In search of light therapy to optimize the internal clock, performance and sleep
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Chapter 7

Epilogue

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7.1 New insights in Light therapy

Over the last decade, light therapy has gained more and more popularity. It has been used over the range from treating winter depression (Meesters & Gordijn 2016) to decreasing neurodegenerative symptoms (reviewed in Shirani & Louis 2009). In addition, it has been extensively used in laboratory studies to phase shift the clock (chapters 1-3). This thesis provides indications that if light is optimally timed, it can even shift sleep and may improve objective sleep quality (chapter 3,5).

It should be taken into account that we also found limits to the use of light therapy. While optimally timed, short blue light pulses were effective in phase shifting the circadian rhythm of melatonin concentration and sleep (chapter 2,3), with preservation of performance during the day (chapter 3), but longer periods of blue light during office hours seemed not beneficial and were sometimes even disadvantageous (chapter 4,6). In addition, we found indications that objective sleepiness increased over the day under blue light exposure compared to bright light exposure (more theta power) and compared to office light exposure (longer RT in the 2-back task) (chapter 6). The timing of periods with blue light during common office hours should also be taken into account (chapter 3): in real-life circumstances, subjects will expose themselves to varying amounts of light with varying blue content at different times of the day, and therefore at different individual circadian phases.

7.2 A role for extra light exposure during the day towards increased melatonin production at night.

The first effect that deserves renewed attention is the influence of light during the day on sleep and on melatonin production during the night. In chapter 5 we measured melatonin at night after one day of extra light and in the study in chapter 2 with more days of extra light. In both cases we found indications for an increased melatonin production. Next to the increased melatonin production, these two studies found positive effects on sleep quality. The question arises whether or not increased melatonin production in an individual is an indication of a higher circadian amplitude of the clock and whether it is related to the observed improved sleep quality. A long lasting debate is going on about the relationship between melatonin and sleep. While researchers seem to agree on the chronotherapeutic effects of melatonin (Cajochen et al. 2003, van Geijlswijk et al. 2010, van Maanen et al. 2016), effects on sleep quality parameters have not always been found. When sleep consolidation parameters were tested, positive effects of a higher melatonin concentration during sleep have indeed been found (to note: these studies use different dosages and various timing of melatonin administration): melatonin can reduce sleep onset latency (Zhdanova & Wurtman 1997, Cajochen et al. 2003, Rajaratnam et al. 2004), can reduce awakenings during the night (Zhdanova & Wurtman 1997), can to some extend increase sleep efficiency (Brzezinski et al. 2005, Wyatt et al. 2006) and in a few studies an increase in REM sleep has been found (Dijk et al. 1997, Dijk & Cajochen 1997). However when homeostatic variables were tested, such as effects on slow wave sleep (Wyatt et al. 2006, Arbon et al. 2015) no
effects have been found. Thus, it seems that a higher melatonin concentration promotes sleep during the night probably by inhibiting the wake promoting drive (Wyatt et al. 2006, Skeldon et al. 2016). However it does not significantly influence the depth of sleep. In all of the previous studies mentioned above, sleep was analysed after exogenous melatonin ingestion. The melatonin concentration is then artificially and drastically increased, which may not reflect a normal melatonin rhythm. Indeed in blind people who needed doses of exogenous melatonin to stay entrained, lower doses appeared to be more effective than higher doses (Lewy et al. 2005). In addition, the timing and concentration of exogenous melatonin with respect to one’s own melatonin rhythm is important to elicit effects (Lewy et al. 2005, 2010, van Geijlswijk et al. 2010).

If one’s own melatonin concentration is naturally increased during the night under the influence of light during the day, the effects on sleep consolidation may be much stronger as the amplitude is increased at just the right time. Manipulating light levels during the day may also influence sleep homeostasis processes. This will be discussed in the next paragraph.

### 7.3 A role for light in sleep homeostasis in humans

In chapter 3 we found indications that not only sleep was shifted earlier after morning blue light therapy, but that sleep quality was also improved. This raises the question whether sleep was more consolidated because of boosting the amplitude of the clock (as suggested by a larger area under the curve of melatonin concentration), or because blue light influenced sleep homeostasis, or both. Earlier mouse studies make this latter hypothesis worthwhile to investigate because it was found that the intensity and color of light can influence sleep homeostasis in mice, probably through the melanopsin pathway (Altimus et al. 2008, Tsai et al. 2009). Such a role for the melanopsin pathway is also suggested by Hubbard et al 2013 and Legates & Hattar 2014. In chapter 6 we tested the influence of light on sleep homeostasis in people with mild sleep problems. In good sleepers this has been tested before, however without yielding significant results (Takasu et al. 2006). In that study there might have been a ceiling effect on sleep quality. Another explanation is the light exposure period that lasted for 16 hours. This, therefore, included light exposure in the evening, where light can negatively influence subsequent sleep quality (Münch et al. 2006). In our study, presented in chapter 6 we applied light for 8 hours from 09:00-17:00 and participants were only selected if the timing of this light was optimal for their chronotype (only boosting their circadian amplitude). In our study, extra light during the day indeed increased sleep consolidation and lowered sleepiness scores the next morning. It also showed a trend towards a higher accumulation rate of deep sleep. However, we could not disentangle the relative contributions of the two processes: The influence of light on the clock and the influence of light on sleep homeostasis. This will be a new challenge in further research.
7.4 Individual differences in the effectiveness of light therapy

While in chapter 3 of this thesis, a positive effect of morning blue light therapy was found for late chronotypes, in chapter 4 we revealed that blue light in the morning might sometimes be disadvantageous, maybe in particular for early chronotypes. It suggests that identifying an individual’s circadian phase before starting with light therapy seems to be an important aspect in improving personalized light therapy. Until now the most common and easy way to assess circadian phase is calculating one’s chronotype with the MCTQ (Roenneberg et al., 2003). Indeed, it is known that the timing of midsleep on freedays (MSF), is highly correlated to the timing of dim light melatonin onset (DLMO) (Kantermann et al. 2015). Still, a lot of variation is seen between DLMO and the phase angle of sleep. In the study of Chapter 3 DLMO ranged from 5.40 hours before sleep onset to 0.26 after sleep onset. In our DLMO calculations we found that there are a lot of people with a relative early DLMO time and a late sleep onset (40% of the participants in the study of chapter 3 had a DLMO time that was earlier than 3 hours before sleep onset), which has been found before (Sletten et al. 2010).

An intriguing question is why different chronotypes, defined by their sleep phase, exist for the same DLMO’s. Recent studies have searched for other DLMO predictors (Gil et al. 2013, Woelders et al. 2017). In both of these recent studies the amount of light during the day seems important for the timing of DLMO, which is a finding that is in consistence with our results in chapter 5. The answer may also be found in the dynamics of sleep pressure. Studies by Mongrain and Colleagues suggested that late chronotypes have different dynamics for sleep pressure compared to early chronotypes. The data revealed a lower amplitude of slow wave activity (SWA) in the first sleep cycles of late types (Mongrain et al. 2006b, Schmidt et al. 2012). This was interpreted as to demonstrate a lower built-up of sleep pressure during wakefulness as well as a slower decay of SWA during sleep (Mongrain et al. 2006a, Schmidt et al. 2012) in late types compared to early types. As a consequence of such characteristics of the regulation of sleep pressure, late types would sleep later in the evening, and they would wake up later in the morning, while their DLMO might not be late. In accordance with this work, being a ‘late chronotype’ would not always mean having a late endogenous clock.

The data of Mongrain et al (2007) may also be explained in another way. The amount of SWA in the first cycle is not only dependent on the accumulation of sleep need during the day, but also on the duration of the cycle. This is caused by the fact that SWA rises in the beginning of the nonREM episode and reaches a high asymptote in the later part of the episode (Achermann et al. 1993). In short cycles, low values dominate, while in long cycles high values are more abundant. Hence episode duration influences slow wave activity independent from the built-up of sleep need. If chronotype is related to REM latency, this would explain Mongrain et al’s data (2007) without the need of assuming differences in the dynamics of process S. Without complete knowledge of the relationship between chronotype and REM latency, it seems safe to suggest that it may also be a combination of a late endogenous clock and different dynamics of sleep pressure. The recent model of
Skeldon et al. (2016), developed with the purpose to explain why people tend to sleep later during adolescence and become earlier later in life, support the theory that clock- as well as sleep pressure dynamics should be part of the model.

Recent literature also proposes another way by which sleep pressure dynamics influences sleep timing. This concerns the presence in the population of a polymorphism of the PER3 clock gene, which is related to sleep pressure dynamics. The PER3 clock gene has a PER34/4 form, which is linked to an evening preference and a PER35/5 form which is linked to a morning preference (reviewed in Dijk & Archer 2010). People with the PER34/4 gene have also a slower built up of sleep pressure compared to people with a PER35/5 gene (Viola et al. 2007, Dijk & Archer 2010, Hasan et al. 2014). Interestingly, people with a PER34/4 polymorphism have stronger brain responses to blue light in the morning (Vandewalle et al. 2011).

All these observations strongly suggest that there exist different types of chronotypes, depending on the clock as well as on sleep architecture. The findings of the study of Vandewalle at al. 2011 also support that different chronotypes will not always react in the same way to (blue) light during particular moments of the day, which is in line with our finding in chapter 4.

7.5 Future prospects: Optimizing light exposure patterns

With the new insights gained 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 it is worthwhile to investigate how extra light with different spectral intensities should be applied optimally in the individual, since the effects differ between individuals. Personalized light therapy is needed. Also gaining insight about the mechanisms behind the effects of light on boosting the circadian amplitude and about the effects of light on homeostatic sleep dynamics in humans will help to optimize light therapy. In developing personalized light therapy, the next step would be to answer the question how to expose humans to an optimal individual light scheme. From the results in this thesis it is evident that only applying longer periods 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. There may however be other general (bright) light schemes wherefrom people in general may benefit. 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 studies in this thesis have made clear that optimizing light in humans is a powerful tool to improve performance, entrain the clock and boost sleep.