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Heidi Jurvelin

TRANSCRANIAL BRIGHT LIGHT – THE EFFECT ON HUMAN PSYCHOPHYSIOLOGY

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Abstract

In addition to the visual information, external light causes non-image-forming (NIF) effects that modulate brain function and induce psychophysiological effects. The light signal is traditionally assumed to only be mediated via the eyes. Recent studies have suggested the existence of putatively light sensitive structures in the rodent and human brain and penetration of light into the skull and brain tissue has been observed. The brain activation observed during transcranial bright light (TBL) exposure indicates a direct light responsivity of brain tissue. The aim of this thesis was to explore the psychophysiological responses related to TBL.

The studies comprising this thesis were conducted in healthy subjects and patients suffering from seasonal affective disorder. TBL exposure was administered via the ear canals in all study settings using light-emitting diodes (LEDs). The comparisons in studies I, II, and III were conducted against the inactivated sham device. Study IV explored the effect of TBL dose.

Neither melatonin nor cortisol secretions were altered when acutely exposed to nocturnal TBL. Circadian profiles in TBL setting were in parallel to control conditions for both hormones. Intermittent TBL exposure led to alleviation of jet lag symptoms. Overall post-travel jet lag symptoms as well as subjective feelings of fatigue, inertia, and forgetfulness were reduced. The time to execute the motor response i.e. motor time with a visual warning signal was improved by the TBL treatment. TBL alleviated both depressive and anxiety symptoms related to seasonal affective disorder (SAD). A dose-response relationship regarding the intensity of dose administered via the ear canals was not found.

Altogether, TBL seems to affect human brain function by alleviating symptoms of jet lag and SAD and improving psychomotor performance. The acute effect is suggested to be mediated via structures unrelated to acute melatonin secretion i.e. the retinohypotalamic tract (RHT). These results support the light sensitivity of the human brain although the mechanism of action is not yet established.

Keywords: cortisol, jet lag, melatonin, mood, psychomotor speed, seasonal affective disorder, sleepiness

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Tiivistelmä

Visuaalisen informaation lisäksi valo aiheuttaa käytöksellisiä ja fysiologisia vaikutuksia, jotka eivät liity kuvan muodostamiseen. Yleisesti vaikutuksen ajatellaan välittyvän aivoihin ainoastaan silmien kautta. Viimeaikaiset tutkimukset ovat havainneet jyrsijöiden ja ihmisten aivoissa mahdollisesti valolle vasteellisia rakenteita. Valon on osoitettu lisäksi läpäisevän kallon ja saavuttavan aivokudoksen. Aivojen aktivoituminen kallon läpi annettavan valoaltistuksen aikana viittaa myös suoraan aivojen valovasteellisuuteen. Tämän väitöskirjan tavoitteena oli tarkastella vaikuttaako kallon läpi annettava valo ihmisen psykofysiologiaan.

Tähän väitöskirjaan sisällytetyt tutkimukset tehtiin terveillä vapaaehtoisilla tutkittavilla ja kaamosmasennuspotilailla. Ledin avulla tuotettu valo annettiin kaikissa tutkimusasetelmissa korvakäytävien kautta. Tutkimukset I, II ja III tehtiin lumekontrolliasetelmassa. Tutkimuksessa IV tarkasteltiin valon annosvastetta.

Akuutin yöaikaisen valoaltistuksen ei havaittu muuttavan melatoniinin tai kortisolin eritystä. Molempien hormonien vuorokausierityksprofiilit olivat kontrolliasetelman kaltaiset. Jaksottaisen valoaltistuksen havaittiin lievittävän aikaerorasituksen kokonaisoireita ja vähentävän väsymystä, inertiaa ja hajamielisyyttä. Motorisen nopeuden havaittiin paranevan kolmen viikon valohoitojakson aikana. Lisäksi neljän viikon valohoitojakso lievitti kaamosmasennukseen liittyviä masennus- ja ahdistusoireita. Vaikutuksessa ei havaittu eroa eri valoannoksen saaneiden ryhmien välillä.

Kallon läpi annettava kirkasvalo näyttäisi vaikuttavan ihmisen aivotoimintaan lievittämällä aikaerorasituksen ja kaamosmasennuksen oireita sekä parantamalla psykomotorista suorituskykyä. Vaikutus ei ole yhteydessä akuuttiin melatoniinin erityksen estämiseen. Tämän tutkimuksen tulokset tukevat ajatusta aivojen valovasteellisuudesta. Kallon kautta annettavan valon vaikutusmekanismia ei kuitenkaan tiedetä vielä.

Asiasanat: aikaerorasitus, kaamosmasennus, kortisoli, melatoniini, mieliala, psykomotorinen nopeus, uneliaisuus

"When the sun is shining, I can do anything: no mountain is too high, no trouble too difficult to overcome." Wilma Rudolph

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I want to express my deepest appreciation to my supervisors Professor Markku Timonen, Docent Timo Takala, and Professor Pirkko Riipinen. At the beginning of my doctoral thesis the idea of administering light directly into the brain was and still is controversial and the mechanism of action is still not understood. Recent studies on this topic have, however, extended knowledge on the effect of external light on human psychophysiology.

I want to thank my research fellows MSc Juuso Nissilä, Docent Vesa Kiviniemi, MSc Jari Jokelainen, PhD Melanie Rüger and PhD Jari Karhu who have supported me during the thesis project. I would also like to thank Docent Mikko Tulppo, Professor Emeritus Seppo Saarela, Docent Olli Vakkuri, Professor Emeritus Juhani Leppäluoto, Docent Antti Kiviniemi, Docent Arto Hautala, PhD Eka Roivainen and MSc Lilli Heberg for their valuable knowledge during the thesis project.

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Finally, I thank my family for all their support during this journey.

February 2018 Heidi Jurvelin

Abbreviations

ACTH	adrenocorticotropic hormone
AUC	area under curve
BDI	Beck Depression Inventory
BL	bright light
CAR	cortisol awakening response
CRH	corticotrophin releasing hormone
CRYs	cryptochromes
DLMO	dim light melatonin onset
DSM-IV	the Diagnostic and Statistical Manual of Mental Disorders
EEG	electroencephalography
EOG	eye movement electrooculographic
fMRI	functional magnetic resonance imaging
HAM-A	the Hamilton Rating Scale for Anxiety
HAMD	the Hamilton Depression Rating Scale
HPA	hypothalamic-pituitary-adrenal
ipRGCs	intrinsically photosensitive ganglion cells
IR	infrared
KSS	Karolinska sleepiness scale
LEDs	light-emitting diodes
LORETA	low-resolution electromagnetic activity
MEQ	Morningness-Eveningness Questionnaire
MINI	Mini International Neuropsychiatric Interview
NIF	non-image-forming
NMDA	N-methyl-D-aspartate
OPN3	opsin 3, encephalopsin
OPN4	opsin 4, melanopsin
OPN5	opsin 5, neuropsin
OJS	overall jet lag symptoms
POMS	Profile of Mood States
PRC	phase response curve
QEEG	quantitative electroencephalography
QoS	quality of the sleep
RHT	retinohypothalamic tract
RIA	radioimmunoassay
SAD	seasonal affective disorder

SCN	suprachiasmatic nucleus
SIGH-SAD	the Structured Interview Guide for the Hamilton Depression Rating scale – Seasonal Affective Disorder
SRT	simple reaction time
STAI-Y1	Spielberger State-trait Anxiety Inventory, Form Y-1
T_{min}	minimum temperature
TBL	transcranial bright light
TMT	Trail-making test
UV	ultraviolet
VAS	visual analogue scale

Original publications

This thesis is based on the following publications, which are referred throughout the text by their Roman numerals:

I Jurvelin H, Takala T, Heberg L, Nissilä J, Rüger M, Leppäluoto J, Saarela S & Vakkuri O (2014) Transcranial bright light exposure via ear canals does not suppress nocturnal melatonin in healthy adults – A single-blind, sham-controlled, crossover trial. Chronobiol Int 31(7): 855-60.

II Jurvelin H, Jokelainen J & Takala T (2015) Transcranial bright light and symptoms of jet lag – A randomized, placebo-controlled trial. AMHP 86(4): 1-7.

III Tulppo MP, Jurvelin H, Roivainen E, Nissilä J, Hautala AJ, Kiviniemi AM, Kiviniemi VJ & Takala T (2014) Effects of bright light treatment on psychomotor speed in athletes. Front Physiol 5: 184.

IV Jurvelin H, Takala T, Nissilä J, Timonen M, Rüger M, Jokelainen J & Räsänen P (2014) Transcranial bright light treatment via the ear canals in seasonal affective disorder: a randomized, double-blind dose-response study. BMC Psychiatry 14: 288.

Contributions in the publications: for publication I, I participated in the planning and designing of the study, coordinated the study, participated in collecting the data, data analysis and drafting the manuscript. For publication II, I participated in planning and designing the study, coordinated the study, participated in the data analysis and drafted the manuscript. For publication III, I participated in planning and designing the study, coordinated the delivering of study devices and participated in drafting the manuscript. For publication IV, I participated in planning and designing the study, coordinated the study, participated in collecting the data, participated in data analysis and drafted the manuscript.

Contents

1 Introduction

The effect of environmental and artificial light on human psychophysiology has been a topic of interest to scientists over the past three decades. Studies have revealed a wealth of information about how the human is affected by light. Knowledge from these studies has improved our understanding of the acute and long-term effects of light. During the past few years, the development of technology has also brought with it new research tools to obtain information on this issue. The improvement of brain research in both functional and molecular methodological imaging has led to a more in-depth insight into the functioning of brain networks and structure of brain tissue.

Environmental or artificial light has plenty of psychophysiological effects. In addition to visual perception, light exposure induces non-image-forming (NIF) effects such as circadian entrainment and shifts the timing of circadian rhythms. Several bodily functions i.e. hormone secretion, heart rate, body temperature and the sleep-wake cycle follow biological rhythm synchronised with external dark-light oscillation. In addition, external light has been found to acutely suppress melatonin secretion, cause pupillary constriction, elevate alertness and improve cognitive brain responses and performance. (Altimus *et al.* 2008, Chellappa *et al.* 2011b, Hankins *et al.* 2008, Vandewalle *et al.* 2009)

The effect of light in humans has been thought to be mediated solely via the eyes by three types of membrane cells; rods, cones and intrinsically photosensitive retinal ganglion cells (ipRGCs) all located in the retina (Tosini *et al.* 2016). Direct perception of external light through extraocular photoreceptors has been reported in birds and lower vertebrates (Vigh *et al.* 2002). However, there is also evidence that a significant amount of external light can penetrate the cranium and reach the mammalian (Ganong *et al.* 1963), including the human brain (Persinger *et al.* 2013). Penetration of light through the human cadaver skull has been revealed in a very recent study (Sun *et al.* 2016). In addition to melanopsin (OPN4) (Brainard *et al.* 2001, Nissilä *et al.* 2017, Provencio *et al.* 1998), potentially photosensitive molecules such as encephalopsin (OPN3) (Blackshaw & Snyder 1999), neuropsin (OPN5) (Tarttelin *et al.* 2003, Yamashita *et al.* 2014), glutamatergic N-methyl-D-aspartate (NMDA) (Leszkiewicz *et al.* 2000) and cryptochromes (CRYs) (Foley *et al.* 2011) have also been found to exist in the mammalian brain. The physiological roles of these structures are not yet known; however, the existence of these extra-retinal structures in the brain suggests that ambient light has important direct targets in the human brain outside the retinohypothalamic tract (RHT) (Nissilä *et al.* 2017).

Visual opsins have also been suggested to participate in mediating the NIF effects of light (Ho Mien *et al.* 2014, Vandewalle *et al.* 2009).

Conventional bright light (BL) treatment is administered via the eyes although the exact mechanism of action of BL is still unknown (Najjar & Zeitzer 2016). Interestingly, transcranially administered light has also been found to modulate the neural networks of the human brain (Starck *et al.* 2012). Immediate transcranial bright light (TBL) treatment increased functional connectivity and activity in the sensorimotor and visual cortices when compared with sham treatment in healthy subjects studied by means of functional magnetic resonance imaging (fMRI) (Starck *et al.* 2012). TBL stimulation through the occipital bone was also recently observed to enhance quantitative electroencephalographic (QEEG) power and low-resolution electromagnetic activity (LORETA) in the parahippocampal areas (Persinger *et al.* 2013). Furthermore, transcranially administered extra-ocular BL has been shown to abolish normal emotional modulation of attention-related brain response (Sun *et al.* 2016). Thus, it appears reasonable to explore whether the effects of light on brain functioning can also be mediated via the extra-retinal routes.

To date, there have been few studies performed on the effects of transcranial light on human psychophysiology. Despite recent observations of putatively light-sensitive structures and direct activations of the brain, studies exploring the psychophysiological and clinical effect of TBL are needed.

2 Literature review

Light is electromagnetic radiation that can be detected by the retina of the human eye with the spectrum ranging approximately from 400 nm to 700 nm. However, the spectrum regions adjacent to the visual band, i.e. ultraviolet (UV) and infrared (IR), is also often referred to as light. Visible spectrum of light can be divided into bands that the human eye interprets as different colours i.e. violet (380 - 450 nm), blue (450 - 490 nm), green (490 - 560 nm), yellow (560 - 590 nm), orange (590 - 630 nm) and red (630 - 760 nm) (Fig. 1). White light consists of a continuous spectrum of light. The human eye is not equally sensitive to all spectrum wavelengths. Under bright conditions, the maximum luminous effect is observed at a green wavelength of around 550 nm (Rovamo *et al.* 1996). The luminous efficacy is the term used for artificial light sources to describe how well the source converts energy to electromagnetic radiation and how well the radiation is detected by the human eye. Part of the input energy of the light source is lost as heat, UV and/or IR radiation. Depending on the light source the efficacy varies. Since light-emitting diodes (LEDs) do not provide UV radiation and IR radiation, the only loss for the LED is heat loss. LED efficacy varies between 12% - 20% (Cheng & Cheng 2006). In addition to the wavelength, the intensity, duration and mode of administration are the parameters which can be used to characterise the light.

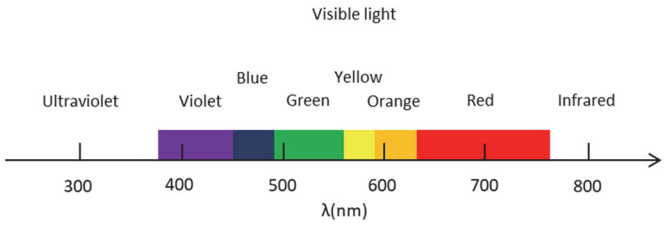

Fig. 1. The visible spectrum of light ranges from 380 nm to 760 nm. The adjacent ultraviolet and infrared are also often referred to as light.

The main source of light on Earth is the Sun. Adaptation of behaviour and physiology to changes in the ambient light level is of critical importance to life. Humans and other mammals can detect light using two systems. The classical visual system is responsible for image formation. The system that detects environmental irradiance and contributes to the modulation of physiological, behavioural, and cognitive functions of living organs beyond conscious image

perception is called NIF pathway. (Cajochen *et al.* 2005, Daneault *et al.* 2016, Golden *et al.* 2005, West *et al.* 2011)

Phototransduction is the process by which a photon of light captured by a photosensitive molecule generates an electrical response in a photoreceptor cell and converts it into a neuronal signal (Ray *et al.* 2016). Retinal phototransduction is mediated by three types of photoreceptors: cones, rods and the intrinsically photosensitive ganglion cells (ipRGCs) (Tosini *et al.* 2016). Rods and cones are responsible for image forming vision, whereas NIF effects of light are mainly mediated by ipRGCs (Koorengevel *et al.* 2001, Vandewalle *et al.* 2009, Wehr *et al.* 1987). The non-image forming phototransduction system is a pathway that runs from ipRGCs, via the retinohypothalamic tract (RHT) to the endogenous master circadian pacemaker (biological clock) located in the suprachiasmatic nucleus (SCN) of the anterior hypothalamus (Brainard *et al.* 2001, Daneault *et al.* 2016, Provencio *et al.* 1998). This NIF photoreceptive system is also known to communicate with various brain areas including the pineal gland, brain stem, limbic system, and cerebral cortex (Paul *et al.* 2009, Vandewalle *et al.* 2006a, Vandewalle *et al.* 2009).

The ipRGCs contain blue-light-sensitive membrane protein, OPN4, which is thought to be mainly responsible for NIF phototransduction (Peirson *et al.* 2009, Vandewalle *et al.* 2007). However, all photoreceptor classes are also suggested to contribute to influencing SCN and playing a role in circadian responses to light (Walmsley *et al.* 2015). Recent findings suggest that SCN is also sensitive to colour in addition to brightness, providing a reliable indicator for the time of day based on spectral composition of the solar cycle and twilight transition (Walmsley *et al.* 2015). Compared to rods and cones, melanopsin ipRGC has also been observed to be able to integrate the photic energy over long time periods (Berson *et al.* 2002, Hattar *et al.* 2002, Panda *et al.* 2002, Provencio *et al.* 2000). Thus, although different in terms of the respective functions, classical visual and NIF systems also seem to communicate (Daneault *et al.* 2016).

The physiology of NIF photo response in humans is not entirely understood (Najjar & Zeitzer 2016). To date it has been shown that light stimulus characteristics such as light intensity, wavelength, duration and temporal pattern of light have an effect on the photoreceptor's contribution to specific NIF responses (Daneault *et al.* 2016). External light has been found to have various long-term and acute NIF effects on behaviour and brain activation in humans (Fig. 2). Long-term NIF effects include circadian entrainment and shift the timing of circadian rhythms such as hormone secretion, heart rate, body temperature and the sleep-wake cycle.

These phase-shifting effects are detected in the next circadian cycle following light exposure. Acute effects such as melatonin suppression, pupillary constriction, alertness, cognitive brain responses and performance improvement are detected faster. (Altimus *et al.* 2008, Chellappa *et al.* 2011b, Hankins *et al.* 2008, Vandewalle *et al.* 2009)

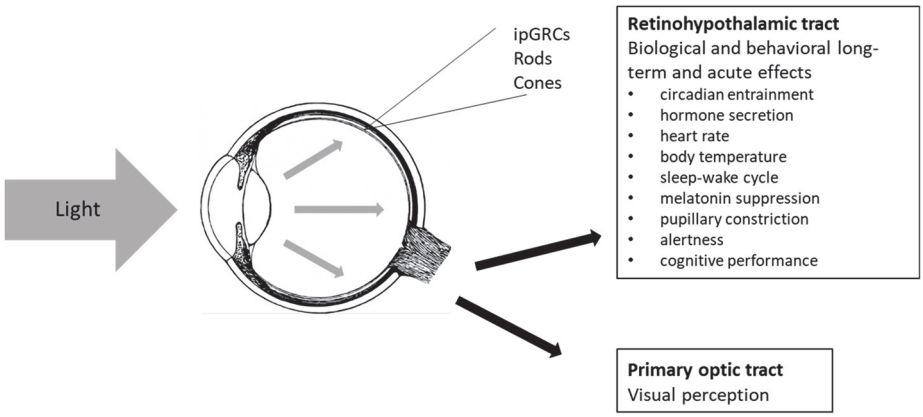

Fig. 2. The effects of light are mediated via the primary optic tract and retinohypothalamic tract (RHT).

2.1 Circadian rhythm and light

Under natural conditions, several physiological and behavioural variables follow circadian rhythm (Golombek & Rosenstein 2010). This rhythm also persists in the absence of environmental stimuli (zeitgebers = time givers) (Berson *et al.* 2002, Gnocchi & Bruscalupi 2017) and shows endogenously generated rhythm (Golombek & Rosenstein 2010). The average period of this innate autonomous oscillation i.e free-running rhythm is approximately, but not exactly, 24 hours (Berson *et al.* 2002, Silver & Kriegsfeld 2014). Under a constant environment, the endogenous circadian timing system is synchronised to the 24-h solar day (Kumar Jha *et al.* 2015). Light is the strongest external cue to regulate the innate free-running rhythm and entrain internal clocks with the external time, but other cues such as social contacts, (Mistlberger & Skene 2004), sleep/wake schedules (Houben *et al.* 2009), feeding (Saper *et al.* 2005), drugs (Mistlberger & Skene

2005), temperature (Buhr *et al.* 2010), and exercise (Flores *et al.* 2016) can also have an effect on human circadian rhythms.

Regular adaptation to external light-dark rhythm is mediated by sensory inputs that report changes in the physical environment providing a useful proxy for time of day. It is regulated by a synchrony between environmental cues and endogenous circadian timing system (Walmsley *et al.* 2015). Endogenous rhythms are governed by a central circadian clock, located in the SCN of the hypothalamus (Takahashi *et al.* 2008). The electrical activity produced in the SCN is transmitted to the rest of the brain and peripheral districts of the body through neural and hormonal signals (Gnocchi & Bruscalupi 2017). SCN acting as a master pacemaker for the other organism drives rhythms in activity and rest, feeding, body temperature and hormones (Mohawk *et al.* 2012).

In recent years, the discovery of self-sustained oscillations in several tissues throughout the body including different regions of the brain and peripheral organs has challenged the idea of one central oscillator (Golombek & Rosenstein 2010, Kyriacou & Hastings 2010). As a matter of fact, it seems that nearly every level of the circadian system participates in the regulation (Mohawk *et al.* 2012). It seems that the role of the SCN is to keep local clocks in synchrony with each other and with the solar cycle (Kyriacou & Hastings 2010).

2.1.1 Melatonin

Circadian clock also has an effect on hormonal homeostasis. The circadian oscillations of melatonin and cortisol hormones are well established (Gnocchi & Bruscalupi 2017). The ability of light to adjust melatonin secretion is one of the most known non-image forming effects of light (Zawilska *et al.* 2009). Melatonin (5-methoxy-N-acetyltryptamine) is a hormone mainly secreted by the pineal gland situated at the centre of the brain. Melatonin is also produced in the retina, gut, skin, platelets and bone marrow. It is synthesised from the essential amino acid tryptophan, which is first transformed into serotonin and then converted into melatonin (Claustrat *et al.* 2005).

The endogenous rhythm of melatonin synthesis and secretion is entrained to the external light-dark cycle (Arendt *et al.* 1995) and can be estimated by measuring the time of melatonin onset, peak or offset (Skene & Arendt 2006). The synthesis of melatonin in the pineal gland is regulated by the internal clock utilising the sympathetic nervous system (Reilly *et al.* 2009). External photic information is transferred as a neural projection from the SCN to the pineal gland (Blackshaw &

Snyder 1999, Hannibal 2002, Moore 1997, Rea *et al.* 2005, Reiter *et al.* 2011). Exposition of light causes acute suppression of melatonin secretion and is maintained for as long as light signals are transmitted from the retina to the SCN and to the pineal gland (Wright & Lack 2001).

Under normal environmental conditions melatonin is secreted at night and it is at its greatest at midnight (02.00 - 04.00 am). During daytime melatonin level is very low. The plasma melatonin profile directly reflects pineal activity, since hormone is not stored in the pineal gland and thus it can be considered as a marker of a circadian phase (Reiter 1991). Plasma melatonin concentration is very reproducible from day to day in a same subject and represents one of the most robust circadian rhythms (Claustrat *et al.* 2005).

Light-induced melatonin suppression in humans was initially reported at light intensities greater than 2000 lux (Lewy *et al.* 1980, Partonen *et al.* 1997). Later studies have shown that depending on the spectrum of light, the suppression of melatonin also occurs at smaller light intensities (Brainard *et al.* 2001, Figueiro & Rea 2010, Lockley *et al.* 2003, Zawilska *et al.* 2009) even through closed eyelids (Figueiro & Rea 2012). Melatonin suppression has been found to be non-linearly related to illuminance with saturating responses around 1000 lux (Zeitzer *et al.* 2000). Compared to longwave light, short wavelength light has been shown to block melatonin secretion and promote shifting of circadian rhythm more (Wright & Lack 2001). To be precise, the mechanism of action has been shown to be mediated via the blue-light sensitive retinal melanopsin having its maximum spectral sensitivity approximately at 480 nm (Berson *et al.* 2002, Qiu *et al.* 2005). However, high intensity red light has also been found to elicit melatonin suppression referring to possible involvement of classical visual photoreceptors (Hanifin *et al.* 2006). The ability of light to suppress melatonin secretion has been found to also depend on the time of day, the preceding ambient light level, and the duration of light exposure (Zawilska *et al.* 2009). In addition, individuals receiving less BL exposure may become more sensitive to lower levels of light (Owen & Arendt 1992).

2.1.2 Cortisol

The hypothalamic-pituitary-adrenal (HPA) axis is known to be responsible for regulation of the physiological stress response. A healthy HPA axis is characterized by a distinctive circadian pattern of cortisol secretion (Ryan *et al.* 2016); thus, level of cortisol has also been used in many circadian studies to indicate the effect of

physical and mental stress factors on circadian rhythm (Dickerson & Kemeny 2004, King & Hegadoren 2002).

Steroid hormone cortisol is the final product of the HPA axis (de Weerth *et al.* 2003). The release and production of cortisol on the cortex of the adrenal gland is stimulated by adrenocorticotropic hormone (ACTH) secreted by the anterior lobe of the pituitary gland. Corticotrophin releasing hormone (CRH) of the hypothalamus regulates the production of ACTH. The synthesis and release of both CHR and ACTH is controlled by cortisol via a feedback inhibition process (Buckley & Schatzberg 2005).

Cortisol is secreted in a pulsatile fashion that displays a circadian rhythm (de Weerth *et al.* 2003). The pattern of cortisol secretion is regulated by the SCN (Buijs *et al.* 2003). In healthy subjects, the daily pattern of cortisol is not affected by gender (Lovallo *et al.* 2010) or season (Thorn *et al.* 2011). The cortisol level in blood and saliva falls to a nadir at approximately midnight and begins to rise about 2–3 h after sleep onset (Buckley & Schatzberg 2005). Cortisol usually peaks early morning within 30–45 min of waking and is associated with arousal. (Chida & Steptoe 2009, Clow *et al.* 2010). The gradual decline in cortisol level occurs over the waking hours (Buckley & Schatzberg 2005).

The main measurable parameter of diurnal rhythm is the cortisol awakening response (CAR), which is the rise in cortisol following awakening (Adam & Kumari 2009). CAR regulation is relatively distinct from cortisol secretion across the rest of the day. It is initiated by a direct neural input to the adrenal cortex by the sympathetic nervous system via an extra-pituitary pathway from the suprachiasmatic nucleus (Clow *et al.* 2010). The other parameter is the rate of decline in cortisol levels across the day, the diurnal cortisol slope (Adam & Kumari 2009).

Stressful factors potentiate cortisol awakening response (Chida & Steptoe 2009, Clow *et al.* 2010). External photic exposure has also been found to stimulate cortisol secretion (Leproult *et al.* 2001). The exposure of BL is dependent on time of day - light induces an immediate elevation in cortisol levels early morning but not at other times of the day or night (Leproult *et al.* 2001, Rüger *et al.* 2006). Chronic disruption of circadian rhythm e.g. repeated travelling across several time zones may result in elevated levels of basal cortisol (Cho *et al.* 2000). An alteration in diurnal cortisol pattern has been found to be involved in various endocrine, behavioural and cardiovascular risk profiles (Collomp *et al.* 2016).

2.2 Jet lag and light

Physical and mental performances also follow circadian rhythm. Typically, performance is strongest in the early evening when bodily internal temperature is at its highest. However, there are no studies conducted on the relationship between the maximum temperature and performance. The optimal time for mental performance depends on the complexity of the task. Compared to complex tasks, capacity to perform a simple task diminishes later. (Reilly *et al.* 2009)

Jet lag is a phenomenon that occurs when the endogenous circadian timing system becomes desynchronised from external time due to rapid travel across several time zones. It has been classified as a circadian rhythm disorder in the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-V) (American Psychiatric Association 2014) and as a chronobiological sleep disorder (ICD-10) (Partinen 2008). Symptoms of jet lag include sleep disturbances, drowsiness during the day, reduced alertness, poor overall performance, cognitive deficits, fatigue, irritation, anxiety, depression, and gastrointestinal dysfunction (Sack *et al.* 2007). The severity of jet lag symptoms depends on the number of time zones crossed, the direction of travel, the time of day of the flight, and possibly the time of year (Waterhouse *et al.* 2007), as well as individual parameters such as age and physical health (Baehr *et al.* 2000, Reilly *et al.* 2009). Travelling over three time-zones almost invariably results in jet lag (Jackson 2010). There is also a large individual variation in how jet lag is subjectively perceived, but to date there is no clear explanation for that. It is possible that younger people with flexible sleep rhythm and in better physical shape experience fewer jet lag symptoms (Reilly *et al.* 2009). However, there are also controversial findings on the effects of age on jet lag symptoms (Sack *et al.* 2007, Waterhouse *et al.* 2002). In addition, circadian preference i.e. chronotype ("early bird" or "night owl") may influence perceived jet lag symptoms (Auger & Morgenthaler 2009).

Jet lag symptoms dissipate as the internal clock shifts gradually toward the external time (Eastman *et al.* 2005). It is generally agreed that without any external boosting methods the biological clock shifts by one hour per day in the travel destination. However, when travelling eastward, shifting of the internal clock to the new time is slower than when travelling westward. The individual free-running period (natural circadian rhythm) also has an effect on the rate of phase shifting. (Eastman *et al.* 2005). For individuals, whose circadian period is shorter than 24 hours, advancing rhythm occurs more easily. For Individuals with free-running

rhythm longer than 24h, entrainment is achieved more easily by delaying (Duffy & Wright 2005).

Light is the strongest environmental signal (Zeitgeber) to synchronise our biological clock to the environment (Khalsa *et al.* 2003). In a laboratory setting, correctly timed BL has been found to shift the internal biological rhythm of humans (Arendt 2009, Auger & Morgenthaler 2009, Eastman *et al.* 2005). The timing of the treatment, as well as the intensity and spectrum of the light have an effect on the magnitude of the shift (Chang *et al.* 2012, Khalsa *et al.* 2003, Rüger *et al.* 2013, St Hilaire *et al.* 2012).

The phase response curve (PRC) of light can be used to determine the connection between the timing of the light stimulus and the magnitude of the phase shift at different phases of circadian rhythm (Khalsa *et al.* 2003) (Fig. 3). All organisms including humans are more sensitive to light stimuli during the biological night compared to the biological day (Czeisler *et al.* 1989). The advancing and delaying of the phase is related to the minimum body temperature (T_{min}) and the timing of the light exposure. Human body temperature typically reaches its lowest value, nadir, at early morning a couple of hours before voluntary wake up time. If light exposure occurs before minimum temperature (biological late evening), the phase tends to be delayed. Light exposure after the minimum temperature (biological early morning) causes the phase advance (Eastman *et al.* 2005). When delaying the rhythm, light exposure should be administered at most six hours before the temperature minimum and when advancing the phase, light exposure needs to be administered at most six hours after temperature minimum. Based on the light response curve phase, shifting is greatest when exposure is administered about three hours before or after temperature minimum (Khalsa *et al.* 2003). Intermittent light exposure has been found to elicit circadian changes comparably or even more effectively than continuous light (Burgess *et al.* 2003, Gronfier *et al.* 2004, Najjar & Zeitzer 2016).

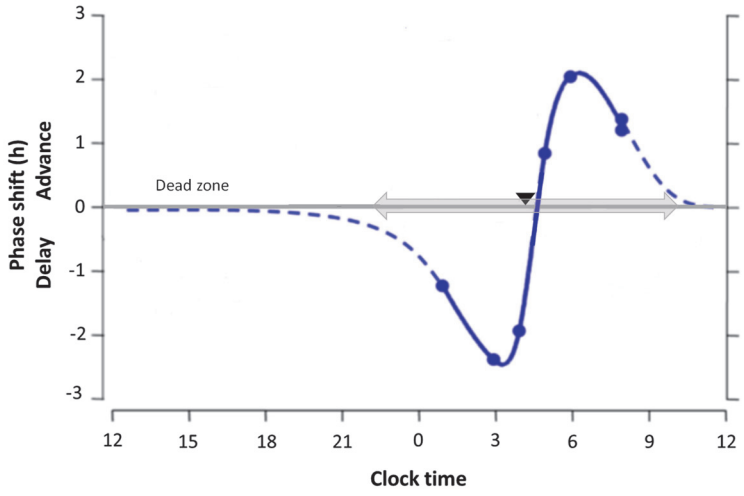

Fig. 3. Phase response curve (PRC) for BL exposure. Light exposure before temperature nadir (T_{min}) induces delaying of the circadian rhythm whereas exposure after T_{min} advances the rhythm. The black triangle shows the typical time of T_{min}. The active window for the entraining effect of light starts 6 h before and ends 6 h after the T_{min}. Modified from (Eastman & Burgess 2009).

Exposure to BL shifts the circadian clock forward or backward depending on the timing of light exposure (Khalsa *et al.* 2003). Thus, artificial or natural light is generally thought to be beneficial in facilitating faster adaptation to a new time zone. In addition to light, jet lag symptoms are treated with melatonin, strategic scheduling of sleep and pharmacological drugs such as hypnotics and stimulants (Sack 2010, Waterhouse *et al.* 2007). Studies mainly focus on treating the underlying cause for jet lag, i.e. the internal desynchronisation of the biological clock. The effect of light on jet lag has been studied extensively under laboratory conditions, but to a lesser extent under authentic jet lag conditions (Gooley 2008). There are only a few field studies exploring the usage of a light device or exposure to ambient light (Boulos *et al.* 2002, Lahti *et al.* 2007, Sasaki *et al.* 1989, Thompson *et al.* 2013) to facilitate adaptation of the biological clock and/or to alleviate the symptoms of jet lag. The field studies on jet lag conducted to date have shown a modest entraining effect (Boulos *et al.* 2002) and increased sleep effectiveness (Sasaki *et al.* 1989), but no effect on performance or subjective jet lag symptoms (Boulos *et al.* 2002, Lahti *et al.* 2007, Thompson *et al.* 2013).

2.3 Psychomotor speed and light

Endogenous circadian rhythm modulates cognitive performance such as alertness, learning and memory. Desynchronisation or misalignment of circadian oscillators can lead to decreased cognitive performance (Czeisler & Gooley 2007, Kyriacou & Hastings 2010). Cognitive deficits are also amongst the symptoms reported for depression (Michalon *et al.* 1997) and are suggested to present themselves as impaired performance in attention and executive function (Porter *et al.* 2003).

Cognitive performance is also one of the important factors in sport performance, specifically in those sports requiring fast decision-making and execution skills. Fatigued athletes often report impaired concentration and cognitive performance (Nederhof *et al.* 2006) especially during a busy and high strained competition schedule (Nederhof *et al.* 2006, Nederhof *et al.* 2007). Training status, physiological and psychological strain and environmental conditions such as seasonal darkness may also significantly influence fatigue and cognitive performance in athletes (Halson 2014, Rosen *et al.* 1996). Cognitive performance, especially psychomotor performance has been observed to be impaired due to overreaching (Rietjens *et al.* 2005), and can be used as an early marker of this (Hynynen *et al.* 2008, Nederhof *et al.* 2006, Nederhof *et al.* 2007). Overreaching is a condition when "immediately after the period of overload training performance will usually be impaired" and recovery to the normal performance level takes days to weeks (Nederhof *et al.* 2007). Psychomotor performance can be examined objectively by measuring the minimal time needed to respond to a stimulus i.e. simple reaction time (SRT) (Cajochen 2007). SRT reflects the brain's speed of information processing (Woods *et al.* 2015).

Light has been found to have an acute effect on cognitive performance and alertness in humans (Cajochen *et al.* 2000, Cajochen *et al.* 2005, Chellappa *et al.* 2011a, Chellappa *et al.* 2011b, Gabel *et al.* 2015, Phipps-Nelson *et al.* 2003, Rüger *et al.* 2013, Sahin & Figueiro 2013, Vandewalle *et al.* 2006, Vandewalle *et al.* 2009). It is well demonstrated that acute light exposure can activate cortical and subcortical networks involved in arousal, attention and memory (Vandewalle *et al.* 2009). It is not entirely known whether the effects of light on performance are mediated via the image-forming or non-image forming system (Tam *et al.* 2016).

Most earlier studies have explored the effect of nocturnal light on cognitive performance in humans and partly due to that it has been suggested that measurements of the effects of light on alertness are linked to light's ability to suppress melatonin (Cajochen *et al.* 2000, Figueiro *et al.* 2007, Okamoto &

Nakagawa 2015, Sahin & Figueiro 2013). Interestingly, an acute improvement of cognitive performance following the day time light exposure has been revealed in several recent studies (Cajochen *et al.* 2000, Gabel *et al.* 2015, Okamoto & Nakagawa 2015, Rüger *et al.* 2013, Sahin & Figueiro 2013), utilizing both short and long wavelength light exposures.

It is well known that night-time melatonin secretion in humans is effectively suppressed by short-wavelength (blue) light (Brainard *et al.* 2001) and is not affected by low levels of long-wavelength (red) light (Ho Mien *et al.* 2014). However, long wavelength light has been observed to increase alertness both at night and in the middle of the afternoon when melatonin levels are low, as shown by a reduction in alpha, alpha-theta and theta power in electroencephalography (EEG) activity (Sahin & Figueiro 2013, Sahin *et al.* 2014). In addition, a recent study revealed that morning exposure to both short- and long-wavelength lights affected alertness by reducing alpha power (Okamoto & Nakagawa 2015). Long-wavelength light has also been found to modulate nocturnal brain activity without suppressing nocturnal melatonin (Figueiro *et al.* 2009). Thus it has been suggested that eliciting direct activating effects of light may be mediated by mechanisms other than those exclusively sensitive to short-wavelength light (Gabel *et al.* 2015, Okamoto & Nakagawa 2015) and that melatonin suppression is not needed to elicit an alerting effect (Sahin & Figueiro 2013).

2.4 Seasonal affective disorder and light

Disturbances in circadian rhythms have been associated with various types of depression (Srinivasan *et al.* 2012). A temporary feeling of depression is a normal emotional reaction related to different losses, failures and disappointments. According to the DSM-V (American Psychiatric Association 2014) depression is considered clinical when symptoms have lasted longer than two weeks and also symptoms other than a depressed state of mind, including fatigue and loss of energy and interest are involved.

The seasonal form of depression called seasonal affective disorder (SAD) was first reported by Rosenthal and colleagues in 1984 (Rosenthal *et al.* 1984). SAD is characterised by recurrent episodes of depression, lack of energy and loss of interest during the specific season (American Psychiatric Association 2014). Since SAD is more prevalent in the winter compared to the summer (Magnusson 2000, Magnusson & Partonen 2005), the term SAD usually refers to winter SAD and is used accordingly in this thesis hereafter. The prevalence of SAD varies from 0% to

9.7% in the general population (Magnusson 2000). Climatological, geographical latitude, social and cultural and genetic factors have been reported to have an influence on the prevalence of SAD (Magnusson 2000, Mersch *et al.* 1999, Rosenthal *et al.* 1984).

People suffering from SAD experience typical and atypical depressive symptoms i.e. lowered mood, energy loss, excessive sleep with difficulty waking, craving for carbohydrates, weight gain, irritability, social withdrawal, daytime fatigue, loss of concentration and impaired cognitive functioning (Michalon *et al.* 1997, Rosenthal *et al.* 1984, Tam *et al.* 1997). Seasonal affective disorder is also associated with anxiety, hopelessness, sadness and suicidal thoughts (The Finnish Association for Mental Health 2016).

The symptoms of SAD recur and dissipate in parallel to day length. They are at their strongest in mid-winter and fully disappear in the summer. SAD is more common among females and younger adults (Magnusson & Partonen 2005). SAD in females is usually characterised by minor depressive episodes, whereas males more commonly experience major depression (Blazer *et al.* 1998), even though males seem to underreport SAD symptoms (Lucht & Kasper 1999).

The precise pathogenesis of SAD is uncertain, despite several explanatory theories such as photoperiod and phase-shifted circadian rhythms, neurotransmitter functions, and/or a genetic basis (Lam & Levitan 2000, Sohn & Lam 2005).

BL has been found to alleviate mood symptoms and is the treatment of choice in SAD (Eastman *et al.* 1998, Ravindran *et al.* 2009, Terman & Terman 2006). It has also been established to be an effective treatment in other forms of depression (Golden *et al.* 2005, Tuunainen *et al.* 2004). In a meta-analysis, the effect size for the reduction of depressive symptoms was 0.84 (Golden *et al.* 2005). However, when the results were carefully scrutinised, the evidence was not unequivocal (Martensson *et al.* 2015).

At the very beginning light research focused on the timing and intensity of the light (Eastman *et al.* 1998, Meesters *et al.* 1993, Meesters 1995, Terman *et al.* 1998). A dose-response relationship was reported in a study utilising conventional fluorescent BL sources (Lee & Chan 1999). On the contrary, even low intensity dawn simulation light (250 lux) has been proven to be as effective as 10,000 lux when administered early in the morning (Avery *et al.* 2001, Terman & Terman 2006). Most studies support the superiority of morning light compared to evening light with respect to reducing depression (Lewy *et al.* 1998, Terman *et al.* 2001, Terman *et al.* 1998).

Discovery of light sensitive cells in the retina having a maximum sensitivity to blue light (Berson *et al.* 2002), shifted the focus from timing and intensity to spectral characteristics of light (Anderson *et al.* 2009, Glickman *et al.* 2006). Spectral characteristics of light have been shown to influence the effect of light treatment in SAD, suggesting that low-intensity short-wavelength LED light sources may be comparably effective as high-intensity full spectrum white light (Anderson *et al.* 2009, Glickman *et al.* 2006, Meesters *et al.* 2011) and superior to red light (Glickman *et al.* 2006, Strong *et al.* 2009). On the other hand, results from recent studies did not enable any conclusion to be drawn for or against blue light sources over full spectrum white light sources (Gordijn *et al.* 2012, Meesters *et al.* 2011). The absence of a clear difference in response might be due to a saturation effect based on the high light intensities used. The light intensity at which the light therapy response reaches saturation is still under discussion - recent studies suggest that the effect of light saturates at low light intensities (Meesters *et al.* 2011).

As described above, findings concerning intensity-based dose-response relationships of phototherapy are contradictory. Luminance scales in lux or lumens units have since been adjusted for visual system sensitivity peaking at 555 nm (Lucas *et al.* 2014, Vandewalle *et al.* 2009). Illuminance measurements underestimate the actual illuminance of blue-enriched light sources (peaking 460 - 480 nm). Thus, the use of power measures of light based on the physical properties of the light would describe the light source more accurately.

Despite the vast amount of research conducted on the issue, the exact effect size, optimal duration, intensity and wavelength of BL treatment remains undetermined. According to clinical guidelines, recommended BL exposure is at least 30 up to 60 minutes, employing a light source of at least 2500 lux up to 10,000 lux (American Psychiatric Association 2014). The overall consensus is that BL therapy in SAD patients is to be effective, despite the fact that underlying mechanisms are still under investigation (Golden *et al.* 2005).

Summary of the reviewed literature

Adaptation of behaviour and physiology to changes in the ambient light level is of critical importance to life. Mammals and humans can detect light using two systems, the visual and non-visual system. Phototransduction in the eye is mediated by three types of receptors; rods, cones and ipRGCs all located in the retina (Tosini *et al.* 2016). All photoreceptor classes although different in terms of the respective

functions are suggested to communicate with each other (Daneault *et al.* 2016). This influences the SCN which controls circadian rhythm (Walmsley *et al.* 2015).

External light has been found to have various long-term and acute effects on behaviour and brain activation in humans. Long-term NIF effects include circadian entrainment and shift the timing of circadian rhythms such as hormone secretion, heart rate, body temperature and the sleep-wake cycle. Acute effects of light such as melatonin suppression, pupillary constriction and changes in alertness, cognitive brain response and performance are detected more rapidly (Altimus *et al.* 2008, Chellappa *et al.* 2011b, Hankins *et al.* 2008, Vandewalle *et al.* 2009).

Despite the fact that there are numerous studies on the effect of light on human psychophysiology, the corresponding mechanism of action is still not fully covered (Duffy & Czeisler 2009); the role of spectrum, intensity, length, rhythm and intermittence of light needs to be further investigated (Najjar & Zeitzer 2016).

Recently published studies might indicate a new mechanism of direct, non-visual photo reactivity of the brain that occurs via several inborn opsins which have been found to be expressed in mammalian brains (Blackshaw & Snyder 1999, Nissilä *et al.* 2012, Nissilä *et al.* 2017, Yamashita *et al.* 2014). Physiological roles of the aforementioned brain structures are not known yet. However, the existence of these opsins in the brain could suggest that brain tissue might be intrinsically sensitive to external light.

In addition, recent findings suggest that transcranially administered light is able to modulate the neural networks of the human brain (Persinger *et al.* 2013, Starck *et al.* 2012) and abolish normal emotional modulation of attention-related brain response (Sun *et al.* 2016). Thus, it seems reasonable that the effects of light on brain functioning could also be mediated via extra-retinal routes.

3 Aims of the study

The effects of artificial and ambient light on human psychophysiology have been broadly studied during the past three decades. However, there are only a few studies to date exploring the effects of light on brain-related functions when administered via the route beyond the eyes. Thus, the main objective of this thesis was to investigate whether TBL can affect human psychophysiology by inducing hormonal, mood and cognitive changes that has earlier been observed with conventional bright light exposure. The specific aims were to study:

1. the effect of TBL on nocturnal melatonin and cortisol secretion (I).
2. the effect of TBL treatment on symptoms of jet lag (II)
3. the effect of TBL treatment on psychomotor speed in athletes (III)
4. the effect of TBL treatment on symptoms of seasonal affective disorder (SAD) (IV)

4 Materials and methods

Four experiments were performed to study the effect of TBL on melatonin and cortisol secretion (I), subjective symptoms of jet lag (II), psychomotor performance in athletes (III) and symptoms of seasonal affective disorder (IV). Studies I and IV were conducted on the Valkee research site, Oulu. Study III was conducted in the Department of Sport Medicine in Verve, Oulu. Study II was conducted in Clinius research centre in Helsinki.

4.1 Participants

The studies were conducted according to the Declaration of Helsinki and written informed consent was obtained from all participants. The following diary numbers of the Ethics Committee of Oulu University Hospital are related to the original publications (299/2010; 246/2013). Study IV was registered with ClinicalTrials.gov, number NCT01293409.

TBL and melatonin (Study I)

Eight healthy voluntary subjects (mean age: 27 ± 5 years) took part in the cross-over study. The study was performed during May and June 2011 in northern Finland (latitude 65º). Gender distribution was 3 ♀ and 5 ♂.

TBL and jet lag (Study II)

A total of 55 healthy male participants (mean age: 39 ± 7 years) completed the study. Participants were recruited via advertisements in local newspapers. To minimise inter-individual variation and the impact of cofounding variables, only male subjects were studied. Subjects travelled to North America and spent there at least one week. The study was conducted between July 2013 and January 2014 in southern Finland (latitude 60º).

TBL and psychomotor speed (Study III)

Twenty-two voluntary male ice hockey players (mean age: 25 ± 5 years) from a Finnish National Ice Hockey League team took part in the study. Interventions were

performed during the seasonal darkness (October 2011) in northern Finland (latitude 65º).

TBL and SAD (Study IV)

Initially ninety voluntary participants (68 ♀, 22 ♂) suffering from seasonal depressive symptoms were recruited via advertisements in local newspapers. Participants were diagnosed by experienced psychiatrists (M.T. & P.R) to suffer from recurrent major depression (moderate or severe) with seasonal pattern according to the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) (American Psychiatric Association 2014) using Mini International Neuropsychiatric Interview (MINI) (Sheehan *et al.* 1998). In addition, subjects had to have a score of at least 20 on the Structured Interview Guide for the Hamilton Depression Rating scale – Seasonal Affective Disorder (SIGH-SAD) (Williams *et al.* 1988), including a score of 10 or more on the Hamilton Depression Rating Scale (HAMD) and a score of 5 or more on atypical symptom score.

The study was performed during the darkest period of the year (from November 2010 to March 2011) in northern Finland (latitude 65º). The final sample was reduced to 89 due to a subject's unexpected trip abroad during the study period. The mean age of the remaining participants was 43 ± 11 years.

4.2 Randomisation and placebo design

In single-blind cross-over study I the order of the active or placebo exposure was randomised and only subjects were blind to the order of the exposures. Participants were randomly assigned to study groups in studies II, III and IV. In these studies, randomisation was planned and implemented by a person outside the research group to ensure that both subjects and researchers were blind to the group assignment.

Studies I, II and III included a control group, which received placebo treatment. The set-up for the placebo group was the same as in the TBL treatment group except that the device's ability to produce light was eliminated. In studies II and III, the earpiece led did not turn on in the sham device, although the device seemed to work properly externally i.e. the device's indicator light turned on. During the TBL or placebo exposures in study I, participants' eyes were covered by goggles, which were impermeable to light, ensuring that the subjects were blind to the given exposure. The exposures were supervised by a researcher. To create a placebo

design in study II the headset part of the device was covered using customised earmuffs during the exposures for both study groups, to ensure that subjects and researchers were blind to the condition subjects received. Earmuffs were equipped with detectors that ensure that the exposure was automatically discontinued if the device was used inappropriately, displaced or removed during the treatment (Fig. 4).

Fig. 4. TBL device. Customised version with earmuffs. Earmuffs equipped with detectors that stop the treatment in case of inappropriate use. Figure originally published in Study II. Published with permission from AMHP.

In study III, subjects were told that the effective/treating light wavelengths are not necessarily visible and it is not possible to decide externally whether or not the treatment device is sham.

4.3 Study exposures

Transcranial light or placebo exposures were administered transcranially via both ear canals using an active or sham device. The blue-enriched TBL was produced using two LEDs and was transmitted into both ear canals by an optical fibre. The light exposures spectra are shown in Figure 5.

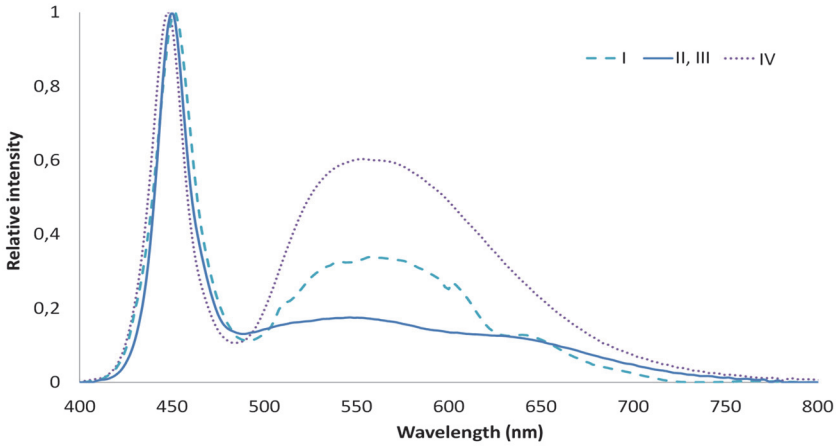

Fig. 5. Spectral distributions of the TBL produced by the light-emitting diode (LED) in studies I-IV.

The exposure in study I was initiated and turned off by the supervising researcher. In studies II, III and IV treatment duration was fixed in the device settings and the device turned off automatically. Subjects received low (1 lumen), intermediate (4 lumen) or high dosage (9 lumen) of TBL in study IV. In studies I, II and III the intensities of TBL exposures were 8.5, 3.5 and 3.5 lumens, respectively. The administered light exposures in studies I, II, III and IV are summarised in Table 1.

Table 1. Physical details of the light devices.

Study	Spectral characteristics	Luminous flux (lumen)	Illuminance (lux)	Irradiance (mW/cm^2)	Photon density ($photons/cm^2/s$)
I					
TBL	$\lambda_{max} \approx 450$	8.5	-	7.28	1.94×10^{16}
sham	-	-	-	-	-
II					
TBL	$\lambda_{max} \approx 448$	3.5	9100	4.3	1.13×10^{16}
sham	-	-	-	-	
III					
TBL	$\lambda_{max} \approx 448$	3.5	9100	4.3	1.13×10^{16}
sham	-	-	-	-	-
IV					
Group 1	$\lambda_{max} \approx 448$	1	2386	0.72	2.00×10^{15}
Group 2	$\lambda_{max} \approx 448$	4	9542	2.88	7.98×10^{15}
Group 3	$\lambda_{max} \approx 448$	9	21470	6.48	18.0×10^{15}

Illuminance and photon density were measured 1 cm from the light source.

4.4 Protocols

TBL and melatonin (Study I)

In the ten-day single-blind crossover study protocol (Fig. 6) subjects spent two nights (6th and 8th) in the laboratory in the same light/dark rhythm (16L:08D, lights off at 11 pm and on at 7 am). Physical activity (Fitbit Inc., San Francisco, CA) was measured throughout the study period to ensure that participants followed normal daytime rhythm. During laboratory nights, saliva and urine samples were collected at pre-determined time points: noon, 6 pm, hourly between 9 pm and 3 am, and hourly between 6 am and 9 am. Participants were exposed in random order to the 24 minutes treatment or sham at 01:10 during the two study days (6th and 8th) in a laboratory environment. The timing and duration of the treatments are summarised in Table 2.

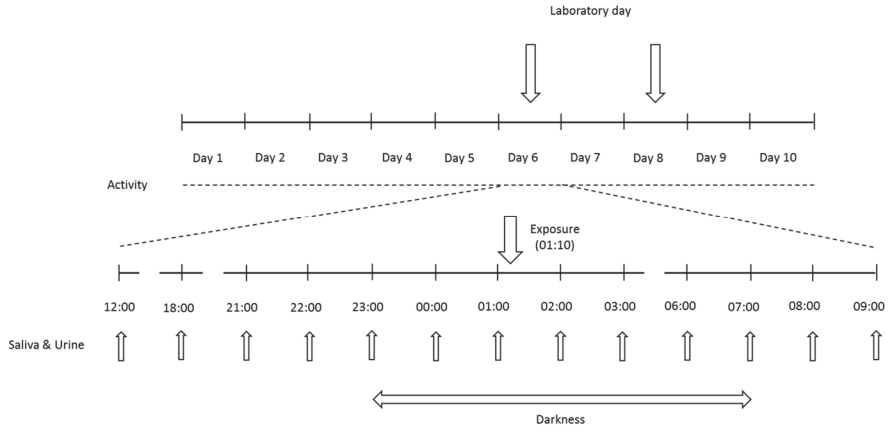

Fig. 6. Melatonin study protocol (Study I). A ten-day cross-over study. During the laboratory nights (6th and 8th) saliva and urine samples were collected at pre-determined times between noon and 09:00 and the sham or TBL exposure was administered at 01:00. The order of the sham and TBL exposure was randomised.

TBL and jet lag (Study II)

The randomised, placebo-controlled and double-blind field study consisted of three consecutive periods: baseline period (1 week), travel period (at least 1 week) and post-travel period (1 week) (Fig. 7). Subjects were split into TBL treatment and placebo groups. The daily 12 minutes treatment exposure was administered intermittently every two hours starting at 8 am (post-travel day 0) or at 10 am (post-travel days 1-6). During the first study day (baseline) and the post-travel period, subjective jet lag symptoms were measured at home using self-rating questionnaires at pre-determined times twice a day (noon and 5 pm). A sleep diary was filled out daily after awakening. The timing and duration of the treatments are summarised in Table 2.

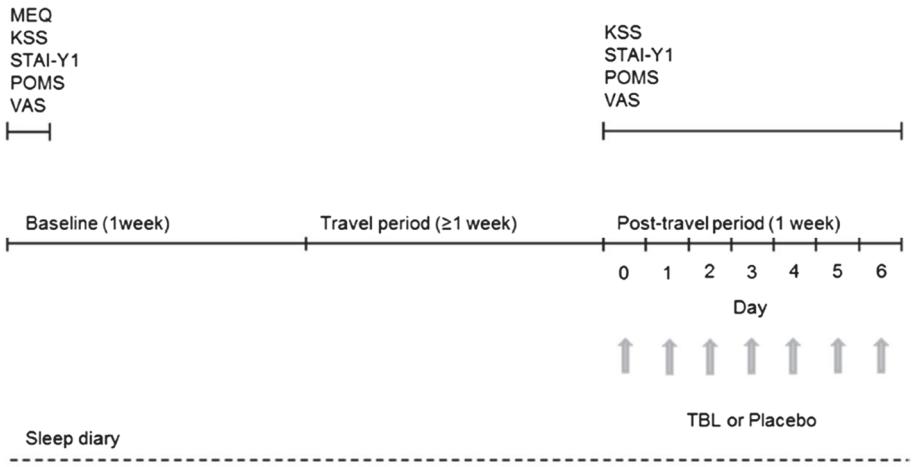

Fig. 7. Jet lag study protocol (Study II). Structured questionnaires were filled in twice a day (noon, 5 pm) at first baseline day and during the intervention period. TBL or sham exposure was administered every other hour starting at 8 am at the first intervention day and at 10 am on the rest of the days. Sleep diary was filled in once a day during the whole study period. Figure originally published in Study II. Published with permission from AMHP.

TBL and psychomotor speed (Study III)

The design of the 24-day field study was randomised, double-blind and placebo-controlled (Fig. 8). Participants' psychomotor speed was monitored before and after the intervention period. Participants were divided into the light treatment and placebo group. Randomisation was performed in groups of four. The daily 12 minutes treatment exposure was administered between 8 am and noon. The timing and duration of the treatments are summarised in Table 2.

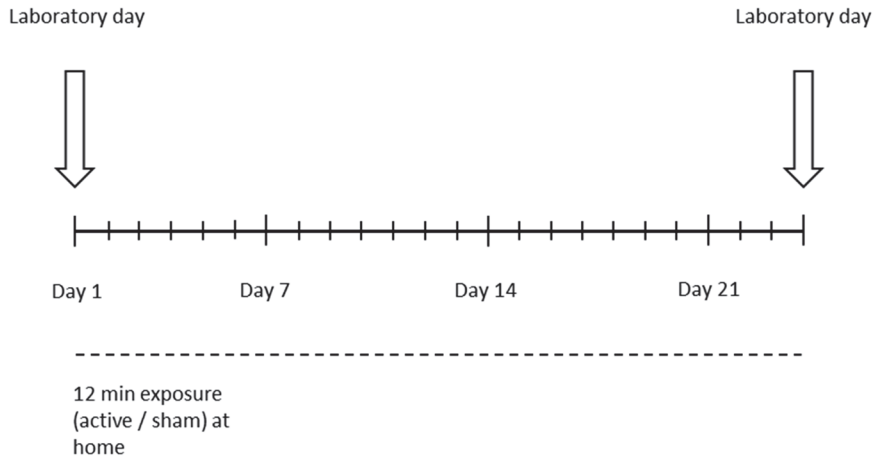

Fig. 8. Psychomotor speed study protocol (Study III). Psychomotor speed was measured at the beginning and end of the study. TBL or sham exposure (12 min) was administered daily at home between 8 am and noon.

TBL and SAD (Study IV)

The four weeks randomised dose-response field study consisted of two visits in research centre at the beginning and end of the study (Fig. 9). During the visits, participants' depressive and anxiety symptoms were measured by experienced psychiatrists using structured interviews. In addition, participants fulfilled self-rating questionnaire monitoring depression symptoms once a week at home. Participants were divided into three intervention groups (low, intermediate and high dosage) at the beginning of the study period. The daily 12 minutes treatment exposure was administered under field conditions between awakening and noon. The timing and duration of the treatments are summarised in Table 2.

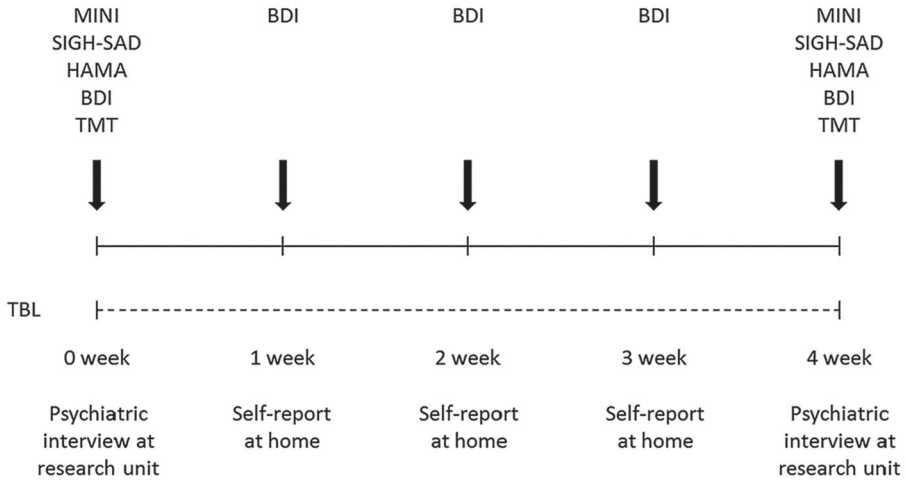

Fig. 9. SAD study protocol (Study IV). A 12-minute TBL daily dose was administered transcranially via the ear canals after awakening. The intensity of the TBL was 1, 4 and 9 lumens in treatment groups 1, 2, and 3, respectively. Depressive symptoms were evaluated using the SIGH-SAD, HAM-A, and BDI measurements. Cognitive performance was measured using the Trail-Making Test (TMT) part A and B. For more details on measurements please see chapter 4.5. The figure was originally published in Study IV. Published with permission from Biomed Central.

Table 2. Timings of treatment administrations.

Study	Exposure timing	Exposure duration (min)
I	01:10	24
II		
post-travel day 0	8 am, 10 am, noon, 14 pm	4 x 12
post-travel days 1-6	10 am, noon, 14 pm and 16 pm	4 x 12
III	between 8 am and noon	12
IV	between awakening and noon	12

4.5 Measurements

4.5.1 Melatonin and cortisol measurements

Melatonin and cortisol levels can be measured non-invasively from the saliva and urine sample (Vakkuri 1985). The correlation between night-time serum and saliva

melatonin concentrations has been proven to be 0.95 (de Almeida *et al.* 2011, Laakso *et al.* 1990). So as not to suppress melatonin, saliva and urine were sampled in a dim red light. Samples were stored frozen at -20 ºC until they were analysed. Before analysing with the radio-immunoassay (RIA), both samples were centrifuged (12 000 x g; 10 min). For the melatonin assay, a 1 mL sample was extracted with chloroform. After evaporation of chloroform phase, the residue was dissolved into phosphate-buffered saline buffer for radioimmunoassay, pipetted using melatonin specific antiserum and 125I-labelled melatonin as tracer (assay sensitivity (95% binding): 1.5 pmol/mL, intra-assay CV 7.4, inter-assay CV 3.7%). For the cortisol assay, 150 µg was assayed using cortisol-specific antiserum and 123I-cortisol tracer in coated tube radioimmunoassay (assay sensitivity (95% binding): 0.8 nmol/L, intra-assay CV 1.3, inter-assay CV 13.7%). Cortisol and melatonin levels were measured from the saliva and urine samples in study I.

4.5.2 Self-rating questionnaires

Beck Depression Inventory (BDI) (IV)

The Beck Depression scale (Beck *et al.* 1961) is a well-established 21-item self-report questionnaire measuring depressive symptom severity rated on a 0 to 3 scale. Each BDI item consists of four statements indicating different levels of severity of a particular symptom experienced over the past week. Higher score indicates the greater severity of depression. Scores for all 21 items are summed to yield a single depression score. Subjective depressive symptoms were measured in study IV. Detailed information on the administration of the questionnaire is shown in Table 3.

Table 3. The questionnaires, tests and samples used in studies I, II, III and IV.

Measurement	Study I	Study II	Study III	Study IV	Administration
Radio-immuno assay					
Melatonin secretion	X				a
Cortisol secretion	X				a
Self-rating questionnaires					
BDI				X	b
KSS		X			c
MEQ		X			d
POMS		X			c
Sleep Diary		X			e
STAI-Y1		X			c
VAS (OJS)		X			c
VAS (QoS)			X		e
Cognitive and psychomotor performance					
Motor time			X		f
Reaction time			X		f
TMT				X	f
Interviews					
HAM-A				X	f
MINI				X	d
SIGH-SAD				X	f
Activity measurement					
Accelerometer	X				

a During the laboratory days at noon, hourly between 9 pm and 3 am, 6 am and 9 am

b Weekly during the study period

c Twice a day at the first study day and during the post-travel period at predetermined times

d Pre-study visit

e Daily during the study period

f Pre- and post-study visits

g Continuously throughout the study period

Karolinska Sleepiness Scale (KSS) (II)

Karolinska sleepiness scale (KSS) (Akerstedt & Gillberg 1990, Kaida *et al.* 2006) is commonly used for evaluating instantaneous subjective sleepiness (Kaida *et al.* 2006). The scale has been validated against alpha and theta EEG activity and slow eye movement electrooculographic (EOG) activity (Akerstedt & Gillberg 1990, Kaida *et al.* 2006). It is a 9-point verbally anchored scale with the following steps: “extremely alert” (score 1), “very alert” (2), “alert” (3), “rather alert” (4), “neither

alert nor sleepy" (5), "rather sleepy" (6), "sleepy, but no effort to stay awake" (7), "sleepy, some effort to stay awake" (8), "extremely sleepy, about to fall asleep, great effort to stay awake" (9). Subjective sleepiness was measured in study II. Detailed information on the administration of the questionnaire is shown in Table 3.

Morningness-Eveningness Questionnaire (MEQ) (II)

The shortened 6-item Morningness-Eveningness Questionnaire modified from the Horne-Östberg morningness-eveningness questionnaire (Horne & Ostberg 1976) measures the subject's chronotype preference. Each item consist of a four-point scale. The sum gives a score ranging from 5 to 27; scores of 12 and below indicate "evening types", scores from 13 to 18 indicate "intermediate types" and scores of 19 and above indicate "morning types". The participant's chronotype was assessed in study II. Detailed information on administration of the questionnaire is shown in Table 3.

Profile of Mood States (POMS) (II)

The shortened Finnish version of POMS (Hänninen 1989, McNair *et al.* 1981) is an adjective checklist measuring effects during the preceding week. The POMS includes 38 items comprising the following subscales: tension, depression, irritability, vigour, fatigue, inertia, confusion and forgetfulness. Higher values on the scales other than vigour indicate worse emotional well-being. On the vigour scale the relationship is inverse. The POMS was used to measure mood changes in study II. Detailed information on the administration of the questionnaire can be found in Table 3.

Sleep Diary (II)

Sleep diary is widely used to measure the subjective parameters of sleep. A structured sleep diary used in study II included items for recording parameters commonly used to quantify sleep: total sleep time, sleep onset latency, number of awakenings and wake after sleep onset. Subjects were also asked how rested they felt after sleep on a scale ranging from 0 (fully rested) to 5 (not rested at all). In addition, time and duration of naps, consumption of caffeinated beverages and alcohol were monitored.

Spielberger State-trait Anxiety Inventory, Form Y-1 (STAI-Y1) (II)

Spielberger State-trait Anxiety Inventory form Y1 (Spielberger *et al.* 1983) measures the severity of state anxiety symptoms. It contains 20 items rated on a scale ranging from 1 "not at all" to 4 "very much so". Scores for all 20 items counted using a scoring key and summed to yield a single anxiety score. Higher anxiety scores indicate higher anxiety symptoms. STAI-Y1 questionnaire was used to measure the change of anxiety symptoms in study II. Detailed information on the administration of the questionnaire is shown in Table 3.

Visual analogue scale (VAS) (II, III)

Visual analogue scales are used to measure the severity and change of variety of symptoms. The VAS is a 100-mm long line. Participants are asked to view the line as representing their personal range of feelings and to place a mark on the line indicating their current feeling. In study II subjects rated the severity of overall jet lag symptoms (OJS) ranging from "no symptoms at all" (left end of the line) to "very severe symptoms" (right end of the line). In study III subjects were asked how they would rate the quality of their sleep (QoS) last night ("very bad" on the left end of the line and "very good" on the right end of the line. Detailed information on administration of the scale is shown presented in Table 3.

4.5.3 Cognitive performance testing

Reaction time tests (III)

The simple reaction time test (Vienna Test System, Schuhfried, GmbH, Moedling, Austria) assesses reaction time and time to execute the motor response i.e. motor time in response to simple visual (yellow light) or acoustic signal (a beep). The subject is instructed to press a reaction key when specific stimuli are presented and return the finger immediately to the rest key after pressing. Mean reaction time (stimulus onset – reaction key pressed) and mean motor time (rest key released – reaction key pressed) is calculated as a mean time for the 28 repetitive signals (Fig 10). Detailed information on administration of the test is outlined in Table 3.

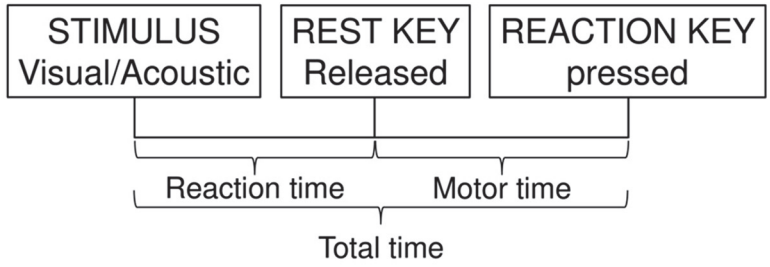

Fig. 10. The deviation of total time into reaction time and motor time. The figure was originally published in Study III. Published with permission from Frontiers.

Trail-Making test (IV)

Trail-making test consisting of two parts measures attention (part A) and mental flexibility (part B) skills (Ayers *et al.* 2007, Crowe 1998). Subjects were asked to draw lines to connect encircled numbers in a numerical sequence (part A; i.e. 1-2-3, etc.) or numbers and letters in an alternating numerical and alphabetical sequence (part B; 1-A-2-B.etc.) as fast as possible (Salthouse 2011). The score on each part represents the amount of time required to complete the task. Detailed information on administration of the test is shown in Table 3.

4.5.4 Interviews

Psychiatric interviews for diagnosing the mental disorder and measuring the severity of depressive symptoms were used in study IV. Interviews were conducted by two trained raters who were blind to the treatment condition. Inter-rater reliability was assessed in a pilot measurement.

Hamilton Rating Scale for Anxiety (HAM-A) (IV)

The clinician-rated HAM-A (Hamilton 1959) assessment device is a widely used semi-structured public domain assessment scale in treatment outcome studies of anxiety. The device consists of 14 items measuring the severity of anxiety symptoms. It is also sensitive to detect the change in symptoms during anxiolytic treatment. The HAM-A interview was used in study IV to assess the severity

anxiety symptoms of SAD patients. Detailed information on administration of the interview is shown in Table 3.

Mini International Neuropsychiatric Interview (MINI) (IV)

The diagnostic interview tool (Mini International Neuropsychiatric Interview, MINI) (Sheehan *et al.* 1998) is used to diagnose mental disorder according to the Diagnosis and Statistical Manual of Mental Disorders (DSM-V) (American Psychiatric Association 2014). The MINI is a structured interview exploring the axis I diagnosis, prioritising identification of current disorders. The MINI is not designed to systemically explore, symptom by symptom, the probes for severity, disability or problems accounted for physically or to identify diagnostic subtypes of psychotic disorder (Lecrubier *et al.* 1997). In study IV two trained psychiatrists diagnosed recurrent major depression with seasonal pattern and excluded subjects with bipolar disorder using the MINI diagnostic tool. Detailed information on the administration of the interview is presented in Table 3.

Structured Interview Guide for the Hamilton Depression Rating Scale – Seasonal Affective Disorder (SIGH-SAD) (IV)

The SIGH-SAD (Williams *et al.* 1988), the most commonly used clinical assessment device for detecting changes in SAD symptoms in light therapy research. The semi-structured interview includes the 21-item Structured Interview Guide for the Hamilton Rating Scale for Depression (HAM-D) and a supplementary 8-item subscale to assess atypical depressive symptoms associated with SAD. Scores for all 29 items are summed to yield a total score for depression. SAD symptoms were measured using SIGH-SAD in study IV. Detailed information on administration of the interview is presented in Table 3.

4.5.5 Activity measurements

Activity monitoring based on an accelerometry sensor is a useful method for obtaining objective information on physical activity patterns (Kumahara *et al.* 2004). To ensure a normal daytime rhythm during the study period, the daily sleep-wake rhythm was measured using an accelerometer (Fitbit Inc., San Francisco, CA) in study I. Detailed information on the administration of the interview is shown in Table 3.

4.6 Data analysis

Data are presented as a percentage or as the mean and 95% confidence intervals, standard deviation or standard error.

Study I: Differences between sham and TBL exposure concerning saliva and urine samples were analysed using one-way ANOVA (repeated measures) with Tukey test. Stineman function of KaleidaGraph (Synergy Software, Reading, PA) was used to analyse circadian rhythm data (acrophase, peak duration and area under the curve; AUC). *P*-values <0.05 were considered statistically significant.

Study II: Data analysis were performed using SAS (version 9.3, SAS Institute Inc, Cary, NC, USA) and OriginPro (OriginLab Corporation, Northampton, MA). Data were analysed using the intent-to-treat method. Baseline values were compared using two-sample independent *t*-tests, Chi-Square test and Fisher's Exact test. The effect of treatment on each variable intergroup and between groups was analysed with two-way repeated measures analysis of variance with time x group interaction. Post hoc analyses were conducted using Bonferoni correction for multiple comparisons. To account for possible baseline differences, data were normalised as a function of the baseline population mean and SD across all subjects (z-score transformation) before the analysis. In the recovery analysis, a criterion for recovery was determined such that subjects were defined as 'recovered' from jet lag if their normalised VAS score was less than 2 by the end of the post-travel period. *P*-values <0.05 were considered statistically significant.

Study III: Data analysis were performed using SPSS (SPSS 19.0 for Windows, IBM, Armonk, NY, U.S.). Standard statistical methods were used to calculate means, standard deviations, and standard errors. Normal Gaussian distribution of the data was verified by the Kolmogorov-Smirnov goodness-of-fit test ($z > 1.0$). The effect of treatment on each variable was assessed using analysis of variance for repeated measures with time x group interaction. The analysis was conducted with and without an appropriate covariate, age, since it is known to impact motor and reaction times. Post hoc analyses were conducted using Bonferoni correction for multiple comparisons. In addition, the independent *t*-test followed by adjustment for age (ANCOVA) was used to calculate the relative changes and group-difference for the values of the psychomotor test. *P*-values <0.05 were considered statistically significant.

Study IV: Data were analysed using SAS (version 9.2, SAS Institute Inc, Cary, NC, U.S.) and the intent-to-treat method. Baseline values were compared using Student *t*-tests. Categorical variables were compared by either a Chi-Square test or

Fisher's Exact test as appropriate. The effects of treatment on each variable within group and between groups were analysed with repeated measures of analysis of variance (ANOVA). The response criterion was defined as a decrease in baseline scores of 50% or more. To fulfil the remission criteria, the total score had to be no more than a cut-off score and the decrease of 50% or more. *P*-values <0.05 were considered statistically significant.

5 Results

5.1 The effect of TBL on nocturnal melatonin and cortisol secretion (Study I)

Melatonin and cortisol concentrations in urine and plasma did not differ significantly during the active TBL and sham experiments in healthy subjects. Melatonin onset (22-23 h), peak (03 h) and offset took place in parallel in both TBL and control conditions (Fig. 11). The cortisol awakening response occurred between 06h and 09h peaking at 08h in both sessions, without any statistically significant differences between the conditions. A potentiated CAR effect was not observed in our study.

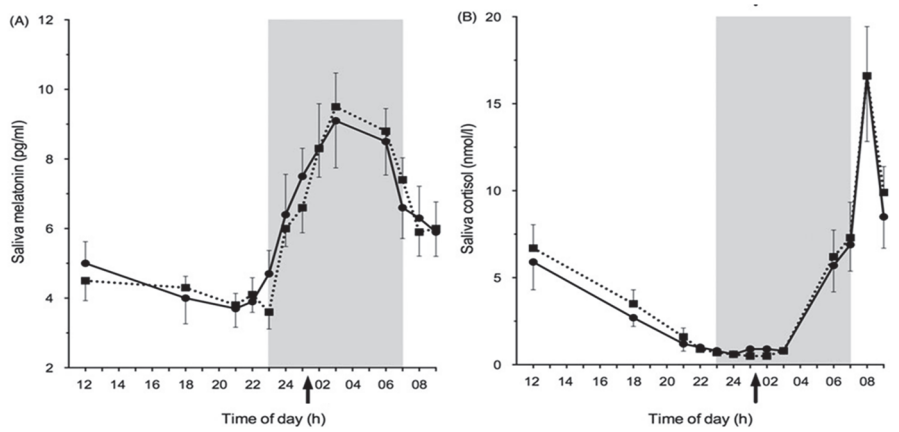

Fig. 11. Circadian rhythm of saliva (A) melatonin and (B) cortisol during the TBL (broken line) and control (solid line) experiments in study I. Values are presented as mean ± sem. The arrow indicates the beginning time of 24 minutes TBL or sham exposure. The lights off period (23h-07h) is marked with a grey colour. The secretion curves of melatonin and cortisol during the TBL intervention experiment were in parallel to the secretion of the control experiment. The figure originally presented in Study I. Published with permission from Chroninobiol Int.

5.2 The effect of TBL on jet lag symptoms (Study II)

In subjects suffering from jet lag symptoms, the effect of TBL was found after four to five days of TBL treatment. Subjects receiving TBL treatment reported

significantly less fatigue, inertia and forgetfulness (POMS), sleepiness (KSS) and overall jet lag symptoms (VAS) compared to the placebo control group (Fig. 12). There was no statistically significant difference between the study groups during the first three intervention days, suggesting a cumulative effect of TBL.

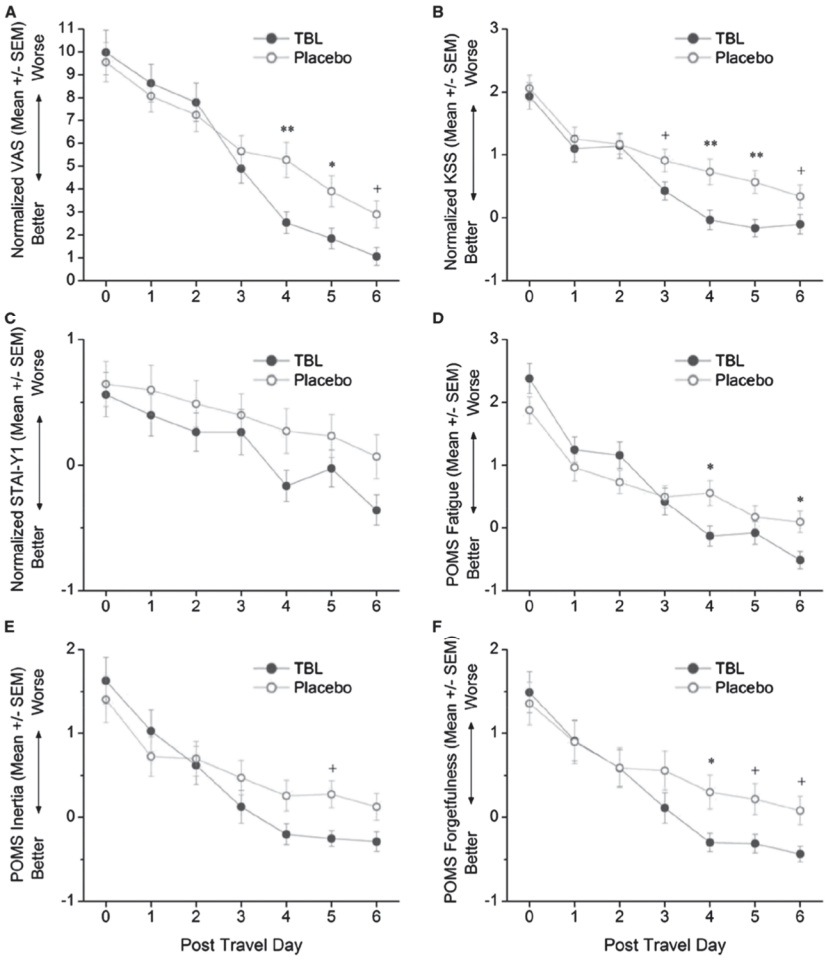

Fig. 12. The effect of TBL treatment on subjective symptoms of jet lag (Study II) measured by Visual Analogue Scale (VAS), Karolinska Sleepiness Scale (KSS) and State-Trait Anxiety Inventory (STAI-Y1) for the jet lag symptoms and Profile of Mood States (POMS) subscales for fatigue, inertia and forgetfulness. Positive values on the y-axis represent a Z-score worse than the pre-travel baseline value, negative values indicate a Z-score better than baseline and 0 indicates a Z-score equivalent to baseline. Data are represented as mean ± SEM, $^{+}P<0.1$; $^{*}P<0.05$; $^{**}P<0,01$. A) Results for the VAS,

B) Results for the KSS, C) Results for the STAI-Y1, D) Results for the POMS fatigue scale, E) Results for the POMS inertia scale and F) Results for the POMS forgetfulness scale. Figure originally published in Study II. Published with permission from AMHP.

According to the recovery analysis, more subjects in the TBL group had recovered compared with the placebo group by post-travel day 6 (Fisher's Exact Test, Mantel-Haenszel $\chi 2(1) = 4.3036$, $P = 0.0380$). The normalised VAS score of 2 or less was defined as a threshold for recovery (Fig. 13).

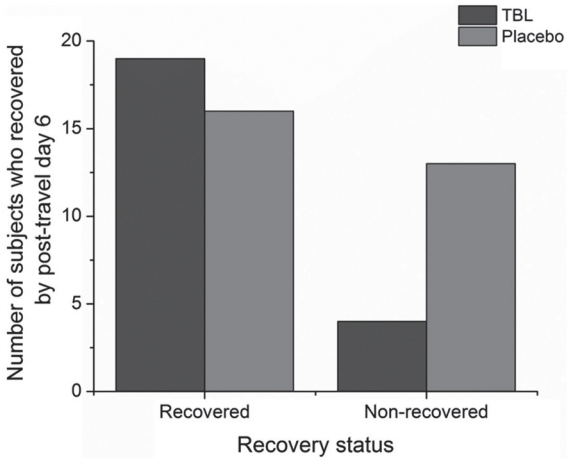

Fig. 13. Recovery analysis in Jet lag study (Study II). Results of the number of subjects who recovered by the end of the treatment period based on the Visual Analogue Scale (VAS) for jet lag symptoms (Fisher's Exact Test, Mantel-Haenszel $\chi^2(1) = 4.3036$, $P = 0.0380$). The figure was originally published in Study II. Published with permission from AMHP.

5.3 The effect of TBL on psychomotor parameters (Study III)

The motor time for visual stimulus improved in TBL group compared to the placebo group (P=0.024, adjusted for age) (Fig. 14). The relative changes in TBL group and sham groups were -24±16% and -10±15%, respectively (P=0.023, adjusted for age). No statistically significant changes in any parameters were reported in the audio warning test or memory test in either the treatment or sham group.

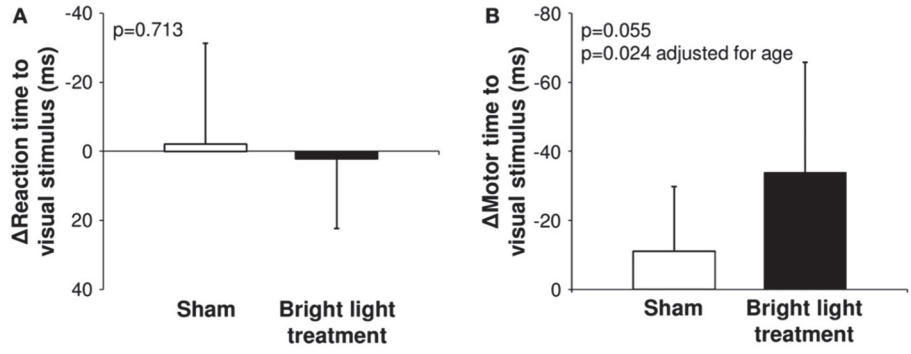

Fig. 14. The change of reaction time (A) and motor times to visual stimulus after 24 days TBL or sham treatment in study III. Figure originally published in Study III. Published with permission from Frontiers.

5.4 The effect of TBL on symptoms of SAD (Study IV)

The total number of participants who completed the study was 89. One participant was excluded from the study due to an unexpected trip abroad. Transcranially administered BL treatment alleviated the mood symptoms in subjects suffering from the SAD. The effect was observed by psychiatric interviews (SIGH-SAD, HAM-A) after a four week study period and after one week by self-rating questionnaire (BDI) (Fig. 15).

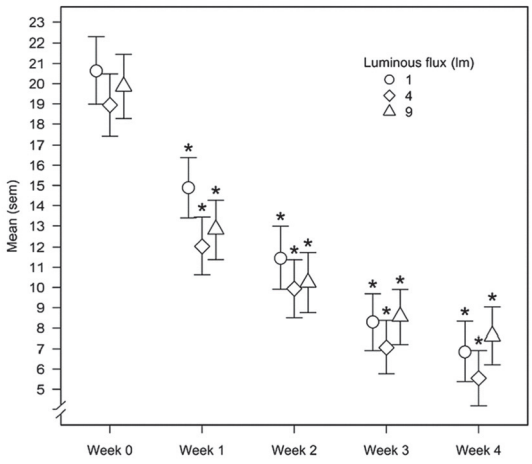

Fig. 15. BDI sum scores during the four-week study period in study IV. Depression symptoms measured by BDI decreased equally in all intervention groups receiving TBL exposure of 1, 4 or 9 lumens. BDI, Beck Depression Inventory. Values are reported as mean ± sem, *$P < 0.05$. The comparison was calculated in relation to the baseline. Figure originally published in Study IV. Published with permission from Biomed Central.

The intensity of light exposure (1, 4, and 9 lumens) did not appear to impact the absolute or relative decrease of symptoms or the response attained or remission rate. The percentage improvement measured by the BDI varied from 63% to 67% in the three treatment groups. Corresponding variations for the SIGH-SAD and the HAM-A were 44%-47% and 47%-50%, respectively. The response rates measured by the BDI varied from 74% to 79% in the three treatment groups. Corresponding variations for the SIGH-SAD and the HAM-A were 35-45% and 47-62%, respectively (Fig. 16).

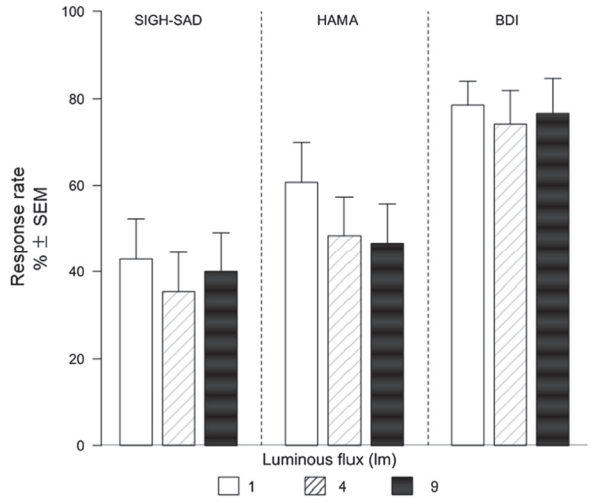

Fig. 16. The response rate measured by the SIGH-SAD, HAM-A and BDI after the four weeks TBL treatment in three study groups receiving light exposures of 1, 4 or 9 lumens in study IV. No statistically significant differences between groups were observed. Figure originally published in Study IV. Published with permission from Biomed Central.

The ameliorated cognitive performance measured by TMT was also found after the treatment period. The attention, measured by the TMT-A, improved significantly in all three treatment groups. The significant improvement in mental flexibility (TMT-B) was observed only in group 2 (Table 4).

Table 4. Changes in Trail-making test A and B.

Change	%	95%CI	*P*-value	%	95%CI	*P*-value	%	95%CI	*P*-value
TMT-A	-9.7	-2.2 - -17.3	0.0066	-18.0	-11.6 - -24.4	<0.0001	-18.7	-12.3 - -25.1	0.0004
TMT-B	-6.5	5.0- -18.1	0.1104	-11.2	-4.9 - -17.4	0.0009	-7.9	-1.2 - -16.9	0.1060

6 Discussion

In this thesis, the effect of alternative route of delivering light was studied in healthy participants and participants suffering from symptoms of SAD and jet lag.

6.1 Overview of the results

The main findings of this doctoral thesis corresponding with the aims presented in the original publications were:

I Nocturnal TBL exposure did not alter the melatonin or cortisol secretions in any of the sampling points. Circadian profiles of both melatonin and cortisol paralleled the profiles measured under control conditions. There were no differences found in any of the rhythm characteristics studied i.e., acrophase, peak duration, and AUC. The TBL exposure did not modulate either the subsequent circadian pattern of melatonin excretion into urine.

II Intermittent TBL exposure appears to alleviate jet lag symptoms. Up to four doses of TBL per day significantly reduced overall post-travel jet lag symptoms as well as subjective feelings of fatigue, inertia and forgetfulness. On average, subjects in the TBL group showed a greater rate of overall recovery based on their VAS scores than subjects in the placebo group. Interestingly, a significant effect of TBL was not observed until post-travel day 4, which may indicate a cumulative effect of the TBL treatment.

III Motor time with a visual warning signal was improved by the TBL treatment in professional ice-hockey players during the competition season in the dark time of the year. Interestingly, auditory cued reaction speed was not altered after TBL treatment.

IV Transcranially administered BL treatment seems to alleviate both depressive and anxiety symptoms related to SAD. However, a proper placebo condition was not included in the study setting. Consequently, no strong conclusion can be drawn from the results of the study. No statistically significant differences in the improvement of depressive or anxiety symptoms were found between groups receiving intensity of 1 to 9 lumens of TBL via the ear canals.

6.2 TBL, melatonin and cortisol

The effect of BL was originally thought to be strictly associated with secretion of melatonin by the pineal gland. However, it is by now established that the alerting

effects of BL are present during the day in the virtual absence of melatonin (Phipps-Nelson *et al.* 2003, Rüger *et al.* 2006). Daytime light exposure has been found to activate the various brain areas (Vandewalle *et al.* 2006, Vandewalle *et al.* 2007). The effect also exists without disturbing nocturnal melatonin secretion on longer wavelengths (Rahman *et al.* 2011, Rahman *et al.* 2013). Furthermore, exposure to flashes of broad spectrum white light has been found to reset human circadian rhythms without affecting melatonin concentration (Zeitzer *et al.* 2011).

These results provide new insights to understand the psychophysiological and clinical effects of transcranially administered BL. As seen in this study, TBL was not found to have acute suppressive or phase-shifting effects on the circadian rhythm of melatonin or cortisol. This parallels the recent findings showing that light administered via the ear canals does not affect pineal melatonin secretion (Bromundt *et al.* 2014). Consequently, it seems that the putative effects of TBL are thus mediated via routes not involving melatonin suppression.

6.3 TBL and Jet lag

Most earlier studies on jet lag were conducted under highly controlled laboratory settings and mainly focused on treating the underlying cause for jet lag; the internal desynchronisation of the biological clock (Gooley 2008, Sack 2010). According to the guidelines for the management of jet lag by the American Academy of Sleep Medicine, the use of melatonin, scheduling sleeping times and BL exposures as well as administering hypnotics and stimulants are supported (Morgenthaler *et al.* 2007).

There are few studies exploring the effect of bright or ambient light administration on jet lag symptoms under authentic field conditions and they were performed with considerably small subject groups (Boulos *et al.* 2002, Daan & Lewy 1984, Lahti *et al.* 2007, Sasaki *et al.* 1989, Suhner *et al.* 2001b, Thompson *et al.* 2013). In the first field study with light two subjects were exposed to ambient light after eastward flight (9 time-zones). The intention was to delay the circadian rhythm of one subject and advance that of the other subject, as was observed (Daan & Lewy 1984). However, according to the subsequently published human PRC, used light administration times should have delayed both circadian rhythms (Boulos *et al.* 1995). BL was subsequently observed to increase sleep effectiveness in a study conducted with four subjects travelling eight time-zones eastward (Sasaki *et al.* 1989). However, due to the small sample size - two subjects per condition - individual differences could be ruled out (Sasaki *et al.* 1989). In the

dim-light controlled setting with nine subjects travelling eastward across six time-zones, BL was not found to shift the circadian rhythm (Suhner *et al.* 2001b). On the other hand, Boulos *et al.* (2002) conducted a study with 20 subjects travelling westwards across six time-zones. The BL was found to modestly entrain the circadian rhythm. However, no effects on sleep, performance or subjective jet lag symptoms were found (Boulos *et al.* 2002). Furthermore, the alleviation of subjective symptoms of jet lag was not observed either in a field study by Lahti *et al.* (2007) - conducted with fifteen aircrew members taking part in long-haul flights and exposed to natural or bright light (Lahti *et al.* 2007) - or in a study by Thompson *et al.* (2013), with 22 female athletes travelling eastwards from USA to Europe (Thompson *et al.* 2013). Consequently, the amount of authentic jet lag studies that have been performed following actual travel is small, studies are conducted with a few subjects and in the main, without a proper control setting. Although laboratory studies have revealed the shifting of circadian rhythm by the BL, well-controlled field studies are needed to ascertain whether the light exposure is effective on reducing jet lag symptoms (Waterhouse *et al.* 2007)

The results in study II showing alleviation of jet lag symptoms are promising and also comparable with findings in corresponding field-based jet lag studies conducted with melatonin (Arendt *et al.* 1986, Claustrat *et al.* 1992, Petrie *et al.* 1989, Petrie *et al.* 1993), stimulants (Beaumont *et al.* 2004) and hypnotics (Suhner *et al.* 2001a) reporting decreased sleepiness and overall symptoms of jet lag and increased mood. Study II aimed to explore the effect of TBL on alleviating the symptoms of jet lag without treating the underlying cause of the disorder, i.e. the internal de-synchronisation. Thus, only measurements evaluating alleviation of subjective symptoms were utilised. Consequently, any conclusion on the shifting of the internal rhythm by TBL cannot be drawn.

6.4 TBL and Psychomotor speed

Transcranially administrated BL treatment was found to improve the motor component of cognitive performance in response to a visual stimulus in professional athletes. The intervention period occurred during the darkest time of the year and during the busy competition season, which together might induce psychomotor slowness as an early marker of overreaching. The alteration of reaction speed with an auditory warning signal was not observed after the light treatment. This is in line with the results of the early fMRI study by Starck et al., (2012) reporting the reactivity of visual and motor - but not auditory cortex - to

acute light exposure (Starck *et al.* 2012); Correspondingly, increased functional connectivity in visual and sensomotor networks has been observed in SAD patients (Abou Elseoud *et al.* 2014).

Conventional BL has been found to improve cognitive performance (Badia *et al.* 1991, Cajochen *et al.* 2000, Campbell & Dawson 1990, Chellappa *et al.* 2011b, Daurat *et al.* 1993, Phipps-Nelson *et al.* 2003). Since the light-induced suppression of melatonin is accompanied by an improvement of sleepiness, alertness and performance, the effect induced by BL has been interpreted to be related to suppression of melatonin (Rüger *et al.* 2005). As discussed earlier, conventional BL exposure has been found to enhance day-time cognitive performance when melatonin is even undetectable (Phipps-Nelson *et al.* 2003, Rüger *et al.* 2006). Thus, improved cognitive performance is at least partly mediated via other mechanisms than melatonin suppression (Phipps- Nelson et al., 2003; Rüger et al., 2005). Since acute TBL exposure was not found to suppress melatonin (Study I), it is reasonable to assume that the improvement of motor time in this study is entirely mediated via a pathway beyond the RHT.

6.5 TBL and SAD

The depression and anxiety symptoms of SAD patients alleviated significantly in all three treatment groups during the four-week TBL treatment (Study IV). The mean decrease in depression score measured by self-rated BDI was 66%. The corresponding decreases for psychiatry-rated SIGH-SAD and HAM-A scores were 46% and 49%, respectively. The alleviation of the depression and anxiety symptoms parallels earlier studies conducted with conventional BL devices or pharmacological therapy in the treatment of SAD or anxiety (Avery *et al.* 2001, Eastman *et al.* 1998, Flory *et al.* 2010, Hartford *et al.* 2007, Lewy *et al.* 1998, Meesters *et al.* 2011, Stein *et al.* 2008, Terman *et al.* 1998, Terman & Terman 2006). The impairment of cognitive functioning is a commonly reported symptom related to major depression (Hammar & Ardal 2009) and deficits in cognitive functioning have also been observed in SAD (Michalon *et al.* 1997). Conventional light exposure has been found to have an effect on cognitive performance and alertness in humans (Chellappa *et al.* 2011a). The improvement of cognitive function measured by the trail-making test was also observed in all treatment groups. The alleviation of anxiety and depressive symptoms were also equal in all three treatment groups despite the different intensity of light received. The lack of dose-response relationship between the different light intensities found in the study has

raised questions. However, neither the earlier findings concerning intensity-base dose-response relationships of phototherapy are consistent (Avery *et al.* 2001, Baxendale *et al.* 2013, Terman & Terman 2006). As seen in earlier studies with conventional BL devices, the absence of a clear difference in response might be due to a saturation effect based on the high light intensities used. The saturation intensity for light therapy response has not yet been established. However, recent studies suggest that this occurs at low light intensities (Meesters *et al.* 2011). Thus, the lack of dose-response in this study might be due to the saturation effect. Since there was no proper placebo group in this study, the observed alleviation of the symptoms in different study groups could also be due to placebo. The dose response in this study was only examined as an intensity-dependent variable, while the duration of treatment is also known to impact the response (Terman & Terman 2005). In addition, the exact timing of the treatment and a detailed analysis of the sleep/wake cycles of patients was not included in the study.

6.6 Theoretical discussion

The mechanism of action of TBL has not yet been established; the concept of direct phototransduction is presented in this thesis. The idea of extraocular phototransduction is not entirely new. The idea of an extra-ocular method of light therapy was presented by Campbell & Murphy (Campbell & Murphy 1998). In the initial study light exposure was administered by the fibre optic pads placed behind the knee (popliteal fossa area). The mechanism underlying extraocular phototransduction being discussed concurrently was the absorption of photic energy by bilirubin. The same method is used to treat newborn infants suffering from hyperbilirubinemia (Hansen 2011). The initial finding by Campbell & Murphy was not found to be replicable (Eastman *et al.* 2000, Koorengevel *et al.* 2001, Wright & Czeisler 2002), and the idea of extra-retinal methods was rejected. The proposed mechanism underlying the effectiveness of TBL in this thesis is, however, different from the bilirubin absorption theory (Oren 1997). In addition, the exposure site (ear canal) differs essentially from an earlier study of Campbell *et al.* (1998).

The exact underlying mechanism of action for conventional BL is not determined either (Najjar & Zeitzer 2016). Traditionally, the effect of natural and artificial light is thought to be mediated only via the eyes (Tosini *et al.* 2016). Since the early 2000s, circadian research has made great strides towards characterising the mechanisms behind photic exposure identifying and characterising light-

sensitive opsins in the retina. Direct perception of external light through extraocular photoreceptors has, however, been reported in birds and lower vertebrates (Vigh *et al.* 2002). Tissue staining studies have also discovered potentially light-sensitive structures outside of the retina in mammalian, including human brains (Blackshaw & Snyder 1999, Kojima *et al.* 2011, Koyanagi *et al.* 2013, Kumbalasiri & Provencio 2005, Leszkiewicz *et al.* 2000, Nissilä *et al.* 2012, Nissilä *et al.* 2017, Tarttelin *et al.* 2003, Yamashita *et al.* 2014).

Interestingly, recent studies have revealed that extraocular light delivered via ear canals abolishes normal emotional modulation of attention-related brain responses (Sun *et al.* 2016) and increases neural activity and connectivity in certain areas of the brain (Persinger *et al.* 2013, Starck *et al.* 2012). These same areas have been shown to be activated during daytime ocular BL administration related to alerting effects (Vandewalle *et al.* 2006, Vandewalle *et al.* 2007, Vandewalle *et al.* 2009). In rodent and human studies of Nissilä *et al.* (2012, 2017), these areas also have been suggested to contain OPN3 (Nissilä *et al.* 2012) and OPN4 (Nissilä *et al.* 2017) proteins. Thus, the underlying mechanism of TBL is at least partly proposed to be based on the functionality and activation of extra-retinal light sensitive opsins in the brain. Further studies are needed to clarify the mechanisms associated with ear light exposure.

6.7 Strength of the studies

One of the strengths of the studies included in this thesis is the representable sample sizes. Compared to studies with conventional BL devices on SAD, the number of patients (n=90) in study IV is among the largest; The average sample size of studies included in the meta-analysis of evidence of BL treatment was 20 and the largest study included 85 patients (Golden *et al.* 2005). Correspondingly, the sample size (n=55) in the jet lag study (II) is greater than existing field studies conducted with ambient or bright light ranging from one to 22 (Boulos *et al.* 2002, Daan & Lewy 1984, Sasaki *et al.* 1989, Suhner *et al.* 2001b, Thompson *et al.* 2013).

The second strength of this thesis is that the study exploring the effect of TBL on jet lag symptoms was conducted in an authentic environment. So far, most of the studies exploring the effect of BL on jet lag symptoms have been performed in laboratory settings (Sack 2010). The laboratory environment helps to control the confounding variables, and enables the use of objective demanding laboratory measurements such as collecting melatonin samples. Although laboratory studies provide important information, laboratory environment is only a simulation of a

real life, and thus cannot replace actual field studies since they do not fully reproduce the external conditions and features related to the phenomenon (Boulos *et al.* 2002).

Thirdly, many of the current BL treatments have been claimed to be impractical since receiving BL via conventional BL devices requires sitting in front of the devices for at least 30 minutes per day. The objectively measured adherence in BL treatment has been found to be lower than reported by subjects (Michalak *et al.* 2002). Shorter and more effective light exposures might thus improve adherence in treatment. Especially in case of travelling across time zones, the mobile study device is more practical and enables beginning the treatment whilst travelling. In contrast to conventional BL, in studies I, II, III and IV the duration of treatment was significantly shorter i.e. 12 min vs. at least 30 min up to 60 min. The device mobility enabled participants to move during exposure, which might have resulted in elevated adherence.

Furthermore, creating a proper placebo setting in light studies has been a challenge for studies using traditional BL devices (Meesters *et al.* 2011). The placebo setting in study II disables the visible recognition of the exposure, and, thus might be a better approach to solve this problem. However, the warm sensation related to light absorption into the structures surrounding the ear canal might also enable the recognition of the exposure.

The measurements, questionnaires and interviews used in this thesis are commonly accepted measurements for exploring melatonin and cortisol secretion, for measuring psychomotor speed and for evaluating SAD and jet lag symptoms.

6.8 Limitations of the studies

Several shortcomings of this study should be noted. The first limitation of this thesis concerns the control settings in studies III and IV. The difficulty in having proper placebo conditions lies in the treatment's nature, i.e. being visible light. The lack of placebo condition is the greatest challenge for studying the effects of BL (Desan *et al.* 2007, Meesters *et al.* 2011). Placebo effect on average accounts for 20% to 40% of any given treatment for depression, and for the BL it has been measured to be approximately 30% (Walsh *et al.* 2002). At the beginning of the BL research dim red light served as a placebo in several BL studies (Glickman *et al.* 2006, Michalon *et al.* 1997, Rosenthal *et al.* 1984). However, subjects allocated to dim red light might have been aware of its placebo use resulting in higher expectations for BL (Eastman *et al.* 1998). A statistically significant difference

between the dim red light placebo group and the BL group was not always found (Avery *et al.* 2001), and some studies has revealed that dim red light might have psychophysiological effects (Sahin & Figueiro 2013, Sahin *et al.* 2014), indicating the importance of having a proper, inactive treatment placebo.

Recent studies have employed a disabled negative ion generator as a placebo (Eastman *et al.* 1998, Flory *et al.* 2010, Terman *et al.* 1998). Assuming the placebo response of TBL to be in line with the placebo effect found in earlier studies, the alleviation of seasonal symptoms in study IV might not be entirely accounted for by means of a placebo effect. In addition, the reduction of symptoms observed for the BDI (76%) and SIGH-SAD (39%) in study IV were comparable to the response rates seen in earlier BL studies (Avery *et al.* 2001, Flory *et al.* 2010, Meesters *et al.* 1993, Meesters 1995, Meesters *et al.* 2011, Strong *et al.* 2009). The findings showing altered emotion-attention interaction due to transcranial light is also consistent with a potential effect of BL on mood (Sun *et al.* 2016). SAD symptoms are known to be at their strongest during the darkest period of the year and prone to alleviate when the days start to get longer (Gorman *et al.* 2001). Since study IV was conducted partly under field conditions, several confounding factors such as unexpected life events, physical activity and nutrition may affect an individual's mood which enables symptoms to either alleviate or intensify. The conclusions drawn from study IV are therefore limited by the absence of a proper placebo group.

In study III an inactivated light device was used as a control device. Subjects were notified that effective light wavelengths are not necessarily visible, and it is not possible to decide externally whether the treatment device is a sham. The subjects knew that this study was a BL study and, therefore, some subjects may know their group membership. However, this kind of approach was also used in an earlier BL study showing that both the active and the placebo alternative showed high response rates (Levitt *et al.* 1996). In studies I and II the interventions were conducted either under the supervision of the investigator or with a customised device that enables prober placebo setting.

The second limitation of this thesis is the lack of female participants in studies II and III. The lack of females is also reported to be common practice in earlier circadian rhythm research (Bailey & Silver 2014). Given that no statistically significant gender differences in any of the measured parameters were found in the study of TBL in SAD which included both men and women (study IV) and that none of the existing field studies on BL in jet lag show a gender effect, i.e., both men and women benefited (Boulos *et al.* 2002) or fail to benefit (Lahti *et al.* 2007) from the tested interventions in equal measures, it is reasonable to assume that the

response to TBL of both genders is in parallel. It is, however, well known that women experience changes in sleep quality, sleep duration, and mood based on hormonal changes throughout their menstrual cycle (Baker & Driver 2007, Hachul *et al.* 2010, LeRoux *et al.* 2014). In addition, sex differences have been detected in several circadian timing system functions (Bailey & Silver 2014). Furthermore, the findings on sex-related difference in simple reaction time has been reported (Dykiert *et al.* 2012). However, results are not consistent (Woods *et al.* 2015) and a trend towards reduced sex di□erences has been reported possibly reflecting increased female participation in fast-action sports and driving (Silverman 2006). To minimise all possible inter-individual variation other than the administration of TBL, studies were comprised of men only.

The lack of objective measures in study II is the third limitation of the thesis. Depending on the choice between investigating treatment alternatives for jet lag symptoms under laboratory or field conditions, or treating underlying cause i.e. internal desynchronisation or symptoms such as increased daytime sleepiness, fatigue, impaired cognition, feelings of anxiety and depression, the metrics used differ. For laboratory studies that enable a high degree of experimental control, the "gold standards" to measure circadian adaptation to a new time zone are dim light melatonin onset (DLMO) measured in blood, saliva or urine, core body temperature or sleep/wake EEG and subjective scales and self-rating to assess the alleviation of symptoms. However, under field conditions and when solely assessing the alleviation of symptoms most of the studies have used the same commonly used standardised and validated instruments as in this study. The shifting of internal rhythm was not measured in study II. Thus, based on the results no conclusion on entraining effect of transcranial light can be drawn. The relatively low number of participants is a limitation in study I. However, the number of participants is in line with earlier physiological studies concerning melatonin secretion (Scholtens *et al.* 2016). In addition, since study I was conducted using cross-over design, participants were allocated into both interventions (light exposure and sham). The effect of confounding variables was thus controlled more efficiently. The results of study I parallels earlier founding (Bromundt *et al.* 2014); thus it is not obvious that an increase in the number of participants would have led to different results.

6.9 Future directions

The results from this thesis and previously observed NIF effects such as changes in brain functions (Persinger *et al.* 2013, Starck *et al.* 2012, Sun *et al.* 2016),

improvements in mood (study IV), motor time (study III) and jet lag symptoms (study II) associated with ear light exposure suggest that there might be an additional route for NIF effects beyond RHT.

In sum, the results on this thesis support the idea that TBL appears to impact some aspects of human psychophysiology. However, there is still a lot to learn about the effects of TBL. Although knowledge of the NIF effects of transcranial light on human psychophysiology has increased in recent years, the mechanism of the action of light is still unknown. Based on the results, we propose that there might be additional routes for NIF effects besides RHT. These routes do not appear to be dependent on the structures regulating melatonin secretion.

Further studies are needed to clarify the mechanisms associated with ear light exposure. The external ear canal consists of an outer cartilaginous portion and an inner bony portion. The adult ear canal forms a definite "S" shape and its length ranges from 2.5 to 3.0 cm. The skin covering the ear canal is thin (0.2 mm – 1 mm), adhered directly to the perichondrium or periosteum and has a profuse blood supply. The ear canal is surrounded by several nerves. The most important nerves innervating the ear canal are an auricular branch of the vagus nerve and the auriculotemporal nerve. The main external ear canal veins are branches of the temporal vein and the posterior auricular vein (Alvord & Farmer 1997). When administering light exposure via ear canals, the light absorbs into the surrounding tissues and eventually turns into heat. Heat exposure has been found to have focal tissue effects. It breaks the molecular bonds, accelerates chemical reactions and putatively perturbs the transmembrane potential generating action potentials (Chernov & Roe 2014). In addition to the putative direct photosensitivity of the brain and local thermal effects in surrounding tissues, delivering BL via ear canals may elicit effects via the nerve branches in the ear. Since electrical stimulation of the left anterior auditory canal has been suggested to stimulate vagal afferents (Kraus *et al.* 2013, Polak *et al.* 2017), the effect of TBL on vagal activation also needs to be explored. Further studies related to shift work and sleep could throw new light on the practical implications of TBL. In addition, studies with proper placebo setting on the effect of TBL on symptoms of seasonal affective disorder are needed.

The effects of artificial and ambient light on human psychophysiology have been broadly studied during the past three decades. The direct photosensitivity of the brain has been shown to exist in birds and lower vertebrates (Vigh *et al.* 2002). However, there are only a few studies to date exploring the effects of light on brain-related functions when administered beyond eye-mediated routes. The aim of this

thesis was to explore whether TBL can affect human psychophysiology. The outcomes of this thesis suggest that transcranially administered BL might have some psychophysical effects on humans. The mechanism of action of TBL is, however, unknown. In addition to the brain's direct photosensitivity, the thermal influences and neural effects of light might contribute to mediating the observed effects. Thus, further studies are warranted to confirm these outcomes and define the actual mechanism of action.

7 Conclusions

1. Transcranially administered acute nocturnal BL exposure does not have an acute suppressive or phase-shifting effect on the human circadian rhythm of melatonin or cortisol. Since TBL was not found to suppress melatonin, it cannot disturb nocturnal melatonin secretion either. The existence of a distinct route beyond RHT mediating the putative NIF effect of TBL is suggested.
2. Intermittent TBL was found to alleviate the subjective symptoms of jet lag under authentic field conditions. The effect was found to emerge at days 3-4 post-travel suggesting the cumulative effect of the TBL treatment.
3. TBL treatment was observed to improve psychomotor speed in professional athletes during the strenuous competition season. Faster reaction speed was found only in relation to the visual but not after the auditory signal.
4. TBL treatment may alleviate the symptoms of SAD. All participants were exposed to visible light. A dose-response effect between the doses administered was not observed. The similar response might be due to the saturation effect or could be interpreted as a placebo effect. Since a proper placebo was not implemented in the study set-up, strong conclusions on the effect of TBL on SAD cannot be drawn. Further investigations are needed.

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