Clocks in Action

Exploring the impact of internal time in real life

Céline Vetter

Inaugural-Dissertation

zur Erlangung des Doktorgrades

der Philosophie an der Fakultät für Psychologie der Ludwig-Maximilians-Universität

München

Vorgelegt von

Céline Vetter
aus München

München, 7.Oktober 2010

Erstgutachter: Prof. Dr. Rainer Schandry

Zweitgutachter: Prof. Dr. Till Roenneberg, Prof. Dr. Gisela Grupe

Tag der mündlichen Prüfung: 3. Februar 2011

Table of Contents

So schwer mir das Aufwachen fiel, so schwer fiel mir das Einschlafen.
Ich war noch nicht fertig mit dem Tag, wenn die Nacht übergriff.
Ich war noch nicht fertig mit der Nacht, wenn der Tag aufkam.
Eigentlich hetzte mich immer die Sonne.
Martin Walser, Halbzeit

1. General Introduction

He wakes up every morning, to perpetually re-live every minute of the same day again, and again. Every morning, the alarm wakes him at 6 a.m. Every morning, he showers, has coffee. And is forced to re-live the "Groundhog Day", a festivity celebrated in Pennsylvania - until he can break the curse and finally pursue a new, better life on 3rd of February.

"The Groundhog Day" with Bill Murray (1993)

The exaggeration of a cruel time loop used in the movie "Groundhog Day" builds up a nightmare of never-ending repetitions. But in its exaggeration, it also illustrates the temporal structure humans are living in. Those temporal structures of our everyday life are not arbitrary, or solely socially determined. A central pacemaker in the brain (and coupled, so-called "body clocks") governs cyclic behaviour, with the most obvious one being sleep and wake behaviour. The underlying complex, biological system follows its internally generated time frame, ignorant of watches, alarm clocks and other mechanical time keepers providing us with the external, social time. This project investigates the role of internal time (the clock) in real life (in action). Three types of populations were at the core of the studies: office workers, shift workers and researchers themselves.

The Leitmotiv of this thesis revolves around the translation, the relevance, and applicability of fundamental research results to real life. Is the reported cyclic variation in reaction times detectable in noisy factory settings? Is sleep influenced by lighting conditions in office environments, even if our alarm clock rings at the same time anyways? If we know that metabolism and brain activity is *inter alia* influenced by internal time, is this important for neuro-functional imaging studies?

I will outline the theoretical background of the research before the three studies of this thesis project are described.

1.1. The circadian clock

All living organisms, from cynobacteria, yeast, plants and insects, to new-world apes and humans, are governed in their behaviour and physiology by the circadian[1] clock. It has evolved - under selection pressure - to anticipate periodic changes in our environment (Paranjpe & Kumar Sharma, 2005): over the year, seasons change and with them, vital resources vanish or re-appear and day length varies. Within 24 hours, the lighting and temperature of the surrounding environment changes dramatically. Predators (from bacteria to crocodiles) have specific hunting times and activity profiles. The circadian clock (lat. *circa*: approximately, *dies*: day) permits an anticipation of cyclic environmental (external) changes, and in turn, adaptation. Such an endogenous, adaptive mechanism will lead to an evolutionary advantage, as the organism can benefit from a temporal ecology (e.g. Daan, 1981), aside from spatial or social ones. This thesis will only include the notions of circannual (i.e. seasonal) and circadian rhythms. Additional information about tidal and lunar cycles and their influence on humans has recently been reviewed by Roenneberg and Foster (2008).

1.1.1. A BRIEF HISTORY OF CLOCK RESEARCH

Over 250 years ago, Christoph Wilhem Hufeland, the medical doctor of J.W. von Goethe, described a "(…) unit of the chronology of nature". He was referring to the period of the 24h earth rotation, supposedly conveyed to all humans on earth. This unit would be reflected in the cycling of bodily functions (Hufeland, 1797, cited from ; Lemmer, 2009). This – by then speculative - association between an external, cyclic signal and the variable functions of living organisms has been reported even earlier, in 1729, by the French astronomist Jean Jacques de Mairan. In his chamber, he evicted a *mimosa pudica* plant from the day and night cycle to constant darkness. Still, it unfolded its leaves before sunrise and closed it in the evening hours - as if it was internally orchestrated (de Mairan, 1729).

[1] Franz Halberg has coined this term in the scientific, biological language (Lemmer, 2009).

In humans, Nathanial Kleitman[2] engaged in a similar procedure as de Mairan. He lived on a 21h and 28h schedule, investigating the effects on physiology and sleep and wake behaviour, while secluded from external temporal hints like daylight. The sleep- and temperature recordings maintained oscillating cycles, pertaining the existence of an endogenous, self-sustained timing mechanism. Self-sustainability today represents one of the major characteristics of the circadian clock[3]. Kleitman already reported inter-individual differences in the period length of the respective rhythms (1987). Wever and Aschoff went one step further: they built a bunker in Andechs, Germany, to potentially shield and control for all external variables from the study participants. In those lengthy studies (i.e. participants remained in the sites for up to 8 weeks), Aschoff and his colleagues observed very different period lengths of temperature, loco-motor activity and sleep and wake cycles. They coined the term *free-running period* (or tau, τ), i.e. the period length as measured when uninfluenced from external temporal cues. Between subjects, just as reported by Kleitman, this free-running period could range from as little as 21h up to 28h (Aschoff, 1993). On average, similar to what Wever reported in 1979, the intrinsic period τ corresponds to approximately 24.2h in humans (Czeisler et al., 1999). It was suggested that the room lightning conditions of the previous bunker experiments may have accounted for the relatively high variation in free-running periods (Klerman et al., 1996). The physiological and genetic underpinnings of the free-running period and their functional mechanisms are being investigated since then with increasing success, as put forward by Hastings and colleagues (Hastings et al., 2008). Amongst many discoveries, the identification of the suprachiasmatic nucleus as *the* central pacemaker of the mammal circadian system in 1973 represented a crucial tipping point. It inspired research resulting in a large body of evidence with regards to the functionality of the circadian clock (Weaver, 1998).

[2] Nathaniel Kleitman is nowadays known as the "father of sleep research", dedicating his career to the investigation of REM-sleep, dreams, etc.

[3] Colin Pittendrigh's experiments with *drosophila pseudoobscura* revealed a second important clock attribute: it is temperature-compensating, i.e. the phase of entrainment remains relatively stable in the range of physiological temperature environments (e.g., Pittendrigh, 1966). Yet, the fruit flies can be synchronized to temperature cycles (e.g., Zimmermann et al., 1968).

1.1.2. THE SUPRA-CHIASMATIC NUCLEUS (SCN)

The suprachiasmatic nuclei are located bilaterally above the crossing (*lat.* chiasma) of the optic nerves, in the anterior hypothalamus (Foster & Kreitzman, 2004; Hastings, 1998; Klein et al., 1991). With its approximately 20.000 neurons, it constitutes the circadian master clock. Albeit lesion studies in the 1970ies already pointed towards the significant role of the SCN in the circadian system (e.g. Weaver, 1998), it was not until the seminal work of Lehman and colleagues (1987) that the SCN was acknowledged its role as the principal circadian pacemaker. They transplanted foetal SCN tissue into lesioned, and thus arrhythmic, golden hamsters. After grafting, the hamsters exhibited re-established loco-motor activity cycles. With the key structure identified, the mechanisms of this time-keeping system were still unknown.

The route for understanding the underlying mechanisms of the oscillating SCN was set in 1997, when first clock genes were identified in mammals (Antoch et al., 1997; King et al., 1997; Sun et al., 1997; Tei et al., 1997). *period* (*per*1, 2 and 3), *clock, bmal1* as well as *chryptochrome* (*cry*1 and 2) are considered the key genes in the mammalian, auto-regulatory, transcription-translation negative feedback loop (Dunlap, 2002; Hastings et al., 2008). The molecular clock has been studied in single cells, and even been built "in a tube" by Nakajima and colleagues (2005) using just three cynobacterial clock proteins. At this rudimentary level, the artificial oscillator still showed the three principal features of the clock: the rhythm is conserved in constant conditions with a period length near 24h, shows temperature-compensation, and can be synchronized (or entrained, see Chapter 1.1.3.) to external cycles. This illustrates that the molecular clock mechanisms are largely preserved across species (e.g. Kyriacou & Hastings, 2010). On the other hand, Nakajiamas results also pointed to a role of metabolic factors in the molecular clock, an idea (see also Roenneberg & Merrow, 1999; Roenneberg & Merrow, 2005) gaining increasing support recently (Marcheva et al., 2010; Nakahata et al., 2009; Ramsey et al., 2009).

Today, it is clear that the SCN rather plays the role of "(…) the central coordinator of a plethora of tissue-based, autonomously active cellular clocks dispersed across the body" (Hastings et al., 2008). One main function of the SCN

relates to the synchronization to the external light/dark (LD) cycle, to integrate peripheral, local clocks in the temporal structure. As such, a maximal adaptive function would be ensured (Hastings et al., 2003). The SCN is synchronized to the LD cycle by a non-visual (or non-imaging forming) pathway in the brain, the retino-hypothalamic-tract (RHT). Intrinsically photosensitive receptors in the ganglion cell layer (ipRGC, Berson, 2003; Berson et al., 2002) transmit via the RTH the light signal to the ventrolateral SCN, the lateral geniculate nucleus and the pretectum (Lockley & Gooley, 2006). The photopigment melanopsin (Foster & Bellingham, 2002; Gooley et al., 2003; Peirson & Foster, 2006; Provencio et al., 2000) conveys the light signals to the SCN where neurons are tuned to exactly 24h by GABA-ergic regulation (*gamma*-Amionbutyric acid, Liu & Reppert, 2000). Rods and cons were initially thought to be irrelevant for circadian photoperception, but experiments with e.g. melanopsin-knockout mice challenged this view: the mice could still entrain to a LD regimen (Ruby et al., 2002). These results suggest that both, the receptors of the image and the non-image forming pathways may be important in the transmittance of light signals to the SCN (Dijk & Archer, 2009; Menaker, 2003).

In humans, the relative sensibility of the receptors can be assessed indirectly by melatonin suppression or pupillary constriction. The resulting action spectrum for non-visual responses to light peaks in the short wavelength range between 420nm and 480nm (Brainard et al., 2001; Brainard et al., 2008; Revell et al., 2005; Thapan et al., 2001; Warman et al., 2003; Wright & Lack, 2001; Wright et al., 2004). Similar results in participants lacking the outer retina endorse those findings (Van Gelder, 2007; Zaidi et al., 2007). Equally, peak sensitivity of the key protein in non-visual photoreception – melanopsin – lies in the blue, short-wavelength spectrum of light (Berson et al., 2002; Dacey et al., 2005). The circadian system draws on the transitions from dusk to dawn and the annual variation in photoperiod (i.e. daylight length) to create a timing system in reference to external time (Foster & Kreitzman, 2004).

1.1.3. SLEEP AND WAKE BEHAVIOUR

While the exact function of sleep is still under debate (Born & Wagner, 2004; Frank, 2006; Krueger & Obal, 2003; Krueger et al., 2008; Tonino & Cirelli, 2006), the alternation between sleep and wake states within 24h is the most obvious behavioural cycle. The disruption of this cycle, leading to sleep deprivation, has been associated with deficiencies of the immune system, impaired cognitive performance, psychological distress (up to severe depressive symptoms) and general health problems (Banks & Dinges, 2007; Cappuccio et al., 2010; Durmer & Dinges, 2005; Knutson & Van Cauter, 2008; Kopasz et al., 2010; Meerlo et al., 2008; Van Cauter et al., 2008).

In general, the regulation of sleep and wake behaviour within 24h relies on two mechanisms: the circadian system, defining the optimal time frame for sleep, and the homeostatic system, building up sleep pressure with increasing wakefulness (Foster & Wulff, 2005; Saper et al., 2005). The importance of the circadian clock for sleep regulation has for instance been demonstrated in a case study with an SCN-lesioned patient. Albeit sleep still occurred, it was fragmented and suggested therefore that the increasing homeostatic sleep pressure was merely "slept off" (Cohen & Albers, 1991).

Borbély (1982) defined a model of sleep regulation termed the *two-process model of sleep regulation*. It posits a wake-promoting, *circadian process, "C",* modelled by a sinusoidal curve, and corresponding to the circadian system. The process C interacts with the *process "S"*, reflect the progressive augmentation sleep pressure as a function of time awake, see fig. 1.1., panel A. The interplay between the two processes has been refined in further theoretical, computational and experimental approaches (Achermann, 2004; Achermann & Borbély, 2003a; Borbély, 1982; Borbély & Achermann, 1992, 1999). The interaction between those two processes has been proposed to predict time awake and time asleep. In extension to this model, Folkard and Åkerstedt (Åkerstedt & Folkard, 1995; Folkard & Åkerstedt, 1992) developed the three-process model, aiming at predicting alertness, and later on sleep latency and performance (see fig. 1.1., panel B, Åkerstedt & Folkard, 1997). While the process S and C were conserved with their main assumptions, an additional process – process "W" – was introduced. Its incorporation aimed at

accounting for low levels of alertness and performance after forced wake-up, a state referred to as sleep inertia[4] (Tassi & Muzet, 2000).

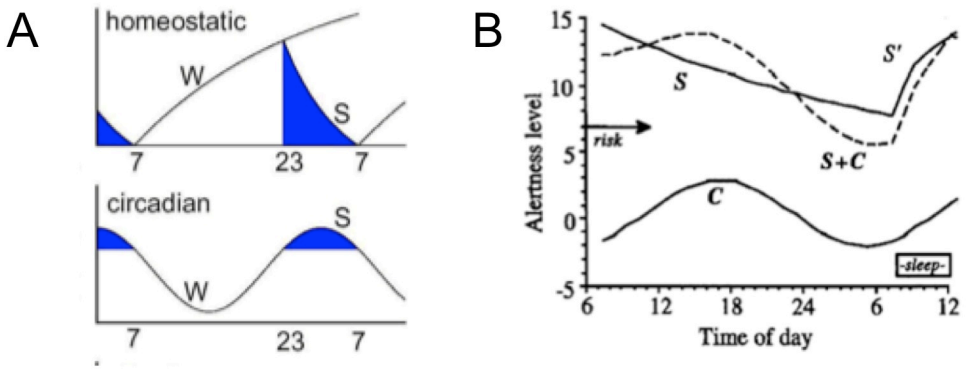


FIGURE 1.1. Panel A: the two-process model of sleep regulation. The upper panel depicts the progressive built-up in sleep pressure (homeostatic process S) during wakefulness (W) and its dissipation during sleep (S). The lower panel shows the sinusoidal function reflecting the circadian oscillation, the process C (Source: Achermann & Borbély, 2003b). Panel B: The three-process model for alertness: the processes S and C correspond approximately to those proposed by Borbély. S' reflects sleep dissipation. The combined output, S+C, predicts the alertness level over time (Source: Åkerstedt & Folkard, 1995).

Major advancements in the conceptualization of sleep and wake behaviour and its relationship to performance emerged from these seminal models. Yet, the validation with accident data has not been fully satisfying. First, it has been suggested that accident frequency and fatigue follow a non-linear relationship. Second, the speed of sleep dissipation was overestimated. Mathematical models grasping the relationship between fatigue, sleep, alertness and performance in the field thus require further refinement (Folkard & Åkerstedt, 2004b; Folkard et al., 1999).

The regulation of sleep in humans and other diurnal mammals entails *inter alia* rhythmic physiological variations in core body temperature (CBT) and blood pressure. Both parameters decrease prior to sleep, with a CBT peak observed in the early morning hours, prior to wake-up (Monk et al., 1997; Wright et al., 2002). Concurrently, melatonin, produced in the pineal gland, is involved in the human sleep and wake cycle. The SCN contains high numbers of melatonin receptors,

[4] In chapter 3, sleep inertia is further defined and discussed in relation to its impact on performance.

and is inhibited by the hormone especially during dawn and dusk (Stehle et al., 1989). Melatonin is released at night and suppressed by light – daylight as well as artificial light during night. An augmentation of melatonin levels usually precedes sleep initiation by 2 h (see fig. 1.2., Arendt & Skene, 2005; Brown et al., 1997).

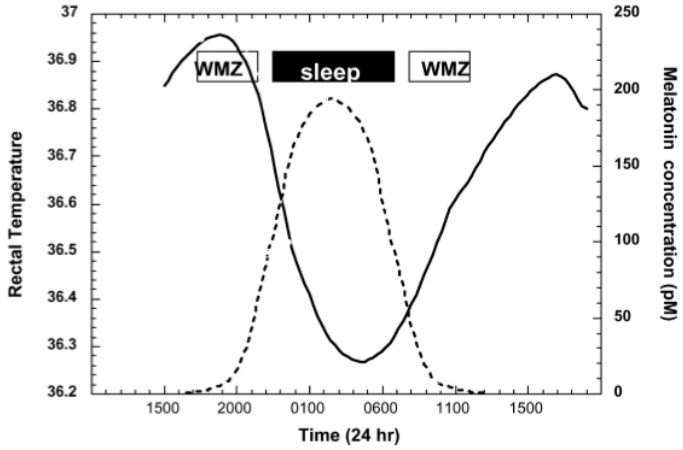


FIGURE 1.2. Core body temperature and melatonin over 24h: temperature (full line) peaks on average around 20:00 o'clock., coinciding with the wake-maintenance zone (WMZ, denotes time zones when the probability to spontaneously fall asleep is very low, see also Chapter 3), and its nadir around 6:00 o'clock. Melatonin rhythms (dotted line) show a reversed pattern with highest plasma concentrations around 3:00 o'clock. During the day, melatonin is usually not detectable as it is suppressed by light (Source: Lack & Wright, 2007).

The role of melatonin in sleep and wake behaviour has also been pertained in multiple shift work studies where adaptation to night shifts (and subsequent sleep duration) was ameliorated by administration of exogenous melatonin (e.g., Burgess et al., 2002; Folkard et al., 1993; Revell & Eastman, 2005; Sharkey & Eastman, 2002; Sharkey et al., 2001). In general, there is a robust association between the melatonin offset, CBT minimum and wake-up times, at least in healthy (and not shift working) individuals (Benloucif et al., 2005). Thus, melatonin secretion and inhibition is not only influenced by the SCN output (in turn influencing SCN activity, constituting the feedback loop between the SCN and the pineal gland, Sack et al., 1998), but can be employed to indirectly assess the phase of the circadian master clock (Arendt, 2000).

As briefly mentioned in the section on the history of clock research, there is a large inter-individual variation in sleep timing, revealing the relationship between the intrinsic period of the clock and the synchronized phase. With an average of 24.2h and a standard deviation of only 8min, the variation of *tau* appears rather

small (Czeisler et al., 1999). Nevertheless, a 6min difference in the intrinsic period was reported to result in a 1h difference in sleep and wake cycle (Duffy et al., 2001). The mechanisms of synchronisation between the internal, circadian clock and an external LD cycle are sketched in the following section.

1.1.4. ENTRAINMENT

The adjustment between the intrinsic, individual period *tau* and an external LD cycle of 24h is an active process coined entrainment, derived from the French word "entraîner" (*engl.* carry over, sweep along). Light is the most prominent external cue for entrainment or *zeitgeber* (German for time-giver, see section 1.1.5. for more information on zeitgebers). The deviation in intrinsic period from 24h supplies the necessary flexibility to "(…) fine-tune biological function to specific times during day and night" (Roenneberg, Daan et al., 2003). When in constant conditions (a state never encountered in the real world, but exclusively in experimental conditions, Johnson et al., 2003), the clock runs free. This is another fundamental aspect of the circadian clock: it is an oscillator itself, and not just passively synchronizing to external changes. Entrainment represents one of three main characteristics - and perhaps the most crucial one, of circadian clocks besides temperature compensation and a free-running rhythm that will not dampen over time (Pittendrigh, 1960).

Zeitgebers can reset and shift the phase of the clock. The relationship between the external and internal time is referred to as *phase angle* or *phase of entrainment*, predicting the "(…) timing of a given circadian event (e.g. activity onset) within a 24h day" (Roenneberg, Daan et al., 2003). The phase of entrainment is not fixed, and its flexibility is limited to a certain *range of entrainment*. The parameters determining the phase of entrainment are: *tau*, the period of the zeitgeber cycle, zeitgeber length and zeitgeber strength. The limits of entrainment, though, are given by the free-running period and its response characteristics to the LD cycle. Stable entrainment is the result of the correction (phase shift) of the difference between the external cycle length (T) and the free-running period (e.g., Daan, 2000). Two major theoretical accounts, sketched below, have been proposed to predict the response characteristics of the circadian clock.

From the 1960ies onwards, Colin Pittendrigh systematically investigated the reactions in fruit flies and nocturnal rodents to transient light bouts while held in constant darkness (DD, Pittendrigh, 1966; Pittendrigh & Daan, 1976b). Light bouts can be thought as an analogy to dawn and dusk in the natural environment. As Pittendrigh's model (Pittendrigh, 1981; Pittendrigh & Minis, 1964) focuses on the phase response characteristics of transient zeitgebers, it was also termed *discrete* or *non-parametric* model of entrainment. It postulates distinct and abrupt phase shifts as a function of when the circadian pacemaker is exposed to the external signal. Those responses are summarized in phase response curves (PCRs, fig. 1.3., panel A). Therefore, PRCs represent the descriptive result and the predictive model for entrainment, a problem discussed further below (Roenneberg et al., 2010b).

In general, paralleling the features of a mechanical oscillator, one may illustrate the effects of a light bout on the circadian pacemaker as a push upon a swing with a given period length, i.e. 24h (fig. 1.3., panel B, Roenneberg, Daan et al., 2003). If you push the swing at a given point, the integration of that push will depend upon the position of the swing: at the extreme poles (6/18), where the swing stops, a push towards the centre will cause a *phase advance,* while a push directed against it causes a *phase delay*.

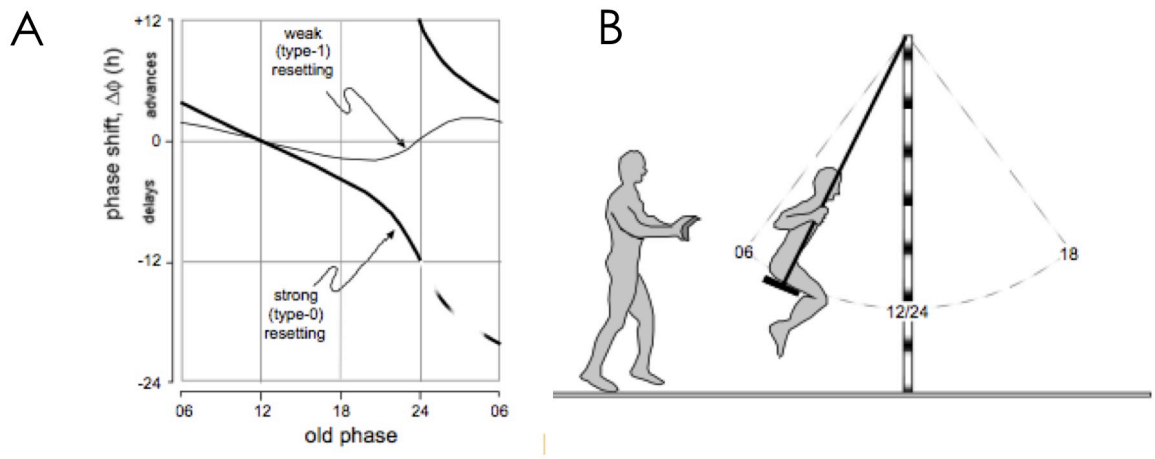


FIGURE 1.3. Panel A: Phase response curves (PRCs). Depending upon the strength of a push and the phase of the swing, different PRCs are obtained predicting the phase shifts. They are plotted as a function of the old circadian phase and subsumed in a PCR (Source: Roenneberg, Daan et al., 2003). Panel B: The swing as an analogy to the process of entrainment: the zeitgeber equals the push. Depending on the phase of the swing, the push will have specific effect. The phase relationship between these two is coined phase of entrainment.

Several scenarios are predicted when the swing is pushed within the two poles: at time point 6, where the swing is relatively slow in speed, a push towards the centre will trigger phase advance. The swing takes up in speed during its travel to the midpoint of the oscillation and the phase advance produced is smaller. When reaching the "dead zone" at the inflection point, a push will have no effect[5]. When the swing returns from the extreme, i.e. point 18, a push will lead to a phase delay.

The non-parametric theory has difficulties predicting the phase of entrainment with longer "pushes" or perturbations (e.g., Roenneberg et al., 2010b). Yet, in real life, those longer perturbations typically arise, as for example by an 8h light exposure. The integration of prolonged light exposure (and the effect of different light intensities) into the conceptualization of entrainment was at the heart of Aschoff's *continuous* or *parametric* approach (Aschoff, 1964; Swade, 1969). His observations that light intensity modulates the free-running period led to the conclusion that light had a continuous action upon the organism's cycle length (i.e. velocity change). At the same time, Aschoff postulated this process of entrainment affected the "(…) average level around which an oscillation moves" (Daan, 2000).

Integrative accounts were proposed, as in velocity response curves (VRCs), where *tau* was to be predicted from differential light intensities and the PRC (Daan & Pittendrigh, 1976). PRC approaches -- and VRCs can be counted as a PRC approach, as they are obtained by a linear transformation of the PRC (Roenneberg et al., 2010b) – on the other hand assume a stable *tau* and PRC itself. The observation of after-effects of entrainment, when released in constant conditions (e.g., Beersma et al., 1999; Diegmann et al., 2010; Pittendrigh, 1981; Pittendrigh & Daan, 1976b), suggests limitations to these approaches (Roenneberg et al., 2010b).

A new theoretical framework of entrainment has recently been proposed by Roenneberg and colleagues (2010b) to integrate previous findings and models into one coherent account. The circadian integrated response characteristic (CIRC), predicts the effects of any given light signal (from light bouts to extended and multiple light exposure, fig. 1.4., panel B-D). The effect of an external signal on

[5] In circadian oscillators, this dead zone can be larger as compared to mechanical oscillators, where only point 12/24 exactly corresponds to the dead zone (Roenneberg, Daan et al., 2003).

the intrinsic period is predicted by the CIRC's shape and asymmetry. The shape of the curve defines the dead zone, while the asymmetry indicates the direction of the phase shift (advancing or delaying). The basic assumption posits a compression of the internal cycle with light exposure around subjective dawn. Conversely, light around subjective dusk expands the internal cycle and thus leads to a phase delay (see fig. 1.4., panel A.).

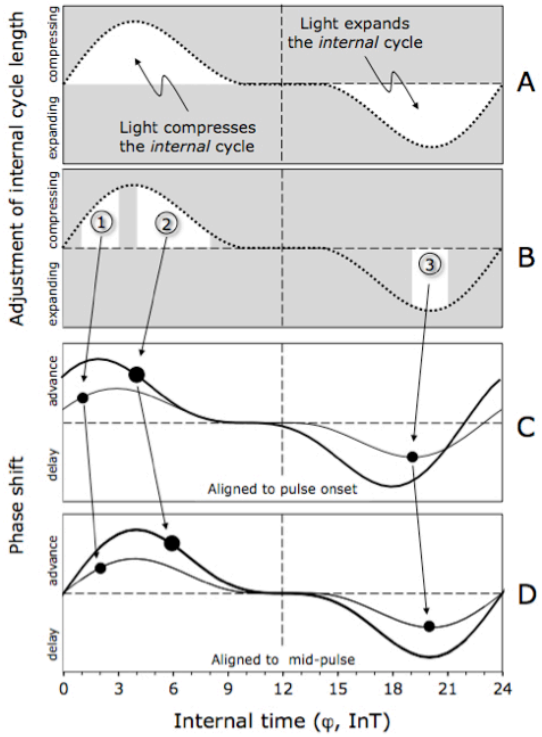


FIGURE 1.4. The CIRC. Panel A: the main assumption of the CIRC refers to compression and expansion of the internal cycle as a function of timing of the light exposure. Panel B to D depict the construction of exemplary PRCs for a given light exposure (Source: Roenneberg et al., 2010b).

1.1.5. ZEITGEBER

Despite light being the most important zeitgeber (for the master pacemaker SCN), other environmental signals were shown to have entraining power as well. The effect of any given zeitgeber on the phase of entrainment depends upon its strength (Aschoff & Pohl, 1978), its duration (Comas et al., 2006) and on individual clock characteristics, as internal period (Wever, 1975) and phase (Roenneberg, Daan et al., 2003). In general, studying the influence of a certain zeitgeber on entrainment, as for instance on the circadian rhythm of melatonin, all other influencing factors need to be controlled for. Furthermore, circadian

rhythms cannot only be influenced by other zeitgebers, but may additionally be masked. Masking is an acute reaction of an organism to an external (e.g., food, light etc.) or internal (e.g., motivation, stress level or digestion) parameter (Blatter & Cajochen, 2007), yet no stable phase angle between the intrinsic cycle and the external rhythm is established (Mrosovsky, 1999; Rietveld et al., 1993). Masking can conceal, but also mimic a rhythmic circadian clock output. In real life however, masking is suggested to be part of the entrainment process. The organism's own activity for instance can influence its phase of entrainment, and as such, masking may be part of the process of entrainment (Roenneberg & Merrow, 2007).

Given the predominance of light in the entrainment of the circadian clock, the investigation of other zeitgebers can only take place in constant darkness or in blind, free-running individuals[6]. Constant darkness, however, poses compliance and ethical concerns, especially for prolonged study periods. As an alternative, dim light conditions (< 100lx) have been chosen for studying the circadian clock. These studies have been extremely fruitful, despite them still bearing a potential light confound: even very dim light conditions (< 5lx) may be effective at resetting the clock and suppressing melatonin (e.g., Kronauer et al., 1999; Wright et al., 2001). In addition, the sensitivity of the circadian system might even be enhanced by prolonged dim light exposure (Hebert et al., 2002; Smith et al., 2004).

Studying the circadian clock and its characteristics in humans has two main objectives: 1) the investigation of the effect of particular zeitgebers on the phase of entrainment and 2) a differentiation between the circadian and homeostatic modulation on a certain parameters like CBT, melatonin or cognition. For this, two types of set-ups have been devised; both are extremely costly, time-consuming, laborious, and require a high level of motivation of the participants. In

[6] Several types of blindness exist: in case of deficient retinal processing, visual perception is impaired. Yet, if the retino-hypothalamic tract (RHT) is intact, those "perceptually blind" individuals will still be entrained to the 24h day: some exhibit melatonin suppression and phase shifts in response to bright light stimulation (e.g., Klerman et al., 2002). Others, with bilateral SCN lesions, were reported to free-run, despite strong social and other nonphotic zeitgebers (Klerman et al., 1998; Lockley et al., 1997; Skene et al., 1999). More details are reviewed for instance by Mistlberger and Skene (2005).

real life settings, such elaborate experiments are not accomplishable. Yet, the insights from such experimental set-ups build the basis for research questions and experimental designs in real-life settings.

Constant Routines (CR)

Participants of a CR (Czeisler et al., 1986; Mills et al., 1978) are subjected to more than 24h wakefulness in constant conditions, i.e. constant ambient dim light and temperature, ideally constant semi-recumbent position in bed, isocaloric meals served in regular intervals and controlled liquid intake. Additionally, participants are in total isolation from external, social time cues such as watches, TV or radios. In such an experimental set-up, the circadian modulation and the influence of increasing sleep pressure will be reflected in the variables of interest, usually measured in equally spaced time intervals. In cognitive performance, typically a "rescue" (or improvement) of the measured parameter emerges in the morning of the next day after a progressive impairment over the night. This rescue is ascribed to circadian-driven arousal enhancement and only assessable with CR of minimally 28h (for a review, see Blatter & Cajochen, 2007; Schmidt et al., 2007).

Napping protocols

Napping protocols are conducted in CR settings, yet, controlled napping in regular intervals controls for the build-up of sleep pressure, thus reducing the impact of process S. The resulting data are presumed to reflect the "endogenous" circadian rhythmicity in, for example, CBT or cognitive function, although it has been argued that the homeostatic component is not entirely controlled (Blatter & Cajochen, 2007).

Forced desynchrony (FD) protocols

FD protocols (Czeisler et al., 1995; Minors & Waterhouse, 1989) impose LD or rest/activity cycles on the participants -- outside the range of entrainment, as for instance 20h, 28h or 30h. For a de-synchronisation between the artificial sleep and wake cycle from the influence of the intrinsic pacemaker to occur, FD protocols necessitate a number of cycles (e.g. 12). As the external period lies outside of the range of entrainment, the circadian clock starts free-running, as measurable in its

output like melatonin or CBT. Similar to CR protocols, no time cues are available to the participants.

Both kinds of set-ups have led to plethora of results disclosing circadian rhythms in physiological parameters as well as in motor and cognitive functions (Bratzke et al., 2009; Jasper et al., 2009; Johnson et al., 1992).

The role of nonphotic zeitgebers has been described as weak, and will depend upon the presence and intensity of other zeitgebers, especially light. Despite their weak effect in humans, nonphotic zeitgeber can be potent and lead to phase shifts. Hence, their consideration (and investigation) is of importance (Mistlberger & Skene, 2005). Sleep and wake behaviour itself can act as a zeitgeber (e.g., Danilenko et al., 2003). Food uptake synchronizes mainly peripheral oscillators, but not the SCN (Mendoza, 2007). Irregular food uptake during night can lead to an internal de-synchronisation between the master pacemaker and the peripheral body clocks and thus be involved in metabolic disease pathways (see Padilha et al., 2010, for a succinct summary of previous studies and latest findings about altered metabolites of shift workers in the morning shift). Physical exercise may serve as a zeitgeber and facilitate phase shifts e.g. in shift workers (Buxton et al., 1999; Eastman et al., 1995), but findings are heterogeneous (Baehr et al., 1999; Cain et al., 2007). Edwards and colleagues (2009) reviewed the research of the past decades and concluded that exercise is a potent zeitgeber for various age and population groups, but encourage further research aiming better de-masking procedures. Mistleberger and Skene (2004, 2005) reviewed the evidence for the impact of social zeitgebers, a body of research mainly built up in the 1960ies. The dominance of light, and in this case, daylight, as the main zeitgeber in humans has been demonstrated amongst a large sample of participants in all of Germany ($n \approx 21.500$, Roenneberg, Kumar et al., 2007). When analysing the phase of entrainment as a function of the geographical location (longitudinal bins, from east to west) of their respective homes, a clear relationship between timing of sleep wake behaviour and sunrise was found. The more east a person lives (i.e. the earlier the sun rises), the earlier he or she gets up. The authors concluded that "the human circadian clock entrains to sun time", not to social time. In rural areas

(with less "light pollution"[7]), the relationship was even stronger, addressing the influence of zeitgeber intensity.

In summary, light is *the* zeitgeber in humans, but nonphotic ones can interact with and support its effect. The particular temporal relationship of an individual to a zeitgeber is reflected in the time difference between, for instance, dawn and the trough in CBT. This phase of entrainment differs between individuals, and this inter-individual difference is termed *chronotype* (Roenneberg, Wirz-Justice et al., 2003).

1.1.6. CHRONOTYPE

In a given species, the intrinsic (free-running) period is distributed around a specific mean (Pittendrigh & Daan, 1976a). In humans the average intrinsic period was reported to be 24.2h with a standard deviation of 8min (Czeisler et al., 1999).

As individuals embed differentially into the LD cycle depending on their intrinsic period (e.g. phase angle between dawn and CBT nadir or wake-up), chronotype can be assessed in entrained conditions (Roenneberg, Wirz-Justice et al., 2003). Sleep is one of the most obvious human behavioural pattern and its timing is controlled by the circadian clock. The Munich ChronoType Questionnaire, MCTQ (see Appendix, fig. A1.1. for an illustration of the questionnaire, Roenneberg, Wirz-Justice et al., 2003), is a simple questionnaire that permits the quantification of chronotype. By asking for exact sleep times on free and work days separately, the parameter "mid-sleep on free days" (i.e. the mid-point of sleep on free days, MSF), corrected for potential sleep debt accumulated over the workweek (MSFsc), is extracted. For instance, a person going to sleep at 1:00 o'clock at night on a free day and wakes up at 9:00 o'clock has a mid-sleep of 5:00 o'clock. The MSFsc correlates with physiological phase markers like melatonin and cortisol as well as actimetry and sleep log data (Havel, 2010; Roenneberg, Kuehnle et al., 2007). Test-retest reliability is high (Juda, 2010). Furthermore, the MCTQ data well matches the results of the Morningness-Eveningness

[7] Two factors may explain this phenomenon: on the one hand, relative zeitgeber intensity is stronger, as the nights are darker than in urban areas. Second, one may assume that rural populations are less daylight-deprived than urban inhabitants.

Questionnaire (MEQ, Horne & Østberg, 1976) - a widely used tool for the assessment of diurnal preference (Zavada et al., 2005). In comparison to the MEQ score, that relies on a subjective estimation, the MCTQ delivers exact, parametrical descriptives of individuals sleep and wake behaviour. This represents a major advantage in the precise phenotyping[8] of populations on which genetic studies built their validity (Allebrandt & Roenneberg, 2008). Chronotype has been associated with genetic polymorphisms (e.g., Toh et al., 2001), but research in this respect is ongoing.

MCTQ studies, with now approximately 90.000 participants in the database, revealed that chronotype was age (Carskadon et al., 1999; Dijk et al., 2000; Roenneberg, Kuehnle et al., 2007) and sex dependent with women being in general earlier chronotypes than men (Roenneberg, Kuehnle et al., 2007). With increasing age children grow later and later chronotypes. The peak in "lateness" is reached at the age of 19 years in women and around 21 years in men. After that, the phase of entrainment progressively gets earlier again, until inter-sex differences vanish approximately at the average age when men and women reach andro- or menopause, respectively. The tipping point, when young adults start progressing into an earlier phase of entrainment, has been suggested to correspond to a marker for the end of adolescence (Roenneberg et al., 2004). In the German population, chronotypes show a slightly skewed normal distribution (see fig. 1.5.). Extremely early and extremely late chronotypes are coined "larks" and "owls".

The quantitative variable MSFsc spans from 0:00 to 12:00 in the population. MSFsc is a continuous measure and in statistical analyses, a usage as a continuous variable appears sensitive. However, some questions may necessitate a categorical usage of the chronotype variable. For this, arbitrary categories have been design ranging from extremely early types (< 1:59), moderately early (2:00 to 2:59), slightly early (3:00 to 3:59), intermediate (4:00 to 4:59), slight late (5:00 to 5:59), moderately late (6:00 to 6:59) up to extremely late (> 7:00). In case a less fine-grained analysis is needed, a split into three or two categories is possible.

[8] For genetic studies of chronotype, the MCTQ disposes of an age- and sex correction algorithm (Roenneberg, Kuehnle et al., 2007).

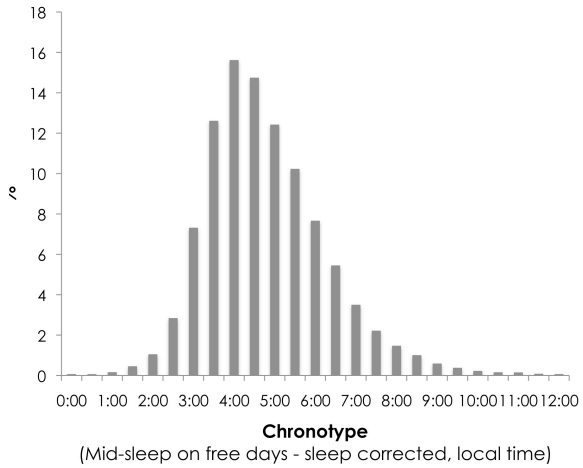


FIGURE 1.5. The chronotype distribution: each bar of the graph represents the percentage of individuals in one of the chronotype bins (0.5h bins). The data were obtained by the online MCTQ (n=79.901). Extremely early chronotypes are shown to the left, the late ones to the right. Sixty-five % of the population have an MSFsc between 3:30 and 5:30. An exemplary participant sleeping on average 8h per night and an MSFsc of 4:30 would thus go to bed at 0:30 and wake-up at 8:30.

Sleep duration is similarly distributed amongst early and late types, with as many short-sleepers in early chronotypes as in late ones (and accordingly for late chronotypes, Roenneberg, Kuehnle et al., 2007).

1.2. The circadian clock in real life

In field studies, individuals are always embedded in the LD cycle and thus entrained. The study of the circadian clock in humans in real life conditions moreover implies – for most of the population – an involvement in working conditions. The interface between the biological, internal and social time is a challenging one: working times, and especially shift work schedules, are until now widely neglecting the importance of sleep itself, but also inter-individual differences (Foster & Wulff, 2005). The study of the circadian clock in real-life settings allows 1) to investigate and quantify the impact of internal time on health, sleep and wake behaviour, cognition and wellbeing within our society, and 2) to reveal new opportunities to improve health and wellbeing. The link between sleep and health, or between sleep deprivation and health, has been established in a large number of epidemiological and experimental studies (Åkerstedt et al., 2010; Banks & Dinges, 2007; Cappuccio et al., 2010; Dinges, 2009; Ingre et al., 2008;

Knutson & Van Cauter, 2008; Kripke et al., 2002; Leger, 1994; Van Cauter et al., 2008; Webb, 1995). Sleep deprivation for example was associated with overweight, diabetes, increased heart attack risk, hypertension and decreased immune function (Irwin et al., 1996; Taheri et al., 2004; Vgontzas et al., 2002). The extent of artificial work time structures becomes evident in the results reported by Wittmann and colleagues (2006) on *social jetlag*.

1.2.1. SOCIAL JETLAG

In analogy to jetlag, social jetlag refers to a misalignment between the internal time and the external, social time. Transmeridian flights across several time zones lead to a de-synchronisation between the entrained phase and the current LD cycle, i.e. *jetlag*. After a couple of days in the new time zone, individuals are usually entrained to the external zeitgeber cycle. In everyday life, Roenneberg and colleagues described the phenomenon of social jetlag (Roenneberg, Kuehnle et al., 2007; Roenneberg, Wirz-Justice et al., 2003; Wittmann et al., 2006). Based on the MCTQ data base - and the differentiation between work days and free days – the authors reported reduced sleep duration on workdays for late chronotypes as compared to weekends (see fig. 1.6.).

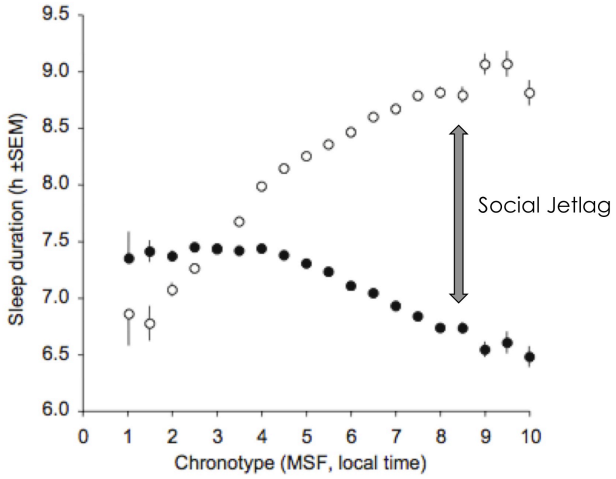


FIGURE 1.6. Sleep duration on work and free days: sleep duration is plotted as a function of chronotype (hourly bins) for work (filled black circles) and free days (white circles) separately (n= 60.000). The discrepancy is largest for late chronotypes, where it appears that they catch up on free days for the sleep deprivation accumulated over the workweek. Social jetlag in early chronotypes is not as pronounced, but is nevertheless in the 45min range when free days are compared with workdays (modified graph, source: Roenneberg, Kuehnle et al., 2007).

Early chronotypes in contrast display reduced sleep durations on free days. This difference between mid-sleep on free days and mid-sleep on workdays quantifies the extent of social jetlag of an individual. In late chronotypes, this sleep debt during the workweek is caused by relatively late "biological", internally regulated sleep onset times. The concomitant forced wake-up by an alarm clock hence artificially reduces sleep length. In early chronotypes, the social pressure of weekend activities taking place during the late evening delays sleep onset. Being regulated by the circadian clock, sleep offset however will occur in the early morning hours in early chronotypes, resulting in reduced sleep duration. As shown previously in the MSFsc-distribution, approximately 88% of the German population display a later MSF than 3:00 and 75% later than 3:30. As such, most the work schedules seem to collide with sleep timing of a large percentage of the population. The partial sleep deprivation resulting from the imposed work schedules "(…) conflicts with our basic biology and is suboptimal for our health" (Foster & Wulff, 2005).

1.2.2. SHIFT WORK

At least 20% of the western population adhere to working times that imply duty before 7:00 o'clock or after 19:00 o'clock (Kreitzman, 1999) and can consequently be qualified as shift workers (see Kantermann et al., 2010 for a critical overview of definitions of shift work). Rotating shift workers as well as permanent morning or night shift workers are even more affected by social jetlag as compared to regular day workers (see fig. 1.7.).

The impact of chronotype on sleep and wake behaviour, but also on health and wellbeing, in shift workers has been reported by Myriam Juda (2010) in a large set of field studies. In summary, the results of those studies comprising over 300 shift workers demonstrated that shift work research neglecting internal time jeopardizes its validity. As an example, the assessment of shift-specific sleep duration in shift workers without considering chronotype would result in similar sleep durations for morning. Yet, major differences are revealed only if chronotype categories are considered: early chronotypes sleep an hour more than late chronotypes during morning shifts, whilst late types sleep an hour more after night shifts (Juda, 2010).

Late chronotypes sleep up to two hours more during evening shift than in morning shifts. Early types in contrast sleep on average merely one hour less on morning shifts as compared to evening shifts. To understand the effects of shift work on health, performance and wellbeing, chronotype represents a key factor. Figure 1.7. reflects the differential burden on a more fine-grained scale with hourly MSF-bins.

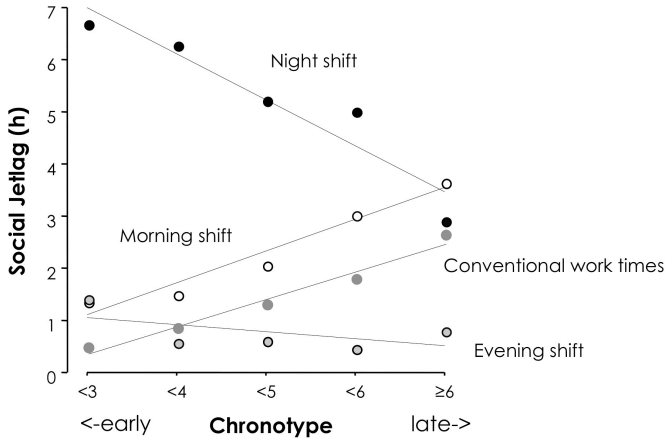


FIGURE 1.7. Social jetlag in shift workers: the highest discrepancy between sleep on free and workdays was reported for early chronotypes working night shift (full black circles). For late types, the morning shift (black and white circles) is associated with similarly high social jetlag as the night shift. The evening shift (grey circles with black contour) represents the least wearing shift for all shift workers. In its dynamics amongst chronotypes, the morning shift can be understood as an extreme version of conventional work times (grey circles; unpublished data, Juda, Vetter, & Roenneberg, 2010).

The outlook of optimized and healthier shift schedules can only be achieved when integrating for instance the differential levels of social jetlag as a function of shift and chronotype. The main prerequisite for the conduction of field studies in the light of chronotype is its fast and cheap assessment.

1.2.3. ASSESSING CHRONOTYPE IN FIELD STUDIES

A panoply of methods can measure the individual phase of entrainment, or chronotype. There are however restrictive criteria in the context of field studies. First, compliance of the participants (and their company, if applicable) is a high-ranking priority. The field studies presented in this thesis were all time-intense, and thus require a high level of compliance. Additionally, exact replications of

such studies are not possible[9] thereby leading to the assessment of a large set of parameters. Therefore, a minimization of interventions serves compliance. The studies also comprise a large number of participants, as dropouts can difficultly be replaced. For this reason, the assessment of chronotype should not be too costly. Last, participants at their work place are supposed to fulfil a task within their work time. To ensure the support of colleagues, managers and the participants themselves, the assessment of chronotype (as all other tests) should be the least time-consuming possible.

Physiological phase markers

Until recently, the non-invasive assessment of physiological, circadian phase markers was difficult. Melatonin is one of the most reliable phase markers of the circadian clock and has been used to quantify the phase of entrainment in the field. Steven Folkard (2008) reviewed seven studies on the adaptation to permanent night shift work by analyzing phase-shifts of melatonin rhythms. Out of those seven studies, only one was conducted in the field, with saliva samples taken every 2h (Koller et al., 1994). The study sample comprised 14 permanent night shift workers. The reliability of saliva samples however can be endangered by nicotine, caffeine and other variables interacting with saliva secretion and composition (e.g., Van Someren & Nagtegaal, 2007). Extraction of melatonin profiles from blood or urine samples appear more laborious and invasive for the participants. The methodological restrictions in the assessment of melatonin profiles risk the feasibility of large-scale field studies. However, technological developments in melatonin assessment could lead to a promising, reliable and practical physiological phase marker.[10] Another approach could be derived from the successful chronotyping of participants by extracting clock gene expression from fibroblasts (Brown et al., 2005; Brown et al., 2008). Yet, for large-scale field studies, biopsies remain rather impractical and too invasive. A new molecular

[9] The replication of a study implies an exact reconstruction of the circumstances. In field studies taking place in enterprises, economical, social and strategic changes within the company impede such equal study environments.

[10] Bühlmann Laboratories, Switzerland, are improving the methods of melatonin assessment in cooperation of the scientists involved in EUCLOCK, part of the FP7 program of the European Union.

approach accomplished reliable chronotype-prediction from only three samples of hair follicle cells, interleaved by three-hourly intervals (Akashi et al., 2010). The authors applied their approach also to a small sample of shift workers, yielding consistent results. This method appears very promising and minimally invasive. Future field research might greatly benefit from these advances in molecular biology. Up to now, all the physiological phase markers have not been established – or imply extensive logistical and monetary efforts - for large-scale field studies.

Questionnaire-based chronotype assessment

A simple way to assess phase of entrainment is a questionnaire. As mentioned above, most studies use the MEQ (Horne & Østberg, 1976), a questionnaire relying on subjective appraisal of one's sleep and wake behaviour. Questions are formulated in hypothetical terms, i.e. "If you were entirely free to plan your evening and had no commitments the next day, at what time would you choose to go to bed?". This kind of procedure has yielded good results. Yet, for research interested in real-life sleep and wake behaviour, it is essential to grasp the actual behaviour. In that sense, the MCTQ and the MCTQ^{shift} represent a quick, valid and quantitative assessment of chronotype. Juda (2010) developed the MCTQ^{shift} based upon the identical principals as the MCTQ (see Appendix A1.2. for an example of the questionnaire). The shift workers are asked to indicate their sleep timing on their respective shifts, but also for the free days following those shifts. Chronotype is in general quantified as the mid-sleep on free days after evening shifts (MSF^{E}). Both, the day worker and the shift worker questionnaire versions were validated by physiological (i.e. melatonin, cortisol and temperature rhythms), behavioural (actimetry) and daily sleep logs (Havel, 2010; Juda, 2010; Kühnle, 2006). The MCTQ takes approximately 5 to 10min to answer, the MCTQ^{shift} circa 20min, as it asks for sleep and wake behaviour as well as light exposure for each shift and free day as a function of shift, respectively. The measurement of chronotype is crucial for the scope of this research and the MCTQ represents an optimal instrument in the fast, large-scale assessment of phase of entrainment in regular employees, students and shift workers.

1.3. Scope of this research

To date, knowledge about the impact of circadian rhythms and chronotype in real-life settings is scarce. Fundamental research in laboratory settings has built-up a large body of evidence regarding the regulation and timing of sleep and wake behaviour and its effects upon cognition and wellbeing. In such settings, sleep timing and duration itself is manipulated or set by the experimental design. How inter-individual differences, especially chronotype, interact with sleep and wake behaviour and cognitive functioning in real life has not been explored extensively so far. The chronotype-specific modulation of sleep duration and social jetlag reported above suggest major modulations of sleep and wake behaviour in office workers and shift workers, potentially modulating performance, wellbeing and health in everyday life.

Light is the main zeitgeber for the mammalian circadian clock. Multi-facetted laboratory experiments have investigated the effects of light intensity, the spectral composition of the light source or of exposure duration on sleep and wake behaviour or physiological phase markers like CBT and melatonin. Also the effect of light on cognitive functions is in the sphere of interest, as well as most recently its effects on the neural activity patterns underlying cognitive performance (e.g., Aschoff & Pohl, 1978; Comas et al., 2006; Honma et al., 1987; Revell & Skene, 2007; Vandewalle et al., 2006; Vandewalle et al., 2007; Vandewalle et al., 2010). Up to now, field studies have hardly provided information about the objective effects of different light sources in indoor buildings – even though the largest part of the Western society spends approximately 65% of their time awake there. The lack of lighting systems adapted to the biological needs of humans was proposed to be part of a causal mechanism underlying health problems and performance impairments. This phenomenon has also been referred to as the "ill-lighting syndrome" (Begemann et al., 1997). In **chapter two**, a field study in an office setting is described. Two light environments were compared with regards to their effect upon sleep and wake behaviour and wellbeing. One light environment was relatively similar to daylight in its spectral composition (i.e. blue-enriched light), whilst the other one represented classical office lighting. The main objective was

to quantify the effects of this poly-chromatic, blue-enriched light on sleep and wake behaviour and wellbeing – as compared to a control group with no light change, but working in the same company and building. Objective measures of sleep and wake behaviour were obtained by actimetry and daily sleep log entries. Wellbeing ratings were tracked daily. Given the higher percentage of short-wavelength light in the new lighting environment, and the sensitivity of the circadian system to such spectral compositions, the light change was hypothesized to lead to (chronotype-dependent) phase-shifts. The positive effects of "blue" light on subjective wellbeing and mood have been described in patients (depression, seasonal-affective disorder etc., Wirz-Justice et al., 2009) and healthy populations (Dumont & Beaulieu, 2007; Knez, 1995), but barely portrayed in everyday life settings, like offices. The findings of this study have generated new propositions of how to design light environments in work settings potentially promoting health and sleep.

In **chapter three**, a field study investigating the impact of internal time on performance is delineated. Participants in this study were the most-challenged ones regarding social jetlag: rotating shift workers. The present study aimed at quantifying the influence of chronotype upon simple reaction time during morning, evening and night shifts. Furthermore, performance was expected to be influenced by the interaction between chronotype, type of shift, and sleep duration, as sleep duration within shifts itself is chronotype-dependant. The progressive built-up of homeostatic sleep pressure, especially in the night shift, and its impact on reaction times was demonstrated. Through reporting these results, chapter three describes the translation of laboratory research to applied, real life settings and endorses the importance of considering chronotype in shift work research. Moreover, this chapter suggests that the optimization of shift work schedules can be approached on a more fine-grained level; for instance the integration of performance profiles over shifts as a function of work place requirements could result in lower levels of work accidents and mistakes (Dorrian et al., 2005).

Chapter four describes a study in which the effect of time-of-day on the neural correlates of task switching was examined. This study was motivated by the recent

findings that simple reaction time tasks elicit chronotype-dependent neural activation patterns in a functional magnetic resonance imaging (fMRI) experiment (Schmidt et al., 2009). Again, light affects not only behaviour, but also brain activation patterns are modulated by previous light exposure, concurrently influencing neural response to a cognitive task (Vandewalle et al., 2009). Those first results suggest a major role for the circadian system in brain activation patterns. Yet, the understanding of the neural mechanisms of sleep and wake regulation in relation to cognition is at the very beginning. Besides the need of further research aiming at a better comprehension of those complex interactions, those results reveal a major caveat for fundamental cognitive research. If time-of-day and chronotype influence the neural patterns underlying task performance, as assessed with fMRI technology, then researchers should carefully integrate external and internal time in their protocols. The task switching paradigm used in the present fMRI study has been previously found to be modulated by internal time and homeostatic sleep pressure in its behavioural parameters – again, in entrained conditions. The participants were assessed with the MCTQ; sleep and wake behaviour was tracked by actimetry and sleep logs. The measurements took place at four times within one day and represented typically laboratory appointment times. This work has implications for the entire field of cognitive neuroscience, since significant time-of-day effects appeared.

In **chapter five**, the findings of the three studies are summarized and implications for future research and work settings are explored. The main conclusion of the present line of research is that internal time significantly influences behaviour, cognition, and physiology in real life. The described impact of internal time in real life suggests that sensible work schedules (i.e. day work, shift work or experimental laboratory work) should not be geared to logistical requirements, and thus external time only, but integrate the internal, individual time scale. The potential of this approach is so far unexplored.

2. Lights on: tracking the effects of blue-enriched light on sleep, activity, and wellbeing in office workers

"We are living in a biological night"[11] one might say considering the work environment most people live in the Western world. Modern lighting technologies have now developed lamps with near-daylight spectral qualities. This chapter will examine the effect of office light on sleep and wake behaviour and wellbeing – in daytime workers, just as most of us are.

2.1. Introduction

The field study described in this chapter stands at a crossroad as it combines the lastest lighting technologies with chronobiological research. It adresses the question of generalizability of laboratory findings to real-life conditions. Light plays a major role in entrainment 24h light-dark cycle being the main zeitgeber in circadian regulation of physiology and behaviour. In contrast to our phylogenetical ancestors, modern humans spend their time indoors, especially during work times. This in turn leads to a reduction of the natural zeitgeber exposure - both in terms of duration and intensity. All light environments – artificial and natural – influence the phase of entrainment of the circadian clock. The mechanisms underlying the interaction of internal phase and lighting environments have been receiving increasingly attention over the past decades.

As an example, the Society of Light Treatment and Biological Rhythms organises an annual congress covering topics such as light treatment in psychiatric and neurological conditions, design and architecture in harmony with natural light environments, or Light-at-Night theories in shift work contexts. Light has been shown to influence wellbeing, vitality, physiology in disease and health various working contexts. In the present study, the effect of artificial lighting in standard office work places was in the center of interest. In particular, the impact of blue-enriched indoor-lighting on sleep and wake parameters and subjective wellbeing was explored. So far, similar questions have been studied in laboratory conditions,

[11] Till Roenneberg, personal communication.

but only scarcely in real-life working conditions: most people in the Western hemisphere spend their majority of time awake in indoors offices.

2.1.1. THE EFFECT OF LIGHT ON HUMANS: LABORATORY STUDIES

Light synchronises the circadian clock to the 24h rotation of the earth – an active process called entrainment[12]. Light is by far the most dominant zeitgeber for the entrainment of circadian clocks in most plants and animals - including humans (Aschoff et al., 1969). In mammals, the clock's central pacemaker is located in the suprachiasmatic nucleus (SCN). It receives light information via retinal photoreceptors, predominantly via the recently discovered, non-visual light receptor melanopsin (Foster & Hankins, 2007; Gooley et al., 2003; Provencio et al., 2000). The action-spectrum for non-visual light responses in humans (pupillary constriction, melatonin suppression) peaks in the blue range between 420nm to 480nm (see fig. 2.1., Brainard et al., 2001; Brainard et al., 2008; Revell et al., 2005; Thapan et al., 2001; Wright & Lack, 2001; Zaidi et al., 2007).

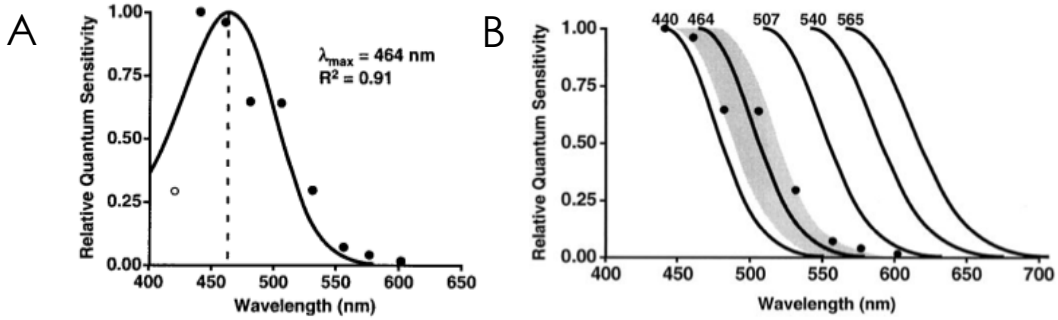


FIGURE 2.1. Panel A shows the percent control-adjusted melatonin suppression action spectrum in humans (n=72). The peak in suppression is achieved in the "blue" short wavelength part of the colour spectrum, at 464nm. The filled circles are the result of stimulations with eight wavelengths (max. response plotted against relative sensitivity, see Brainard et al. 2001 for more details). In Panel B, the action spectrum of melatonin suppression (peak 464nm ± standard deviation, SD) is compared to the ones of visual perception, i.e. rod (peak: 507nm) and cones (peaks: 440nm, 540nm & 565nm). Source: Brainard et al., 2001.

The effect of light on SCN activity is phase-dependent (Mitchell et al., 1997; N. Okudaira, Kripke, & Webster, 1983; T. J. Savides, Messin, Senger, & Kripke, 1986) – exposure to bright light around subjective dawn shortens the internal day

[12] Please see Chapter 1.1.3. for details on the process of entrainment.

and lengthens it around subjective dusk (Beersma & Daan, 1993; Czeisler et al., 1989; Honma et al., 1987; Khalsa et al., 2003). The degree to which the clock's internal cycle length is shortened or lengthened by light depends on its intensity (Aschoff & Pohl, 1978) and duration (Comas et al., 2006) as well as on individual clock characteristics like period (Wever, 1975) and internal phase (Roenneberg, Daan et al., 2003). When the clock is entrained, it establishes a specific phase relationship with the zeitgeber cycle (phase of entrainment, e.g. the time difference between the body temperature minimum and dawn). This phase of entrainment, i.e. chronotype, shows large inter-individual differences characterised by a positively skewed normal distribution.

Laboratory studies with humans living in constant conditions have demonstrated that even single bright light pulses can shift the circadian phase of both physiological (such as melatonin or CBT, Dawson et al., 1993; Gronfier et al., 2004; Khalsa et al., 2003) and behavioural rhythms (e.g., the sleep and wake cycle, Honma et al., 1987). Yet, not only the light's intensity but also its spectral composition determine its capacity to shift the clock's phase, with blue enriched light being in general more effective than long-wavelength light (Brainard et al., 2008; Cajochen et al., 2005; Revell et al., 2005; Warman et al., 2003; Wright et al., 2004). Smith and colleagues (Smith & Eastman, 2009; Smith et al., 2009) reported similar phase-advancing and phase-delaying properties of a 2h blue-enriched light pulse (17.000K) when compared to a 2h bright light (4.100K) pulse. In turn, monochromatic, short-wavelength light sources are less effective in suppressing nocturnal melatonin than polychromatic light sources, pointing to the importance of the whole colour spectrum of a light source and its potential impact on the non-image forming photic responses (Revell & Skene, 2007). Besides its direct effects on the circadian clock, short wavelength light is also more effective than longer wavelength light in increasing subjective alertness (Cajochen et al., 2005; Lockley et al., 2006).

2.1.2. The influence of light in office settings

Urban life style and indoor work deprive humans of natural daylight, and weaken the strength of the zeitgeber for entrainment (Roenneberg, Daan et al., 2003).

Compared to daylight, in-door lighting typically consists of low colour temperature (measured in K, Kelvin) – it appears warmer and less blue. Artificially blue-enriched light therefore gives indoor lighting more daylight qualities. Office settings with blue-enriched light environments could consequently increase zeitgeber duration and intensity. In the laboratory, blue-enriched light has proved itself to be a powerful agent in influencing physiological phase markers like melatonin suppression and core body temperature (see above).

In field studies, the effects of blue-enriched or bright light have rarely been examined. Bright morning and bright evening light pulses (2500lx, 2h) in office settings increase self-reported mood, alertness, energy and productivity (Avery et al., 2001), regardless of the timing of the bright light pulses. Blue-enriched light (17.000K) has been studied in two studies. Mills and colleagues (2007) reported improved ratings in subjective wellbeing, productivity and sleepiness ratings, especially during the first seven (out of 14) weeks after the light administration. Viola et al. (2008) compared the effects of the same 17.000K lighting to no, and 4.000K white light on self-reported mood, alertness, performance and fatigue. After a four-week study period, participants in the blue-enriched light showed less evening fatigue and improved performance and alertness. Light exposure (i.e. the amount of light reaching the eye) in office workers has also been reported to modulate sleep quality (Hubalek et al., 2010).

The few studies in real-life settings show a clear trend: at least on the subjective level, participants tend to feel better and perceive themselves as more alert and less tired. As such, laboratory results and field study data point to bright light as a potentially powerful agent.

2.1.3. Research aim

This study explores how changes in the colour temperature of office light from 4.000K to blue-enriched (8.000K) light affect sleep, activity and wellbeing. Sleep and wake behaviour as well as loco-motor activity were chosen 1) to evaluate the effects of blue-enriched light quantitatively and 2) to examine the effect of the light exposure on subjective wellbeing ratings on a longer time scale.

It is predicted that the effects of the blue-enriched light parallel the effects usually observed in spring time, such as increased wellbeing (Wirz-Justice et al., 2003) and advanced timing of activity and sleep- and wake behaviour. This prediction is in line with previous results demonstrating that humans track sun- instead of social time (Kantermann et al., 2007; Roenneberg, Kumar et al., 2007).

As the light change represents an increase in zeitgeber strength, one should expect that the timing of sleep and activity of the employees working under blue-enriched light is altered compared to those exposed to the "warmer" light source. The working hours at the study site were early with most of the employees starting between 7:00 and 8:30 o'clock. Given the early onset of increased zeitgeber strength and the finding that the majority of the population displays a later phase of entrainment (Roenneberg, Kuehnle et al., 2007), an advance in the timing of mid-sleep on free days is expected in the experimental group, above changes observed in the control group - where no light change will occur (**hypothesis 1**).

Previous findings indicate that loco-motor activity is a more sensitive measure than sleep-logs when investigating behavioural responses to environmental changes like transitions in and out of daylight savings time (DST, Kantermann et al., 2007). Hypothesis 2 hence predicts an advance in loco-motor activity independent of whether this advance becomes apparent in sleep log data (**hypothesis 2**).

In light of observed mood-improving effects of blue-enriched light (e.g. Mills et al., 2007) in field and laboratory studies, the assessment of subjective wellbeing should result in an improvement of the ratings superior to potential changes observed in the control group (**hypothesis 3**).

As stated earlier, it is known that the phase of entrainment, or chronotype, correlates with the timing of sleep and wake behaviour and loco-motor activity. It is thereby hypothesized that chronotype will be related to the timing sleep and activity measures, with earlier chronotypes showing an earlier timing in sleep- and wake behaviour as well as earlier activity peaks than late chronotypes (**hypothesis 4**).

Given the predictions of the circadian integrated response curve (CIRC, refer to Chapter 1 for more details, Roenneberg et al., 2010a), one could furthermore

expect a differential effect of the increase in zeitgeber strength as a function of chronotype (**hypothesis 5**). Early chronotypes, with an internal period (τ) shorter than 24h (T – the external cycle, i.e. earth rotation), should delay when exposed to a stronger zeitgeber (see fig. 2.2., panel F), as compared to a weak zeitgeber (fig. 2.2., panel C).

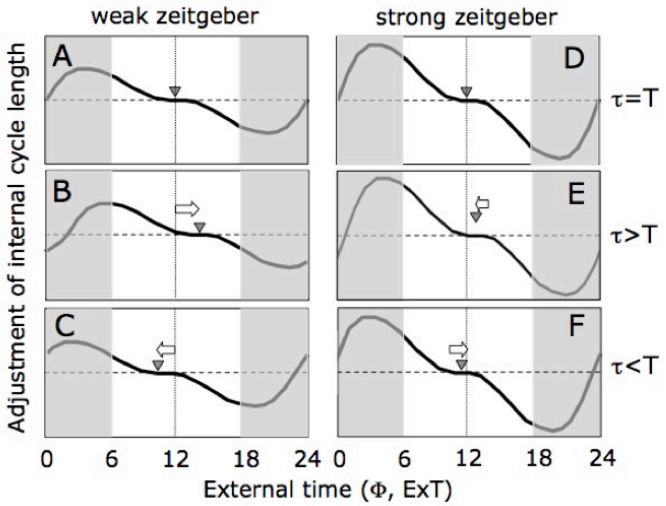


FIGURE 2.2. This figure illustrates the predictions of CIRC (circadian integrated response curve) with regards to the adjustment of internal cycle length as a function of zeitgeber strength and internal period (τ). The triangle indicates the position of τ, the white arrow points towards the expected adjustment. Source: Roenneberg et al., 2010.

Late chronotypes (τ > T) should in contrast show an advance in phase of entrainment in a light environment with a stronger zeitgeber (fig. 2.2., panel E, see panel B for the case of a weaker zeitgeber). If internal phase is identical to external phase, increasing zeitgeber strength should not result in any changes in the phase of entrainment, as the in the compression and expansion sections under the CIRC balance each other out (see fig. 2.2., panel A and D).

2.2. Materials and methods

This study obtained ethics approval by the ethics committee of the Department of Psychology, Ludwigs-Maximilians-University, Munich. All participants signed an informed consent and were aware of their possibility to withdraw from the study at any point. All study materials were recoded to assure anonymous data handling and data analyses.

2.2.1. STUDY DESIGN

The study was performed in the offices of OSRAM GmbH headquarters in Munich, Germany, between January 14th and February 17th 2008. During the first two weeks, the office lighting was identical for all participants (4.000K; OSRAM 840 LUMILUX® Cool white, see fig. 2.3., panel A, for the spectral power composition). Over the weekend of the 26th and the 27th of January 2008, three offices floors were switched to 8.000K lighting (polychromatic blue-enriched 8.000K lamps, OSRAM 880 LUMILUX SKYWHITE®, see fig. 2.4., panel B), while 2 office floors continued to be illuminated by the 4.000K light source.

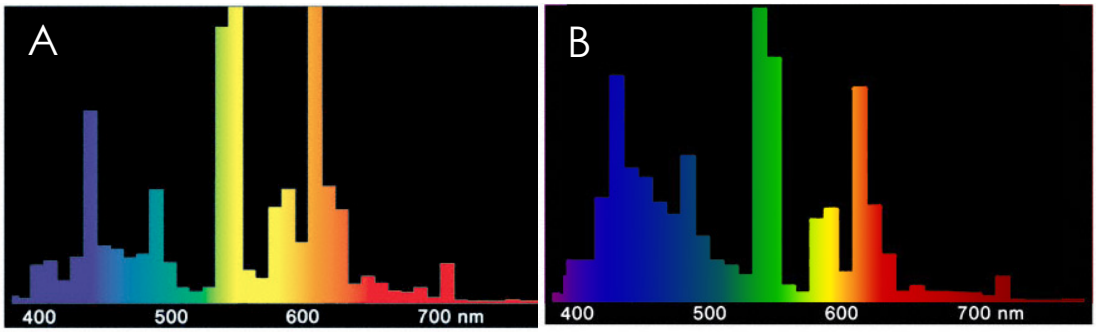


FIGURE. 2.3. Spectral composition of the light sources: panel A shows the spectral composition of the LUMILUX cool white lamps, the standard lighting in the OSRAM headquarters. Panel B: in comparison, the spectrum of the LUMILUX SKYWHITE is clearly enriched in the short-wavelength part, but also shows relatively more medium wavelengths ("green").

Figure 2.4. illustrates the study setting after the light change: the top three floors encompassed the experimental group (exposed to the light change; n=27) while the lower two floors featured the control group (without change in lighting; n=27). The ground floor containing the cafeteria and a reception area was excluded from the study. Participants filled out daily sleep-logs and wore actimetry devices over the entire study period. The individual chronotype of all volunteers was assessed by the MCTQ (see 2.2.3.) at the beginning of the study.

FIGURE 2.4. The OSRAM GmbH Headquarters in Munich, Germany during the study: in the top three floors, the illumination was changed to a blue-enriched light environment (LUMILUX SKYWHITE), while the lower ones remained with their initial lightning over the course of the study period.

2.2.2. PARTICIPANTS

A total of 66 employees agreed to participate in this study. Of these, 12 were excluded due to *a priori* and *post-hoc* exclusion criteria. *A priori* exclusion criteria were applied in case of home officing, part time contracts, foreseeable commitments outside of the office building (more than once a week), and planned business trips. *Post-hoc* exclusion criteria were applied to the participants who did not complete sleep-logs, took more than three days off or had to take short notice business trips. Those rigid criteria aimed at assuring within and between group comparability. The 54 participants (26 men and 26 women, two not indicated) between the age of 24 and 63 years (mean age= 40.33 ±8.9) were analysed for their sleep-wake behaviour based on sleep logs. Of these, 27 participants could be analysed for their daily loco-motor activity by means of actimeters, after the exclusion of 17 due to missing data (that could not be explained by the watch protocol nor the sleep log data). The participants in the two groups did not differ in terms of work rank or in their educational achievement.

2.2.3. MATERIALS

Sleep logs

Sleep-logs were filled out during the entire five week study period (see Appendix, fig. A2.1. for an example). Following parameters were assessed: bed-time (BT), sleep latency (Sl_Lat), sleep offset (Sl_Off), time to get up (sleep inertia, Sl_In), use of an alarm clock, wellbeing (from 0 = not at all to 10 = extremely well), whether the day in question was a free or a workday and in the case of the latter, exact times spent at the work place. Additional space was available in case the participants had comments regarding their sleep quality or timing. Participants were instructed to fill out the sleep log every morning after wake-up. The main variables used to assess daily sleep timing were mid-sleep on free days (MSF) and mid-sleep on workdays (MSW). In addition, subjective wellbeing was assessed on a day-to-day basis.

Actimetry

To record loco-motor activity, 27 subjects continuously wore a waterproof device around their preferred wrist (Daqtometer Version 2.4 by Daqtix GmbH, Oetzen, Germany, see fig. 2.5.) and were instructed to keep a log about the times when they did not wear the device (see Appendix, fig. A2.2.). Activity data was coded for free days or workdays on the basis of sleep log entries, so that individual differences in work presence could be accounted for (more than three days off work resulted in the exclusion from the study).

FIGURE 2.5. The Daqtometer - continuous recordings of both, changes in dynamic and static acceleration (i.e. motion and gravity) allow for an appreciation of loco-motor activity for up to six months.

The Munich ChronoType Questionnaire (MCTQ)

The MCTQ (Roenneberg, Kuehnle et al., 2007) provides a robust and reproducible measure for assessing chronotype by self-reported sleep habits. The MCTQ differentiates between free days and workdays. Chronotype is quantified by the mid-point between sleep onset (Sl_On) and sleep offset (Sl_Off), corrected for sleep deficit accumulated during the workweek (Wittmann et al., 2006). Here, the recently redefined algorithm by Myriam Juda (2010) is employed for the computation of MSFsc (mid-sleep on free days corrected for sleep debt, see section 2.2.4 for details).

2.2.4. DATA PROCESSING

Sleep log data

Sleep log data was used for the weekly computation of the following variables: Mid-sleep on workdays (MSW), mid-sleep on free days (MSF) as well as an average of weekly wellbeing judgments. For an overview of the variables, their derivates and the underlying computations, consult table 2.6 on the following page.

Loco-motor activity

The Daqtocontrol© software was used for the standardized set-up of the actimetry devices and data extraction. The actimeters were all programmed with this software following the standard protocol. Data were consolidated in 10-min bins. The variable extracted from the loco-motor activity recordings was the Centre of Gravity (CoG, ψ_{act}), as this one has been shown to be independent of the individual shape of the profiles (Kenagy, 1980) and to be sensitive to environmental changes (Kantermann et al., 2007). ψ_{act} was computed with ChronOSX program (Roenneberg & Taylor, 2000) by fitting a one harmonic cosine for each free weekend of the study period, resulting in a total of five $\psi_{act\text{-}f}$ values as well as an average for each workweek ($\psi_{act\text{-}w}$). The data was 24h trend-corrected and non-smoothed. To insure comparability within and between groups,

workdays on weekends as well as free days during the workweek were excluded from analyses.

Sleep Log and MCTQ Variables

Obtained Parameters	Derivative	Derivative Work Days / Free Days
1 Bed Time	BT	BT_w / BT_f
2 Sleep Latency	Sl_Lat	Sl_Lat_w / Sl_Lat_f
3 Sleep Offset	Sl_Off	Sl_Off_w / Sl_Off_f
4 Use of Alarm Clock	A	A_w / A_f
5 Sleep intertia	Sl_In	Sl_In_w / Sl_In_f
Computed Parameters	**Derivative**	**Derivative Work Days / Free Days**
1 Sleep Onset	Sl_On	Sl_On_w / Sl_On_f
Algorithm	BT + Sl_Lat	
2 Sleep Duration	Sl_D	Sl_D_w / Sl_D_f
Algorithm	Sl_Off - Sl_On	
3 Mid-Sleep	MS	MSW/MSF
Algorithm	Sl_On + Sl_D/2	
4 Average Sleep Duratic	Ø SD	none
Algorithm	(SD_w * xw + SD_f * xf) / (xw + xf)	

* xw = relative number of workdays / xf = relative number of free days

TABLE 2.6. The underlying computations of the essential variables were identical for the MCTQ and sleep logs. All parameters, but the average sleep duration, exist for free days and workdays. To calculate chronotype, additional computations are necessary as defined in this section under *MCTQ*.

Wellbeing

Daily wellbeing ratings were averaged for each week of the study period by computing a weighted score (see below for the algorithm).

Wellbeing Computation

Obtained Parameters	Derivative	Derivative Work Days / Free Days
Mean Wellbeing	WB	WB_w / WB_f
Algorithm	(ΣWB_w)/xw or (ΣWB_f)/xf	
Computed Parameters		
Weighted av. Wellbeir	Av_WB	-
Algorithm	(WB_w*xw+WB_f*xf)/(xw+xf)	

* xw = relative number of workdays / xf = relative number of free days

The Munich ChronoType Questionnaire

The computation of the participants' chronotype (MSFsc) was based on the MCTQ data obtained during the first study week. The formula is shown below (fig. 2.7.). The weighted and averaged sleep duration was computed to correct for potential sleep debt (see table 2.6.).

MSFsc Computation	
Case 1	
	SD_f > SD_w ➔ MSF - ((SD_f - Ø SD/2)
Case 2	
	SD_f < SD_w ➔ MSF

TABLE 2.7. Few people sleep less on free days than on workdays (see General Introduction, 1.2.1.); in case 2, a sleep debt correction would result in an over-estimation of "earliness", thus the differentiation was shown to be necessary and more sensible (M. Juda, 2010).

2.2.5. STATISTICAL ANALYSES

All data sets were analysed with Excel 2008 and SPSS 17.0 and 18.0 for Mac OS X. The changes across the five week study period in MSW, MSF, wellbeing and loco-motor activity ($\psi_{act\text{-}w}$ and $\psi_{act\text{-}f}$) were assessed by means a set of repeated-measures ANOVAs (rANOVA). Separate computations were performed for the control and the experimental group. Due to missing values, the sample sizes may differ between different computations.

Variables not known to be normally distributed, i.e. the wellbeing ratings, were tested for normality by means of the Kolmogorov-Smirnov-Test. If the normality assumption did not hold true, Friedmans ANOVA was additionally reported. In case of a violation of sphericity, the Greenhouse-Geisser correction was applied. As post-hoc tests, Bonferroni-corrected pairwise comparisons were calculated; effect size (Cohen, 1988) was estimated by means of partial η^2.

Calculations were done separately for each group, as one might expect non-linear effects of the light change in the experimental group, threatening the validity of a between-subject rANOVA. All variables expressing times of day (MSW, MSF, $\psi_{act\text{-}w}$, $\psi_{act\text{-}f}$) are reported in decimal units, i.e. 13:30 is 13.5.

2.3. Results

The participants in the two groups (experimental and controls) matched in age and chronotype as shown by Students t-tests for independent samples (all p-values > .4; see in table 2.8.).

	Sleep Logs		**Loco-motor activity**	
Groups	experimental	control	experimental	control
N	27	27	14	13
Age in yrs (±SD)	39.92 (±8.72)	40.37 (±9.18)	38.21 (±8.45)	41.08 (±7.14)
MSFsc (±SD)	3.81 (±0.85)	3.59 (±0.93)	3.65 (±0.97)	3.58 (±0.93)

TABLE 2.8. Demographic data of the sample: average age and chronotype (MSFsc; ±SD) as a function of group and condition.

2.3.1. SLEEP AND WAKE BEHAVIOUR

Mid-sleep on workdays (MSW)

Table 2.9. gives an overview of the sleep- and wake behaviour during the study's five workweeks.

MSW-times		
	Exp. Group	Control Group
n	22	23
Week 1	2.78 (±0.80)	2.80 (±0.74)
Week 2	2.80 (±0.83)	2.79 (±0.67)
Week 3	2.92 (±0.86)	2.82 (±0.12)
Week 4	3.00 (±1.14)	2.73 (±0.63)
Week 5	2.81 (±0.82)	2.78 (±0.55)

TABLE 2.9. The average MSW-times as a function of study group (±SD).

For both, the control group and the experimental group sleep timing was neither being advanced n or delayed across the five weeks (non significant rANOVAs with the factor week, all p-values > .3).

Mid-sleep on free days (MSF)

In regards to the experimental group, the timing of sleep- and wake behaviour on free days remained constant over the course of the study (see table 2.10. for an overview of the mean MSF-times).

MSF-times		
	Exp. Group	Control Group
n	24	25
Week 1	4.34 (±1.18)	4.21 (±1.05)
Week 2	4.39 (±1.33)	3.98 (±1.07)
Week 3	4.29 (±1.08)	4.17 (±1.14)
Week 4	4.36 (±1.25)	3.76 (±0.86)
Week 5	4.24 (±0.78)	3.73 (±0.98)

TABLE 2.10. The average MSF-times as a function of study group (±SD).

The control group, in contrast, became significantly earlier across the five weeks (see fig. 2. 11.; rANOVA with between-subject factor "chronotype"; significant main effect of "week", $F(4,92)= 3.304$, $p= .014$, $\eta^2= .13$). Weeks one and three were significantly later from week five (p-values < .05); they also showed the same trend with regards to week four ($p= .052$ and .085 respectively) as assessed with Bonferroni-corrected, post-hoc comparisons.

Timing of sleep was dependent upon chronotype in the control group (main effect of "chronotype", $F(1,23)= 16.47$, $p= .000$, $\eta^2= .42$, see fig. 2.12., panel A, next page), but both early and late chronotypes exhibited a similar pattern in advance over the course of the study (non-significant interaction between "week" and "chronotype).

Chronotype also influenced the timing of sleep and wake behaviour in the experimental group, $F(1,22)= 15.79$, $p= .001$, $\eta^2= .41$. Just like in the controls group, no differences between early and late types in the timing of sleep could be observed over the five study weeks, see fig. 2.12., panel B.

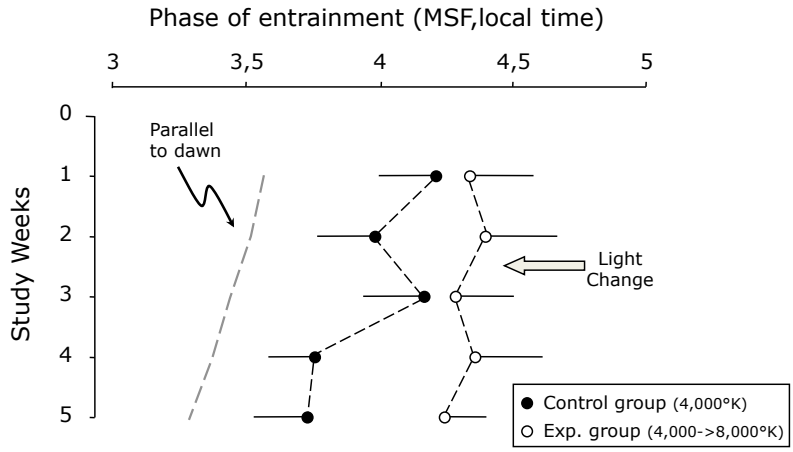


FIGURE 2.11. Average mid-sleep on free days (MSF ± standard error of the mean, SEM) as a function of study-week, separately for the control group (black dots) and the experimental group (open circles). The light change occurred between week two and week three. While the sleep-wake behaviour in the control group advanced, it remained constant in the experimental group.

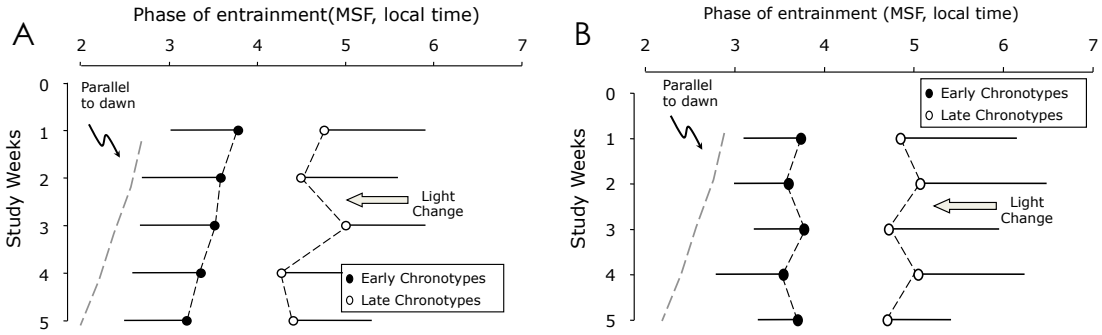


FIGURE 2.12. In panel A, MSF-times (± SD) of the control group are plotted by chronotype (early: n=14, late: n=11) and as a function of study weeks. Panel B follows the same logic, but for the experimental group (early: n=11 and late chronotypes: n=13).

2.3.2. LOCO-MOTOR ACTIVITY

Loco-motor activity on workdays ($\psi_{act\text{-}w}$)

The main differences in the sleep and wake behaviour between the two groups emerged on free days. These results are coherent with the activity data: the centre of gravity ($\psi_{act\text{-}w}$) on workdays in both groups remained constant over the study period (see table 2.13. for the descriptives; p-values > 0.5, respectively).

CoG in loco-motor activity ($\psi_{act\text{-}w}$) on workdays		
	Exp. Group	Control Group
n	14	13
Week 1	14.33 (±1.01)	14.08 (±1.33)
Week 2	14.63 (±1.18)	13.96 (±1.37)
Week 3	14.80 (±1.09)	14.00 (±1.37)
Week 4	14.51 (±1.02)	13.97 (±1.53)
Week 5	14.51 (±1.02)	13.89 (±1.43)

TABLE 2.13. Mean $\psi_{act\text{-}w}$ (±SD) fitted to the daily activity recordings over the five weeks of the study separately for the control and the experimental group.

Loco-motor activity on free days ($\psi_{act\text{-}f}$)

The phase of activity on free days ($\psi_{act\text{-}f}$) showed significant changes over the 5-week study period for the control group, but not for experimental one (significant effect of "week" on $\psi_{act\text{-}f}$ in the control condition, $F(3.55, 39.03)= 6.34$, $p= .001$, $\eta^2= .37$, see fig. 2.14.).

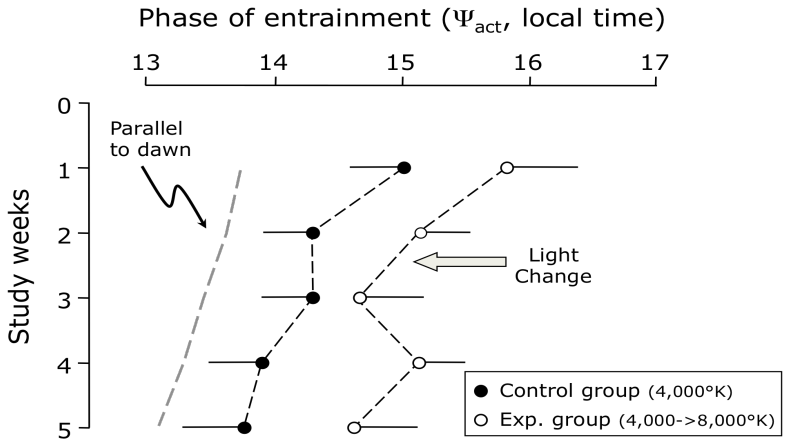


FIGURE 2.14. Changes in phase of loco-motor activity on free days ($\psi_{act\text{-}f}$). The circles represent means (± SEM), with the filled ones referring to the control group.

Table 2.15. summarises the means of $\psi_{act\text{-}f}$ by group and for each week of the study. In the control group, $\psi_{act\text{-}f}$ times in week one were significantly later than

week four and week five, as well as $\psi_{act\text{-}f}$ of week three compared to week five (Bonferroni-corrected, post-hoc comparisons, all p-values < .01). A similar trend was detected for week one compared to week three, p= .06.

CoG in loco-motor activity ($\psi_{act\text{-}f}$) on free days		
	Exp. Group	Control Group
n	14	13
Week 1	15.82 (±2.12)	15.01 (±1.52)
Week 2	15.14 (±1.48)	14.29 (±1.38)
Week 3	14.66 (±1.90)	14.30 (±1.43)
Week 4	15.13 (±1.39)	13.90 (±1.50)
Week 5	14.62 (±1.90)	13.75 (±1.74)

TABLE 2.15. Average $\psi_{act\text{-}f}$ (mean ±SD) is given as a function of group and study week.

In both groups, chronotype influenced the timing of loco-motor activity (main effect of chronotype; controls: $F(1,11)= 7.03$, p= .02 and experimental: $F(1,12)= 26.19$, p= .00), i.e. the earlier the chronotype, the earlier the centre of gravity, $\psi_{act\text{-}f}$. For visualization of this effect both groups were split in an early and late chronotype group (early < MSFsc = 4.5 > late); however, the sample sizes were to small to draw further calculations (see fig. 2.16., panel A for controls, and panel B for the experimental group).

Early chronotypes in the control group showed a more pronounced advance than the late types – this visual trend was confirmed by the significant interaction between chronotype and $\psi_{act\text{-}f}$ ($F(3.5,39.03)= 3.63$, p= .03, $\eta^2= .25$). For the experimental group, no interaction between the effect of chronotype and the effect of study weeks was detected (p> .2).

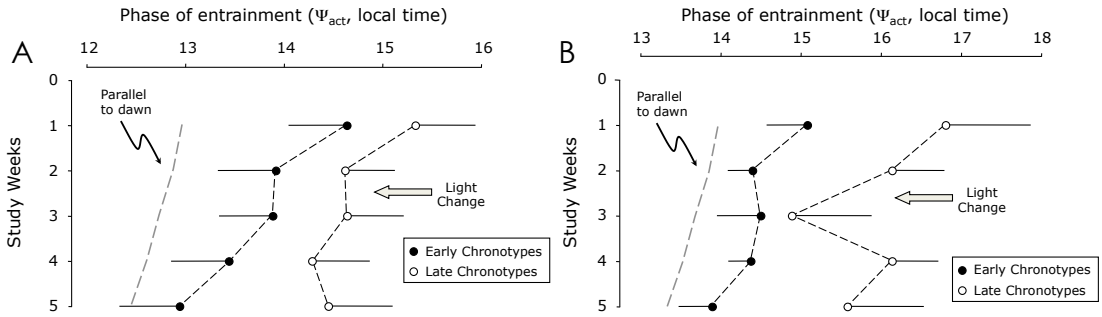


FIGURE 2.16. Panel A: chronotype-specific loco-motor activity in the control group. The early chronotypes (filled circles, n=6) show a more pronounced average progression of the course of the five weeks as compared to the late chronotypes (open circles, n=7). In the experimental group, panel B, the early chronotypes (filled dots, n=8) had in general a significantly earlier $\psi_{act\text{-}f}$ than the late chronotypes (open dots, n=6).

2.3.3. WELLBEING

Wellbeing ratings were averaged for each week of study period, see table 2.17. for an overview.

Wellbeing scores		
	Exp. Group	Control Group
n	21	22
Week 1	6.54 (±0.28)	5.95 (±0.36)
Week 2	6.72 (±0.31)	6.53 (±0.32)
Week 3	6.46 (±0.25)	6.80 (±0.25)
Week 4	6.73 (±0.24)	6.61 (±0.31)
Week 5	6.61 (±0.37)	6.75 (±0.33)

TABLE 2.17. Mean subjective wellbeing ratings are shown for each study week, separately for the experimental and the control group chronotypes (weekly average ±SD).

Subjective wellbeing reports of the participants did not change significantly over the 5-week study period, neither in the control not in the experimental group (rANOVA with the factor "week" and the covariate "chronotype", effect of week, $p > .09$).

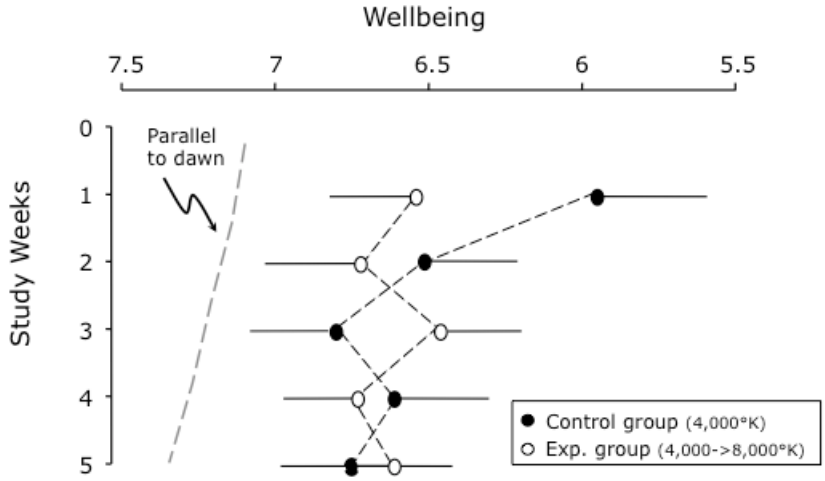


FIGURE 2.18. Changes in subjective wellbeing ratings (weekly average ±SD, separately for the control and the experimental group). The variations in the data did not show a systematic trend during the study.

In general, early chronotypes felt significantly better in the control group (rANOVA with the between-subject factor chronotype, $F(1,20)=6.62$, $p= .018$; see fig. 2.19., panel A).

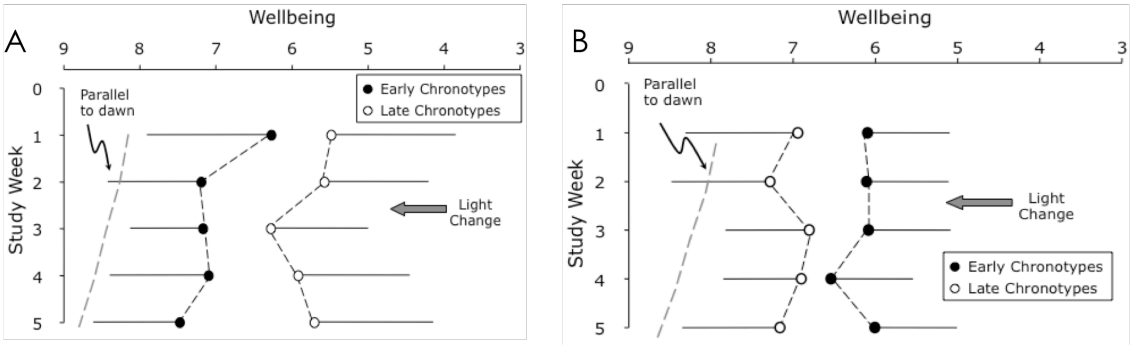


FIGURE 2.19. Panel A: Early chronotypes in the control group displayed a slight (but non-significant) increase in wellbeing throughout the study period (average wellbeing ±SD, black circles, n=13), while late chronotypes (open circles, n= 9) remain on a constant level. Panel B: The ratings in the experimental group (average wellbeing ±SD) did not change significantly over the five weeks, neither for early chronotypes (black circles, n=11), nor for late ones (open circles, n=10).

The wellbeing ratings in the control group showed a slight rise in early chronotypes, but this trend did not reach significance. Late chronotypes remained constant across the five week study period, just as the scores in the experimental group wellbeing (see fig. 2.19., panel B).

2.4. Discussion

The aim of this field study was to investigate whether polychromatic, blue-enriched light in an office setting affects the timing of sleep and wake behaviour, activity and subjective wellbeing. For five continuous weeks, participants kept sleep logs to report their daily sleep timing, subjective wellbeing and wore devices around their wrists for the recording of their loco-motor activity.

Over the study period, the timing of sleep on free days advanced significantly in the control group, but remained stable in the experimental group, which experienced the light change. The timing of activity matched the observed findings in sleep and wake timing: On free days, the timing of loco-motor activity advanced significantly in the control group, but not in the experimental group. Wellbeing ratings in contrast did not show variations, neither as a function of study period nor of group. The exposure to blue-enriched light in the experimental group was locked to office times. It appears that the continuous and highly regular light exposure entrained the experimental group to work times. This implies that the increase in zeitgeber strength and duration of the indoor lighting competes with natural LD cycle. While the control group followed the seasonal changes in photoperiod, the experimental group entrained to the artificial light signal.

The observed advances in the timing of sleep and wake behaviour of the control group are consistent with a greater association between the timing of human sleep and wake behaviour and sun-time than social time. Roenneberg and colleagues have shown (2007) that the timing of sleep and wake behaviour in the German population progressively advanced from East to West in accordance to longitudinal differences in dawn. Sleep and wake behaviour is also strongly influenced by season, specifically by the changing dawn times in spring and autumn (Kantermann et al., 2007). During the course of the present study, sunrise advanced by 42 minutes from 8:00 (beginning of week 1) to 7:18 o'clock (end of week five; for an overview of the sunrise times, see Appendix, table A2.3.), matching the observed advancement in the control group. In contrast, the experimental group shows a remarkable absence of effects throughout the course

of the study, suggesting that daily exposure to blue-enriched light during office hours interfered with the seasonal adjustment of sleep and wake behaviour and loco-motor activity. Blue-enriched light exposure appears to override the influence of sunlight that entrains the circadian clock in the general population (Roenneberg, Kumar et al., 2007; Roenneberg & Merrow, 2007).

Laboratory studies have shown phase-shifting properties of bright and blue-enriched light (Dawson et al., 1993; Gronfier et al., 2004; Honma et al., 1987; Khalsa et al., 2003; Revell et al., 2005; Wright & Lack, 2001; Wright et al., 2004). On the basis of these findings and in accordance with the predictions from the CIRC (Roenneberg et al., 2010a), **hypotheses 1** and **2** expected a phase-advance in sleep and wake behaviour and loco-motor activity as a consequence of blue-enriched light exposure. A recent study conducted during the polar winter quantitatively investigated the effects of different colour temperatures on sleep and wake behaviour (sleep logs and actimetry), general health and circadian phase[13] (Mottram et al., 2010). With a complex, inter-leaved intervention design, the effects of the different light environments were measured amongst 15 employees. The blue-enriched light significantly advanced circadian phase and sleep onset as compared to white light, along with a reduction in sleep latency. Just as in the study at hand, blue-enriched light showed to be a more powerful zeitgeber than white light. The study was conducted in the total absence of natural light signals, i.e. constant darkness during polar winter. Consequently, its research question could be qualified as a laboratory study as this real-life situation is extreme and rare. Transitions in and out of the polar winter and interactions with artificial light environments have not yet been studied. Hence, in the absence of competition between natural and artificial light, blue-enriched light sources yield a phase advance, as quantified by Mottram and colleagues (2010).

By exploring white and blue-enriched light environments in office workers in an everyday situation, the present study in contrast involves exposure to a natural light/dark cycle outside of office hours. The phase-shift in the timing of sleep and activity in the experimental group was not only of a smaller than the phase-

[13] Circadian phase was assessed via melatonin profiles, i.e. urinary 6-sulphatoxymelatonin rhythm.

advance observed in the control group, but absent in both of the assessed behavioural indices. **Hypotheses 1** and **2** have thus to be refuted.

Wellbeing ratings did not reveal significant dynamics over the study period. Typically, an increase in mood is observed in early spring increase, correlating with photoperiod (Wirz-Justice et al., 2003). Changes in photoperiod in spring and autumn have been shown to affect wellbeing ratings in the general population - with this relationship being more pronounced in individuals with seasonal affective disorder (SAD). Bright and blue-enriched light is successfully used in the treatment of SAD, but also other mood disorders (Glickman et al., 2006; Strong et al., 2009; Terman, 2007; Wirz-Justice, 1998; Wirz-Justice et al., 2009). In one field study, timed and transient exposure to bright light in the field has yielded positive effects: employees reported an overall improvement in subjective assessments of performance, mood and alertness (Avery et al., 2001). Those studies employing continuous blue-enriched light exposure did not focus on quantifying the effects with regards to sleep and wake behaviour or mood, but rather on the subjective and performance effects of the light intervention (Mills et al., 2007; Viola et al., 2008). The comparison between the distinct studies is difficult. One, the nature of the assessed variables was different. Second, the interval between the assessments varied significantly across them. In view of the ratings in this study, they appear not sensitive enough to track seasonal modulation of mood. As the generally reported increase of wellbeing with photoperiod has not been observed in the control group, no conclusions for the wellbeing ratings are drawn here; consequently **hypothesis 3** remains subjected to future research.

Chronotype-specificity could be replicated: sleep- and wake behaviour, as well as loco-motor activity was modulated by the individuals' chronotype, independent of the group affiliation. Hence, **hypothesis 4** can be accepted.

Hypothesis 5 addressed the question of whether light exposure would result in phase advances in late chronotypes and in phase delays in early chronotypes. Laboratory results suggest that expected effects of blue-enriched light should not only depend on factors such as duration of light exposure (Comas et al., 2006), but also on the internal phase of the individuals being exposed to light (Roenneberg, Daan et al., 2003). Chronotype has not been used as a variable of

interest in the previously described studies involving office settings (Avery et al., 2001; Mills et al., 2007; Viola et al., 2008). Only in the study by Mottram et al. (2010), diurnal preference was assessed with the MEQ (Horne & Østberg, 1976). Melatonin profiles served as an indicator of circadian phase. The study sample was nearly homogeneous in its distribution, and included only one early type. MEQ-scores were not sensitive to the light manipulation but they were sensitive to actimetry-based sleep parameters. As shown by Kantermann et al. (2007), activity recordings are more sensitive than sleep logs in tracking adaptation to environmental changes. Here, sleep and wake behaviour remained constant over the whole study period in the experimental group, independent of chronotype. Sleep logs may however not be sensitive enough to conclude that there was not chronotype-specific reaction to blue-enriched light. A visual inspection of loco-motor activity data in the chronotype-subgroups exposed to the light change (experimental group) suggests that especially for the late chronotypes, a transient phase advance (week 3) may have occurred. Even though this trend did not reach significance, it could represent a short-term reaction to the change in zeitgeber strength. A replication with a larger sample may shed light on this question. Taken together, the data suggest that chronotype plays a central role when assessing sleep- and wake behaviour in office settings. Loco-motor activity seems to be more sensitive to chronotype differences in the field than sleep parameters, even in a small sample.

Conclusion

The findings of this field study show that blue-enriched light acts as a powerful agent, even in non-therapeutic, every-day settings and it has the potential to override seasonal adaptive behaviours. It is important to note however that the sample size in this study was relatively small. Further large-scale field studies are needed to address the generalisability of the present findings.

3. Validating the golden standard in the field – psychomotor vigilance performance in rotating shift workers

"Owls" and "larks" could share a bed, if they wanted to: chronotype influences sleep and wake behaviour in shift workers substantially. The question how reaction times are influenced by chronotype and sleep parameters in at different times of day, is one question. But how much of this remains important in real-life work situations like in rotating shift workers? Chapter 3 describes a field study where shift workers accomplished a reaction time task around the clock - in their factory.

3.1. INTRODUCTION

Circadian rhythms in cognition have played a central role in human chronobiological research in the past decades. Laboratory studies have established a solid body of evidence for circadian rhythms as well as modulations due to the homeostatic component of various cognitive functions, such as language, motor skills, executive functions, and attention. Highly controlled, artificial settings are essential for identifying the underlying mechanisms of performance variations and the crucial factors influencing time-of-day effects in cognition. Yet, translational research, from laboratory to real-life settings, has lately received growing attention, aiming at evaluating the effect size and the applicability of research results.

Variations in cognition as a function of chronotype and social time are of interest for all kind of work situations: when is a meeting optimally scheduled to receive the full attention of all attendees? How should we regulate work processes to reduce error rates and accidents in factory settings? When is the creative mind at the peak of its sharpness? All those questions relate to laboratory results, however, the translation into the real world is not trivial: does the noise in the external world jeopardize the application of laboratory results relating to cognition in real life? Or are the circadian rhythms observed robust enough to be relevant outside the laboratory?

Rotating shift workers cover the entire range of 24h within a working schedule. If there are systematic fluctuations in cognitive functions, shift workers should be affected at some point in one of their shifts, depending upon their chronotype. Also the impact of the well-described influence of sleep duration on performance patterns becomes a new twist in the field: how does differential sleep duration affect performance of a shift worker within his working conditions?

A sensible investigation of circadian rhythms in cognition in field settings is challenging: the control of influencing factors is minimal and the paradigms used for studying circadian rhythms need to be adapted to the constraints (i.e. time, direct and indirect costs, test situation, integrity of work processes etc.) given in field studies. Furthermore, field studies beyond questionnaire-related work have hardly been conducted. Experience with chronobiological paradigms in the field is scarce. The optimal paradigm to investigate circadian and homeostatic modulation in the field seems thus to be one highly sensitive to sleep deprivation and circadian rhythms. As such, the golden standard of chronobiological research, the psychomotor vigilance test (PVT), appears an adequate choice; Blatter and Cajochen (2007) state with regards to the PVT that "(…) it seems that this is the only test known so far to provide all the prerequisites to accurately measure both circadian rhythms in performance and the effects of sleep deprivation". It has been precisely characterised in numerous laboratory experiments regarding its sensitivity to sleep loss, the circadian component and its ecological and internal validity (e.g. Dorrian et al., 2005).

The research presented in this chapter aims at 1) translating the golden standard in cognitive paradigms into an adequate field version, 2) testing for time-of-day and homeostatic effects in PVT performance and 3) integrating the concept of inter-individual differences in internal time into shift work research.

3.1.1. PVT PERFORMANCE IN THE LABORATORY

The PVT (Dinges & Powell, 1985) is a test of sustained attention, i.e. assessing the ability to attend to a stimulus and to detect changes as to subsequent react with a simple motor response to this change (for a comparison with and overview of other attentional tasks, please refer to Schmidt et al., 2007). It can be classified a

simple reaction time task, as opposed to choice reaction time tasks (Dorrian et al., 2005). The task itself requires a button press, as soon as a digital counter starts running. Each trial is separated by randomly timed intervals, usually between 2s and 10s. The dependent variables assessed with the PVT are lapses (i.e. reactions > 500ms) and reaction time, whereby reaction time is usually divided into *optimal reaction times* (i.e. fastest 10%), *slowest performance* (i.e. slowest 10%) and *general performance* (i.e. either median reaction time or 10-90% of the reaction time distribution). The differentiation between performance levels has recently received validation by neuro-imaging data: Drummond and colleagues (2005) reported that fastest reaction times were associated with both, activations in the cortical attention network and in the cortico-subcortical motor network. Slowest PVT performance in contrast coincided with increased activations along the frontal midline, comprising areas of a network coined the "default mode" network (Raichle et al., 2001). The authors (Drummond et al., 2005) argued that this increase in activation reflects a partial attentional disengagement that in turn results from a diminished allocation of resources to the attention and motor network. On a behavioural level, this would then lead to impaired or bad performance.

In the past decades, numerous studies have shown that PVT performance parallels core body temperature rhythms (one of the physiological key measures of circadian rhythms) - but only if test times are extended into biological night (Cajochen et al., 1999; Dijk et al., 1992; Edwards et al., 2008; Johnson et al., 1992; Monk et al., 1997; Wright et al., 2002; Wyatt et al., 1999), such as in constant routine protocols. Yet, a direct, causal relationship between performance and core body temperature, as proposed by several authors (Kleitman, 1987; Williams et al., 1959), seems unlikely (see Blatter & Cajochen, 2007).

Typically, peak performance is measured in the late afternoon and early evening (Graw et al., 2004; Strogatz et al., 1987). After approximately 16h of stable performance, both reaction time measures and lapses start to increase (Cajochen et al., 1999; Dijk et al., 1992; Doran et al., 2001; Graw et al., 2004; Kleitman, 1923). It is assumed that the circadian drive counter-acts the rising build-up of sleep pressure (Schmidt et al., 2007), resulting in stable performance measures

within this time frame. With the extension of time-awake, performance starts deteriorating and this sensitivity of the PVT to sleep pressure is well-documented (e.g. Blatter et al., 2006; Rogers et al., 2003). Especially the slowest performance is affected by increasing sleep pressure (see fig. 3.1.), while optimal performance exhibits time-of-day effects of lower amplitude. General performance measures typically show time-of-day effects in between the two extremes (see also Graw et al., 2004).

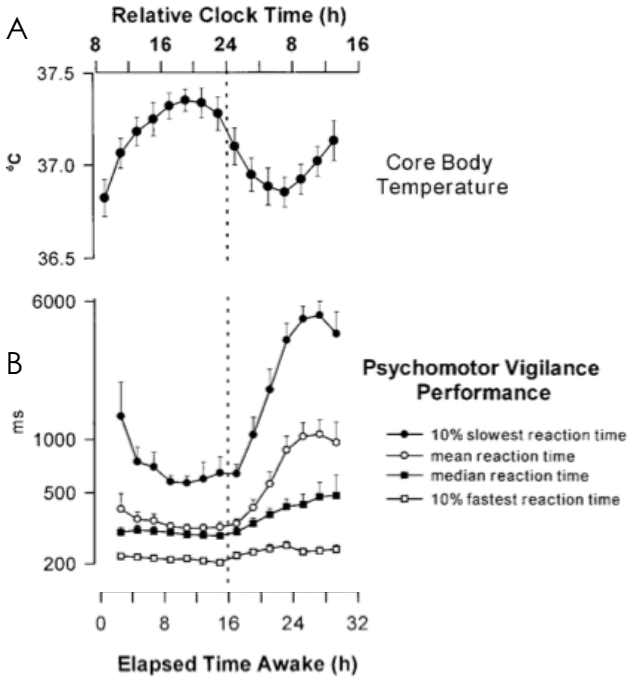


FIGURE 3.1. CBT (panel A) and PVT performance (panel B) are plotted in 2-hourly bins expressed as a function of elapsed time since scheduled wake-up. Performance remains stable for approximately 16h; at temperature nadir, performance is at its lowest, in particular regarding the 10% slowest reaction times. Data was averaged across ten participants (mean ± SE, graph modified, source: Cajochen et al., 1999).

After reaching the most prominent performance decrements at around 8:00 o'clock, performance ameliorates again, indicating the influence of the circadian-driven wake signal (Blatter & Cajochen, 2007; Bratzke et al., 2009; Carrier & Monk, 2000; Dorrian et al., 2005; Graw et al., 2004; Horne & Pettitt, 1985; Jasper et al., 2009; Jasper et al., 2010; Rogers et al., 2003; Schmidt et al., 2007; Valdez et al., 2008; Van Dongen & Dinges, 2000, 2005; Wyatt et al., 1997).

Yet, the postulation of one, causative global arousal variation cannot be fully accepted, as PVT performance was shown to be not predictive of executive

function performance (Frey et al., 2004), despite both tasks necessitating attentional resources.

The PVT belongs to a class of tests used in the experimental, stimulus-response approach (Dorrian et al., 2005) that is based on a repeated stimulus presentation requiring a timed response. This allows for a quantification of the consequences of both, sleep deprivation and circadian rhythms. Several theoretical frameworks have been proposed on the grounds of the plethora of experimental results obtained with the PVT and other tests of behavioural alertness. The "arousal theory" (Colquhoun, 1971) postulates that circadian modulation of performance reflects the variability of basal arousal levels. Previous accounts suggested that distinct oscillators were driving several types of performance, as phase-offsets were reported between different tasks (Folkard et al., 1983). Yet, if testing is extended to the biological night, task differences dissolve, challenging the multiple oscillator approach. Furthermore, factors like motivation, caffeine consumption, posture and food intake may mask the circadian rhythm - constant routines or forced desynchrony protocols allow for the control of these variables (Schmidt et al., 2007). Studies with this type of experimental set-up reported a homogeneous picture: a through in performance in the night and performance peaks in the late afternoon, early evening (Cajochen et al., 1999; Dijk et al., 1992; Wright et al., 2002; Wyatt et al., 1999). This only holds with participant samples of similar chronotype; experiments investigating the correspondence between test time and chronotype evoke benefits in case of synchrony (the "synchrony effect", e.g. Hasher et al., 2005; May, 1999).

The "lapse hypothesis" (Williams et al., 1959) suggests that the deterioration of performance during sleep deprivation is due to a "microsleep" (i.e. moments of low arousal), entailing an omission of reaction or *lapse*[14] (e.g. Dorrian et al., 2005). Yet, not only lapse frequency increases with rising sleep pressure, but also performance variability, a fact that the lapse hypothesis cannot account for. Typically, subjective performance and effort ratings do not follow the objectively

[14] Lapses can be defined as 1) omitted reactions, 2) as all reactions above 500 ms (Dorrian et al., 2005) and 3) also as reactions double the individual´s mean (Williams et al., 1959).

measured performance decrements observed during extended sleep deprivation (Dinges et al., 1992; Odle-Dusseau et al., 2010).

The wake "state instability" hypothesis (Balkin et al., 2004; Doran et al., 2001; Dorrian et al., 2005) stresses the variability of performance as an echo of dysregulated mechanisms of sleep-initiation and wake-promotion (Mignot et al., 2002; Saper et al., 2005). Here, sleep-loss derived lapses (Doran et al., 2001; Durmer & Dinges, 2005) are integrated into the more general concept of performance variability. On the other hand, compensatory effort permits normal performance, at least for a short time (Doran et al., 2001; Williams et al., 1959).

In summary, circadian modulation and the effects of sleep deprivation on PVT performance are well documented. The PVT consequently appears to be an optimal choice for first field studies. The finding that the PVT is insensitive to practice effects (i.e. a 1 to 3 trial learning curve, Balkin et al., 2004; Dinges et al., 1997; Dinges & Powell, 1985; Dorrian et al., 2005; Jewett, Dijk et al., 1999; Kribbs & Dinges, 1994; Lee et al., 2009; Van Dongen, Maislin et al., 2003) renders the test an optimal choice. Interestingly, participants seem unaware of this, as they themselves judge their own performance as improving over repeated test sessions (Lee et al., 2009).

3.1.2. PVT PERFORMANCE IN SHIFT WORKERS

Although many simulated shift work studies have been conducted in the past years, the assessment of PVT performance in real-life shift working condition is rare. Most of the simulation studies focused on night shift performance and adaptation with the help of pharmaceutical agents (e.g. melatonin, trialozam, zolpidem etc.), bright light or behavioural interventions (Boivin & James, 2005; Kantermann et al., 2010; Revell & Eastman, 2005). As we stated in a recent review, "(…) simulated shift-work experiments can only explore short-term, transient effects in carefully chosen participants (mostly shift-work-naïve volunteers), and many of the suggested countermeasures (e.g. wearing dark sunglasses or scheduled exercise) are unlikely to be implemented by workers in real-life settings" (Kantermann et al., 2010). The focus on the night shift is problematic, as sleep debt (Banks & Dinges, 2007; Van Dongen, Rogers et al.,

2003) in shift workers is chronotype- and shift-dependent. Late chronotypes get especially short sleep in the morning shift as compared to early types and *vice versa* for the morning shift (Juda, 2010). The focus on night shift work thus leads to an underestimation and misjudgement of the impact of morning shifts on sleep and wake behaviour, health and performance.

Amongst the rare field studies exploring (PVT) performance in the field, two examined the influence of napping during the night shift. In health workers, nocturnal performance and subjective sleepiness ratings improved with a 30min nap as compared to no napping (Smith et al., 2007). In marine pilots taking opportunistic naps, no positive effect was reported, probably because naps were taken at high sleep propensity times and thereby prevented severe performance decrements rather than improving it (Fergueson et al., 2008). In a recent study, the relationship between lapses and sleep duration was explored amongst a large sample of police academy recruits (Neylan et al., 2010). The authors reported a significant reduction in lapse frequency with increasing sleep duration (3.5% less lapses for each h of sleep). In addition, increasing time awake reduced the number of lapses by 0.9% in this day-working sample. All three studies used the 5min PVT version, as opposed to the classical 10min version. Even though the short version was shown to be less sensitive than the 10min version, it is reliable enough for the appreciation of sleep deprivation effects (Lamond et al., 2005; Lamond et al., 2008; Roach et al., 2006). Furthermore, maximal test duration in field settings should be held as short as possible. This will increase compliance on the participants and on their employers' side, as the costs and the non-work time are minimized.

Some studies on the effects of jetlag on fatigue, sleep and vigilance also employed the PVT (Lamond et al., 2006; Petrilli et al., 2006). In summary, these studies reported that long layovers are beneficial for sleep, sleepiness and reaction times (Lamond et al., 2006) and that sleep duration in pilots (most prominent in the

second half of a flight pattern[15]) leads to impaired performance and increased self-rated fatigue.

Such studies bear their importance in the fact that fatigue and increased reaction time measures are associated with accident risk. They thus help elucidate the key factors involved in integrating new work schedules aiming at minimizing that risk. Leger (1994) estimated the accruing costs of fatigue and sleep deprivation related accidents to be 40 billion U.S. dollars per year (but see Webb, 1995). A graphical representation of sleep-related accidents and PVT impairment as a function of time-of-day (see fig. 3.2.) suggests that the PVT also holds ecological validity (Dorrian et al., 2005). Recent work has reported a significant relationship between sleep debt and accident rates (Lombardi et al., 2010).

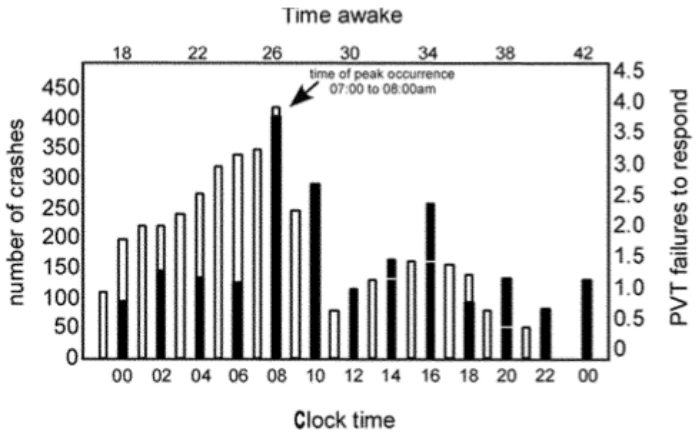


FIGURE 3.2. Frequency of motor vehicle crashes (hourly bins, n=4333) and PVT sleep attacks (i.e. no reaction after 30s, 2h-bins, n=14, 42h sleep deprivation paradigm) are plotted as a function of time-of-day. The peak of accidents coincides with the peak of sleep attacks and the following improvement in PVT performance concurs with lower accidents. In case soberness of the driver was doubted, data were excluded (Source: Dorrian et al., 2005).

Only two studies have tested PVT performance in regular intervals (i.e. several times within a shift without pharmaceutical or napping intervention) in shift workers - again, only the night shift was considered. Bjorvatn and colleagues (2006) examined the adaptation to a week of 12h night shifts (n=14) as compared to a week of 12h day shift (n=12) amongst oil rig workers in the north sea. PVT performance was assessed in 3-hourly intervals in night and day shift (e.g.

[15] A flight pattern is a certain flight path of an aircraft. In this context, one pilot may subserve a flight pattern of Australian to Asia, Asia to Europe, Europe to Asia and Asia to Australia. This would correspond to one full flight pattern.

midnight, 3:00 o'clock and 6:00 o'clock for the night shift) during the 1st, 3rd and 6th day of the respective shift.

Night shift performance was reported to gradually improve over the sessions, while daytime performance was stable and comparable to the data obtained during the last night shift. The authors concluded that shift workers continually adapted to the night shift. However, several aspects of this study may be critical to its outcome: first, no training was conducted with the participants. Even though the PVT has a low learning curve, one could assume that the Pocket PC handling may be unfamiliar for many participants. In particular, the high reaction times in the first session point towards this explanation. Second, the study was conducted with participants who explicitly complained about night work. This suggests a motivational confound, potentially biasing PVT performance.

Another study examined age-related differences in PVT performance amongst metallurgy shift workers (Kandelaars et al., 2006). Assessment was also scheduled at three time points during 12h shifts and showed that performance in older shift workers declined faster during night shifts than for in their younger colleagues. As the authors pointed out, the results are preliminary, as sample size was very small for a between-subject design (n=20).

Overall, most shift work field studies found impaired performance in the night shift, as measured either with psychometric tests (Denisco et al., 1987; Dula et al., 2001; Galy et al., 2008; Hossain et al., 2004; Monk & Carrier, 2003; Monk et al., 1996; Tilley et al., 1982; Wojtczak-Jaroszowa et al., 1978) or by sampling work performance (e.g. Åkerstedt, 2007; Bjerner et al., 1955; Dinges, 2009; Folkard & Åkerstedt, 2004a; Smith et al., 1994), but not all (Costa et al., 1979; Lowden et al., 1998). Despite this trend, two major caveats can be stated: on the one hand, data regarding morning shift performance is scarce and thus comparability jeopardized. First results indicate that early morning work is challenged by increased sleepiness or fatigue (Lowden et al., 1998), resulting probably from sleep dept. On the other hand, internal time (i.e. chronotype) has not been considered. Recent work suggests a major influence of chronotype on shift work tolerance, sleep duration, sleep quality, wellbeing and health (Juda, 2010).

In general, a characterisation of PVT performance in the field, over all shifts is missing. Additionally, none of the above mentioned studies took internal time into consideration. Given the clear circadian and homeostatic modulation in PVT performance described in the first part of this chapter, and the predominant role of chronotype with regards to sleep duration in shift workers, a comprehensive study was designed to examine those aspects in real-life condition.

3.1.3. RESEARCH AIMS

The PVT is the golden standard of vigilance measures in Chronobiology and sleep research. After being well characterised in sleep deprivation studies and constant routines, one main aspiration of this research aims to quantify PVT performance in rotating shift workers under entrained conditions in the field (i.e. rotating between morning, evening and night shifts). Furthermore, this study attempts to elucidate the relationship between sleep duration, performance and chronotype within the respective shifts. The important new factor in this approach is *chronotype*, as the concept of internal time has so far only scarcely been considered in shift work field studies (Kantermann et al., 2010).

More specifically, this study intends to quantify PVT performance in the field in the morning, evening and night shift in a within-subject design. It is assumed that the 5min PVT version does show systematic variations, even if measured in the field. As best performance is usually observed in the late afternoon and early evening, hence, the evening shift is assumed to show peak measures. In contrast, PVT performance was lowest in the early morning of CR protocols. PVT performance is thus expected to be most impaired during the second half of the night shift (**hypothesis 1**). In general, lapses are not expected, as participants are not sleep deprived such as in sleep deprivation protocols.

The circadian influence on PVT performance has been reported extensively; as a proxy to this, PVT performance is assumed to vary as a function of internal time, and in addition to variations accounted for by external time (**hypothesis 2**).

Fastest reaction times are supposed to remain unaffected by growing sleep pressure – as predicted in the context of the state instability hypothesis (e.g. Doran et al., 2001); yet, a circadian modulation has been reported in the

laboratory, and this modulation did not differ between a napping and a sleep deprivation protocol (Graw et al., 2004). Thus, fastest reaction times are hypothesized to vary as a function of internal and external time, but not as a function of time awake (**hypothesis 3**)**.** In contrast, growing sleep pressure affected slower reaction times and general performance in CR protocols (Graw et al., 2004). Increasing time awake coincides with a progressive build-up in sleep pressure, resulting in performance decrements. Unlike in sleep deprivation protocols, though, shift workers get to sleep in real-life settings. Prolonged wakefulness in shift workers is thus not comparable to the experimentally induced states of sleep deprivation. It is approximately after 16h to 18h of time awake that performance decrements are observed in simple reaction time tasks like the PVT; only the night shift allows for such long time awake intervals, at least within work and thus test times. As such, performance decrements as a function of time awake are only expected in the night shift and in slower RT and general performance only (**hypothesis 4**).

In general, sleep duration and sleep need varies between individuals (Allebrandt et al., 2010; Van Dongen & Dinges, 2001). In shift workers, a large-scale questionnaire and sleep log study reported that sleep duration in distinct shifts is chronotype-dependent (Juda, 2010). In turn, the impact of sleep duration (or more precisely, sleep debt) on PVT performance has to date been described in the context of total sleep deprivation settings and in studies investigating chronic sleep deprivation including multiple nights with partial sleep deprivation (e.g. Van Dongen & Dinges, 2005; Van Dongen, Maislin et al., 2003). Even though partial sleep deprivation is common in modern societies, it has received much less scientific attention than total sleep deprivation studies (Banks & Dinges, 2007). It is predicted that sleep debt is associated to impaired PVT performance (**hypothesis 5**). Moreover, sleep debt on a given shift is itself assumed to be dependent of chronotype, i.e. late chronotypes should get less sleep in the morning shift than early types, and vice versa for the night shift.

3.2. MATERIALS AND METHODS

Ethical approval was obtained by the Psychology Department of the Ludwigs-Maximilians-University, Munich. Participants signed an informed consent and were aware of their possibility to withdraw from the study at any point in time. Each participant was attributed a study code that was used for all materials and experimental sessions, allowing for the cross-validation and association between tests. For feedback purposes, the link between the participants´ names and consigned code was deposited with the company's physician, who is obliged to medical confidentiality. All participants received self-selected presents with a maximum value of 35€ as remuneration as well as a feedback letter with their individual results if desired.

3.2.1. STUDY DESIGN

The study took place from the 26th of May 2008 to the 11th of July 2008. All participants worked at Siemens, Cham, Germany in the same shift schedule. The lighting in the fabrication hall was equal for all participants. The factory produces low voltage controls and all participants worked in assembly lines. The shift schedule is depicted in fig. 3.3. Working times corresponded to the classical shift times: the morning shift took place from 6:00 to 14:00 o'clock, the evening shift from 14:00 to 22:00 o'clock and the night shift from 22:00 to 6:00 o'clock.

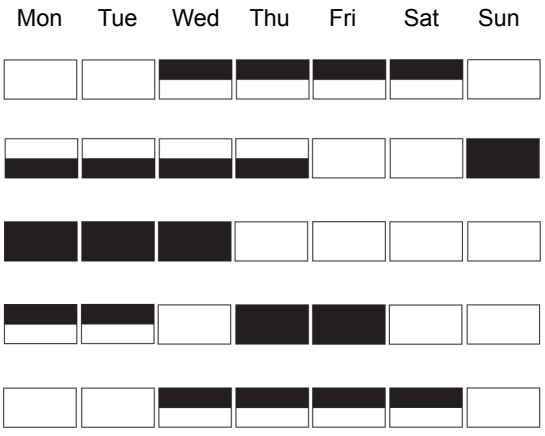


FIGURE 3.3. The Vario 4 shift schedule. The shift schedule of all participants comprised morning shifts (upper case black), evening shifts (lower case black), and night shifts (black block), regularly dispersed by free days (empty blocks). This figure shows a full rotation of four weeks with the first week of the second rotation, i.e. the last line, starting again with four morning shifts.

All participants were tested on the third day of the morning, evening and night shift to avoid carry-over effects from previous free days. Within each shift, participants were assessed four times in 2-hourly intervals at fixed times, i.e. 7:00 to 13:00 o'clock in the morning shift, 15:00 to 21:00 o'clock in the evening shift and 23:00 up to 5:00 o'clock in the night shifts. Time points were chosen to avoid interference with any social or technical routines established in the factory. Counter-balancing of the starting shift, i.e. keeping the number of participants constant who would first start with a morning, evening or night shift, was aimed for. Counter-balancing was impossible due to the voluntary participation, the time restrictions and dropouts. This issue will further be discussed under the participants' section.

Lighting in the factory hall was measured in all three shifts (morning shift: 10:00 to 11:00 o'clock, evening shift: 18:00 to 19:00 o'clock and night shift: 3:30 to 4:30 o'clock) at identical locations using the Colormeter HTC-99D (with a multi-channel sensor CT-4501-4, Gigahertz-Optik, Türkenfeld, Germany). No map of the factory hall can be shown here due to confidentiality obligations. Light measurements (Kelvin, K and lux, lx) took place at 35 equally distanced locations at a height of 1.4m and were effected within 24h ($17^{th}/18^{th}$ June 2008). While light intensity (in lx) differed significantly between the shifts ($F(2,68)= 9.6$, $p < .000$, partial $\eta^2= .22$), colour temperature of the lighting (in K) remained constant ($F(1.1,37.9)= 3.1$, $p > .05$, application of the Greenhouse-Geisser correction as Mauchley's test revealed a violation of sphericity; repeated-measures ANOVA with the between-subject factor "shift" {3}). Bonferroni-adjusted post-hoc comparisons revealed that light intensity in the night shift was significantly lower than in the morning or the evening shift (please find the raw data in the Annexe, table A.3.1).

3.2.2. PARTICIPANTS

Participants were recruited amongst rotating shift workers from the Siemens factory in Cham, Germany. *A priori* inclusion criteria encompassed no vacation during the study period, no history of neurological or psychiatric illness, normal or

corrected-to-normal vision, a minimum of three year shift work experience, full time employment as well as the affiliation to the Vario 4 shift system.

Out of approximately 100 shift workers fulfilling the inclusion criteria, 33 participants took part in the complete study. Twelve additional participants dropped out of the study either for health reasons, leaving the company or not completing the experimental tests and/questionnaires. In the latter case, either demographic data or more than two experimental test session had to be missing. The remaining participants (n=33) showed a very heterogeneous age distribution, with the majority of the participants being under 35 years old. As not only psychomotor vigilance performance (Blatter et al., 2006), but also chronotype depends on age (Roenneberg, Kuehnle et al., 2007), only data of the 24 participants under the age of 35 years was taken into account. Thus, nine participants were excluded *post hoc*.

The remaining 24 participants (eight male) had an average age of 25.33 years (± 4.5) and a mean chronotype (or $MSF^{E}sc$[16]) of 5.62 (± 1.95). All but five chronotype-estimates were extracted from the MCTQ. In case of the five participants who did not hand in the MCTQ, a sleep-corrected mid-sleep on free days after evening shifts was computed on the basis of sleep log data. The two measures highly correlate (Juda, 2010).

When the study began, participants could either be engaged in a morning shift, an evening shift, a night shift or in a split week of their shift schedule rotation (see section 3.2.1 for more details). In case of a split week, participants started the test sessions within their first full morning shift week, as all assessments took place on the 3rd day of a given shift. In total, 50% of the participants started with a morning shift, 16.7% with an evening shift test as well as 33.3% with a night shift test.

[16] $MSF^{E}sc$: Mid-sleep on free days after evening shifts, corrected for accumulated sleep debt. This is the variable derived from the $MCTQ^{shift}$ used as a quantitative measure of chronotype. The algorithm is defined in section 2.2. Yet, in rotating shift workers, free days after evening shifts are used instead of free days in general.

3.2.3. MATERIALS

Sleep Logs

The participants filled out sleep logs during the entire five week study period. Instruction on the sleep logs stressed to fill out the logs shortly after wake up. The assessed variables were: daylight exposure (Light, in h and min), wellbeing (from 0 = not at all to 10= very well), napping (Nap, time), bed-time (BT), sleep latency (Sl_Lat), sleep offset (Sl_Off), time to get up (sleep inertia, Sl_In), use of an alarm clock, sleep quality (Sl_Qual, from 0 = not at all to 10 = extremely good), whether the day in question was a morning shift (MS), evening shift (ES), night shift (NS) or a free day (Free). Any disturbance, health or mental condition that may have disrupted sleep could be indicated in an extra commentary field. The use of this commentary field was strongly encouraged. See Appendix, A3.2. for an example of the sleep log used.

Munich ChronoType Questionnaire shift (MCTQ^{shift})

To quantitatively assess chronotype in shift workers, Myriam Juda devised the MCTQ^{shift} (Juda, 2010), based on the standard MCTQ (Roenneberg, Kuehnle et al., 2007). The MCTQ^{shift} distinctly asks for sleep and wake behaviour on morning, evening and night shifts as well as on the respective free days. Juda (2010) reported that in case of a shift schedule including evening shifts, the free days following evening shifts are best suited for assessing chronotype. This result was validated by cortisol and melatonin profiles, sleep log and actimetry data (Havel, 2010).

3.2.4. PSYCHOMOTOR VIGILANCE TEST (PVT)

The PVT is a key paradigm in sleep and chronobiological research (Dinges & Powell, 1985; Lim & Dinges, 2008; Van Dongen & Dinges, 2000). In the laboratory, less time constraints act upon the choice and the length of tasks, and the duration of the task itself may sometimes be of interest. Yet, in the field, only short tasks can be used as to minimize the disturbance of the usual workflow and the potential costs related to the discontinued workflow. Lamond and colleagues

(Lamond et al., 2005) have developed a 5min PVT version on hand-held Palms validated against a 10min version. The authors concluded that the 5min version was equally useful in detecting the effects of prolonged wakefulness as the 10min version.

The PVT was implemented on a hand-held pocket PC (Hewlett Packard, HP iPAQ hx2400 Family, see fig. 3.4.). The pocket PCs disposed of WiFi, Bluetooth and mobile phone functions: they were all disabled to prevent any interference. The operation system on the Pocket PC was Microsoft .Net Compact Framework 2.0; Visual Studio 2005 was used for the implementation. The pocket PCs had a Marvell PXA270 processor with 520 MHz, a 3.5inch TFT display (64.000 colours), 64 MB RAM and 128 MB integrated ROM.

FIGURE 3.4. The HP iPAQ pocket PC (sketched on the left side) was ideally suited for the field experiments (see right side for a Pocket PC in use during the field study). It disposed of a relatively large screen and the two outer buttons could be used as response buttons.

PVT performance was always assessed last following two other tests (visual analogue scales for subjective states as well as a visual search task; not further described in here). Each PVT session lasted 5min in total. The number of trials within each assessment depended on the reaction times. In general, participants responded to 55 to 65 trials per session. In each trial, the outlines of a black square appeared in the centre of the screen on a white background (see fig. 3.5.). In the middle of the square, a "0" was displayed and served as a counter. After 3000 to 7000ms (randomly chosen, with 500ms intervals), the "0" started counting

upwards, with a maximum possible reaction time of 1200ms. Beyond this time frame, the trial was coded as unanswered (*lapsus*). The visual feedback did not correspond to the internal ms-timer, as the refresh rate of the screen could not represent these. The counter served as an indirect feedback for the participants. Participants were instructed to press the response button as soon as the counter started on the side corresponding to their dominant hand.

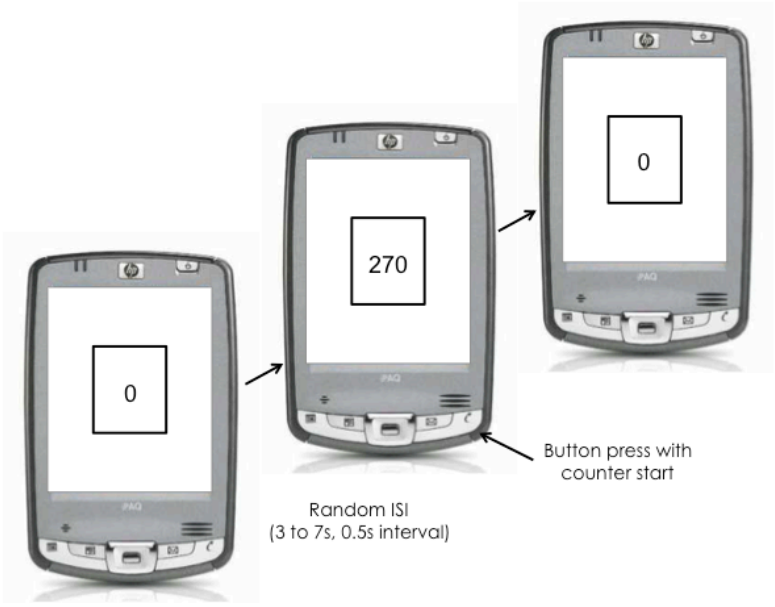


FIGURE 3.5. Trial sequence: participants were instructed to respond with the large left or right button to the start of the counter as fast as they could. After response, the counter was set back to "0" and the next trial started after the pseudo-random inter-trial interval (ITI). After five minutes, the task was automatically finished and the participants were reminded of the next test session with a goodbye message.

3.2.5. PROCEDURE

The first approach to the Siemens factory in Cham went through a large-scale questionnaire-based study from November 2007 to January 2008. Most of the findings of this enquiry are found in the dissertation by Myriam Juda (2010). During this period, shift worker rotating between the morning, evening and night shift were informed about the present experimental study. In May 2008, participants working in the Vario4 shift schedule were invited to join the study. In the week before their first experimental testing (individually tailored training plan, from 26th of May to the 5th of June 2008), all participants were trained with the

pocket PCs and the PVT whereby they all completed the experiment at least three times. Additional training was conducted either on the participants' request or in case the study team observed mal-handling of the device and/or mistakes during the task. The MCTQ^{shift} (Juda, 2010), the sleep logs and an overview of the respective test sessions were handed out to the participants from the 26th to the 30th of May 2008. The leading scientists (M. Juda and C. Vetter) were always available for further questions, feedback, or further training requests by phone or in person.

During the test session in the morning, evening and night shifts, the leading scientists prepared the pocket PCs and presented the study assistants to the participants. Every two hours, the team distributed the pocket PCs to the participants at their workstation. Participants were reminded to use the earplugs provided by the Siemens AG to reduce noise variability between workstations. Each participant was allocated to one responsible study assistant or scientist to whom to address all questions that may arise during the test session. The scientific teams also assured that the participants were not disturbed by their colleagues during the total of 15min test time. After the testing, the pocket PCs were collected, data was secured on an external hard drive and prepared for the next test session.

3.2.6. DATA PROCESSING

For the assessment of chronotype, MSF^{E}sc was computed as indicated in fig. 2.9., Chapter 2. The underlying variables were extracted from the free evening shift data sets of the MCTQ^{shift} instead of the free days section of the MCTQ.

Sleep log data provided following relevant parameters: Sl_Off, to compute individual time awake each test time point, shift-specific sleep duration before a test day (morning shift: SD_ms, evening shift: SD_es and night shift, SD_ns) and an averaged, weighted night sleep duration (SD_Av). The basis for the computation of SD_Av was the respective average SD for morning, evening and night shifts, both for work and free days. Values were weighted as a function of the relative occurrence of each work and free day. To account for inter-individual differences in average sleep duration (or sleep need, Allebrandt et al., 2010; Van

Dongen, Rogers et al., 2003), sleep duration before a test day is subsequently expressed as percental proportion of the individual sleep need (approximated by SD_Av) and will later on be referred to as *normalized sleep duration* (SD_norm).

Raw RT data are shown in the first part of the results section. For further analyses, all RT data were transformed into the percental deviation from individual mean over all test times point. This procedure corrects for inter-individual differences in baseline reaction time speed. The main variables of interest were median RT of all trials (referred to as *general* performance), top 15% of trials (*fastest* RT) and worst 15% of the trials (*slowest* RT).

As no sleep deprivation *per se* was expected, all non-responses within the 1200ms time frame were counted as lapses and those trials were not included in the analyses. Still, lapse frequency was recorded. Only complete data sets were considered for analyses.

3.2.7. STATISTICAL ANALYSES

Data sets were analysed with Excel 2008, SPSS 17.0 and 18.0, Kaleidagraph ® 3.6.4. (Synergy Software, Reading, Pennsylvania, U.S.), CircWave 1.4 (Hut, 2007) and Statistix ® 8 (Analytical Software, Tallahassee, Florida, U.S.) for Mac OS X. Variables expressing times of day (MSF^{E}sc and T_awake) are reported in decimal units, i.e. 13:30 is 13.5.

To assess time-of-day effects in the data, percental deviations from individual means were fitted one harmonic cosine functions with 24h trend-correction as a function of internal time, external (local) time and time awake. This type of analyses was conducted with Kaleidagraph. Local time corresponds to CET (UTC +2) in summer. In addition to the reported regression coefficient (r), fit amplitude is reported.

To assess the influence of time awake and sleep duration on PVT performance, polynomial fits were used. Additionally, data was de-trended in order to remove the circadian influence and to further elucidate the effect of time awake on PVT performance. This was achieved by subtracting the obtained one harmonic cosine fit function of internal time during the 12 test sessions (Carrier & Monk, 2000; Monk et al., 1997; Valdez et al., 2010).

Additionally to the rhythmicity analyses, repeated-measures ANOVAs (rANOVA) and Bonferroni-adjusted post-hoc tests assessed differences test sessions and the shifts. Effect sizes are estimated by partial η^2 (Cohen, 1988). All variables were normally distributed as assessed with the Kolmogorov-Smirnov test. The Greenhouse-Geisser correction was applied if the assumption of sphericity was violated.

3.3. RESULTS

3.3.1. GENERAL PVT PERFORMANCE

Average PVT performance is listed as a function of shift in table 3.6. The type of shift significantly modulated PVT performance (main effect of shift, $F(2,40)= 6.7$, $p< .01$, $\eta = .25$, rANOVA with the within-subject factor "shift" {3} and "session" {4}, covariates age and $MSF^{E}sc$, sex as a between-subject factor). Results for session are not reported, as the assumption of independence for rANOVAs is violated in this study design (Field, 2009). All three shifts were significantly different from one another (post-hoc tests, $p< .001$). Not age, but chronotype ($MSF^{E}sc$) significantly influenced performance (main effect of $MSF^{E}sc$, $F(2,20)= 8.7$, $p< .01$, $\eta^2= .30$) in general, but also as a function of shifts (significant interaction shift*$MSF^{E}sc$, $F(2,40)= 3.8$, $p< .05$, $\eta^2= .16$).

Average PVT performance		
Shift	Raw (in ms)	Normalised (in %)
Morning	394.6 (±49.9)	- 10.33 (±16.5)
Evening	377 (±50.7)	+ 6.83 (±12.7)
Night	380.5 (±55.5)	+ 3.42 (±12)

TABLE 3.6. PVT performance was averaged over all 4 sessions per shift; raw data (mean ±SD) was normalised to the deviation from individual baseline (mean ±SD; negative values indicate slower performance, positive faster than average performance).

A double-plot of the normalized data is shown below (fig. 3.7., following page) Lapse frequency was below 5% and did not vary as a function of shift, rANOVA

with mean number of lapses by shift, p> .05. Please consult the appendix for a closer appreciation of the raw data, table A.3.3.

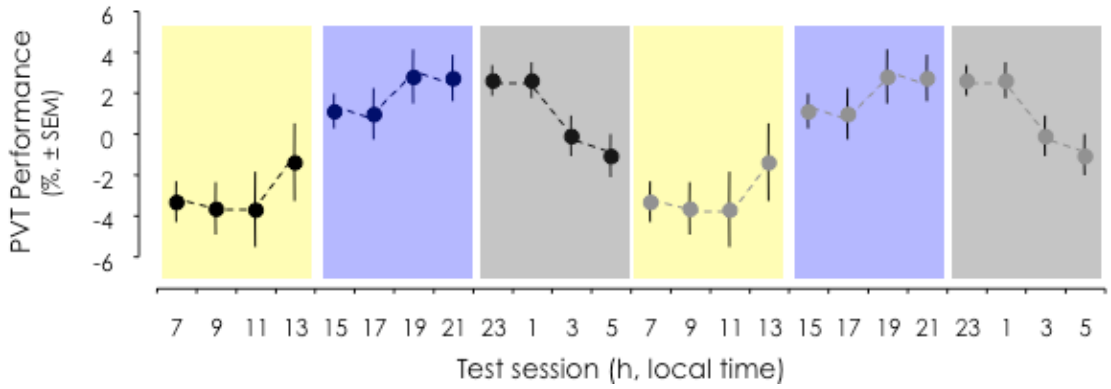


FIGURE 3.7. This double plot shows the PVT performance (mean, ± standard error of the mean, SEM) as a deviation from ind. baseline across all participants. The morning (yellow), evening (violet) and night (grey) shift all contained four test sessions, equally separated by 2h intervals.

3.3.2. PVT PERFORMANCE AS A FUNCTION OF INTERNAL AND EXTERNAL TIME

General performance was modulated by internal (r= .36, p< .000, n=288, df= 2, fig. 3.8., panel A) and by external (r= .37, p< .000, n=288, df= 2, panel B) with similar amplitudes (6.6% and 6.5%, respectively). For an example fit shown on raw data, please consult the appendix, fig A3.4.

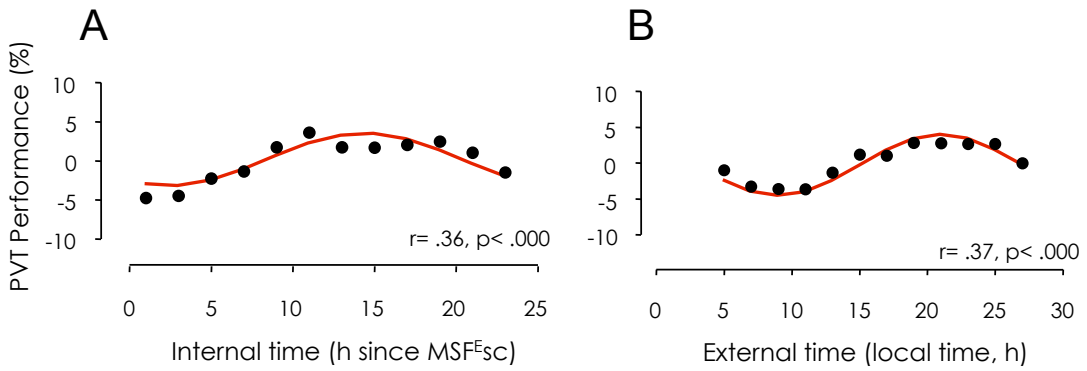


FIGURE 3.8. Binned PVT performance (deviation from ind. baseline, in %) is plotted as a function of internal (panel A) and external (B) time. The better the performance, i.e. the faster, the higher the positive percental deviation. All computations are based on raw data, as are the r-values shown here.

To examine whether internal time influences performance beyond the variation accounted for by external time, linear regression models with external time only

and both, external and internal time, were calculated; see table 3.9. for an overview of the regression models and their parameters.

Multiple regression model summary

DV	Parameter	residual SS	df	
PVT performance	ExT modell	10269.20	285	
	Ext & InT modell	9859.50	283	
		Δ residual SS	Δ df	p
		409.70	2	0.003

TABLE 3.9. The multiple regression model either included the parameter ExT (local, external time, in h) or ExT and InT (internal time, h since $MSF^{E}sc$) to account for the variation in PVT performance. The residual sum-of-squares (SS) as well as the degrees of freedom (df) are reported for both models. The deviance change is indicated under Δ residual SS and the corresponding change in the degrees of freedom are denoted as Δ df.

The multiple regression model gained explanatory power when both, internal and external time, were included (i.e. the residual sum of squares were significantly reduced, $F(2,285)= 5.88$, $p< .01$).

3.3.3. PVT PERFORMANCE AND TIME AWAKE

Time awake by test session

Sleep offset was modulated by shift ($F(2,40)=7.3$, $p< .01$, $\eta^2= .27$) and chronotype ($F(1,20)=8.7$, $p< .01$, $\eta^2= .3$). Within shifts, chronotype additionally modulated the wake-up time of shift workers (significant interaction between shift and chronotype, rANOVA, $F(2,40)=3.8$, $p< .05$, $\eta^2= .16$). Conversely, time awake was significantly different as a function of shift ($F(2,120)= 6.7$, $p< .01$, $\eta^2= .25$) and chronotype, $F(1,20)=8.7$, $p< .01$,$\eta^2= .3$. The night shift coincided with the longest time awake amongst all three shifts (post-hoc pairwise comparison, $p< .000$). Please consult table 3.10. for an overview of the mean time awake of the participants.

Time awake (in h)			
Test session	Morning shift	Evening shift	Night shift
1st	2.3 (±.3)	5.6 (±1.7)	9.3 (±1.5)
2nd	4.3 (±.3)	7.6 (±1.7)	11.3 (±1.5)
3rd	6.3 (±.3)	9.6 (±1.7)	13.3 (±1.5)
4th	8.3 (±.3)	11.6 (±1.7)	15.3 (±1.5)

TABLE 3.10. Ind. time awake (mean ±SD) was assessed with sleep logs for each test session allowing for a fine-grained analysis with regards to its effects on performance. In the morning shift, shift workers have the smallest variation in time awake, while evening and night shift display more variability.

General PVT performance

Given the significant influence of shift upon time awake, data were analysed as a function of shift. Performance in the night shift was associated to time awake (polynomial regression, r= -.37, p< .001, df=2, n=96). In the morning and the evening shift, time awake did not relate to performance variability. The de-trended data showed a similar pattern: again, morning and evening shift performance was not associated with time awake (p-values> .2), whilst night shift performance correlated highly with time awake, (r= -.57, p< .001, df=2, n=96, fig.3.11.).

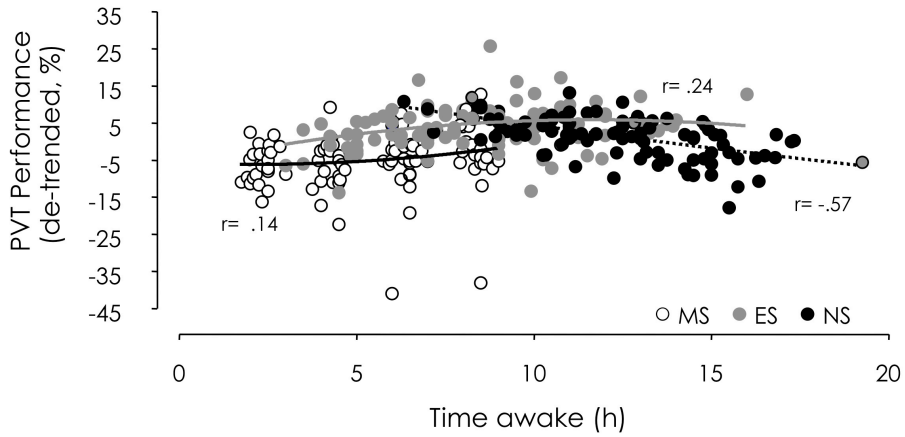


FIGURE 3.11. Polynomial fits through de-trended PVT performance as a function of shift (morning shift: white circles, black line; evening shift: grey circles and line; night shift: black circles and dotted line).

Slowest PVT performance

The 15% slowest reaction times were modulated by internal (one harmonic cosine fits, r= .24, p< .001, n=288, df= 2) and external time (r= .23, p< .001, n=288, df= 2). As for the general PVT performance, only night shift performance was significantly associated with time awake (polynomial regression analyses, r= -.38, p< .001, n=96, df= 2), while no relationship was established for the morning or the evening shift performance (p-values> .1). Again, de-trended data showed the same results: in the night shift, performance decreased with time awake (r= -.49, p< .000, n=96, df= 2).

Fastest PVT performance

Average raw data of the fastest responses are shown in table 3.12. Neither shift, nor test session significantly influenced fastest performance (rANOVA; within-subject factor shift {3} and test session {4}, age as a covariate, sex as a between-subject factor). Figure 3.13. (panel A) shows the fastest performance over all three shifts.

Fastest PVT performance		
Shift	Raw (in ms)	Normalised (in %)
Morning	317.4 (±62.3)	- 5.24% (±21)
Evening	294.3 (±76.1)	4.43% (±15)
Night	304.3 (±75.9)	0.8% (±18.9)

TABLE 3.12. Mean fastest reaction times (± SD) as well as the normalized data are listed as a function of shift (± SD).

Fastest PVT performance was significantly modulated by internal time (r= .16, p< .01, n=288, df= 2, amplitude 8.4%) and external time (r= .21, p< .001, n= 288, df=2, amplitude 11.1%), see fig. 3.13., panel B.

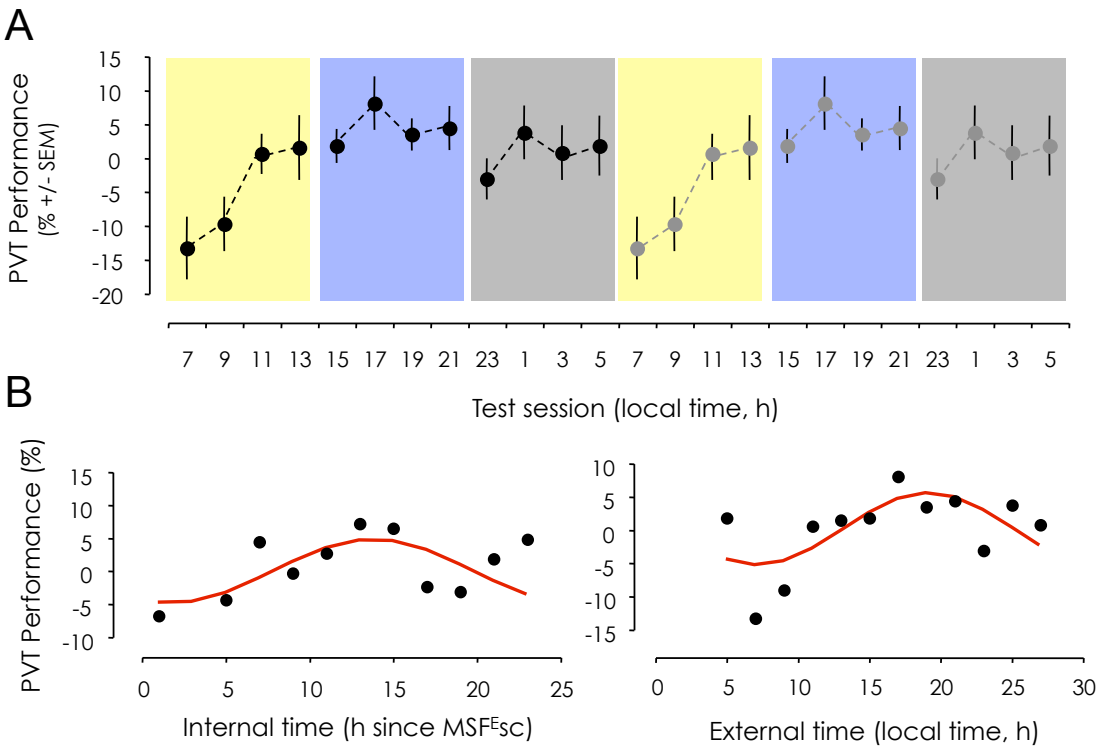


FIGURE 3.13. Panel A shows the fastest PVT performance (deviation from ind. baseline, in %, ± SE) in a double plot across all three shifts (morning: yellow, evening: violet, night: grey), measured within 2h intervals. Panel B: Fastest performance (binned data) is modulated by internal and external time.

For the shift-specific analyses, three outlier values were excluded from the morning-shift data set. A significant relationship between time awake and the fastest performance was observed uniquely in the morning shift ($r = .39$, $p < .001$, $n=84$, $df= 2$, see fig. 3.14.), but not in the evening or night shift.

The de-trended data corroborate the findings of the relationship between time awake and fastest PVT performance in the morning shift ($r = .33$, $p < .01$, $n=84$, $df= 2$), whilst evening and the night shift data remained unaffected by increasing time awake ($p > .1$).

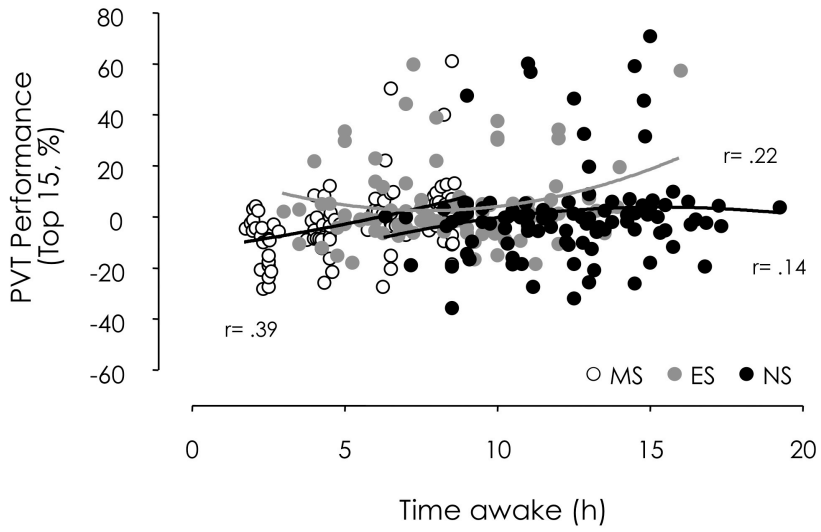


FIGURE 3.14. Fastest performance and time awake: for each test session, fastest performance was plotted as a function of time awake. The colours code the respective shift: morning = white circles and black line, evening = grey circles and line, and night = black circles and dotted line. R-values refer to the shift-specific polynomial regression analyses where only the relationship between time awake and the morning shift performance reached significance.

3.3.4. SLEEP DURATION AND ITS EFFECT ON PVT PERFORMANCE

Sleep duration by shift

Shift workers slept most in the evening shift as compared to the morning and the night shift (Bonferroni-corrected post-hoc tests, p-values< .000; average normalized sleep duration is given in table 3.15.). The main effect of shift did not reach significance, $F(2,34)= 1.7$, $p> .1$. The interaction between chronotype and shift was marginally significant ($F(2,34)= 3.2$, $p= .052$). Sleep duration has previously already been reported to be modulated by chronotype and shift type (Juda, 2010). The computations only comprised 21 participants, as three morning shift sleep duration values were missing.

SD_norm (in %)	
Morning shift	67.7 (±21.6)
Evening shift	104.1 (±15.4)
Night shift	83.1 (±17.5)

TABLE 3.15. Normalized sleep duration: SD_norm was approximated by the percentage of average sleep duration a participant had before his or her respective test day. The table shows the means (±SD).

Average performance levels per shift were computed to investigate the relationship between sleep duration and PVT performance. Two participants slept below 20% of their average sleep duration and sleep logs indicated private difficulties. The data were hence excluded from the analyses. Polynomial regression analyses showed a highly significant connection between sleep duration and performance in the morning shift (r= .7, p< .001, n=19), but not in the evening or night shift. Short sleep duration is associated to decrements in average performance, as illustrated in fig. 3.16.

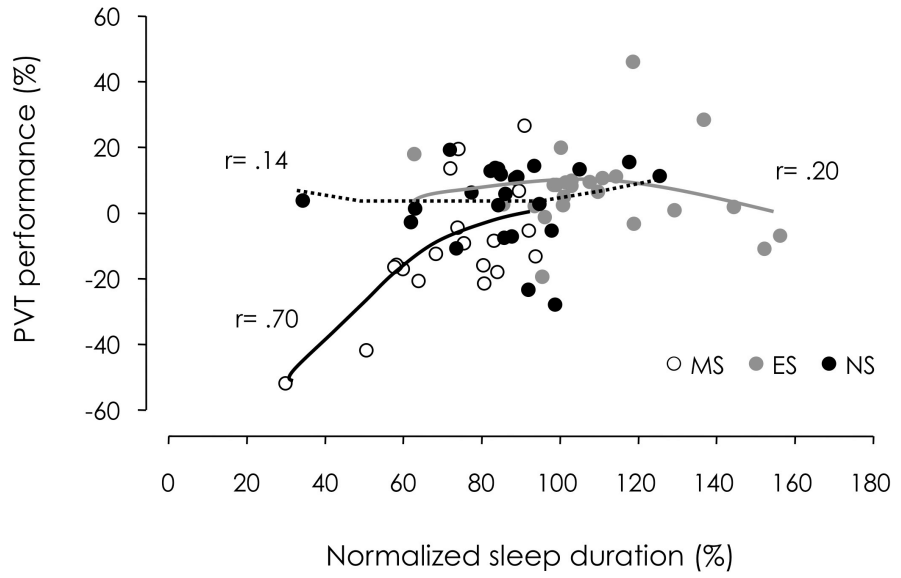


FIGURE 3.16. Sleep duration and performance: sleep duration (normalized to the percentage of ind. average sleep duration) before a test day was associated with PVT performance in the morning shift (white circles, black trend line); this is the shift in which the present sample of shift workers was sleeping the least as compared to evening (grey circles and line) and night (black circles and dotted line) shift sleep duration.

3.4. DISCUSSION

In this field study, PVT performance was assessed in real-life conditions amongst rotating shift workers. Young shift workers (< 35 yrs) were tested every two hours in the morning, evening and night shift. A 5xmin PVT version was implemented on a hand-held pocket PC. Shift workers kept daily sleep logs as to extract time awake on a test day, estimate individual sleep need and calculate shift-associated

sleep duration. PVT performance across all shifts was analysed with regards to chronotype (internal time), external time, time awake and sleep duration.

PVT performance in general showed a time-of-day effect with worst performance in the morning shift and best performance in the evening shift. Best performance was predicted in the evening shift, as constant routines have reported lowest reaction times in the late afternoon (e.g. Graw et al., 2004). Late afternoon also coincides with the latter part of the rising core body temperature rhythm, a time range coined "wake-maintenance zone" (Cajochen et al., 2006; Strogatz et al., 1987). During this period of approximately two to three h, participants - already awake –tend to maintain wakefulness and corresponds well to the stable and good performance recorded during the evening shift.

Worst performance in contrast was expected in the early morning hours of the night shift, as suggested by previous research in controlled conditions (e.g. Graw et al., 2004; Schmidt et al., 2007) and work accidents data (e.g. Åkerstedt, 2007; Bjerner et al., 1955; Dinges, 2009; Folkard & Åkerstedt, 2004a; Smith et al., 1994). The performance decrements were supposedly linked to extended wakefulness and increasing sleep pressure. In the present study, worst performance was observed in the morning shift, leading only to a partial acceptance of **hypothesis 1**. In the laboratory findings previously reported, the influence of chronotype was not considered; and this may in turn account for the phase difference in the performance through. In controlled conditions, participants are usually screened as to represent "normal", intermediate chronotypes. Thus, the conclusions drawn from those studies may be valid for the "average" population. Re-visiting the participants' MSF^{E}sc of 5.62 suggests that the studied sample is later than the average shift work population (MSFEsc = 4.21, Juda, 2010). An additional application of age and sex correction (to a virtual, 30 year old participant, please see Roenneberg, Kuehnle et al., 2007 for the underlying computation) confirms this impression: the shift workers in this study can be qualified as relatively late with an offset of +1.09 from the mean of the average chronotype (see fig. 3.17.). The relative lateness of the present study sample may explain the better night shift performance; conversely, the same explanation may hold up for the performance decrements in the morning shift. Especially late chronotypes struggle with sleep

debt during morning shift weeks (Juda, 2010), a potential reason for deteriorated performance that will be further elucidated below.

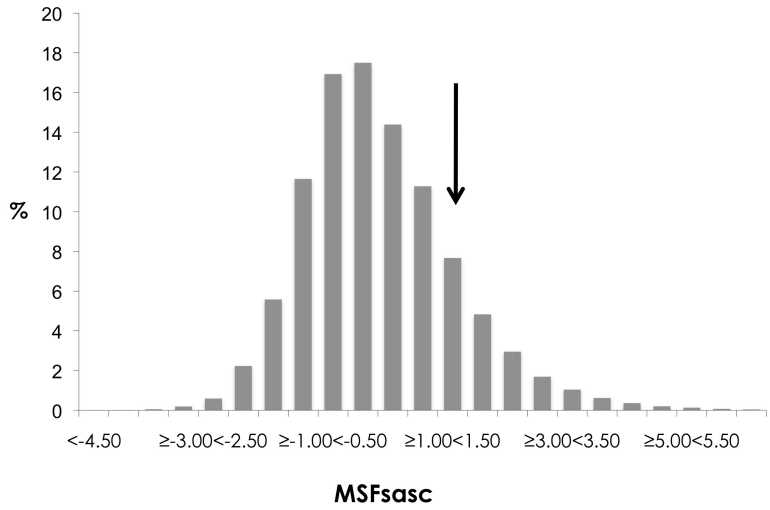


FIGURE 3.17. The MSFsasc-distribution (MSFsasc: sex, age and sleep-deficit corrected chronotype). The x-axis gives to the difference to the sex, age and sleep deficit corrected average chronotype of a participant (0.5 h bins). The distribution is based upon 70.983 MCTQ entries (in %). Here, participants had an offset of 1.09; the arrow points to the corresponding bin of the distribution.

The frequency of lapses, i.e. omissions of reactions, was very low overall shifts. Possibly, the definition criteria was set too high, as only reaction times above 1200ms were counted as lapses. This criterion was chosen, as there was very little knowledge about speed of reaction times in real-life settings. Future studies may define lower thresholds in case lapses represent the main concern. Here, the principal interest was a detailed characterisation of simple reaction times.

PVT performance in laboratory environments was significantly modulated by internal and external time. In the present study, PVT performance was systematically influenced by both, internal and external time. Furthermore, the variation pattern was significantly better explained when considering both time scales. **Hypothesis 2** can thus be accepted. This is, to my knowledge, the first experimental field study reporting systematic variations of PVT performance with regards to both, internal and external time.

Reaction time data measured with the PVT are usually divided into fastest and slowest RT as well as general performance. A differential effect of time awake was expected upon performance measures: fastest RT should be dependent upon internal and external time, but not time awake (Graw et al., 2004). A theoretical background for this assumption is given by the wake state-instability hypothesis (Doran et al., 2001; Williams et al., 1959), postulating that transient top performance was possible due to compensatory mechanisms - even though general and slowest performance measures deteriorated progressively. As predicted, fastest reaction times were significantly modulated by internal and external time. However, regression analyses of fastest RT as a function of time awake revealed a significant, adverse impact of *short* time awake in the morning shift. This result was unexpected and leads to a partial rejection of **hypothesis 3**. A possible explanation for this finding may be that participants were in a state of sleep inertia, not allowing for full access to compensatory mechanisms. The relatively bad performance levels observed in the morning shift corroborate such an assumption. Sleep inertia is a "(…) transitional state of lowered arousal occurring immediately after awakening from sleep and producing a temporary decrement in subsequent performance" (Tassi & Muzet, 2000). Jewett and colleagues (1999) reported that sleep inertia should dissipate after a time range of 2h to 3h. Performance would remain impaired, independent of whether participants stayed in bed, had a shower or ate breakfast. In the present study, participants were tested at 7:00 o'clock the first time in the morning shift and got up on average 2.3h beforehand. It is therefore plausible to suggest an influence of sleep inertia on performance levels in general, and on the fastest reaction times in particular. Yet, other studies demonstrated that even small doses of caffeine purge the detrimental effects of sleep inertia on PVT performance (Van Dongen et al., 2001). Even though participants did not report their caffeine consumption before and during a test day, one can suppose that the shift workers consumed caffeine-containing drinks (e.g. Boggild & Knutsson, 1999; Knutsson, 2004). Yet, the impact of caffeine consumption in the field amongst shift workers and its link to sleep inertia remains to be elucidated in future studies.

The influence of homeostatic sleep pressure was presumed to affect general and slowest RT selectively and in the night shift only. Several constant routine experiments have shown that it is uniquely after 16h to 18h of time awake that performance declines (Cajochen et al., 1999; Dijk et al., 1992; Doran et al., 2001; Graw et al., 2004; Kleitman, 1923). As predicted, general performance and slowest RT declined with increasing time awake, affirming **hypothesis 4**. The de-trended PVT performance showed even more severe decrements, indicating a "rescue" of psychomotor vigilance performance by the circadian drive in the early morning hours. The time point coincides with the end of the night shift. Thus, without the circadian input, performance should be more impaired, as observed in the present study. In addition, early chronotypes display the longest times awake in the night shift, as they usually get up early in the morning, even after night shifts (Juda, 2010).

Sleep duration in shift workers depends on chronotype and shift (Juda, 2010), a result replicated amongst this sample. Late chronotypes sleep less during morning shift weeks than early chronotypes and *vice versa* in the night shift. Here, an association between sleep duration, i.e. sleep debt, and performance was found solely in the morning shift, corroborating the role of chronotype, and thus, **hypothesis 5**. As the study sample comprised on average late chronotypes, impaired performance parameters were particularly expected for the morning shift. The results are in accordance with previous studies amongst police academy recruits, performing better (i.e. reduced number of lapses) as a function of previous night sleep duration. Yet, the present study expands these findings, as it shows that also reaction times depend upon sleep duration. Last, the role of chronotype in studies linking sleep duration to cognition is enforced, as sleep duration itself is chronotype-dependent.

Limitations of the study

The cognitive profiles established amongst rotating shift workers in a field study setting are to my knowledge the first of their kind. In general, the results obtained in this noisy real-life setting are coherent with laboratory-derived hypotheses. Yet, the present study has several limitations: First, counter-balancing of the groups

within the shift schedule failed. Ideally, an equal number of participants would have started the performance tests in the morning, evening and night shift. Due to deliberate participation, dropouts, and the impossibility to re-schedule all participants of the study, this was not achieved. Fifty percent of the participants had their first test in the morning shift, i.e. the shift in which worst performance patterns were recorded. One may argue that this was the reason for the observed performance decrements. However, the learning curve in the PVT corresponds to one to three trials (Balkin et al., 2004; Dinges et al., 1997; Dinges & Powell, 1985; Dorrian et al., 2005; Jewett, Dijk et al., 1999; Kribbs & Dinges, 1994; Lee et al., 2009; Van Dongen, Maislin et al., 2003) and all participants completed three entire 5-min PVT sessions before the study started. Even though the possibility that failed counter-balancement influenced the results cannot entirely be excluded, it seems very unlikely.

Second, light environment could not be controlled, but only be taken into account. In all three shifts, and at all workstations of the participating shift workers, colour temperature (in Kelvin, K) and light intensity (in lux, lx) were measured. Statistical analyses revealed a constant level of colour temperature. Light intensity though, was lowest during the night shift. Bright light is an effective zeitgeber for the circadian system (Beersma & Daan, 1993; Czeisler et al., 1989; Honma et al., 1987; Khalsa et al., 2003). In simulated night shift studies, ambient bright light (1.000lx) led to enhanced subjective and objective performance measures as opposed to dim light (30lx, Campbell & Dawson, 1990). During the night shift of the present study, ambient light had on average 590 lx, a light intensity that cannot be qualified as a dim light condition. Additionally, colour temperature, i.e. the spectral composition of the light source, is of major importance for its circadian efficiency[17] (Brainard et al., 2008; Cajochen et al., 2005; Revell et al., 2005; Warman et al., 2003; Wright et al., 2004). Here, colour temperature was comparable between shifts, and the differences in light intensity are within the range of usual light environments. Therefore, the probability that

[17] Please refer to the General Introduction and Chapter 2 for more information about the zeitgeber light, the underlying physiological mechanisms, its influence on the circadian system as well as on sleep and wake behaviour, mood and performance.

differential light environments biased performance patterns in the night shift is small.

Last, sample size was relatively small and especially for the association between sleep duration and cognitive performance, replication studies are needed. The range of sleep debt in the morning shift was relatively narrow: only four participants obtained below 60% of their average, needed sleep duration. More data in the range of 30 to 60% of sleep duration need to be sampled, especially as inter-individual differences in vulnerability to sleep deprivation has been described (Van Dongen & Dinges, 2001). Any analysis considering potential inter-individual differences relies on larger sample sizes, even more so if the data was collected in the field.

Conclusion

This study demonstrates that internal and external time modulate performance in rotating shift workers within a range of approximately 10% across all shifts. In a sample of relatively late chronotypes, the morning shift represents the major challenge for performance levels. Short sleep duration (as usually observed in late chronotypes during morning shift) may be causative for performance decrements in the morning shift itself; additionally, the short time awake of shift workers in the morning shift contributes or indirectly influences performance in the morning shift. Extended wakefulness, as typically associated with night shifts, jeopardises performance, even in populations of late chronotypes. With PVT performance now being well characterised in a real-life situation, further experimental paradigms examining higher cognitive functions can be introduced to the field (Schmidt et al., 2007).

4. Time-of-Day effects in task switching performance: a functional magnetic resonance imaging study

Understanding the impact of internal time on the brain's metabolism and energy consumption is a pre-requisite for fundamental research. The state-of-the-art methods investigating the brain "in action" rely on a reproducibility and comparability between measurements. This chapter tries to quantify the influence and thus derive the relevance of chronotype and time awake upon the neural underpinnings of cognition in classical, everyday research settings.

4.1. INTRODUCTION

In the past two decades, functional magnetic resonance imaging (fMRI) has become a golden standard for the investigation of cognitive processes and their neural correlates. The blood-oxygen level dependent (BOLD) signal recorded during experimental sessions is thought to reflect relative energy consumption of the brain and hence task-specific activation or inhibition (Gazzaniga, 2009). A literature search of neuro-scientific databases (Pubmed & Sciencedirect) resulted in up to 25.113 hits with the keywords "fMRI" and "cognitive". In the quest of understanding human behaviour and reasoning, the non-invasive *in vivo* tracking of brain activation during many different types of processing, i.e. sensory processing, pain perception, cognitive functioning or meditation, can provide information about the brain's plasticity, functional connectivity and specialisation.

A wide range of cognitive functions, such as vigilance, selective attention, executive functions and language, is influenced by the homeostatic and the circadian component on the behavioural and physiological level (Schmidt et al., 2007). To date, those aspects 1) have hardly been studied with fMRI and 2) not been considered as a potential source of variability in the BOLD signal associated with cognitive functions. The present study tries to understand the impact of internal time and time awake (the homeostatic component) on the neural correlates of time-of-day dependent behaviour. In case of systematic variations, future fMRI research designs should be realigned not only to social time, but also

to internal time. Previous research has mainly manipulated arousal states – sleep deprivation paradigms, pharmacological agents, or circadian factors as light and extreme chronotypes. This study takes place within the typical time frame of usual fMRI studies (8:00 to 20:00 o'clock), raising the question whether the combined influence of circadian and homeostatic processes within a day systematically modulates the BOLD signal.

For this investigation, the chosen test is task switching, a paradigm investigating the mechanisms of cognitive control. Below, an overview of the task itself, its theoretical background and its neural correlates is given. Then, the results of the few previous studies investigating time-of-day effects in cognition and their neural correlates are reported. Yet, this research is not aiming at an investigation of task switching mechanisms *per se*. The task switching paradigm is used as a proxy for cognitive tasks modulated by the circadian and homeostatic component on a behavioural level in general.

4.1.1. THE TASK SWITCHING PARADIGM: THEORY AND NEURAL CORRELATES

A brief theoretical background

In the late 1920ies Jersild devised for the first time a task switching paradigm, asking his participants to time themselves while performing two simple arithmetic tasks (Jersild, 1927). A list of two-digit, fully visible numbers was presented to the subjects and they either had to subtract three or to add six. In case the two mathematical calculations were mixed within one list, participants took more time to finish it as compared to their blocked performance. Hence, the mixing of the two tasks resulted in *costs* (see also Allport et al., 1994; Monsell, 1996; Monsell, 2003; Rogers & Monsell, 1995). In another series of experiments, Jersild showed that participants were much faster in finishing a mixed list – this time, the addition task was exchanged with a simple antonym-naming task (e.g. word: man, the correct response would be: woman). The conclusions that Jersild drew from these results about 80 years ago are still valid today: 1) switching between two tasks causes "*switch costs"*, but only in case of ambivalent stimuli, i.e. that stimuli are not evocative the nature of the task. 2) The switch costs are substantially reduced (or even turned into an acceleration) if the stimulus is uniquely associated to one task,

as for the antonym-naming task. In other experiments, Jersild also demonstrated that 3) task complexity increased the switch costs, e.g. by using 2-digit numbers for the arithmetic operations. Even though Jersild's work has been replicated with more objective reaction time methods by Biederman and Spector in a series of experiments (Biederman, 1972; Spector & Biederman, 1976), it was not before the 1990ies that the interest in cognitive control mechanisms in task switching paradigms resuscitated (Monsell, 2003).

Cognitive control mechanisms are active in every deed, behaviour and thinking process of ever day life: we need to adapt our actions, "procedural schemes" (Norman & Shallice, 1986) or "task sets" (Monsell, 1996) to achieve goals, may they be to make coffee or wash the dishes. All those activities involve *inter alia* visual search, memory processes to maintain the goals, sequencing of movements, guiding of attention and updating the goals to potentially re-direct behaviour. Monsell (2003) suggests that "(...) effective cognition requires a delicate "just-enough" calibration (…) of endogenous control": on the one hand, the ongoing task should be protected from nuisances. On the other hand, fast adaptation and flexibility to environmental changes represent major criteria for an efficient control system.

Several task switching paradigms have emerged since Jersild's experiments: alternating-run paradigms (Rogers & Monsell, 1995) comprise two tasks (A and B), but to reduce the memory load, the participants know *in advance* that every n^{th} trial the tasks change in a predictable, constant manner (AABBAABB…). By modulating the inter-stimulus-interval (ISI), *preparation time* before the next trial can be manipulated. Yet, this practice concomitantly also varies time for the last task-set to dissipate (Monsell, 2003), potentially reducing interference. The quantification of switch costs relies on the comparison between switch trials (AB or BA) and repetition trials (AA and BB, see fig. 4.1. for a schematic illustration). The second common task switching paradigms relies on cueing whilst the task sequence itself is unpredictable for the subject: cue onset either precedes the task or coincides with it. The cue can be explicit or rather implicit, i.e. the location on the screen indicates the task to engage into. Again, a variation of the stimulus

onset asynchrony (the time between the cue and the onset of the stimuli, SOA), allows a manipulation of preparation times[18].

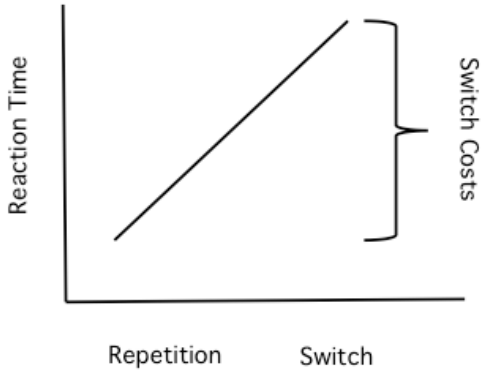


FIGURE 4.1. Switch cost computation: repetition trial RT (AA & BB) is subtracted from switch trial RT (AB & BA) to quantify switch costs between two task sets.

Long SOAs usually result in reduced reaction times (RT) and switch costs (Logan, 2003; Monsell, 2003; Monsell et al., 2003). This interpretation refers to the reconfiguration view (Monsell & Driver, 2000) suggesting that the longer one has time to "re-set" the mental configuration, the lower the switch costs. In contrast, the encoding view attributes this effect to basic perceptual and mnemonic processes interfering with efficient task solving. Consequently, long SOAs support the dissipation of the previous task set and hinder priming effects. Furthermore, consistent preparation effects may *inter alia* be ascribed to an experimental bias of within-subject designs (Altmann, 2004, 2007; Logan & Bundesen, 2003; Logan et al., 2007). In general, switch costs most-probably depend on multiple causes (Monsell, 2003) and echo enhanced demands upon cognitive control mechanisms in order to control for (perceptual, mnemonic and top-down) interference (Allport et al., 1994; Logan, 2004; Rubinstein et al., 2001).

Neural correlates of task switching performance

Patients with frontal lobe lesions generally show deficits in "executive" tasks, i.e. impairments in the organization of goal-oriented action, inhibition deficits (e.g.

[18] Preparation time and residual costs (reaction time costs remaining independent of the amount of preparation time given to the participants) and their relation to cognitive control and consciousness is discussed elsewhere (Meiran et al., 2002).

prepotent response suppression), decreased focused attention and the organization of action sequencing (for a conceptual overview of executive functions, see Alvarez & Emory, 2006; Logan, 1985; Norman & Shallice, 1986; Stuss & Alexander, 2000). Cognitive control is an inherent component to all those tasks. Patients with focal left-hemispherical lesions were reported to show deficits in task switching performance, suggesting that the left frontal, but not the right frontal lobe plays a specific role in cognitive control (Rogers et al., 1998). This specialization of the left-hemispheric network has subsequently been corroborated using positron emission tomography (PET). Meyer and colleagues (1997) compared the neural activity associated to a single task with the one recorded during the dual task condition. The authors described mainly left-hemispheric activation patterns. An fMRI study amongst patients with focal left- or right-hemispheric frontal lobe lesions conducted by Aron et al. (2004) support the predominant role of the left hemisphere in cognitive control. Impaired switch performance in right-hemispheric lesion patients was attributed to deficitary inhibition of prepotent responses. Impaired task switch performance in patients with left-hemispheric lesions however was linked to weakened cognitive top-down control.

In the PET study by Meyer and colleagues (1997), the brain regions supporting dual-task performance were the dorsolateral prefrontal cortex, the posterior parietal lobe, the anterior cingulate (brain regions all associated with attention networks, Corbetta et al., 2000; Corbetta & Shulman, 2002; Gitelman et al., 1999; Mesulam, 1990; Posner & Petersen, 1990) as well as the premotor area – i.e. an area of anticipatory goal-oriented movement. The only right-hemispheric activity that Meyer and colleagues (1997) detected was localized in the cerebellum.

Subsequent fMRI and EEG studies investigating the functional neuroanatomy of cognitive control in task switching performance report consistent pattern of left-hemispherical activation in following areas: (lateral and medial) prefrontal cortex, insula, supplementary motor area (SMA) and pre-SMA, intra-parietal sulcus (IPS), cuneus, precuneus, posterior cingulate gyrus, and bilaterally in the thalamus (Brass & von Cramon, 2002; Braver et al., 2003; E.A. Crone et al., 2006; D´Esposito et al., 1995; Derrfuss et al., 2005; Dove et al., 2000; Dreher et al., 2002; Gurd et al.,

2002; Hyafil et al., 2009; Kimberg et al., 2000; MacDonald et al., 2000; Ravizza & Carter, 2008; Rubinstein et al., 2001; Rushworth et al., 2002; Serences et al., 2004; Sohn et al., 2000; Szameitat et al., 2002; Yantis et al., 2002; Yeung et al., 2006). The thalamic regions, the (pre) frontal cortex, parietal regions, the SMA, as well the cingulate cortex and the cerebellum are functionally inter-connected by the fronto-striatal and fronto-cerebellar circuits (Heyder et al., 2004).

4.1.2. TIME-OF-DAY EFFECTS IN TASK SWITCHING PERFORMANCE

Early studies on time-of-day effects in cognition led to the conclusion that the best time to performance a task would depend upon the nature of the task (Folkard, 1983): the time points of troughs and peaks in performance were substantially differing from one task to another. Subsequent studies explicitly focused on the investigation of the underlying mechanisms in time-of-day effects in cognition in forced desynchrony protocols or constant routines. In those artificial lab settings, the dip in cognitive performance rhythms could be tackled between 5:00 and 7:00. The large between-task offset in rhythmicity vanished and performance decrements gathered around core body temperature nadir (Cajochen et al., 1999; Dijk et al., 1992; Johnson et al., 1992; Monk et al., 1997; Wright et al., 2002; Wyatt et al., 1999). Recently, Kyriacou and Hastings (2010) pointed out the double-role of the circadian oscillator on cognitive performance: The "(…) circadian oscillator mediates cognitive performance directly, as well as indirectly, through sleep." In natural day-night conditions, with no suspension of sleep, the combined output of the two processes can be diverse in terms of phase and amplitude, and diverge from the typical parallelism to core body temperature observed in constant routines and sleep deprivation protocols (Rogers et al., 2003).

On a behavioural level, three studies have investigated time-of-day effects in task switching performance. Couyoumdjian and colleagues (2009) reported increased switch costs after a night of total sleep deprivation – even after correcting for the decrease in general arousal levels. A second study by Heuer et al. (2004) investigated whether sleep deprivation equally influenced shifts in stimulus-

response mapping and shifts between two types of judgments. While the switch costs derived from the 20% of the slowest reaction times were equally affected by sleep deprivation, the switch costs obtained from the 20% of the fastest reaction times showed an increase after a night of sleep deprivation, but only in the domain of judgement shifting. Hence, sleep deprivation seems to affect performance in mental set-shifting in particular, over and above the influence of arousal levels and motor-response mapping.

In a 28h constant routine, Bratzke et al. (2009) investigated task switching performance with regards to both, the circadian oscillator and the homeostat. Task switching performance was tested every three hours in an alternating-run switch paradigm, adapted from Heuer's experiments (2004). General reaction times and switch costs showed a profile consistent with the influence of both, circadian and homeostatic processes: up to 21:00 o'clock, performance and switch costs improved with a subsequent decline reaching its minimum at around 4:00 o'clock. Ensuing performance improved again in the morning, reaching near-baseline levels from the previous day – even though the participants were still sleep deprived. This dynamic suggests a circadian-driven improvement of performance. Subjectively, participants started to feel progressively tired only after 21:00 o'clock.

To date, no investigation of the time-of-day effects in relation to the neural activations underlying task switching performance has been conducted. However, there is a growing body of evidence for neural correlates of time-of-day effects in cognitive performance. A recent study by Schmidt et al. (2009) demonstrated differential activation in the locus correlus and the supra-chiasmatic area for the fastest reaction times in extreme chronotypes. Late chronotypes exhibited significantly enhanced task-related neural activity in the evening as compared to early types. In turn, early types had higher thalamic activations in the evening than late ones. This enhanced BOLD response was linked to increased measures of global reaction times: late chronotype reacted faster in the evening, exhibiting approximately one third of the relative thalamic activation.

The thalamus serves as a relay station for arousal signals to the cortex (Aston-Jones, 2005; Portas et al., 1998). By manipulating arousal levels (e.g. sleep

deprivation or pharmacological agents), the results of previous studies corroborate that low arousal levels usually coincide with enhanced thalamic activation (Coull et al., 2004; Foucher et al., 2004; Portas et al., 1998; Schmidt et al., 2009; Thomas et al., 2000; Vandewalle et al., 2009; Vandewalle et al., 2006). Portas et al. (1998) suggested that this increase in relative neural activity would subserve a compensatory mechanism, maintaining attentional performance despite low arousal levels. After the first 24h of sleep deprivation, PET-study results suggest that thalamic areas are significantly *deactivated*, just as prefrontal and parietal regions (Thomas et al., 2000). The authors suggested that task complexity and task duration influence the neural recruitment and the potential "rescue" of performance during sleep deprivation: in case of a simple task, short-term enhancement of the neural response may be possible and potentially prevent performance decrements.

In summary, task switching performance (general reaction times as well as switch costs) is modulated by the homeostatic and the circadian process when investigated in the sleep deprivation context. The neural underpinnings of task switching have not been examined in the light of internal time. Few fMRI studies have up to now integrated both, the circadian and the homeostatic component in their research questions, but those who have, suggest that systematic variations in reaction times come hand in hand with modulations of the neural response (but see Schroeter et al., 2006 for an example of stable neural response patterns in the primary visual cortex during a 10h test day).

4.1.3. RESEARCH AIM

This study was designed to investigate and systematically quantify potential time-of-day effects in the BOLD signal in the task switching network – a task *known* to show circadian and homeostatic influences in its behavioural output.

Participants are measured four times a day to allow for a quantification of the diurnal dynamics. The task switching experiment is intertwined with control blocks, exclusively requiring a motor response to stimuli appearance. To exclude novelty or sequence effects as an explanation for variations in the neural activation, an additional sample of participants was measured with the identical

tasks, but with a temporal offset of 2.5h. Internal time and time awake of the participants was taken into account and quantitatively assessed.

In line with laboratory results of behavioural task switching indices, a decrease in both, RT performance and switch costs, over the day is expected (**hypothesis 1**). In general, as the control condition only requires simple motor responses to the stimuli appearance, task-specific reaction times and switch costs should be higher in the experimental condition. Variations in basic vigilance levels may similarly modulate RT in the control and the experimental condition. Consequently, a task switching specific time-of-day effect should only be observed in task-specific switch costs. Subjective sleepiness scores are not expected to increase, but to rather stay constant, as earlier work suggests an augmentation only later in the evening. Task performance (switch costs and reaction times) and relative neural activations, especially in the thalamus, are therefore assumed to be independent of subjective sleepiness ratings.

There are, as described above, not many studies demonstrating time-of-day effects using fMRI technology. As circadian and homeostatic components modulate the behavioural output, time-of-day effects in the neural network underlying task switching performance are expected (**hypothesis 2**).

The thalamus represents a key structure in the mediation of arousal to cortical regions. The present study attempts to quantify the dynamics in thalamic activity over the course of a day without a manipulation of arousal levels *per se*. The thalamic BOLD signal is assumed to vary systematically (**hypothesis 3**) as a function of time-of-day. Whether the variations in relative thalamus activity relate to behavioural output in the task switching performance is an open question to be explored.

4.2. MATERIALS AND METHODS

This study obtained ethics approval by the ethics committee of the Medical Faculty of the Ludwigs-Maximilians-University, Munich. All participants signed an informed consent and were aware of their possibility to withdraw from the study at any point. Study materials were recoded to assure anonymous data handling and data analyses. Participants received 100€ as remuneration as well as a DVD with their anatomical MRI scans.

4.2.1. STUDY DESIGN

The main study took place from the 19th of July 2009 and the 9th of August 2009 at the University Clinic Großhadern in Munich, Germany. Each participant was measured on one weekend day, i.e. a Saturday or a Sunday. A maximum of four participants spent the day in the Radiology Department of Großhadern. The total number of participants was 15. Four scanning sessions took place between 8:30 and 19:30 o'clock, from now on referred to as time point 1 to time point 4 (TP_1 to TP_4). Participants were allotted to one out of four chronotype categories (MSFsc[19] 3:00 to 3:59, 4:00-4:59, 5:00-5:59 and 6:00-6:59) to reduce variability between subjects. During a test day, one participant per category was measured. Participants arrived at the scanning facilities 45min before their respective first scan, i.e. the earliest chronotype was scanned first, followed by the participant of category 2 and so forth. As it has been suggested that light exposure influences the BOLD signal to subsequent cognitive task performance (Vandewalle et al., 2007; Vandewalle et al., 2010), participants were not allowed to exit the Radiology Department during the experimental day.

To differentiate between time-of-day effects and sequence effects, a second sample of participants (n=4) was assessed only from TP_2 to TP_4. This second study took place on the 18th of October 2009 and will in the following be referred to as *sup-sample* (derived from supplementary). Figure 4.2. on the following page summarizes the study design.

[19] MSFsc is the abbreviation for mid-sleep on free days with sleep debt correction and is a quantitative measure of chronotype. The MCTQ and the underlying computation are detailed in the Materials part of this chapter.

The scans were scheduled before the weekend of transition to wintertime, a change known to influence human activity profiles (Kantermann et al., 2007) and thus sleep and wake behaviour - important variables in the context of this study.

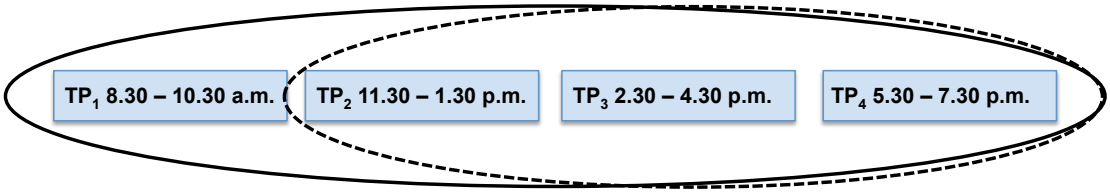


FIGURE 4.2. Study design: the participants of the main study underwent four scans, i.e. TP_1 to TP_4 (continuous line), while the sup-sample only participated in three scans, TP_2 to TP_4 (dotted line). Between each of the 30min long assessments, participants had constant pause intervals of 2.5h. The order of the participants within a test day remained constant.

4.2.2. PARTICIPANTS

Participants were recruited amongst medical students of the Ludwig-Maximilians-University, Munich. Fifteen students fulfilled the a *priori* inclusion criteria, namely an MSFsc between 3:00 and 6:59, a lateralization quotient (L.Q.) above 70 as assessed with the Edinburgh Handedness Questionnaire, aged under 30 years, non-smokers and no record of psychiatric or neurological disease. For safety reasons, students with large-scaled tattoos or implants were excluded from the study. All female participants took a pregnancy test before being admitted to the scanning facilities. The same inclusion and exclusion criteria were entailed on the second sample of four participants. All participants had normal or corrected-to-normal vision.

Out of the 15 main study participants, RT was lost for four of them due to technical problems and leading to their *post hoc* exclusion. For three other participants, RT data was not recorded for the first test session. Yet, the remaining three data sets were judged sufficient to infer about their task comprehension and compliance to the instructions. Additionally, RT data from two participants in the sup-sample were lost due to technical problems for TP_2. The two remaining data sets were used to assess their compliance and understanding of the task, but were excluded from analyses.

All together, eleven participants (six female) composed the sample of the main study. On average, they were 23.8 years old (±3.54) and had a mean MSFsc of

5.04 (±1.07). The sup-sample (n=4, three female) did not differ in age or chronotype from the main study sample (average age = 24.75 yrs ±1.71 and mean MSFsc = 4.08 ±1.09) as examined by a t-test for independent samples ($p > .05$).

4.2.3. PROCEDURE

Before the study, all potential participants filled out the Munich ChronoType Questionnaire (MCTQ, Roenneberg, Kuehnle et al., 2007) and the Edinburgh Handedness Inventory (Oldfield, 1971). Ten days before their respective scanning dates, all participants fulfilling the inclusion criteria, wore actimetry devices and continuously filled out sleep logs. Training sessions for the task switching paradigm (three runs) were scheduled one to three days before the actual measurement day and refreshed in the morning of the test day itself (one complete session). By means of the Karolinska Sleepiness Scale (KSS, Åkerstedt & Gillberg, 1990) levels of subjective sleepiness was assessed before each scanning session. During each of the four scanning sessions the participants engaged in the task switching experiment, after having completed anatomical scans, and two other, non-cognitive tasks not further described here. Altogether, each scanning session took 32min, with the task switching part lasting 11min.

4.2.4. MATERIALS

Sleep Logs

All participants kept a 10-days sleep log whereby following parameters were assessed: bed-time (BT), sleep latency (Sl_Lat), sleep offset (Sl_Off), time to get up (sleep inertia, Sl_In), use of an alarm clock, alertness to bed and when waking up (from 0 = not at all to 10 = extremely alert), whether the day in question was a free or a workday (incl. work times) and the amount of time they spent outdoors. A commentary field was available for comments the participants qualified as being important with regard to their sleep timing and/or quality. See Appendix for an illustration of a sleep log (fig. A2.1.). The instruction emphasized to fill in the sleep log every day after wake-up. The mid-sleep on work and free days (MSW

and MSF) were calculated for each participant and Sl_Off served to calculate time awake on the test day.

Karolinska Sleepiness Scale (KSS)

The KSS was developed by Åkerstedt and Gillberg (1990) to assess subjective levels of sleepiness. In this study, a German version of the KSS (see Appendix, fig. A4.1.) with the original 9-point Likert scale was used. Five verbal anchors ranging from "very alert" (*dt.* sehr aufmerksam, 1), "alert" (*dt.* aufmerksam, 3), "neither alert nor sleepy" (*dt.* werder aufmerksam noch schläfrig, 5) to "sleepy, but no difficulty remaining awake" (*dt.* schläfrig, kann aber die Augen offen halten, 7) and finally "extremely sleepy – fighting sleep" (*dt.* sehr schläfrig – schlafe fast ein, 9) servd as orientation labels for the Likert scale.

Actimetry

All subjects continuously wore an activity-recording device (Daqtix GmbH, Oetzen, Germany; see section 2.2. for a description) around their preferred wrist for ten days before the testing day. See appendix A2.2. for an example of the actimetry log where subjects could track the time intervals they did not wear the device.

Munich ChronoType Questionnaire (MCTQ)

All participants filled out the MCTQ (Roenneberg, Kuehnle et al., 2007) prior to their participation in the study. Please refer to section 2.2. for a detailed description of the MCTQ. The main variable of interest was the MSFsc as an estimator of chronotype.

Edinburgh Handedness Inventory

The German version of the Edinburg Handedness Inventory (Oldfield, 1971, see Appendix, fig. A4.2.) allows for a quick approximation of lateralization by computing a laterality quotient (L.Q.). A L.Q. of a minimum of 70 (i.e. primarily right-handed) served as inclusion criteria for the participants to control for

potential inter-individual differences in lateralization. Participants are asked ten questions relating to preferential hand-use, e.g. "Which hand do you use when cutting with scissors?" or "With which hand would you light a match". Participants are instructed to indicate their preference by putting "+" signs for either the right or left hand with emphasizing exclusive hand use by "++". In case of no preference, a "+" sign is to be put in both columns, left and right hand. Two additional questions ask for foot and eye preference.

4.2.5. THE TASK SWITCHING PARADIGM

The task switching paradigm was adapted from Heuer and colleagues (2004) and Bratzke et al. (2009). In each trial, two numbers appeared on the screen, where a fixation cross marked the centre. The central number was always located directly above or below of the fixation cross. The second number, the "flanker", appeared in the periphery, either to the left or to the right of the central number (see fig. 4.3.). The task was cued implicitly and contingent with the spatial location of the 2 numbers, i.e. above (task A) or below (task B) the fixation cross. This experiment can be categorized as a task-cueing paradigm, yet spatial location of the stimuli (cue) would not predict the task in the *next* trial, but define the *current* one (i.e. implicit, simultaneous cueing; Meiran, 1996; Monsell, 2003). In task A, participants had to judge whether the central number belonged to the lower magnitude set (numbers 1 to 4) or to the higher magnitude set (numbers 6 to 9; magnitude judgement task). Alternatively, task B required a location judgment of the flanker number, i.e. indicating whether the flanker was positioned on the left or on the right of the central number (spatial task). Responses were given by a button press with the right hand: for the lower magnitude set and the left flanker position, participants were to press the left button with their index finger, whilst high magnitude sets and the right flanker positions necessitated a right button with the middle finger.

The control condition for this block design study was created by replacing the digits by symbols (n=9, in accordance with the number of stimuli in the task switching paradigm, see Appendix, fig. A4.3.). Participants were instructed to respond to stimuli onset by pressing either of the two response buttons.

At the beginning of each block, a fixation cross appeared in the centre of the screen. After 3000ms, the first trial of a block was presented with a fixed presentation time of 2250ms. Pauses separated the trials from one another, with a counter-balanced variable inter-stimulus interval (ISI) of 300ms up to 1200ms (in 300ms intervals; per block total pause duration was kept constant with 6000ms). See fig. 4.3. for an illustration of a trial sequence within a block.

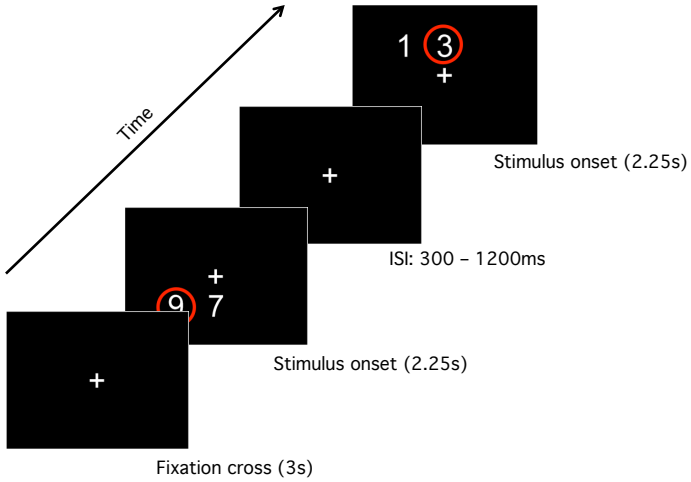


FIGURE 4.3. Task switching trial sequence: each block started with a fixation cross, independent of the task condition. The panels show the task switching displays, the first one presented is task B (the flanker is the target, circled) and participants were instructed to respond with a left button press. The top panel illustrates task A. As the target digit is below five, a left button press would be the accurate response. The situation sketched above represents a switch trial (task B is followed by task A).

Between blocks, pauses lasted between 9 and 21s (with 3s intervals), again counter-balanced between participants. The task sequence within each block was randomized. Instructions were given at the training two to three days before the test day and at the final training just before the first scan; speed and accuracy were stressed.

In each session, participants were presented 16 blocks (eight task switching and eight control condition blocks) in a pseudo-randomized order. The position of the target stimuli was counter-balanced across all trials within a session. Each block comprised eight trials, resulting in 64 trials per condition and session. Stimuli were presented under computer control (Presentation© software, Neurobehavioral Systems, Albany, USA), through a magnetically shielded video projector, onto a translucent screen. Participants viewed the screen inside the

scanner via a head coil-compatible mirror system. Timing of the stimulus presentation was triggered by a pulse produced by the scanner at the start of each run.

4.2.6. fMRI IMAGE ACQUISITION

Experiments were conducted in a 3.0-T whole body system (Magnetom VERIO, Siemens, Germany) equipped with a standard A TIM head coil. Foam cushions securely but comfortably fastened the subject's head in order to minimize head movements. To provide an anatomical reference and rule out morphological anomalies, a sagittal high-resolution 3D T1-weighted Magnetization Prepared Rapid Gradient Echo (MPRAGE) sequence was aquired with the following parameters: repetition time (TR) = 2400ms, echo time (TE) = 3.06ms, flip angle (FA) = 9°, number of slices = 160, field of view (FOV) = 240 x 256mm, matrix = 224 x 256 and rect. FOV = 7/8. For BOLD functional imaging, a T2*-weighted Echo-Planar Imaging (EPI) sequence was carried out (TR = 3000ms, TE = 30ms, FA = 80°, number of slices = 36, slice thickness = 4mm, inter-slice gap = 0.4mm, interleaved acquisition, FOV = 192 x 192mm, matrix = 64 x 64, in-plane resolution = 3 x 3mm). Functional images were acquired in axial orientation (parallel to the AC-PC line), covering the whole brain. Anatomical measurement lasted approximately five minutes, the functional measurement session approximately eleven minutes.

4.2.7. DATA PROCESSING

For the computation of the Center of Gravity (ψ_{act}), data was read out with the Daqtocontrol© software and further analysed with ChronOSX 2.1 (Roenneberg & Taylor, 2000). The motor activity data was consolidated in 10min bins and missing data, as indicated by the activity logs, excluded. ψ_{act} (Kenagy, 1980) was computed with ChronOSX by fitting a one harmonic cosine over the 10-day study period. Data was 24h trend-corrected and non-smoothed. The extracted ψ_{act}-value was only used for validation of the MCTQ and sleep log data.

The computation of the MSFsc (MCTQ) is described in section 2.2. (fig. 2.9.). The value allowed for a staggered, individually-tailored design in which participants were invited to the testing sessions as a function of their "early- or lateness". The critical variables emerging from sleep log data were mid-sleep on free days (MSF), mid-sleep on work days (MSW) and sleep offset (Sl_Off) on the test day. The individual number of free and work days during the study period was also extracted. As the participants had highly varying numbers of free days during the study, a weighted mid-sleep ($MS_{weighted}$) was computed in order to validate the ψ_{act} and MCTQ data, with $MS_{weighted}$ = (MSW* nb of workdays + MSF* nb of free days)/(nb of workdays + nb of free days).

KSS scores were used for correlational analyses as raw individual scores (range: 1-9). The L.Q. computation of the Edinburgh Handedness Questionnaire relies on an easy calculation algorithm shown below. It can be used as a cut-off criteria or as a quantitative trait-estimator.

L.Q. Computation

$$\sum_{right} - \sum_{left} \; / \; (\sum_{right} + \sum_{left}) \; *100$$

fMRI preprocessing

BrainVoyager® QX 2.0.7 was used for the pre-processing of the fMRI data. Anatomic labelling of the regions of interest (ROIs) was done with the AAL atlas (automated anatomical labelling atlas of Tzourio-Mazoyer et al., 2002, transformed into Tailerach space) and the Tailarach Demon (Lancaster et al., 2000).

The first five functional volumes were discarded due to T1 saturation effects. The remaining data were realigned to the first volume, 3D motion corrected (6 parameter rigid-body trilinear interpolation) and high-pass filtered with a filter cut-off of two cycles in time course (removal of low-frequency drifts). Subsequently, functional data were aligned to the structural images, normalized into the Talairach stereotactic space, re-sampled to 3x3x3mm^3 voxels, and spatially

smoothed to minimize noise and residual inter-subject differences in anatomy (isotropic Gaussian kernel of 8mm full-width half maximum).

4.2.8. STATISTICAL ANALYSES

Data sets were analysed with Excel 2008 and SPSS 17.0 and 18.0 for Mac OS X . BrainVoyager® QX 2.0.7 was used for statistical analyses of the fMRI data. The MCTQ was cross-validated by correlation analyses with the sleep-log based $MS_{weighted}$ and the CoG (ψ_{act}). All variables expressing times of day (MSFsc and ψ_{act-}) are reported in decimal units, i.e. 13:30 o'clock corresponds to 13.5.

Statistical analyses of fMRI data sets

A random effects general linear model (RFX GLM) with mask was used for the extraction of the functional task-related network. BOLD signal time course was normalized by z-transformation. Experimental conditions were modeled with boxcar regressors, convolved with the hemodynamic response function (two-gamma HRF). Statistical maps for the specific contrasts were calculated as t-statistic on a voxel-wise basis. To avoid an increase of type I errors that is contingent with multiple comparisons, a dual thresholding method was employed, i.e. a Monte Carlo simulation with 1000 iterations. The corrected alpha level corresponded to $p < .005$ and minimal cluster size for the ROIs was set at $600mm^3$.

Assessment of time-of-day effects in the fMRI data sets

Individual values for each ROI, each participant and each scanning session were extracted (only activations are considered). From there, deviations from individual mean over all four time points, were computed and expressed in percent whereby inter-individual variations in baseline activation are controlled for. Raw scores are reported in the beginning of the results section. An outlier correction was applied, based on the all over variability of the individual neural responses of the main and the sup-sample: all deviations from individual mean that exceeded two standard deviations, i.e. ± 263.25%, are excluded (4.1%; the result section will specify the

underlying number of measurements for each cluster and the corresponding degrees of freedom).

Systematic variations in the BOLD signal may rather be linked to internal time, sleep pressure (or time awake) or to sequence (or novelty) effects. To examine the nature and systematics of the variations, one part of the analyses focused on the temporal characteristics of the variability in the signal. To do so, an amplitude correction was applied to all individual data sets of each ROI. The computation underlying the amplitude correction is specified below:

Amplitude Correction Algorithm

1st step Identify maximum individual deviation (TP_1....TP_4)

2nd step Amplitude corrected deviation from individual mean

➔ TP_x / Max $_{(TP1...TP4)}$ *100

*with TP pointing to the individual scanning sessions

To acknowledge the potential complexity in the signal, two harmonic cosine fits were used to examine the stability or variability in the task-related neural network (see fig. 4.4.). The amplitude-corrected data were fitted to individual time since MSFsc (as an approximation of individual internal time) and time awake.

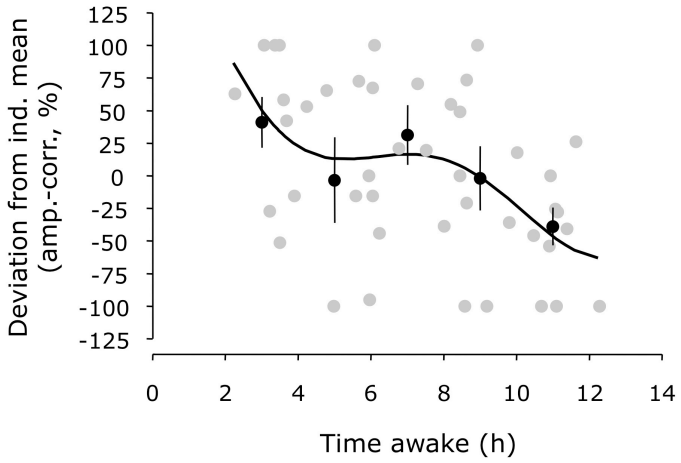


FIGURE 4.4. Thalamus activation as a function of time awake: two harmonic cosine fit upon the amplitude-corrected deviation from individual mean neural activity (grey dots, in %) in the task switching paradigm as a function of time awake (h) in the left thalamus, r= .49, p< .01. The dark dots represent the binned data for 2h-intervals (± SEM).

In case the fitting functions reached significance, a bootstrapping method probed the validity of the effect and thereby allowed for a differentiation between sequence and time-of-day effects. For each ROI, the match between the data of the sup-sample and the main study was compared by a least sum of square (SS) bootstrapping method (see fig. 4.5.).

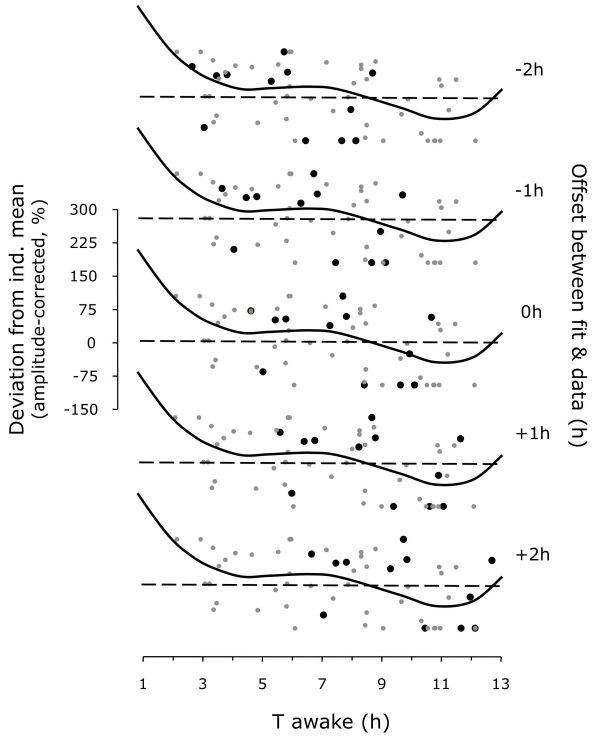


FIGURE 4.5. Bootstrapping method: the activation in the left thalamus of the sup-sample (red dots) is integrated in the fit obtained amongst the main study participants (light grey dots), here shown with a 1h-interval. The best match between the theoretical prediction of the main study fit and the actual values of the sup-sample is determined by the least SS, see fig. 4.6.

The two harmonic fit parameters from the main study group served as a basis for predicting the sup-sample values. The intervals used for these analyses comprise – in 0.25h steps – up to 3h around 0, with 0 corresponding to no offset between TP_2 in the main group and in the sup-group. In case the best fit was obtained with an offset close to 0, a time-of-day effect was assumed. Alternatively, the best match (i.e. least distance from the predicted and significant two harmonic fit function as shown by least SS; see fig. 4.6.) between the sup-sample and the main study group could be located at -3h.

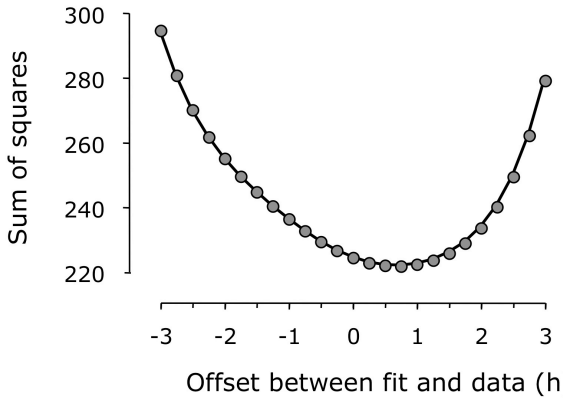


FIGURE 4.6. Classification of effects by the least sum of square method: the activation in the left thalamic region of the sup-sample matches best with the main study activation at an offset of 0.25h, suggesting that time awake plays a significant role in the systematic variation of the activation pattern.

If the best fit was obtained for -3h, this would indicate an equality e.g. between TP_1 main study group and TP_2 and the sup-group, and thus a displaced neural response by one scanning session. A displacement of -3 h would consequently suggest a sequence (or novelty) effect in a given ROI. The decision criteria for allocating either a time-of-day effect for both, either driven by internal time or time awake, as well as a sequence effect are shown below.

Cut-off Criteria Bootstrapping

Time-of-Day Effect	Least SS at offset -1h to 1h
Sequence Effect	Least SS at offset -2h to -4h

SS : sum of squares

Time-of-day effects either refer to internal time or time awake. In case the best fit occurred at any other offset, no conclusion was drawn and the variation was qualified as non-systematic.

Last, the range of oscillation was computed for each ROI to estimate the extent of variation in the signal. To do so, the same data as for the time-of-day effect calculations were used, yet, without amplitude correction. By extracting the parameters of the two harmonic cosine fit, the maximum and minimum of the function within 24h (10min bins) was extracted. The range of oscillation within 24h was calculated by subtracting the minimum from the maximum of the function. Correlations between data sets were conducted with the raw beta values.

RT analyses

The reaction to the first trial of each block was discarded from analyses, irrespective of its accuracy. Median (correct) RT and task switching costs were the variables of interest for both, the task and the control condition, see below for the underlying computations.

Switch Cost Computation

Median RT	∑ correct median RT / nb of trials
Switch Costs	RT switch - RT repetition
RT repetition	(RT aa + RTbb)/ nb of trials (aa+bb)
RT switch	(RT ab + RTba) / nb of trials (ab+ba)

Only RT of accurate trials were taken into account for the computations; in the control conditions, all responses are adequate, as only a button press was required as a response.

As the scanner setting might promote lapses or microsleeps, the analyses was based on median RT rather then average RT (Horowitz et al., 2003). RT data were normalized to percental deviation from individual mean. Linear regressions were used to assess whether RT data and switch costs decreased over the day, as asserted in hypotheses 1.

Due to the exclusion of 50% of the sup-group for RT data analyses, no bootstrapping or further analyses is possible; the study will thus focus on the main group data. All TP_1 calculations are based on a sample of eight participants, TP_2 to TP_4 comprises eleven participants. Thus, all within-subject rANOVAs are reported on the basis of eight participants. In case of violations of sphericity, Greenhouse-Geisser correction is applied (e.g. Field, 2009). Effect sizes are estimated by partial η^2.

4.3. RESULTS

4.3.1. MCTQ VALIDATION

The sleep log-based chronotype estimation ($MS_{weighted}$) correlated significantly the MSFsc obtained from the MCTQ, r= .82, p< .001, n=11. The correlation of the timing of motor activity (ψ_{act}) and the chronotype measure MSFsc did not reach

significance, but showed the right trend, i.e. late chronotypes (MSFsc) also exhibited later ψ_{act} and vice versa for the early types, r= .54, p= .07, n=11. Yet, $MS_{weighted}$ and ψ_{act} were significantly correlated, r= 0.64, p< .05, n=11.

4.3.2. KAROLINSKA SCALE

Mean subjective sleepiness levels are listed in table 4.7. The sleepier, the lower the score, whilst high alertness levels are indicated by higher scores. The participants were not significantly sleepier at a certain time during the test day (rANOVA with the between-subject factor "session" {4} and the covariate "chronotype" demonstrated, F(3,27)= .15, p > .9).

Karolinska Sleepiness Scores	
Session	Main study group
TP_1	3.5 (±1.1)
TP_2	3.0 (±1.2)
TP_3	3.8 (±1.5)
TP_4	3.2 (±0.8)

TABLE 4.7. Average KSS scores by session: the sleepiness scores remained constant across the four time points (average KSS score ± standard deviation, SD).

4.3.3. REACTION TIMES ANALYSES

Only correct RT were taken into account. Accuracy was high: the all-over error rate corresponded to 0.88%. The first session was slightly more error prone than the other three time points (1.77% versus 0.99%, 0.43% and 0.53%, respectively). Yet, this did not reach significance, p >.3.

Median RT

Median RT of the task switching condition will be further on referred to as "general RT". Raw data are shown in table 4.8. Reaction times in the control condition were significantly faster than in the task switching condition (rANOVA with the within-subject factors condition {2}, and session {4}, F(1,410)= 973.5 p< .000, η^2= .70).

Median RT (raw data)		
	Main study group	
Session	Task Condition	Control Condition
TP_1	766.1 ms (±204.4)	487.1 ms (±171.9)
TP_2	719.7 ms (±200.9)	456.7 ms (±172.5)
TP_3	701.8 ms (±212.5)	521.3 ms (±281.3)
TP_4	703 ms (±221.6)	473.5 ms (±207.7)

TABLE 4.8. The average RT (±SD) of the main study group as a function of condition.

The testing session influenced general RT ($F(2.9, 1185.8)= 8.4$, $p< .000$, $\eta^2= .02$), but the modulation over the day differed between conditions, (significant interaction between condition*session, $F(2.75,1128.3)= 12.1$ $p< .000$, $\eta^2= .03$). While general performance during task switching declined (see fig. 4.9.), control RT did not show systematic variations.

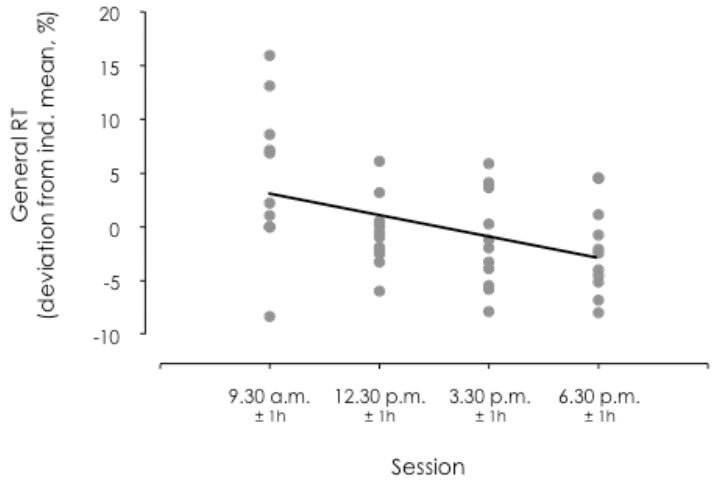


FIGURE 4.9. General RT speed significantly declined in the task switching paradigm over time and measurements. Negative percentages indicate that participants were reacted faster compared to their mean individual performance, while positive values point to a deceleration.

Switch Costs

Participants showed higher switch costs in the task switching condition than in the control condition, $F(1,11.4)= 21.8$, $p= .002$, $\eta^2= .76$, see table 4.10. for the raw data. The session succession itself did not significantly influence the switch costs;

also, the modulation within the conditions across the day was similar (non-significant interaction between the factors condition and session).

Switch costs (raw data)		
	Main study group (n=11)	
Session	Task Condition	Control Condition
TP_1	47.2 ms (±63.1)	-22.1 ms (±28.3)
TP_2	65.3 ms (±49.7)	7.9 ms (±51.6)
TP_3	29.9 ms (±63.3)	-32 ms (±49.1)
TP_4	72.3 ms (±40.9)	15 ms (±83.2)

TABLE 4.10. Switch costs (±SD) are listed as a function of session and condition.

Subjective sleepiness levels during the day did neither relate to general task switching nor control condition performance, as shown with linear regression analyses (all $p > .1$). Also, switch costs and subjective sleepiness levels were not linked to each other, all p-values of the linear regressions exceeded 0.5.

4.3.4. TIME-OF-DAY EFFECTS IN THE TASK SWITCHING NETWORK

Definition of the task switching network

For the definition of the task-related neural activations, the pooled control condition blocks were subtracted from the pooled task switching blocks. Only the resulting activations are reported, please refer to table 4.11. for an overview. The coordinates refer to the peak within significantly activated cluster.

	x	y	z	t-value	Cluster size (mm^3)	Associated BA
Premotor Area (PMA)	-30	-7	48	8.04	2871	6
Inferior Parietal Lobule	-39	-44	55	10.79	6840	7 & 40
Superior Parietal Lobule	-39	-43	56	11.61	8232	7 & 40
Precuneus	-9	-61	43	9.18	4958	7
Precuneus {r}	12	-52	52	6.70	1983	7
Thalamus	-18	-15	16	8.42	3840	-
Thalamus {r}	9	-21	18	6.46	1702	-
Occipital Lobe	-30	-58	31	12.98	3342	18 & 19
Cerebellum	-21	-34	-41	13.02	13148	-
Cerebellum {r}	24	-40	-41	12.82	24524	-
Vermis	4	-61	-23	9.02	7281	-

TABLE 4.11. The task switching network: cortical and sub-cortical structures showed a relative BOLD signal enhancement during the task-switching paradigm as compared to the control condition. All regions are located in the left hemisphere (also indicated by the negative values in the x-plane), unless stated otherwise: {r} corresponds to the right hemisphere. T-values are significant by $p < .005$. The x, y and z coordinates refer to the Tailarach stereotactic space; BA: Brodmann Area

Compared to the control condition, cognitive performance during task-switching trials activated motor areas, parietal regions, subcortical structures as the thalamus, and the cerebellum. Figure 4.12. depicts the task-switching network.

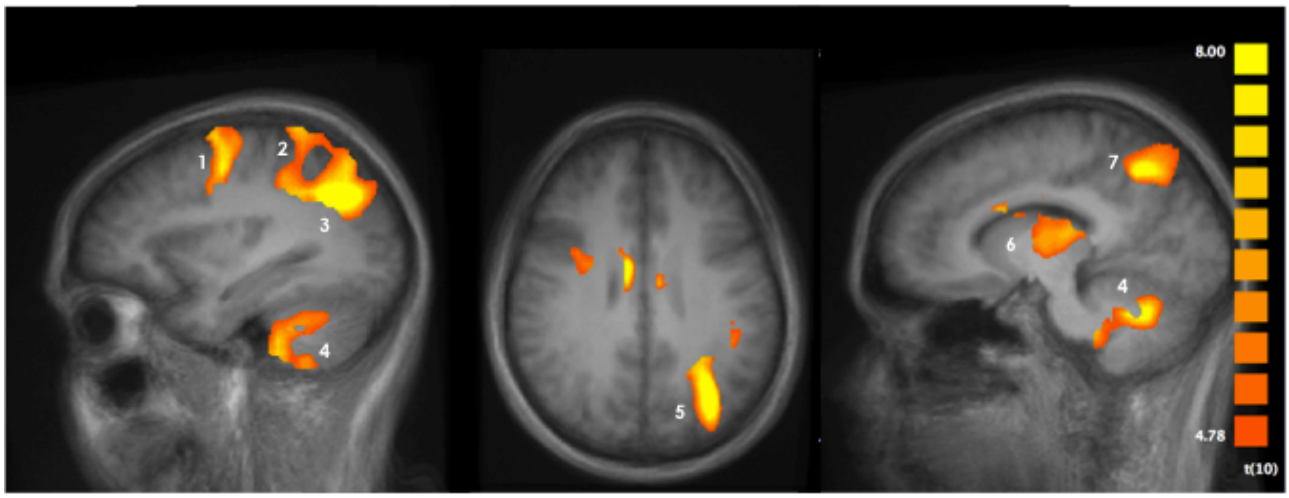


FIGURE 4.12. The task-switching network as obtained amongst the main study participants (n=11) comprises the pre-motor area (1), superior (2) and inferior (3) parietal structures and the occipital lobe (5) in the left hemisphere; the precuneus (7) in the parietal lobes, the cerebellum (4) and the thalamus (6) showed bilaterally significant activations. Only activations and no deactivations are shown; left sagittal plan x= -31, middle transversal plane z=30, right sagittal plane x= -11.

Examination of the network stability

First, all areas in the task-switching network were examined with regards to systematic modulation as a function of a) internal time, b) time awake and for c) sequence effects. Second, the non-amplitude corrected data is used to estimate the range of oscillation within a given cluster over 24h. Relative cluster activations of the main study group (outlier and amplitude corrected) were fitted with a two harmonic cosine fit. The following part summarizes the results of the bootstrapping analyses.

Internal time

For the left-hemispheric PMA and the right cerebellum, the best fit between the main and the sup-sample data was obtained with an offset between -1h and +1h. The PMA showed a decreasing trend with a slight increase approximately 13h after individual MSFsc (see fig. 4.13.), as shown by the main study fit r= .61, p < .001, n=43, *df*= 39. Confrontation with the sup-sample data revealed the best fit at an offset (t offset) of -1h, SS= 232.87.

Cerebellar activation in the right hemisphere decreased steadily as a function of MSFsc, r= .37, p< .05, n=44, *df*= 40. Least sum of squares was obtained for t offset = +0.25h, SS= 218.84.

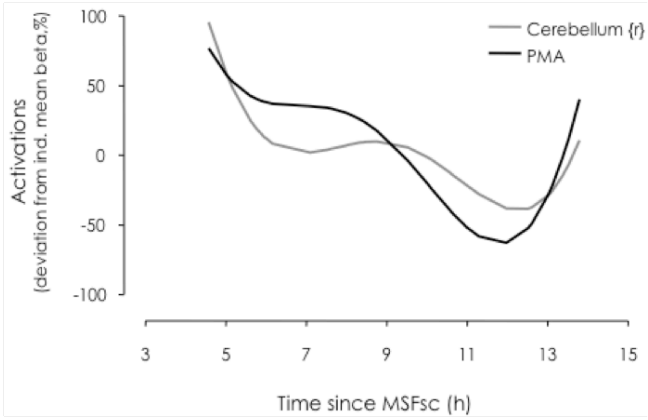


FIGURE 4.13. Systematic modulation of motor areas by internal time: the two harmonic fits obtained on the basis of the main study data (amplitude corrected) is plotted as a function time since ind. MSFsc. Both, the PMA in the left hemisphere and the right cerebellum exhibit the most pronounced relative deactivation around 12h after MSFsc, i.e. for an intermediate chronotype with a MSFsc of 4.5 this would correspond to 16:30 o'clock.

Sequence effects

In the left cerebrum, the BOLD signal in both, the inferior parietal lobe and the thalamus showed sequence effects (inferior parietal area: r= .39, p< .01, n=44, *df*= 40, t offset = -3, SS= 266.27; thalamus: r= .52, p< .001, n=42, *df*= 38, t offset = -2, SS= 225.98). Additionally, relative activity was enhanced for the first session in the vermis of the cerebellum with decreasing tendency for the following ones, r= .52, p< .001, n=42, *df*= 38, t offset = -2, SS= 225.98. Figure 4.14. depicts the sequence effect as modelled by the two harmonic cosine fits.

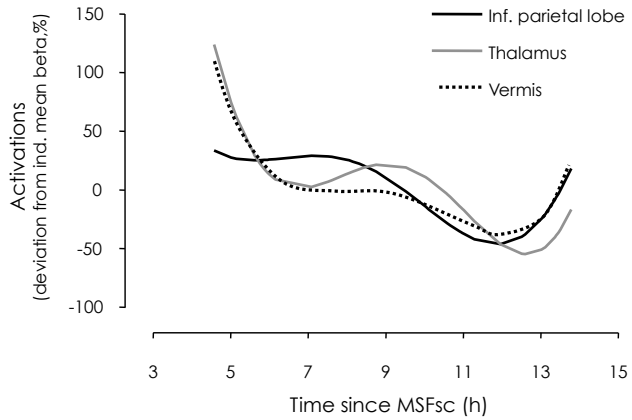


FIGURE 4.14. Sequence effects: the fit on the main study data obtained the best correspondence with the sup-sample data with an offset of 3h. Thus, a sequence effect in the BOLD response (i.e. in this case an enhanced response for the first session) is assumed. Inferior parietal lobe and the thalamus are both located in the left hemisphere.

The thalamus and the vermis exhibited an enhanced BOLD signal early on, approximately 5h after MSFsc, corresponding to the first scanning session. The inferior parietal lobe showed a similar activation pattern with a relative decrease in the signal, yet, the range of the signal change appears smaller (refer to the next chapter *range of oscillation* for precise amplitude information).

Time awake effects

Time awake significantly modulated the BOLD signal in parietal structures, the thalamic areas and the right cerebellum. Please refer to table 4.15. for a summary of the results.

	r	n _ df	t offset	SS
Inferior Parietal Lobule	0.40*	44 _ 40	0.25	246.10
Superior Parietal Lobule	0.40*	44 _ 40	-1.00	225.04
Precuneus	0.45**	44 _ 40	0.25	251.25
Precuneus {r}	0.57***	44 _ 40	0.75	234.64
Thalamus	0.49**	42_38	0.75	221.76
Thalamus {r}	0.49**	41_37	0.25	248.94
Cerebellum {r}	0.32*	44 _ 40	-1.00	228.66
		* p< .05	** p < .01	*** p < .001

TABLE 4.15. Time awake modulations: individual time awake systematically influenced neural activity in the parietal lobe, subcortical thalamic structures and the right cerebellum: the reported r is based on the main study day with a sample size of n; the corresponding degrees of freedom (df) for the two harmonic fit are specified in the second column. T offset = time point of the best fit between the main and the sup-sample data, SS= sum of squares of the best fit. * indicate the significance levels of the respective regressions.

Figure 4.16. illustrates in two panels the activation patterns in the parietal lobe structures (panel A) as well as the thalamic and cerebellar modulation (panel B) in the BOLD signal. Parietal activations followed a similar pattern, revealing a double peak throughout the experimental day. Thalamic and cerebellar activations showed a progressive decline.

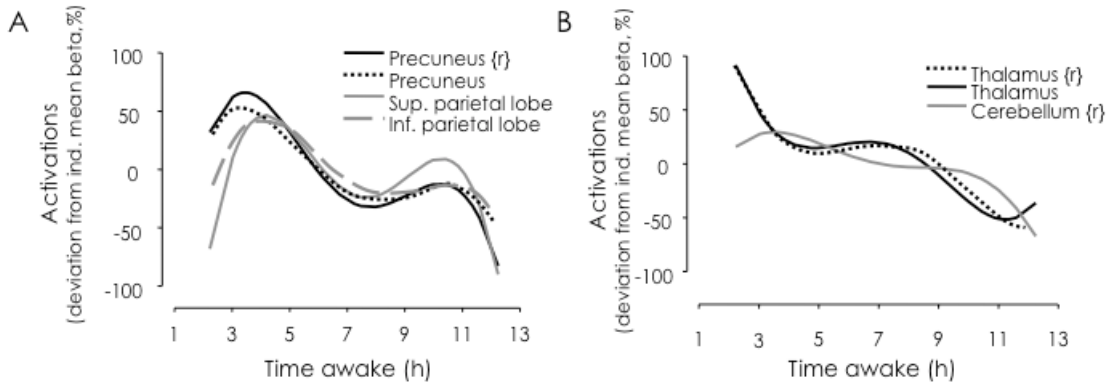


FIGURE 4.16. All parietal areas with systematic changes in the BOLD signal over the day were sensitive to time awake (Panel A); activity modulation in the thalamus is consistent across hemispheres and shows a decrease with a plateau from approximately 5 to 8.5 h after wake-up (panel B). Cerebellar activity decreases steadily. {r} denotes the right hemisphere; the graphs are all based on amplitude-corrected data of the main study group and shows the two harmonic fit.

Stable areas within the task-switching network

Two harmonic regression analyses of the BOLD signal in the left occipital lobe and the left cerebellum of the main study group resulted in a significant fit for both, time awake and internal time. Yet, the bootstrapping approach with the sup-

sample data set could not confirm systematic variations for either of them. The best fits between the sup-sample and the main study's fit laid outside the cut-off criteria defined in the methods part.

Range of oscillation

The range of oscillation within 24h predicted the extent of the modulation within the task-specific network. Table 4.17. gives an overview of the range of oscillation for all significantly modulated structures, may they vary as a function of internal time, time awake or of sequence.

	Range of oscillation
Premotor Area (PMA)	85.94
Inferior Parietal L. $^{T\ Awake}$	245.44
Inferior Parietal L. ^{Sequence}	234.15
Superior Parietal Lobule	970.21
Precuneus	873.28
Precuneus {r}	1436.2
Thalamus $^{T\ Awake}$	456.86
Thalamus ^{Sequence}	1163.9
Thalamus {r}	456.12
Cerebellum {r} $^{Internal\ T}$	1182.42
Cerebellum {r} $^{T\ Awake}$	498.40
Vermis	1197.72

TABLE 4.17. Range of oscillation within the network: the two harmonic regression function of the main study group was used to estimate the range of oscillation for all task-related brain areas exhibiting systematic time-of-day effects; amplitude of the respective structures were highly variable within 24h.

In the case of significant time-of-day effects related to more than one factor, i.e. influence of sequence AND the homeostat, both functions and ranges of oscillations are described.

4.3.5. THALAMIC ACTIVATION, REACTION TIMES AND THE HOMEOSTAT

Thalamic structures were significantly involved in task-switching performance as shown in Fig. 4.18. when compared to activations during the control condition (pooled TP_1-TP_4, respectively).

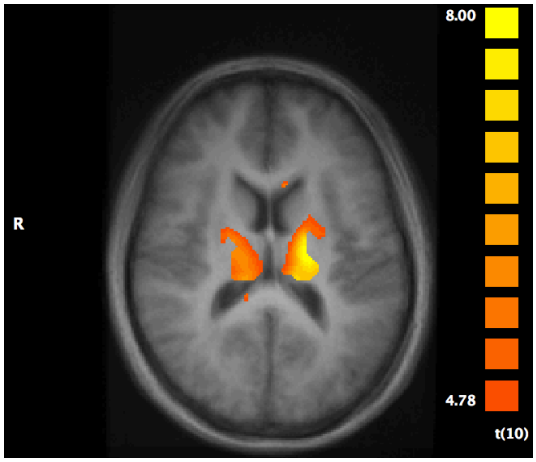


FIGURE 4.18. This figure shows the thalamic clusters (transversal plane, z= 15) activated during the task-switching blocks (TP_1 to TP_4, main study; task-switching 1 to 4 > control condition 1 to 4) on the averaged anatomical scans of the participants (main study). Orientation follows radiology conventions (right cerebrum = left side, left cerebrum = right side).

BOLD signal of the thalamus was significantly dependent upon time awake. The modulation of the task-related response is shown for the raw data plotted by scanning session (fig. 4.19., panel A) and the amplitude-corrected data as a function of time awake (r= .49, p< .001, respectively, panel B).

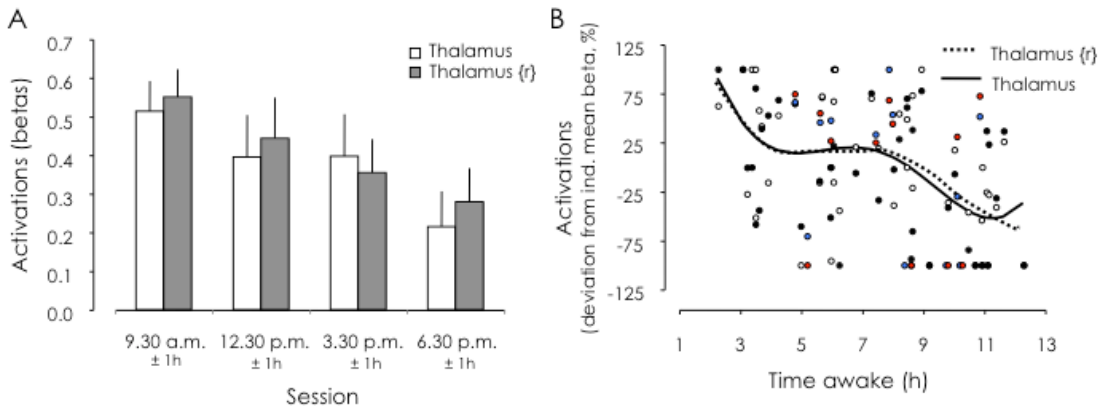


FIGURE 4.19. Thalamic activity declines over the course of the study (Panel A); sleep pressure that is building up the longer participants are awake explains a substantial part of the variability in the signal (Panel B: all data points are shown as a percental deviation from individual mean with amplitude correction; main study data is shown in black and white, sup-saple data in colour; filled black and blue circles > left thalamus; white and red circles > right thalamus). The depicted two harmonic fits are based on the corresponding main study data and individual h since wake up.

The effect session in BOLD signal of the left and the right thalamus was marginally significant, rANOVAs, $F(3,30) > 3.23$, $p < .1$, respectively. Effect sizes for the factor session corresponded – for both structures – to $\eta^2 = .19$. Activation levels between the first and the last session were significantly different from one

another in the left thalamus (post-hoc pairwise comparisons, mean difference .298, p= .035).

Enhancement in thalamic activation and improvement of general reaction times correlated significantly with each other (see fig. 4.20., left thalamus r= -.41, p< .01, right thalamus r= -.31, p< .05). For the control RT, the correlation with the thalamic activation patterns tended towards significance (right thalamus, r= -.29, p= .06, left thalamus, r= -.33, p< .05).

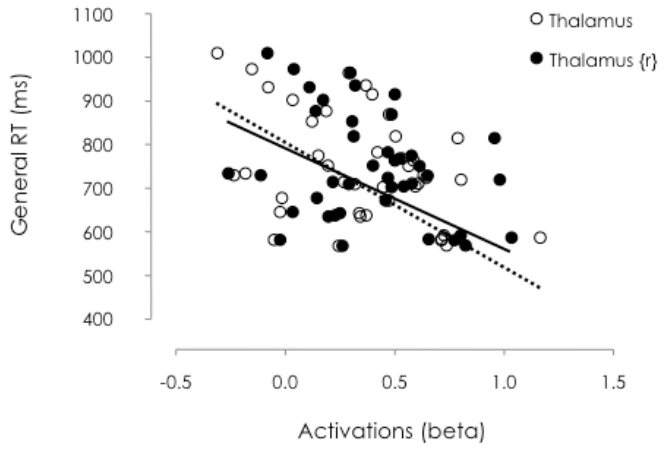


FIGURE 4.20. High activity in the thalamus coincided with better task performance, i.e. faster reactions. {r} = right hemisphere; the dotted line corresponds to the linear fit for the left thalamus.

Task switch costs in the experimental paradigm were not dependent upon thalamic activation, correlation coefficients did not exceed -.26 and remained above the significance level of p= .1. Switch costs in the control condition did not show any systematic relationship with thalamus activity, p-values > .65.

Furthermore, decreasing Karolinska scores, indicating less subjective sleepiness, coincided with increased BOLD signal in the right and left thamalus (r= -.33 and r= -.36, p< .05 respectively).

To tackle the determining factor underlying the fluctuations in general RT, a multiple linear regression (backward method) was calculated with following predictors: time awake, time since MSFsc, session (TP), Karolinska score, average RT in the control condition as well as the beta coefficients of the right and left thalamus. Even though the parameters used in this linear regression are assumed to expose non-linear dynamics within 24h (e.g. thalamic activity or general RT), their variability could well be described in a linear fashion for the study time

frame. Thus, the variables were assumed to fulfil the underlying criteria of a linear regression analyses in terms of linearity.

The model predicting general performance during task-switching best included the left and the right thalamus, time awake and RT during the control condition, $F(1,40)= 16.08$, $p< .000$, $r^2= .64$. Please consult Appendix, table A.4.4. for the model summery.

4.4. DISCUSSION

The present study examined potential time-of-day effects in neural activation associated to task-switching with fMRI – within an usual experimental day. Participants engaged in task-switching were scanned four times during one day, in the morning, midday, afternoon and early evening. Internal time and time awake significantly modulated the task-switching network. Activity patterns in the thalamus - as a central structure in mediating homeostatic sleep pressure and arousal to the cortex – were associated with time awake and predicted *inter alia* performance levels.

Behavioural task-switching performance

On the behavioural level, general reaction times in task-switching showed an improvement over the day. Yet, switch costs across the four sessions did not show systematic variations. The general reaction time results partly replicate previous findings by Bratzke and colleagues (2009) and may reflect circadian influence on performance (e.g. Monk et al., 1997). Practice effects cannot entirely be dispelled, as the repetition of a task, especially of a task involving cognitive control, usually results in better task performance. Training effects are usually well described by a saturating exponential function (Blatter & Cajochen, 2007; Jewett et al., 2001; Wright et al., 2006) with a steady improvement in performance at the beginning of task execution and a subsequent plateau of performance (asymptotic level of performance). The improvement of general reaction times over the four test sessions may partly be attributed to practice effects. However, all participants received extensive training before the test day (and one complete

training session before testing). Given the asymptotic increase in practice effects, it has been suggested that pre-training is a valid method to prevent practice effects (Blatter & Cajochen, 2007). Additionally, practice effects would also affect the switch costs as a specific marker for cognitive control – especially as tasks estimating cognitive control and inhibition performance seem particularly vulnerable to training effects (Schmidt et al., 2007) – which was not the case.

The task-switching reactions were significantly slower than those associated to the simple control blocks. This result undermines the validity of the control blocks for the fMRI block design comparison. Similarly, the switch costs computed from the control condition for monitoring reasons were distributed around zero. As the switch between the two control stimuli sets did not imply any conceptual or task set, no costs were expected to emerge from the perceptual switch, the latter one being irrelevant for the correct response (i.e. simple button press). The result that only reaction times, but not switch costs improved over the day, points to a non-specific, rather arousal-driven (e.g. Schmidt et al., 2007) effect on task-related reaction times that did not attaint switch costs. The effort of switching between conceptual tasks sets hence remained stable across the day. When compared to Bratzke et al. (2009), the differences between the first four assessments (ranging from 9:00 to 18:00 o'clock in 3h intervals) did not show a significant time-of-day effect in isolation from the subsequent 31h of constant routine. Switch costs are higher at 9:00 o'clock with higher variability, but seem comparable from 12:00 to 18:00 o'clock. Possibly, this trend was prohibited with intense training, exceeding the training that the participants obtained before the constant routine.

In summary, **hypothesis 1** can be partially accepted, as time-of-day effects emerged in reaction times, but not switch costs, suggesting that cognitive control mechanisms remained constant over the day, while reaction times were subjected to basic vigilance fluctuations.

The neural network underlying of task-switching performance

Previous investigations of the neural network of task-switching has reported activation in the prefrontal cortex, the supplementary motor area (SMA), parietal regions, thalamic structures, and the right cerebellum (e.g. Braver et al., 2003; E.

A. Crone et al., 2006; Dove et al., 2000; Dreher et al., 2002; Kimberg et al., 2000; Meyer et al., 1997; Sohn et al., 2000). The network emerging in this study is largely consistent with the structures earlier described in task-switching performance.

One main difference is that this study and the contrast between the task and the control blocks did not yield significant relative activation in the prefrontal cortex, an area often associated to switch trials within a task block (Dove et al., 2000; Meyer et al., 1997; Sohn et al., 2000) and more specifically to the transient (anterior PFC) and sustained demands (ventro- and dorsolateral PFC) on cognitive control (Braver et al., 2003). Yet, apart from being involved in the cognitive control process during task-switching itself, prefrontal cortex activation was specifically linked to predictable task sequences. In the present study, the use of a specific task strategy may represent an advantage and thus the prefrontal cortex is also postulated to be involved in maintaining and updating task strategies (Sohn et al., 2000). The paradigm employed in the present study did not rely on predictable sequences and foreknowledge manipulation (one main difference as compared to the study by Bratzke et al., 2009). Specific strategies were thus unnecessary and would not have enhanced performance. This, in turn, may have reduced prefrontal implication during task-switching.

Furthermore, participants received more training than in typical experimental settings to reduce training effects potentially confounding with time-of-day effects (e.g. Blatter & Cajochen, 2007). Intensive training reduces the need in cognitive control and in turn would result in decreased relative PFC activity, as postulated by the dual mechanisms of control account by Braver and colleagues (Braver et al., 2007; Braver et al., 2009). Recent studies support this claim, even though direct experimental evidence is lacking. In the perceptual domain, previously trained items specifically elicited less activation in the PFC than novel items (Eriksson et al., 2008). By lessening the level of cognitive control demands by intense training in a memory task amongst elderly participants, the BOLD signal in frontal areas including the PFC was significantly reduced (Velanova et al., 2007).

Last, most task-switching studies on cognitive control using fMRI technology chose event-related designs. Switch trials are compared to repetition trials and preparation time effects can be examined. This study did not investigate task-

switching *per se*, but a cognitive task known to be influenced by time-of-day and hence opted for a block design. In this situation, a block comprises switch trials and repetition trials, the latter ones showing largely reduced PFC activation as compared to switch trials (Meyer et al., 1997).

In addition, both trial types recruit parietal networks: in this study, superior and inferior parietal structures supported the task-related network, potentially leading to the activation pattern as described here. Sohn and colleagues (2000) argue that the parietal cortex supports a task meta-strategy, especially in cases where task sequence is non-predictable. Increased BOLD signal in the superior parietal cortex also reflect processes associated with the online reconfiguration and updating of task-set information immediately following a switch in task (e.g. Braver et al., 2003; Dove et al., 2000; Dreher et al., 2002; Sohn et al., 2000). The superior parietal lobe seems implicated in dynamics changes between stimulus-response mapping (E. A. Crone et al., 2006) – just as the PMA. As the same motor responses were required for ambivalent stimuli sets, the involvement of the PMA in this task-switching paradigm is plausible. (e.g. Sohn et al., 2000).

In summary, the task-switching network here has been largely replicated and the missing prefrontal activations may be explained by 1) the non-predictable task sequence, 2) reduced prefrontal recruitment due to practice, and 3) block design methodology. Yet, one has to point out that " (…) cognitive control is not restraint to the prefrontal cortex and task-switching networks involve also other cortical and subcortical structures" (Dove et al., 2000).

Time-of-day effects the neural substrates of task-switching performance

Almost all structures of the network underlying task-switching performance showed significant time-of-day effects that could either be attributed to internal time, to time awake or to sequence effects, supporting **hypothesis 2**. Only left-lateralized activations in the occipital lobe and the left cerebellum showed inconclusive, i.e. non-systematic, signal variability.

Internal time modulated the relative activity of the left PMA as well as the right cerebellum, two areas involved in the so-called "motor network" (along with the motor cortex, sensorimotor cortex, thalamus and the basal ganglia, Alexander &

Crutcher, 1990), but also in movement planning and adaptation. They showed similar patterns over the course of the experimental day. Motor behaviour itself, as for example assessed with self-paced finger tappin (Moussay et al., 2002), exhibits a clear circadian rhythm. Unpublished results from Peres et al. (in preparation) report systematic modulations of the motor network during self-paced finger tapping as a function of time awake and internal time over the course of 12 hours.

Increasing time awake had a considerable impact on numerous task-relevant structures. Bilateral thalamic activation and ventral and dorsal parietal lobe structures were systematically modulated by time awake – parietal areas all demonstrated a similar temporal dynamic, different from the thalamic modulation which in turn was comparable between the right – and the left-hemispheric thalamus. The thalamus is an important structure in conveying arousal levels to the cortex (Aston-Jones, 2005; Portas et al., 1998) and shows differential activity patterns during cognitive tasks as a function of chronotype (Schmidt et al., 2009) and sleep pressure (Vandewalle et al., 2009). Parietal lobe activity has previously not been described in the context of time-of-day effects. Yet, parietal and thalamic structures are interconnected, as reported by Behrens and colleagues using diffusion tensor imaging (DTI, 2003).

In the left hemisphere, the thalamus and the inferior parietal lobe were additionally affected by the scanning sequence: the first assessment resulted in significantly higher activation patterns than the subsequent ones. Sequence effects may be linked to enhanced emotional processing, adaptation to the scanner set-up etc.; an in-depth discussion of those results would go beyond the scope of this research, but represent an interesting approach for future studies.

The time-of-day effects – as based on phase-specific analyses – give one impression of the variability of the BOLD signal during a cognitive task. The effect size of those modulations was estimated by the range of oscillation: all but the PMA exceeded the 100% of rhythm amplitude within 24h. If only the 12h of

scanning time are considered, the systematic modulations within each study participant still surpass the 100%, representing a major source of variation in the signal.

Thalamic activation, reaction times and the homeostat

The BOLD signal in the thalamus during task-switching decreased continuously over the day, corroborating **hypothesis 3**. Relative activation values halved over the course of the experimental day and the modulation was systematically associated to time awake. Thus, within a normal day/night regimen without sleep deprivation, thalamic activation during task-switching decreases continuously over the day. This is the first quantification of thalamic activation during daytime, non-confounded with internal time, as participants were assessed with an individually tailored chronotype-ranked experimental design. Best reaction times were recorded in the evening where in general relative activity in the thalamus was lower than in the morning. Concomitantly, correlational analyses revealed that higher thalamic activity concurs with better reaction times, but not switch costs, implying an unspecific, vigilance-based effect. A multiple regression analyses additionally corroborates that the relationship between thalamic activity and performance seems non-task-specific but rather arousal driven: general RT was best explained by the thalamic activation, reaction times in the control condition and time awake.

Previous research manipulating arousal levels or circadian factors (e.g. light, sleep deprivation or chronotype) reported an increase in thalamic activation with low arousal levels (Coull et al., 2004; Foucher et al., 2004; Portas et al., 1998; Schmidt et al., 2009; Thomas et al., 2000; Vandewalle et al., 2009; Vandewalle et al., 2006). Yet, none of those studies has attempted to quantify the variation in thalamic activity within a regular day while controlling for internal and external time. The results reported here consequently add to the knowledge about the diurnal dynamics of thalamic activation during a cognitive task.

Is there a relationship between performance, subjective sleepiness and the BOLD activation?

As anticipated from the results by Bratzke and colleagues (2009), subjective sleepiness levels remained constant from morning to early evening sessions. Conversely, performance measures and thalamic activation patterns over the course of the experimental day did not relate to subjective sleepiness patterns. The finding that subjective sleepiness levels do not relate to reaction times (as an objective vigilance measure) has been described previously in daytime experiments (Hoch et al., 1992) and in constant routine protocols (e.g. Frey et al., 2004). In general, the position that the concepts of sleepiness and alertness reflected reciprocal states of consciousness has recently been challenged (Moller et al., 2006). However, to ensure comparability to other studies, this standard scale was chosen for the assessment of subjective sleepiness.

Limitations of the study

This study gained many insights with regards to time-of-day effects in the neural underpinnings of task-switching performance. Yet, critical points may be discussed and furthermore improved in future research tackling similar questions.

First, Ttme-of-day effects were distinguished from sequence effects by comparing the BOLD signal of the participants assessed over the entire day with the one obtained amongst a small sample, starting the measurements one time point later than the main sample. The small, supplementary sample only comprised four participants. This may have jeopardized the detection power of time-of-day and sequence effect. Some areas of the task-switching network were not ascribed any systematic variation (as defined with the bootstrapping method and the corresponding cut-off criteria), albeit exhibiting highly significant two harmonic cosine fits within the main study sample. Hence, the risk of missing a significant time-of-day or sequence effect is not negligible. On the other hand, many areas were successfully identified as showing systematic modulations during the study. In consequence, the bootstrapping method based upon a small sample may have led to a small percentage of omissions, but for most areas effect sizes were large enough to be detected with the data sets.

Second, recent research reported significant variations in the BOLD signal as a function of light exposure preceding cognitive testing in the scanner (Vandewalle et al., 2007). The present study did not empirically control for light exposure, even though participants were not allowed to go outside during the test day. Nonetheless no objective assessment of light exposure took place. Future studies could make use of the LightWatcher (Sowoon/EuClock®, Holland), a portable and light-weighted device sensitively measuring light exposure at the eye level. As a result, the participants' light exposure could 1) be used as a covariate in statistical analyses and 2) be more thoroughly controlled for.

Last, analysis methods in this research have been highly influenced by statistics usually employed in chronbiological research; yet, a combination of those methods with more advanced fMRI analyses approaches like independent component analysis (ICA, e.g. Calhoun et al., 2001; Jung et al., 2001; McKeown et al., 2003) may be useful in future projects. ICA can be especially useful in exploratory research questions as *a priori* assumptions are reduced to a minimum.

Conclusion

In conclusion, this study quantified time-of-day effects on the behavioural and neural level associated to task-switching performance. Systematic time-of-day effects are supposedly associated to the circadian oscillator and the homeostatic drive. For an in-depth investigation of the BOLD response to a cognitive task as a function of the circadian and homeostatic component, future research may employ constant routine, forced desynchrony or napping protocols. This study shows that the effortful, costly and time-consuming endeavour necessary for a constant routine - and for disentangling the influence of the two components - may be fruitful, given the reported effect sizes. Moreover, the results reported here point towards a potentially substantial confound in studies in the field of cognitive neuroscience. The concept of internal time therefore may be helpful in the forthcoming studies of neural networks underlying cognition and behaviour.

5. General Conclusions

This research aimed at translating the knowledge about the mechanisms and functionality of the circadian system into "action", into real-life conditions. Understanding the impact of internal time in real life is not a project *despite* this natural environment. Biological systems such as the circadian clock have evolved in exactly this complexity of real-life conditions, being inherently noisy. The re-integration of the study of internal time in the context it evolved in was the main goal of this research. Three field studies were devoted to investigate the interaction between internal and external time on cognition, sleep and wake behaviour as well as physiology. For this, a plethora of methods derived from the fields of psychology, biology and neuroscience was employed. To apprehend multifaceted behaviour in complex environments research needs to engage in interdisciplinary work. In turn, the combination of multiple research methods results in a potentialisation of caveats inherent to the methodological and epistemological background of the respective disciplines.

This chapter summarizes the main findings of the three field studies. Furthermore, recommendations for improving human living conditions and implications for future research are presented.

Continuous blue-enriched light exposure affects sleep and wake behaviour in office workers

Office workers are exposed to light that in general assures visibility, but widely neglects the importance of light for the human biology (Begemann et al., 1997). Especially short-wavelength light, perceived as with relatively cold, bluish light, synchronises the circadian system to the 24h LD cycle (e.g., Brainard et al., 2001; Thapan et al., 2001). New lighting sources have been developed that increasingly resemble the spectral composition of day light, and as such comprise a relative high proportion of short-wavelength. In office environments, the continuous exposure to blue-enriched light environments – as compared to classical "warmer" light conditions" – appears to override the signals of the natural LD cycle. Sleep and wake behaviour on free days, as assessed with daily sleep logs and actimetry, remained constant across the study period in the group exposed to the

blue-enriched light. These results suggest that the group entrained to the fixed office light schedule. It appears that continuous blue-enriched light exposure, in combination with fixed work schedules, may interfere with seasonal adaptation. The control group (i.e. standard 4.000K light environment) in contrast followed in their sleep and wake behaviour the progression in photoperiod, as it is typical in springtime. In contrast to previous findings, subjective wellbeing ratings did not vary over the study period and were independent of the light environment (Mills et al., 2007).

The spectral composition of light sources in offices is a powerful factor influencing human behaviour, as shown in the present study. This result is in accordance with recent work conducted in an Antarctic base reporting blue-enriched light to dispose of the strongest phase-shift properties (Mottram et al., 2010). Even though the authors described a rather unique and secluded study setting exposed to extreme LD cycles, they observed that the best sleep (and sleep timing) occurred under natural light conditions –underlying the importance of dynamic, naturalistic light systems. Indoor lighting systems should thus be oriented towards daily and annual dynamics in the LD cycle in order to maximise beneficial effects for the employees. Second, Mottram et al. (2010) proposed that an increase in the absolute amount of light exposure might represent a key element, irrespective of the spectral composition of the light source. This observation corresponds to the general claim of zeitgeber lack in Western civilizations, but a systematic examination of the effects of distinct light spectra within field studies has yet to be conducted. Previous research has mainly employed very high colour temperature light environments (with blue-enriched light, 17.000K, Mills et al., 2007; Mottram et al., 2010; Viola et al., 2008). The results of the present study underline the biological efficacy of light sources with 8.000K, suggesting a large range interval of potentially powerful light sources.

Future research is also necessary to understand optimal timing in dynamic lighting exposure as well as regarding its spectral composition at certain time of day. Settings such as offices, hospitals or elderly homes are designed to the needs and demands of distinct populations whereby the range of applications of light environments corresponds to those requirements. An office might simply aim at

preventing a zeitgeber lack, while clinical settings could additionally aim at tackling (subclinical) mood disorders as the seasonal affective disorder (e.g., Wirz-Justice et al., 2009; Wirz-Justice et al., 2003). Specific light regime pinpoint specific needs inherent to the setting.

Additionally, the role of inter-individual differences, such as chronotype or age, remain to be examined with regards to dynamic real-life light environments. In general, dynamic lighting has to date scarcely been investigated systematically and results are inconclusive (e.g. Spreeuwenberg et al., 2010). The ecological validity of dynamic lighting, in context with the results of the present study, renders it a promising tool and further studies are necessary.

Cognitive performance profiles in rotating shift workers and the influence of sleep

Artificial temporal structures in humans are carried to extremes in shift workers. Those "(…) imposed structure conflicts with our basic biology and is suboptimal for our health", as stated by Foster and Wulff (2005). Good performance is expected at any time of day. Yet, the present study amongst young rotating shift workers demonstrated the dependency of reaction times upon internal and external time. The performance profiles assessed in the factory during a total of 12 time points across 24h underline the importance of chronotype; not only with regard to shift-specific sleep duration as already reported by Juda (2010), but also for intra- and inter-shift performance levels. Prolonged waking times – as observed in particular (in early chronotypes) during night shifts – is associated with performance impairments, and may potentially be explicative of elevation in work accidents during night shifts (Folkard & Åkerstedt, 2004a; Smith et al., 1994; Smith et al., 1998). Last, the present study revealed an even stronger association between sleep duration and performance with severe performance decrements wit a sleep duration below 60% of the individual sleep need. In turn, sleep duration in shift workers is mediated by chronotype (Juda, 2010). Those results apply to more than 20% of the population, working between 19:00 and 7:00 o'clock in the morning, and thus, outside of the traditional work range (Kreitzman, 1999).

In general, real-life study settings are inherently noisy as compared to well-controlled laboratory conditions. For instance, body posture, caffeine and nicotine

consumption or food intake were not controlled for[20]. By deliberately including those confounding factors into the study, a maximal approximation to real-life situations was intended. It has even been suggested that in real life, masking may be part of the entrainment process itself (Roenneberg & Merrow, 2007). The results obtained in the present shift work study fit into the theoretical context deployed by the findings of laboratory studies. This suggests on the one hand the (at least partial) transferability of laboratory-derived conclusions, even into noisy and uncontrolled conditions. On the other hand, the results of the present study underline the importance of internal time, whilst laboratory findings reported the largest effect sizes for the effect of the homeostatic component. In the real world, however, internal time may be of relatively more importance, as total sleep deprivation rather represents an artificial condition that is scarcely encountered.

The demographic development in most countries of the Western hemisphere endorses future research to investigate the effects of shift work upon elderly workers in the light of internal time. As chronotypes get progressively earlier with age (Roenneberg, Kuehnle et al., 2007), the detrimental effects on health and performance in shift workers are even more pronounced. To date, whilst it is known that older shift workers exhibit more health problems than younger ones, the exact mechanisms remain unknown (Costa, 2005). Hence, age- and chronotype-specific consequences of shift work represent one of the major topics in future shift work research.

In addition, future field studies should assess further cognitive functions such as cognitive control, visual search or working memory. With the profile of PVT performance in the field being established, future field studies can employ the 5min PVT task as a golden standard, as it has been the norm in laboratory experiments for the last few decades. This will facilitate the interpretation of the results obtained with other cognitive tasks. Furthermore, an expedient transposition of experimental paradigms into field settings can be achieved in close cooperation with industry and ergonomists, as particular work processes can

[20] Factors like activity, body posture, caffeine or cigarettes for instance affect the circadian system and can acutely "mask" the phase of entrainment, but not resulting in a stable phase angle. Please refer to section 1.1.5. for an overview and Mrosovsky (1999) or Rietveld et al. (1993) for comprehensive reviews.

vary significantly from one site to another. Emergency rooms employees for instance rely substantially on language processing and fine-motor skills, while monitoring and reparation tasks demand fast visual orienting. Thus, the relevance of a particular cognitive function within a specific work environment and work place can diverge. Amelioration of working conditions relies on inter-disciplinary work integrating laboratory knowledge with on-site expertise. The first step in this direction has been made, as a first profile of simple reaction times as a function of internal and external time is established.

In summary, a sensible recommendation of new, health and wellbeing promoting work schedules need to consider chronotype, or internal time, in addition to external time, as both, performance and sleep are linked to one another and in turn depend upon the individual chronotype. The assumption that discipline and determination allow for a adaptation to irregular working schedules cannot be held up: even 20 years of night shift for instance do not result in adapted permanent night shift workers (Folkard, 2008; Rajaratnam & Arendt, 2001).The present study provides further evidence for this, based on data sampled in real-life conditions.

Time of day modulates neural activity in the task switching network

Functional MRI is one of the methods of choice to investigate the neural correlates of the human mind and the scheduling of experiments and participant appointments is mostly based on convenience and availability, as scanning facilities are a valuable scientific and clinical resource. Many behavioural correlates of cognitive functions show cyclic variations (Schmidt et al., 2007), whilst little is known about the modulation of the neural ones. Recently, differences in performance levels between extremely early and late chronotypes have been tackled in the neural substrates (Schmidt et al., 2009).

To date, neither external time nor internal time played an explicit and important role in the design of neuro-scientific study designs. The present study employed a task switching paradigm and demonstrated major time-of-day effects in the neural network underlying task performance. Time-of-day effects were associated with internal time and with time awake, underlining the importance of internal time for

everyday research and the interpretation of neuro-functional data sets. The significant variations observed in the BOLD signal over the day can be considered as a major methodological confound for most neuro-scientific studies, as the majority of fMRI research is based on group analyses. If the participant groups are composed of distinct chronotypes, and in case they are assessed at different time points, merging the participants introduces a critical signal variation that is independent of the task or action itself. Given the distribution of chronotypes in the population, it appears probable that study participants differ in internal time. Conclusions may therefore be biased. This study emphasizes the importance of internal time even within a chronotype-staggered design, reducing the impact of chronotype-variability to a maximum. The results of the present study also suggest even higher signal variations in case participant samples include extreme chronotypes.

The source of the variation can be linked to the sleep and wake regulating systems. Future research is essential to disentangle the influence of the circadian drive from the one of the homeostatic component on the task switching network. The influence of the systems regulating sleep and wake behaviour on neural activation patterns can be examined by repeated scanning and the usage of protocols such as constant routines. The systematic investigation of the interplay between cognitive performance, sleep and wake behaviour, and internal time requires the combination of those two expensive and effortful research methods and should thus be conducted in larger research networks.

The variations in the BOLD signal reported in this study did not appear to be task-specific. Other cognitive functions need to be examined to conceive similarities between particular functions and the influence of the circadian and the homeostatic components, respectively.

In case the impact of internal time on neural activation is not in the centre of fMRI researches, the control of this potentially confounding variable time-of-day is feasible with minor effort. First, internal time can be quantified by the MCTQ (Roenneberg, Kuehnle et al., 2007) providing a reliable approximation of the individual phase of entrainment or chronotype. Chronotype can then either be used as a covariate for statistical analyses, or allows for individually tailored

research designs. The aim of such research designs would be to keep the phase angle between internal and external time constant for each participants. As such, the integration of internal and external time appears relatively easy and the major confound revealed in the present study is controlled for.

Summary

The main conclusion of this doctoral dissertation is that internal time significantly influences behaviour, cognition, and physiology in real life conditions. The impact of internal time in real life suggests that sensible work schedules (i.e. day work, shift work or experimental laboratory work) should not be geared to logistical requirements, and thus external time only, but integrate the internal, individual time scale. The potential of this approach is so far unexplored.

6. Acknowledgements

6.1. To colleagues, friends, and family

First, I would like to thank my supervisor, Prof. Rainer Schandry, for supporting and believing in this project all along. Prof. Till Roenneberg is my mentor, I thank him for enlightening discussions and guidance, but also for giving me the freedom to follow my interests. I would also like to thank Prof. Gisela Grupe who has welcomed and supported this thesis project.

My colleague and friend, Dr. Myriam Juda, has welcomed me in the first place to the challenges and caveats of fieldwork. Without her, nothing would have been the same. I miss our conversations, debates, the soy latte and the genuine feedback.

The Institute of Medical Psychology gave me an inspiring, academic home, and I want to whole-heartedly thank my colleagues for giving valuable feedback and the best food I have ever encountered (in a work place): Dr. Cornelia Madeti, Manfred Gödel, Susanne Kantermann, Ildiko Meny, Dr. Thomas Kantermann, Dr. Julia Diegmann, Tanja Radic, Dr. Karla Viviani Allebrandt, Rosa Levandovsky, Prof. Ernst Pöppel, Susanne Piccone, Christiane Zündt Freiin von Kentzingen and Petra Carl.

The ClockWork project was my extended home. In particular, I would like to thank Dr. Isabelle Jasper, Andreas Häusler, Dr. Daniel Bratzke, Michael Steinborn, Patrizia Hölzle, PD Dr. Joachim Hermsdörfer, Prof. Rolf Ulrich, Kathrin Pusch und Anna Jessen for stimulating and productive teamwork. Christian Tatarau and his programming talent made a substantial contribution to the project.

Most precious help was provided by Gabriela Wypior, Franziska Scheller, Alexandra Obermayr, Lena Schwarzer and Simone Scharl: they intelligibly and carefully supported the data entry and study preparations.

Learning about neuro-imaging methods has always been on my agenda, but it was Dr. Evgeny Gutyrchik who gave me the opportunity to join the team of Systems Neurosciences at the IMP and of the Radiology Department. Thank you so much

for this unexpected development and incredible chance. The studies conducted with Isabella Peres, Dr. Thomas Meindl, Dr. Janusch Blautzik and Ute Coates were challenging and exciting.

Clever and critical minds surrounding me were of substantial help by giving me feedback, and hope, while writing this thesis: Dr. Myriam Juda, Dr. Agnieszka Wykowska, Isabella Peres, Dr. Cornelia Madeti, Martina Rieder, Dr. Evgeny Gutyrchik, Jennifer Bruder and Prof. Hans Distel. You made this even more than bearable. Dr. Christine Stenzer, in our mutual understanding I find comfort.

My friends. Thank you for travelling with me and making me the person I am: Alexandra Obermayr, Martina Rieder, Nadja Maki, Dr. Christine Stenzer, Silvia Neulinger, Dr. Agnieszka Wykowska, Jennifer Bruder, Katarina Groth, Dr. Christian Pohl, Anne Rolvering, Mark Schneider.

Ernst Kölnsperger, Dr. Anton Stroh, Andrea Gruhn-von Schlippe: you were there, all my life, tickling my mind, assisting my education, telling me about foreign horizons. Thank you so much.

Manuel Chwalinski, your support, understanding, lightness, love and wit, makes me laugh and realize the important things. Thank you for being the person you are.

My parents, Françoise and Klaus, and my brother Nicolas are the beginning. Your love and trust gave me the confidence to believe in me. This is for you.

6.2. To industry partners

First of all, I am grateful to have known the curious, open-minded and committed participants of these studies. Not only were they the pillar of this research. Interesting interactions permitted mutual understanding and learning.

The OSRAM GmbH trusted us in accompanying the light change in their headquarters; this is the result of a long-lasting and confident cooperation. I would like to particularly thank Dieter Lang, Dr. Andreas Wojtysiak and Alfred Wacker for their time and their open-mindedness in lengthy, fruitful discussions.

The shift work study was made possible by our partner, the Siemens AG. Wolfgang Kloke bore the responsibility and always believed in the success of this enterprise. His colleagues have provided valuable time, immense effort and excellent ideas in promoting chronobiology in shift work field research. I would like to thank the whole department of CT T DE TC2, especially Bea Alice Löhr, Julian Konrad, Dr. Nadja Schmiedl, Michael Quade, Mark Mohnke, Johannes Zettl, and Friedrich Dürst. In the field studies, nothing would have been possible without the help and understanding of employees on-site, in Cham and Berlin. Thank you, Dr. Friederike Dunkel-Benz, Wolfgang Eichinger, Eberhard Patzer, Martina Heinrich, Michael Schindler, Matthias Mettig, Bernd Koch, and Olaf Bolduan.

Finally, I would like to sincerely thank the Siemens AG, the OSRAM GmbH, the Daimler-Benz Foundation as well as EUCLOCK, a program of the European Union, FP7, for financial support.

7. Deutsche Zusammenfassung

Die innere Uhr des Menschen beeinflusst nicht nur maßgeblich das Schlaf- und Wachverhalten und das Schlafdefizit in Abhängigkeit der Arbeitszeiten (insbesondere bei Schichtarbeitern), sondern zudem die gesamte Physiologie und kognitive Leistungsfähigkeit. Die Anpassung der individuellen inneren Uhr an die externe 24-Stunden-Rotation der Erde und dem daraus resultierenden Licht-Dunkel-Wechsel (LD-Wechsel) weist starke interindividuelle Unterschiede auf. Diese variierende Einbettung in den 24-Stunden-Tag wird als *Chronotyp* bezeichnet. In einer Reihe einschlägiger Laborstudien zeigte sich die Bedeutung des Lichts (oder des LD-Wechsels) als Haupt-*Zeitgeber* für die innere Uhr. In der urbanen westlichen Gesellschaft sind Lichtmangel und eine daraus resultierende „Zeitgeberschwäche" weitverbreitet. Dieser Umstand erschwert nicht nur die saisonale Anpassung des Menschen an Jahreszeiten (und forciert so z.B. Grippewellen), sondern beeinträchtigt überdies auch dessen Anpassung an den externen LD-Wechsel, wodurch sich eine „Desynchronisation" (z.B. die Phasenverschiebungen infolge eines ‚Jetlags' oder im Rahmen von Schichtarbeit) einstellen kann. Schlafdeprivation, Schlafstörungen, eine verminderte physische und/oder kognitive Leistungsfähigkeit sowie unterschiedlichste kardio-vaskuläre und gastro-intestinale gesundheitliche Risiken zählen hierbei zu den häufigsten der – weder von Arbeitnehmern noch von Arbeitgebern – keinesfalls zu unterschätzenden Konsequenzen.

Mit der vorliegenden Arbeit wurde ein erster Versuch unternommen, diese soeben kursorisch angeführten Laborergebnisse „im echten Leben" zu untersuchen und durch entsprechend konzipierte Feldstudien zu examinieren. Die nachfolgend vorgestellten drei Studien (Studie 1: Auswirkung Tageslicht-ähnlicher Beleuchtung am Arbeitsplatz, Studie 2: Der Einfluss von Innenzeit und Schlafparametern auf die Reaktionsfähigkeit bei rotierenden 3-Schicht-Mitarbeitern, Studie 3: Tagesrhythmische Schwankungen der neuronalen Korrelate von kognitiven Funktionen) beleuchten die Effekte der individuellen inneren Uhr des Menschen auf das Schlaf- und Wachverhalten und die kognitive Leistungsfähigkeit unter

besonderer Berücksichtigung der extern vorgegebenen Arbeitszeitbedingungen sowie der spezifischen Lichtumgebung. Die Wichtigkeit und die potentiell vielschichtigen Implikationen des Chronotyps haben bis dato im Arbeits- und Wissenschaftsalltag kaum Beachtung gefunden.

Studie 1: Auswirkung Tageslicht-ähnlicher Beleuchtung am Arbeitsplatz

Die Mehrheit der Bevölkerung in der westlichen Hemisphäre verbringt den Großteil des Tages in Büroräumen, die hinsichtlich ihrer Lichtumgebung primär auf eine optimale visuelle Informationsverarbeitung abzielen und nur in seltenen Fällen auch auf das biologische, circadiane System des Menschen. Das Tageslichtspektrum beinhaltet einen relativ hohen Anteil an kurzwelligem („blauen") Licht. Wie in neuesten Studien nachgewiesen, wird das circadiane System insbesondere durch den kurzwelligen Anteil des Lichtspektrums synchronisiert. Die meisten konventionellen künstlichen Lichtquellen jedoch weisen in ihrer spektralen Zusammensetzung einen relativ geringen kurzwelligen Anteil auf. Die Lichtumgebung in Bürogebäuden stellt somit für den Menschen eine „biologische Dunkelheit" dar.

In Nachfolge einschlägiger Laborstudien, die eine Verbesserung des Wohlbefindens der Versuchspersonen durch den Einsatz von Tageslicht-ähnlicherem Licht nachweisen konnten, wurde im Rahmen der Studie 1 der Einfluss von entsprechenden Lichtquellen auf das Schlaf-Wachverhalten und das subjektive Wohlbefinden von Büroangestellten untersucht: Die Mitarbeiter der OSRAM GmbH in München führten hierfür in einem Zeitraum von 5 Wochen (14.01.-17.02.2008) eigens konzipierte „Schlaftagebücher" (n=49), trugen Aktimetrie-Uhren (n=27) und wurden in ihrer ursprünglichen Lichtumgebung mit dem „Munich ChronoType Questionnaire" (MCTQ) in ihrem Chronotyp erfasst. Das Schlaf-Wachverhalten wurde anhand der Mitte des Schlafes (aus Schlaftagebuchdaten) sowie der Mitte der Aktivitätsverteilung an Arbeits- und an freien Tagen (Aktimetriedaten, centre of gravity, ψ_{act}) quantifiziert. Die wöchentlichen Wohlbefindenswerte wurden ebenfalls durch die Schlaftagebücher ermittelt. Nach der zweiwöchigen Erfassung der Ausgangsdaten fand einzig in den oberen 3 Stockwerken die zu untersuchende Lichtumstellung von 4.000K auf

8.000K, mithin eine Annäherung auf das Tageslichtspektrum statt. Während somit die dort arbeitende experimentelle Gruppe (Schlaftagebücher n=27, Aktimetrie n=14) einer signifikant erhöhten Lichttemperatur (durch Anreicherung des Lichtspektrums v.a. im kurzwelligen Bereich) ausgesetzt war, verblieb die Kontrollgruppe (Schlaftagebücher n=27, Aktimetrie n=13) in ihrer gewohnten Lichtumgebung. Obgleich sich beide Gruppen weder in ihrer Alters-, Geschlechts- und Chronotyp-Zusammensetzung unterschieden, zeigten Analysen (Messwiederholungs-ANOVAs), dass die experimentelle Gruppe über die 5-wöchige Studienzeit hinweg in ihrem Schlaf- und Wachverhalten (Aktimetrie und Schlaftagebücher) an freien Tagen konstant blieb. Die Kontrollgruppe hingegen wies eine jahresrhythmische Anpassung der Schlafzeitpunkte und der Aktivitätsprofile an den Wochenenden auf, die dem progressiv früher-werdenden Sonnenaufgang folgten (während der Studie um 44 Minuten). Die modifizierte Lichtquelle des Arbeitsplatzes scheint demzufolge für die experimentelle Gruppe als Hauptzeitgeber zu fungieren, wobei die jahreszeitliche Veränderung der Photoperiode nur eine untergeordnete Rolle spielt. Das Wohlbefinden der Probanden zeigte weder in der Kontroll-, noch in der experimentellen Gruppe statistisch signifikante Veränderungen. Dieser Befund lässt eine geringe Sensibilität der Schlaftagebücher für die saisonale Dynamik des subjektiven Wohlbefindens vermuten und steht in Kontrast zu einer Reihe entsprechender Studien.

Als wesentliches Resultat der Studie 1 lässt sich ein durch Tageslicht-ähnliche Lampen am Arbeitsplatz hervorgerufener quantifizierbarer Effekt auf das Schlaf- und Wachverhalten der Arbeitnehmer benennen – ein Effekt, der den des Tageslichts sogar übertreffen kann. Gleichwohl sollte auf dieses Potential im Hinblick auf die im Laufe eines Jahres stetig variierende Tageslänge und die daraus resultierende saisonale Anpassung des Menschen mit Bedacht zurückgegriffen werden. Die Resultate dieser Studie unterstützen insbesondere die Entwicklung und Erforschung von jahreszeitlich-gesteuerten, dynamischen Beleuchtungssystemen.

Studie 2: Der Einfluss von Innenzeit und Schlafparametern auf die Reaktionsfähigkeit bei rotierenden 3-Schicht-Mitarbeitern

Wie Voruntersuchungen gezeigt haben, können Studien mit Schichtarbeitern nur dann zu validen und vergleichbaren Resultaten führen, wenn sie die Innenzeit, also den individuellen Chronotyp der Probanden berücksichtigen, der die Schlaflänge nach einer Schicht signifikant determiniert. Die bei Schichtarbeitern vielfach evidente Teilschlafdeprivation führt nicht nur zu gesundheitlichen und psychischen Belastungen, sondern erhöht auch die Arbeitsunfallquote. Da bis dato weder der Zusammenhang zwischen kognitiver Leistung und Schlafparametern (Wachzeit und Schlafdauer) in Abhängigkeit der Innenzeit noch chronotyp-spezifische Leistungsprofile von Schichtarbeitern vorliegen, erfolgte in Studie 2 eine eingehende Untersuchung des Zusammenspiels von Chronotyp, Kognition und dem Schlaf- und Wachverhalten.

Eine Studie mit jungen Schichtarbeitern (n=24, < 35 J.) testete in der Früh-, Spät- und Nachtschicht die einfache Reaktionsgeschwindigkeit (Psychomotor Vigilance Test, PVT) in 2-Stunden-Intervallen. Der hierfür auf einem PocketPC implementierte Test stellt eine klassische Reaktionszeitaufgabe dar, die im Labor zur Untersuchung von Tagesrhythmik und dem Einfluss von Schlafdeprivation eingesetzt wird. In Nachfolge entsprechender Laborergebnisse wird die schlechteste Leistung in den frühen Morgenstunden, die beste Leistung gegen 19:00 Uhr sowie ein Leistungseinbruch nach 16 bis 18 Stunden Wachzeit bei konstant bleibenden schnellsten Reaktionen (10%) erwartet. Weiterhin wurde der Zusammenhang zwischen Schlafdauer und Reaktionszeit untersucht. Insgesamt wurde die Reaktionsschnelligkeit über 12 Messzeitpunkte hinweg (4 pro Schicht) erfasst. Zur Ermittlung der exakten Schlaflänge vor einem Testtag und der Wachzeit zu einem gegebenen Testzeitpunkt führten alle zuvor mittels des $MCTQ^{shift}$ chronotypisierten Schichtarbeiter über den gesamten Studienzeitraum (5 Wochen, Juni/Juli 2008) Schlaftagebücher. Die durchschnittliche Reaktionsgeschwindigkeit der Mitarbeiter zeigte sich signifikant und additiv von der Innen- und der Außenzeit beeinflusst (signifikante Verminderung des least sum of square, Regressionsmodell). Die schlechteste Leistung wurde in der Frühschicht festgestellt, die beste in der Spätschicht. Leistungsminderungen

korrelierten mit steigender Wachzeit sowie verkürzter Schlafdauer. Nachweislich verlangsamte Reaktionsgeschwindigkeiten in der Frühschicht machten hierbei entgegen ursprünglicher Annahmen deutlich, dass eine optimale Reaktionszeit dort nicht abgerufen werden kann. Die signifikante Korrelation mit der kurzen Wachzeit in der Frühschicht deutet insofern auf einen Ermüdungszustand *(sleep inertia*) hin, welcher selbst transiente Leistungssteigerungen zu verhindern scheint.
Im Rahmen der Studie 2 konnten in Abhängigkeit von der Außen- und Innenzeit signifikante Unterschiede in den Reaktionszeiten der an ihrem Arbeitsplatz untersuchten rotierenden Schichtarbeiter festgestellt werden. Zudem ist die Reaktionszeit signifikant durch die Wachzeit sowie durch die schichtspezifische Schlafdauer beeinflusst, die ihrerseits durch den individuellen Chronotypen determiniert ist.

Studie 3: Tagesrhythmische Schwankungen der neuronalen Korrelate des Aufgabenwechsels

Wie bereits in einschlägigen Studien nachgewiesen, weist der Metabolismus des zentralen Nervensystems tagesrhythmische Schwankungen auf. Zudem unterliegt ein Großteil der behavioralen Messwerte kognitiver Funktionen systematischen Variationen, die mit der Innen-, der Außen- sowie der Wachzeit zusammenhängen. Bis heute sind potentielle Schwankungen der neuronalen Aktivitätsmuster bei kognitiven Paradigmen nicht systematisch beschrieben. Im Rahmen der neuro-funktionellen Studie 3 wurden die neuronalen und behavioralen Korrelate des Aufgabewechsels (*engl.* task-switching) aufgezeichnet, wobei die Leistung bei gleichbleibender Aufgabe mit der Leistung bei einem Wechsel zwischen zwei (perzeptuell gleichen) Aufgaben verglichen wird. In der zugrunde liegenden Aufgabe wurde der Einfluss der Wachzeit und der circadianen Komponente auf die Reaktionsfähigkeit und die Wechselkosten zwischen zwei Aufgaben bereits belegt. Die vorliegende Studie zielte auf eine Quantifizierung der möglichen tageszeitlichen Schwankungen des aufgabenspezifischen neuronalen Netzwerks unter Berücksichtigung des Chronotyps ab. Signifikante Modulationen dieses Netzwerks würden weitreichende Implikationen für gemeinhin irrespektiv

von Innen- und Außenzeit durchgeführte neurowissenschaftliche Studien bedeuten.

Mit einem nach Chronotypen gestaffelten Studiendesign wurden in einem Zeitraum von 8:30 bis 19:30 Uhr die Reaktionszeiten, die Fehler und die neuronalen Korrelate der elf Versuchspersonen registriert: die Teilnehmer bearbeiteten im 3-Tesla Magnetresonanztomographen vier Mal die Aufgabe und eine Kontrollaufgabe (im Blockdesign) in Intervallen von 2,5 Stunden. Vier weitere Probanden wurden – bei identischen Intervallen zwischen den Messungen – um eine erste Messung zeitversetzt und insofern in 3 Durchläufen gemessen. Die neuronale Aktivität, die über alle Messzeitpunkte hinweg während der Kontrollaufgaben registriert, was die Extraktion des aufgabenspezifischen Netzwerks erlaubte. Die auf diese Weise definierten Areale – linker Parietalcortex, linker prämotorischer Cortex, bilaterale thalamische Strukturen sowie das rechte Cerebellum – wurden bereits zuvor mit Aufgabenwechseln assoziiert. Cosinus-Anpassungen wurden für alle Areale als Funktion der Innen- sowie der Wachzeit vorgenommen. Anschließend wurden die Daten der Areale mit signifikant schwankenden Aktivierungsmustern mit denjenigen der 4 Probanden verglichen, die an den Messzeitpunkten 2 bis 4 ermittelt wurden. Dieses spezielle Studiendesign zielte auf eine präzise Differenzierung anhand eines Bootstrapping-Verfahrens zwischen Tageszeiteffekten (aufgrund der Innenzeit, der Wachzeit, oder beidem) und Sequenzeffekten (Lern- oder Gewöhnungseffekte). Es konnte eine signifikante Assoziation zwischen Schwankungen in den thalamischen Strukturen, den parietalen Areale sowie dem Cerebellum und der voranschreitenden Wachzeit nachgewiesen werden. Gleichermaßen sind die Aktivitätsmuster des Cerebellums und des prämotorischen Cortex im Laufe eines Tages abhängig von der Innenzeit. Der linke Thalamus, der inferiore linke Parietallappen sowie das Vermis wiesen zudem Sequenzeffekte auf. Analog zu eintägigen Schlafdeprivations-Experimenten nahmen auch im Rahmen der vorliegenden Studie die Reaktionszeiten der Probanden progressiv ab, wobei Trainingseffekte durch vorherige Trainingsdurchläufe ausgeschlossen werden konnten. Des Weiteren korrelierte eine nachweisbare Verbesserung der Reaktionszeit signifikant mit der Thalamusaktivität, einer Relaisstruktur in der

Regulation des Schlaf- und Wachverhaltens. Die Effektgröße der oben angeführten Schwankungen wurde anhand des Oszillationsbereichs der Cosinusfunktionen geschätzt und entsprach bis zu 100% der Signalstärke (Abweichung vom individuellen Mittel). Insgesamt machen die Ergebnisse der Studie 3 deutlich, dass Untersuchungen kognitiver Funktionen und deren neurofunktionaler Grundlagen nur unter entsprechender Berücksichtigung der Innenzeit valide und vergleichbare Resultate erzielen.

Schlussfolgerungen

Die soeben kursorisch vorgestellten Studien betonen die Relevanz der inneren Uhr: Büromitarbeiter zeigen sich signifikant von ihrer jeweiligen Lichtumgebung beeinflusst. Lampen mit spektraler Ähnlichkeit zum Tageslicht vermögen das von der inneren Uhr gesteuerte Schlaf- und Wachverhalten zu regulieren und den Einfluss des Außenlichts zu dominieren. Reaktionszeiten in der Früh-, Spät- und Nachtschicht von Schichtarbeitern sind – unmittelbar am Arbeitsplatz gemessen – signifikant von deren individueller Innen- und Außenzeit abhängig. Leistungseinbußen sind mit verlängerten Wachzeiten und verkürzter Schlafdauer assoziiert. Schlafdauer und Wachzeit sind wiederum vom individuellen Chronotypen eines Schichtarbeiters abhängig. In dem neuronalen Netzwerk, das einer kognitiven Aufgabe zugrunde liegt, lassen sich je nach Messzeitpunkt und individueller Innenzeit signifikant unterschiedliche Aktivierungsniveaus belegen. Ob Theorie oder Praxis, wissenschaftliche Untersuchung oder Arbeitswelt – die individuelle Innenzeit ist als zusätzlicher Maßstab zur sozialen Zeit unabdinglich für den Erkenntnisgewinn.

8. Curriculum Vitae

Céline Marie-Claire Désirée **Vetter**

*12.08.1980 in Munich

2007 - PhD Student
Biological Psychology, Department of Psychology, LMU, Munich
Prof. Dr. Rainer Schandry

2007 - Research Associate
Institute of Medical Psychology, Department of Medicine, LMU, Munich
Prof. Dr. Till Roenneberg

2006 - Postgraduate Research Fellowship

2007 Department of Psychology, University of Warwick, U.K.
Prof. Dr. Adrian von Muehlenen & Prof. Derrick Watson, PhD

2006 Master Thesis *"Psychopathology and Visual Search" (1,0)*
Max Planck Institute of Psychiatry, Munich, Germany
Prof. Dr. Josef Zihl

2004 - M.Sc.-Studies in neuro-cognitive Psychology

2006 Department of Psychology, LMU, Munich

2001 - Licence and D.E.U.G. of Psychology (Bachelor equivalent)

2004 Department of Psychology, Université Louis Pasteur,
Strasbourg, France

2000 Abitur at Gymnasium Ottobrunn

9. References

Achermann, P. (2004). The two-process model of sleep regulation revisited. *Aviation, Space, and Environmental Medicine, 75*(3, Suppl.), A37-A43.

Achermann, P., & Borbély, A. A. (2003a). Mathematical models of sleep regulation. *Frontier in Biosciences, 8*, S683-S693.

Achermann, P., & Borbély, A. A. (2003b). Mathematical models of sleep regulation. *Frontiers in Biosciences, 8*, s683-s693.

Akashi, M., Soma, H., Yamamoto, T., et al. (2010). Noninvasive method for assessing the human circadian clock using hair follicle cells. *Proc Natl Acad Sci USA, epub ahead of print, 23.08.2010*.

Åkerstedt, T. (2007). Altered sleep/wake patterns and mental performance. *Physiology & Behavior, 90*, 209-218.

Åkerstedt, T., & Folkard, S. (1995). Validation of the S and C components of the three-process model of alertness regulation. *Sleep, 18*(1), 1-6.

Åkerstedt, T., & Folkard, S. (1997). The three-process model of alertness and its extension to performance, sleep latency, and sleep length. *Chronobiology International, 14*(2), 115-123.

Åkerstedt, T., & Gillberg, M. (1990). Subjective and objective sleepiness in the active individual. *International Journal of Neuroscience, 52*(1-2), 29-37.

Åkerstedt, T., Kecklund, G., & Selén, J. (2010). Early morning work - prevalence and relation to sleep/wake problems: a national representative survey. *Chronobiology International, 27*(5), 975-986.

Alexander, G. E., & Crutcher, M. D. (1990). Functional architecture of basal ganglia circuits: neural substrates of parallel processing. *Trends in Neurosciences, 13*(7), 266-271.

Allebrandt, K. V., & Roenneberg, T. (2008). The search for circadian clock components in humans: new perspectives for association studies. *Brazilian Journal of Medical and Biological Research, 41*, 761-721.

Allebrandt, K. V., Teder-Laving, M., M., A., et al. (2010). CLOCK gene variants associate sleep duration in two independent populations. *Biological Psychiatry, 67*(11), 1040-1047.

Allport, D. A., Styles, E. A., & Hsieh, S. (1994). Shifting intentional set: exploring the dynamic control of tasks. In C. Umilta & M. Moscovitch (Eds.), *Attention and Performance XV* (pp. 421-452). Hillsdale: Erlbaum.

Altmann, E. M. (2004). The preparation effect in task-switching: Carryover of SOA. *Memory & Cognition, 32*(1), 153-163.

Altmann, E. M. (2007). Comparing switch costs: Alternating runs and explicit cueing. *Journal of Experimental Psychology: Learning, Memory, and Cognition, 33*(3), 475-483.

Alvarez, J. A., & Emory, E. (2006). Executive function and the frontal lobes: a meta-analytic review. *Neuropsychology Review, 16*(1), 17-42.

Antoch, M. P., Song, E. J., Chang, A.-M., et al. (1997). Functional identification of the mouse circadian Clock gene by transgenic BAC rescue. *Cell, 89*, 655-667.

Arendt, J. (2000). Melatonin, circadian rhythms and sleep. *New England Journal of Medicine, 343*, 1114-1116.

Arendt, J., & Skene, D. (2005). Melatonin as a chronobiotic. *Sleep Medicine Reviews, 9*, 25-39.

Aron, A. R., Monsell, S., Sahakian, B. J., et al. (2004). A componential analysis of task-switching deficits associated with lesions of left and right frontal cortex. *Brain, 127*(Pt 7), 1561-1573.

Aschoff, J. (1964). Die Tagesperiodik Licht- und Dunkelaktiver Tiere. *Revue Suisse Zoologique, 71*, 528-558.

Aschoff, J. (1993). On the relationship between motor activity and the sleep-wake cycle in humans during temporal isolation. *Journal of Biological Rhythms, 8*(1), 33-46.

Aschoff, J., & Pohl, H. (1978). Phase relations between a circadian rhythm and its zeitgeber within the range of entrainment. *Naturwissenschaften, 65*, 80-84.

Aschoff, J., Pöppel, E., & Wever, R. (1969). Circadian rhythms in men under the influence of light-dark cycles of various periods. *Pflugers Archives, 306*, 58-70.

Aston-Jones, G. (2005). Brain structures and receptors involved in alertness. *Sleep Medicine 6*(Suppl 1), S3-S7.

Avery, D. H., Kizer, D., Bolte, M. A., et al. (2001). Bright light therapy of subsyndromal seasonal affective disorder in the workplace: morning vs. afternoon exposure. *Acta Psychiatrica Scandinavica, 103*, 267-274.

Baehr, E. K., Fogg, L. F., & Eastman, C. I. (1999). Intermittent bright light and exercise to entrain human circadian rhythms to night work. *Am J Physiol Regul Integr Comp Phyiol, 277*, R1598-R1604.

Balkin, T. J., Bliese, P. D., Belenky, G., et al. (2004). Comparative utility of instruments for monitoring sleepiness-related performance decrements in the operational environment. *Journal of Sleep Research, 13*(3), 219-227.

Banks, S., & Dinges, D. F. (2007). Behavioral and physiological consequences of sleep restriction. *Journal of Clinical Sleep Medicine, 3*(5), 519-528.

Beersma, D., Daan, S., & Hut, R. (1999). Accuracy of circadian entrainment under fluctuating light conditions: contributions of phase and period responses. *Journal of Biological Rhythms, 14*, 320-329.

Beersma, D. G., & Daan, S. (1993). Strong and weak phase resetting by light pulses in humans? *Journal of Biological Rhythms, 8*, 340-347.

Begemann, S. H. A., van den Beld, G. J., & Tenner, A. D. (1997). Daylight, artificial light and people in office environment, overview of visual and biological responses. *International Journal of Industrial Ergonomics, 20*, 231-239.

Behrens, T. E. J., Johansen-Berg, H., Woolrich, M. W., et al. (2003). Non-invasive mapping of connections between human thalamus and cortex using diffusion imaging. *Nature Neuroscience, 6*(7), 750-757.

Benloucif, S., Guico, M. J., Reid, K. J., et al. (2005). Stability of melatonin and temperature as circadian phase markers and their relation to sleep times in humans. *Journal of Biological Rhythms, 20*, 178-188.

Berson, D. M. (2003). Strange vision: ganglion cells as circadian photoreceptors. *Trends in Neurosciences, 26*(6), 314-319.

Berson, D. M., Dunn, F. A., & Takao, M. (2002). Phototransduction by retinal ganglion cells that set the circadian clock. *Science, 295*, 1070-1073.

Biederman, I. (1972). Human performance in contingent information processing tasks. *Journal of Experimental Psychology, 93*, 219-238

.

Bjerner, B., Holm, Å., & Swensson, Å. (1955). Diurnal variation of mental performance. A study of three-shift workers. *British Journal of Industrial Medicine, 12*, 103-110.

Bjorvatn, B., Stengenes, K., Øyane, N., et al. (2006). Subjective and objective measures of adaptation and readaptation to night work on an oil rig in the north sea. *Sleep, 29*(6), 821-829.

Blatter, K., & Cajochen, C. (2007). Circadian rhythms in cognitive performance: methodological constraints, protocols, theoretical underpinnings. *Physiology & Behaviour, 90*, 196-208.

Blatter, K., Graw, P., Münch, M., et al. (2006). Gender and age differences in psychomotor vigilance performance under differential sleep pressure conditions. *Behavioural Brain Research, 168*, 312-317.

Boggild, H., & Knutsson, A. (1999). Shift work, risk factors and cardiovascular disease. *Scandinavian Journal of Work, Environment & Health, 25*(2), 85-99.

Boivin, D. B., & James, F. O. (2005). Light treatment and circadian adaptation to shift work. *Industrial Health, 43*(1), 34-48.

Borbély, A. A. (1982). A two process model of sleep regulation. *Human Neurobiology, 1*, 195-204.

Borbély, A. A., & Achermann, P. (1992). Concepts and models of sleep regulation: an overview. *Journal of Sleep Research, 1*, 63-79.

Borbély, A. A., & Achermann, P. (1999). Sleep homeostasis and models of sleep regulation. *Journal of Biological Rhythms, 14*, 557-568.

Born, J., & Wagner, U. (2004). Awareness in memory: being explicit about the role of sleep. *Trends in Cognitive Sciences, 8*, 242-244.

Brainard, G. C., Hanifin, J. P., Greeson, J. M., et al. (2001). Action spectrum for melatonin regulation in humans: evidence for a novel circadian photoreceptor. *Journal of Neuroscience, 21*, 6405-6412.

Brainard, G. C., Sliney, D., Hanifin, J. P., et al. (2008). Sensitivity of the Human Circadian System to Short-Wavelength (420-nm) Light. *Journal of Biological Rhythms, 23*(5), 379-386.

Brass, M., & von Cramon, D. Y. (2002). The role of the frontal cortex in task preparation *Cerebral Cortex, 12*, 908-914.

Bratzke, D., Rolke, B., Steinborn, M. B., et al. (2009). The effect of 40 h constant wakefulness on task-switching efficiency. *Journal of Sleep Research, 18*(2), 167-172.

Braver, T. S., Gray, J. R., & Burgess, G. S. (2007). Explaining the many varieties of working memory variation: Dual mechanisms of cognitive control. In A. R. A. Conway, C. Jarrold, M. J. Kane, A. Miyake & J. N. Towse (Eds.), *Variation in working memory* (pp. 76-106). Oxford: Oxford University Press.

Braver, T. S., Paxton, J. L., Locke, H. S., et al. (2009). Flexible neural mechanisms of cognitive control within human prefrontal cortex. *Proceedings of the National Academy of Sciences, 106*(18), 7351-7356.

Braver, T. S., Reynolds, J. R., & Donaldson, D. I. (2003). Neural mechanisms of transient and sustained cognitive control during task switching. *Neuron, 39*(4), 713-726.

Brown, E. N., Choe, Y., Shanahan, T. L., et al. (1997). A mathematical model of diurnal variations in human plasma melatonin levels. *American Journal of Physiology, 272*, E506-E516.

Brown, S. A., Fleury-Olela, F., Nagoshi, E., et al. (2005). The period length of fibroblast circadian gene expression varies widely among human individuals. *PLoS Biology, 3*(10), 1813-1818.

Brown, S. A., Kunz, D., Dumas, A., et al. (2008). Molecular insights into human daily behavior. *Proceedings of the National Academy of Sciences 105*(5), 1602-1607.

Burgess, G. S., Sharkey, K. M., & Eastman, C. (2002). Bright light, dark and melatonin can promote circadian adaptation in night shift workers. *Sleep Medicine Reviews, 6*(5), 407-420.

Buxton, O. M., Frank, S. A., L'Hermite-Balériaux, M., et al. (1999). Roles of intensity and duration of nocturnal exercise in causing phase delays of human circadian rhythms. *American Journal of Physiology, Endocrinology and Metabolism, 273*, E536-E542.

Cain, S. W., Rimmer, D. W., Duffy, J. F., et al. (2007). Exercise distributed across day and night does not alter circadian period in humans. *Journal of Biological Rhythms, 22*, 534-542.

Cajochen, C., Khalsa, S. B., Wyatt, J. K., et al. (1999). EEG and ocular correlates of circadian melatonin phase and human performance decrements during sleep loss. *American Journal of Physiology 227*, R640-R649.

Cajochen, C., Münch, M., Knoblauch, V., et al. (2006). Age-related changes in the circadian and homeostatic regulation of human sleep. *Chronobiology International, 23*(1&2), 461-474.

Cajochen, C., Münch, M., Kobialka, S., et al. (2005). High sensitivity of human melatonin, alertness, thermoregulation, and heart rate to short wavelength light. *The Journal of Clinical Endocrinology & Metabolism, 90*(3), 1311-1316.

Calhoun, V. D., Adali, T., Pearlson, G. D., et al. (2001). A method for making group inferences from functional MRI data using independent component analysis. *Human Brain Mapping, 14*, 140-151.

Campbell, S. S., & Dawson, D. (1990). Enhancement of nighttime alertness and performance with bright ambient light. *Physiology & Behavior, 48*(2), 317-320.

Cappuccio, F. P., Délia, L., Strazzullo, P., et al. (2010). Sleep duration and all-cause mortality: a systematic review and meta-analysis of prospective studies. *Sleep, 33*(5), 585-592.

Carrier, J., & Monk, T. H. (2000). Circadian rhythms of performance: new trends. *Chronobiology International, 17*(6), 719-732.

Carskadon, M. A., Labyak, S. E., Acebo, C., et al. (1999). Intrinsic circadian period of adolescent humans measured in conditions of forced desynchrony. *Neuroscience Letters, 260*, 129-132.

Cohen, J. (1988). *Statistical power analysis for the behavior sciences* (2nd Edition ed.). New Jersey: Lawrence Erlbaum.

Cohen, R. A., & Albers, H. E. (1991). Disruption of the human circadian and cognitive regulation following a discrete hypothalamic lesion: a case study. *Neurology, 41*, 726-729.

Colquhoun, W. P. (1971). Circadian variations in mental efficiency. In W. P. Colquhoun (Ed.), *Biological rhythms and human performance*. London: Academic Press.

Comas, M., Beersma, D. G., Spoelstra, K., et al. (2006). Phase and period responses of the circadian system of mice (Mus musculus) to light stimuli of different duration. *Journal of Biological Rhythms, 21*(5), 362-372.

Corbetta, M., Kincade, J. M., Ollinger, J. M., et al. (2000). Voluntary orientating is dissociated from target detection in posterior parietal cortex. *Nature Neuroscience, 3*, 292-297.

Corbetta, M., & Shulman, G. (2002). Control of goal-directed and stimulus driven attention in the brain. *Nature Reviews Neuroscience, 3*, 201-215.

Costa, G. (2005). Some considerations about age, shift work and work ability. *International Congress Series, 1280*, 67-72, Assessment and Promotion of Work Ability, Health and Well-being of Ageing Workers.

Costa, G., Gaffuri, E., Perfranceschi, G., et al. (1979). Re-entrainment of diurnal variation of psychological and physiological performance at the end of a slowly rotated shift system in hospital workers. *International Archives of Occupational Health, 44*, 165-175.

Coull, J. T., Jones, M. E., Egan, T. D., et al. (2004). Attentional effects of noradrenaline vary with arousal level: selective activation of thalamic pulvinar in humans. *NeuroImage, 22*, 315-322.

Couyoumdjian, A., Sdoia, S., Tempesta, D., et al. (2009). The effects of sleep and sleep deprivation on task-switching performance. *Journal of Sleep Research, 19*(1-I), 64-70.

Crone, E. A., Wendelken, C., Donohue, S. E., et al. (2006). Neural evidence for dissociable components of task-switching. *Cerebral Cortex, 16*(4), 475-486.

Crone, E. A., Wendlken, C., Donohue, S. E., et al. (2006). Neural evidence for dissociable components of task-switching. *Cerebral Cortex, 16*, 475-486.

Czeisler, C. A., Allan, J. S., & Kronauer, R. E. (1986). A method to assess the intrinsic period of the endogenous circadian oscillator. *Sleep Research, 15*, 266.

Czeisler, C. A., Duffy, J. F., Shanahan, T. L., et al. (1995). Reassessment of the intrinsic period of the human circadian pacemaker in young and older subjects. *Sleep Research, 24A*, 505.

Czeisler, C. A., Duffy, J. F., Shanahan, T. L., et al. (1999). Stability, precision, and near-24-hour period of the human circadian pacemaker. *Science, 284*(2177-2181).

Czeisler, C. A., Kronauer, R. E., Allan, J. S., et al. (1989). Bright light induction of strong (type 0) resetting of the human circadian pacemaker. *Science, 244*, 1328-1333.

D´Esposito, M., Detre, J. A., Alsop, D. C., et al. (1995). The neural basis of the executive system of working memory. *Nature, 378*, 279-281.

Daan, S. (1981). Adaptive daily strategies in behavior. In J. Aschoff (Ed.), *Biological Rhythms* (Vol. 4, pp. 275-298). New York, London: Plenum Press.

Daan, S. (2000). Colin Pittendrigh, Jürgen Aschoff, and the natural entrainment of circadian systems. *Journal of Biological Rhythms, 15*(3), 195-207.

Daan, S., & Pittendrigh, C. S. (1976). A functional analysis of circadian pacemakers in nocturnal rodents. III. Heavy water and constant light: homeostasis of frequency? *Journal of Comparative Physiology, 106*, 276-290.

Dacey, D. M., Liao, H. W., Peterson, B. B., et al. (2005). Melanopsin-expressing ganglion cells in primate retina signal colour and irradiance project to the LGN. *Nature, 433*, 749-754.

Danilenko, K. V., Cajochen, C., & Wirz-Justice, A. (2003). Is sleep per se a zeitgeber in humans? *Journal of Biological Rhythms, 18*(2), 170-178.

Dawson, D., Lack, L. C., & Morris, M. (1993). Phase resetting of the human circadian pacemaker of a single pulse of bright light. *Chronobiology International, 10*(2), 94-102.

de Mairan, J. J. (1729). Observation botanique. *Histoire de l'Academie Royale des Sciences*, 35-36.

Denisco, R. A., Drummond, J. N., & Gravenstein, J. S. (1987). The effect of fatigue on the performance of a simulated anesthetic monitoring task. *Journal of Clinical Monitoring, 3*, 22-24.

Derrfuss, J., Brass, M., Neumann, J., et al. (2005). Involvement of the inferior frontal junction in cognitive control: meta-analyses of switching and stroop studies. *Human Brain Mapping, 25*, 22-34.

Diegmann, J., Stück, A., Madeti, C., et al. (2010). Entrainment elicits period aftereffects in neurospora crassa. *Chronobiology International, 27*(7), 1335-1347.

Dijk, D.-J., & Archer, S. N. (2009). Light, sleep, and circadian rhythms: together again. *PLoS Biology, 7*(6), e1000145.

Dijk, D.-J., Duffy, J. F., & Czeisler, C. A. (1992). Circadian and sleep/wake dependent aspects of subjective alertness and cognitive performance. *Journal of Sleep Research, 1*(2), 112-117.

Dijk, D.-J., Duffy, J. F., & Czeisler, C. A. (2000). Contribution of circadian physiology and sleep homeostasis to age-related changes in human sleep. *Chronobiology International, 17*, 285-311.

Dinges, D. (2009). An overview of sleepiness and accidents. *Journal of Sleep Research, 4*(2), 4-14.

Dinges, D. F., Kribbs, N. B., Steinber, K. N., et al. (1992). Do we lose the willingness to perform during sleep deprivation? *Sleep Research, 21*, 318.

Dinges, D. F., Pack, F., Williams, K., et al. (1997). Cumulative sleepiness, mood disturbance, and psychomotor vigilance performance decrements during a week of sleep restricted to 4-5 h per night. *Sleep, 20*, 267-277.

Dinges, D. F., & Powell, J. W. (1985). Microcomputer analyses of performance on a portable, simple visual RT task during sustained operations. *Behavior Research Methods, Instruments & Computers, 17*, 652-655.

Doran, S. M., Van Dongen, H. P. A., & Dinges, D. F. (2001). Sustained attention performance during sleep deprivation: evidence of state instability. *Archives Italiennes de Biologie, 139*, 253-267.

Dorrian, J., Rogers, N. L., & Dinges, D. F. (2005). Psychomotor vigilance performance: Neurocognitive assay sensitive to sleep loss. In C. A. Kushida (Ed.), *Sleep Deprivation*. New York: Marcel Dekker Inc.

Dove, A., Pollmann, S., Schubert, T., et al. (2000). Prefrontal cortex activation in task switching: an event-related fMRI study. *Brain research Cognitive brain research, 9*(1), 103-109.

Dreher, J.-C., Koechlin, E., Ali, S. O., et al. (2002). The roles of timing and task order during task switching. *NeuroImage, 17*, 95-109.

Drummond, S. P. A., Bischoff-Grethe, A., Dinges, D. F., et al. (2005). The neural basis of the Psychomotor Vigilance Task. *Sleep, 28*(9), 1059-1068.

Duffy, J. F., Rimmer, D. W., & Czeisler, C. A. (2001). Association of intrinsic circadian period with morningness-eveningness, usual wake time, and circadian phase. *Behavioral Neuroscience, 115*, 895-899.

Dula, D. J., Dula, N. L., Hamrick, C., et al. (2001). The effect of working serial night shifts on the cognitive functioning of emergency physicians. *Annals of Emergency Medicine, 38*(2), 152-155.

Dumont, M., & Beaulieu, C. (2007). Light exposure in the natural environment: relevance to mood and sleep disorders. *Sleep Medicine, 8*, 557-565.

Dunlap, J. C. (2002). Molecular bases for circadian clocks. *Cell, 96*, 217-290.

Durmer, J. S., & Dinges, D. F. (2005). Neurocognitive consequences of sleep deprivation. *Seminars in Neurology, 25*(1), 117-129.

Eastman, C. I., Hoese, E. K., Youngstedt, S. D., et al. (1995). Phase-shifting human circadian rhythms with exercise during the night shift. *Physiology & Behavior, 58*(6), 1287-1291.

Edwards, B., Reilly, T., & Waterhouse, J. (2009). Zeitgeber-effects of exercise on human circadian rhythms: what are alternative approaches to investigating the existence of a phase-response curve to exercise? *Biological Rhythm Research, 40*(1), 53-69.

Edwards, B., Waterhouse, J., & Reilly, T. (2008). Circadian rhythms and their association with body temperature and time awake when performing a simple task with the dominant and non-dominant hand. *Chronobiology International, 25*(1), 115-132.

Eriksson, J., Larsson, A., & Nyberg, L. (2008). Item-specific training reduces prefrontal cortical involvement in perceptual awareness. *Journal of Cognitive Neuroscience, 20*(10), 1777-1787.

Fergueson, S. A., Lamond, N., Kandelaars, K., et al. (2008). The impact of short, irregular sleep opportunities at sea on the alertness of marine pilots working extended hours. *Chronobiology International, 25*(2&3), 399-411.

Field, A. (2009). *Discovering statistics using SPSS* (3rd ed.). Los Angeles, CA.: Sage.

Folkard, S. (1983). Diurnal variation in human performance. In G. R. J. Hockey (Ed.), *Stress and fatigue in human performance* (pp. 245-272). Chichester, England: Wiley.

Folkard, S. (2008). Do permanent night workers show circadian adjustment? A review based on the endogenous melatonin rhythm. *Chronobiology International, 25*(2), 215-224.

Folkard, S., & Åkerstedt, T. (1992). A three-process model of the regulation of alertness-sleepiness. In R. J. Broughton & R. D. Ogilvie (Eds.), *Sleep, arousal, and performance*. Boston: Birkhäuser.

Folkard, S., & Åkerstedt, T. (2004a). Trends in the risk of accidents and injuries and their implications for models of fatigue and performance. *Aviation, Space, and Environmental Medicine, 75*, A161-167.

Folkard, S., & Åkerstedt, T. (2004b). Trends in the risk of accidents and injuries and their implications of fatigue and performance. *Space Environ Med, 75*(3).

Folkard, S., Åkerstedt, T., Macdonald, I., et al. (1999). Beyond the three-process model of alertness: estimating phase, time on shift and successive night effects. *Journal of Biological Rhythms, 14*(6), 579-589.

Folkard, S., Arendt, J., & Clark, M. (1993). Can melatonin improve shift workers' tolerance to night shifts: preliminary findings. *Chronobiology International, 10*(5), 315-320.

Folkard, S., Wever, R. A., & Wildgruber, C. M. (1983). Multi-oscillatory control of circadian rhythms in human performance. *Nature, 305*, 223-226.

Foster, R., & Bellingham, J. (2002). Opsins and melanopsins. *Current Biology, 12*(16), R543-544.

Foster, R., & Hankins, M. (2007). Circadian vision. *Current Biology, 17*(17), 746-751.

Foster, R. G., & Kreitzman, L. (2004). *Rhythms of Life: the biological clocks that control the daily lives of every living thing*. London: Profile Books.

Foster, R. G., & Wulff, K. (2005). The rhythm of rest and excess. *Nature Reviews Neuroscience, 6*, 407-414.

Foucher, F. R., Otzenberger, H., & Gounot, D. (2004). Where arousal meets attention: a simultaneous fMRI and EEG recording study. *NeuroImage, 22*, 688-697.

Frank, M. G. (2006). The function of sleep. In T. L. Lee-Chiong (Ed.), *Sleep: a comprehensive handbook* (pp. 45-48). New Jersey: Wiley-Liss.

Frey, D. J., Badia, P., & Wright, K. P. (2004). Inter- and intra-individual variability in performance near the circadian nadir during sleep deprivation. *Journal of Sleep Research, 13*, 305-315.

Galy, E., Mélan, C., & Cariou, M. (2008). Investigation of task performance variations according to task requirements and alertness across the 24-h day in shift workers. *Ergonomics, 51*(9), 1338-13351.

Gazzaniga, M. S. (2009). *The Cognitive Neurosciences* (4th ed.): MIT Press.

Gitelman, D. R., Nobre, A., Parrish, T. B., et al. (1999). A large-scale distributed network for covert spatial attention. Further anatomical delineation based on stringent behavioural and cognitive controls. *Brain, 122*, 1093-1106.

Glickman, G., Byrne, B., Pineda, C., et al. (2006). Light therapy for seasonal affective disorder with blue narrow-band light-emitting diodes (LEDs). *Biological Psychiatry, 59*(6), 502-507.

Gooley, J. J., Lu, J., Fischer, D., et al. (2003). A broad role for melanopsin in nonvisual photoreception. *The Journal of Neuroscience, 23*(18), 7093-7106.

Graw, P., Kräuchi, K., Knoblauch, V., et al. (2004). Circadian and wake-dependent modulation of fastest and slowest reaction times during the psychomotor vigilance task. *Physiology & Behavior, 80*, 695-701.

Gronfier, C., Wright, H. R., Kronauer, R. E., et al. (2004). Efficacy of a single sequence of intermittent bright light pulses for delaying circadian phases in humans. *American Journal of Physiology, Endocrinology and Metabolism, 287*(1), E174-E181.

Gurd, J. M., Amunts, K., Weiss, P. H., et al. (2002). Posterior parietal cortex is implicated in continuous switching between verbal fluency tasks: an fMRI study with clinical implications. *Brain, 125*(5), 1024-1038.

Hasher, L., Goldstein, D., & May, C. P. (2005). It´s about time: Circadian rhythms, memory, and aging. In C. Izawa & N. Ohta (Eds.), *Human learning and memory: Advances in theory and application* (4th ed., pp. 199-218). Mahwah, N.J.: Lawrence Erlbaum Associates.

Hastings, M. H. (1998). The brain, circadian rhythms, and genes. *British Medical Journal, 317*, 1704-1707.

Hastings, M. H., Maywood, E. S., & Reddy, A. B. (2008). Two decades of circadian time. *Journal of Neuroendocrinology, 20*, 812-819.

Hastings, M. H., Reddy, A. B., & Maywood, E. S. (2003). A clockwork web: circadian timing in brain and periphery, in health and disease. *Nature Reviews Neuroscience, 4*, 649-661.

Havel, M. (2010). *Synchronisation der inneren Uhr an die Nachtschicht durch gezielte Lichtexposition unter Berücksichtigung des Chronotyps: Eine Feldstudie.* Unpublished Doctoral Dissertation, Department of Medicine, Ludwig-Maximilians-University, Munich.

Hebert, M., Martin, S. K., Lee, C., et al. (2002). The effects of prior light history on the suppression of melatonin by light in humans. *Journal of Pineal Research, 33*, 198-203.

Heuer, H., Kleinsorge, T., Klein, W., et al. (2004). Total sleep deprivation increases the costs of shifting between simple cognitive tasks. *Acta Psychologia, 117*, 29-64.

Heyder, K., Suchan, B., & Daum, I. (2004). Cortico-subcortical contributions to executive control. *Acta Psychologica, 115*, 271-289.

Hoch, C. C., Reynolds, C. F., Jennings, J. R., et al. (1992). Daytime sleepiness and performance among healthy 80 and 20 year olds. *Neurobiology of Aging, 13*, 353-356.

Honma, K., Honma, S., & Wada, T. (1987). Phase-dependent shift of free-running circadian rhythms in response to a single bright light pulse. *Experientia, 43*, 1205-1207.

Horne, J. A., & Østberg, O. (1976). A self-assessment questionnaire to determine morningness-eveningness in human circadian rhythms. *International Journal of Chronobiology, 4*, 97-110.

Horne, J. A., & Pettitt, A. N. (1985). High incentive effects on vigilance performance during 72 hours of total sleep deprivation. *Acta Psychologica, 58*, 123-139.

Horowitz, T. S., Cade, B. E., Wolfe, J. M., et al. (2003). Searching night and day: a dissociation of effects of circadian phase and time awake on visual selective attention and vigilance. *Psychological Science, 14*(6), 549-557.

Hossain, J. L., Reinish, L. W., Heslegrave, R. J., et al. (2004). Subjective and objective evaluation of sleep and performance in daytime versus nighttime sleep in extended-hours shift-workers at an underground mine. *Journal of Occupational and Environmental Medicine, 46*(3), 212-226.

Hubalek, S., Brink, M., & Schierz, C. (2010). Office workers' daily exposure to light and its influence on sleep quality and mood. *Lighting Research Technologies, 42*, 33-50.

Hufeland, C. W. (1797). *Die Kunst das menschliche Leben zu verlängern*. Jena: Akademische Buchhandlung.

Hut, R. (2007). CircWave (Version 1.4.). Groningen, The Netherlands.

Hyafil, A., Summerfield, C., & Koechlin, E. (2009). Two mechanisms for task switching in the prefrontal cortex. *The Journal of Neuroscience, 29*(16), 5135-5142.

Ingre, M., Kecklund, G., Åkerstedt, T., et al. (2008). Sleep length as a function of morning shift-start time in irregular shift schedules for train drivers: self-rates health and individual differences. *Chronobiology International, 25*(349-358).

Irwin, M., McClintick, J., Costlow, C., et al. (1996). Partial night sleep deprivation reduces natural killer and cellular immune responses in humans. *The FASEB Journal, 10*, 643-653.

Jasper, I., Häußler, A., Baur, B., et al. (2009). Circadian variations in the kinematics of handwriting and grip strength. *Chronobiology International, 26*(3), 576-594.

Jasper, I., Roenneberg, T., Häußler, A., et al. (2010). Circadian rhythm in force tracking and in dual task costs. *Chronobiology International, 27*(3), 653-673.

Jersild, A. T. (1927). Mental set and shift. *Archives of Psychology, 89*.

Jewett, M. E., Dijk, D.-J., Kronauer, R. E., et al. (1999). Dose-response relationship between sleep duration and human psychomotor vigilance and subjective alertness. *Sleep, 22*, 171-179.

Jewett, M. E., Wright, K. P., Hull, J. T., et al. (2001). Practice effects observed over a month-long 28-hour forced desynchrony protocol in a cognitive

throughput task are well described by a saturating exponential function. *Sleep, 24*(A4).

Jewett, M. E., Wyatt, J. K., Ritz- De Cecco, A., et al. (1999). Time course of sleep inertia dissipation in human performance and alertness. *Journal of Sleep Research, 8*, 1-8.

Johnson, C. H., Elliott, J. A., & Foster, R. G. (2003). Entrainment of circadian programs. *Chronobiology International, 20*(5), 741-774.

Johnson, M. P., Duffy, J. F., Dijk, D.-J., et al. (1992). Short-term memory, alertness and performance: A reappraisal of their relationship to body temperature. *Journal of Sleep Research, 1*, 24-29.

Juda, M. (2010). *The importance of chronotype in shift work*. Unpublished doctoral dissertation, Department of Psychology, Ludwig-Maximilians-University, Munich.

Jung, T.-P., Makeig, S., McKeown, M. J., et al. (2001). Imaging brain dynamics using independent component analysis. *Proceedings of the IEEE, 89*(7), 1107-1122.

Kandelaars, K., Baulk, S. D., Fletcher, A., et al. (2006). Observations of age-related differences in neurobehavioral performance in a 12-hour shift system. *Sleep and Biological Rhythms, 4*, 171-174.

Kantermann, T., Juda, M., Merrow, M., et al. (2007). The human circadian clock's seasonal adjustment is disrupted by daylight saving time. *Current Biology, 17*(22), 1996-2000.

Kantermann, T., Juda, M., Vetter, C., et al. (2010). Shift-work research: Where do we stand, where should we go? *Sleep and Biological Rhythms, 8*(2), 95-105.

Kenagy, G. J. (1980). Center-of-gravity of circadian activity and its relation to free-running period in two rodent species. *Journal of Interdisciplinary Cycle Research, 11*, 1-8.

Khalsa, S. B., Jewett, M. E., Cajochen, C., et al. (2003). A phase response curve to single bright light pulses in human subjects. *Journal of Physiology, 549*, 945-952.

Kimberg, D. Y., Aguirre, G. K., & D´Esposito, M. (2000). Modulation of task-related neural activity in task-switching: an fMRI study. *Cognitive Brain Research, 10*, 189-196.

King, D. P., Zhao, Y., Sangoram, A. M., et al. (1997). Positional cloning of the mouse circadian Clock gene. *Cell, 89*(641-653).

Klein, D. C., Moore, R. Y., & Reppert, S. M. (1991). *Suprachiasmatic nucleus: the mind´s clock*. New York: Oxford University Press.

Kleitman, N. (1923). The effects of prolonged sleeplessness on man. *American Journal of Physiology, 66*, 67-92.

Kleitman, N. (1987). *Sleep and wakefulness* (Midway Reprint ed.). Chicago, London: University of Chicago Press.

Klerman, E. B., Dijk, D.-J., Kronauer, R. E., et al. (1996). Simulations of light effects on the human circadian pacemaker: implications for assessment of intrinsic period. *American Journal of Physiology Regulatory Integrative Comparative Physiology, 270*, R271-R282.

Klerman, E. B., Rimmer, D. W., Dijk, D.-J., et al. (1998). Nonphotic entrainment of the human circadian pacemaker. *American Journal of Physiology, 274*, R991-R996.

Klerman, E. B., Shanahan, T. L., Brotman, D. J., et al. (2002). Photic resetting of the human circadian pacemaker in the absence of conscious vision. *Journal of Biological Rhythms, 17*, 548-555.

Knez, I. (1995). Effects of indoor lighting on mood and cognition. *Journal of Environmental Psychology, 15*(1), 39-51.

Knutson, K. L., & Van Cauter, E. (2008). Associations between sleep loss and increased risk of obesity and diabetes. *Annals of the New York Academy of Sciences, 1129*, 287-304.

Knutsson, A. (2004). Methodological aspects of shift work research. *Chronobiology International, 21*(6), 1037-1047.

Koller, M., Härmä, M., Laitinen, J. T., et al. (1994). Different patterns of light exposure in relation to melatonin and cortisol rhythms and sleep of night shift workers. *Journal of Pineal Research, 16*, 127-135.

Kopasz, M., Loessl, B., Hornyak, M., et al. (2010). Sleep and memory in healthy children and adolescents - a critical review. *Sleep Medicine Reviews, 14*(3), 167-177.

Kreitzman, L. (1999). *The 24 Hour Society*. London: Profile Books.

Kribbs, N. B., & Dinges, D. F. (1994). Vigilance decrement and sleepiness. In R. Harsh & R. D. Ogilvie (Eds.), *Sleep onset mechanisms* (pp. 113-125). Washington, D.C.: American Psychological Association.

Kripke, D. F., Garfinkel, L., Wingard, D. L., et al. (2002). Mortality associated with sleep duration and insomnia. *Archives of General Psychiatry, 59*, 131-136.

Kronauer, R. E., Forger, D. B., & Jewett, M. E. (1999). Quantifying human circadian pacemaker response to brief, extended, and repeated light stimuli over the phototopic range. *Journal of Biological Rhythms, 14*, 501-516.

Krueger, J. M., & Obal, F. J. (2003). Sleep function. *Frontiers in Biosciences, 1*(8), d511-519.

Krueger, J. M., Rector, D. M., Roy, S., et al. (2008). Sleep as a fundamental property of neuronal assemblies. *Nature Reviews Neuroscience, 9*(12), 910-919.

Kühnle, T. (2006). *Quantitative analysis of human chronotype*. Unpublished doctoral dissertation, Department of Medicine, Ludwig-Maximilians-University, Munich.

Kyriacou, C. P., & Hastings, M. H. (2010). Circadian clocks: genes, sleep, and cognition. *Trends in Cognitive Sciences, 14*(6), 259-267.

Lack, L. C., & Wright, H. R. (2007). Chronobiology of sleep in humans. *Cellular and Molecular Life Sciences, 64*, 1205-1215.

Lamond, N., Dawson, D., & Roach, G. D. (2005). Fatigue assessment in the field: validation of a hand-held electronic psychomotor vigilance task. *Aviation, Space, and Environmental Medicine, 76*(5), 486-489.

Lamond, N., Petrilli, R. M., Dawson, D., et al. (2006). Do short international layovers allow sufficient opportunity for pilots to recover? *Chronobiology International, 23*(6), 1285-1294.

Lamond, N., S.M., J., Dorrian, J., et al. (2008). The sensitivity of a palm-based psychomotor vigilance task to severe sleep loss. *Behavior Research Methods, 40*(1), 347-352.

Lancaster, J. L., Woldroff, M. G., Parsons, L. M., et al. (2000). Automated Tailarach atlas labels for functional brain mapping. *Human Brain Mapping, 10*, 120-131.

Lee, J. H., Wang, W., Silva, E. J., et al. (2009). Neurobehavioral performance in young adults living on a 28-h day for 6 weeks. *Sleep, 32*(7), 905-913.

Leger, D. (1994). The cost of sleep-related accidents: a report for the National Commission on Sleep Disorders Research. *Sleep, 17*(1), 84-93.

Lehman, M. N., Silver, R., Gladstone, W. R., et al. (1987). Circadian rhythmicity restored by neural transplant. Immunocytochemical characterization of the graft and its integration with the host brain. *The Journal of Neuroscience, 7*(6), 1626-1638.

Lemmer, B. (2009). Discoveries of rhythms in human biological function: a historical overview. *Chronobiology International, 26*(6), 1019-1068.

Lim, J., & Dinges, D. F. (2008). Sleep deprivation and vigilant attention. *Annals of the New York Academy of Sciences, 1129*, 305-322.

Liu, C., & Reppert, S. M. (2000). GABA synchronizes clock cells within the suprachiasmatic circadian clock. *Neuron, 25*(1), 123-128.

Lockley, S. W., Evans, E. E., Scheer, F. A. J. L., et al. (2006). Short-wavelength sensitivity for the direct effects of light on alertness, vigilance, and the waking electroencephalogram in humans. *Sleep 29*, 161-169.

Lockley, S. W., & Gooley, J. J. (2006). Circadian photoperception: spotlight on the brain. *Current Biology, 16*(18), R795-R797.

Lockley, S. W., Skene, D., Arendt, J., et al. (1997). Relationship between melatonin rhythms and visual loss in the blind. *Journal of Clinical Endocrinology and Metabolism, 82*, 4502-4505.

Logan, G. D. (1985). Executive control of thought and action. *Acta Psychologica, 60*, 193-210.

Logan, G. D. (2003). Executive control of thought and action: In search of the wild homunculus. *Current Direction in Psychological Science, 12*, 45-48.

Logan, G. D. (2004). Working memory, task switching, and executive control in the task span procedure. *Journal of Experimental Psychology: General, 133*(2), 218-236.

Logan, G. D., & Bundesen, C. (2003). Clever Homunculus: Is there an endogenous act of control in the explicit task-cueing paradigm? *Journal of Experimental Psychology: Human Perception and Performance, 29*(3), 575-599.

Logan, G. D., Schneider, D. W., & Bundesen, C. (2007). Still clever after all these years: Searching for the Homunculus in explicitly cued task switching.

Journal of Experimental Psychology: Human Perception and Performance, 33(4), 978-994.

Lombardi, D. A., Folkard, S., Willetts, J. L., et al. (2010). Daily sleep, weekly working hours, and risk of work-related injury: US national health interview survey (2004-2008). *Chronobiology International, 27*(5), 1013-1030.

Lowden, A., Kecklund, G., Axelsson, J., et al. (1998). Change from a 8-hour shift to a 12-h shift, attitudes, sleep, sleepiness and performance. *Scandinavian Journal of Work, Environment and Health, 24*(3), 69-75.

MacDonald, A. W., Cohen, J. D., Stenger, V. A., et al. (2000). Dissociating the role of dorsolateral prefrontal and anterior cingulate cortex in cognitive control. *Science, 228*, 1835-1838.

Marcheva, B., Ramsey, K. M., Affinati, A., et al. (2010). Clock genes and metabolic disease. *Journal of Applied Physiology, 107*, 1638-1646.

May, C. P. (1999). Synchrony effects in cognition: the costs and a benefit. *Psychonomic Bulletin & Review, 6*(1), 142-147.

McKeown, M. J., Hansen, L. K., & Sejnowski, T. J. (2003). Independent component analysis of functional MRI: what is signal and what is noise? *Current Opinion in Neurobiology, 13*, 620-629.

Meerlo, P., Sgoifo, A., & Suchecki, D. (2008). Restricted and disrupted sleep: effects on autonomic function, neuroendocrine stress systems and stress responsivity. *Sleep Medicine Reviews, 12*(3), 197-210.

Meiran, N. (1996). Reconfiguration of processing mode prior to task performance. *Journal of Experimental Psychology: Learning, Memory and Cognition, 2*, 1423-1442.

Meiran, N., Hommel, B., Bibi, U., et al. (2002). Consciousness and control in task switching. *Consciousness and Cognition, 11*, 10-33.

Menaker, M. (2003). Circadian photoperception. *Science, 299*, 213-214.

Mendoza, J. (2007). Circadian clocks: setting time by food. *Journal of Neuroendocrinology, 19*(2), 127-137.

Mesulam, M. M. (1990). Large-scale neurocognitive networks and distributed processing for attention, language, and memory. *Annals of Neurology, 28*(597-613).

Meyer, E. D., Evans, J. E., Lauber, E. J., et al. (1997). *Activation of brain mechanisms for executive mental processes in cognitive task switching*. Paper presented at the Meeting of the Cognitive Neuroscience Society.

Mignot, E., Taheri, S., & Nishino, S. (2002). Sleeping with the hypothalamus: emerging therapeutic targets for sleep disorders. *Nature Neuroscience, 5*, Suppl. 1071-1075.

Mills, J. N., Minors, D. S., & Waterhouse, J. M. (1978). Adaptation to abrupt time shifts of the oscillator(s) controlling human circadian rhythms. *Journal of Physiology, 285*, 455-470.

Mills, P., Tomkins, S., & Schlangen, L. J. (2007). The effect of high correlated colour temperature office lighting on employee wellbeing and work performance. *Journal of Circadian Rhythms, 5*, 2.

Minors, D. S., & Waterhouse, J. M. (1989). Masking in humans: the problem and some attempts to deal with it. *Chronobiology International, 6*, 29-53.

Mistlberger, R. E., & Skene, D. J. (2004). Social influences on mammalian circadian rhythms: animal and human studies. *Biological Reviews, 79*(3), 533-556.

Mistlberger, R. E., & Skene, D. J. (2005). Nonphotic entrainment in humans? *Journal of Biological Rhythms, 20*(5), 339-352.

Moller, H. J., Devins, G. M., Shen, J., et al. (2006). Sleepiness is not the inverse of alertness: evidence from four sleep disorder patient groups. *Experiemental Brain Research, 173*(2), 258-266.

Monk, T. H., Buysse, D. J., Reynolds, C. F., et al. (1997). Circadian rhythms in human performance and mood under constant conditions. *Journal of Sleep Research, 6*, 9-18.

Monk, T. H., & Carrier, J. (2003). Shift worker performance. *Clinics in Occupational and Environmental Medicine, 3*, 209-229.

Monk, T. H., Folkard, S., & Wedderburn, A. J. (1996). Maintaining safety and high performance on shift work. *Applied Ergonomics, 27*, 17-23.

Monsell, S. (1996). Control of mental processes. In V. Bruce (Ed.), *Mysteries of the Mind: Tutorial Essays on Cognition* (pp. 93-148). Hove: Erlbaum.

Monsell, S. (2003). Task switching. *Trends in Cognitive Sciences, 7*(3), 134-140.

Monsell, S., & Driver, J. S. (2000). Banishing the control homunculus. In S. Monsell & J. S. Driver (Eds.), *Control of cognitive processes: Attention and performance XVIII* (pp. 3-32). Cambridge: MIT Press.

Monsell, S., Sumner, P., & Waters, H. (2003). Task-set reconfiguration with predictable and unpredictable task switches. *Memory & Cognition, 31*(3), 327-342.

Mottram, V., Middleton, B., Williams, P., et al. (2010). The impact of bright artificial white and "blue-enriched" light on sleep and circadian phase during the polar winter. *Journal of Sleep Research*, doi: 10.1111/j.1365-2869.2010.00875.x; online publication ahead of print.

Moussay, S., Dosseville, F., Gauthier, A., et al. (2002). Circadian rhythms during cycling exercise and finger-tapping. *Chronobiology International, 19*(6), 1137-1149.

Mrosovsky. (1999). Masking: History, definitions, and measurement. *Chronobiology International, 16*(4), 415-429.

Nakahata, Y., Sahar, S., Astarita, G., et al. (2009). Circadian control of the NAD+ salvage pathway by CLOCK-SIRT1. *Science, 324*, 654-657.

Nakajima, M., Imai, K., Ito, H., et al. (2005). Reconstitution of circadian oscillation of cynobacterial KaiC phosphorylation in vitro. *Science, 208*, 414-415.

Neylan, T. C., Metzler, T. J., Henn-Haase, C., et al. (2010). Prior night sleep duration is associated with psychomotor vigilance in a healthy sample of police academy recruits. *Chronobiology International, 27*(1), 1493-1508.

Norman, D. A., & Shallice, T. (1986). Attention to action: willed and automatic control of behaviour. In R. J. Davidson, G. E. Schwartz & D. Shapiro (Eds.), *Consciousness and self-regulation: advances in research and theory* (Vol. 4, pp. 1-18). New York, London: Plenum.

Odle-Dusseau, H. N., Bradley, J. L., & Pilcher, J. J. (2010). Subjective perceptions of the effects of sustained performance under sleep-deprivation conditions. *Chronobiology International, 27*(2), 318-333.

Oldfield, R. C. (1971). The assessment and analysis of handedness: The Edinburgh Inventory. *Neuropsychologia, 9*, 97-113.

Padilha, H. G., Crispim, C. A., Zimberg Zalcman, I., et al. (2010). Metabolic responses on the early shift. *Chronobiology International, 27*(5), 1080-1092.

Paranjpe, D. A., & Kumar Sharma, V. (2005). Evolution of temporal order in living organisms. *Journal of Circadian Rhythms, 3*(7), doi:10.1186/1740-3391-1183-1187.

Peirson, S., & Foster, R. (2006). Melanopsin: another way of signalling light. *Neuron, 49*(3), 331-339.

Peres, I., Gutyrchik, E., Vetter, C., et al. (in preparation). Time-of-Day modulates neural activity in the motor system.

Petrilli, R. M., Roach, G. D., Dawson, D., et al. (2006). The sleep, subjective fatigue, and sustained attention of commercial airline pilots during an internal pattern. *Chronobiology International, 23*(6), 1347-1362.

Pittendrigh, C. S. (1960). Circadian rhythms and the circadian organization of living systems. In *Cold Spring Harbor Symposia on Quantitative Biology. Biological Clocks* (Vol. 25).

Pittendrigh, C. S. (1966). The circadian oscillation in Drosophila pseudoobscura pupae: a model for the photoperiodic clock. *Zeitschrift für Pflanzenphysiologie, 54*, 275-307.

Pittendrigh, C. S. (1981). Circadian systems: entrainment. In J. Aschoff (Ed.), *Handbook of Behavioral Neurology. Volume 4. Biological Rhythms* (pp. 95-124). New York: Plenum Press.

Pittendrigh, C. S., & Daan, S. (1976a). A functional analysis of circadian pacemakers in nocturnal rodents. I. The stability and lability of circadian frequency. *Journal of Comparative Physiology, 106*, 223-252.

Pittendrigh, C. S., & Daan, S. (1976b). A functional analysis of circadian pacemakers in nocturnal rodents. IV. Entrainment: pacemaker as clock. *Journal of Comparative Physiology, 106*, 291-331.

Pittendrigh, C. S., & Minis, D. H. (1964). The entrainment of circadian oscillations by light and their role as photoperiodic clocks *The American Naturalist, 98*, 261-294.

Portas, C. M., Rees, G., Howseman, A. M., et al. (1998). A specific role for the thalamus in mediating the interaction of attention and arousal in humans. *The Journal of Neuroscience, 18*(2), 8979-8989.

Posner, M. I., & Petersen, S. E. (1990). The attention system of the human brain. *Annual Reviews of Neuroscience, 13*, 25-42.

Provencio, I., Rodriguez, I. R., Jiang, G., et al. (2000). A novel human opsin in the inner retina. *Journal of Neuroscience, 20*, 600-605.

Raichle, M. E., MacLeod, A. M., Snyder, A. Z., et al. (2001). A default mode of brain function. *Proceedings of the National Academy of Science USA, 98*(2), 676-682.

Rajaratnam, S. M., & Arendt, J. (2001). Health in a 24-h society. *Lancet, 358*, 999-1005.

Ramsey, K. M., Yoshino, J., Brace, C. S., et al. (2009). Circadian clock feedback cycle through NAMPT-mediated NAD biosynthesis. *Science, 324*, 651-654.

Ravizza, S. M., & Carter, C. S. (2008). Shifting set about task switching: behavioural and neural evidence for distinct forms of cognitive flexibility. *Neuropsychologia, 46*(12), 2924-2935.

Revell, V., & Skene, D. (2007). Light-induced melatonin suppression in humans with polychromatic and monochromatic light. *Chronobiology International, 24*(6), 1125-1137.

Revell, V. L., Arendt, J., Terman, M., et al. (2005). Short-wavelength sensitivity of the human circadian system to phase-advancing light. *Journal of Biological Rhythms, 20*, 270-272.

Revell, V. L., & Eastman, C. I. (2005). How to trick mother nature into letting you fly around or stay up all night. *Journal of Biological Rhythms, 20*(4), 353-365.

Rietveld, W. J., Minors, D. S., & Waterhouse, J. M. (1993). Circadian rhythms and masking: an overview. *Chronobiology International, 10*(4), 306-312.

Roach, G. D., Dawson, D., & Lamond, N. (2006). Can a shorter psychomotor vigilance task be used as a reasonable substitute for the ten-minute psychomotor vigilance task? *Chronobiology International, 23*(6), 1379-1387.

Roenneberg, T., Daan, S., & Merrow, M. (2003). The art of entrainment. *Journal of Biological Rhythms, 18*(3), 183.

Roenneberg, T., & Foster, R. G. (2008). Human responses to the geophysical daily, annual and lunar cycles. *Current Biology, 18*, R784-R794.

Roenneberg, T., Hut, R., Daan, S., et al. (2010a). *A new approach to understanding entrainment.*Unpublished manuscript.

Roenneberg, T., Hut, R., Daan, S., et al. (2010b). Entrainment concepts revisited. *Journal of Biological Rhythms, 25*(5), 329-339.

Roenneberg, T., Kuehnle, T., Juda, M., et al. (2007). Epidemiology of the human circadian clock. *Sleep medicine reviews, 11*(6), 429-438.

Roenneberg, T., Kühnle, T., Pramstaller, P. P., et al. (2004). A marker for the end of adolescence. *Current Biology, 14*(24), R1038-1039.

Roenneberg, T., Kumar, C. J., & Merrow, M. (2007). The human circadian clock entrains to sun time. *Current Biology, 17*(2), R44-45.

Roenneberg, T., & Merrow, M. (1999). Circadian systems and metabolism. *Journal of Biological Rhythms, 14*(6), 449-459.

Roenneberg, T., & Merrow, M. (2005). Circadian clocks: translation lost. *Current Biology, 15*(12), R470-473.

Roenneberg, T., & Merrow, M. (2007). *Entrainment of the human circadian clock*. Paper presented at the Cold Spring Harbor Symposia on Quantative Biology.

Roenneberg, T., & Taylor, W. (2000). Automated recordings of bioluminescence with special reference to the analysis of circadian rhythms. *Methods in Enzymology, 205*, 104-119.

Roenneberg, T., Wirz-Justice, A., & Merrow, M. (2003). Life between clocks - daily temporal patterns of human chronotypes. *Journal of Biological Rhythms, 18*, 80-90.

Rogers, N. L., Dorrian, J., & Dinges, D. F. (2003). Sleep, waking and neurobehavioral performance. *Frontier Biosciences, 8*, S1056-S1067.

Rogers, R. D., & Monsell, S. (1995). Costs of a predictable switch between simple cognitive tasks. *Journal of Experimental Psychology: General, 124*, 207-231.

Rogers, R. D., Sahakian, B. J., Hodges, J. R., et al. (1998). Dissociating executive mechanisms of task control following frontal lobe damage and Parkinson's disease. *Brain, 121*, 815-842.

Rubinstein, J., Meyer, E., & Evans, J. E. (2001). Executive control of cognitive processes in task switching. *Journal of Experimental Psychology: Human Perception and Performance, 27*(4), 763-797.

Ruby, N. F., Brennan, X. X., Cao, V., et al. (2002). Role of melanopsin in circadian responses to light. *Science, 298*, 2211-2213.

Rushworth, M. F. S., Hadland, K. A., Paus, T., et al. (2002). The role of the human medial frontal cortex in task-switching: a combined fMRI and TMS study. *Journal of Neurophysiology, 87*(2577-2592).

Sack, R., Lewy, A., & Hughes, R. J. (1998). Use of melatonin for sleep and circadian rhythm disorders. *Annals of Medicine, 30*, 115-121.

Saper, C. B., Scammell, T. E., & Lu, J. (2005). Hypothalamic regulation of sleep and circadian rhythms. *Nature, 437*(27), 1257-1263.

Schmidt, C., Collette, F., Cajochen, C., et al. (2007). A time to think: circadian rhythms in human cognition. *Cognitive Neuropsychology, 24*(7), 755-789.

Schmidt, C., Collette, F., Leclercq, Y., et al. (2009). Homeostatic sleep pressure and responses to sustained attention in the suprachiasmatic area. *Science, 324*, 516-519.

Schroeter, M. L., Bücheler, M. M., & Scheid, R. (2006). Circadian variability is negligible in primary visual cortices as measured by fNIRS. *International Journal of Psychophysiology, 62*, 9-13.

Serences, J. T., Schwartzbach, J., Courtney, S. M., et al. (2004). Control of object-based attention in human cortex. *Cerebral Cortex, 14*, 1346-1357.

Sharkey, K. M., & Eastman, C. (2002). Melatonin phase shifts human circadian rhythms in a placebo-controlled simulated night-work study. *Am J Physiol Regul Integr Comp Phyiol, 282*, R454-R463.

Sharkey, K. M., Fogg, L. F., & Eastman, C. I. (2001). Effects of melatonin administration on daytime sleep after simulated night shift work. *Journal of Sleep Research, 10*(3), 181-192.

Skene, D., Lockley, S. W., James, K., et al. (1999). Correlation between urinary cortisol and 6-sulphatoxymelatonin rhythms in field studies of blind subjects. *Clinical Endocrinology, 50*, 715-719.

Smith, K. A., Schoen, M. W., & Czeisler, C. A. (2004). Adaptation of human pineal melatonin suppression by recent photic history. *Journal of Clinical Endocrinology and Metabolism, 89*, 3610-3614.

Smith, L., Folkard, S., & Poole, C. J. M. (1994). Increased injuries during night shift. *Lancet, 334*, 1137-1139.

Smith, L., Hammond, T., Macdonald, I., et al. (1998). 12-h shifts are popular but are they a solution? *International Journal of Industrial Ergonomics, 21*(3-4), 323.

Smith, M., & Eastman, C. (2009). Phase delaying the human circadian clock with blue-enriched polychromatic light. *Chronobiology International, 26*(4), 709-725.

Smith, M., Revell, V., & Eastman, C. (2009). Phase advancing the human circadian clock with blue-enriched polychromatic light. *Sleep Medicine, 10*(3), 287-294.

Smith, S. S., Kilby, S., Jorgensen, G., et al. (2007). Napping and nightshift work: Effects of a short nap on psychomotor vigilance and subjective sleepiness in health workers. *Sleep and Biological Rhythms, 5*, 117-125.

Sohn, M.-H., Ursu, S., Anderson, J. R., et al. (2000). The role of prefrontal cortex and posterior parietal cortex in task switching. *Proceedings of the National Academy of Sciences, 97*(24), 13448-13453.

Spector, A., & Biederman, I. (1976). Mental set and mental shift revisited. *The American Journal of Psychology, 89*(4), 669-679.

Spreeuwenberg, M. D., Willems, C., Verheesen, H., et al. (2010). Dynamic lighting as a tool to influence the day-night rhythm of clients with psychogeriatric disorders: a pilot study in a Dutch nursing home. *Journal of the American Geriatrics Society, 58*(5), 981-982.

Stehle, J., Vanecek, J., & Vollrath, L. (1989). Effects of melatonin on spontaneous electrical activity of neurons in rat suprachiasmatic nuclei: an in vitro iontophoretic study. *Journal of Neural Transmission, 78*, 173-177.

Strogatz, S. H., Kronauer, R. E., & Czeisler, C. A. (1987). Circadian pacemaker interferes with sleep onset at specific times each day: role in insomnia. *Am J Physiol Regulatory Integrative Comp Physiol, 253*, 172-178.

Strong, R., Marchant, B., Reimherr, F., et al. (2009). Narrow-band blue-light treatment of seasonal affective disorder in adults and the influence of additional nonseasonal symptoms. *Depression and Anxiety, 26*(3), 273-278.

Stuss, D. T., & Alexander, M. P. (2000). Executive functions and the frontal lobes: a conceptual overview. *Psychological Research, 63*, 289-298.

Sun, Z. S., Albrecht, U., Zhuchenko, O., et al. (1997). RIGUI, a putative mammalian ortholog of the Drosophila period gene. *Cell, 90*, 1003-1011.

Swade, R. H. (1969). Circadian rhythms in fluctuating lightcycles: towards a new model of entrainment. *Journal of Theoretical Biology, 24*, 227-239.

Szameitat, A., Schubert, T., Müller, K., et al. (2002). Localization of executive function in dual-task performance with fMRI. *Journal of Cognitive Neuroscience, 14*(8), 1184-1199.

Taheri, S., Austin, D., Young, T., et al. (2004). Short sleep duration is associated with reduced leptin, elevated ghrelin and increased body mass index. *PLoS Medicine, 1*(3), 210-217.

Tassi, P., & Muzet, A. (2000). Sleep inertia. *Sleep Medicine Reviews, 4*(4), 341-353.

Tei, H., Okamura, H., Shigeyoshi, Y., et al. (1997). Circadian oscillation of a mammalian homologue of the Drosophila period gene. *Nature 389*, 512-516.

Terman, M. (2007). Evolving applications of light therapy. *Sleep medicine reviews.*

Thapan, K., Arendt, J., & Skene, D. (2001). An action spectrum for melatonin suppression: evidence for a novel non-rod, non-cone photoreceptor system in humans. *Journal of Physiology, 535*, 261-267.

Thomas, M., Sing, H., Belenky, G., et al. (2000). Neural basis of alertness and cognitive performance impairments during sleepiness. I. Effects of 24 h of sleep deprivation on waking human regional brain activity. *Journal of Sleep Research, 9*, 335-352.

Tilley, A. J., Wilkinson, R. T., Warren, P. S. G., et al. (1982). The sleep and performance of shift workers. *Human Factors, 24*, 624-641.

Toh, K. L., Jones, C. R., He, Y., et al. (2001). An hPer2 phosphorylation site mutation in familial advanced sleep phase syndrome. *Science, 291*, 1040-1043.

Tonino, G., & Cirelli, C. (2006). Sleep function and synaptic homeostasis. *Sleep Medicine Reviews, 10*, 49-62.

Tzourio-Mazoyer, N., Landeau, B., Papathanassiou, D., et al. (2002). Automated anatomical labeling of activations in SPM using a macroscopic anatomical parcellation of the MNI MRI single-subject brain. *NeuroImage, 15*(1), 273-289.

Valdez, P., Ramírez, C., García, A., et al. (2010). Circadian and homeostatic variation in sustained attention. *Chronobiology International, 27*(2), 393-416.

Valdez, P., Reilly, T., & Waterhouse, J. (2008). Rhythms of mental performance. *Mind, Brain and Education, 2*(1), 7-16.

Van Cauter, E., Spiegel, K., Tasali, E., et al. (2008). Metabolic consequences of sleep and sleep loss. *Sleep Medicine, Suppl 1*, S23-S28.

Van Dongen, H. P. A., & Dinges, D. F. (2000). Circadian rhythms in fatigue, alertness, and performance. In M. H. Kryger, T. Roth & W. C. Dement (Eds.), *Principles and Practice of Sleep Medicine* (3rd ed., pp. 391-399). Philadelphia, Pennsylvania: WB Saunders.

Van Dongen, H. P. A., & Dinges, D. F. (2001). Modeling the effects of sleep debt: on the relevance of inter-individual differences. *Sleep Research Society Bulletin, 7*(3), 69-72.

Van Dongen, H. P. A., & Dinges, D. F. (2005). Sleep, circadian rhythms, and psychomotor vigilance. *Clinics in Sports Medicine, 24*, 237-249.

Van Dongen, H. P. A., Maislin, G., Mullington, J. M., et al. (2003). The cumulative cost of additional wakefulness: dose-response effects on neurbehavioral functions and sleep physiology from chronic sleep restriction and total sleep deprivation. *Sleep, 26*(2), 117-128.

Van Dongen, H. P. A., Price, N. J., Mullington, J. M., et al. (2001). Caffeine eliminates psychomotor vigilance deficits from sleep inertia. *Sleep, 24*(7), 813-819.

Van Dongen, H. P. A., Rogers, N. L., & Dinges, D. F. (2003). Sleep debt: theoretical and empirical issues. *Sleep and Biological Rhythms, 1*, 4-12.

Van Gelder, R. N. (2007). Non-visual photoreception: sensing light without sight. *Current Biology, 18*(1), R38-R39.

Van Someren, E. J. W., & Nagtegaal, E. (2007). Improving melatonin circadian phase estimates. *Sleep Medicine, 8*, 590-601.

Vandewalle, G., Archer, S. N., Wuillaume, C., et al. (2009). Functional magnetic resonance imaging-assessed brain responses during an executive task depend on interaction of sleep homeostasis, circadian phase, and PER3 genotype. *The Journal of Neuroscience, 29*(25), 7948-7956.

Vandewalle, G., Balteau, E., Phillips, C., et al. (2006). Daytime light exposure dynamically enhances brain responses. *Current Biology, 16*, 1616-1621.

Vandewalle, G., Gais, S., Schabus, M., et al. (2007). Wavelength-dependent modulation of brain responses to a working memory task by daytime light exposure. *Cerebral Cortex, 17*, 2788-2795.

Vandewalle, G., Maquet, P., & Dijk, D.-J. (2010). Light as a modulator of cognitive brain function. *Trends in Cognitive Sciences, 13*(10), 429-438.

Velanova, K., Lustig, C., Jacoby, L. L., et al. (2007). Evidence for frontally mediated controlled processing differences in older adults. *Cerebral Cortex, 17*, 1033-1046.

Vgontzas, A. N., Zoumakis, E., Bixler, E. O., et al. (2002). Adverse effects of modest sleep restriction on sleepiness, performance, and inflammatory cytokines. *The Journal of Clinical Endocrinology & Metabolism, 89*(5), 2119-2126.

Viola, A. U., James, L. M., Schlangen, L. J. M., et al. (2008). Blue-enriched white light in the workplace improves self-reported alertness, performance and sleep quality. *Scandinavian Journal of Work, Environment & Health, 34*(4), 297-306.

Walser, M. (1990). *Halbzeit*. Frankfurt a.M.: Suhrkamp.

Warman, V. L., Dijk, D.-J., Warman, G. R., et al. (2003). Phase advancing human circadian rhythms with short wavelength light. *Neuroscience Letters, 34*, 37-40.

Weaver, D. R. (1998). The suprachiasmatic nucleus: A 25-year retrospective. *Journal of Biological Rhythms, 13*(2), 100-112.

Webb, W. B. (1995). The cost of sleep-related accidents: A reanalysis. *Sleep, 18*(4), 276-280.

Wever, R. (1975). The circadian multi-oscillator system of man. *International Jorunal of Chronobiology, 3*, 19-55.

Williams, H. L., Lubin, A., & Goodnow, J. J. (1959). Impaired performance with acute sleep loss. *Psychological Monographs: General and Applied, 73*, 1-26.

Wirz-Justice, A. (1998). Beginning to see the light. *Archives of General Psychiatry, 55*(10), 861-862.

Wirz-Justice, A., Benedetti, F., & Terman, M. (2009). *Chronotherapeutics for affective disorders. A clinician's manual for light and wake therapy*. Basel: Karger.

Wirz-Justice, A., Graw, P., Krauchi, K., et al. (2003). Seasonality in affective disorders in Switzerland. *Acta Psychiatrica Scandinavica*.

Wittmann, M., Dinich, J., Merrow, M., et al. (2006). Social Jetlag: Misalignment of Biological and Social Time. *Chronobiology International, 23*(1-2), 497-509.

Wojtczak-Jaroszowa, J., Makowska, Z., Rzepecki, H., et al. (1978). Changes in psychomotor and mental task performance following physical work in standard conditions. *Ergonomics, 21*, 801-809.

Wright, H. R., Hughes, R. J., Kronauer, R. E., et al. (2001). Intrinsic near-24-h pacemaker period determines limits of circadian entrainment to a weak synchronizer in humanes. *Proceedings of the National Academy of Science, 98*(24), 14027-14032.

Wright, H. R., Hull, J. T., & Czeisler, C. A. (2002). Relationship between alertness, performance, and body temperature in humans. *American Journal of Physiology. Regulatory, Integrative and Comparative Physiology, 283*, R1370-R1377.

Wright, H. R., & Lack, L. C. (2001). Effect of light wavelength on suppression and phase delay of the melatonin rhythm. *Chronobiology International, 18*, 801-808.

Wright, H. R., Lack, L. C., & Kennaway, D. J. (2004). Differential effects of light wavelengths in phase advancing the melatonin rhythm. *Journal of Pineal Research, 36*, 140-144.

Wright, K. P., Hull, J. T., Hughes, R. J., et al. (2006). Sleep and wakefulness out of phase with internal biological time impairs learning in humans. *Journal of Cognitive Neuroscience, 18*(4), 508-521.

Wyatt, J. K., Dijk, D.-J., Ronda, J. M., et al. (1997). Interaction of circadian and sleep/wake homeostatic processes modulate psychomotor vigilance test (PVT) performance *Sleep Research 26*(759).

Wyatt, J. K., Ritz- De Cecco, A., Czeisler, C. A., et al. (1999). Circadian temperature and melatonin rhythms, sleep, and neurobehavioural function in humans living on a 20-h day. *American Journal of Physiology, 277*, R1152-R1163.

Yantis, S., Schwartzbach, J., Serences, J. T., et al. (2002). Transient neural activity in human parietal cortex during spatial attention shifts. *Nature Neuroscience, 5*, 995-1002.

Yeung, N., Nystrom, L. E., Aronson, J. A., et al. (2006). Between-task competition and cognitive control in task switching. *Journal of Neuroscience, 26*(5), 1429-1438.

Zaidi, F. H., Hull, J. T., Peirson, S., et al. (2007). Short-wavelength light sensitivity of circadian, pupillary, and visual awareness in humans lacking an outer retina. *Current Biology, 17*(24), 2122-2128.

Zavada, A., Gordijn, M., Beersma, D., et al. (2005). Comparison of the Munich Chronotype Questionnaire with the Horne-Östberg's Morningness-Eveningness score. *Chronobiology International, 22*(2), 267-278.

Zimmermann, W. F., Pittendrigh, C. S., & Pavlidis, T. (1968). Temperature compensation of the circadian oscillation in Drosophila pseudoobscura and its entrainment by temperature cycles. *Journal of Insect Physiology, 14*(5), 669-684.

10. Appendix

FIGURE A1.1. The Munich ChronoType Questionnaire (MCTQ).

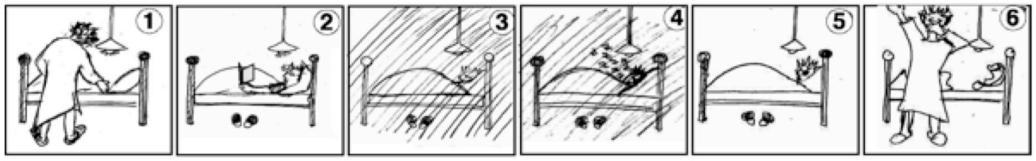
Munich Chronotype Questionnaire (MCTQ)

Ich gehe einer regelmäßigen Arbeit nach (schließt Hausfrau oder Hausmann ein):

Ja ☐ ich arbeite an 1☐ 2☐ 3☐ 4☐ 5☐ 6☐ 7☐ Tagen in der Woche.

Nein ☐

Ist Ihre Antwort „*Ja, an 7 Tagen*" oder „*Nein*" dann überlegen Sie bitte, ob sich Ihre Schlafzeiten nicht dennoch an allgemeinen ‚Werktagen' und ‚Wochenenden' unterscheiden und füllen den MCTQ entsprechend aus.



Zeiten bitte anhand der 24 Stunden Skala angeben (z.B. 23.00 statt 11.00 abends)!

Arbeitstage

Zeichnung 1: Ich gehe ins Bett um _____ Uhr.

Zeichnung 2: Manche Menschen bleiben noch eine Weile wach, wenn sie im Bett liegen!

Zeichnung 3: Ich bin bereit einzuschlafen um _____ Uhr.

Zeichnung 4: Um einzuschlafen, brauche ich _____ Minuten.

Zeichnung 5: Ich wache um _____ Uhr auf.

Zeichnung 6: Ich stehe auf nach _____ Minuten.

Ich benutze einen Wecker an Arbeitstagen: Ja ☐ Nein ☐

Wenn „Ja": Ich wache regelmäßig VOR dem Weckerklingeln auf: Ja ☐ Nein ☐

Freie Tage

Zeichnung 1: Ich gehe ins Bett um _____ Uhr.

Zeichnung 2: Manche Menschen bleiben noch eine Weile wach, wenn sie im Bett liegen!

Zeichnung 3: Ich bin bereit einzuschlafen um _____ Uhr.

Zeichnung 4: Um einzuschlafen, brauche ich _____ Minuten.

Zeichnung 5: Ich wache um _____ Uhr auf.

Zeichnung 6: Ich stehe auf nach _____ Minuten.

Meine Aufwachzeit (Zeichnung 5) wird durch einen Wecker bestimmt: Ja ☐ Nein ☐

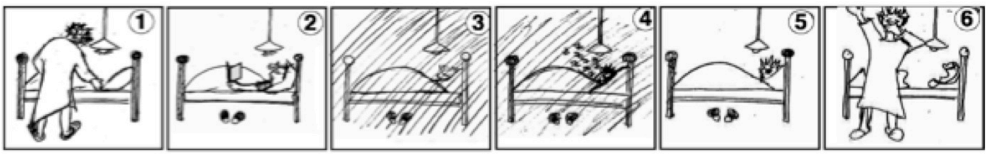
Aus bestimmten Gründen kann ich meine Schlafzeiten auch an freien Tagen nicht selbst bestimmen:

Ja ☐ Wenn „Ja": Kind(er)/Haustier(e) ☐ Hobbys ☐ Andere ☐, zum Beispiel:_____

Nein ☐

FIGURE A1.2. The MCTQ^{shift}

Bitte achten Sie darauf die Uhrzeiten an Hand der 24 Stunden Skala anzugeben (z.B. 23.00 statt 11.00 Uhr)!!!



Zwischen zwei Frühschichten!

Ich gehe ins Bett um _____ Uhr. (Zeichnung 1)

Manche Menschen bleiben noch eine Weile wach, wenn sie im Bett liegen! (Zeichnung 2)

Ich bin bereit einzuschlafen um _____ Uhr. (Zeichnung 3)

Um einzuschlafen, brauche ich _____ Minuten. (Zeichnung 4)

Ich wache um _____ Uhr auf. (Zeichnung 5)

☐ mit Wecker ☐ ohne Wecker

Ich stehe auf nach _____ Minuten. (Zeichnung 6)

Normalerweise mache ich ein Nickerchen ☐ ja ☐ nein

Wenn ja, dann von _____ Uhr bis _____ Uhr

Bitte geben Sie HIER an, falls Sie in dieser Schichtbedingung KEINE Möglichkeit haben Ihre Schlafzeiten selbst zu bestimmen (z.B. wegen eines Haustieres, Kind(er)...):

_____

_____

Zwischen zwei freien Tagen nach einer Frühschicht!

Ich gehe ins Bett um _____ Uhr. (Zeichnung 1)

Manche Menschen bleiben noch eine Weile wach, wenn sie im Bett liegen! (Zeichnung 2)

Ich bin bereit einzuschlafen um _____ Uhr. (Zeichnung 3)

Um einzuschlafen, brauche ich _____ Minuten. (Zeichnung 4)

Ich wache um _____ Uhr auf. (Zeichnung 5)

☐ mit Wecker ☐ ohne Wecker

Ich stehe nach _____ Minuten auf. (Zeichnung 6)

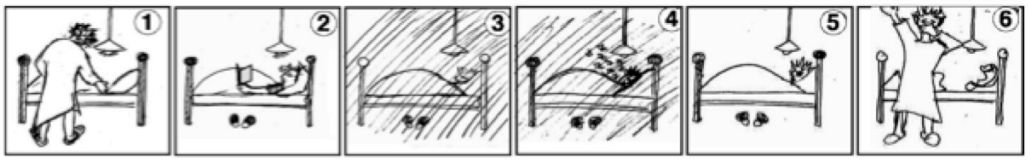
Normalerweise mache ich ein Nickerchen ☐ ja ☐ nein

Wenn ja, dann von _____ Uhr bis _____ Uhr

Bitte geben Sie HIER an, falls Sie in diesem Fall KEINE Möglichkeit haben Ihre Schlafzeiten selbst zu bestimmen (z.B. wegen eines Haustieres, Kind(er)...):

_____

_____



Uhrzeiten bitte an Hand der 24 Stunden Skala (z.B. 23.00 statt 11.00 abends)!!!

Zwischen zwei Spätschichten!

Ich gehe ins Bett um _____ Uhr. (Zeichnung 1)

Manche Menschen bleiben noch eine Weile wach, wenn sie im Bett liegen! (Zeichnung 2)

Ich bin bereit einzuschlafen um _____ Uhr. (Zeichnung 3)

Um einzuschlafen, brauche ich _____ Minuten. (Zeichnung 4)

Ich wache um _____ Uhr auf. (Zeichnung 5)

☐ mit Wecker ☐ ohne Wecker

Ich stehe auf nach _____ Minuten. (Zeichnung 6)

Normalerweise mache ich ein Nickerchen ☐ ja ☐ nein

Wenn ja, dann von _____ Uhr bis _____ Uhr

Bitte geben Sie HIER an, falls Sie in dieser Schichtbedingung KEINE Möglichkeit haben Ihre Schlafzeiten selbst zu bestimmen (z.B. wegen eines Haustieres, Kind(er)...):

_____

_____

Zwischen zwei freien Tagen nach einer Spätschicht!

Ich gehe ins Bett um _____ Uhr. (Zeichnung 1)

Manche Menschen bleiben noch eine Weile wach, wenn sie im Bett liegen! (Zeichnung 2)

Ich bin bereit einzuschlafen um _____ Uhr. (Zeichnung 3)

Um einzuschlafen, brauche ich _____ Minuten. (Zeichnung 4)

Ich wache um _____ Uhr auf. (Zeichnung 5)

☐ mit Wecker ☐ ohne Wecker

Ich stehe nach _____ Minuten auf. (Zeichnung 6)

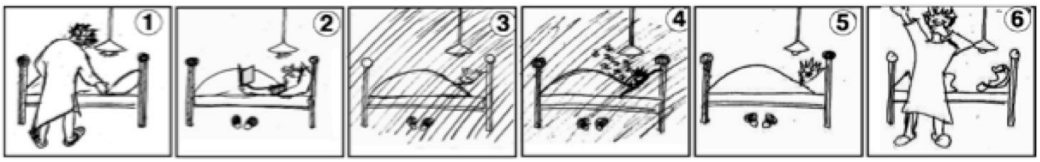
Normalerweise mache ich ein Nickerchen ☐ ja ☐ nein

Wenn ja, dann von _____ Uhr bis _____ Uhr

Bitte geben Sie HIER an, falls Sie in diesem Fall KEINE Möglichkeit haben Ihre Schlafzeiten selbst zu bestimmen (z.B. wegen eines Haustieres, Kind(er)...):

_____

_____



Uhrzeiten bitte an Hand der 24 Stunden Skala (z.B. 23.00 statt 11.00 abends)!!!

Zwischen zwei Nachtschichten!

Ich gehe ins Bett um _____ **Uhr.** **(Zeichnung 1)**

Manche Menschen bleiben noch eine Weile wach, wenn sie im Bett liegen! **(Zeichnung 2)**

Ich bin bereit einzuschlafen um _____ **Uhr.** **(Zeichnung 3)**

Um einzuschlafen, brauche ich _____ **Minuten.** **(Zeichnung 4)**

Ich wache um _____ **Uhr auf.** **(Zeichnung 5)**

☐ mit Wecker ☐ ohne Wecker

Ich stehe auf nach _____ **Minuten.** **(Zeichnung 6)**

Normalerweise mache ich ein Nickerchen ☐ **ja** ☐ **nein**

Wenn ja, dann von _____ **Uhr** **bis** _____ **Uhr**

Bitte geben Sie HIER an, falls Sie in dieser Schichtbedingung KEINE Möglichkeit haben Ihre Schlafzeiten selbst zu bestimmen (z.B. wegen eines Haustieres, Kind(er)...):

_____

_____

Zwischen zwei freien Tagen nach einer Nachtschicht !

Ich gehe ins Bett um _____ **Uhr.** **(Zeichnung 1)**

Manche Menschen bleiben noch eine Weile wach, wenn sie im Bett liegen! **(Zeichnung 2)**

Ich bin bereit einzuschlafen um _____ **Uhr.** **(Zeichnung 3)**

Um einzuschlafen, brauche ich _____ **Minuten.** **(Zeichnung 4)**

Ich wache um _____ **Uhr auf.** **(Zeichnung 5)**

☐ mit Wecker ☐ ohne Wecker

Ich stehe nach _____ **Minuten auf.** **(Zeichnung 6)**

Normalerweise mache ich ein Nickerchen ☐ **ja** ☐ **nein**

Wenn ja, dann von _____ Uhr bis _____ Uhr

Bitte geben Sie HIER an, falls Sie in diesem Fall KEINE Möglichkeit haben Ihre Schlafzeiten selbst zu bestimmen (z.B. wegen eines Haustieres, Kind(er)...):

_____

_____

FIGURE A2.1. Sleep Log Example

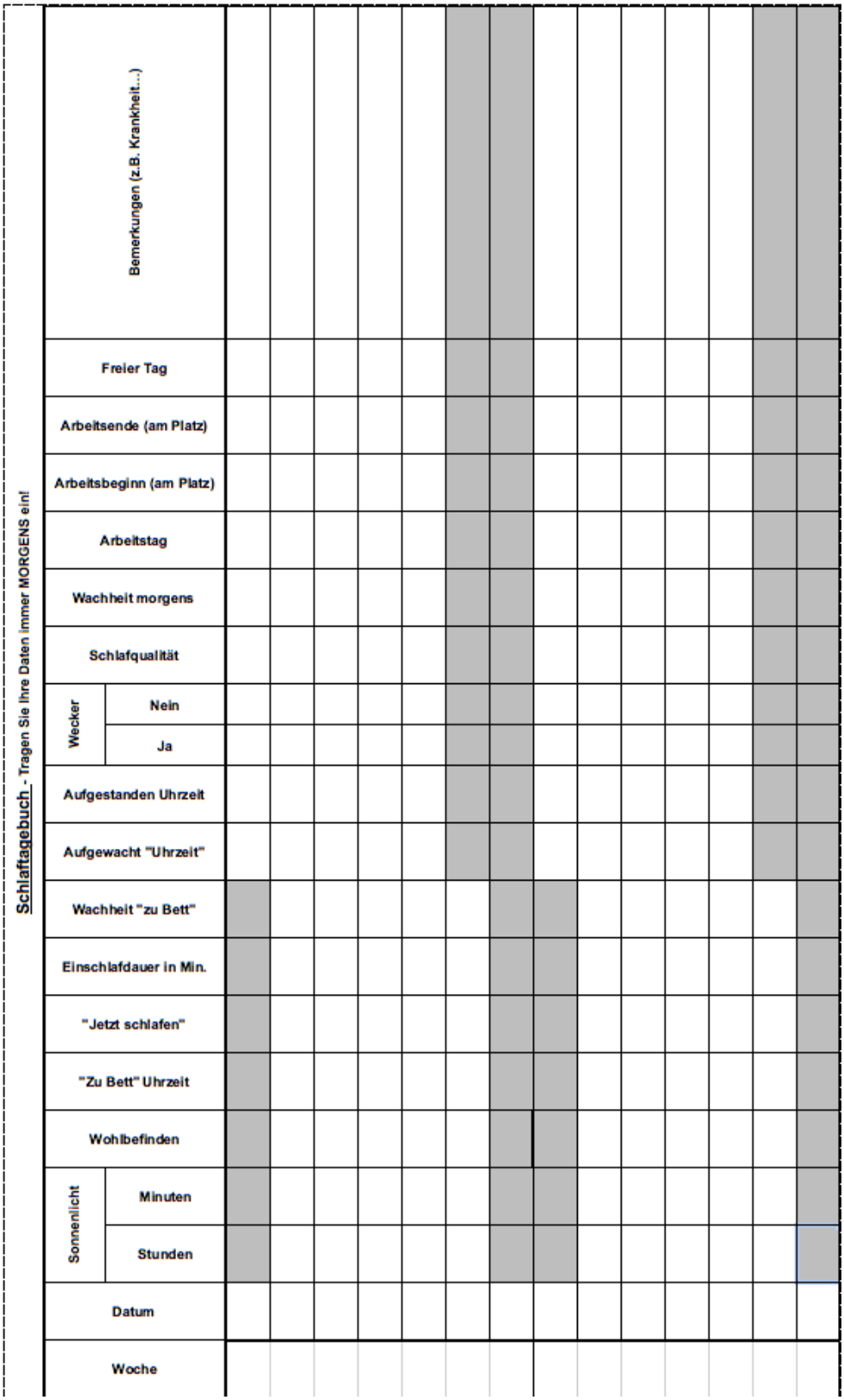
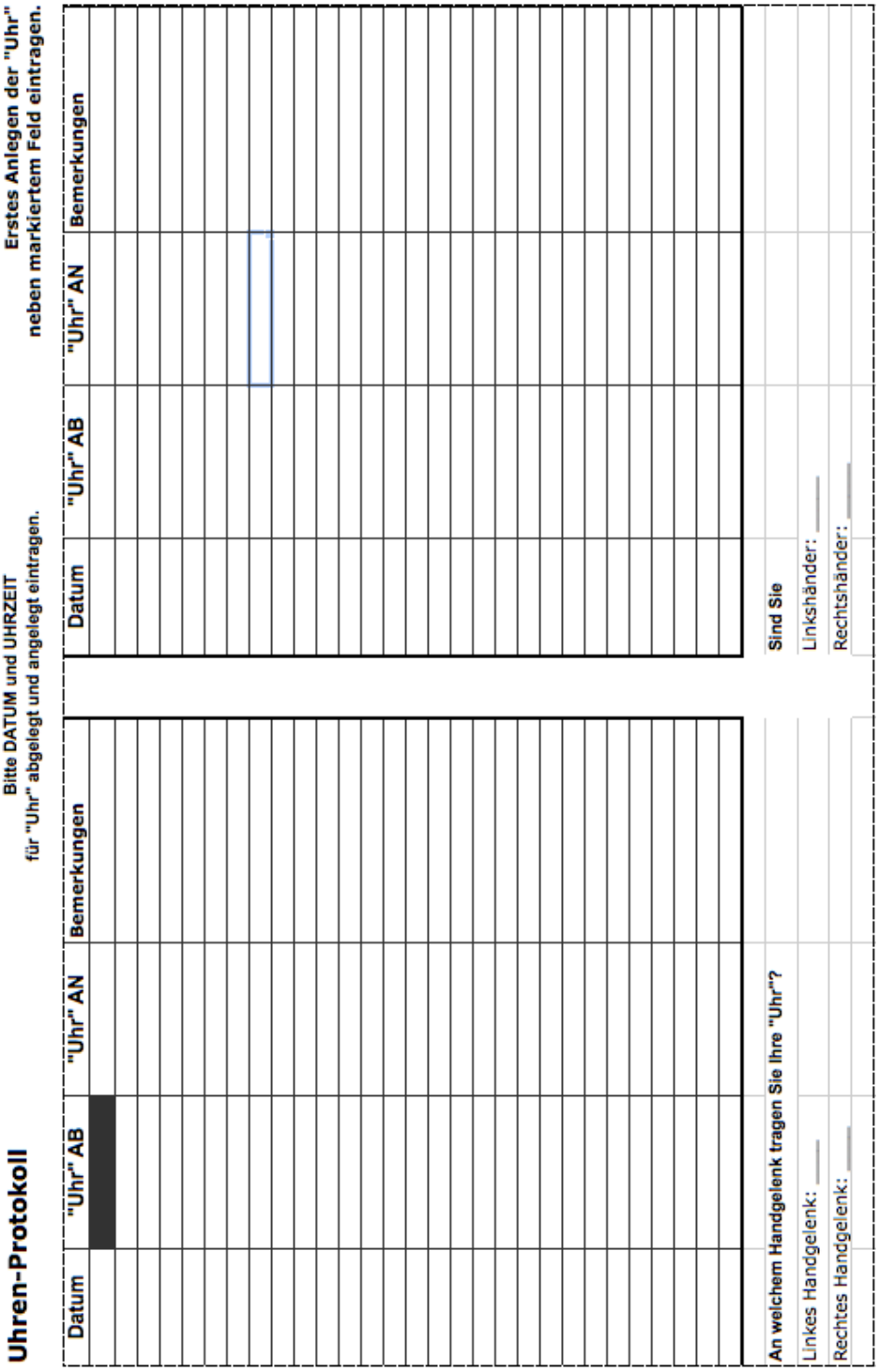


FIGURE A 2.2. Example of an actimetry log



Uhren-Protokoll

Bitte DATUM und UHRZEIT
für "Uhr" abgelegt und angelegt eintragen.

Erstes Anlegen der "Uhr"
neben markiertem Feld eintragen.

Datum	"Uhr" AB	"Uhr" AN	Bemerkungen

Datum	"Uhr" AB	"Uhr" AN	Bemerkungen

An welchem Handgelenk tragen Sie Ihre "Uhr"?

Linkes Handgelenk: ____

Rechtes Handgelenk: ____

Sind Sie

Linkshänder: ____

Rechtshänder: ____

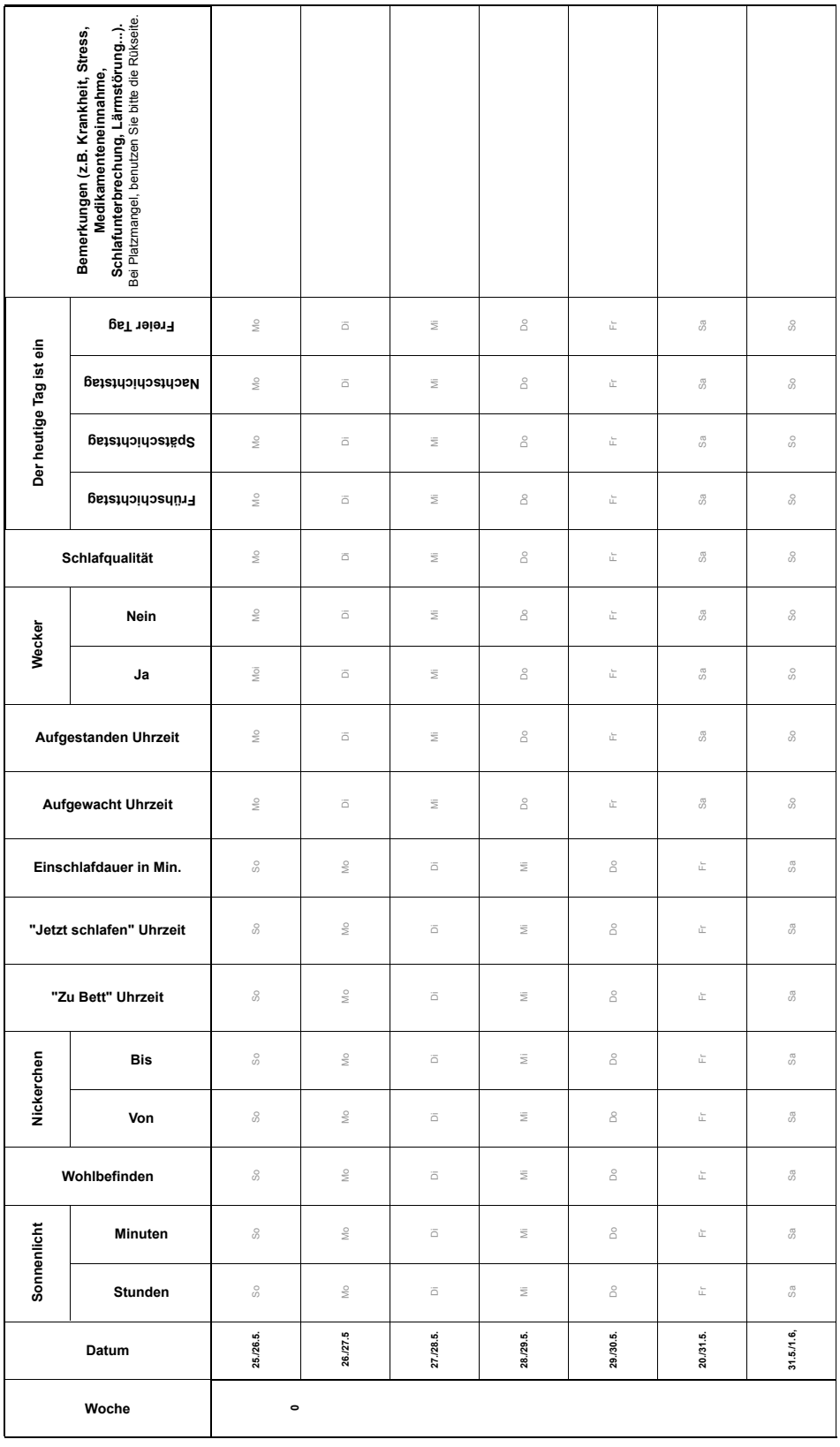
TABLE A 2.3. This table shows time of sunrise (h:min) during the study period from January 14th to February 17th 2008 for Munich, Germany, 11°34', 48°08' (from Sunrise & Sunset Calculator, http://www.timeanddate.com/worldclock/sunrise.html).

	Mon	Tue	Wed	Thu	Fri	Sat	Sun
Week 1 (14th – 20th Jan)	8:00	8:00	7:59	7:58	7:57	7:57	7:56
Week 2 (21st – 27th Jan)	7:55	7:54	7:53	7:52	7:51	7:50	7:49
Week 3 (28th Jan – 3rd Feb)	7:48	7:47	7:45	7:44	7:43	7:41	7:40
Week 4 (4th – 10th Feb)	7:39	7:37	7:36	7:34	7:33	7:31	7:30
Week 5 (11th – 17th Feb)	7:28	7:27	7:25	7:23	7:22	7:20	7:18

TABLE A3.1. Averages (± SD) of the light measurements (lx and K) are listed as a function of shift. The averages are based on 35 sample points that were equally distanced and covered the work whole area of the participants.

Light measurements		
Shift	Colour temperature (in K)	Light intensity (in lx)
MS	5413.5 (± 147)	996.3 (± 577.7)
ES	5442.9 (± 175.6)	992.9 (± 544)
NS	5175.1 (± 863.3)	598.5 (± 348.6)

FIGURE A3.2. Shift work study sleep log



Schlaftagebuch - Tragen Sie Ihre Daten immer NACH DEM AUFSTEHEN ein!

Bemerkungen (z.B. Krankheit, Stress, Medikamenteneinnahme, Schlafunterbrechung, Lärmstörung...). Bei Platzmangel, benutzen Sie bitte die Rükseite.								
Der heutige Tag ist ein	**Früh-schichttag**							
	Spät-schichttag							
	Nacht-schichttag							
	Freier Tag	Mo	Di	Mi	Do	Fr	Sa	So
Schlafqualität		Mo	Di	Mi	Do	Fr	Sa	So
Wecker	**Nein**	Mo	Di	Mi	Do	Fr	Sa	So
	Ja	Mo!	Di	Mi	Do	Fr	Sa	So
Aufgestanden Uhrzeit		Mo	Di	Mi	Do	Fr	Sa	So
Aufgewacht Uhrzeit		Mo	Di	Mi	Do	Fr	Sa	So
Einschlafdauer in Min.		So	Mo	Di	Mi	Do	Fr	Sa
"Jetzt schlafen" Uhrzeit		So	Mo	Di	Mi	Do	Fr	Sa
"Zu Bett" Uhrzeit		So	Mo	Di	Mi	Do	Fr	Sa
Nickerchen	**Bis**	So	Mo	Di	Mi	Do	Fr	Sa
	Von	So	Mo	Di	Mi	Do	Fr	Sa
Wohlbefinden		So	Mo	Di	Mi	Do	Fr	Sa
Sonnenlicht	**Minuten**	So	Mo	Di	Mi	Do	Fr	Sa
	Stunden	So	Mo	Di	Mi	Do	Fr	Sa
Datum		25./26.5.	26./27.5	27./28.5.	28./29.5.	29./30.5.	20./31.5.	31.5./1.6.
Woche		0						

TABLE A3.3. Mean error rates (number of lapsus) are listed as a function of shift and test session.

Mean number of lapsus			
Test session	Morning shift	Evening shift	Night shift
1st	0	0.05 (±0.2)	0
2nd	0.2 (±0.6)	0.05 (±0.2)	0.05 (±0.2)
3rd	0.2 (±0.5)	0	0
4th	0.1 (±0.6)	0.1 (±0.5)	0

FIGURE A3.4. Non-binned performance data (deviation from ind. baseline, %) from all rotating shift workers across all shifts and test sessions. Internal time, as operationalised by h since MSF^{E}sc, influences significantly general performance, r= .36, p <.000 (one harmonic cosine fit regression analyses).

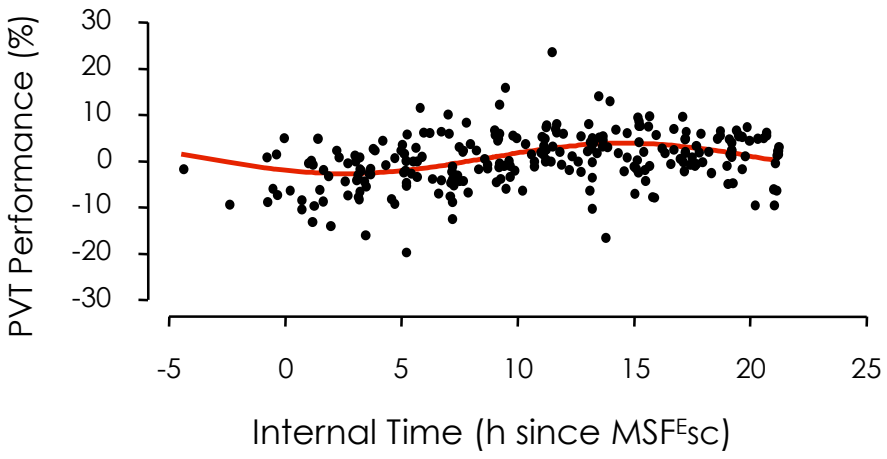


FIGURE A4.1. The German version of the Karolinska Sleepiness Scale was handed to the participants directly before their respective fMRI assessments.

Bitte geben Sie an, wie wach oder schläfrig Sie sich gerade zum jeweiligen Zeitpunkt fühlen!

	Sehr aufmerksam		**aufmerksam**		**Weder aufmerksam noch schläfrig**		**Schläfrig (kann aber die Augen offen halten)**		**Sehr schläfrig (schlafe fast ein)**
1	1	2	3	4	5	6	7	8	9

	Sehr aufmerksam		**aufmerksam**		**Weder aufmerksam noch schläfrig**		**Schläfrig (kann aber die Augen offen halten)**		**Sehr schläfrig (schlafe fast ein)**
2	1	2	3	4	5	6	7	8	9

	Sehr aufmerksam		**aufmerksam**		**Weder aufmerksam noch schläfrig**		**Schläfrig (kann aber die Augen offen halten)**		**Sehr schläfrig (schlafe fast ein)**
3	1	2	3	4	5	6	7	8	9

	Sehr aufmerksam		**aufmerksam**		**Weder aufmerksam noch schläfrig**		**Schläfrig (kann aber die Augen offen halten)**		**Sehr schläfrig (schlafe fast ein)**
4	1	2	3	4	5	6	7	8	9

FIGURE A4.2. The Edinburgh Handedness Inventory assesses relative lateralization and was employed once amongst all potential participants.

Edinburgh Händigkeitsfragebogen

Bitte geben Sie an, welche Hand Sie bei den folgenden Aktivitäten bevorzugen. *Setzen Sie + in die entsprechende Spalte.* Sollte die Präferenz so stark sein, dass Sie nie - wenn nicht absolut notwendig - versuchen würden, die andere Hand zu benutzen, *setzen Sie ++.* Wenn Sie wirklich keine Präferenz haben, *setzen Sie + in beide Spalten.*

Manche Aktivitäten erfordern zwei Hände. In diesen Fällen ist der Aufgabenteil, oder der Objektteil, für welchen Handpräferenz abgefragt wird, in Klammern angezeigt.

Bitte versuchen Sie alle Fragen zu beantworten, und lassen sie eine Zeile nur dann leer, wenn sie überhaupt keine Erfahrung mit dem Objekt oder Aufgabe haben.

		LINKE(R)	RECHTE(R)
1	Schreiben		
2	Malen		
3	Werfen		
4	Schere		
5	Zahnbürste		
6	Messer (ohne Gabel)		
7	Löffel		
8	Besen (obere Hand)		
9	Streichholz zünden (Streichholz)		
10	Schachtel öffnen (Deckel)		
i	Mit welchem Fuß treten Sie bevorzugt einen Gegenstand?		
ii	Welches Auge benutzen Sie, wenn Sie nur eines benutzen?		

L.Q.		Bitte lassen Sie diese Felder leer	DEZIL	

FIGURE A4.3. The symbols were common and known, but meaningless for the participants during the control task. They were asked to observe the stimuli and to randomly press one of the two response buttons. The panels below show four out of the nine possible symbols. Location and stimuli brightness exactly corresponded to the digits in the task switching paradigm.

TABLE A4.4. The backward multiple regression analyses successively excluded parameters (TP = time point, thalamic activity is entered as a param. estimates) that were unnecessary for the prediction of general task performance during the task switching experiment. Unstandardized coefficients are reported in the first two columns (standardized beta-values, B, and their standard errors, Std. Error). Standardized beta coefficients are listed in the third column (Beta). r^2 and adjusted r^2 allow an appreciation of the generalizability of the model: the less the two coefficients differ from one another, the better the cross-validity. Model 4 shows the best explanatory power.

Model		B	Std. Error	Beta	r^2	adjusted r^2
1	Constant	509.93	124.44		0.67	0.60
	Time awake	-42.92	23.00	-0.98		
	Time since MSF	0.48	28.04	0.01		
	TP	89.86	103.92	0.80		
	Karolinska Score	7.40	13.21	0.07		
	Control condition RT	0.60	0.10	0.67***		
	Thalamus left	-316.09	100.91	-0.84**		
	Thalamus right	263.67	114.59	0.65*		
2	Constant	511.57	77.57		0.67	0.61
	Time awake	-43.03	21.71	-0.98		
	TP	91.33	56.88	0.81		
	Karolinska	7.44	12.74	0.07		
	Control condition RT	0.60	0.10	0.67***		
	Thalamus left	-316.38	98.04	-0.84**		
	Thalamus right	263.99	111.40	0.65*		
3	Constant	535.85	64.86		0.66	0.62
	Time awake	-41.45	21.34	-0.94		
	TP	86.21	55.66	0.77		
	Control condition RT	0.61	0.09	0.68***		
	Thalamus left	-317.40	97.10	-0.85**		
	Thalamus right	253.18	108.81	0.62*		
4	Constant	533.58	66.10		0.64	0.60
	Time awake	-9.13	4.55	-0.21		
	Control condition RT	0.59	0.09	0.66***		
	Thalamus left	-282.33	96.24	-0.75**		
	Thalamus right	199.80	105.19	0.49		
		* p< .05	** p < .01	*** p < .001		