In search of light therapy to optimize the internal clock, performance and sleep
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Summary
Under the influence of the earth’s rotation around the sun almost every organism has evolved an internal rhythm close to 24 hours. This internal rhythm of about 24 hours is called a ‘circadian’ rhythm and is generated by the biological clock. In mammals the biological clock is located in the suprachiasmatic nucleus (SCN). In humans, a robust output marker of the SCN is the rhythm of the hormone melatonin. The SCN inhibits the production of melatonin during the day. During the evening this inhibition stops and melatonin will start to be produced in the pineal gland. In general, the melatonin rhythm peaks during the middle of the night and declines in the early morning. Melatonin provides also feedback to the SCN together with other internal time signals, like the internal availability of nutrients and body temperature. The SCN is also under influence of external signals called ‘Zeitgebers’. This adjustment by Zeitgebers is needed, because when there are none the SCN will ‘free-run’ with its own endogenous period, which will lead to erroneous time of day signalling. Therefore the SCN needs to be synchronized daily. Light is the most important Zeitgeber to the SCN.

In humans, the effect of light is gated via the eyes. Photoreceptors which are located in the retina will translate and transport the light signal to the biological clock (SCN) and to other areas of the brain i.e. areas for vision and alertness. While the classical photoreceptors for vision (rods and cones) do contribute to this signal they are not absolutely required. The most important cells for transferring the light signal to the clock are the photosensitive retinal ganglion cells (pRGC’s), because when these cells are not present, the clock is insensitive to light. They contain the protein melanopsin, which is mainly responsible for the translation of the light-signal. Melanopsin is most sensitive for blue light and blue light is therefore most effective for adjusting the clock.

In general, light in the early morning will shift the clock to an earlier time and light in the evening will shift the clock to a later time. Light during the middle of the day will not have phase shifting effects, yet there are indications that light during the day can boost the amplitude of the circadian rhythm of the clock.

In modern society there is a lot of variation between individuals in the pattern of the sleep-wake cycle. In chronobiological research, humans are often classified according to their ‘chronotype’, a term that is based on differences in sleep timing of the population. Chronotype can be quantified with the Munich Chronotype Questionnaire (MCTQ). If someone has an overall sleep timing that is earlier or later than a large part of the population (under the 25th percentile or above the 75th percentile), then this person is called someone with an ‘early chronotype’ or a ‘late chronotype’ respectively. A person with his/her sleep around the average (between the 25th and 75th percentile) is called someone with an ‘average chronotype’.

In addition to this variation in sleep timing, the common habit of the majority of adults is that they like to sleep later on free days than on workdays. Apparently, work- and school schedules start earlier than what people prefer. These work- and school schedules may...
lead therefore to a mismatch of endogenous circadian rhythms (generated by the clock, the SCN) and external environmental rhythms. As a result of the discrepancy in sleep timing on workdays and free days, many adults experience a so-called weekly ‘social jetlag’. As with a ‘normal’ jetlag resulting from travelling to different time zones, sleeping at the wrong internal phase can disturb bodily rhythms. This may lead to stress and health problems. A large number of people in the population could therefore theoretically benefit from a correction of their timing of sleep.

One way to achieve this is by advancing the biological clock. Since light is a strong Zeitgeber, light therapy in the morning is often proposed as a tool to treat the phase of late sleepers. In a clinical setting, light exposure in the morning has already been shown to be effective. However, there is no generally accepted protocol, definitely not for using light therapy at home. For a practical and successful correction of the phase of late sleepers, optimal parameters about light exposure, like the timing, duration, intensity and color of light need to be specified. Also characteristics of individuals that influence the effectiveness of light therapy have to be identified.

The data of this thesis can be useful to improve the treatment of sleep disorders with light therapy and at the same time fundamental questions about the underlying mechanisms related to the influence of light on physiology and behavior (such as sleep and alertness) may be answered.

In chapter 2 we combined some optimal light therapy parameters to see if the duration of light therapy can be shortened in a home situation, while maintaining the effect. The timing of light exposure is one of the parameters we could optimize. For this purpose it is important to know when the melatonin concentration starts to rise in the evening under dim light (also called ‘dim light melatonin onset’, DLMO). Indeed, it is known that light is most effective 9 hours after DLMO for phase advancing the clock. Since we measured the DLMO of the participants before the start of the experiment, we exactly knew when they had to start with light therapy in the morning. The light source itself was a small lamp (Philips Golite Blu) emitting high intensity blue light, which is the color and intensity that should maximize the effect. We examined if high intensity blue light pulses of 30 minutes were as effective as high intensity blue light pulses of 60 minutes. We indeed found that 30 minute blue light pulses were as effective as three blue light pulses of 60 minutes in phase advancing the clock (when they were applied once a day on three consecutive days at an optimal timing). We found also a decrease of sleepiness in the morning at waking up. Furthermore, we found some indications that sleep was shifted to an earlier phase.

These last findings lead to the questions in the next study described in chapter 3. Here we focused on post-treatment effects on sleep itself, which hardly have been studied. Also effects on daytime functioning after light therapy treatment have hardly been reported. Therefore, post-treatment effects on sleep and performance were the main output measures in the study of this chapter. We made use of two light therapy protocols applied
in two groups of participants. These participants were suffering from a ‘social jetlag’ during workdays and wanted to advance their sleep. The two light therapy protocols were exactly the same, except from the light sources used. The light sources emitted either high intensity blue light (using the same lamp as in chapter 2), or amber colored light with the same visible brightness (lux). Melanopsin, and therefore the clock, is less sensitive to amber light. Therefore the amber light could function as a kind of placebo. Differences between the two groups with respect to sleep and performance had to be caused by the color of the light. The protocol consisted of 30 days in total and was performed at home. All participants started with 14 baseline days with no sleep instructions. This was followed by 9 intervention days with every morning either 30 minutes of blue light, or 30 minutes of amber light, along with a sleep advancing scheme. The scheme was based on the habitual sleep offset in the baseline period. Light therapy started at habitual sleep offset and was then advanced by 1 hour every 3 days. This scheme was followed by 7 post-treatment days (the period that measured the eventual preservation of the effects) without sleeping instructions and no use of light treatment devices. We analyzed saliva samples to estimate the start of melatonin production in the evening (DLMO) and to calculate the phase shift of the clock. Light exposure was recorded continuously to check the compliance. Sleep was monitored through an activity watch (sensitive for movement). Performance was measured with a reaction time task on a portable mini-computer. As expected, the phase advance of the melatonin rhythm was significantly larger in the blue light exposure group, compared to the amber light exposure group. Interestingly, the wake-up times were still a bit earlier in the post-treatment period in the participants who were exposed to blue light, while they were slightly later in the amber light group. In addition we found that the quality of sleep, measured with the activity watch, was somewhat reduced in the amber light group. This was accompanied with a worsened performance during the whole day in the amber light group. This was only the case in the morning during the post-treatment period in the blue light group. Thus, sleep and performance (to a large extend) were kept stable in the blue light group, despite the fact that the participants had to wake up earlier. We concluded that the blue light was able to compensate for the sleep quality reduction and to a large extent for the performance decrement that was observed in the amber light condition. From these results we could generate new questions for the next study. Was the effect of (blue) light on sleep due to the effective phase shifting of the clock or was there maybe also another effect of blue light on sleep quality? And are there also direct effects of blue light on performance during the day or is there only an indirect effect via the clock?

This last question was addressed in Chapter 4. We examined if it was possible to fight a subjective energy dip at the office with 3 hours of extra blue light. The question was whether alertness and performance are affected by the timing of light exposure and whether these effects are dependent on someone’s chronotype. The study applied one experimental day and one control day, randomized across participants, in their own office environment. On the control day participants were exposed to their regular office lighting; on the experimental day, 3 hours of extra blue light was added to the regular office light. Blue light was provided by a blue LED-lightstrip at a distance of 60 cm. (280x25 mm2; peak transmission 480 nm;
500 mlux; prototype Philips, Drachten, The Netherlands) which was placed on top of the computer monitor. Participants showed their energy dip before the start of the experiment by drawing a line in a graph with the time scale of their working day. Lowered energy was indicated by a lowering of the line in this graph. The extra blue light was then applied around one’s energy dip either at the beginning, middle or end of the working day. We measured sleepiness with a specialized sleepiness scale (Karolinska Sleepiness Scale, KSS). Performance was examined with several performance tasks, varying from a simple reaction time task to a more cognitive memory task. The output measures, to compare the differences between conditions, were average reaction times and the number of errors. Extra blue light seemed beneficial for people that experienced an energy dip in the afternoon, because blue light stabilized cognitive performance during this time. At noon the blue light was effective in improving performance during light exposure, but after turning off the light, performance showed a deterioration. Participants also consumed less drinks with caffeine when they were exposed to light at noon. For those that suffer from reduced energy during the first morning hours at work, the extra blue light did not seem to be helpful. Interestingly it seemed that especially early types performed worse under morning light exposure. We indeed found an interaction between the moment of light exposure and chronotype for different energy dip groups. No significant effects of extra blue light exposure on sleepiness were observed, although there was a trend for being less sleepy under extra blue light in the afternoon. We concluded that extra blue light can have different effects during different energy dip moments, and early types performed different from late types during different blue light exposure moments.

In chapter 5 we addressed the other question raised from the study in chapter 3: Is there a positive effect of extra light during the day on sleep quality during the night? Sleep is under the influence of two processes, namely a homeostat which is responsible for an increase in the need for sleep during waking and a decrease in that need during sleeping, and the biological clock, which sets daily optimal limits to wake up and to fall asleep. According to this two-process model of sleep regulation, two mechanisms can be proposed to explain the impact of light on sleep quality. One is the possible influence of light on the need for sleep, the other one is the influence of light on the clock. The possible influence of light on both these mechanisms was examined in a laboratory setting, described in chapter 5.

Participants were exposed to three conditions: Either to one simulated working day (09:00-17:00) with moderate intensity ‘office light’, one working day with high intensity bright light, or to one working day with extra blue light (provided by the same lightstrip as used in chapter 4) on top of the ‘office light’. We measured the influence of this daylight on the clock via melatonin analysis and we measured sleep quality/homeostasis after the experimental days with electroencephalography (EEG) measurements during subsequent sleep. If light had an effect on the need for sleep we expected to find an increase in the built-up of slow wave activity, in other words, we expected to find slow waves with more power at the beginning of the sleep period. If light had an effect on the clock, we expected to find changes in sleep consolidation (being less awake).
We found that the melatonin onset was earlier in the bright light condition as well as in the blue light condition compared to the office light condition. This result may not only be explained by an advance of the melatonin rhythm, but can also be explained by a higher amplitude of the clock in the conditions with extra light. Unfortunately, we could not determine which of the two explanations was right, because melatonin data was only available in the evening and not during sleep. More research is needed to confirm this potentially interesting finding. Sleep efficiency was higher in the bright light condition compared to the office light condition as well was the percentage of REM sleep. Also the build-up of slow wave activity was significantly higher in the bright- as well as in the blue light condition compared to the office light condition. From these results we concluded that light intensity during the day can influence sleep via the clock and via influencing sleep homeostasis; with higher light intensities leading to more consolidated and deeper sleep.

The last study of this thesis is described in chapter 6. During the study of chapter 5, we were also interested in alertness and performance measures under the 3 different light conditions. Therefore, participants performed tests-batteries with various performance tasks (similar tasks as described in chapter 4) on the computers available in the rooms at different moments of the working day (8:00, 10:00, 12:00, 14:00, 16:00, 19:00). Also, physiological aspects of alertness were analyzed with help of EEG recordings, while the subjects were awake.

The results revealed that prolonged bright light exposure had advantageous effects on subjective and objective alertness as well as on performance, whereas prolonged blue light exposure showed no effects or even negative effects during the second half of the working day. The wake EEG under blue light exposure also showed an increase in sleepiness compared to the bright light exposure period.

From this thesis it seems evident that increasing daily light exposure is a practical and effective tool to increase performance and sleep quality. However, it has also revealed that effects differ between individuals. Personalized light therapy is needed. From the results in this thesis it is evident that only applying several hours of extra blue light exposure is not the solution. Prolonged blue light exposure can have various effects at different times of the working day and the effects may differ between chronotypes. The combination of these degrees of freedom makes it extremely difficult to find the exposure schedule that for everyone leads to optimal performance during the day and to optimal sleep during the night. We cannot rule out that such a scheme exists. On top of that, individual light therapy, with customized intensity and color exposure may be used, for instance when a phase shift of the clock is needed or performance needs to be optimized at certain times of the day.

Although the multidimensionality of the system is a complicating factor and our knowledge is still limited, the optimization of light exposure in humans is a powerful tool to improve performance, entrain the clock and boost sleep.