	Costa et al.	1980	3x8 h shifts	clockwise
2	Ellingsen et al.	2007	3x8 h shifts	clockwise
3	Harma et al.	1998	3x8 h shifts	clockwise
4	Karlsson et al.	2005	3x8 h shifts	clockwise
5	Knutsson et al.	1986	3x8 h shifts	clockwise
6	Knutsson et al.	1988	3x8 h shifts	clockwise
7	Knutsson et al.	1989	3x8 h shifts	clockwise
8	Knutsson et al.	1990	3x8 h shifts	clockwise
9	Lac and Chamoux	2004	3x8 h shifts	clockwise
10	Nakamura et al.	1997	2x8 h shifts	clockwise
11	Nikolova et al.	2000	3x8 h shifts	clockwise
12	Ohira et al.	2000	3x8 h shifts	clockwise
13	Oishi et al.	2005	3x8 h shifts	clockwise
14	Romon et al.	1992	3x8 h shifts	clockwise
15	Sakata et al.	2003	3x8 h shifts	clockwise
16	Sookoian et al.	2007	2x12 h shifts	clockwise
17	Suwazono et al.	2006	3x8 h shifts	clockwise
18	Di Lorenzo et al.	2003	3x8 h shifts	counterclockwise
19	Garbarino et al.	2002	4x6 h shifts	counterclockwise
20	Ishii et al.	2004	3x8 h shifts	counterclockwise
21	Ishii et al.	2005	3x8 h shifts	counterclockwise
22	Jansen et al.	2003	3x8 h shifts	counterclockwise
23	Karlsson et al.	2003	3x8 h shifts	counterclockwise
24	Morikawa et al.	2005	2x8 h shifts	counterclockwise
25	Morikawa et al.	1999	3x8 h shifts	counterclockwise
26	Prunier-Poulmaire et al.	1998	3x8 h shifts	irregular
27	Wolfhagen et al.	1994	3x8 h shifts	irregular + counterclockwise
28	Burch et al.	2005	night shift	permanent
29	Drake et al.	2004	night shift	permanent
30	Estryn-Behar et al.	1990	night shift	permanent
31	Ingre and Akerstedt	2004	night shift	permanent
32	Lasfargues et al.	1996	night shift	permanent
33	Lee	1992	night shift	permanent
34	Niedhammer et al.	1994	night shift	permanent
35	Sternberg et al.	1995	night shift	permanent
36	Yamasaki et al.	1998	night shift	permanent
37	Ueno et al.	1984	night shift	permanent
38	Ahlborg et al.	1996	night-, 3x8, 2x8 h shifts	permanent and rotating
39	Kubo et al.	2006	night shift	rotating night
40	Viswanathan	2007	night shift	rotating night
41	Davis et al.	2001	night shift	rotating night
42	Hansen et al.	2001	night shift	rotating night
43	Lie et al.	2006	night shift	rotating night
44	O´Leary et al.	2006	night shift	rotating night
45	Schernhammer et al.	2001	night shift	rotating night
46	Schernhammer et al.	2003	night shift	rotating night
47	Schernhammer et al.	2006	night shift	rotating night
48	Tynes et al.	1996	night shift	rotating night
49	Ohayon et al.	2002	2x8 h shifts	varios/not defined
50	Peter et al.	1999	2x8 h shifts	varios/not defined
51	Virtanen and Notkola	2002	2x8 h shifts	varios/not defined
52	Parkes	1999	2x12 h shifts	weekly changes

Table 2 List of final articles from the literature survey on shift-work and health, after applying the exclusion criteria (Table 1). The articles in this table are sorted by shift-work rotation (right column).

The selected 52 publications cover examinations of a total number of 347 586 subjects (195 873 shift-workers / 151 713 day workers) from 45 different studies, which were set in the USA, Japan, Western and Eastern Europe (Figure 17). The publications cover 57% cross-sectional, 24% retrospective and 19% prospective examinations (Figure 18).

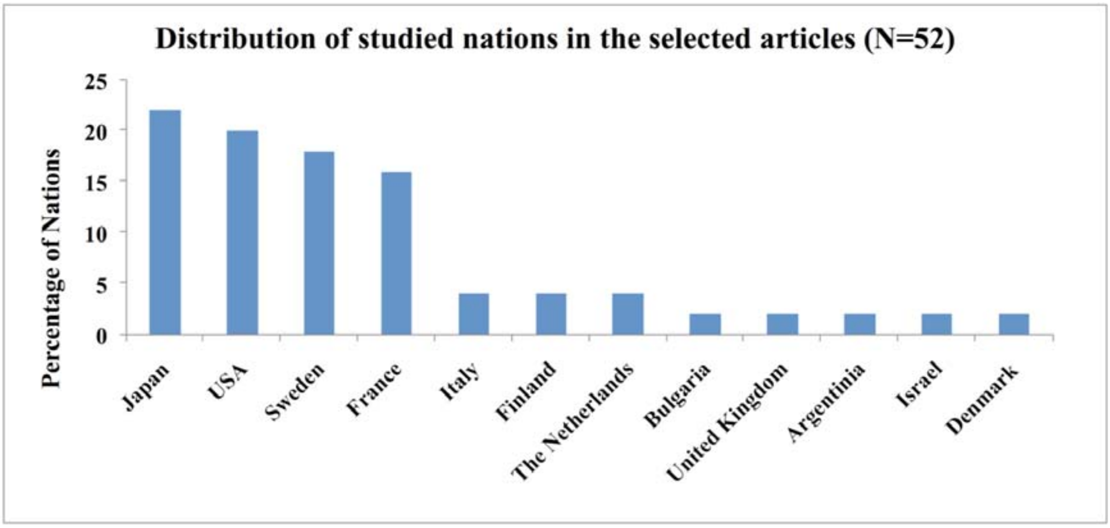


Figure 17 Distribution of nations from the selected 52 articles. The majority of studies have been performed in Japan, the United States of America and Sweden.

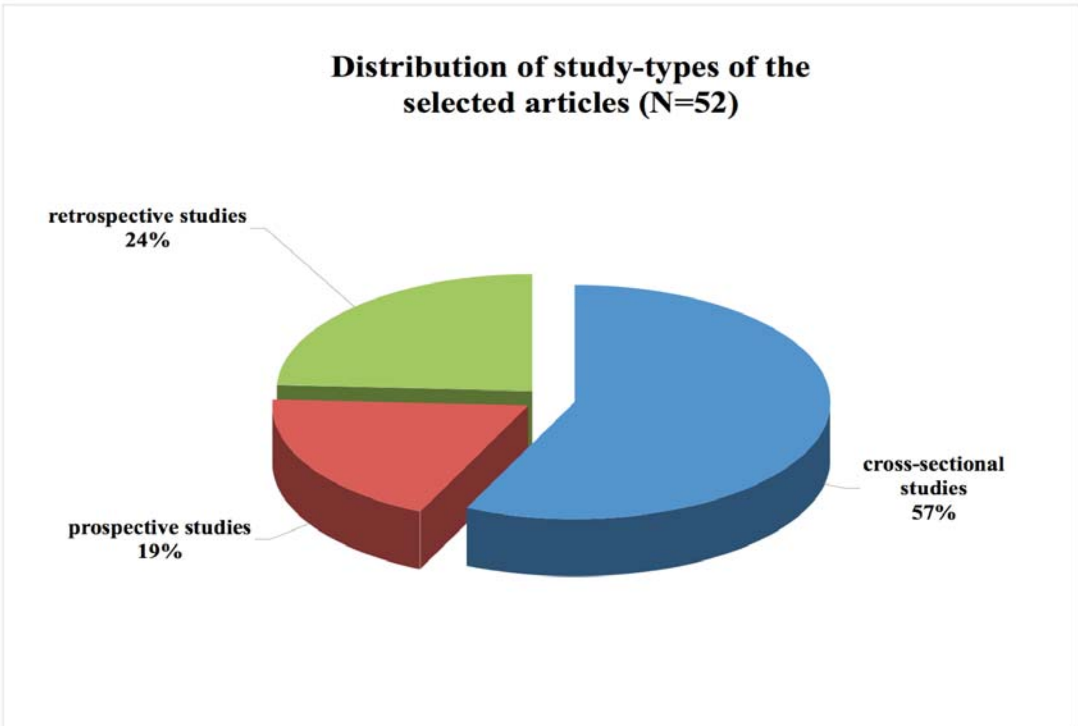


Figure 18 Distribution of study types in the selected 52 articles. Most studies are cross-sectional studies (57%), followed by similar equal numbers of retrospective and prospective studies (24% and 19%, respectively).

The initial idea was to perform a statistical meta-analysis on the data from the selected articles. This idea has been skipped for the reasons mentioned in the next section.

4.4.1. Why no Meta-Analysis?

The profit of a statistical meta-analysis is a combinatory and quantitative evaluation of the selected studies (Cochrane Handbook for Systematic Reviews of Interventions, 2006 ; Spector and Thompson, 1991). In most cases, meta-analyses are performed to summaries results from clinical trials to provide physicians and clinicians with a comprehensive overview to a certain subject. To do a meta-analysis, the most important prerequisite of the material is comparability in methods and outcomes. The studies selected from the literature search in this thesis do not fulfil these two minimal prerequisites and therefore do not allow performing a meta-analysis. The idea to perform a statistical meta-analysis on the shift-work literature for this thesis has additionally been skipped because of diversity in and an incomparability of the:

- … methods (e.g. objective or subjective evaluations of heart diseases)
- … statistics (e.g. odds ratios, relative risks or only percentage differences)
- … duration of studies and number of follow up investigations
- … outcomes (e.g. diagnostic criteria are often uncertain)
- … definitions of shift-work and differences in the shift schedules
- … occupations and workplaces of the shift-workers
- … occupations of the control group, if different to the shift-workers
- … control for confounders and other statistical bias

This incomparability of the shift-work studies strongly underlines one of the biggest weaknesses of epidemiological shift-work research. Unlike as in clinical trials, which are in most cases designed to be comparable to other trials, the health examinations on shift-workers are highly individual, and further often depend on the methodological possibilities in the field and not on the necessary examinations that would allow for such comparability. There are finally no two studies that would stand a direct comparison. Therefore, to avoid meaningless conclusions and to not obscure the differences in the studies, a narrative, informative form in presenting the studies' characteristics and findings has been chosen for this literature survey. The results presented for the shift-workers in this health survey are significantly different from the results of the non-exposed control group, otherwise it is explicitly stated. Where relative risks or odds ratios are given, these are listed separately in each chapter. Chapter 4.5 presents the results from the articles on health and shift-work. The selected articles that passed the exclusion criteria are indicated by an asterisk (*), to distinguish these from references that did not fulfil the exclusion criteria but that have been added for explanatory purposes, especially in terms of background information on certain variables. The following sections will handle background information to the selected articles. These sections focus on the key epidemiological studies (section 4.4.1), studied occupations (section 1), studied sexes/genders (section 4.4.4), and the data acquisition by questionnaires and interviews (section 4.4.5).

4.4.2. Key epidemiological Studies

The workers that have been studied in the identified examinations either were recruited from certain individual work places or via data from large-scale epidemiological cohorts. The key epidemiological cohorts were:

1. Long Island Breast Cancer Study Project (LIBCSP) (Gammon et al., 2002)
2. Seattle Case-Control Study (SCCS) (Davis et al., 2001)
3. Danish Case-Control Study (DCCS) (Hansen, 2001)
4. Japan Collaborative Cohort Study for the Evaluation of Cancer Risk (JACC) (Ohno and Tamakoshi, 2001; Tamakoshi et al., 2005)
5. Work Lipids and Fibrinogen Study (WOLF) (Peter et al., 1998; Alfredsson et al., 2002)
6. Nurses Health Study I and II (NHS-I and II) (Colditz et al., 1997)
7. Maastricht Cohort Study on Fatigue at Work (MC) (Kant et al., 2003)
8. Helsinki Heart Study (HHS) (Frick et al. 1987; Manttari et al., 1987)
9. Swedish Midwives Association (SMA) (Ahlborg et al., 1996)
10. Telecom cohort (TC) (Tynes et al., 1996)
11. Fertility cohort (FC) (Tynes et al., 1996)
12. Female occupational cancer cohort (OC) (Tynes et al., 1996)
13. Swedish Twin Register (Lichtenstein et al., 2002)

4.4.3. Occupations

The majority of studies were done on workers from the industrial sector. These workers were blue-collar-workers, for example workers from paper-and-pulp, steel or chemical industry, or from nuclear plants. The second group constituted workers from the health care sector (nurses and midwives). About 1/3 of the studies did not list the workers´ occupations. The latter therefore constitute a heterogeneous working population in respect to the occupations and work-related exposures. Controls in all studies were regular (white-collar) day workers, which not always have the same comparable occupational background. White-collar workers in most cases are employed in administrative jobs, instead of doing tasks, for example, at an assembly line.

4.4.4. Sexes / Genders

43% of the studies examined exclusively male subjects, 30% studied exclusively female subjects, 22% investigated both sexes, but not separately, and 5% of the studies presented results separately for females and males (Figure 19). Male-dominated works were mostly industrial jobs like steelworkers and workers at nuclear power plants, whereas female-dominated works were health care occupations like nurses and midwives. Some authors excluded women from the study population, either when they were underrepresented or to eliminate any effect of the menstrual cycle.

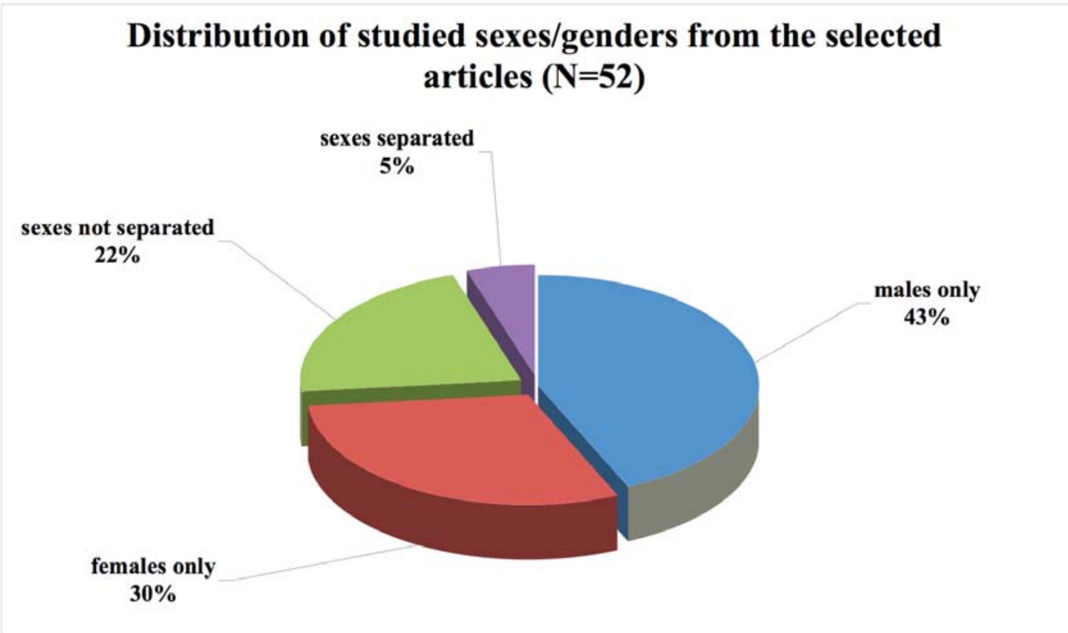


Figure 19 Distribution of sexes/genders studied in the selected 52 articles. The majority of studies investigated exclusively male subjects (43%, 'males only'), followed by 30% of studies with female subjects only. One fifth (22%) of the studies did not give the information on the female/male ratio ('sexes not separated'). Only 5% of the studies listed the results separately for females and males.

4.4.5. Questionnaires and Interviews

The use of questionnaires and interviews is very common in shift-work studies and epidemiological research in general. From the literature, there was no common or standard shift-work questionnaire or interview-procedure identifiable. The questionnaires that have been used in the selected studies were:

- Eppworth Sleepiness Scale, ESS (Johns, 1991)
- General Health Questionnaire (GHQ-28) (Goldberg and Hillier, 1978)
- Morningness-Eveningness Questionnaire (MEQ) (Horne and Ostberg, 1976)
- The Standard Shiftwork Index (Barton et al., 1995)
- The Job Content Questionnaire (JCQ) (Karasek et al., 1998)
- Stanford Sleep Questionnaire and Assessment of Wakefulness (SQAW) including General Sleep Disturbances Scale (GSDS) (Douglass et al., 1986)
- Neuroticism scale from the Eysenck Personality Questionnaire (Eysenck et al., 1985)
- Framingham Type-A scale (Haynes et al., 1978)

Additionally used were:

- National Health Insurance Records
- Company records
- Investigator developed self-administered questionnaires on sleep or diet

The questionnaires have been filled out by the workers themselves or by the investigators, either in face-to-face or telephone interviews. Estimations of prevalent sleep problems were done using diagnostic manuals, mostly the ICSD (Thorpy 1990; 1997; 2001) (International Classification of Sleep Disturbances) or otherwise by comparing the scores from the used scales quantitatively. Medical evaluations have been performed due to criteria of the DSM-IV (1994) or the ICD-6 to -10 (1952-1957; 1958-1968; 1969-1986; 1987-1996; 1997-2002), and the ICD-O (1976).

4.4.5.1. Pros and Cons of Questionnaires

One advantage of using questionnaires in shift-work research is them being quickly implemented, covering various health and social aspects and giving the researcher the possibility to reach large number of subjects in a non-cost-expensive and short lasting time. Questionnaires are definitely useful to obtain information about certain behavioural aspects, as for example about sleeping or lifestyle habits.

The most mentioned disadvantage is that questionnaires are subjective and can give no clear results on, for example, organic diseases like cardiovascular problems. For example, in Kivimäki et al. (2006) , the prevalence of cardiovascular diseases (CVD) has been estimated by answers to the question: “Have you ever been told by a physician that you have or have had any of the following diseases?”. CVD in this study was determined by answering yes to the options “myocardial infarction”, “angina pectoris” and “hypertension (ICD-10 codes I10-I15)”. This method likely leads to misclassifications, as it inherits the risk of recall bias. Furthermore, giving an affirmative answer to the question on hypertension (ICD-10 codes I10-I15), does not automatically indicate the prevalence of CVD.

Further problems with special focus on shift-work research are, that the questionnaires …

- … are self-structured and not comparable and not validated and verified in prospective studies
- … do not account for inter-cultural differences (e.g. coping behaviours)
- … not standardised for shift-work studies
- … are individually interpreted by the investigators (highly interpretive) and therefore entail the risk of miss-classification due to differences in answers

4.5. Findings from the selected Articles

This chapter presents the most potent results on health and shift-work that have been evaluated from the selected 52 articles. If not mentioned explicitly, all results presented in this chapter show significant differences between the shift- and day-workers (all studies had a control group of workers that were not exposed to shift-work, see exclusion criteria chapter 4.3). The health topic from the selected n=52 articles have been separated due to 4 main health categories. The Figure 20 shows the distribution of the articles by the 4 main health categories (i) cardiovascular, (ii) sleep, (iii) metabolism and (iv) cancer. Most of the articles focused on cardiovascular problems (31% of the articles), followed by sleep and metabolism (each with 25%), and finally cancer diseases (19%). These four topics are confirmed by findings from previous articles and will be dealt with in the next chapters.

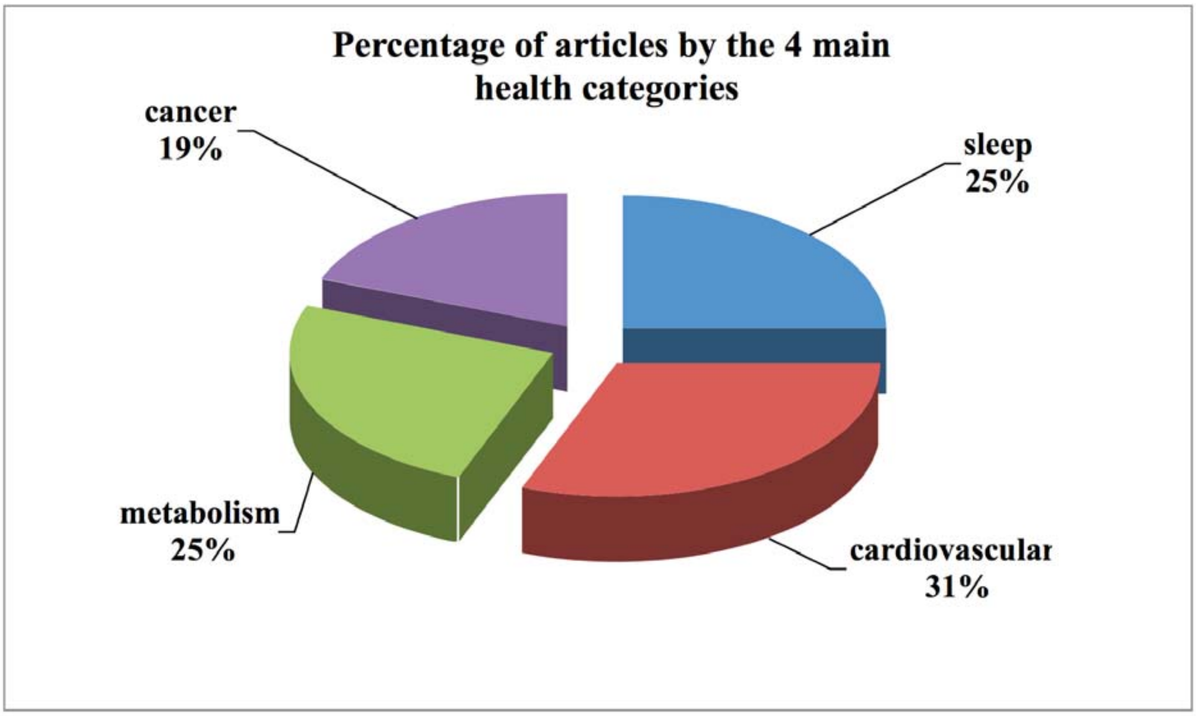


Figure 20 Distribution of the selected 52 articles due to the 4 main health categories. The majority of articles publishes results on cardiovascular problems (31%), followed by sleep and metabolism (with each 25%) and finally 19% on cancer diseases.

The results will be presented in the following sequence, with (i) sleep problems (section 4.5.1), (ii) cardiovascular problems (section 4.5.3; focus on altered blood pressure, heart rate and Coronary Heart Disease) and lifestyle risk factors, (iii) cancer (section 4.5.5) and (iv) metabolic and digestive problems (section 4.5.7). These sections will be followed by a discussion on methodological problems and difficulties with interpreting the results (chapter 4.6).

4.5.1. Shift-Work and Sleep

Sleep problems are the most mentioned problems by shift-workers. These are most consistently discomforts, in both women and men equally, which emerge soon, even after only one or two night shifts in a row. Sleep problems have been examined only subjectively (no electroencephalographic evaluations (EEG), for example) and have been gathered mainly in cross-sectional examinations from self-administered questionnaires, both validated ones and/or investigator developed tools. Interviews either were done at the workplace (mostly during annual health check-ups by the occupational physicists) or via telephone surveys, sometimes by random-digit dialling procedures.

Sleep problems have been described to derive from a shortage of sleep duration, either by difficulties falling asleep or premature awakening, or both, especially after a night shift (period) (*Ohayon et al., 2002 ; *Parkes, 1999 ; *Lee, 1992 ; *Prunier-Poulmaire et al., 1998 , *Ingre and Akerstedt, 2004 , *Estryn-Behar et al., 1990 and * Burch et al., 2005). Also daytime sleep after a night shift is shortened, as it is often accompanied by acoustic disturbances and further marked by a difficulty in falling asleep due to a lack of sleep propensity from the internal clock, as daytime sleep for humans is “sleep at the wrong time” (see Two-Process-Model of Sleep, chapter 1.2.1).

In this respect, Kogi in 1982 mentioned, that also sleep satisfaction depends on the time of day one sleeps and that sleep dept often remains unpaid. The author writes, that sleep deficit is not a pure accumulative process, as sleep deficit is not a “real dept”, as, for example, a lack of oxygen that can be paid off accurately.

Kogi (1982) mentioned two possibilities in context of sleep deficit in shift-workers, (i) sleep deficit can be paid off by smaller quantity of sleep of different quality and (ii) the unpaid deficit may be transformed into some remnant effects which may or may not exert long-term effects.

That not only the timing, but also the direction in shift-rotation might have an impact on the accumulation of sleep deficits has been shown. This will be discussed more in detail in chapter 4.7.1, and therefore only briefly added to this section. Basically, in clockwise (forward) rotation, the successively later rising hours over the course of a shift cycle (with early – late –night shifts) allow for sleep debt compensation. In contrast, counterclockwise (backward) rotating shift systems rather increase the sleep dept. This can be attributed to the successive earlier get up times, which cannot be compensated by earlier bed times and lack of sleep propensity from disturbances to the internal clock. In addition to this, *Garbarino et al. (2002) found that sleep before a night shift and an early morning shift is shortest.

Further, night shift (*Lee, 1992 ; *Ueno et al., 1984) and irregular shift-work (*Harma et al., 1998 ; *Niedhammer et al., 1994 ; *Ohayon et al., 2002) have not only been reported to result in the high numbers of sleep disturbance, but further be difficult to arrange with the social life. According to these results, *Lee (1992) wrote that age and family reasons rather modulate sleep problems, than caffeine or alcohol do. Workers delay their sleep times, for social reasons to take part in family activities, meet friends, follow hobbies, and do the household. Further, the sleep hours are shifted because of the work schedule in times of the day, in which the body is not "programmed" to sleep, due to the circadian rhythm. The circadian rhythm does not allow for sleep during the daytime hours. If sleep can be initiated anyhow, acoustic disturbances can more easily wake up the workers. Environmental factors were a too bright bedroom, the „general life in a house", children in the house or on the street, traffic and aircraft noise, construction or renovation works. Workers with shift-work sleep disorder (SWSD; see chapter 4.5.2) showed generally "shorter time in bed", and further higher prevalences of co-morbidities as ulcer or heart diseases and depression. See respective works done by *Garbarino et al. (2002) and *Drake et al. (2004) .

What are the consequences of too few sleep hours and not recreational rest?

The lack of sufficient sleep is found to lead to sleepiness in the middle run, which in turn is leading to a lack of awareness and decreased reaction times. As a long-term consequence of chronic sleep dept, fatigue has been stated to emerge by *Lee, 1992 ;* Drake et al., 2004 ; *Niedhammer et al., 1994 ; *Harma et al., 1998 ; *Parkes, 1999 ; *Garbarino et al., 2002 ; *Ohayon et al., 2002 ; *Jansen et al., 2003 . In addition to this, *Jansen et al. (2003) have found different shift systems leading to different levels of fatigue. Lowest in the group of day workers (18.1%), followed by those doing irregular shifts (19.1%), whereas the latter has defined exactly in the study. 5-shift-workers reported with 23.7% slightly lower levels of fatigue, than 3-shift-workers with 28.6%. Fatigue was stated to be a major reason to change from shift to permanent day work. As night shift is shown to increase sleep dept, studies from *Drake et al. (2004) and *Ohayon et al. (2002) showed that most sleep was gathered by workers on the afternoon shift, followed by the day shift and finally the night shift.

Although not major topic to this thesis, it should be noted that the effects of sleep deficits resultant in daytime sleepiness and fatigue can severely impair the working capacity and increase the risk of accidents (e.g. falling asleep while commuting home after a night shift) and injuries. The most prominent and disastrous examples of consequences of sleep deficits are the incidences at (i) the nuclear power plant Three Mile Island (at 04:00 h on March 28th,1979), (ii) the Davis-Besse reactor (in June 6th, 1985) and (iii) the nuclear plant in Chernobyl (at 01:23 h on April 26th, 1985) or accidents that happened in the NASA space shuttle program (Mitler et al., 1988 ; Folkard, 1997 ; Waterhouse et al., 1993). The common ground of all these disasters is them having happened in the early morning hours and that these are highly attributed to human error, due to sleep loss, lack of attention and alertness. This clearly shows that sleep deficits from shift-work must be seriously regarded as a potential risk factor for the individuals´ and public safety. The fact that these disasters happened during the early morning hours as a result of a lack of alertness from sleep dept, goes in line with finding of this shift-work literature survey, that sleep problems have been found predominantly in fixed night workers and counterclockwise rotators employed in 3x8 h, 5x8 h, 4x6 h and 2x12 systems (which are found to suffer more from sleep curtailments than clockwise rotators, which will be pointed out in chapter 4.7.1).

Overview of the findings on shift-work and sleep problems

The Figure 21 shows a taxonomy of the articles about sleep problems (n=13; representing 25% of the initially selected 52 articles). The results are presented due to shift-work schedule, shift rotation, sexes/genders and occupations, for both significant (↑) and non-significant results (Ø). Each of the end-bars in Figure 21 (with information about shift rotation, sex/gender and occupation) represents one article. If one end-bar concerns more than one article, this is listed in brackets behind the respective shift rotation. Sleep problems have been found for various shift systems as 2-shift, 3-shift, 5-shift work (with 8 hours duration each shift), for 4-shift work (with 6 hours each shift) and for permanent night shift. For permanent night work, the most results have been found with 6 articles (see '6x' in the end-bar). The distribution of sleep problems is equal for females and males. The occupations have not been specified by most authors. Only on article found no difference in sleep problems between permanent night workers and the day working control group (*Niedhammer et al., 1994). Despite the amount of studies that have been performed concerning sleep problems in shift-workers, one question still remains open. This question aims at distinguishing between (i) those that develop sleep problems because of the shift-work schedule and (ii) those that have chosen to do shift-work because they already have sleep problems (*Drake et al., 2004). This dilemma reflects a hen-egg-problem that definitely justifies further research.

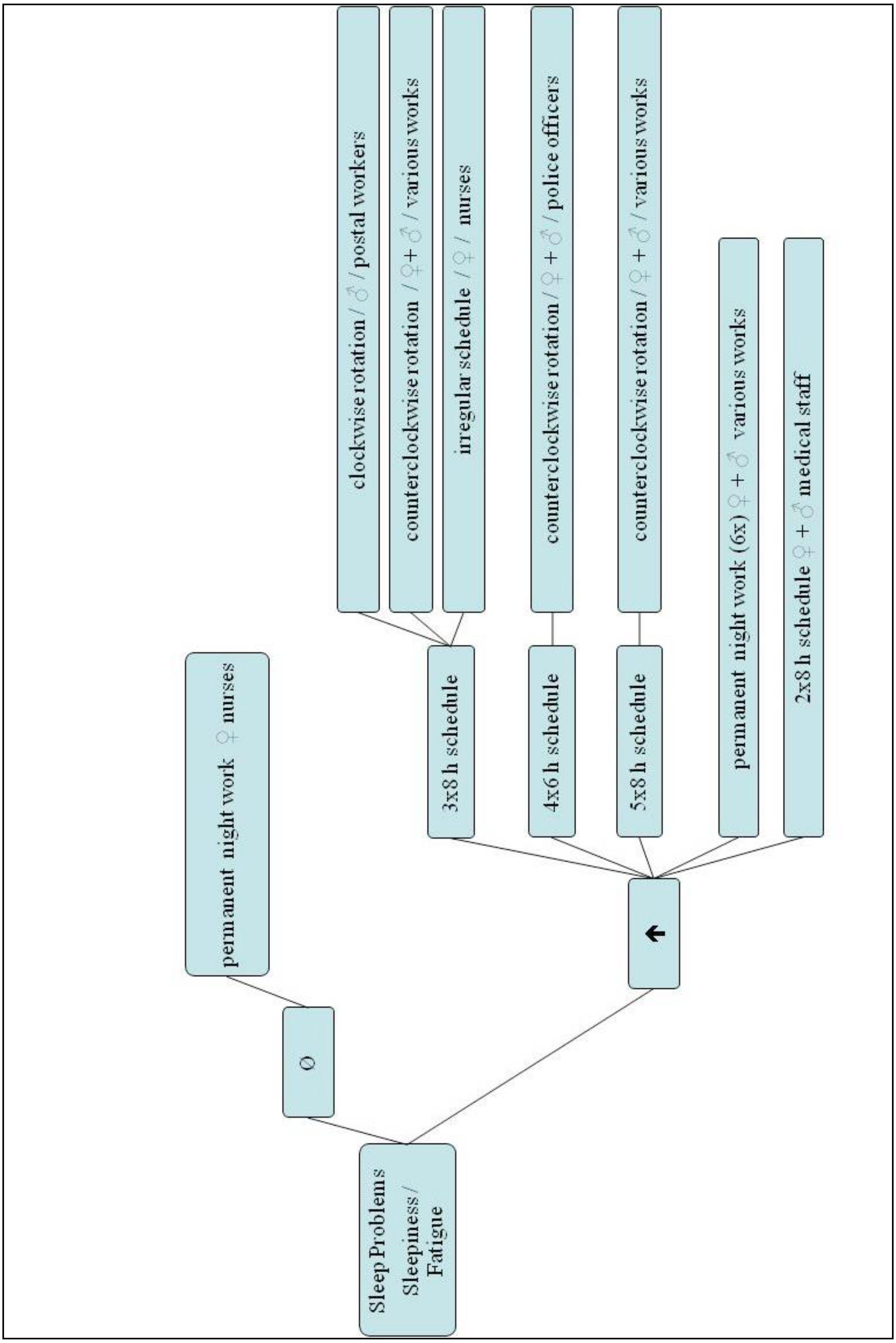


Figure 21 Taxonomy of the selected articles about sleep problems (n=13). The taxonomy shows the distribution of articles showing significant (↑) and non-significant (Ø) differences in sleep problems between the shift-work and control group for the respective work schedule, shift rotation, sexes and occupational group.

4.5.2. Shift-Work Tolerance - Shift-Work Sleep Disorder (SWSD)

As not all shift-workers suffer from their work schedule, several approaches have been performed to measure shift-work tolerance. These attempts base on the finding and intensity of (i) sleep alterations, (ii) persisting fatigue, (iii) changes in behaviour, (iv) digestive troubles and (v) regular use of sleeping pills. Especially the coexistence of (i), (iii) and (v) have been introduced as shift-work intolerance. These criteria show that the consequences of shift-work on the human health mostly regard sleep disturbances and its consequences of sleepiness and fatigue as a central issue.

The concept of shift-work sleep disorder (SWSD) has been introduced to the clinical field and added to the International Classification of Sleep Disorders (codes 307.45-1). Shift-work sleep disorder (ICSD codes 307.45-1) is discussed in relation to the following issues: night shift; irregular work hours; transient insomnia; transient excessive sleepiness; "work shift" change in conventional sleep/wake schedule; acute-phase shift of sleep and frequently changing sleep/wake schedule. There is no obvious difference between the sexes. A family disposition has not been observed. No known anatomical or biochemical pathology has been described. The condition is directly related to the circadian interference with sleep during the morning and evening, which conflicts with the need of the shift-workers to sleep at these times.

Symptoms of shift-work sleep disorders

The symptoms of SWSD (ICSD codes 307.45-1) are insomnia, excessive sleepiness and inability to stay asleep for the usual sleep duration. The latter is especially the case when the sleep is tried to introduce at daytime hours after a night shift (e.g. after 6 a.m.). Sleep length is reduced by about four hours per week and mainly affects the REM sleep and stage 2 of the non-REM sleep, which leads to unsatisfactory and not refreshing sleep.

Improvements of environmental conditions to alleviate sleep initiation and sleep maintenance can bring some profit, but cannot diminish the problems entirely. Especially shifts starting early in the morning (e.g. at 4 a.m.) are related to difficulties in sleep initiation and with awakening. Excessive sleepiness generally is a problem during shifts, and mainly during the night, which is related to a need of napping and a reduced alertness, with decrements in the mental abilities, as reduced performance ability.

The latter is further discussed in context of safety issues. Besides the problems while on shift, the individual spare time must be used for recreation and sleep deficit compensation. Finally, beside such individual struggles, alternating work hours can make it difficult to keep up with social contacts. Although not examined conclusively, an increase in the rate of divorce or decrease in the chance of marriage, for example, might indicate that the working conditions can discredit social relationships. On the long run, shift-workers might run the risk of social marginalization, which in turn must be considered as an additional risk factor (e.g. from changes in behaviour like an increased alcohol or cigarette consumption) in any shift-work related (health) problem.

4.5.3. Shift-Work and the Cardiovascular System

The most potent cardiovascular problems that have been identified from the literature are alterations in (i) blood pressure and risk of hypertension, (ii) heart rate and (iii) an increased prevalence of Coronary Heart Disease (CHD). The evaluation of cardiovascular problems follows two approaches. The first is, to compare (correlate) datasets yielded in large-scale cohort studies (e.g. WOLF-study) and/or occupational files from annual health check-ups at the workplace. The second approach is to collect data in cross-sectional field investigations. The effect of shift-work on cardiovascular risk factors as, for example concerns measures of blood pressure, heart rate and the risk of developing hypertension (ICD-10 codes I10-I15). No difference between females and males were found. The underlying methodology and criteria for the diagnoses remain uncertain in some studies. This makes comparisons of the studies (partly) impossible. Another problem that occurs from is that no information about the time points (or time spans like “incidence happened in the morning hours”, for example) of any cardiovascular events has been regarded. Although it is known that physiological parameters like blood pressure and heart rate do show circadian rhythms, and further that cardiovascular events like stroke or heart attack mostly peak in the early morning hours (between 04:00 and 06:00), such information is completely ignored in the selected studies. None of the studies has evaluated the time points of the respective events or based their analysis adequately on internal time of the workers.

4.5.3.1. Blood Pressure and Hypertension (ICD-10 codes I10-I15)

Shift-workers have been found to exhibit higher levels of blood pressure than their day-working colleagues. High blood pressure is known as one of the most potent reasons for the development of hypertension (ICD-10 codes I10-I15). Statistically elevated levels of blood pressure (BP) have been found by *Ohira et al. (2000) (for systolic blood pressure only), *Yamasaki et al. (1998) , *Morikawa et al. (1999) (OR 3.6, CI: 1.41-9.1), *Oishi et al. (2005) with an RR of 1.23 (CI: 1.05-1.44) (for diastolic blood pressure only) and in a study by *Prunier-Poulmaire et al. (1998) with an RR of 3.1 (CI:1.05-9.1). In contrast, no significant elevations in both systolic and diastolic blood pressure levels in shift-workers were stated by *Knutsson et al. (1988) and *Nikolova et al. (2000) . *Sternberg et al. (1995) compared blood pressure rhythms of day and shift-working bakery workers and found a shifted peak (due to external time) in blood pressure rhythm in the latter. The systolic and diastolic peaks for the day workers were at 23:00 and 22:00 h, respectively. For the shift-workers these peaks were shifted to 04:00 and 03:00 h, respectively. *Sakata et al. (2003) found an increased risk in the development of hypertension (whereas not strictly defined to the ICD-10 codes I10-I15) in clockwise rotating 3-shift-workers with an RR of 1.1 (CI: 1.01-1.97). In a follow-up study by *Oishi et al., 2005 shift-work was furthermore found to propel the development from mild to severe hypertension (ICD-10 codes I10-I15) by 23%. An age effect on the development of hypertension in shift-workers was pointed out by *Morikawa et al. (1999) , with hypertension (ICD-10 codes I10-I15) being significantly more prevalent in the 18-29 year old and in ex-shift-workers, that have switched to day work. BMI, systolic BP and consumption of alcohol showed marginal effects on the results. Shift-work seniority to be an important modulator factor in the aetiology of hypertension (ICD-10 codes I10-I15) was also mentioned by *Ohira et al. (2000) and *Nikolova et al. (2000) . In addition to the adverse effects of the factor shift-work "itself", various other factors have been stated, though without conclusive results, as, for example, a high work load, an effort-reward imbalance, high noise levels at the workplace, stressful work environment, heat, dust exposure, passive smoking and also long walking, prolonged standing, doing monotonous works and stressful contact with customers (= German „nervlich belastender Kundenverkehr"; *Virtanen und Notkola, 2002 ; *Peter et al., 1999 with an RR of 1.7 (CI: 1.15-2.5); *Prunier-Poulmaire et al., 1998). *Virtanen und Notkola, 2002 recently mentioned that stress from psychosocial factors (e.g. high work load and low control) had a stronger impact on health deteriorations than stress from physical and physiological (occupational) factors like noise or sedentary work. Additionally, effects arranging from factors as active smoking, leading a sedentary lifestyle and from elevated age have been pointed out by several authors (*Peter et al., 1999 ; *Prunier-Poulmaire et al., 1998). Finally, shift-work in many studies is the only variable remaining different between the healthy and the affected workers.

4.5.3.2. Heart Rate

Heart rate measurements have been performed using 24-hour ambulatory recorders (e.g. Holter-recorders). Although data on the 24-hour profiles of shift- and non-shift-workers was collected, none of these studies have evaluated the profiles on individual internal time, but rather on external time due to the classical medical criteria (which obviously are not established on populations of shift-workers, but rather on normative day-working populations). The evaluations concentrated on (i) comparison of the profiles´ shape (total daily heart rate rhythm was found to be flattened in shift-workers) and comparisons of the peaks and troughs between day and shift-workers. *Virtanen und Notkola (2002) calculated the reduction in risk of several heart problems for the extinction of the factors like high work load, decision latitude, noise and shift-work (as a general unspecified factor). The authors determined a reduction of death due to cardiovascular disease by 8%, due to myocardial infarction by 10% and due to cerebrovascular disease by 18%. *Ishii et al. (2004) and *Ishii et al. (2005) showed an direct impact of shift-work on heart rate, measuring sympathetic and parasympathetic neuronal activity via ECG. *Yamasaki et al. (1998) additionally found lack of recreation phase in the heart rate profile in shift-workers.

4.5.3.3. Coronary Heart Disease (ICD-10 codes I20-I25)

Coronary Heart Disease (CHD; including the diagnoses of Ischeamic Heart Disease, IHD and Myocardial Infarction, MI; ICD-10 codes I20-I25) are the most mentioned long-term consequences for the cardiovascular system. In most of the studies, the incidences of heart diseases have been calculated in various populations of shift-workers, irrespective of the precise shift-schedule. *Knutsson et al. (1986) studied male clockwise rotating 3x8 blue-collar shift-workers and found an increased risk with an odds ratio (OR) of 2.2 for workers with a shift-work seniority of 11-15 years and with an OR of 2.8 for those having worked in shifts for about 16-20 years, both results for the age group of 45-54 years.

*Karlsson et al. (2005) found an elevated risk for the development of Coronary Heart Disease of + 24% for workers of 30 years of age (OR 1.24, CI: 1.04-1.49). In the same retrospective analysis by *Karlsson et al., 2005 , examining data from 2354 shift-workers and 3088 day workers for the years 1952 to 2001, the authors found no significant elevation in the overall mortality risk of + 2% (range -7% to +11%). A recent study from *Ellingsen et al., 2007 found an increase of 62% (RR 1.62, CI 1.2-2.18) in sample of shift-workers compared to the non-shift-working employees, from a fertilizer plant in the middle east.

Overview of the findings on shift-work and cardiovascular problems

The Figure 22 shows a taxonomy of the articles about the cardiovascular problems Coronary Heart Disease, CHD, and Hypertension (n=16; representing 31% of the initially selected 52 articles). The results are presented due to shift-work schedule, shift rotation, sexes/genders and occupations, for both significant (↑) and non-significant results (Ø). Each of the end-bars in Figure 22 (with information about shift rotation, sex/gender and occupation) represents one article. If one end-bar concerns more than one article, this is listed in brackets behind the respective shift rotation. The results in Figure 22 are mainly found for rotational 3-shift work (with 8 hour shift duration). No study has investigated (permanent) night shift workers. For both CHD and Hypertension significant and non-significant results have been found, whereas the ratio basically is about 50:50 (see also the number of respective articles presented in the figure, indicated in brackets after the shift-rotation which is listed in the end-bars). Mostly males have been studied and the occupational group exclusively was constituted of blue-collar workers. Results on altered heart rate are not included into this taxonomy, because these do not constitute a clear outcome, but rather a risk factor, compared to hypertension and CHD.

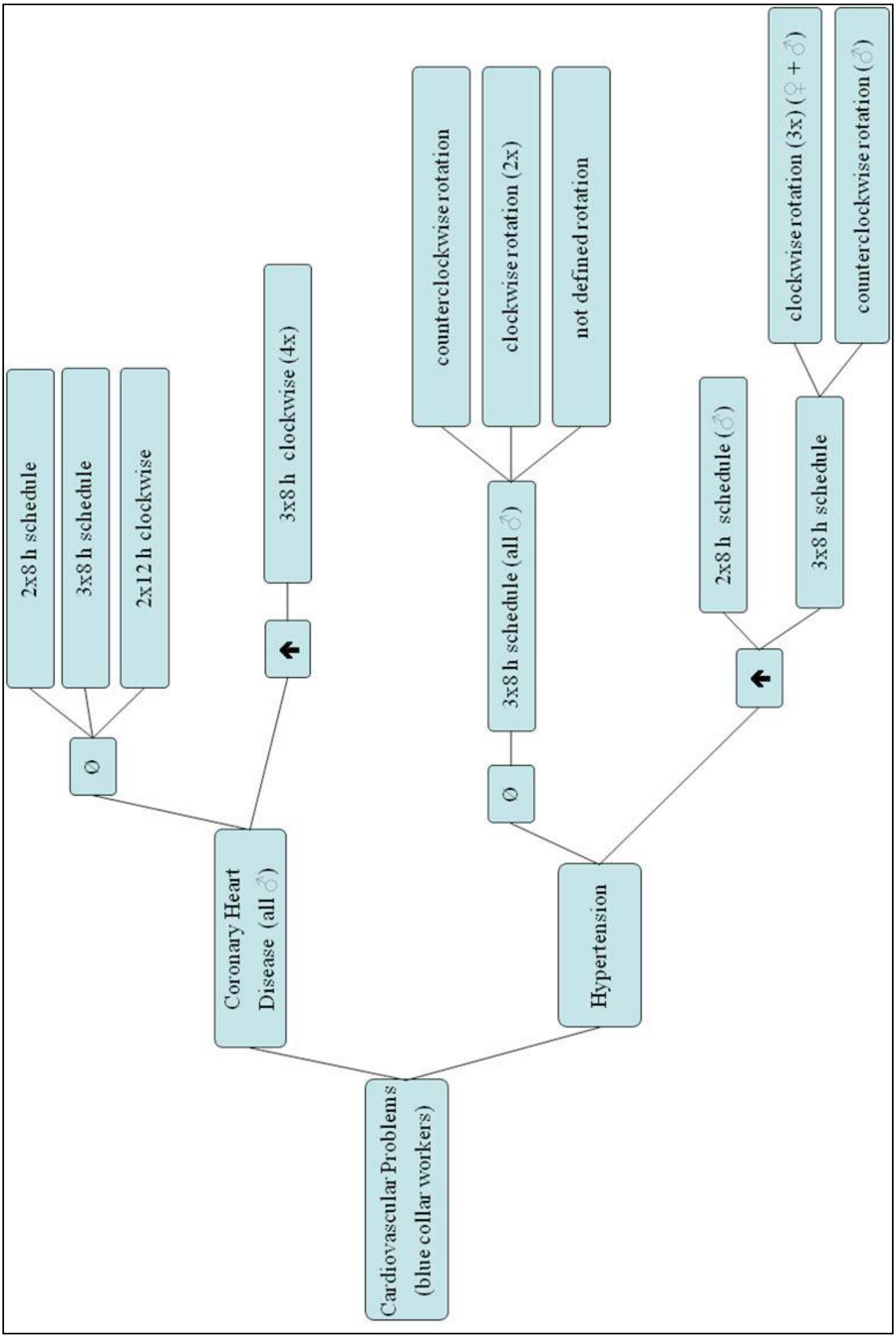


Figure 22 Taxonomy of the selected articles about cardiovascular problems with Coronary Heart Disease and Hypertension (n=16). The taxonomy shows the distribution of articles showing significant (↑) and non-significant (Ø) differences in cardiovascular problems between shift-work and control group, for the respective work schedule, rotation, sexes and occupational group.

4.5.4. Cardiovascular Risk and Lifestyle Factors

Cardiovascular problems are not uniquely found in shift-work populations. They rather represent common epidemiological health problems. Certain risk factors are therefore known, which will be discussed in this chapter. The following section additionally includes information from articles that have not past the initial exclusion criteria. These articles have only been added for purposes of background information. This section further includes articles not primarily on cardiovascular problems, but on metabolic problems in general. The latter will be mainly dealt with in chapter 4.5.7. Some of these articles are mentioned here, as they give information about important risk factors in the aetiology of cardiovascular problems.

The known cardiovascular risk factors can be divided into 4 groups:

a) Uncontrollable factors: age, being male, genetic disposition
b) partially controllable factors: hyperlipidaemia, hyperglycaemia, Diabetes mellitus (ICD-10 codes E10-E14), low-HDL-cholesterin
c) controllable factors: smoking, being overweight, arterial hypertension (ICD-10 codes I10-I15)
d) suggested factors: physical inactivity, emotional stress, personality type

Factors of group **a** are not subject to this thesis, as these are risk factors equally distributed among both day and shift-workers. Factors of group **b** already have partly been discussed in the previous chapters, and shown to be also distributed equally both among day and shift-workers. Factors of group **d** are not subject to this chapter, as studies investigating these factors have not been included in this study. Therefore, with special interest for the following section are the factors of group **c** **(**the “controllable” lifestyle factors).

Lifestyle factors like smoking, alcohol consumption and diet are factors argued to act as compensators against stress. As stress is highly suggested to affect shift-workers more than day workers, these factors will be discussed as fallows.

4.5.4.1. Smoking Behaviour

Smoking behaviour is a standard variable that is commonly collected in health studies, and controlled for, because smoking often is regarded as a confounder. As smoking can also be regarded in terms of coping behaviour, this makes especially smoking a mediator instead of a confounder. A higher rate of smokers is stated to be more pronounced in those shift-workers, that “only have observational” or control tasks to do at night, compared to those who are “heavily” working (e.g. steel workers). Needless to say, that the possibility to smoke on the job additionally plays a role. In jobs pronounced by monotonous tasks, smoking might serve to stay awake and additionally, some might just smoke because of boredom.

As smoking behaviour has never systematically been studied quantitatively (in terms of the number of cigarettes), it can be assumed that most authors are not interested in the possibility that a worker increases the number of smoked cigarettes depending whether he/she is allowed to smoke on the job or not. This means that only the status of “smoker yes/no” has been evaluated. Due to lack of information from these studies, an attribution due to a certain shift system and smoking status is therefore also not possible. As said above, mostly for health examinations the information about smoking behaviour is collected. Therefore, it should be noted that especially studies on sleep problems do not ask for smoking habits. As shift-work as a risk factor for stress might lead to both higher smoking rates and increased sleep problems, thereby indirectly showing the stress-impact of the schedule, this lack of information is not justified.

Anyhow, the majority of studies show smoking behaviour to be more prevalent among shift-workers (Table 3), meaning that the number of smokers is higher among shift-worker populations. As said above, this does not mean that the shift-workers smoke more cigarettes. Table 3 shows studies separated for their result of having found a higher percentage, lower percentage or no difference in the percentage of smokers in the comparison between shift- and day workers. This table also includes those articles, that have initially not passed the exclusion criteria, but which serve in this case to increase the amount of information. Most articles found that shift-workers are more likely smokers than day workers. The number of studies that found no difference between the shift- and day workers in respect to their smoking behaviour is equal to those that did find an elevation. The number of articles that have been chosen for this survey (these are indicated by an asterisk, *) is similar in both groups, with 10 articles in the group of “More smokers among the Shift-Workers” (left column) and 11 articles in the group of “No difference between Shift-Workers and control group” (right column). Interestingly, some authors even found a higher number of smokers among the control group (centre column).

More smokers among the Shift-Workers	More smokers among the control group	No difference between Shift-Workers and control group
Bisanti et al., 1996	*Ishii et al., 2004	*Burch et al., 2005
Chen et al., 2006	Kawachi et al., 1995	*Ellingsen et al., 2007
*Di Lorenzo et al., 2003	Koller et al., 1985	Gordon et al., 1986
Harada et al., 2005	van Amelsvoort, 2001	*Karlsson et al., 2003
*Harma et al., 1998		*Knutsson et al., 1989
*Ishii et al., 2005		*Knutsson et al., 1990
Johansson et al., 1991		*Kubo et al., 2006
Kivimäki and Kuisma, 2001		Murata et al., 2005
*Knutsson et al., 1988		Nakayama et al., 1997
Knutsson et al., 1998		Niedhammer et al., 1996
Knutsson et al., 1999		*Nikolova et al., 2000
*Lasfargues et al., 1996		*Ohira et al., 2000
Mohen et al., 2002		Quera-Salva et al., 1996
*Morikawa et al., 2005		*Romon et al., 1992
Murata et al., 1999		Romon-Rousseaux et al., 1985
Nagaya et al., 2002		*Schernhammer et al., 2003
Nakamura et al., 1997		Smith et al., 1982
*Oishi et al., 2005		*Sookoian et al., 2007
*Sakata et al., 2003		
*Schernhammer et al., 2006		
*Sternberg, 1995		
*Suwazono et al., 2006		
*van Amelsvoort, 2004		
Zhu et al., 2003		
Zhu et al., 2004		

Table 3 List of articles (for each column in alphabetical order) that provide data on the difference in smokers between shift-workers and control group. Most studies found a higher number of smokers among the shift-workers (left column). The number of articles showing no difference is similar (right column). Some authors found a higher number of smokers among the control group (centre column). These data does not reflect the number of cigarettes, but only the status of being a smoker “yes/no” (*Articles from the initial literature search).

4.5.4.2. Alcohol Consumption

Alcohol consumption has in most studies been shown not be higher in shift-workers, instead the day workers are more likely to consume more alcohol. The latter can be explained by the circumstances that (i) day workers have simply more opportunities to drink alcohol, because it is preferably consumed in the evenings, when the usual day worker commonly is not at his workplace, compared, for example, to a night worker. The lack of occasionality to drink alcohol and the fact that alcohol consumption while on duty is not permitted in almost all occupations, directly decrease the number of situations for shift-workers to drink alcohol (Lennernäs et al., 1994 ; Romon-Rousseaux et al., 1985 ; Hermansson et al., 2003 ; Gordon et al., 1986 , *Harma et al., 1998 ; *Morikawa et al., 2005). Exceptions can be suggested for those workers taking alcohol as sleep-substitutes (Ohida et al., 2001), whereas this is not subject to this thesis (see exclusion criterion number 5 in chapter 4.3).

4.5.4.3. Dietary habits

Dietary habits have been investigated by only few authors, showing no or only minor differences between shift- and day workers (Romon-Rousseaux et al., 1985 ; Aptel et al., 1992 ; Lennernäs et al., 1994 ; Niedhammer et al., 1996 ; *Lasfargues et al., 1996). Diet might be an additional factor with a modulator impact on health. The alimentary situation in terms of concrete health risks has not been investigated conclusively.

4.5.4.4. Body Mass Index (BMI)

*Di Lorenzo et al. 2003 examined workers from a chemical plant and found the BMI of 185 shift-workers with 27.7 significantly higher than the BMI of the 134 day workers with 26.6. Also *Kubo et al., 2006 found higher BMI in rotating shift-workers in their study on prostate cancer (RR 3.0, CI 1.2-7.7). The authors did not find differences in body fat. Also *Karlsson et al. (2003) have not found abdominal obesity to be elevated in shift-workers, but the percentage of workers with a BMI of ≥ 30 was higher in the shift-work group (15.0%) than in the comparison group (14.3%), although this difference was not significant. *Lasfargues et al. (1996) and *Suwazono et al. (2006) , both found higher BMI in shift-workers, the former author for women and men separately.

No significant difference in BMI was stated by * Viswanathan (2007) **,** *Nakamura et al. (1997) , *Morikawa et al. (1999) , *Ohira et al. (2000) und Knutsson et al., *1988 , *1989 and *1990 . In contrast, higher BMI for the reference group was found by *Nikolova et al. (2000) , *Sakata et al. (2003) (RR 1.1, CI: 1.01-1.197), *Oishi et al. (2005) und *Ishii et al. (2005) . These results listed here show no consistent findings on this subject.

4.5.4.5. Cholesterol

Also the data on cholesterol is not consistent. Significant elevations of total cholesterol have been found by *Nakamura et al. (1997) , whereas *Karlsson et al. (2003) found decreased total cholesterol for the shift-workers (RR 3.48, CI: 1.18-2.03). A separate analysis for HDL-cholesterol in the latter study has revealed a significant elevation for 3-shift-workers (7.6%; n=659) compared with day workers (3.9%; n=665). *Lasfargues et al. (1996) only found decreased values for male workers on a significance level. No statistical differences between groups shift and day workers were found by *Knutsson et al. (1988) , *Nikolova et al. (2000) , *Sakata et al. (2003) , *Di Lorenzo et al. (2003) und *Oishi et al. (2005) .

4.5.4.6. Triglycerides

As the results on the BMI and cholesterol, so are the results on triglyceride levels not consistent. Significantly higher values of triglycerides in shift-workers have been observed in studies by *Romon et al. (1992) , *Knutsson et al. (1988) , *Lasfargues et al. (1996) (for night shift-working men and women separately) and *Karlsson et al. (2003) (RR 1.83, CI: 1.08-1.4) . The results of the latter study did not differ after control for age, socio-economic status, physical activity, smoking, social support and workload. No statistical difference has been found by *Nikolova et al. (2000) , Knutsson et al., *1989 and *1990 , *Di Lorenzo et al., 2003 , and *Nakamura et al. (1997) . An increased risk for the metabolic syndrome (due to NCEP/ATP III-Definition) has been stated by *Sookoian et al. (2007) , who have analysed indicators for this syndrome as the prevalence of an elevated BMI (>30) and waist/hip circumference (>102/88 cm), higher levels of triglycerides (>150 mg/dl), decreased high-density-lipoprotein (HDL) levels (<40 mg/dl in males and <50 mg/dl in females), higher arterial blood pressure (>130/85 mmHg) and increased fasting glucose levels (>100 mg/dl). (see Grundy et al. (2005) for further background information).

The results from the studies on lifestyle factors and changes in blood parameters, as have been listed above, show that all these factors cannot explain the risk of shift-work on health. Most studies control for these variables in terms of control for confounders, and find that shift-work mostly remains the only difference between health affected workers and not affected workers. Further, as most shift-work jobs are from industry, chemistry, nuclear field etc., occupational exposures have to be taken into account, especially in case of long-term diseases. Additionally, it has to be kept in mind, that many occupational factors like heat, noise, steam, dust, exposure to other chemical components, are not clearly defined in their own risk potential, therefore also unknown in effect in the context of shift-work. The concepts of stress, allostatic load and of circadian misalignment must be scrutinized and broadened in future research, to better account for intra- and interindividual differences in the responses of people to this time-intensive 24-hour society.

4.5.5. Shift-Work and Cancer

In the mid 1990ies, cancer diseases became subject to shift-work research. More precisely, they became subject to studies on night shift-work. This is based on the assumption that light during the nocturnal work hours elevates the risk of tumour development. Due to difficulties in measuring light exposure in humans in the field, ´night work´ has chosen as a surrogate in human epidemiological studies for exposure to light at night. Results exclusively originate from correlations of data mostly gathered in large-scale population surveys via questionnaires and/or data from official health registries. Measurements of light have never been performed in these human epidemiological studies. The keyword in all these studies is the LAN-Theory, building the fundamental hypothesis which will be explained in the following section.

4.5.5.1. Excursion: Light-At-Night (LAN) Theory

Roenneberg and Lucas (2002) have excellently pointed out the quintessence of the LAN-Theory, which will be presented briefly here. The LAN-theory is based on hypothetically linking the following facts to be causal:

1. Melatonin represents internal night under the control of the circadian clock
2. Melatonin levels can be suppressed by light
3. Melatonin is an indolamine
4. Indolamines can act as scavengers of oxygen radicals
5. Oxygen radicals can cause DNA damage
6. DNA damage can cause cancer

This theory bases on a supposed interruption of the nocturnal physiological synthesis and release of melatonin by the pineal gland (Hill and Blask, 1988 ; Blask et al., 1999, 2005 ; Davis et al., 2001) which in turn affects the level of estrogens. An unnaturally elevated level of estrogens is finally supposed to enhance tumour growth. Melatonin is a free radical scavenger and inhibits estrogenic function. This has been shown in *in vitro* and in murine *in vivo* studies (Cardinali and Pevet, 1998 ; Bartsch and Bartsch, 2006 ; Petranka et al., 1999 ; Anisimov, 1997, 2000). Estrogens bind to specific receptors on the surface of tumour cells and promote growth. A lack of oestrogen inhibition caused by a lack of nocturnal melatonin is therefore suspected to lead to tumour growth. Therefore, it is suspected that inhibition of tumour growth being one of the main functions of melatonin (release). The decreased melatonin synthesis is expected to be the main causal link to the development of cancer in night shift-workers.

In the following, the prevalent definitions of "night-work" from the respective studies are listed. One can easily see, that these are, if anyhow, only approximations of any light exposure during the night. These definitions are based on:

- Only one initial question at study entry on how many years in total they had worked *"rotating night shifts with at least three nights per month in addition to days or evenings in that month"*. (see *Schernhammer et al., 2001, 2003, 2006 and *Viswanathan et al., 2007).

- Information on work and cancer status used from (i) the Norwegian Board of Health's registry of nurses and (ii) census data from 1960, 1970, and 1980. Shift-work status was defined by the census' work codes '*nursing*' or '*nursing and other care work*' or the industry code was '*health work*'. (see *Lie et al., 2006).

- Information on *"occupational groups in which employees work predominantly at night"* was obtained from a nationwide interview-based survey on living and working environment conditions in 1976 among 2603 women. (see *Hansen et al., 2001).

- A characterisation of exposure to light at night *"working the graveyard shift"* (between 7:00 p.m. and 9:00 a.m.) in the 10 years before diagnosis of cancer and defined by (i) *ever worked during the graveyard shift*, (ii) *hours per week worked during the graveyard shift based on a weighted average of all jobs in the 10 years before diagnosis*, (iii) *the number of years worked at least one graveyard shift per week* (see *Davis et al., 2001)

- The self-reports from interviews if "ever working in at least one job during the past 15 years that included (i) *any shift-work* (i.e., any evening or overnight shift job), (ii) *any evening shift* (i.e., including jobs with both evening and overnight shift-work), (iii) *evening shifts only* (i.e., excluding jobs with both evening and overnight shift-work), (iv) *any overnight shift* (i.e., including jobs with both overnight and evening shift-work) or (v) *overnight shifts only* (i.e., excluding jobs with both overnight and evening shift-work) (see *O'Leary et al., 2006)

- Estimations from answers to a self-administered questionnaire: *“Which form of work schedule have you engaged in the longest before now: daytime work, fixed-night work, or alternate night and day work (which are referred to as rotating-shift-work)?”* (see *Kubo et al., 2006).

The following section will provide a short excursion on melatonin. After this excursion, a chapter about the details of the respective shift-work-cancer literature will follow.

4.5.5.2. Excursion on melatonin

Melatonin is a pulsatile, synthesised by the pineal gland (Figure 4). The time point of melatonin synthesis and release is (i) under circadian control from the Nucleus suprachiasmaticus (SCN, the major pacemaker) and (ii) also dependent from the intensity of the ambient light level, as light is potent to depress the synthesis and release of melatonin from the pineal gland, via activation of the SCN. The productive machinery of melatonin therefore shows a 24-hour active rhythm, but the final release is mediated by a disinhibition from the SCN, when ambient light levels fall beneath a certain threshold.

Under light-conditions, the SCN exhibits an inhibitory noradrenergic input via the paraventricular nucleus and the superior cervical ganglia to the pineal gland. This results in an inhibition of the synthesis of Melatonin. Tryptophan is processed by the tryptophan hydroxylase to 5-Hydroxytryptophan. The product from the decarboxylation of this intermediate is 5-Hydroxytryptamin (5-HT or serotonin). Finally the arylalkylamine-N-acetyltransferase and the hydroxyindole-O-methyltransferase process N-acetyl-5-methoxytryptamin, the final melatonin. Brzezinski et al. (1997) found the threshold of melatonin inhibition between 200 and 400 Lux. Maximal inhibition has been postulated at an intensity of 600 Lux for the duration of one hour. This correlates with a spectrum of 446 to 477 nm but is based on results from laboratory examinations under well-controlled conditions (Lockley et al., 2003 and Brainard et al., 2001). The nocturnal peak of melatonin is reached between 02:00 and 04:00 a.m., with levels up to 1400 pmol/l. The normal levels of nocturnal melatonin range around 60 pg/ml. The daily levels are about 10 or less pg/ml. Different melatonin receptors have been identified in humans. These are three high affinity receptors (Mel1a, Mel1b, and Mel1c) and one low affinity receptor (MT2). The high affinity receptors are G-protein coupled and their activation leads to an inhibition of adenylate acyclase. These receptors are involved in retinal function, circadian rhythms, and reproduction. The low affinity receptor is also G-protein coupled and implemented in the stimulation of phosphoinositide hydrolysis. This receptors´ distribution in human physiology further is unclear. These receptors have been found in various densities in the retina, other peripheral organs and in about 110 brain structures as, for example, in the internal granular layer, external plexiform layer, lateral septum, septohippocampal nucleus, caudate putamen, bed nucleus of the stria terminalis, nucleus suprachiasmaticus, mediobasal hypothalamic nuclei, paraventricular nuclei of the hypothalamus, paraventricular nuclei of the thalamus, intergeniculate leaflet, central and medial amygdaloidal nuclei, inferior colliculus, fasciculus retroflexus, substantia nigra, frontal, orbitofrontal, parietal cortex, and the pars tuberalis of pituitary, to name just the most prominent structures. Besides the pineal gland, melatonin is also expressed by the retina itself and by cells in the intestinal tract, whereas the full action spectrum of melatonin still needs to be elucidated.

In context of melatonin depression and cancer development, only very few data are available for humans in real life and any causality is highly suggestive nowadays. In the next chapter, the studies on shift-work and cancer in humans will be presented.

4.5.6. Shift-Work Studies on Cancer

Most results have been obtained via retrospective analyses of data from large cohort studies on cancer prevalences and the respective number of years in rotating night work. Markedly, primarily nurses doing rotating night work have been studied. No other shift-work schedules than night work have been examined, as already mentioned because night shift-work has been chosen as a surrogate for light exposure during the night hours (hence, LAN = Light-at-Night Theory). It was not night shift-work in general that propelled this field of research. The more years employed in night work, the higher the prevalence of cancer. Therefore, the studies in cancer risk in shift-workers are somehow different, as these do not explicitly regard the shift system itself of being harmful, but rather the circumstance of altered light/dark regimes. Anyhow, although these studies are more or less only indirectly real shift-work studies, they will be discussed in this thesis as they constitute an important area in shift-work and also chronobiological research, that definitely needs further research. Therefore, I will start with an overview about the shift-work cancer studies, and then proceed with a brief discussion of the intellectual inconsistencies and flaws of these works (see Comment on the LAN-Theory, chapter 4.5.6.1). The cancers that have been evidenced to be propelled in incidence from night work are breast cancer (with the majority of the studies, Table 4), colorectal cancer, prostate cancer and endometrial cancer. The latter three cancers have only been examined in one study each. All studies found that the risk persisted after control for the factors age, age at menarche, age at Menopause, age at birth of first child, parity, changes in body weight between 18^{th} birthday and menopause, BMI, height, family history of cancer, former benign tumour diseases, use of oral contraceptives and postmenopausal hormones, menopausal status and alcohol consumption.

Article	shift-schedule	RR	OR	CI min	CI max	Focus on …
*Davis et al., 2001	rotating night shift		2,3	1	5,3	Breast cancer
*Hansen et al., 2001	rotating night shift		1,5	1,2	1,7	Breast cancer
*Lie et al., 2006	rotating night shift		2,21	1,1	4,45	Breast cancer
*O'Leary et al., 2006	rotating night shift		1,04	0,79	1,38	Breast cancer
*Schernhammer et al., 2001	rotating night shift	1,36		1,04	1,78	Breast cancer
*Schernhammer et al., 2001	rotating night shift	1,79		1,06	3,01	Breast cancer
*Tynes et al., 1996	rotating night shift		1,5	1,1	2	Breast cancer
*Schernhammer et al., 2003	rotating night shift	1,35		1,03	1,77	Colorectal cancer
*Viswanathan, 2007, 2007	rotating night shift	1,47		1,03	2,1	Endometrial cancer
*Kubo et al., 2006	rotating night shift	3		1,2	7,7	Prostate cancer

Table 4 Overview of shift-work studies on cancer risk. Presented are the Relative Risks (RR) and Odds Rations (OR), and the respective Confidence Intervals (CI). The majority of studies have been performed on breast cancer. Only night work schedules have been studied.

Overview of the findings on shift-work and cancer problems

The Figure 23 shows a taxonomy of the articles about cancer problems (n=10; representing 19% of the initially selected 52 articles). The results are presented due to shift-work schedule, shift rotation, sexes/genders and occupations, for both significant (↑) and non-significant results (Ø). Each of the end-bars in Figure 23 (with information about shift rotation, sex/gender and occupation) represents one article. If one end-bar concerns more than one article, this is listed in brackets behind the respective shift rotation. Cancer problems are only investigated in (rotating) night workers, and additionally only in females (one exception only in the study on prostate cancer by *Kubo et al., 2006). All other studies investigated the cancer risk in nurses. None of the articles reported non-significant results.

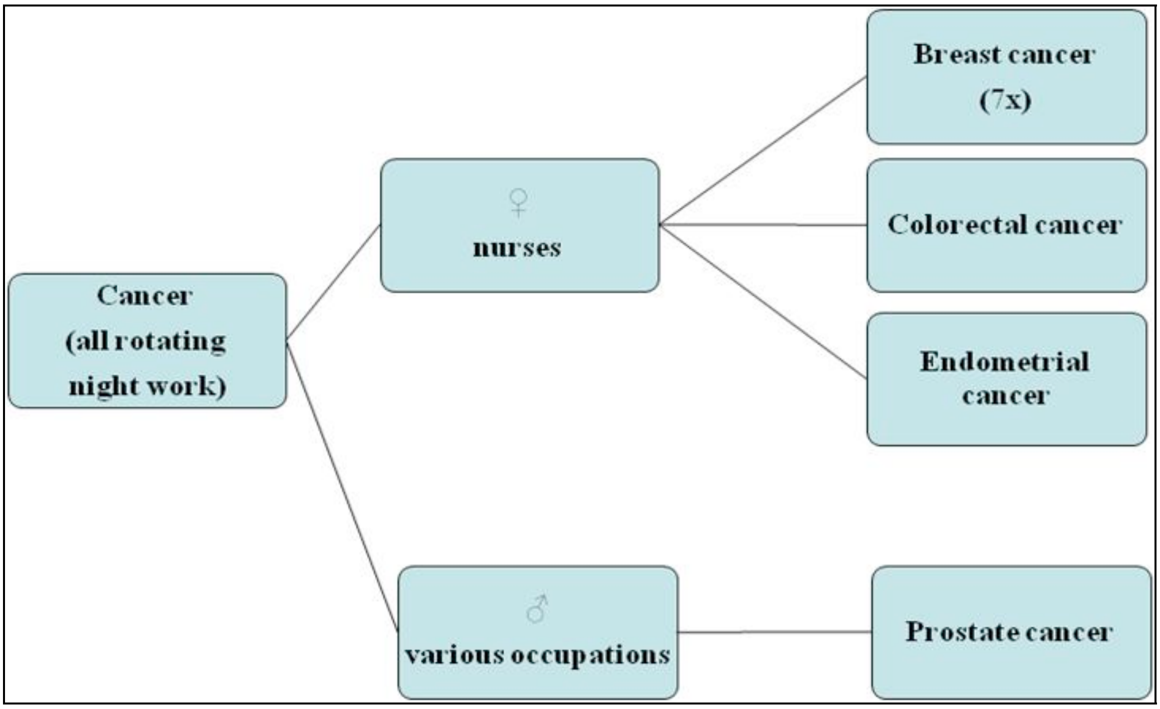


Figure 23 Taxonomy of the selected articles about breast, colorectal, endometrial and prostate cancer (n=10). The taxonomy shows the distribution of articles showing significant increases in cancer for the respective work schedule, rotation, sexes and occupational group.

The weak evidence from the studies has lead the International Agency for Research on Cancer (IARC, a sub-organization of the World Health Organisation, WHO) to constitute an expert meeting that has published in 2007 (http://www.iarc.fr) the results of a respective review and concluded that due to *"limited evidence in humans for the carcinogenicity of shift-work that involves night work"* and *"sufficient evidence in experimental animals for the carcinogenicity of light during the daily dark period (biological night)"* … *"Shift-work that involves circadian disruption is probably carcinogenic to humans"*.

4.5.6.1. Comment on the LAN-Theory

Although, logically, a relationship between light-mediated melatonin suppression and tumour growth cannot be ruled out, such a complex scenario (endocrine system, circadian system, night-shift-work, etc) requires caution in assigning guilt to this one factor. More thorough investigations regarding the specific interactions between the putative causal steps, as well as real-life measurements of actual light environments and individual light perception at the retinal level are necessary to evaluate the impact of LAN on health and specifically on cancer (Roenneberg and Lucas, 2002) .

Further, as the basis of the LAN theory comes from studies on rodents, it must be noted that the circadian system of nocturnal rodents is approximately 10.000 times more sensitive to optical radiation than that of humans (Bullough et al., 2006). Direct comparisons of results from studies on humans and rodents are therefore merely possible. Stress or immune function has neither in rodents nor in humans been elaborated in context of LAN.

Night shift-workers, both working in rotation or constant shifts, differ in many facets from those working under standard conditions: diet, smoking habits and/or alcohol consumption, occupational factors, meal times, and sleep-wake rhythms, to name only a few. Some of these are confounders that have to be controlled for, whereas the lifestyle factors (e.g. smoking or alcohol consumption) must in context of shift-workers be regarded as possible mediators towards disease, as such working regimes can have an effect on coping strategies and health habits. The whole issue is being complicated as the factors listed above further act in concert as a causal basis for the higher tumour risk in night-shift-workers. Some would certainly act as confounders merely by the fact that most of them are bound to correlate with light-suppressed melatonin levels. The actual degree of melatonin suppression in night-shift-workers in context to light exposure has never been examined.

Today it remains unclear if some workers might still produce melatonin during the night hours, in case they are not shifted, and additionally during their day sleep period when lying in darkness. Finally, these workers might be provided with higher levels of melatonin during one shift cycle compared to fixed day workers. As the inhibitory effect of melatonin on tumour growth only appears in small ranges of about 10^{-9} M but not at higher or lower doses, one can also suggest the melatonin level to be overall higher in night workers. This puts emphasize on the importance to regard individual light exposure on both work and free days. From the prevalent results one could also put forward the statement that cancer in night shift-workers rather is caused by no-light-at-day (no-LAD) instead of light-at-night (LAN). No cancer-melatonin association for women with or without cancer was found by Travis et al., 2004 . An elevated melatonin level in fixed night shift-workers on days off was found by Roden et al., 1993 . In addition, it is known fairly little about the actual light levels required to suppress melatonin in real-life situations, especially when history-dependent adaptation levels are taken into account.

Based on this conclusion, more research is strongly recommended to tease apart the causalities behind the health-risks of shift-work but the above summary suggests that it is unlikely that LAN is acting directly via the scenario presented above. An expert meeting on shift-work and breast cancer at the MRC (Medical Research Council) Institute for Environment and Health (November 2004) came to the conclusion that the association between shift-work and cancer is only suggestive so far. Although the relationship appears to be biologically plausible, there is a lack of empirical data. It was mentioned that the measures of shift-work and light-at-night exposure must be improved. This should include duration of shift-working, type and intensity of light exposure, changes in sleep pattern, and variables associated with the circadian rhythm. Further mentioned was the lack of more useful parameters to measure variations in exposure and effect.

4.5.7. Shift-Work and Metabolism

4.5.7.1. Digestive Problems

Digestive problems have most been analysed in cross-sectional studies and workers employed in 3-shift systems. The hypothesis behind the digestive problems is that the alternating work hours lead to alterations in habitual eating times. Especially for social reasons (e.g. to eat together with the family) some workers delay or advance their eating times, depending on the actual work hours (*Lasfargues et al., 1996). *Prunier-Poulmaire et al., 1998 found a correlation between irregular eating hours and loss of appetite and subjective discomforts. Malaise from metabolic consequences like alterations on bowel habits, constipation, diarrhoea, flatulence and heartburn have been described (*Ueno et al. (1984) , *Prunier-Poulmaire et al. (1998) und *Wolfhagen et al. (1994) , *Lasfargues et al., 1996 , * Lac and Chamoux, 2004). *Costa et al. (1980) have found night and 3-shift-work to result in the highest rates of morbidity.

Metabolic (digestive) disorders are found for both females and males and are mainly argued to be an effect of eating at times at which, for example, digestive enzymes are at their physiological nadir and appetite is low, meaning the digestive tract is not prepared to digest during the night. Therefore, these problems would also have a circadian component, because digestion processes are regulated by the internal clock, which can become ill-timed when strong alterations in eating patterns occur as in night work. Some studies already have been discussed in chapter 4.5.4 about cardiovascular problems and the respective risk factors.

4.5.7.2. Diabetes mellitus (ICD-10 codes E10-E14)

*Suwazono et al. (2006) found a higher prevalence (+35%) for Diabetes mellitus (ICD-10 codes E10-E14) in 4-Team/3-Shift-workers. *Morikawa et al., 2005 only found shift-work to be a predictor for 2-shift, but not 3-shift-workers, after control for age, BMI and family history of Diabetes mellitus (ICD-10 codes E10-E14). Concerning Insulin, *Di Lorenzo and co-workers (2003) were not able to find significant differences.

4.5.7.3. Sub-fecundity (ICD-10 code N97)

Higher rates of subfecundity (ICD-10 code N97) were found in a study on midwives by *Ahlborg et al. (1996) . The authors found significantly decreased values for women doing 2-shift-work (-22%, range -35 to -6% / Fertility ratio (FR) of 0.78, CI: 0.65-0.94) and for women in 3-shift-work (-23%, range -40 to -2% / FR 0.77, CI: 0.61-0.98).

Overview of the findings on shift-work and metabolic problems

The Figure 24 shows a taxonomy of the articles about the metabolic problems ulcer and duodenitis, diabetes and subfertility (n=13; representing 25% of the initially selected 52 articles). The results are presented due to shift-work schedule, shift rotation, sexes/genders and occupations, for both significant (↑) and non-significant results (Ø). Some of the articles have already been discussed in chapter 4.5.4 on the lifestyle variables concerning cardiovascular problems. Each of the end-bars in Figure 24 (with information about shift rotation, sex/gender and occupation) represents one article. If one end-bar concerns more than one article, this is listed in brackets behind the respective shift rotation. Metabolic problems have mostly found in rotational 3-shift workers with 8 hour shifts. The results showed no sex/gender differences. Information on the occupations was not provided by all authors. For the three outcomes (i) ulcer and duodenitis, (ii) diabetes and (iii) subfertility, both significant (↑) and non-significant results (Ø) have been found. The risk to develop metabolic problems was not found to be specifically caused by a certain shift system, and is therefore seemingly influenced by various (work related and likely non-work-related) factors.

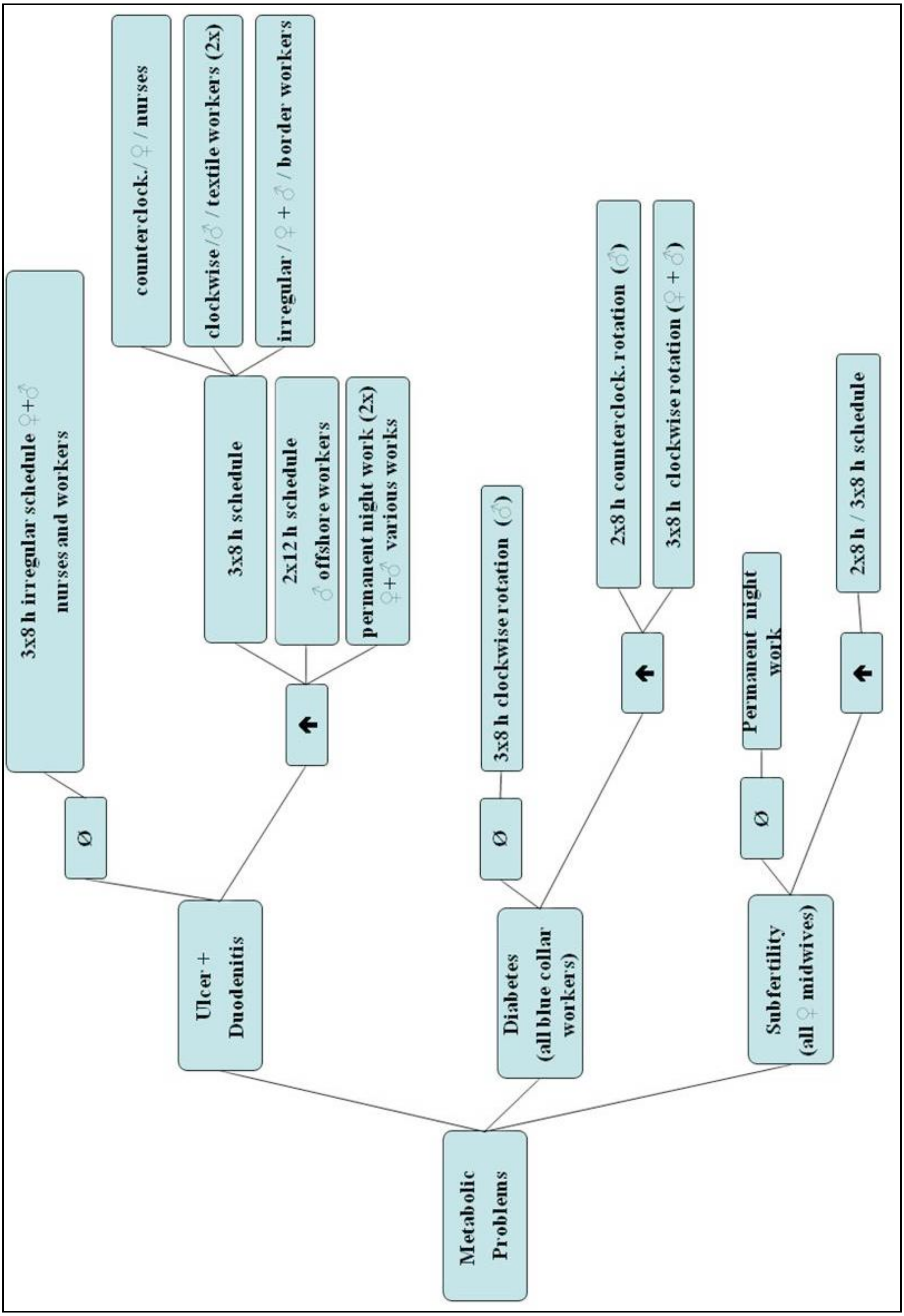


Figure 24 Taxonomy of the selected articles about metabolic problems with ulcer and duodenitis, diabetes and subfertility (n=13). The taxonomy shows the distribution of articles showing significant (↑) and non-significant (Ø) differences in metabolic problems between the shift-work and control group for the respective work schedule, rotation, sexes and occupational group.

4.6. Methodological Difficulties with the Shift-Work Literature

This section is about general methodological difficulties with the shift-work literature. Therefore, it is not limited to the selected articles presented above (n=52). The aim of this section is to give an overview of the main struggles that arise when dealing with epidemiological studies on shift-work. The comparison of the shift-work studies is, as already mentioned above, complicated mostly by the heterogeneity in methodology.

The main differences are (in loose order):

- Shift-work schedules are not separately analysed (e.g. fixed night work has not been separated from rotating schedules)
- The work hours and direction of rotation are not presented
- Shift-work is not defined anyhow
- Weak or non-adjustment of confounders (e.g. lifestyle habits or pre-diseases)
- The time of day of the measurements has not been regarded (no internal time!)
- Mostly only single samplings have been performed instead of daily profiles

In addition to these factors, the interpretation of the results is further complicated by the variance in the following aspects:

a. **Study type:**

   i. Cross-sectional studies are of minor use for the evaluation of causality, as these only represent an actual health state of the population under study. This study type is also highly affective for the "Healthy Worker Effect" (see point **c** in this list).

   ii. Retrospective studies suffer from recall bias or they base on the evaluation of medical records, without reflecting individual work profiles and histories.

   iii. Prospective studies are the only possibility to examine the development of certain diseases in shift-working populations, when these are followed up for a given period and when additionally confounding factors (e.g. lifestyle or shift changes) are accounted for.

b. **The study duration**, in terms of length (number) of follow up studies, often is too short to draw meaningful conclusions.

c. **"Healthy shift-worker"** effect: This effect means that a given shift-worker population constitutes a self-selected sample, by (i) a preselecting process at employment, that only those workers are employed that could endure shift-work burdens, (ii) selection by drop-out, that those who do not stand the shift-work burdens leave shift-work. These processes finally lead to a population of shift-workers that might be healthier then the control groups, as these workers are the “toughest”, in terms of the Darwinian concept of “survival of the fittest”. On average, 20% of a shift-work population leave shift-work due to severe health problems. About 10% show a huge tolerance and withstand the troubles without any complaints. The remaining 70% show different levels of tolerance and problems, which are more or less manifest at different times and with different severity. Cross-sectional studies are often biased by the “Healthy Worker Effect”, as those shift-workers that have left shift-work (and, for example, changed to day work) are not excluded from the sample. Therefore, the sample must be controlled for the number of so-called drop outs. Especially in cross-sectional studies, the shift-workers might appear healthier than the control group. An underestimation of any calculated risk or difference between the groups is likely to obscure the results.

d. **Direction of shift-work rotation** (e.g. clockwise, counterclockwise or permanent night work) and also the speed of rotation (e.g. weekly shift changes or changes every two days) are under discussion to have distinct effects, but are not studied with great detail up to today.

e. **Occupational differences** as the level of demand, different tasks, different number of workers in different shifts (e.g. fewer at night), of supervisors in shifts (e.g. fewer at night), shift durations (e.g. 6-/8-/12-hour shifts), exposures at the workplace (e.g. heat, dust, stress) can constitute completely different working conditions and thereby worksite related exposures and stressors.

f. **The control group is inadequate**, when it differs in too many aspects like the jobs tasks, ages, sexes, socio-economic backgrounds etc.

g. **Subjective or objective data sampling**, meaning (re-) evaluation of data from primary sources (e.g. national health surveys, records from company based annual health check-ups or insurance files etc.), use of questionnaires, interviews or physiological measurements.

h. **Changes and variations in diagnostic criteria** can make comparisons of several studies difficult.

i. **Lifestyle differences** as the socio-economic status, smoking and drinking behaviour, family status, leisure time physical behaviour etc. might additionally play an important role in disease development. Health studies should always take both work and private life into account.

4.7. Discussion

The aim of the literature survey in this thesis was to figure out the state of knowledge about shift-work and health with special considerations from chronobiology. In this respect, two important aspects became apparent that have made this evaluation striking. First, virtually no study has applied thorough chronobiological concepts in field examinations (e.g. to use the individual Chronotype, internal time in prospective examinations) and, second, after analysing those reliable studies that remained (only 52 in total) it must be stated that after decades of shift-work research, the main conclusion that can be drawn reflects the same simple incentive that once has propelled the pioneer shift-work researchers, namely that shift-work affects the health of some workers negatively. Markedly, shift-work research is pronounced by the use of subjunctives and the majority of the results arranges only from correlations of datasets gathered from mostly cross-sectional analyses (57%; Figure 18), and rather superficial studies in which the influence of altered work hours is basically treated as a co-variable, without adequate quantification. In the following section I want to continue first with general statements on the topic of shift-work and health.

Shift-work research is interdisciplinary, combining approaches from biology, pathology, psychology and sociology under the roof of epidemiology. Epidemiology is defined as the discipline that studies the “distribution and causes of disease prevalences in human populations” (MacMahon and Pugh, 1970). By this definition it becomes clear that these studies do not concern the individual worker, but a given population in total, running the risk to loose important information when results are inadequately pooled.

On the one hand, this interdisciplinary approach offers the advantage that the health situation of shift-workers is examined by different expertise. On the other hand, the disadvantage is expressed in the large differences in methodology and concepts (see previous section 4.6) that make comparison difficult. Sad but true, the reader, therefore, finds himself confronted with the fact, that finally there are no two studies that would stand a direct comparison (which, for example, in the field of real clinical studies is far less the case; see, for example, reviews from the Cochrane collaboration).

The aforementioned might be interpreted as a reason why shift-work never has been defined adequately in these studies, neither on external time nor least of all on individual internal time. This also might be a reason, why no statistical meta-analysis on the total shift-work issues has been performed, as it is simply impossible and would not lead to useful results (see section 4.4.1). The idea of a meta-analysis had also been skipped in this thesis. Therefore, the presentation of the material is rather descriptive than statistical. In addition, no systematic longitudinal studies have been found, that would have analysed both certain specific shift-schedules individually for a broad variety of diseases and health effects, to precisely estimate the impact on both sleep and cardiovascular problems, for example.

Another critical aspect is the small number of occupations that have been studied. As shown, shift-workers are employed in many different work sectors (Figure 15), but only few of these have been studied, which is of hindrance to give general statements and recommendation for the general workforce. This is partly reasonable, as there are certain methodological hindrances and obstacles to establish a field-study in running plants and high risky occupational fields (e.g. from the initial compliance of the workers to the limits of research tools in their applicability in real life settings, as for example in the steel industry or during transatlantic flights). Anyhow, the reader should be aware that the knowledge on shift-work health issues is despite its long history rather limited. Anyhow, the huge variability in the studies does also inherit one advantage. Despite the limited interpretability due to the manifold methods and approaches used, it is remarkable that some health outcomes are found with (at least some) consistency over the past decades. These are especially sleep disturbances with its consequences on daytime sleepiness and fatigue on the one hand, and cardiovascular events as long-term effects on the other hand.

Although certain methodological problems have become obvious (chapter 4.6) and although causalities between shift-work and certain diseases are not clear in many aspects today, it must be noted that anyhow the number of shift-work occupations is increasing globally and that the traditional 9-to-5-jobs are about to become extinct. Taking this into account, surely, the awareness of shift-work having detrimental effects on human health is important as the first step, but as long as adequate concepts to ameliorate the situation of shift-workers are missing, the only consequence of this knowledge is, to carry on with more thorough scientific examinations.

A myriad of different shift systems have been introduced worldwide and it seems that nearly every plant uses individual schedules, with some industries using 80 and more different schedules (private communication with a respective occupational physician from a worldwide leading manufacturer of light sources). From this point of view it is interesting, that not much is known about the impact of these plenty shift schedules. One important criterion for the literature selection used in this study was that the investigated shift-schedule had to be listed. Finally, 3-shift systems are studied most, whereas information on the arrangements of the three shifts can hardly be found. Therefore, no optimal (in terms of less interfering) shift schedule could be identified from the results of these articles.

Anyhow, as the number of various shift-work schedules that are worked worldwide is huge, it offers the opportunity to develop not simply production-site adjusted schedules (as is it frequently done today), but further shift-worker adjusted schedules in respect to their individual Chronotype. As mentioned above, despite many methodological differences, certain health problems have been found with some consistency in these studies. This might underline the severity of these problems, even if causalities remain unclear by these approaches. On the next pages the prevalent state of knowledge concerning shift-work and health will be discussed with additionally elaborating strategies for (better) future research.

The most prevalent health problems have been categorised into (i) sleep, (ii) cardiovascular, (iv) cancer and (v) metabolic problems, as presented in the previous chapters in this thesis. In short, sleep problems are named already in the first studies as one of the major struggles of shift-employees, mainly arranging from sleep curtailment and insufficient time for recreation. Cardiovascular problems first appeared in the literature by the 1980ies, have been strongly doubted at that time but have finally been confirmed as a potent long-term consequence in the 1990ies, whereas explanations mainly take elevated stress levels as a key component in disease development. The most recent association between shift-work and disease is a higher incidence of cancer that has first been introduced in the mid-1990ies. As already argued in chapter 4.5.6, cancer diseases are not major topic to this thesis but are mentioned due to the (even if questionable) consistency in the findings. As already pointed out in chapter 4.5.6.1, the argumentative basis (LAN-theory) is elusive today and strongly recommends further investigations. Anyhow, without more insights, the cancer risk must be interpreted to be at least potentially possible.

Finally, digestive problems have been stated to be elevated in shift-workers, which are generally interpreted to be influenced by a combination of (i) low-quality food intake (especially during the night shift hours, due to closed canteens, for example) (ii) adverse lifestyle habits (e.g. smoking and a sedentary lifestyle) and (iii) an unadjusted internal time system, that leads to a food and stimuli consumption at times, at which the body is not prepared properly in terms of enzyme and hormone state. It must be mentioned, that improved diagnostics in medicine have helped to decrease the number of some previously found effects, as for example infections with *H. pylori*, which today are (i) earlier diagnosed and (ii) more effectively treated.

Regarding the field of shift-work research in total, it becomes obvious that since the introduction of cancer diseases in the mid-1990ies, no further major finding has been added to the area. Instead, rather known health effects appeared disguised in new terminology, as for example, the diagnosis of the metabolic syndrome. This syndrome finally just combined already known factors that are found elevated in some shift workers (see chapters 4.5.4 and 4.5.7). The respective factors are an elevated BMI (>30) and waist/hip circumference (>102/88 cm), higher levels of triglycerides (>150 mg/dl), decreased levels of high-density-lipoprotein (HDL; <40 mg/dl in males and <50 mg/dl in females), higher arterial blood pressure (>130/85 mmHg) and increased fasting glucose levels (>100 mg/dl).

Besides the limits mentioned above, the research on shift-work was surely not wasted as it has revealed indeed many health modulators from work- and lifestyle, diet and stimulant consumption and the psychosocial state of employees on various health outcomes. Anyhow, these results have surely strengthened the awareness of the potential effect of shift-work and thereby constitute an excellent basis for upcoming studies, to elaborate the weightings of the individual modulator factors and develop methods to quantify the exposure to shift-work.

This literature evaluation here was confronted with many methodological difficulties, as pointed out above. Finally, one aspect has been identified that gives promising new insights into the field of shift-work research. This aspect is the direction of shift-work rotation, namely the differential impact from clockwise and counterclockwise rotation. It could be shown to differentially affect sleep and cardiovascular outcomes. This means, that there is evidence that indeed the temporal constellations from working in (rotating) shifts play a role in the aetiology of certain shift-work burdens and recommend future research to take the aspect of time more thoroughly into account. The respective hypothesis of the differential impact from shift-work rotation will be figured out more in detail in chapter 4.7.1. The Figure 25 provides an overview of the most significant outcomes due to the shift-work schedules. Most findings have been published for 3x8 h clockwise shift-work. The fewest number of results is listed for shift systems of 5x8 h or 4x6 h rotational shift-work, as this system has fairly been studied.

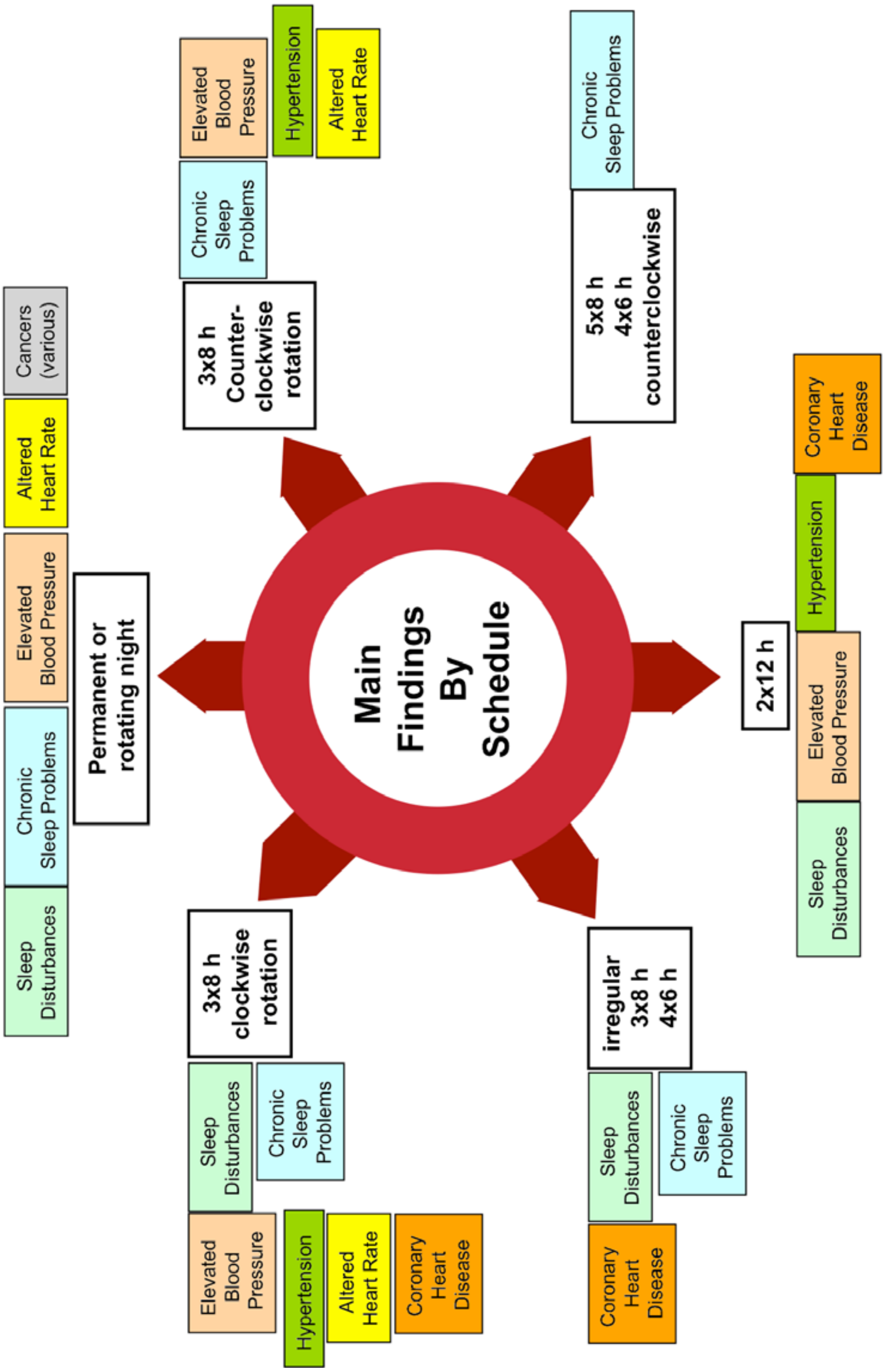


Figure 25 Illustration of the main health effects identified from the selected articles, grouped by shift schedule and direction of rotation. Most findings have been published for clockwise 3-shift systems with 8 hour shift durations. The least number of results has been found for 5x8 h schedules (5-shift systems with 8 hour shifts) and 4x6 h schedules (4shift systems with 6 hour shift).

In the next section I will focus on the evidence found in the literature survey, that the direction in shift-rotation might play a mediating role in stress and maybe also in (long-term) disease development.

Sleep and cardiovascular problems – two sides of the same (shift-work) medal?

As mentioned in the previous paragraph, the two main outcomes that have been identified from this literature evaluation are sleep problems (as an impact on the short run) and cardiovascular problems (as an impact on the long run). Therefore, in the following section these two health issues will be focused on more in detail to figure out the hypothetical title of this section, namely if sleep and cardiovascular problems constitute two sides of the same (shift-work) medal?

As already pointed out in chapter 4.5.1, sleep problems develop soon after entry in a shift-work cycle, mainly on a night shift period and decrease (often also soon) on days off or when switching to day work. Therefore, sleep problems can be interpreted by a rather short-term and transient character. The most prevalent severe and long-term consequences are cardiovascular problems, whereas it remains uncertain if, and in case in which way, these are connected with the sleep problems. One possible and often used explanation for an increased level of heart problems is elevated stress. Measuring stress is highly subjective and stress is further individual and context dependent (see also chapter 4.7.2 below). In the literature that has been scanned for this survey, stress in shift-workers is discussed to originate from various factors as high work load, heat, steam, noise, hectic. Volkholz already mentioned in 1977 that there are several factors at the workplace, which constitute a combined impact on the development of stress and even disease. *Virtanen und Notkola, 2002 wrote in this context, that stress from psychosocial factors (e.g. high work load and low control) had a stronger impact on health deteriorations than stress from physical and physiological (occupational) factors like noise or sedentary work. Needless to say, that of course those combinatory effects not only exist at the workplace but also outside the workplaces, e.g. at home. It is therefore self-evident that an evaluation that does only focus on the worksite-related effects is way too short minded. The psychosocial impact from conflicts with the family and friends has been mentioned and lead Tenkanen et al. (1998) and Harma et al., (1990, 1994, 1996, *1998, 2000) to conclude that shift-work enhances the burdens of negative lifestyle factors.

Stress, as said, can result in adverse lifestyle habits like cigarette smoking or alcohol consumption. Anyhow, increased stress levels are not consistently found in shift-work populations and the ability to smoke, for example, depends on the occupational task and/or the actual work situation. For example, smoking is not possible or even permitted at all workplaces. Nurses would have to leave the station and go out to smoke, whereas some workers on a night duty in an isolated control room might be very well permitted to smoke. A shown, occupational stressors and adverse lifestyle factors cannot fully explain the health deterioration associated with shift-work. Also, these factors (like smoking) appear in most cases as both confounders and also mediators to disease, as already pointed out previously in this thesis. For example, night shift-workers more than day workers have to fight against the tendency of falling asleep when less is to do during the night and cigarette smoking is often used as a stimulant against tiredness.

In the view of chronobiology, shift-workers might besides that discussed above been stressed by another circumstance, which is increasingly discussed in the actual research today. Shift-workers are struggled to "function" at times within a 24-hour period, at which the body is not "adequately prepared", both in terms of cognitive and also metabolic and physiologic resources. The former is expressed in circadian rhythms of alertness, memory and of stress tolerance, for example, whereas the latter affects daily rhythms of hormone, enzyme and even DNA-synthesis. This would mean that, for example, digestion or the bodily stress response itself are "inadequate", as these rhythms might not adjust to the new time regime (given by the work hours) and be still synchronized to a diurnal lifestyle in a night shift-worker who has recently started the nocturnal work period. But, these findings are mostly hypothetical, originating from laboratory studies and need to be proven in real life settings for how and to which extent these affect the health of shift-workers in the short and the long run, respectively.

What the factors are and in which interaction under which circumstances these exactly (might) lead to illness, depends obviously on many individual traits, as for example on the adjustment capacity of the individual internal clock, the respective susceptibility and coping behaviour of the individual worker. Volkholz (1977) pointed out at this melting pot of impacts when he wrote that "*not work itself, but those forms of human work that result in overstraining are problematic*".

Müller (1985) recommended in turn to realize that stresses and strains are objective external factors, that are independent from the workers. Costa in 2003 in addition mentioned that shift-work has to be regarded as a modulator or trigger, that acts as a stress factor which interferes with co-prevalent disorders. It must be noted at this point, that all the health problems that are found and discussed to be elevated in shift-workers (e.g. sleep and cardiovascular events) are definitely not unique for this working population. All these diseases and health problems are known from epidemiology. *The* shift-work health problem has never been identified, whereas seemingly the ways under which shift-workers are affected might differ from that of non-shift-workers. Thereby, the outcome is the same, but the aetiology may not. Further, as we know of most of these population diseases to have a multifaceted origin in genetic, personality, life-style, social conditions and intervening illnesses, shift-work might therefore be also regarded as a factor that likely propels pre-existing diseases and increases adverse lifestyle habits. Equal to a vicious circle, in the long-run health is adversely affected. A thorough pre-screening is therefore strongly recommended before employment.

The appeal that arranges from this argumentation is, to take the individual worker into focus. The epidemiology of the shift-work health problems as it appears today, clearly shows that new concepts are needed, taking the challenge of integrating a new dimension into the established methods of analysis, namely the dimension of internal time (Chronotype; see also chapter 7.1). With the knowledge from chronobiological research, future research on shift-work should strictly regard the individual internal circadian physiology and adjustment capacity of the individual worker, in the context of individual alterations in physiology due to individual alterations in work and sleep hours and the environmental zeitgeber exposure.

In this respect, Aguirre and Foret (1993) argued that "*the physiological explanations given by chronobiological studies are of limited help to account for the complaints of shift workers. Even if plausible, there is no evidence whatsoever that, sleep and alertness problems apart, the physiological consequences of shift-work could be related to repeated disruption of the circadian system*". As the studies in this thesis clearly show, this line of argumentation by Aguirre and Foret can definitely not be agreed upon.

Therefore, a thorough (re-) examinations of shift-employees on the fundament of the previously gathered results from shift-work research and on the basis of chronobiological approaches to ground all investigations on internal time, is very promising to elucidate the weightings of the known modulator and interacting factors:

- Sleep deprivation (with consequences of sleepiness and/or fatigue)
- Mal-nutrition (e.g., elevated intake of snacks, fast-food, alcohol, caffeine, etc.)
- Adverse life-style habits (e.g., smoking, sedentary lifestyle, etc.)
- Elevated (psychosocial) stress (both at work and in the private area at home)
- Internal desynchronisation (from misalignment of internal and external time)

The interplay between the social schedule (e.g. work times) and biological (e.g. dawn and dusk) zeitgebers and the consequences of a mismatch of these two is illustrated in Figure 26. This figure shows that under "normal" conditions, when the social schedule and the biological zeitgebers are synchronised the internal clock (SCN) mediates physiological processes during which the body is internally synchronized (see upper part of the figure at the right side and also chapter 1.3). "Shift-work" (left part of the figure, marked by a red-flash) therefore interferes with this harmonic synchronization of social and biological time, leading to possibly altered alimentation (eating times) and social routines, whereas the latter can either lead to altered light/dark cycles or directly to states of stress and finally to disease. Further, altered light/dark cycles might also (or maybe most importantly) play a role in the internal desynchronisation of the body, when shielding the worker from the daily light exposure due to, for example, night work. From this point two possible outcomes can be depicted. On the one hand it is possible that the circadian system adapts to the alterations and adjusts properly to the new time regime, getting in synchrony with the new environmental time cues. This must be assumed to be likely, because not all shift-workers show complaints or are found to become ill. On the other hand, the circadian system does not adjust and the body becomes internally desynchronised (destabilized) which results in the adverse health outcomes reported in this study at hand (see "stress and disease" in Figure 26).

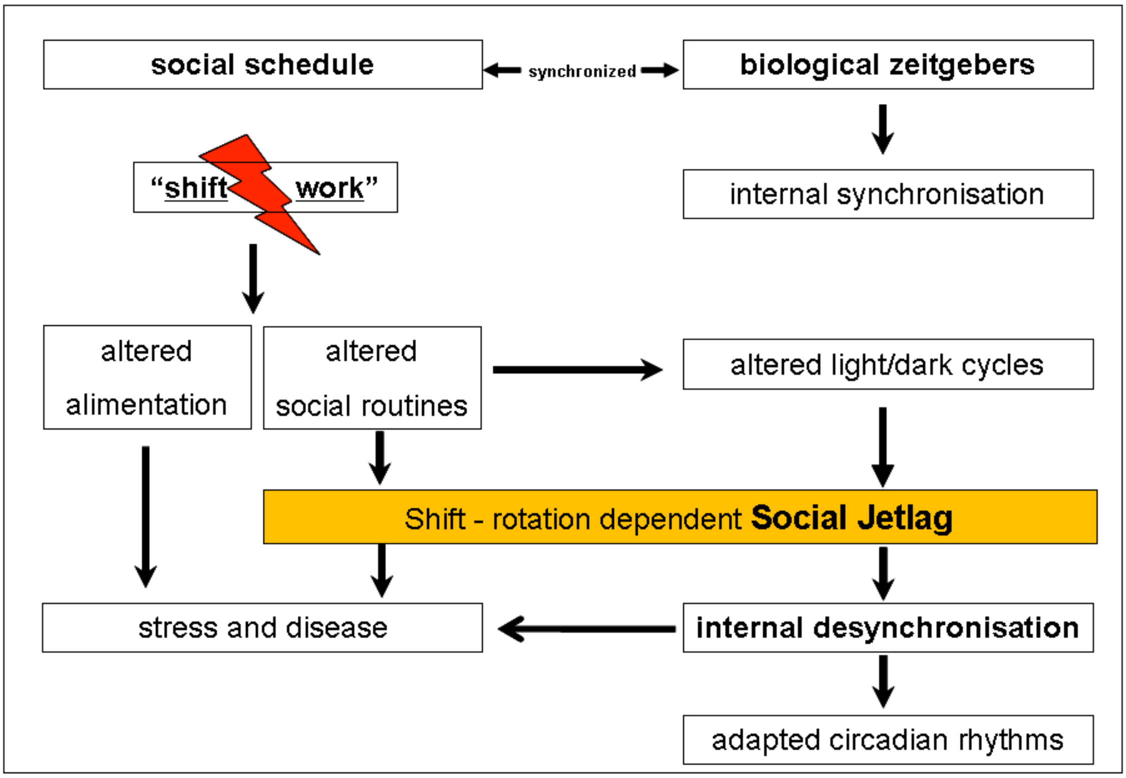


Figure 26 Illustration of the interplay of social schedule and biological zeitgebers and consequences of a mismatch between these. Shift-work (indicated by a red flash) represents a social factor that disturbs this interplay. The two possible results from this disturbance are 'stress and disease' (left side) or 'adapted circadian rhythms' (right side).

This shows, that circadian desynchrony does not inevitable lead to disease, but can result also in "adapted circadian rhythms". Social Jetlag (yellow field in Figure 26) has been introduced as a mediating variable leading to internal desynchronisation is supposed a very good marker for the calculation of the impact of shift-work on humans.

As mentioned at the beginning of this Discussion, there is evidence that certain health outcomes are shift-schedule depended, with special regard of the direction (clockwise vs. counterclockwise) in which the shifts rotate. This will be further illuminated in the next chapter, starting with an overview of the studies on the direction of shift-work rotation.

4.7.1. The Direction of Shift-Work Rotation

4.7.1.1. Review of the Literature

Only few studies have compared clockwise and counterclockwise shift-systems in respect to impacts on health. These studies have investigated mostly the effect on sleep and social factors, like the arrangement of work and private life. Some studies investigated physiological rhythms of body temperature and cortisol (Costa et al., 1994 ; Lavie et al., 1992 ; Hakola and Harma, 2001 ; Takahashi et al., 2008 ; Kecklund et al., 2008). These will be discussed below. Anyhow, there is no study that has focused on long-term health effects, like Coronary Heart Disease for example, in a longitudinal examination on shift-workers due to the direction of the worked shifts.

Substituted by findings from studies on Jetlag after time zone travel, which indicate that adjustment after westward (delaying) flights is easier to manage for the internal clock than adjustment after eastward (advancing) travels, several authors (and seemingly workers, too) favour clockwise rotation as this work regime allows for better adjustment of the sleep/wake cycles and circadian clock, which is mainly supported by subjective self-reports showing shift-workers to better cope with clockwise work regimes (*Jansen et al., 2003 ; van Amelsvoort et al., 2004). To be mentioned in this context is, that the main reasons to leave shift-work are high levels of sleepiness and fatigue, increased need for recovery that cannot be accomplished for, further poor sleep quality and general malaise, combined with being dissatisfied from insufficient time for leisure activities, and increased work-family conflicts (van Amelsvoort et al., 2004).

Orth-Gomer (1983) and Barton and Folkard (1993) came to the conclusion that clockwise rotation has fewer effects on the general health status and feelings of well-being. Barton et al. (1995) found longer night shift periods to be of advantage, judged from results obtained with the Standard Shiftwork Index: "*Results showed clearly the impact of the number of consecutive nights worked on health and well-being, not directly, but indirectly through the impact on sleep duration and sleep quality. Sleep duration was shown to increase with more consecutive nights worked. This in turn was found to predict sleep quality, which in turn was found to be the stronger direct predictor of psychological and physical ill-health i.e.*

better health was associated with longer and better quality sleeps."(cited from Barton et al. (1995). This *indirect* evidence mentioned by Barton et al. (1995) only bases on suggestive interactions between "sleep duration – sleep quality – psychological and physical ill-health".

Anyhow, a better adjustment of the sleep/wake cycles in clockwise rotation was also found by Lavie et al. (1992) and Hakola and Harma (2001) using actimetry and sleep-logs. Knauth and co-workers in several studies (1983, 1993, 1995a,b, 1996) have compared clockwise and counterclockwise rotation in respect to physiological, psychological and social factors. They argue that clockwise rotation decreases problems with time-budgeting, the sleep deficit and circadian disturbances, whereas the latter finding concerns shifts in the acrophases of hormones. In addition to the direction of shift rotation, the amount of free days between the shifts, to compensate for sleep deficits, was found to correlate with the attitude of shift-workers towards their actual work schedule (Kecklund et al., 2008), and shift-systems with longer night shift periods are known to lead to higher levels of sleep problems, as presented in chapter 4.5.1. This was also found in a recent work by Takahashi et al. (2008) , who compared sleep problems among caregivers employed in various shift systems. The hypothesis has been put forward that shift-workers´ health problems are <u>mediated</u> by an impact on the internal clock in terms of internal desynchronisation has already been introduced to this thesis at several chapters, but it must be mentioned again, that results on this area are debatable. Gibbs et al. (2002) are one the few authors, that have realized that the initial phase position of the internal clock determines the impact of the shift schedule and its direction in rotation.

As the studies mentioned above mainly focus on sleep and related factors, the next section will focus on those studies that have looked at the influence of shift-work on physiological parameters. It must be noted, that these studies have mostly been performed under laboratory controlled or semi-controlled conditions, and therefore have been excluded from the initial pool of hits from the literature survey in this study (chapter 4.3).

Barnes et al., (1998) have shown that workers on 12-hour duties, with work hours from 00:00 h to 12:00 h, advanced their aMT6s (the metabolic product of melatonin, which is commonly used as a phase marker in physiological studies) rhythms and workers in a similar setting, but working from 18:00 h to 06:00 h, showed a phase delay in the respective aMT6s rhythm (Gibbs et al. (2002). Also Nesthus et al. (2001) have presented "*surprisingly*" the result of a delay in circadian temperature acrophase in workers studied in counterclockwise rotation, with two evening, two early morning and one midnight shift in a row. The results from Nesthus et al. (2001) underline that the initial phase position of the internal clock is of importance. Further, Nesthus et al. (2001) studied the circadian temperature rhythm in shift-workers and found an attenuation of the amplitude and a delay in the acrophase. In a later study by the same group, Boquet et al. (2004) also found lower amplitude and delay in acrophase of the rectal temperature rhythms, but failed to find differences in cortisol, melatonin. The authors finally concluded that not the direction in rotation, but the actual shift (early morning and night work especially) are detrimental in effect.

On the contrary, some recent studies do not find significant differences in the effect of shift rotation. Tucker et al. in 2000 found no difference between advancing and delaying shift-schedules and reasoned, that "*the absence of negative effects of advancing shifts upon the chronic outcome measures accorded with previous evidence that advancing shifts may not be as harmful as early research indicated*." In a study by Cruz et al. (2003), sleep/wake behaviour, subjective sleepiness, sleep quality and mood were not found to differ between workers employed in clock- and counterclockwise rotational systems. The authors argue that shift type is more important concerning sleep problems than the direction of shift-work. De Valck et al. (2007) found no impact on the cortisol level and subjective sleepiness, and also argue in favour to regard of shift type instead of shift direction.

In addition to the direction of shift rotation, the speed in rotation has been emphasized by Costa et al. (1994) for clockwise rotating nurses showing that sleep/wake behaviour, temperature rhythms and plasma-/urinary parameters better adjust to fast rotating clockwise shifts (meaning shift changes every 2 or 3 days). Vokac et al. (1981) for experimental counterclockwise rotation came to a similar conclusion, that fast rotating systems do not markedly disturb the internal clock. They further argued that partially observed phase shifts of temperature rhythms for example, are rather due to masking effects than "true phase shifts (entrainment)". Another example is, that 12-hour shifts are favoured by some employers with the aim to offer the employees more free time for the arrangement of work-, social- and family life. A recent publication from Loudoun (2008) otherwise found no benefit from 12-hour shifts compared to 8-hours shifts on the reconciliation of work- and non-work life, among a sample of machine workers. The diversity in the findings and different interpretations on the effect of the shift-work direction have lead some authors to state that there is no optimal direction (Turek et al., 1986) and no optimal speed (Monk et al., 2000) in shift rotation.

The discussion on the effect of the direction in rotation is, as can be seen from the examples above, is marked by controversies and inconsistencies. These data further indicate that the underlying mechanisms are more tangled as some scientist might have initially thought. Therefore, the articles selected for the shift-work literature survey (n=52) have been examined in respect to the direction of the shift-schedule rotation, and as already mentioned above, there is evidence of a difference in effect between clockwise and counterclockwise rotation.

4.7.1.2. Evidence from the articles on the effect of the direction in shift rotation

As introduced in the previous sections, direct comparisons of the studies and their results are merely possible due to the heterogeneity from the interdisciplinary approaches used in the various shift-work studies. Anyhow, there is one difference emerging when comparing the direction in shift-work rotation especially between the studies on sleep and those on cardiovascular events. We find cardiovascular problems pronounced in workers employed in clockwise than counterclockwise rotation. Sleep problems in turn are found more often for counterclockwise rotational shift-work and with its highest number in permanent night workers (Figure 27). One can also see that cardiovascular problems are not represented by studies on fixed night work. Cancer in turn has exclusively been studied in night working populations, but not in other schedules. This limit in findings might partly bias the observation mentioned here, but I rather assume that the non-finding of respective articles belongs to the overall bias that mostly only those studies are published, that report to find significant differences, whereas those studies that do not are not published. Therefore, I argue that the non-publishing of more articles on cardiovascular problems in counterclockwise rotation falls into this circumstance. Figure 28 shows the result exclusively for sleep and cardiovascular problems, as these will be mainly focused on in the following course of this thesis.

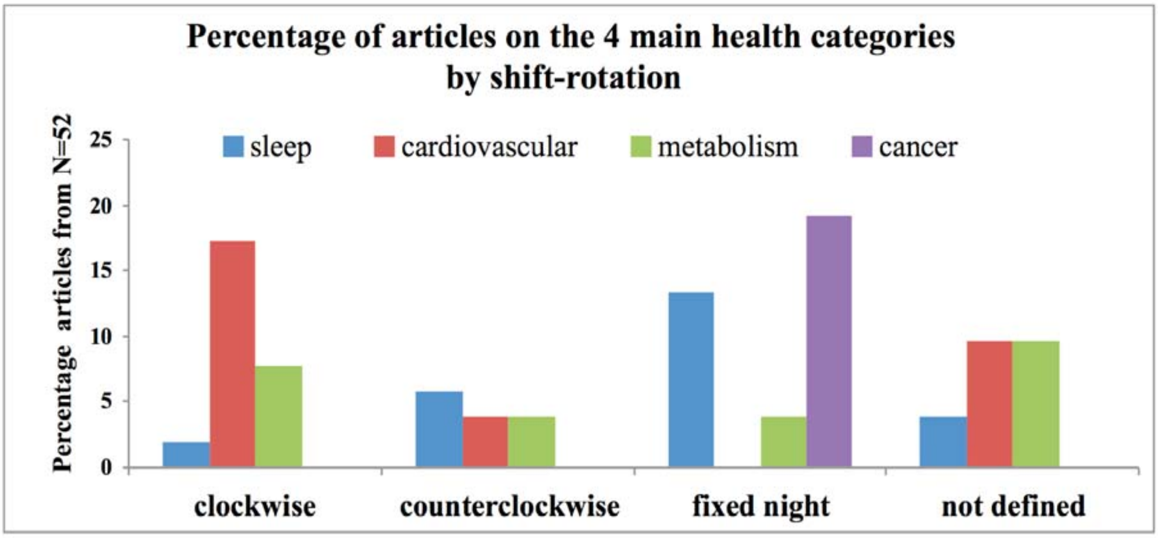


Figure 27 Distribution of the 4 major health categories sleep (blue bars), cardiovascular (red bars), metabolic (green bars) and cancer problems (purple bars). The results are presented by the shift rotations, namely clockwise (forward), counterclockwise (backward) and fixed night work. The results from studies that did not name the direction of shift rotation are grouped under 'not defined'.

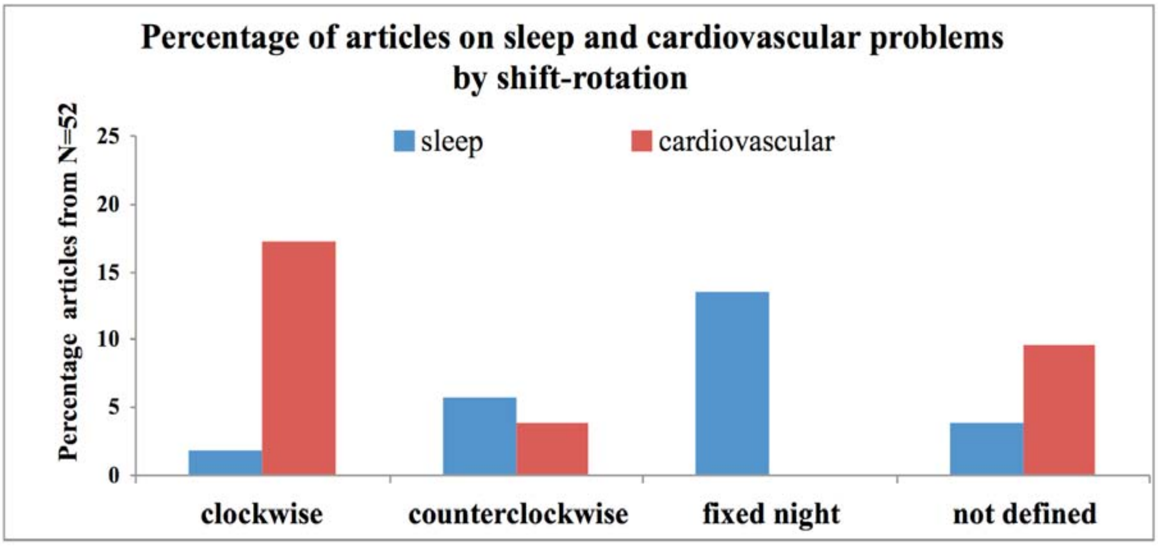


Figure 28 Distribution of the 2 most consistent health outcomes sleep and cardiovascular problems. The results are presented by the different shift rotations, namely clockwise (forward), counterclockwise (backward) and fixed night work. The results from studies that did not name the direction of shift rotation are grouped under ´not defined´.

The separate analysis of these studies on the direction in shift rotation revealed an age difference for the average ages of the studied workers. Table 5 shows the average ages of the workers, separated by health category and direction of the shift-work schedule. For reasons of completeness, the average ages of the studies from all four categories (sleep, cardiovascular, cancer and metabolic problems, respectively) and also the ages for night workers have been added to the table.

Rotation / health topic	clockwise	counterclockwise	fixed night work
Sleep problems	38	36	35
Cardiovascular problems	36	41	42
Cancer diseases	NA	NA	47
Metabolic problems	39	49	38

Table 5 Presented are the average ages of the workers by the 4 main health categories. Most evident is the age difference of the workers studied on cardiovascular and sleep problems (36 and 41 years, respectively) for the both shift-work directions clockwise and counterclockwise (NA=no ages, due to no available studies for this group, because cancer has not been studied in other shift schedules than night work).

From Table 5 it can be seen that certain age differences appear in the groups. The importance of these differences will in the following section be discussed.

Why might this age difference be important?

As already said, clockwise rotation, compared to counterclockwise rotation, is often preferred (by both employees and employers, for mostly subjective reasons) as the latter leads earlier and to more sleep problems, social disarrangements and it thereby makes it difficult for some workers to arrange both work and family life. In addition, counterclockwise rotating systems are worked in many cases by newly employed and therefore assumingly most likely by younger workers. Table 5 shows that sleep problems appear about two years earlier in counterclockwise than clockwise rotation, which is in line with the finding mentioned above. Pronounced night work also shows to lead earlier to sleep problems. Interestingly, the opposite holds true for the finding of cardiovascular problems, and slightly also for metabolic problems, as in these studies the workers in counterclockwise rotation are the oldest (on average). The point that I want to make here is, if counterclockwise rotation forces workers to leave shift-work early in their career, the clockwise workers from these studies cannot be former counterclockwise workers (hypothetically spoken), as these are already older (36 vs. 41 years, respectively). Based on these simple observations, the direction of shift rotation can be evidenced to play a role in the aetiology of both short- and long-term health outcomes in shift-workers, found here for sleep and cardiovascular problems, respectively. As these shift-workers can be assumed not to differ in respect in their overall exposure to risk factors and as also the course in development of cardiovascular problems can be assumed to be equal in both groups, the only difference found here is the direction in shift rotation.

The hypothesis for the next part of this thesis therefore is that workers employed in counterclockwise rotation are affected in older ages (later) by cardiovascular problems than their colleagues from clockwise rotation. Further, it can be hypothesised that the benefit of less sleep and social disarrangements from clockwise rotation (as reported in many subjective evaluations) might be replaced by a higher risk of developing severe heart problems on the long run. This would mean that there is a true difference in effect to the physiology by the direction of shift-work rotation that needs further investigation. Sleep problems and cardiovascular problems therefore appear as the two sides of the (shift-work) medal. Before I will come to discuss how to measure such a difference, I will first argue on the possible basis of this difference, to further illustrate the hypothesis.

What might be the basis of this difference in findings for the different shift rotations?

Cardiovascular problems develop slowly with time, mostly over years. CHD has been shown to be significantly elevated after shift-work seniority of at least 10 years, with increasing risk prevalence with increasing years on shift-work (chapter 4.5.3.3). Further, it can be assumed that (mostly subjective) first signs and indicators on heart problems are almost always not perceived by an affected person. This means, that the factors leading to disease are very likely prevalent at least for some years, but the indicators and risk factors are not always clear to the people. Studies have shown an impact of shift-work on known cardiovascular risk factors as smoking, adverse diet, altered heart rate and blood pressure, whereas this impact is found not to be shift-work rotation dependent. Therefore, the aetiology of heart disease is equal to the shift-workers, irrespective of the shift-system they are employed in. This strengthens the finding of the difference in shift rotation to have a distinct impact.

Further, in contrast to heart problems, sleep and digestive disturbances are very well noticed by a subject pretty soon (with symptoms like altered bowel habits, constipation, diarrhoea, flatulence and heartburn). This gives an affected worker directly the opportunity to establish countermeasures against the adverse impact (e.g. leaving shift-work in worst case). In the following section it will therefore be tried to illustrate how such an individual outcome might emerge. The concept of stress will be adapted again as it has been introduced to this discussion; chapter 4.7.

4.7.2. Direction of Shift-Work Rotation and Stress

Shift-work research lacks standard operating procedures (SOP) that would allow for accurate comparisons of the studies and results, as pointed out in detail in chapter 4.6. Further, there is no defined parameter that could be used as a risk estimate for a certain shift-work constellations. The concept of internal desynchronisation has been introduced in shift-work research, but many aspects of this concept are still uncertain and to be elucidated. Despite the open questions in the concept of internal desynchronisation (see also chapter 1.3.2.1) it is a promising approach in the basis of chronobiological concepts. Therefore, it will be used to explain the impact of shift rotation (clock- vs. counterclockwise) on the mismatch of internal and external time.

A mismatch between social and biological zeitgebers from, for example, constant nychthermal work-shifts, might cause a desynchronisation of the internal physiology (chapter 1.3.2.1), that throws people out of their habitual chronotope (chapter 1.3). Laboratory studies have shown that body rhythms differ in their temporal adaptation to changes zeitgebers, which indicates that single cell and organ clocks become uncoupled from the rhythm of the SCN (Yamazaki et al., 2000 ; Hara et al., 2001 ; Waterhouse et al., 1999). Core body temperature for example has been shown to adapt after several days to a shift in sleep times in night workers, but only if these keep their permanent nocturnal routines. Stokkan et al. in 2001 have shown that rodent livers adapt slower than the SCN after phase shifts in light exposure.

In respect to the direction of shift rotation, a different response to advances and delays in humans had been observed (Folkard et al., 1978 and 1980 ; Goh et al., 2000 ; Persson et al., 2006 van Amelsvoort, 2004). In a night shift simulation study it has been shown, that both central and peripheral circadian rhythms adapt to new work hour regimes, but that it had taken several days and that peripheral clock adapted later than central ones (James et al., 2007a,b). Adjustment in cortisol pattern in shift-workers has been shown to be only partial, as additionally the re-adjustment to day work schedules (advance) was slower than the adjustment to the shift schedule (delay) (Karlsson et al., 2006). Most of the results are not easy to interpret and further it has also been mentioned that more work needs to be done to learn more about definite and conclusive markers of the circadian clock in humans (Sack et al., 2007a,b).

Although the impact of internal desynchronisation on the development of long-term health problems still remains uncertain and so far mostly hypothetical (Brown et al., 2008 ; Martino et al., 2008), this concept has been introduced to explain the observed problems in shift-workers, for both transient sleep disturbances and long-term deteriorations of cardiovascular functions. Circadian misalignment appears to be plausible explanation for a destabilization of the internal physiological status, leading to elevated (chronic) levels of stress.

In the literature, disturbances in circadian rhythms in humans are in most cases described in context of an altered sleep/wake rhythm. The effects of shifted sleep/wake cycles therefore are interpreted to cause circadian misalignment by disrupting the endogenous circadian rhythms. As light is the primary zeitgeber for the human internal clock, the effect of shift-work on the internal clock likely is an effect of altered or weakened zeitgeber exposure from altered exposure to the light-dark cycle (e.g. lower light levels while working at night). Due to the altered work and sleep times, the workers are not able to expose their internal clocks to light at proper times, which in turn weakens the internal system and thereby weakens the ability to sleep and function adequately.

Although neither the term “circadian alignment” nor the term “circadian misalignment” has ever been defined properly, for the following explanations, internal desynchronisation will be regarded as a (maybe *the*) potent underlying mechanism that weakens the physiological ability to cope with stressors and to reach homeostasis (Greek *homeo* = same and *stasis* = stable) by a chronically elevated level of allostatic load (allostasis = active adaptation process to maintain stability through change). For further information I would like to refer to the excellent article on this subject from Korte et al., 2005 . To illustrate how a mismatch of internal and external time might lead to an increased level of stress, the functioning of the Hypothalamic-Pituitary-Axis (HPA) in stress response will be used.

In day oriented workers, normally cortical starts to rise before waking up to provide the body with sufficient levels of cortisol for the start into the day, for example at 07:00 o’clock in the morning. In terms of shifting to night work (meaning an ad-hoc external shift in 8 hours or more), the cortisol rhythm might not adjust immediately to the new time regime. Therefore, the worker might not be provided with sufficient cortisol when getting up (for example at noon or later), but still at 07:00 o’clock when still lying in bed. Cortisol therefore is not available in situations of (acute) stress when needed most, and further impairs sleep by activating the body at the wrong time (at 7 o’clock, when the night-worker wants to sleep).

This example can of course be adapted for all physiological parameters that can become misaligned with the external world. If thereby, the body is not capable to adequately react to stressors, an increase in allostatic load might be the result. The allostatic load then leads to physiological, energetic exhaustion and a chronic stress level, until homeostasis is reached again. If the latter is not possible, long-term consequences become likely and sooner or later, elevated stress can lead to adverse health conditions for compensation (e.g. smoking or alcohol consumption). (See also Akana et al., 1992 ; McEwen et al., 1998 ; Dallman et al., 2006 ; de Kloet et al., 2005 ; Joels et al., 2008).

Finally, the effect of altered work hours and the repeated adjustment-re-adjustment processes that shift-workers have to manage, point at a strongly exhaustive impact and the following two questions emerge: What are the parameters (physiological correlates) leading to allostatic load (stress) and how to measure these? To answer these questions, is subject to the chapter 5. The next chapter will first give an example that underlines the importance of developing tools and measures to adequately quantify the impact from shift-work on humans, by calculating the monetary aspect of shift-work health problems. Therefore, an exemplified calculation of the potential costs arranging from shift-work in terms of cardiovascular problems has been performed.

4.7.3. Potential Health Costs from Shift-Work

As presented above, the evaluation of the health risks that are associated with shift-work is complicated due to the heterogeneity in these evaluations (see additionally chapter 4.6). To calculate the most potential costs of shift-work health problems, I have chosen the most reasonable severe long-term consequence that could be identified in terms of consistency in results obtained in the literature survey in the thesis at hand, namely Coronary Heart Disease (CHD; ICD-10 codes I20-I25; chapter 4.5.3).

CHD has chosen to explain the potential health costs from shift-work because CHD (i) shows a high prevalence among the general population (males: 8.9% / females: 6,1% / both sexes: 7,3%), (ii) causes half the deaths among the general population (McGraw-Hill 2001), (iii) therefore is one of the major lethal factors worldwide, (iv) is clearly defined due to its diagnosis by the ICD code and (v) is the most cost intensive outcome with grant total costs with 156.4 billion Dollar.

The grand total costs include direct costs from hospital, nursing home, physicians/other professionals, drugs/other medication, home health care, and also indirect costs from lost productivity/morbidity/mortality. Data on the prevalences was taken from those of the selected studies where extraction of the respective data was possible (Table 6). The background data and the costs for the calculation of the potential health costs form shift-work on the risk of CHD have been extracted from the "Heart Disease and Stroke Statistics – 2008 Update, American Heart Association ". As the number of shift-workers varies between the different countries (Figure 14), an amount of 20% shift-workers among the general workforce has been chosen for the calculations here.

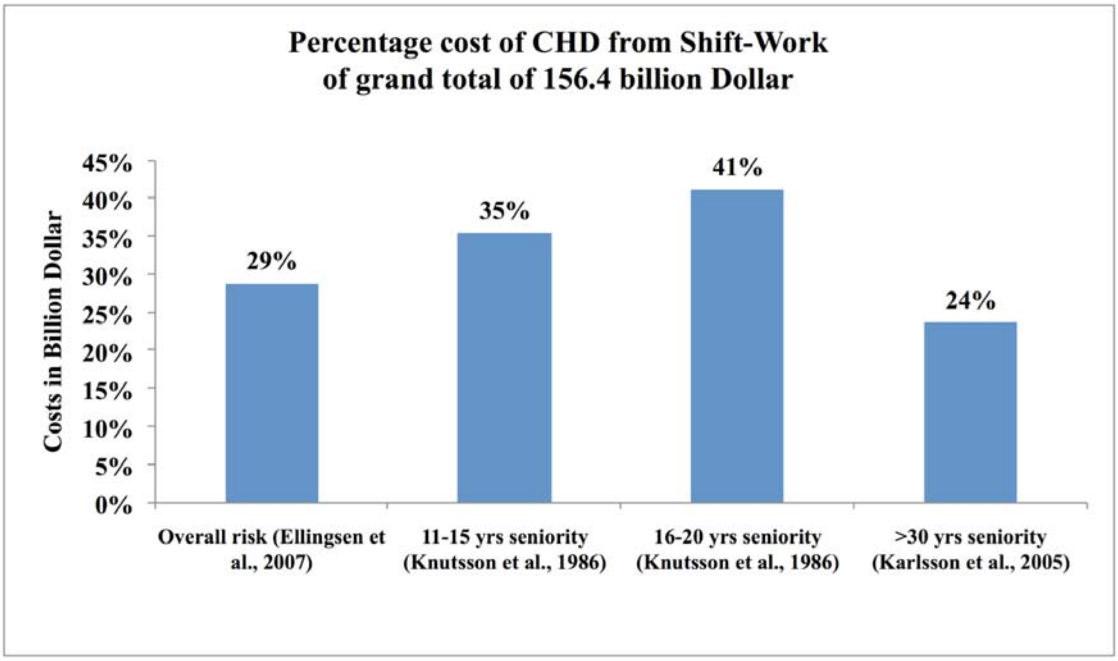
Diagnosis	**Article**	**Schedule**	**Rotation**	**Sex**	**OR/RR**
CHD overall	Ellingsen et al., 2007	3x8 h	clockwise	males	1,62
CHD (11-15 yrs seniority)	Knutsson et al., 1986	3x8 h	clockwise	males	2,2
CHD (16-20 yrs seniority)	Knutsson et al., 1986	3x8 h	clockwise	males	2,8
CHD (>30 yrs seniority)	Karlsson et al., 2005	3x8 h	clockwise	males	1,24

Table 6 Overview studies that have been used for the calculation of the potential cost from shift-work on health.

The following formula was used to calculate the percentage of affected shift-workers from the total workforce (with SW=shift-workers and DW=day workers):

$$\% \text{ affected SW} = N_{affectedSW} / (N_{affectedSW} + N_{affectedDW})$$

The percentage Dollars from the grand total costs for CHD calculated for the shift-workers ranges between 24% and 41%, as shown in Figure 29. Both costs and risk decrease with higher shift-work seniority (>30 years). The highest costs are found for shift-workers with a seniority between 16 and 20 years (*Knutsson et al. (1986). The decrease in risk of CHD with increased shift-work seniority of more than 30 years might be due to the "Healthy Worker Effect". This effect describes that by time a certain number of workers (for health reasons, fro example) quit shift-work. The remainder than constitutes a population of "survivors" which might turn out to be healthier or less affected than the control group. This selection effect concerns especially cross-sectional studies if the data is not corrected/controlled for the quitters (see also chapter 4.6). Anyhow, although the risk and the costs decrease with longer duration on shift-work than 30 years, it still is about 24% increased compared to non-shift-workers (Table 6).



Diagnosis	Article	Schedule	Rotation	Costs bill. $	% from grant total
CHD overall	Ellingsen et al., 2007	3x8 h	clockwise	45,1	29%
CHD (11-15 yrs seniority)	Knutsson et al., 1986	3x8 h	clockwise	55,5	35%
CHD (16-20 yrs seniority)	Knutsson et al., 1986	3x8 h	clockwise	64,4	41%
CHD (>30 yrs seniority)	Karlsson et al., 2005	3x8 h	clockwise	37,0	24%

Figure 29 The figure shows the potential health costs (in billion Dollar) arranging from shift-work on the development of Coronary Heart Disease (CHD). A trend can be seen that costs increase with shift-work seniority up to 10 years and then decrease for longer time in shift-work. For explanations on this finding see text. The table below the figure shows total costs in billion Dollars and percentage costs from grant total 156.4 billion Dollars.

5. Shift-Work/Social-Jetlag-Model

5.1. Introduction

As already introduced above, the hypothesis of an individual impact from clock- and counterclockwise rotating shift-work on human health has been built upon the results from the shift-work literature survey (chapter 4). Furthermore, the previous chapter (4.7.3) on the potential costs of shift-work has shown that there is also strong monetary need to decrease the impact of shift-work on both health and the health care system. This chapter will focus on a new concept to quantitatively examine the impact of shift-work, aiming at developing beneficial concepts in the future. As already introduced in section 4.7.1.1, there are virtually no studies that have investigated the impact of distinct shift-systems, neither in the short- nor on the long run, on any concrete health effect or even disease development (as for example of heart diseases). Most of these studies mainly focused on susceptibilities and sleep problems. As found in our study on the impact of the transitions to and from daylight saving time (DST) (see chapter 3), even small shifts in environmental zeitgebers (in this case of “only one hour”) are found to lead to a measurable effect on the internal clock. The adjustment of the subjects´ internal clocks, to the advance of this single hour in external time, was not complete even four weeks after the transition to DST in spring, especially in the late Chronotypes (Figure 12 A and B).

5.2. Rationale for the Shift-Work/Social-Jetlag-Model

From the assumption, that sleep and cardiovascular problems in shift-workers are affected differently depending on shift-work directions (counterclockwise vs. clockwise) the question has risen of how to quantitatively measure the impact of different shift-work schedules and rotation on the human internal clock? A modified concept of Social Jetlag (Wittmann et al., 2006 ; see also chapter 1.3.2.2) has been proposed by Roenneberg et al. (in preparation) to calculate the impact of shift-work on the internal clock and further to estimate the differential effect of different directions of shift-work rotations. Social Jetlag is a valid parameter to calculate the discrepancy between internal and external time, and is thereby useful as an indicator for internal desynchronisation in different Chronotypes (Wittmann et al., 2006).

Therefore, the purpose of the Shift-Work/Social-Jetlag-Model is to quantify the shift-work effects (a) shift-schedule specific and (b) Chronotype specific.

5.3. Methods

Theory behind the Shift-Work/Social-Jetlag-Model

In terms of calculating the discrepancy between internal and external time, the Shift-Work/Social-Jetlag-Model bases on the Chronotype of the workers (meaning their initial phase position from their phase of entrainment on free days, MSF, chapter 1.3.1). This approach is also recommended by the results from Gibbs et al. (2002) and Nesthus et al., 2001 showing that the initial phase position depicts the phase movement of individual rhythms. Therefore, dependent on the initial phase position at entry into a shift cycle (meaning if someone is an earlier or later Chronotype), workers have to adjust to an individual degree to the subsequent shift. For example, a late Chronotype on a morning shift will advance his phase, whereas an early Chronotype will have to advance less or even not. If in turn the shift cycles starts on a night shift, both early and late Chronotypes will delay their phase, but to a different extent, respectively. In the following examples, the work schedules will be represented by capital letters with M=morning shift, L=late shift, N=night shift, F=free shift/day off. As said above, a shift schedule in a clockwise direction as, for example,

FFFFF – EEEEE – LLLLL - NNNNN

is by most authors argued to cause less problems (please see additionally the review of the literature on this topic in chapter 4.7.1). The workers can adjust better, especially to the night shifts at the end of the cycle, because the clockwise rotating shift cycle can be regarded as “preparing” the worker by successive delays over the course of the shift cycle for the night work period (NNNNN). If true, the worker’s internal clock would need to be re-set after switching to an early shift or days off. The reset (readjustment period) therefore falls into the period of the free days. When starting again with the early shifts of the cycle, the worker might be (almost) readjusted to the daily routine. The sleep deficit in this example will occur either on the night shift period and/or on the days off.

In contrast, in this scenario a counterclockwise worker on a schedule as, for example,

FFFFF – NNNNN – LLLLL - MMMMM

will not adjust that easily to the night shifts, because he/she starts the shift cycle with a night shift. The gap for the internal clock to adjust ad-hoc to the night work (i) is larger and (ii) the shift is additionally to the opposite direction than for the workers in clockwise rotation, for whom the adjustment to the night work is facilitated by successive delay through the previous shifts. Therefore, the internal clock of a worker on a counterclockwise system does not adjust to the night work period and already is advanced when switching to the late shift and the early shift. The struggles for the counterclockwise worker are that he/she gathers a higher sleep deficit on the night shift period, which he/she carries over to the late and early shift. The workers therefore have to recreate on the shift, whereas the clockwise workers is able to recreate on the free days after the night shifts. Taken together, there is evidence that the impact on the internal clock is less in counterclockwise rotation, and further dependent on the Chronotype (meaning an earlier or later phase of entrainment). The next chapter is about using Social Jetlag as a parameter to estimate this respective impact.

Calculation of Social Jetlag with the Shift-Work/Social-Jetlag-Model

In the following, the Shift-Work/Social-Jetlag-Model will be used to figure out the difference between clockwise and counterclockwise rotational schedules in terms of Social Jetlag (SJL) as a variable accounting for the discrepancy between internal and external time. The output of the Shift-Work/Social-Jetlag-Model is the daily amount of Social Jetlag in hours (as proposed by Roenneberg et al., in preparation). The Shift-Work/Social-Jetlag-Model does not only allow to predict different amounts of Social Jetlag on the internal clock by both the direction and the speed of a shift schedule, but further to show differential impact on different Chronotypes (meaning workers with a different phase of entrainment at the start of a shift-work cycle, Roenneberg et al., 2003a,b). Table 7 gives an example of the calculation procedure of Social Jetlag for a worker employed in a standard 3-shift system, with shift durations of 8 hours each shift and shift rotation in a clockwise direction. The shift-work hours have been set from 06:00 h to 14:00 h for the morning shift, from 14:00 h to 22:00 h for the late shift and for the night shift from 22:00 h to 06:00 h, in respect to common 3-shift system mentioned for example in *Knutsson et al. (1988). The calculation of Social Jetlag bases on the differences in hours (orange field in Table 7), between a hypothetical internal point of time on two successive days (yellow and brown fields in Table 7, days 18 and 19, respectively) by a hypothetical shift (advances, which are indicated by a minus sign (-) and delays = grey field in Table 7). The values for Social Jetlag can be then computed for different Chronotypes, separately for work days and free days or as a mean over the entire shift schedule (see field "mean SJL" in the upper right corner in Table 7). The midpoint of the external day is the middle of the period the worker is awake (between getting up from and to bed) that varies on the different shifts, because the wake up time is different on a morning shift than on a night shift, for example (blue fields in the most left column in Table 7). For days off the Mid-Sleep on Free days (MSF, green fields in the most left column in Table 7) is used.

Shift	Day	**Midpoint of** external day from schedule	**Midpoint of** internal clock	ΔPhi	Social Jetlag	mean SJL
day off	1	15,5	15,5	0	0	1,5204082
morning shift	2	12,5	15	-0,5	0,5	
morning shift	3	12,5	14,5	-0,5	2	
morning shift	4	12,5	14	-0,5	1,5	
morning shift	5	12,5	13,5	-0,5	1	
day off	6	15,5	14,5	1	2	
day off	7	15,5	15,5	1	0	
day off	8	15,5	15,5	1	0	
day off	9	15,5	15,5	1	0	
late shift	10	17	16,5	1	1	
late shift	11	17	17	1	0	
late shift	12	17	17	1	0	
late shift	13	17	17	1	0	
day off	14	15,5	16,5	-0,5	0,5	
day off	15	15,5	16	-0,5	0,5	
day off	16	15,5	15,5	-0,5	0	
day off	17	15,5	15,5	-0,5	0	
night shift	18	23	16,5	1	1	
night shift	19	23	17,5	1	5,5	
night shift	20	23	18,5	1	4,5	
night shift	21	23	19,5	1	3,5	
day off	22	15,5	19	-0,5	4	
day off	23	15,5	18,5	-0,5	3	
day off	24	15,5	18	-0,5	2,5	
day off	25	15,5	17,5	-0,5	2	

Table 7 Hypothetical example for an intermediate Chronotype with a MSF of 3.5 (internal Mid-Activity is 3.5 + 12 = 15.5 as indicated on days off, green fields), "employed" in a clockwise 3-shift schedule (with morning, late and night shifts; indicated as blue fields). The calculation of Social Jetlag (orange field) bases on the difference between internal time (column in the middle for internal clock) and external time (column for external day), due to the shift-work schedule. For details on the calculation, see text. ΔPhi gives the amount of hours the internal clock is shifted, with a ΔPhi of 1 meaning a delay of 1 hour and a ΔPhi of -0.5 meaning an advance of half an hour.

The wake- and bed hours have been estimated for this example hypothetically by adding time to the shift start and end times for (i) getting up, (ii) commute to and from work, and (iii) for social interactions after the shift. For the following simulation, the corresponding hours of being awake at certain shift-work days are on the morning shift from 04:00 h to 21:00 h (midpoint = 12.5), on the late shift from 10:00 h to 00:00 h (midpoint = 17.0) and on the night shift from 14:00 h to 08:00 h (midpoint = 23.0). These times are highly individual and depend on manifold influences, as pointed out chapter 4.5.1. For the simulation described hereafter, the mentioned times have been chosen as an example. The next section will focus on the applicability of this Shift-Work/Social-Jetlag-Model to calculate individual levels of advance and delay for three different Chronotypes, namely early, intermediate and late.

Application of the Shift-Work/Social-Jetlag-Model

The most difficult part of modelling Social Jetlag in shift-workers is that the advance/delay capacity of humans in real life is largely not known. The advance/delay capacity simply describes the amount of "time" (e.g. minutes or even hours) that the internal clock is capable of shifting within one day, e.g. from one shift-day to the subsequent. If advance and delay capacity are balanced, one can assume that the internal clock is shifted equally in both directions. Therefore, the adjustment in a shift cycle with equal numbers of shifts (5xE-5xL-5xN, e.g.) would theoretically be balanced. From studies on Jetlag after travelling across time-zones it has been observed that for the most people the capacity to advance is less than the capacity to delay. Hence, it takes longer for the internal clock to adjust travelling eastwards compared to a westward travel. In analogy, the amount of the advance/delay capacity can be hypothised to depict the amount of Social Jetlag.

The best way to prove the Shift-Work/Social-Jetlag-Model for its applicability and parameters (meaning advance/delay ratios), is the validation against data collected in the field. The data that has been used for this validation was collected in a field study on shift-workers at a German automobile plant (courtesy Miriam Havel, Havel et al., 2006) . These data (the "Automobile-Test-Sample") compromised measures on various psychological parameters from 55 workers employed in a clockwise 3-shift system (with morning, late, night shift), with a duration of each shift of 8 hours and changeover times at 06:00, 14:00 and 22:00 o'clock (as in the example presented in the previous section).

The shift schedule of these workers at the automobile plant was as follows (44 days in total): ***FF-MMMMM-FF-LLLLL-FFF-NNNN-FFF-NNNN-FFF-NNNN-FFF-NNNN-FF***

The following variables have been assessed daily for one shift cycle: (i) sleep quality, (ii) Basler score, (iii) “intrapsychic Balance”, (iv) “social extrovertism”, (v) vigilance and (vi) vitality. For further information on these variables, sampling and methods, please see Havel et al., 2006 . A program (the “Shift-Work/Social-Jetlag-Model”) has been developed to automate the calculations (Roenneberg et al., in preparation). Furthermore, the program enables an upload of certain shift systems, to set start and end times of each shift and to set the individual Chronotype (based on MSF) as the initial parameter.

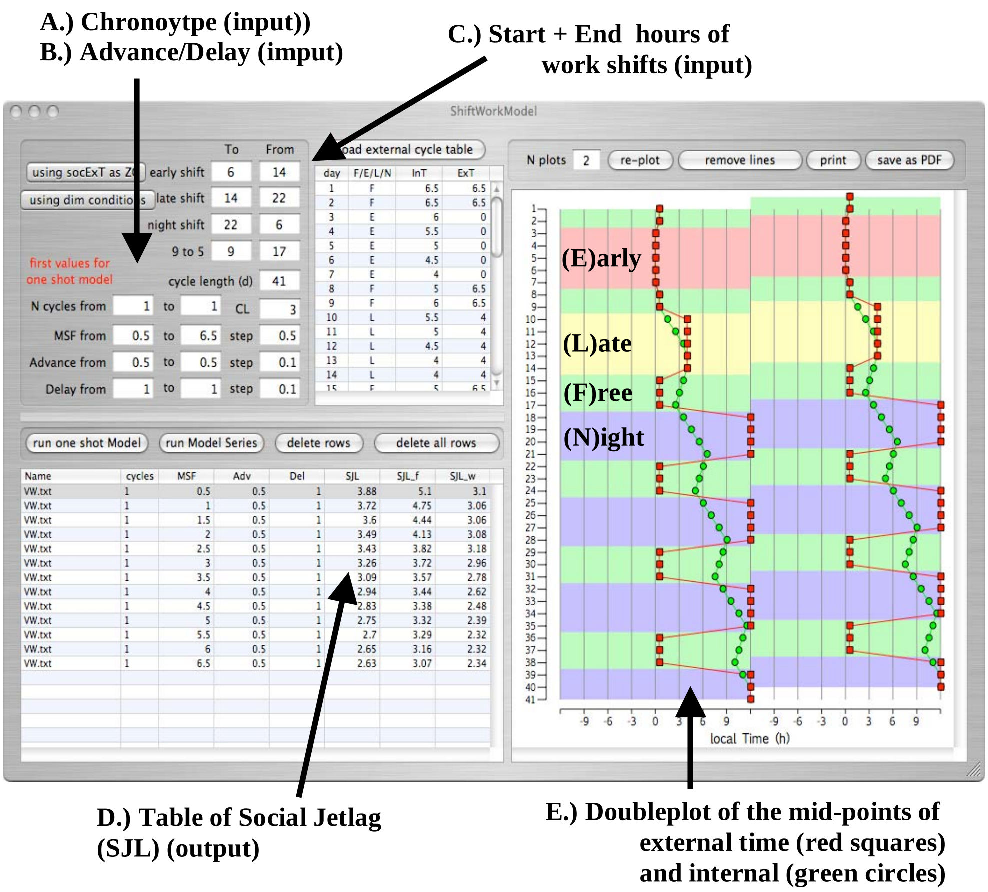


Figure 30 Screenshot of the Shift-Work/Social-Jetlag Model (Roenneberg et al., in preparation). The main functions are indicated, with the options to enter Chronotype (A) as an input variable, to set the advance and delay capacities (B), and to set the start and end times of the work shifts (C). Additionally the program contains a data table (D) with information about the resultant values of Social Jetlag. The corresponding double-plot (E) graphically shows the relationship between internal time (green circles) and external time (red squares, given by the work hours) for one shift-cycle.

The calculation of external mid points follows in analogy to the procedure described in the previous chapter. The program then calculates the chronotype-specific levels of Social Jetlag as illustrated in Table 7.

Figure 30 and Figure 31 present screenshots of the program, exemplifying the calculation of Social Jetlag for the Automobile-Test-Sample. In the background of the plot (right side) the respective shift schedule can be seen, whereas each shift (early, late, night, and free) is represented by a different colour.

In Figure 31 the discrepancies between internal (green circles) and external time (red squares) differing in respect to Chronotype and worked shift are shown. Exemplified for an early (left) and a late Chronotype (right), one can see that the early Chronotype accumulates most Social Jetlag on the night shifts, whereas the late Chronotype accumulates highest Social Jetlag on the morning shifts, respectively.

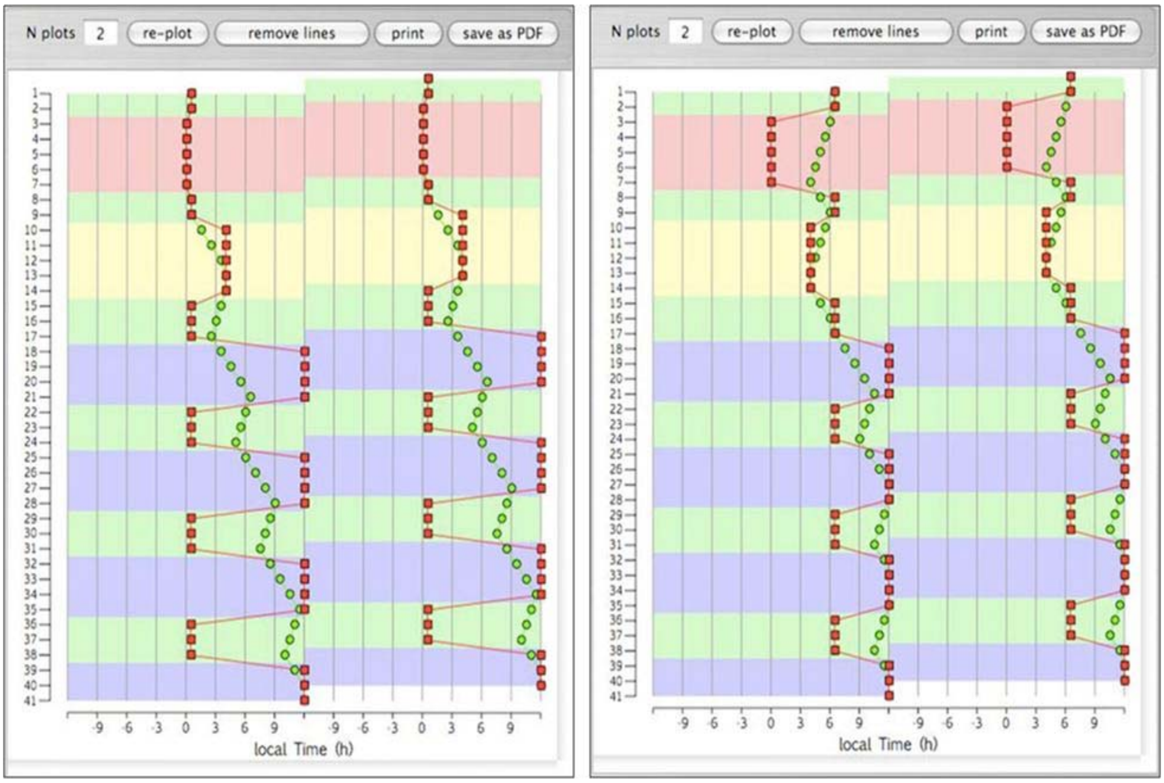


Figure 31 Two double-plots yielded from the Shift-Work/Social-Jetlag-Model (Roenneberg et al., in preparation) showing the differences between an early (left figure) and late Chronotype (right figure). It is conspicuous, that the early Type (left) on the early shift (red area) does not accumulate Social Jetlag, whereas the late (right) Type does. In turn, on the night shifts (blue areas) the late Type does not accumulate that much Social Jetlag as the early Type.

The data from the Automobile-Test-Sample has been validated against the values of Social Jetlag from the model to calculate the most realistic advance/delay capacity of the shift-workers. The advance/delay ratio showing the highest correlations with the field data will then be used to proof or disproof the initial hypothesis, stating that *'early and late types will develop different amounts of Social Jetlag in comparison of clockwise and counterclockwise rotation'*. To this end, Social Jetlag has been modelled for an early, intermediate and late Chronotype (with an average MSF of 1.5, of 3.6 and of 5.6, respectively), which in this example are hypothetically "employed" in a clockwise and counterclockwise rotating system. Statistics on the results have been performed using Prism Version 4.0c for Macintosh.

5.4. Results

The average Chronotype of the Automobile-Test-Sample from the shift-work field study used for this exemplified validation was 4.7 (Figure 32). The distribution of Chronotypes in this population was Gaussian-like, with more late types, therefore slightly skewed rightwards. The validation of the field data with the calculated Social Jetlag values from the model revealed significant correlations for an advance/delay capacity of about <u>0.5 hours</u> (with a Pearson r of about 0.3). The Figure 33 shows the different amounts of Social Jetlag (as average hours for a total shift cycle from a real existing clockwise work schedule and the corresponding hypothetical counterclockwise schedule.) for early (average MSF of 1.5), intermediate (average MSF of 3.6) and late Chronotypes (average MSF of 5.6), based on the validated advance/delay ratio of 0.5 hours.

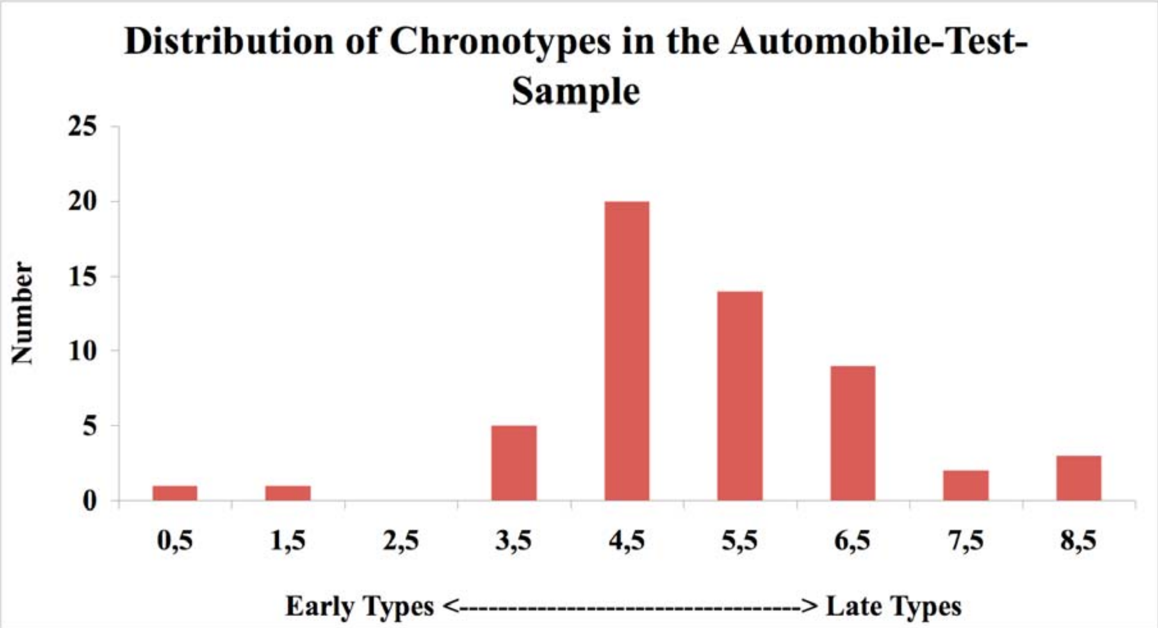


Figure 32 Distribution of MSF in the shift-work population of the Automobile-Test-Sample. The distribution is slightly skewed rightwards; with a higher number of late Chronotypes. The average Chronotype of the sample is 4.7.

To compare the two calculations of Social Jetlag, these have been treated statistically as representative data from the same population, which has been tested under the two different conditions (i) clockwise and (ii) counterclockwise rotation. Pre-testing of the Social Jetlag values for normal distribution, D'Agostino & Pearson omnibus normality test was used showing inconsistent results. Therefore, Mann-Whitney-U-test for nonparametric statistics has been used to compare the levels of Social Jetlag in early, intermediate and late Chronotypes.

The analysis revealed a statistically significant difference in the amount of Social Jetlag for each of the three different Chronotypes (with Early $p=0.0009$; Intermediate $p<0.0001$; Late $p<0.0001$). Further, the difference is largest for the Late-Types (average MSF of 5.6) with a mean difference in Social Jetlag of 0.34 h. Therefore, the benefit from counterclockwise rotation in terms of Social Jetlag reduction is highest in this group. The respective differences for early and intermediate Chronotypes were 0.2 h and 0.25 h. Additionally, late types show less Social Jetlag in the counterclockwise rotation than early types (compare right and left part of Figure 33). Figure 33 shows that clockwise rotation leads to higher Social Jetlag levels in the three Chronotypes.

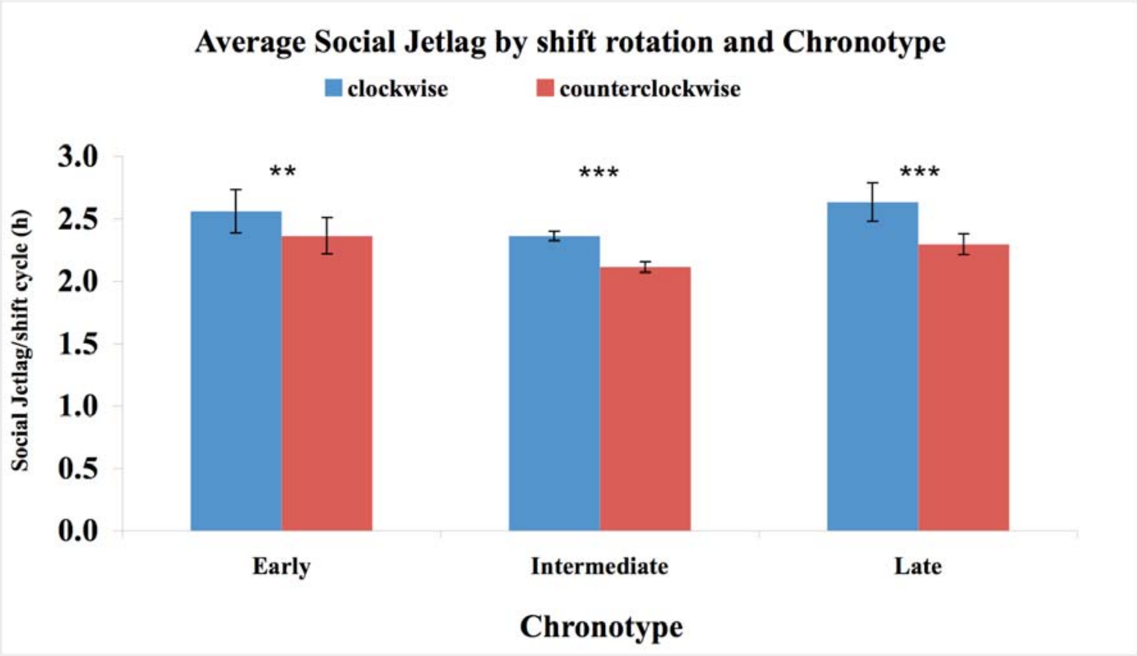


Figure 33 Calculation from the Shift-Work/Social-Jetlag-Model for the comparison of the levels of Social Jetlag, accumulated in one shift cycle in a clockwise (blue bars) and a counterclockwise (red bars) rotational shift cycle. Clockwise shift rotation always leads to significantly elevated levels of Social Jetlag, for all three Chronotypes (** $p<0.001$ / *** $p<0.0001$; Early $p=0.0009$, Intermediate $p<0.0001$, Late $p<0.0001$; Mann-Whitney-U-test).

5.5. Discussion

It has been observed that for shift-workers the effects on health differ according to the direction of the shift-rotation (see chapter 4.7.1). A special program (the “Shift-Work/Social-Jetlag-Model”) to calculate such differences has been proposed and developed by Roenneberg et al. (in preparation). This program uses Social Jetlag (modified from Wittmann et al., 2006) as the outcome variable. Validation with fieldwork data revealed an advance/delay capacity of about 0.5 hours. This estimated circadian adjustment capacity found is supported by earlier simulated shift-work studies, taking rectal temperature as a circadian marker (0.5 hours/day (Eastman et al., 1994), 0.8 hours/day (Moog and Hildebrandt, 1987). In addition, also full laboratory studies have yielded similar results (0.2 hours/day (Czeisler et al, 1990), 0.8 hours/day (Campbell, 1995 , Dawson and Campbell, 1991), 1.3 hours/day (Harma et al., 1994) and 1.4 hours/day (Dawson et al., 1995). It should be emphasized here, that the results on the shift capacity found by the Shift-Work/Social-Jetlag-Model used in this study is best reflected in the results obtained in simulated field shift-work studies (Eastman et al., 1994 ; Moog and Hildebrandt, 1987). The laboratory based examinations seem to overestimate the capacity of the human clock to be shifted in real life.

Finally, the calculations of Social Jetlag for clockwise and counterclockwise shift systems are found to lead to significantly different amounts of Social Jetlag. This finding proves the initial hypothesis stating that '*early and late types will develop different amounts of Social Jetlag in comparison of clockwise and counterclockwise rotation*'.

This initial approach of the Shift-Work/Social-Jetlag-Model is promising and underlines the applicability of the concept of using Social Jetlag as a parameter in shift-work studies. In a next step, the Shift-Work/Social-Jetlag-Model can be used to validate not only against psychological variables, as done in this study, but further against physiological measures yielded in field studies (e.g. melatonin, cortisol, body temperature, pH changes in the stomach, etc). As pointed out in chapter 1.3.2.1 on the internal desynchronisation, one can assume that there are differences in circadian phases, not only between organs but even between single cells from the same tissue. To elucidate the principles of internal desynchronisation, various parameters must be compared and validated. This has been done in the underlying study utilising Social Jetlag and the psychological measures from the Automobile-Test-Sample.
Consequences on the cardiovascular system might be regarded as being perceived less/later than sleep problems (which are the predominate afflictions reported during counterclockwise rotation). The results in chapter 4.7.1 show that cardiovascular events occur less frequently and on average six years later in counterclockwise rotators. This underlines the finding that Social Jetlag is a silent stressor that is not perceived as immediate and intense as a sleep deficit and social problems. Longitudinal studies now have to proof if the amount of Social Jetlag varies with the shift rotation and if it therefore constitutes a mediating factor in the aetiology of long-term effects from shift-work on health, like an increase in Coronary Heart Disease.

The main reasons to leave or change the shift-work system are: high levels of fatigue, the need for recovery, poor sleep quality, poor general health, insufficient leisure time, and work-family conflicts (van Amelsvoort et al., 2004). These factors (which obviously are dependent from each other!) might be reducible by applying new shift systems with help of the Shift-Work/Social-Jetlag-Model. The development of shift-schedules that allow for sufficient sleep in respect to internal time (Chronotype) can be beneficial for certain workers. Future research is recommended to further unveil variables in the puzzle leading to the creation of healthier shift-schedules.

6. Conclusion

6.1. Daylight Saving Time (DST) and the Human Clock (see Chapter 3)

The influence of the transitions to and from Daylight-Saving-Time (DST) on the human physiology has merely been studied previously and the few previous examinations came to the conclusion that the "one-hour transition" to and from this artificial summertime does not cause major problems for humans to cope with. Adjustments after one week have been found, whereas these examinations (i) seldomly lasted longer than for one week after the change and (ii) have not based the analysis on internal time. We for the first time are able to show that the human internal clock does not adjust to DST within at least 4 weeks after the change to DST, which especially holds for the late Chronotypes.

Further, the transition to DST (advance) takes longer for the internal clock to adjust than the transition from DST (delay) back to standard time. This finding is in accordance with observations from studies on Jetlag after time zone travel. Additionally we show that even small changes on first sight ("only one hour" as it is often argued) indeed can have a measurable effect in interfering with the synchronisation of internal and external time. Future research has to elucidate in a next step the magnitude of this disturbance on the internal clocks´ seasonal adjustment in the context of prevalences of, for example, seasonal occurring diseases by comparing populations that use DST with those that do not on a worldwide level.

6.2. Shift-Work and the Human Clock (see Chapter 4)

Although shift-workers have been subject to many studies, only few of these studies are useful to draw conclusions for the real life other than that shift-work is not good for the health of the employees. Certain diseases, both transient sleep problems and also long-term effects on the cardiovascular system have been found with some consistency, but causalities and explanations are still to be elaborated. In addition, *the* shift-work health problem could not be identified. As we have seen in the study on the effect of the transitions to and from Daylight Saving Time, internal time definitely is a valid variable that physiological studies should be based on. Further, the discriminative value of Chronotype in medical research should have been also found in the shift-work literature survey, but unfortunately no study could be identified taking internal time into account for the examination of concrete health problems.

6.2.1. Potential Health Costs from Shift-Work (see Chapter 4.7.3)

To illustrate the monetary aspect of shift-work health burdens, a calculation has been performed for the most potential costs from Coronary Heart Disease (CHD, ICD-10 codes I20-I25). CHD represents the most severe and consistent long-term outcome found in the literature on shift-work and health and further is responsible for half the death among the general workforce/population. It was found that shift-workers account for 24 to 41% of the total costs arranging from CHD in the USA, with an estimated percentage of shift-workers of 20% of the general workforce. This shows that shift-work does not only have a chronobiological effect, but further a monetary aspect that is not ignorable and both justify further intense research.

6.3. Shift-Work/Social-Jetlag-Model (see Chapter 5)

There is no real life study on any long-term health effect on shift-workers employed in different shift-work directions. As shown in the previous two sections, there is evidence of a measurable effect when internal time would be taken as a basis. The Shift-Work/Social-Jetlag-Model (Roenneberg et al., in preparation) used for the estimation of Social Jetlag in shift-workers, as a measurement for the discrepancy between internal and external time, has also shown that there are significantly different effects ($p<0.001$) measurable for early, intermediate and late Chronotypes. The Shift-Work/Social-Jetlag-Model allows quantifying the influence of alternating wake-sleep hours from shift-work schedules onto the human clock. Although the Shift-Work/Social-Jetlag-Model at this point is in a simple form, it has already proven the initial hypothesis stating that '*early and late types will develop different amounts of Social Jetlag in comparison of clockwise and counterclockwise rotation*'. This proof makes the Shift-Work/Social-Jetlag-Model highly potential for future applications (see also next chapter 6.4).

6.4. Outlook on the applicability of the Shift-Work/Social-Jetlag-Model

The Shift-Work/Social-Jetlag-Model (Roenneberg et al., in preparation) presented here in its simple form to estimate the amount of Social Jetlag for different Chronotypes "employed" in different shift-work schedules already shows that indeed different amounts of Social Jetlag can be calculated in respect to the shift system. The differences are significant ($p<0.001$) and found for early, intermediate and late Chronotypes (MSF 0.5 through 6.5). This preliminary simulation shows that the approach followed in this study, to evaluate the advance/delay capacities of the workers´ internal clocks from real life studies, and to improve thereby the applicability of the Shift-Work/Social-Jetlag-Model to elaborate new (chronotype-specific) shift-schedules, needs further effort, but is already promising at this developmental stage.

Our workgroup is currently running field experiments with both blue and white collar workers from various industries in Germany and Luxembourg. Myriam Juda and Céline Vetter are the leading investigators in these studies investigating effects of different shift-work and also lighting conditions on the internal clock. Therefore, both psychological (e.g., alertness, cognitive functioning, reaction times) and physiological (e.g. sleep times, activity profiles) parameters are being estimated, which then would be an optimal source for further validations and applications of the Shift-Work/Social-Jetlag-Model. That the combination of sleep-logs and actimetry is perfectly suited to measure even smaller impacts on the internal clock than from shift-work, was shown in this thesis in the study on the effects from DST (chapter 3). As in shift-work the workers are shifted by several hours each day (up to 12 hours in contrast to the one hour from the DST transitions), these methods are promising for upcoming studies. In addition, as already mentioned in the discussion on the results from the Shift-Work/Social-Jetlag-Model (chapter 5.5), further examinations of the phenomenon of internal desynchronisation are needed. Cross-correlations of data from physiological measures on, for example, melatonin, cortisol, body temperature, pH values of the stomach, etc. against the data from the Shift-Work/Social-Jetlag-Model would be a possible point to start from. An additionally important future perspective of the Shift-Work/Social-Jetlag-Model is to implement lighting profiles, based on the chronobiological knowledge on internal time and entrainment (chapter 4.7.2). Individual effects of light on the human clock dependent from the individual phase of entrainment (Chronotype) are known, which makes it highly interesting to incorporate such information into the Shift-Work/Social-Jetlag-Model. Obviously, depending on the certain shift (morning-late-night), workers are exposed to different levels of light which in turn differently affects the adjustment to the shift-work schedule. Therefore, additionally ambient light profiles from workers at the worksite will be collected (via light sensitive wrist worn devices) in the running studies in our workgroup. The future perspective of the model therefore will be (i) to prove prevalent theories and scrutinise results from both laboratory and field studies and (ii) to develop new approaches and shift-schedules on the basis of internal time, taking Chronotype and the individual shift-capacity of people into account.

7. Summary

This thesis gives a contribution to the understanding of the behaviour of the internal human clock in real life, exemplified by influences from (i) the transitions to and from Daylight Saving Time (DST) and (ii) Shift-Work employment. The results show that there is evidence that future research on human physiology and disease management profits by taking internal, biological time as the basal time scale.

The key results from this thesis are:

Chapter 3: A clearly **measurable chronotype-specific impact** from the transitions to and **from Daylight Saving Time** (DST) on the seasonal adjustment of the human internal clock could be identified.

Chapter 4: **Increased rates of health problems** and diseases in shift-workers have been presented, which are **suggested** to result **from alterations between external zeitgebers and internal physiological states**. **Conclusions** on any causality **cannot be given** from the selected studies. Overall, a mixture of the influences from both work and private life are suspected to mediate the health outcomes in shift-workers. *Virtanen und Notkola, 2002 recently mentioned that stress from psychosocial factors (e.g. high work load and low control) had a stronger impact on health deteriorations than stress from physical and physiological (occupational) factors like noise or sedentary work.

A potential **cost analysis showed** a clear **monetary dimension for shift-work related health outcomes**, exemplified for CHD, accounting **for 24 to 41%** of the grand total costs.

Chapter 5: A newly developed **program** (the **“**Shift-Work/Social-Jetlag-Model”, Roenneberg et al., in preparation) **for the quantification of shift-work effects** on the human clock calculated as Social Jetlag **showed significant chronotype-specific effects** for different directions in shift rotation (clockwise vs. counterclockwise).

The following section gives a hypothetical example to underline the importance of taking Chronotype into account in biological, physiological, psychological and medical research.

7.1. Appeal: Importance of Chronotype in Medical Research

The results of the studies performed for this thesis do clearly underline the importance of analysing physiological data on internal time. This is supported by numerous studies from chronobiological research that have accumulated results showing, that entrainment of the internal clock plays a pivotal role in health and body function. The information of external time (social time) in medical issues is of minor use, for the following reason. Concerning internal time, two individuals living under the same environmental conditions, are from their physiological state closer to each other at the same external time of the day (e.g. at noon), as the same persons compared to themselves 12 hours apart. In respect to shift-work, the individual impact of a night shift, e.g. with working hours between 2200 h and 0600 h, is assumingly pretty different for a late Chronotype than for an early Chronotype. It has been stated (Harrington, 1978, 2001) that about 10% of a shift-work population see certain advantages in their shift-work schedule. From our own MCTQ-database we can see that around 10% of the population constitutes extreme late types, which are active most of their time during the night hours. Further the ability to withstand shift-work burdens decreases with age (Harma et al., 1994; Harma and Kandolin, 2001), and people become also earlier Chronotypes with age (Roenneberg et al., 2007a). Taking into account that the difference in Chronotype depicts the differences in physiology, it becomes apparent that comparisons of physiological processes only make sense when interpreted on the basis of internal time. The importance and advantage of estimating Chronotype in shift-work research becomes apparent in the following simple example. Working the night shift would be less problematic for workers with habitual bedtimes of 03:00 h in the morning (defined as a very late Chronotype) than for those preferring to go to bed at 22:00 h (defined as a corresponding early Chronotype). For late Chronotypes in turn, early rising for the morning shift (starting at 06:00 a.m. forces workers to get up at 05:00 h or even earlier) would be much more stressful and exhaustive than for their earlier counterparts. In simple terms, night shifts may be better than normal shifts for some individuals, leading to less Social Jetlag and stress, for example (see

Chapters 1.3.2.2 and 4.7.2). It may, therefore, be possible that not the “shift-work schedule” itself or certain tasks at work are adverse in effect. It might turn out that living against ones individual internal biological clockwork turns out to be the culprit. This assumption is proven by the results from this thesis. In the study on the effect of Daylight Saving Time on the internal clock (Chapter 3), differential impact on early and late Chronotypes has been shown. Further, the results from the shift-work literature survey (Chapter 4) and the results from the Shift-Work/Social-Jetlag-Model (Chapter 5) additionally point into the direction of chronotype-specific effects, especially from the direction in rotation of the shift-schedule. Chronotype has been shown to play a role in various physiological and psychological parameters. Therefore, estimating Chronotype is recommended to accurately interpret results from shift-work research and finally all types of health studies for the benefit of all those investigated. In analogy, no one would chose average sized hiking shoes to climb the Mount Everest and risk ones life, when she/he is clearly aware that individual fitting footwear is available nearby.

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9. Figure list

Figure 1 Spectrum of biological rhythms in a human body. The spectrum of circadian rhythms is presented in this figure at the level of period duration of 1 day (log 105), indicated by rhythms of ‘sleep-wakefulness’ (left side) and ‘earth rotation (right side) (Figure taken from Moser et al., 2006)..3
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11.Erklärung

Hiermit erkläre ich, dass ich die vorliegende Arbeit selbsständigt angefertigt und nur die angegebenen Hilfsmittel und Quellen verwendet habe. Ich habe bisher keinen Versuch unternommen, diese oder eine andere Dissertation, auch nicht in Teilen, einer anderen Prüfungskommision vorzulegen, noch habe ich mich erfolglos einer Doktorprüfung unterzogen.

München, den 17.07.2008

Thomas Kantermann

12.Curriculum vitae

Name	Thomas Kantermann
Address	Perlacherstrasse 5 81539 Munich
Birth date	26.02.1979
Birthplace	Gütersloh, Germany
Family status	married
Languages	English (fluent) Spanish (basic)
Hobbies	Playing guitar, song-writing, literature, sports

University Education

10/1998 – 06/2003	Biology and Psychology, University Bielefeld
06/2003	Diploma in Neurobiology on "*Epigenetic influences on the maturtion of GABA-interneurons in the basolateral amygdala in Meriones unguiculatus*" (Prof. Teuchert-Noodt)

Jobs

08/1999 – 08/2001	Lycos (Tripod) Database Editor for the categories music and science (Mrs. Niederluecke)
11/2001 – 09/2003	Assistant at the University Library Bielefeld, Faculty of Mathemaics and Economics (Mr. Kuekenshoener)

Scientific positions

04/2004 – 11/2005	Scientific Assistant at the Medical Faculty, Department of Anatomy/Neuroembryology at the University Rostock (Prof. Ulfig)
Since 12/2005	Ludwig-Maximilians-University Munich, PhD-student at the Department for Chronobiology; Institute for Medical Psychology (Prof. Roenneberg)

Certificates

02/2005	Rhetoric course with training based on theater methods (University Rostock)
03/2005	"Methodenwerkstatt" (course on lecture methods, University Rostock)
03/2006	Cochrane-Workshop on "Evidence-based Medicine", Freiburg
07/2006	Mind-Mapping Workshop (Ludwig-Maximilians University Munich)

Invited Talks

06/2008	*Invited attendee at the 2nd DIN-Expert meeting on "Light and Health", Berlin*
10/2008	*Invited speaker at the 13th Meeting of the European Neuroendocrine Association (ENEA), Antalya/Turkey* Kantermann, T. "The human circadian clock, sleep regulation and challenges from real life"

Talks and Posters

08/2006	*Talk and Poster at the 15th European Summer-School for Chronobiology (Euclock), Trest/Czech Republic* Kantermann, T. "Shift-Work and Human Health"
11/2006	*Talk at the Clockwork colloquium, Gottlieb-Daimler und Karl-Benz Foundation, Ladenburg* Kantermann, T., "Shift-Work and Human Health"
06/2007	*Talk at the Minisymposium Chronobiology, Max-Plank-Institute for Ornithology, Andechs, Germany* Kantermann, T. "Daylight Saving Time"
12/2007	*Talk at the Clockwork colloquium, Gottlieb-Daimler und Karl-Benz Foundation, Ladenburg* Kantermann, T., "Shifted zeitgebers and circadian aligment"
01/2008	*Talk and Poster at the 2nd annual Euclock meeting, Frauenchiemsee/ Germany* Kantermann, T., Juda, M., Merrow, M. & Roenneberg, T. "The Human Circadian Clock's Seasonal Adjustment is disrupted by Daylight Saving Time"
05/2008	*Poster at the 11th meeting of the Society for Research on Biological Rhythms (SRBR), Sandestin/Florida* Kantermann, T., Juda, M., Merrow, M. & Roenneberg, T. "The Human Circadian Clock's Seasonal Adjustment is disrupted by Daylight Saving Time"

Memberships and Networks

Since 2005	Member of the CLOCKWORK network www.clock-work.org
Since 2006	Member of the EUCLOCK network www.euclock.eu
Since 2006	Project manager at KORA-F4 (Cooperative Health Research in the Region Augsburg at the Helmholtz-Centre Munich; former GSF-Munich)
Since 2006	Project Investigator at EUCLIS (Euclock Information system) http://www.bioinfo.mpg.de/euclis/
Since 2007	Online content manager at www.theWeP.eu (the Worldwide experimental platform)
Since 2008	Member of the Society for Research on Biological Rhythms

Grant Awards

05/2008	Travel award from the Gottlieb-Daimler and Daimler-Benz Foundation for the Biannual Meeting of the Society for Research on Biological Rhythms (SRBR)

Teaching experience

2004/2005	Courses and exams in Neuroanatomy, Histology, Embryology, macroscopic Anatomy at the University Rostock
Since 2005	Courses and seminars in Medical Psychology and Sociology at the Ludwig-Maximilians University Munich

Publications

1. **Kantermann, T.**, Juda, M., Merrow, M. & Roenneberg, T. "The Human Circadian Clock's Seasonal Adjustment Is Disrupted by Daylight Saving Time." Current Biology 17(22): 2007
2. Roenneberg, T., Kuehnle, T., Juda, M., **Kantermann, T.**, Allebrandt, K., Gordijn, M. & Merrow, M. "Epidemiology of the human circadian clock." Sleep Medicine Reviews 11(6): 2007
3. **Kantermann, T.** "Schichtarbeit und Gesundheit", DIN (German Institute of Norms, Berlin), 2007 – *remittance work, unpublished* -
4. Roenneberg, T., Vetter C., Juda M. & **Kantermann, T.** „ Quantifying the effects of shift-work on health and well-being by the accumulative discrepancy between internal and external time" *in preparation*

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“Acknowledgment”

Definition I: (social) *“a written thank you note expressing gratitude for gifts, assistance, or expressions of sympathy”* (www.wikipedia.org, June-2008)

Definition II: *“a short text at the beginning or end of a book where the writer names people or other works that have helped in writing the book”* (Cambridge Advanced Learner´s Dictionary online, June 2008)

The phrasing of an answer to a question varies with the ´source´ of information, and with the number of sources the diversity in the final answer increases, which should be regarded as a chance to learn. Therefore, I express my gratitude to whom provided me with such diversity:

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