FATIGUE IN MULTIPLE SCLEROSIS:

EARLY DISEASE COURSE AND EFFICACY OF A NOVEL

LIGHT THERAPY INTERVENTION

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vorgelegt von

Julia Ottersbach

aus Neukirchen b. Sulzbach-Rosenberg

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Universität Regensburg

Gutachter: Prof. Dr. Mark W. Greenlee

Gutachterin: Prof. Dr. Angelika Lingnau

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Look at the light, and you'll find your way.

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PREFACE

The underlying aetiologies of many neurodegenerative disorders such as multiple sclerosis (MS) remain a mystery. When searching for "Multiple Sclerosis Epstein Barr Virus" in the PubMed database (https://pubmed.ncbi.nlm.nih.gov/; search date: 25th June 2025), the earliest mention of a potential connection between early-age infection with Epstein–Barr Virus (EBV) and the development of MS was written by Adams in 1972. It then took 50 years of research and debate until Bjornevik et al. (2022) provided compelling evidence for this link, demonstrating that people with EBV seropositivity showed a 32-fold increased risk of developing MS compared to people with EBV seronegativity. This led to the assumption that a previous EBV infection is causative for the development of MS (Aloisi et al., 2023). These findings, along with knowledge on the complex interplay between genetic and environmental factors in MS, have paved the way for modern efforts in preventing MS.

Progress in disease prevention is inherently slow and is not necessarily accompanied by the development of a cure; however, patients who currently live with MS are in need of more. With the implementation of and recommendation for first-line disease modifying therapies for MS as early as possible after diagnosis, much effort is being put into controlling inflammatory events and future disability (Coerver et al., 2025; Rae-Grant et al., 2018). However, studies have also shown that some MS symptoms progress in severity independently of the progression of the disease itself and that these symptoms can be very prevalent even during remission. One of these symptoms is fatigue, which is often described as the most impairing MS symptom and is responsible for reduced quality of life and early retirement in many patients with MS (Flachenecker, 2023).

This dissertation broadly focuses on MS-related fatigue and consists of three parts:

Part I gives a general introduction, which includes the pathology of MS and MS-related fatigue, explores the circadian system, night work, summarizes related findings regarding light therapy, and develops the main rationale for the work performed in this dissertation.

Part II comprises three studies: Study 1 focused on the progression of fatigue, alertness, sleep, and fitness to drive within the first year after de-novo MS diagnosis; this study was published in *Multiple Sclerosis and Related disorders* on August 11th, 2023, and the pre-print version of the article is included herein. As light therapy has shown promising results in the treatment of fatigue in other neurological conditions, a novel light therapy method using portable light glasses was evaluated in Studies 2 and 3. Study 2, as an initial trial, included healthy night shift workers who used the light therapy glasses during the early morning hours of night shift work (near the end of the shift) to evaluate effects on mitigating sleepiness and improving alertness and sustained attention. This study was published in *Somnologie,* on January 25th, 2024, and the pre-print version is included here. In Study 3, patients with MS and fatigue participated in an assessment of the efficacy and feasibility of using light therapy glasses, applied directly after awakening, to reduce MS-related fatigue. This study was submitted to *Scientific Reports* on September 24th, 2025, and the submitted version is included here. The manuscripts have all been formatted within this dissertation according to the American Psychological Association (APA) 7th Edition guidelines (American Psychological Association, 2020). The figures and tables have been numbered in consecutive order within each study. Figures 2.3, 2.4, and 2.6 have been adjusted regarding the time format according to APA guidelines. Otherwise, the text and display items in Studies 1–3 have not undergone further changes.

In Part III of this dissertation, a general discussion and conclusions are provided. This is comprised of a summary of the studies' findings and implications, their general

limitations, directions for future research, and conclusions. All references have been merged into a single list that is provided after Part III. Supplementary Materials are given for each study in the Appendix at the end of this dissertation.

Sometimes, it is possible to find simple approaches to solving complex problems—which attempting to address fatigue in MS clearly is. By means of this dissertation, this simple approach has been sought in the form of light.

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ABSTRACT

Despite great advances in the diagnosis and treatment of multiple sclerosis (MS) within the prior two decades, the treatment and prevention of this degenerative autoimmune disorder remain challenging, as it affects around 2.8 million people worldwide who present with diverse constellations of symptoms. Furthermore, early changes in specific symptoms and functional ability within the first year after initial MS diagnosis have not been thoroughly investigated. One of the most prevalent symptoms described as the most impairing by many patients with MS is fatigue, defined as a feeling of disproportionate tiredness and overwhelming exhaustion, thus severely impacting quality of life. However, fatigue is often undertreated, and effective and feasible countermeasures remain scarce.

The work in this dissertation had three Aims: i) to examine alertness, fatigue, mental health, sleep, and fitness to drive in patients with MS shortly after de-novo diagnosis and 1 year later, with comparisons to a matched healthy control group (Study 1); ii) to evaluate a novel light therapy-based intervention method using blue-enriched bright light (468 nm, 1,500 lux) applied via glasses in healthy participants during the early morning hours of night shift work and comparing these with placebo glasses (dim red light, 660 nm, 150 lux) to assess effects on sleepiness, alertness, and sustained attention (Study 2); and iii) assess the safety and efficacy of the same light therapy glasses applied in Study 2 in patients with MS with fatigue, compared with placebo glasses, directly after awakening in an attempt to reduce fatigue and improve quality of life (Study 3).

Study 1, a prospective observational study, examined psychological, psychometric, and physiological data collected in a prospective pilot study over the course of 1 year, including 25 patients with MS and 25 healthy matched controls. Directly after diagnosis, alertness, fatigue, mental health, sleep, and fitness to drive were similar in patients with de-novo MS and matched healthy controls. Further, no deteriorations in the assessed components were observed 1 year after diagnosis.

Study 2, an intervention study, included a placebo-controlled, randomized, crossover design, examining psychological and psychometric data from healthy participants using light therapy glasses. These experiments involved blue-enriched bright light therapy glasses and placebo glasses (dim red light) and were conducted during night shift work at a sleep laboratory. Usage of both light glasses from 5:00 a.m. to 5:30 a.m. slightly reduced sleepiness but yielded no significant effects on alertness directly after light exposure or on fatigue and sustained attention after the night shift. No side effects were reported, and the acceptance and feasibility of the glasses were good.

Building on the findings of Study 2, Study 3 included the same study design adapted to patients with MS with fatigue, using the glasses directly after awakening in the morning. With a focus on analysing the efficacy and feasibility of the light glasses, we were able to provide evidence of the immediate and prolonged significant reductions in fatigue following blue-enriched light exposure (compared to dim red light) and of clinically significant reductions in fatigue levels after one intervention week. Side effects and their severity were mild, and acceptance levels and feasibility were high.

Within the limitations of these studies, namely limited sample sizes, study settings, and generalizability, these findings contributed to the existing knowledge about the initial development of specific symptoms and functional ability within MS. They further provided evidence for a novel portable light therapy-based intervention method that can help treat a highly debilitating MS symptom, initiating ideas for further research, and extending current treatment options for patients with MS and fatigue.

CONTRIBUTIONS

Contributions for the studies included in this dissertation are listed in Table i for Study 1, Table ii for Study 2, and Table iii for Study 3.

Table i. Contributions to Study 1

Study title	Prospective analyses of alertness, sleep, and fitness to drive one year after de-novo multiple sclerosis diagnosis
Authors	Julia Ottersbach[1,2], Thomas C. Wetter[1], Nicole König[3], Anna Fierlbeck[1], Robert Weissert[3], Roland F. J. Popp[1,*]
Author affiliations	[1] Department of Psychiatry and Psychotherapy, Center of Sleep Medicine, University of Regensburg, Regensburg, Germany [2] Department of Experimental Psychology, University of Regensburg, Regensburg, Germany [3] Department of Neurology, University of Regensburg Hospital, Regensburg, Germany [*] corresponding author. E-mail address: Roland.Popp@medbo.de
Author contributions	J.O analysed and interpreted the data, wrote the original draft, and revised the article. T.C.W. designed and conducted the experiment, proofread, and revised the article. N.K. designed and conducted the experiment, acquired funding, proofread, and revised the article. A.F. designed and conducted the experiment, acquired funding, proofread, and revised the article. R.W. designed and conducted the experiment, acquired funding, proofread, and revised the article. R.F.J.P. designed and conducted the experiment, interpreted the data, proofread, and revised the article.
Study supervision	R.W., R.F.J.P.
Acknowledgement	We are grateful to Bettina May and Lena Adelsberger for their assistance in patient management, data collection, and test evaluation. Additionally, we thank Alexander S. Chockley for English language editing.
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Declaration of Helsinki	Yes
Clinical trial	No
Journal (Impact Factor)	Multiple Sclerosis and Related Disorders (2024 Impact Factor: 2.9)
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Table ii. Contributions to Study 2

Study title	Light therapy glasses during night shift work: a field study
Authors	Julia Ottersbach[1,2,*], Anna-Lena Eich[1,2], Katharina Ringeisen[1,2], Thomas C. Wetter[1], Roland F. J. Popp[1]
Author affiliations	[1] Department of Psychiatry and Psychotherapy, Center of Sleep Medicine, University of Regensburg, Regensburg, Germany [2] Department of Experimental Psychology, University of Regensburg, Regensburg, Germany [*] corresponding author. E-mail address: Julia.Ottersbach@psychologie.uni-regensburg.de
Author contributions	J.O designed and conducted the experiment, analysed and interpreted the data, wrote the original draft, and revised the article. A.-L.E. conducted the experiment, interpreted the data, proofread, and revised the article. K.R. conducted the experiment, interpreted the data, proofread, and revised the article. T.C.W. designed the experiment, proofread, and revised the article. R.F.J.P. designed and conducted the experiment, interpreted the data, proofread, and revised the article.
Study supervision	R.F.J.P.
Acknowledgement	We thank all participants for taking part in the study. Further, we are grateful to Alexander S. Chockley for English language editing.
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Table iii. Contributions to Study 3

Study title	Efficacy and feasibility of light therapy glasses to mitigate fatigue in patients with multiple sclerosis: a randomised, placebo-controlled crossover field study
Authors	Julia Ottersbach[1,2,*], Markus Canazei[3], Sophie K. Bauer[1,2], Celine Hfalek[1,2], Caren Berggold[1,2], Thomas C. Wetter[1], De-Hyung Lee[4], Ralf A. Linker[4], Roland F. J. Popp[1]
Author affiliations	[1] Department of Psychiatry and Psychotherapy, Center of Sleep Medicine, Medbo, University of Regensburg, Regensburg, Germany [2] Department of Experimental Psychology, University of Regensburg, Regensburg, Germany [3] Department of Psychology, University of Innsbruck, 6020 Innsbruck, Austria [4] Department of Neurology, University of Regensburg, Regensburg, Germany [*] corresponding author. E-mail address: Julia.Ottersbach@psychologie.uni-regensburg.de
Author contributions	J.O designed and conducted the experiment, analysed and interpreted the data, wrote the original draft, and revised the article. M.C. designed the experiment, interpreted the data, proofread, and revised the article. S.K.B. conducted the experiment, interpreted the data, proofread, and revised the article. C.B. conducted the experiment, interpreted the data, proofread, and revised the article. T.C.W. designed the experiment, proofread, and revised the article. D.H.L conducted the experiment, proofread, and revised the article. R.A.L. conducted the experiment, proofread, and revised the article. R.F.J.P. designed and conducted the experiment, interpreted the data, proofread, and revised the article.
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Publication status	Submitted September 24th, 2025

LIST OF ABBREVIATIONS

Abbreviations frequently used throughout the text of this dissertation are listed in Table iv.

Table iv. List of abbreviations

AMT	Adaptive Matrices Test
ANOVA	Analyses of Variance
APA	American Psychological Association
ArbZG	Arbeitszeitgesetz, German Working Hours Act
ATAVT	Adaptive Tachistoscopic Traffic Perception Task
BDI-II	Beck Depression Inventory II. Revision
BL	Blue-enriched light
CIS	Clinically–isolated syndrome
CNS	Central nervous system
COG	Cognitrone
CONSORT	Consolidated Standard of Reporting Trials
CSF	Cerebrospinal fluid
D-FIS	Daily Fatigue Impact Scale
D-MEQ	Morningness-Eveningness Questionnaire, German version
DRIVEPLS	Psychological traffic test battery Vienna Test System
DRL	Dim red light
DT	Determination Test
EBV	Epstein–Barr virus
EDSS	Expanded Disability Status Scale
ESS	Epworth Sleepiness Scale
FOSQ	Functional Outcomes of Sleep Questionnaire
FRT	Fastest 10% of reaction times
FSS	Fatigue Severity Scale
h	Hours
ID	Identification
ipRGCs	Intrinsically photosensitive retinal ganglion cells
ISCED	International Standard of Education
IVPE	Inventory of Driving-Related Personality Traits
KSS	Karolinska Sleepiness Scale

Table iv, continued. List of abbreviations

lx	Lux
M	Mean
MCT	Mackworth Clock Test
Mdn	Median
MFIS	Modified Fatigue Impact Scale
min	Minutes
MQLI	Multicultural Quality of Life Index/Inventory
MS	Multiple sclerosis
ms	Milliseconds
MWU	Mann–Whitney U test
n	Sample size
nm	Nanometer
p	P-Value
PLMS	Periodic limb movement in sleep
PP	Peripheral Perception
PPMS	Primary–progressive multiple sclerosis
PSG	Polysomnography
PSQI	Pittsburgh Sleep Quality Index
PST	Pupillographic Sleepiness Test
PUI	Pupillographic Unrest Index
PVT	Psychomotor Vigilance Task
pwMS	People with multiple sclerosis
REM	Rapid eye movement
RIS	Regensburg Insomnia Scale
RLS	Restless Legs Syndrome
RRMS	Relapsing–remitting multiple sclerosis
rt	Reaction time
RTest	Reaction Test
s	Seconds
SAD	Seasonal affective disorder
SAS	Self-rating Anxiety Scale
SCN	Suprachiasmatic nucleus
SD	Standard deviation
SDS	Self-rating Depression Scale

Table iv, continued. List of abbreviations

SE	Standard error of the mean
SPMS	Secondary–progressive multiple sclerosis
SPT	Sleep period time
SRT	Slowest 10% of reaction times
SSA	Self-assessment Scale for Sleeping and Awakening Quality
TST	Total sleep time
VAS_F	Visual Analogue Scale for Fatigue
VIGIL S1	Computerized Mackworth Clock Test Vienna Test System
VPT	Visual Pursuit Test
WRBTV	Vienna Risk Taking Test Traffic
WSRT	Wilcoxon signed-rank test

PART I: INTRODUCTION

1.1 Multiple Sclerosis

1.1.1 Aetiology, pathology, and diagnosis

Multiple sclerosis (MS) is an inflammatory and demyelinating disease of the central nervous system (CNS), often with a chronic disabling course (Makris et al., 2014). Currently, 2.8 million people worldwide live with MS, with prevalences varying by region: in Africa and the Western Pacific, about 5 in 100.000 people have MS, whereas 133 out of 100.000 people have MS in Europe (The Multiple Sclerosis International Federation, 2020).

Aetiology. Only recently did Bjornevik et al. (2022) provide compelling evidence for the cause of MS, demonstrating that the risk of developing MS was 32-fold higher in people with Epstein–Barr Virus serum positivity than in those without, while prior infection with no other common viruses was associated with an increased risk of developing MS. EBV, also known as human gammaherpesvirus 4, most commonly occurs at early ages. Following infection, EBV persists in B lymphocytes throughout life. These B cells play a crucial role in the inflammatory processes of MS, with persistent B-cell activation within the CNS being a diagnostic marker of MS (Aloisi et al., 2023) and a key driver of damage to CNS tissue (Cree et al., 2022). Whether and how EBV affects the clinical onset and ongoing disease in MS remains unclear (Aloisi et al., 2023). However, EBV infection has a high global prevalence, with around 95% of the global population having prior infection (Bjornevik et al., 2022; Henle et al., 1979), and MS does not; therefore, EBV infection may not necessarily cause the development of MS. Rather, there is a complex interplay between the genetic and environmental factors that precede MS development following EBV infection (Aloisi et al., 2023). There is strong evidential support for genetic variants causing susceptibility for developing MS, with a 40-fold risk increase seen in siblings of people with MS and a 300-fold risk increase seen

in monozygotic twins of people with MS. Further, there are environmental risk factors that show strong statistical evidence, including childhood obesity, vitamin D deficiency, low levels of sunlight exposure, and tobacco use (Ebers et al., 1995; Goodin, 2015; Vitturi et al., 2025).

Pathogenesis. Evidence suggests that there is a prodromal phase of 5–10 years before the clinical onset of MS symptoms. This prodrome includes higher rates of depression, changes in health-related behaviour, pain, headache, gastrointestinal symptoms, and sleep disturbances (Tremlett & Marrie, 2021). On a neuro-immunologic level, serum concentrations of neurofilament light chain (a biomarker for neuronal degeneration) increase 6 years before clinical onset in MS (Bjornevik et al., 2022). Further, oligoclonal bands, as a marker for the intrathecal activation of B cells and the synthesis of immunoglobulin, are commonly found in the cerebrospinal fluid (CSF) of patients with MS (Aloisi et al., 2023; Cree et al., 2022). This B-cell activation and immunoglobulin synthesis likely lead to the inflammatory, demyelinating, and neurodegenerating processes primarily seen in the white matter but also in the grey matter areas of the brain in MS (Zettl & Patejdl, 2023). These processes cause the first symptoms during the onset and relapse of MS by disrupting neuronal signals (Makris et al., 2014). On a cellular level, proinflammatory cytokines and antibodies that drive inflammation and cell injury in the CNS are produced by aberrant memory cells arising from faulty peripheral checkpoint controls of T- and B-lymphocyte interactions. Further, microglia can drive inflammatory processes by generating oxidative stress in the CNS (Zettl & Patejdl, 2023).

Diagnosis. The diagnosis of MS is based on the 2017 McDonald diagnostic criteria, which include an examination of the patient's clinical status, magnetic resonance imaging of the brain and spinal cord to determine the spatial (dissemination in space) and temporal (dissemination in time) extend of nerve damage, lesions, and inflammation; and

laboratory analyses of CSF to examine inflammation markers and levels such as CSF-specific oligoclonal bands (Thompson et al., 2018). A standard tool used to assess neurological impairment and disability progression in patients at diagnosis and during disease progression is the Expanded Disability Status Scale, with scores ranging from 0 (normal neurological exam) in steps of 0.5 to 10 (death due to MS) (Kurtzke, 1983).

Delineating MS activity into clinical and radiographic components aids in classifying the specific type of MS and anticipating its clinical course. An early occurrence of relapses with recurrent episodes of symptom development, stabilization, and recovery between relapses leads to the diagnosis of relapsing–remitting MS. This is the most common type, seen in around 90% of all MS cases, with two-thirds of cases seen in women. Progressive disability without relapses is classified as primary-progressive MS, while relapses occurring with this type of MS indicate primary–progressive MS with superimposed activity. In contrast, when a relapsing–remitting course evolves into progressive worsening of disability independent of relapses, it is classified as secondary–progressive MS (Cree et al., 2022; Makris et al., 2014). In addition, clinically isolated syndrome is diagnosed when patients present with a first neurological episode lasting at least 24 hours but not all diagnostic criteria for MS are met (National Multiple Sclerosis Society, 2019).

MS initially occurs during the early years of adulthood with the average age at diagnosis being 32 years worldwide. However, the number of children diagnosed with MS has increased, with at least 30,000 cases under the age of 18 reported in 2020 (The Multiple Sclerosis International Federation, 2020). Depending on the type of MS, disease activity and symptom occurrence and severity can vary over the course of the disease.

1.1.2 MS symptoms and treatment

Once the clinical onset of MS occurs, initial symptoms can include sensory disturbances, limb paraesthesia, and visual impairments. As the disease progresses, further neurologic

symptoms and motor impairments such as vertigo, sensory loss, pain, spasticity, gait difficulties, bladder dysfunction, and sexual dysfunction can occur. Many patients experience fatigue even during remission, or Lhermitte's sign, where neck flexion leads to an electric shock-like painful sensation down the spine and limbs (Makris et al., 2014). Further, patients with MS often show reduced overall and mental health, with increased rates of anxiety, depression, and impaired sleep and cognition (Makris et al., 2014; Noseworthy et al., 2000).

Generally, MS medication target the immune system. Immunosuppressants such as glucocorticoids are administered during acute disease activity. Disease-modifying therapy, including substances such as fingolimod, teriflunomide, or dimethyl fumarate, is also used to modulate immune system activity by targeting lymphocytes; as a relatively new and highly effective therapy, monoclonal antibodies are administered to deplete B cells, preventing or controlling inflammatory events and thus disease progression (Coerver et al., 2025; Cree et al., 2022). This line of treatment has changed the disease course of MS. Combining such therapies with evidence of EBV involvement long before MS onset and during disease activity has inspired research into potential therapies targeting EBV within B cells or selectively eliminating EBV-infected B cells (Cree et al., 2022). Apart from these immunomodulatory treatment methods, multidirectional treatment approaches include physiotherapy and psychotherapy to maintain mobility, prevent and reduce paresis, and to help patients with co-morbid mood disorders and cognitive deficits (Makris et al., 2014; Noseworthy et al., 2000).

1.1.3 Cognition, vigilance, and fitness to drive in MS

Many patients with MS experience cognitive impairments throughout the disease course, even when it is isolated from other neurological disease activity. These arise not only from grey and white matter atrophy due to inflammation and demyelination but also from changes in functional connectivity within the brain. However, the loss of grey matter

seems to be a reliable marker for cognitive decline in MS (Benedict et al., 2020). Commonly, this decline affects processing speed and efficiency, memory, sustained attention, and executive functioning (Sumowski et al., 2018). Detriments in sustained attention, or vigilance, are in turn linked to cognitive slowness, and these symptoms differ from motor- or fatigue-related slowness (Kujala et al., 1995). Initial cognitive impairment can be used to predict long-term decline in cognitive functions, especially in paediatric-onset MS (Benedict et al., 2020). Assessing cognitive detriments as part of the diagnostic process of MS can be difficult as tests are mostly conducted in a quiet laboratory environment without distractions, which does not reflect real-world environments. However, cognitive multi-tasking with nearby distractors is an essential part of real life. This lack of external validity makes it difficult to evaluate the impact of cognitive impairments on everyday life in patients with MS. Additionally, assessing the magnitude of initial cognitive decline is difficult, as data from before cognitive decline are usually not available, and many studies assess cognitive impairments cross-sectionally and not longitudinally. This can lead to an underestimation of cognitive decline and undertreatment with cognitive therapies (Sumowski et al., 2018).

Driving is an everyday activity that demands continuous cognitive multi-tasking and vigilance to ensure both personal and public safety. Driving requires high processing speed, executive functions, and visuo-spatial abilities (Groeger, 2002); if impaired, these factors can lead to risks to the driver as well as other traffic participants. Therefore, as soon as cognitive impairments occur, driving-related cognition will most likely also be affected. Studies on drivers suffering from age-related chronic diseases such as dementia have revealed the effects of cognitive impairments on fitness to drive, which is especially relevant considering the increasing average age of the global population. However, few studies have examined driving and MS, which highlights the need for more research (Morrow et al., 2017). Even fewer studies have assessed fitness to drive in patients with

MS in a longitudinal setting, which makes it difficult to pinpoint at which state of the clinical course impairments in fitness to drive can be expected.

1.1.4 Sleep in patients with MS

Sleep is essential for human health and well-being throughout life, with detriments in sleep quality and quantity causing disruptions in cognitive functioning and mental and physical health (Ramar et al., 2021); as Hobson stated, “sleep is of the brain, by the brain, and for the brain” (Hobson, 2005, p. 1). Given that MS is a neurodegenerative disorder of the CNS, it is not surprising that patients with MS often show impaired sleep, with higher prevalences of sleep disorders such as insomnia, periodic limb movement disorders, restless legs syndrome, and sleep-related breathing disorders than the general population (Popp et al., 2017; Veauthier, 2015). However, sleep disorders in MS remain vastly underdiagnosed and therefore improperly treated (Brass et al., 2014). Assessing sleep and screening for sleep disorders should be an inherent part of the diagnostic process of MS since daily functioning depends on nocturnal sleep (Touzet, 2017). According to the 2023 criteria of the American Academy of Sleep Medicine, the gold standard to for objectively assessing sleep is polysomnography (PSG) (American Academy of Sleep Medicine, 2023; Iber et al., 2007). PSG uses electrooculography, electroencephalography, and electromyography as well as measurements of muscle contraction, breathing patterns, and snoring patterns and, in some cases, video surveillance during sleep. Further, standardized questionnaires concerning specific sleep-related disorders such as the Regensburg Insomnia Scale (Crönlein et al., 2013), the Epworth Sleepiness Scale (Johns, 1991), the Berlin Questionnaire on Obstructive Sleep Apnoea Syndrome (Netzer et al., 1999), or sleep diaries assessing sleep and wake times, subjective sleep quality, and nocturnal awakenings, among others, are used during the sleep-related diagnostic process. Despite the high occurrence of sleep disorders in patients with MS, they are often overlooked and the assessment of sleep is not part of the

standard in the diagnostic process for MS (Thompson et al., 2018; Veauthier, 2015). However, if patients with MS are more prone to experiencing disturbed sleep, reductions in everyday functioning and cognition could be explained not only by neurological changes but also due to a lack of restful sleep. Sleep disturbances occur as early as during the prodromal phase of MS before diagnosis (Tremlett & Marrie, 2021) and may therefore already affect patients during the early phase after diagnosis. This has, however, received little attention in research.

1.1.5 MS-related fatigue

Despite the diversity in MS symptomology and disease courses across patients, up to 90% of patients experience fatigue (Manjaly et al., 2019). Fatigue can commonly occur under normal circumstances, for example after intense or prolonged mental or physical activity; however, as soon as its extent is unpredictable and interferes with everyday life, fatigue becomes clinically relevant. This is the case in a variety of neurological disorders such as narcolepsy, poliomyelitis, MS, myalgic encephalomyelitis/chronic fatigue syndrome, stroke, and traumatic brain injury (Chaudhuri & Behan, 2004; Kluger et al., 2013). Currently, no general definition of fatigue exists, but the concept of fatigue encompasses both a subjective feeling of tiredness and a lack of energy (often described as “fatigue”) as well as objectively measurable reductions in the ability to sustain cognitive or physical performance for a prolonged duration (referred to as “fatigability”) (Flachenecker, 2023; Kluger et al., 2013). MS-associated fatigue is described as a feeling of unproportional tiredness and exhaustion with reduced functioning, with many patients ranking it as one of the most disabling symptoms (Popp et al., 2017). MS-related fatigue presents further challenges as it occurs in all stages of MS (Krupp et al., 1988) independent of the level of neurologic impairment (Fisk, Ritvo, et al., 1994), impacting social and professional quality of life and leading to early retirement in many people with MS (Bakshi, 2003; Giovannoni, 2006; Stuke et al., 2009). Fatigue affects psychomotor vigilance, which is

important for alertness and reaction time and thus, fitness to drive (Rotstein et al., 2012). During the clinical assessment of fatigue, it is important to distinguish between fatigue and daytime sleepiness. Daytime sleepiness manifests in the form of reduced alertness or wakefulness levels with an increased sleep drive and pressure. It also occurs in many patients with MS, but not as frequently as fatigue and is distinct from it, as sleeping mitigates daytime sleepiness but not fatigue (Popp et al., 2017). Commonly used questionnaires to assess fatigue are the Fatigue Severity Scale (FSS, Krupp et al., 1989), the Modified Fatigue Impact Scale (MFIS, Multiple Sclerosis Council for Clinical Practice Guidelines, 1998), the Daily Fatigue Impact Scale (D-FIS, Fisk & Doble, 2002), and a Visual Analogue Scale for Fatigue (VAS_F) ranging from 0 to 100%, which all assess fatigue based on operationalized definitions of the symptom (Flachenecker, 2023; Manjaly et al., 2019).

In the literature, fatigue in MS is categorized into primary and secondary fatigue. Primary fatigue arises from changes directly related to MS, such as neurologic inflammation and demyelination, whereas secondary fatigue is caused by changes that are both associated with the disease, such as medication effects and changes in activity levels or muscle use, and independent of MS itself, such as comorbid mood or sleep disorders (Bakshi, 2003; Flachenecker, 2023). The exact underlying mechanisms that cause MS-related fatigue remain elusive, with four major hypotheses being discussed: structural white and grey matter damage, processes surrounding inflammation, maladaptations in network recruitment, and metacognitive interpretations of brain states linked to helplessness (Manjaly et al., 2019). Flachenecker (2023), in his model on the aetiological factors of fatigue, differentiated further between factors that drive primary fatigue—namely cortical and subcortical network function, orthostatic hypotension, proinflammatory cytokines, endocrine factors, attention deficits, and personality traits—

and factors that drive secondary fatigue, such as comorbidities, medication, and sleep problems.

Since fatigue has a major impact on quality of life in patients with MS even in remitting episodes, it is important to treat it accordingly. Pharmacological treatments such as amantadine, methylphenidate, or modafinil can improve fatigue severity but are often accompanied by adverse side effects and are not more effective than placebo in mitigating fatigue (Nourbakhsh et al., 2021). Non-pharmacological approaches include exercise therapy, psychological approaches, and a mixture of both (Bakshi, 2003; Tur, 2016). Findings regarding exercise therapy have been inconclusive concerning its efficacy to reduce MS-related fatigue, with heterogeneity in effects seen in many studies (Andreasen et al., 2011; Heine et al., 2015) but promising results seen regarding high-intensity resistance training (Englund et al., 2022). Psychological approaches include patient education, mindfulness-based interventions, relaxation, and cognitive behavioural therapy, which all show potential in mitigating MS-related fatigue (Phyo et al., 2018; Wendebourg et al., 2017). To expand and improve the number of available treatment methods, easily-administered, non-invasive therapeutic methods should be explored to reduce levels of fatigue in order to maintain daily functioning in people with MS. In recent years, light therapy has gained attention for treating fatigue in neurologic disorders, and this therapy can be easily implemented into everyday life.

1.2 The circadian system and light therapy

1.2.1 The human pacemaker and light

The sleep-wake cycle, including the patterns of rest and activity that make up a person's circadian rhythm, is regulated by the suprachiasmatic nucleus (SCN) of the hypothalamus. This pacemaker synchronizes physiological and behavioural processes to the day- and night cycle, including pupil size regulation, core body temperature, hormone

production and release, and rest- and activity rhythms (Berson et al., 2002; Spitschan, 2019; Steinberg et al., 2010; Thapan et al., 2001). Projections to the SCN from the intrinsically photosensitive retinal ganglion cells (ipRGCs) in the human eye via the retinohypothalamic tract are of vital importance for this circadian entrainment (LeGates et al., 2014). IpRGCs not only transmit signals from rods and cones, the retinal photoreceptors vital for image forming, but also signals related to the lighting situation by producing melanopsin, a photopigment with a maximum sensitivity to light in the short-wavelength range at around 460 nm. During the day, when enough daylight is available, a signalling cascade via the ipRGCs, SCN, and paraventricular nucleus leads to the suppression of melatonin production. When light levels decrease during the evening, melatonin is produced in the pineal gland and released into the bloodstream, where it signals nighttime to bodily tissues, promoting sleepiness, reducing alertness and arousal, and lowering the core body temperature (Arendt, 1998, 2006; Masters et al., 2014).

Exposure to both bright light at 2,500 lx (Arendt, 2006) and blue-enriched light at around 460 nm can inhibit melatonin production at night (Cajochen et al., 2005; de Toledo et al., 2023). During the day, when melatonin levels are low, the alerting effects of light occur independently of melatonin, possibly via the thalamus and anterior insula (Vandewalle et al., 2006). Apart from these alerting properties, the usage of light as an intervention method can be beneficial in clinical and non-clinical settings.

1.2.2 Usage of light in clinical and non-clinical settings

Bright light interventions use corneal illumination levels between 2,500 and 10,000 lx and constitute standard light treatment (Spitschan, 2024). Explored as a light therapy method in clinical settings, the beneficial effects of bright light therapy have been demonstrated to prevent (Partonen & Lönnqvist, 1996) and mitigate symptoms of seasonal affective disorder (Eastman et al., 1998), major depression (Lam et al., 2016),

and circadian rhythm sleep disorders such as shift work disorder and advanced and delayed sleep phase disorders (Morgenthaler et al., 2007). Regarding fatigue, bright light therapy was proven effective to reduce fatigue following traumatic brain injury (Sinclair et al., 2014) and in patients with cancer (Johnson et al., 2018). Research also provides evidence for the effectiveness of significantly lower illuminance levels such as 750 lx to mitigate symptoms in seasonal affective disorder (Meesters et al., 2011). To date, light boxes are generally used to administer light therapy. These, however, have the disadvantage that patients are required to sit relatively still for the duration of usage, usually for 30–60 minutes.

In an effort to improve the applicability and acceptance of light therapy, glasses using bright light peaking at wavelengths of around 460 nm have gained increasing attention in recent research. These glasses provide light via the frames of glasses, making light therapy portable and more easily integrated into daily life. Research has shown promise for light therapy glasses in treating depression in adolescents (Legenbauer et al., 2024), improving mood and sleepiness in medical inpatients (Formentin et al., 2020), and mitigating fatigue in patients with Parkinson's disease (Raymackers et al., 2019), breast cancer (Bean et al., 2022), and Hodgkin and non-Hodgkin lymphoma (Starreveld et al., 2021).

Regarding the use of light therapy in non-clinical settings, research has been conducted during the commute to and in the workplace. For example, Canazei et al. (2021) reported that in-vehicle daylight supplementation using blue-enriched bright light placed on the sun visor of a passenger car could increase physiological alertness during morning drives. Further, supplementing illumination levels within a truck's cabin with multimodal blue-enriched bright light could increase alertness levels in long-distance truck drivers (Popp et al., 2024). Another study showed reductions in fatigue and vigilance decrements during the post-lunch dip after exposure to blue-enriched bright

light exposure compared to dim red light exposure (Slama et al., 2015). Regarding late work shifts, exposure to bright blue-enriched white light led to increased well-being and reduced objective sleepiness (Rodenbeck et al., 2019). Further, many studies regarding light supplementation at work have concentrated on night shift workers, as they are required to maintain high performance levels during the actual rest phase of the human circadian rhythm.

1.3 Night work

1.3.1 Definition, dangers, and side effects of night work

Working during the night hours poses an especially challenging situation, as it creates a misalignment between natural circadian rhythms and sleep–wake rhythms (Pallesen et al., 2010). Shift work in general and night work in particular create crucial economic value and societal benefits worldwide, from production lines or road construction running around the clock to medical care being administered at all hours. In the German Working Hours Act (*Arbeitszeitgesetz*), working for longer than 2 h between 11:00 p.m. and 6:00 a.m. is defined as night shift work, applying to around 5% of employees nationwide (Bundesministerium der Justiz, 2023; Statistisches Bundesamt, 2022). Night shift work is accompanied by severe risks, with a short-term increased risk for errors and accidents at work and on the commute home (Åkerstedt, 1998; Åkerstedt et al., 2005; de Cordova et al., 2016; D. Fischer et al., 2017) and a long-term increased risk for shift work sleep disorder, cancer, and negative impacts on mental, metabolic, and cardiac health (James et al., 2017; Rodenbeck & Mayer, 2023). Night shift work is accompanied by consistent sleep deprivation, leading to cognitive and motor impairments affecting the professional and private lives of workers (Åkerstedt, 2003; Caruso, 2014; Popp & Fulda, 2004; Schwarz et al., 2016). Further, driving home from work after a night shift can affect the safety of workers and other traffic participants, as driving after a night shift is

accompanied by severely impaired driving performance, increasing the risk for traffic accidents (Lee et al., 2016).

1.3.2 Light during night shift: benefits and current research

Research on methods for mitigating the side effects of night shift work have included health promotion, dietary interventions, and physical activity (Neil-Sztramko et al., 2014), napping (Slanger et al., 2016), and caffeine supplementation (Valck & Cluydts, 2001). These have shown promising effects, yet some are difficult to implement during night shift work. As an alternative, light interventions have recently gained traction. Because they are easily integrated and administered and are non-disruptive to many workflows, portable light interventions such as using light glasses may be a suitable intervention to mitigate the negative effects of night work. Their usage has been tested during night shift work, with assessments of their effects on sleepiness on the commute home (Aarts et al., 2020) and comparisons to the effects of naps on fatigue and well-being (van Woerkom, 2021). However, studies comparing active light glasses to placebo glasses during night shift work as well as examining objective parameters of alertness and sustained attention are currently lacking.

1.4 Light therapy for MS-related fatigue: current research

Low exposure to sunlight and low levels of vitamin D have both been discussed as risk factors for the onset and progression of MS (Lucas et al., 2011; Munger et al., 2004). Knippenberg et al. (2014) showed that increased sunlight exposure, but not increased vitamin D levels, were associated with improved symptoms of depression and fatigue in patients with MS. Evidence showing the positive effects of light therapy in patients with other disorders with significant fatigue suggests that this may be a viable treatment for MS-related fatigue (Bean et al., 2022; Raymackers et al., 2019; Starreveld et al., 2021).

Thus far, two studies have examined whether light therapy can mitigate fatigue in patients with MS.

Mateen et al. (2020) compared a bright-light intervention (10,000 lux) to a sham condition using dim red light (<300 lux) administered using light boxes. Patients were instructed to use the assigned light box twice for 1 hour (once in the morning, starting 2 hours after awakening, and once in the evening, starting 3 hours before bedtime) for 4 weeks. Fatigue was measured using the FSS at baseline, after the 4-week intervention period, and after 4 weeks of washout. Quality of life was also rated using an MS quality of life questionnaire. Voggenberger et al. (2022) utilized the same light boxes in active and sham conditions and instructed patients to use the assigned light box once daily for 30 minutes within 3 hours of awakening over the course of 2 weeks. Fatigue was assessed using the FSS and a VAS_F at baseline, during the participation period using a VAS_F, and using the FSS after the 2-week intervention period and after a 2-week washout phase. Both studies showed significant reductions in MS-related fatigue using both bright and dim light with no significant differences between conditions. Both light interventions were well tolerated and induced no severe adverse effects. The light interventions included light boxes in both studies, which require patients to sit still for an extended period of time during usage, making it difficult for patients with MS to incorporate this kind of light therapy into everyday life. Utilizing portable light glasses might facilitate better applicability, but no study has been conducted using glasses that emit blue-enriched light to mitigate MS-related fatigue. Further, the short-term effects of light therapy, i.e. effects measured immediately after usage and hours later, as well as effects measured within 1 week of usage, have not been researched. Such studies would provide insights into the temporal dynamics of MS-related fatigue within a limited timespan after light therapy. Another important factor regarding interventions for MS-related fatigue is the prevention of adverse effects. During light therapy, adverse effects commonly appear

early, but tend to diminish in severity and occurrence over time (Blume et al., 2019; Wirz-Justice & Bromundt, 2013). To increase the likelihood of treatment continuation during light therapy, it is important to establish a timeframe in which potential side effects and their severity subside. Therefore, studies are needed to assess side effects after each light therapy session instead of at the end of each session week or after discontinuation, as has been done in past research (Mateen et al., 2020; Voggenberger et al., 2022)

1.5 Rationale of this dissertation

MS is a highly impairing disorder with increasing prevalence and incidence globally (Portaccio et al., 2024). In addition to neurologic symptoms such as spasticity, vision impairments, and sensory disturbances, cognitive impairments affecting alertness and fitness to drive, high levels of fatigue, impaired mental health, and sleep disturbances are seen in MS (Makris et al., 2014). However, the occurrence of these symptoms at diagnosis and their development during the first year after diagnosis has not received research attention. Fatigue is especially demanding for people living with MS, as it occurs independent of neurologic impairment in all disease stages and profoundly affects quality of life (Bakshi, 2003; Fisk, Pontefract, et al., 1994; Giovannoni, 2006; Krupp et al., 1988; Stuke et al., 2009). However, effective countermeasures that are easily applicable, effective, and feasible remain scarce. Portable light therapy is a promising non-pharmacologic, psychophysiologic approach to address this issue, and it has been proven effective in various non-clinical (Canazei et al., 2021; Popp et al., 2024; Rodenbeck et al., 2019; Slama et al., 2015; van Woerkom, 2021) and clinical populations (Johnson et al., 2018; Lam et al., 2016; Partonen & Lönnqvist, 1996; Sinclair et al., 2014).

This dissertation addressed three related aims: i) using an observational approach, Study 1 aimed to prospectively assess alertness, fatigue, mental health, sleep, and fitness to drive in patients with de-novo MS at diagnosis and 1 year later; using an intervention

approach, Study 2 and Study 3 aimed to test a light therapy method to assess its efficacy and feasibility by ii) including healthy subjects (Study 2), and iii) patients with MS-related fatigue (Study 3).

Study 1: We conducted an exploratory longitudinal study on 25 patients with MS who were assessed multidimensionally regarding alertness and sustained attention, sleep macrostructure, fitness to drive, fatigue, and psychological symptoms. To compare this group with healthy controls, 25 healthy participants were recruited and matched to each patient in age, sex, and education level, using the same study protocol as for patients with MS. All participants were evaluated at study inclusion (directly after MS diagnosis) and at follow-up (around 1 year later for patients, and around 3 months later for controls). Assessments included objective measures of alertness and sustained attention (using computerized tests), PSG during two nights of assessment (follow-up PSG assessment only included patients), questionnaires (on sleep parameters such as quality, chronotype, and sleep disorders; on mental health such as depression and anxiety; and on quality of life), and a computerized traffic test battery to assess fitness to drive.

Study 2: This study was a randomized, placebo-controlled, crossover field study including healthy participants. The aim of the study was to assess the use of the light glasses and to develop and refine the study design and protocol intended to later assess the efficacy of the light therapy glasses in reducing MS-related fatigue in a non-clinical setting. To this end, 21 sleep-deprived night shift workers were recruited from a sleep laboratory; they participated in the study during two regular night shifts that started at 9:00 p.m. Work consisted of monitoring patients in the sleep lab undergoing PSG and helping with any problems that might arise during the night. The light therapy glasses were used in an active condition, emitting blue-enriched light (468 nm, 1,500 lx), and in a placebo condition, emitting dim red light (660 nm, 150 lx). During both test nights, participants wore the light therapy glasses from 5:00 a.m. to 5:30 a.m. Assessments of alertness,

sleepiness, and fitness were conducted before and after usage. Further, participants provided hourly ratings of sleepiness and fitness, along with an assessment of fatigue during the night and sustained attention after shift completion at 7:00 a.m., and an assessment of acceptance and comfort levels for the glasses in each condition.

Study 3: Based on the experiences and perspectives gained from Study 2, Study 3 was designed to assess the use of the light therapy glasses in patients with MS as a novel approach to counteract MS-related fatigue. Twenty patients with MS with clinically significant levels of fatigue were recruited to participate in a randomized, placebo-controlled, crossover field study, using the light therapy glasses for 20 minutes per day within their own homes over the course of 1 week per condition. Between conditions, participants underwent 6 days of washout without any intervention in order to control for carry-over effects. The light therapy glasses from Study 2 were used directly after waking, with fatigue level assessments performed immediately before and after usage and at 1:00 p.m. Sleep diaries were completed daily during light exposure. Side effects were assessed after each intervention session. Further, quality of life, daily fatigue levels, and fatigue severity were assessed every other day, and acceptance and comfort levels were rated at the end of each intervention week. The aim of Study 3 was to analyse the efficacy and feasibility of the active light therapy glasses in mitigating fatigue in patients with MS.

To summarize, this dissertation aimed at providing an overview of the development and progression of alertness, fatigue, mental health, sleep, and fitness to drive during the first year after de-novo MS diagnosis. Further, the design and assessment of a novel therapeutic approach for the highly prevalent and persistent MS symptom of fatigue was conducted and tested in a healthy control population and in patients with MS with clinically significant fatigue.

PART II: STUDIES

2.1 STUDY 1

PROSPECTIVE ANALYSES OF ALERTNESS, SLEEP, AND FITNESS TO DRIVE ONE YEAR AFTER DE NOVO MULTIPLE SCLEROSIS DIAGNOSIS

Julia Ottersbach, Thomas C. Wetter, Nicole König, Anna Fierlbeck, Robert Weissert, Roland F. J. Popp

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2.1.1 Abstract

Background: The prevalence and functional burden of the chronic demyelinating disease multiple sclerosis (MS) are well documented; however, little is known about the initial clinical course of alertness, sleep, cognitive, and psychological symptoms.

Objectives: This exploratory, prospective, longitudinal study multidimensionally investigated the development and progression of alertness, sleep, fitness to drive, and psychological symptoms in the first year after de novo MS diagnosis.

Methods: Twenty-five people with MS (pwMS) were assessed cognitively, psychologically, and using polysomnography soon after diagnosis and one year later, with outcomes compared to matched healthy controls.

Results: In the early stage of the disease, psychological symptoms of pwMS were comparable with those of controls, and patient conditions did not deteriorate within the first disease year. A small percentage of pwMS experienced increased levels of anxiety and depression after diagnosis. Alertness, sustained attention, and fitness to drive were comparable between both groups, and fatigue levels remained low over the course of the year.

Conclusions: This study highlights patient experiences within the initial clinical course of MS in a small group of patients. Further research is needed to understand the progression of symptoms and impairments in MS over a longer period and in different stages of the disease.

Keywords: multiple sclerosis, alertness, sleep, fitness to drive

2.1.2 Introduction

Multiple Sclerosis (MS) is a neurological disorder that results in inflammation and damage to the myelin sheath surrounding axons in the central nervous system (Makris et al., 2014). The clinical course of MS ranges from relapsing–remitting to primary–progressive or secondary–progressive with or without disease activity (Lublin et al., 2014). In young adults, non-traumatic neurological disabilities most frequently result from MS (Browne et al., 2014).

The cause of MS remains undetermined; however, recent research has suggested that preceding infections with the Epstein–Barr virus are an important contributor to MS aetiology (Bjornevik et al., 2022). The symptoms can vary extensively between people with MS (pwMS); initial symptoms can include sensory disturbances, visual impairments, and limb paresis. With disease progression, further neurological symptoms and motor impairments (e.g., pain, spasticity, gait difficulties, vertigo, sensory loss, bladder dysfunctions) may occur. (Noseworthy et al., 2000). The pathophysiology of MS and its multifaceted physical and psychological symptoms strongly affect quality of life, and pwMS frequently present with overall and mental health problems (Veauthier et al., 2015).

In general, cognitive impairments in pwMS affect processing speed, memory, sustained attention, and executive functioning (Kujala et al., 1995; Sumowski et al., 2018). These processes mainly depend on alertness; specifically, the ability to drive safely can be affected even if vision or motor skills are yet unaffected. When driving a car, constantly maintaining high alertness levels is essential and requires cognitive multitasking between executive function, attention, and visuospatial abilities (Groeger, 2002). If impaired, these factors can lead to safety risks for all traffic participants. Fitness to drive is specifically relevant for pwMS, as restriction of mobility or autonomy may further compromise quality of life. However, only few studies have examined driving-

related abilities in MS, let alone in the context of cognitive impairments or reduced alertness (Morrow et al., 2017). Even fewer studies have analysed fitness to drive in pwMS in a longitudinal setting. Thus, it is difficult to pinpoint at which disease stage and at which levels of symptom severity driving behaviour may become unsafe. The effects of MS on alertness and fitness to drive are often accompanied by disordered sleep, and these processes are highly interconnected.

Poor sleep and sleep disorders such as restless legs syndrome, sleep-related breathing disorders, and insomnia are common in pwMS and can contribute to reduced general daily functioning (Touzet, 2017), reduced sleep quality, fatigue, and excessive daytime sleepiness (Popp et al., 2017). In particular, excessive daytime sleepiness, distinguishable from fatigue in MS (Popp et al., 2017), can be an independent factor for impaired fitness to drive (Schwarz et al., 2016) and affects quality of life both in non-clinical (Thorarinsdottir et al., 2019) and clinical populations (Wanberg et al., 2021; Yoo et al., 2019). However, objective data on sleep in MS are scarce, especially regarding changes in sleep behaviour throughout MS progression, and existing studies have rarely offered case-control data (Tanioka et al., 2020).

Further symptoms and comorbidities that conflict with everyday life of pwMS are depression and anxiety, which about 20–40% of pwMS experience (Beiske et al., 2008). A highly prominent and one of the most disabling symptoms of MS, fatigue can also affect physical and cognitive functioning and is a major contributor to early retirement in pwMS (Bakshi, 2003). It is characterized by feeling tired and exhausted with reduced physical and cognitive functioning (Krupp et al., 1988; Popp et al., 2017). The complex symptomatology of MS complicates assessments of the disease and treatment strategies.

Ensuring multidimensional assessments of MS is crucial, as MS manifests itself in a variety of symptoms across multiple domains. Little is known about the effects of potential MS impairments on sleep, alertness, fitness to drive, fatigue, and psychological

symptoms during the first year after diagnosis. In general, investigating the wide variety of MS symptoms and their associations and development over time is critical for our understanding of MS pathophysiology and patient experiences. Our focus was on objectively assessed symptoms of cognitive dysfunction and impaired sleep quality at an early stage of the disease. Given that MS is a chronic lifelong condition, we felt that a 12-month observation period was appropriate to measure changes at an early stage after the first onset of neurological MS symptoms Thus, the aims of the present exploratory, prospective, longitudinal study were to (i) assess different domains multidimensionally and soon after clinical diagnosis, comparing pwMS with a matched healthy control group and (ii) measure clinically relevant changes at a one-year follow-up. The main outcomes addressed herein were alertness, sleep, and fitness to drive, with the inclusion of fatigue and psychological symptoms as secondary outcomes.

2.1.3 Materials and methods

Study design

Using a prospective, longitudinal within- and between-participant design, pwMS were tested soon after de novo diagnosis (baseline) and one year later (follow-up) in this exploratory analysis. Baseline data were compared with healthy controls and used to match participants based on age, sex, and education. The study was approved by the ethics committee of the University of Regensburg (reference number 13-101-0086) and was conducted in accordance with the World Medical Association Declaration of Helsinki. All participants provided written informed consent.

Measurements

All participants were evaluated using self-reported questionnaires, cognitive assessment batteries (tests on alertness, sustained attention, and fitness to drive), polysomnography

(PSG) recordings, and sleepiness tests. All reported measurements as well as their references and testing dimensions are listed in Table 1.1.

Table 1.1. Subjective and objective measurements used throughout the study, along with the parameters measured and references

Assessment	*Measurements and measures*	References
Screening	• *Berlin Questionnaire Sleep Apnoea*: obstructive sleep apnoea	Netzer et al. 1999
	• *Restless Legs Syndrome diagnostic criteria:* restless legs syndrome	Allen et al. 2014
Mental health, quality of life	• *Nottingham Health Profile:* subjective overall health	Hunt et al. 1985
	• *Multicultural Quality of Life Index:* health and life quality	Mezzich et al. 2011
	• *Beck Depression Inventory II (BDI-II):* depressive symptoms	Beck et al. 1996
	• *Self-rating Depression Scale* (SDS): depressive symptoms	Zung, 1965
	• *Self-rating Anxiety Scale* (SAS): anxiety symptoms	Zung, 1971
Daytime sleepiness, fatigue	• *Epworth Sleepiness Scale* (ESS): overall daytime sleepiness, sleep propensity	Johns, 1991
	• *Karolinska Sleepiness Scale* (KSS): acute level of sleepiness	Åkerstedt & Gillberg 1990
	• *Modified Fatigue Impact Scale* (MFIS): impact of fatigue	Fisk et al. 1994, Fischer et al. 1999
	• *Fatigue Severity Scale* (FSS): fatigue severity	Krupp et al. 1989
Subjective sleep quality	• *Pittsburgh Sleep Quality Index* (PSQI): overall subjective sleep quality	Buysse et al. 1989
	• *Functional Outcomes of Sleep Questionnaire* (FOSQ): overall impact of sleep impairment	Weaver et al. 1997
	• *Regensburg Insomnia Scale* (RIS): psychophysiological insomnia	Crönlein et al. 2013
	• *Self-assessment Scale for Sleep and Awakening Quality* (SSA): sleeping and awakening quality of individual nights	Saletu et al. 1987
Objective sleep quality	*Cardiorespiratory Polysomnography* (PSG): objective assessment of sleep quality and quantity	American Academy of Sleep Medicine 2007
Objective sleepiness, alertness, and sustained attention	• *Pupillographic Sleepiness Test:* Pupil unrest index	AMTech Pupilknowlogy GmbH, Dossenheim, Germany
	• *Psychomotor Vigilance Task* (PVT): Mean RT, refractional RT, lapses, fastest 10% of reaction times, slowest 10% of reaction times as measure for changes in vigilance	Khitrov et al. 2014
	• *VIGIL S1 - Computerized Mackworth Clock Test Vienna Test System*: Mean RT, number of false and true reactions as measure for sustained vigilance under monotonous conditions	Schuhfried GmbH, Mödling, Austria
Psychological traffic test battery - Vienna Test System DRIVEPLS	• *Adaptive Matrices Test* (AMT): Logical reasoning	Schuhfried GmbH, Mödling, Austria
	• *Determination Test* (DT): reactive stress tolerance, divided attention	
	• *Reaction Test* (RT): ability to react	
	• *Cognitrone* (COG): concentration	
	• *Adaptive Tachistoscopic Traffic Perception Task* (ATAVT): overview	
	• *Peripheral Perception* (PP): peripheral perception	
	• *Visual Pursuit Test* (VPT): visual perception	
	• *Inventory of driving-related Personality Traits* (IVPE): psychological personality assessment	
	• *Vienna Risk Taking Test Traffic* (WRBTV): readiness to take risks	

A detailed description of all measurements can be found in Appendix A1.

At baseline, participants were screened for sleep disorders and provided self-reported data on demographics, driving experience, and history of driving accidents. General subjective and mental health (i.e., self-ratings of depression and anxiety), quality of life, subjective sleepiness, fatigue, and subjective sleep quality were measured using standardized internationally established questionnaires (Appendix A1.1-A1.4). PSG was recorded on two nights for control participants and four nights for pwMS (two baseline, two follow-up), followed by an assessment of sleep and awakening quality (Self-assessment Scale for Sleep and Awakening Quality, SSA) each morning. Details of the PSG can be found in Appendix A1.5 and Table A1.

Objective changes in alertness were assessed using a psychomotor vigilance task (PVT) with reaction speed and number of lapses as the main outcome parameters. A 26-min computerized version of the Mackworth Clock Test (MCT) was used to measure sustained attention under monotonous conditions. On a physiological level, objective sleepiness was evaluated using the pupillographic sleepiness test (PST) with the pupillographic unrest index (PUI) as main measure (details on these objective tests can be found in Appendix A1.6). Subjective sleepiness throughout the test batteries was assessed using the Karolinska Sleepiness Scale (KSS).

The DRIVEPLS Fitness to Drive Plus of the Vienna Test System TRAFFIC (Schuhfried GmbH, Mödling, Austria) was also employed. This is an internationally used computer-based psychological traffic test battery consisting of several tests (Table 1.1; Appendix A1.7) that measure driving-related abilities and personality traits. The overall assessment of a person's fitness to drive provided by the test system is based on a neural network validated with real driving performance.

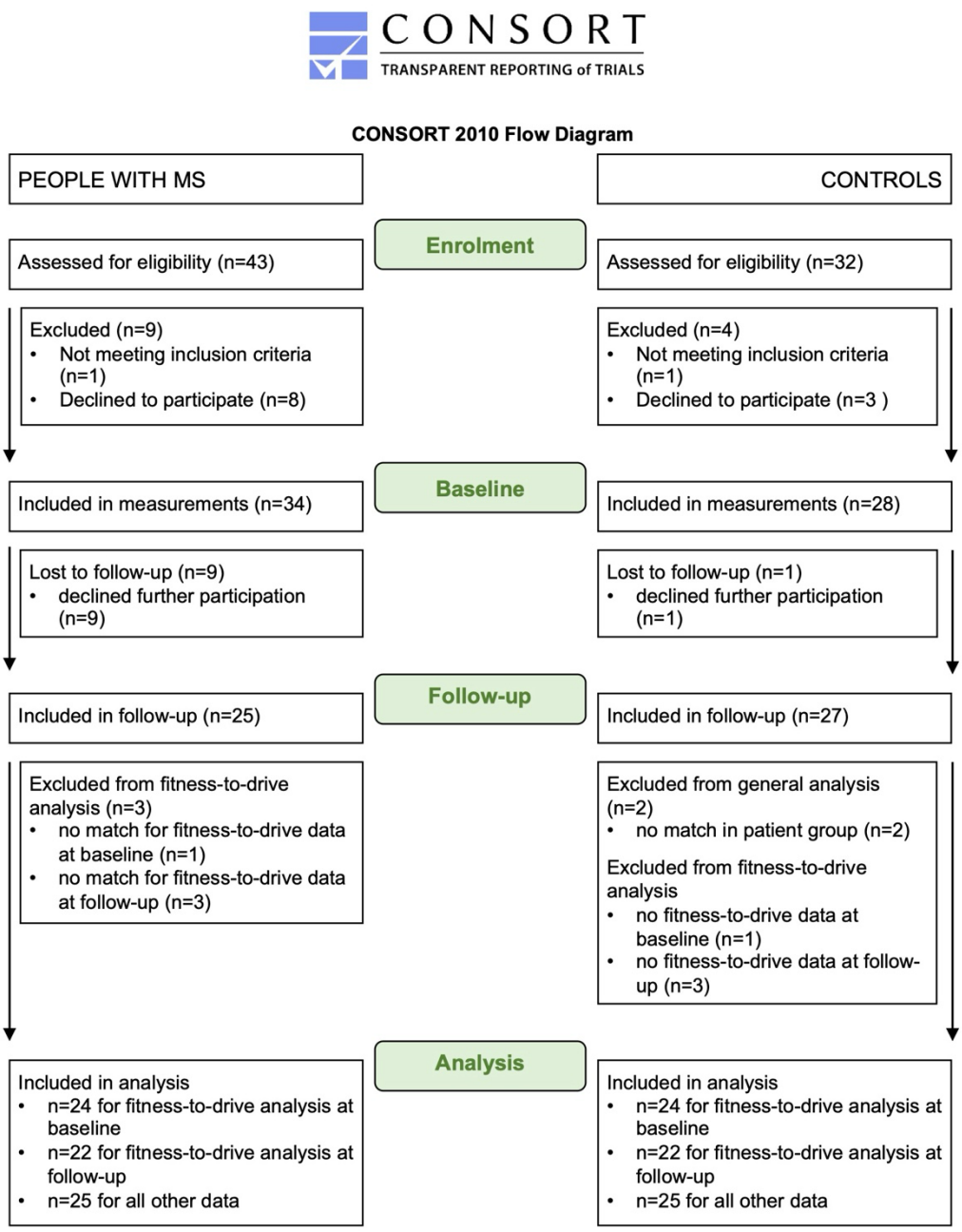
Participants

Forty-three newly diagnosed pwMS from the neurological MS out- and inpatient clinics at the Department of Neurology, University of Regensburg Hospital, Germany were assessed for eligibility, of which 34 participated in baseline measurements. The final sample after follow-up consisted of twenty-five pwMS (M = 33.8, SD = 10.1 years) with a disease duration of M = 0.5, SD = 1.2 years (range: 0-4 years). For the control group, 32 healthy participants individually matched to pwMS based on age, sex, and education (matches pairs) were recruited among hospital staff and via newspaper ads and flyers. Twenty-eight control participants were included in baseline measurements, while the final control sample consisted of 25 participants (M = 34.5, SD = 11.3 years). Figure 1.1 shows the CONSORT flow chart for subject enrolment.

A sample size of 25 per group was considered statistically sufficient (based on a within-subject design of pwMS) to detect relevant differences. Statistical power analyses and sample size determination were calculated with an estimated effect size between 0.5 and 0.6, an α error of 0.05 and a power of 0.95 using known set size effects of the outcome parameters provided by the objective assessments.

All pwMS were diagnosed based on the 2017 McDonald criteria (Thompson et al., 2018) and tested during remission or after completion of inpatient rehabilitative measures. Details on inclusion and exclusion criteria for pwMS and controls can be found in Appendix A2.

Figure 1.1. CONSORT chart for subject enrolment, drop-outs, and exclusions throughout the study.



Note. Due to technical difficulties during various sessions of the fitness-to-drive assessment, data from one control at baseline and three controls at follow-up could not be used for this analysis; therefore, the data from people with MS matched to those controls were also excluded from fitness-to drive analyses. Two controls were excluded from analysis because their matched people with MS declined participation at follow-up.

Procedure

After study enrolment, tests were performed directly after diagnosis (baseline) and at a one-year follow-up (follow-up) for pwMS (*M* = 12.36 months between baseline and follow-up; range, 12–16 months*; SD* = 0.83); for control participants, these were performed after study enrolment (baseline). All control participants were tested again at least 2 months later (follow-up; *M* = 6.81 months between baseline and follow-up; range, 2–18 months, *SD* = 4.64) to control for possible long-lasting learning effects in the fitness-to-drive and vigilance assessments. Participants completed questionnaires regarding their health, psychological well-being, sleepiness, fatigue, and sleep quality. On a different day, the fitness-to-drive assessment, alertness and sustained attention tests, and the PST were administered for 3–4 h, including six KSS ratings between tests. PwMS spent two nights in our sleep laboratory, with assessments of subjective sleep quality (SSA) in the mornings and the neuropsychological assessment (not reported) on the following day. Control participants conducted neuropsychological assessments, the fitness-to-drive assessment, and vigilance tests on the same day, followed by two nights with PSG recordings and morning SSA evaluations.

Data analysis

All data were pseudonymized before storage. Values that deviated more than 3 standard deviations from the group were scrutinized as outliers but left in the dataset due to the exploratory character of the study (5 outliers out of 700 values in vigilance assessment, 4 missing values; 11 outliers out of 1632 values in fitness-to-drive assessment, 8 missing values; sample sizes for fitness-to-drive comparisons in the control group were n = 24 for baseline and n = 22 for follow-up due to technical difficulties during assessment). The Shapiro–Wilk test was used to check data normality. Corrections for multiple comparisons were conducted using Bonferroni correction. For within-participants comparisons, the Wilcoxon signed-rank test was used for skewed data and questionnaire

data, and a paired t-test was used for normally distributed data. Group comparisons were conducted using the Mann–Whitney U test for skewed data and questionnaire data as well as an independent samples t-test for normally distributed data. Included in the main analyses were within-subject comparisons of patients at baseline and follow-up as well as between-subjects comparisons of pwMS and healthy controls at baseline. Additional analyses, including within-subject comparisons of healthy controls at baseline and follow-up as well as between-subjects comparisons of pwMS and healthy controls at follow-up, can be found in Appendix A4. All analyses were performed in SPSS software (v26.0; IBM Corp., Armonk, NY, USA).

2.1.4 Results

Participant overview

Table 1.2 includes an overview of the participants' demographic, driving-related, and clinical data along with the number of pwMS receiving immunosuppressive medication (a detailed list of the specific medications can be found in Appendix A3.1, Table A2). Descriptive data on excluded and drop-out pwMS can be found in Appendix A3.2 and Table A3. Disease duration of pwMS was $M = 0.5$, $SD = 1.2$ years (range: 0–4 years).

Table 1.2. Demographic and clinical characteristics (including driving-related data) of participants.

	pwMS	Controls
n	25	25
Male	9	9
Female	16	16
Age in years *M*±*SD*	33.8±10.1	34.5±11.3
Education status based on ISCED 97		
Low (1–2)	1	2
Medium (3–4)	22	19
High (5–6)	2	4

Table 1.2, continued. Demographic and clinical characteristics (including driving-related data) of participants.

	pwMS	Controls
Years with driving license *M*±*SD*	15.5±9.1	15.9±12.7
Driving hours/week *M*±*SD*	6.5±8.8	5.4±5.1
Previous accidents *M* (*range*)	0.8 (0–7)	0.9 (0–5)
Diagnosis (McDonald criteria 2017)		
Clinically Isolated Syndrome (CIS)	3	NA
Relapsing–Remitting MS (RRMS)	19	NA
Initially CIS, then RRMS	3	NA
Years of disease duration *M*±*SD (range)*	0.5±1.2 (0–4)	NA
EDSS Score*		
Baseline *M*±*SD* (*range*)	0.7±0.8; (0–2)	NA
Follow-up *M*±*SD* (*range*)	0.7±0.9; (0–2)	NA
MS Therapy°		
Medication at baseline (%)	23 (92)	NA
Medication between baseline and follow-up (%)	24 (96)	NA
Medication at follow-up (%)	22 (88)	NA
Screening Questionnaires		
Obstructive Sleep Apnoea (n (%) suspicious)	2 (8)	0 (0)
Restless Legs Syndrome (n (%) suspicious)	1 (4)	1 (4)

Note. pwMS, people with Multiple Sclerosis; n, number; *M*: mean, *SD*: standard deviation, ISCED 97: International Standard Classification of Education; MS, multiple sclerosis; EDSS: Expanded Disability Status Scale.

*EDSS scores can range from 0 = "normal neurological exam, no disability in any functional system" in steps of 0.5 to 10 = "death due to MS"; Patient scores ranged from 0 to 2 = "minimal disability in one functional system".

°All medications were immunosuppressive and included alemtuzumab, dimethyl fumarate, fingolimod, glatiramer acetate, interferon beta 1a, interferon beta 1b, natalizumab, teriflunomide, and cortisone for acute therapy only.

Alertness and sustained attention

Table 1.3 provides an overview of all applied measures of alertness and sustained attention. With an adjusted p-value of $\alpha < 0.014$, no significant differences were found within or between groups.

Acute daytime sleepiness levels

Measuring acute sleepiness on a physiological level using pupillography, PUI values were significantly higher in controls (5.6 ± 2.1) compared with those in pwMS at baseline (baseline: 3.8 ± 1.4; $p = 0.001$; Table 1.3).

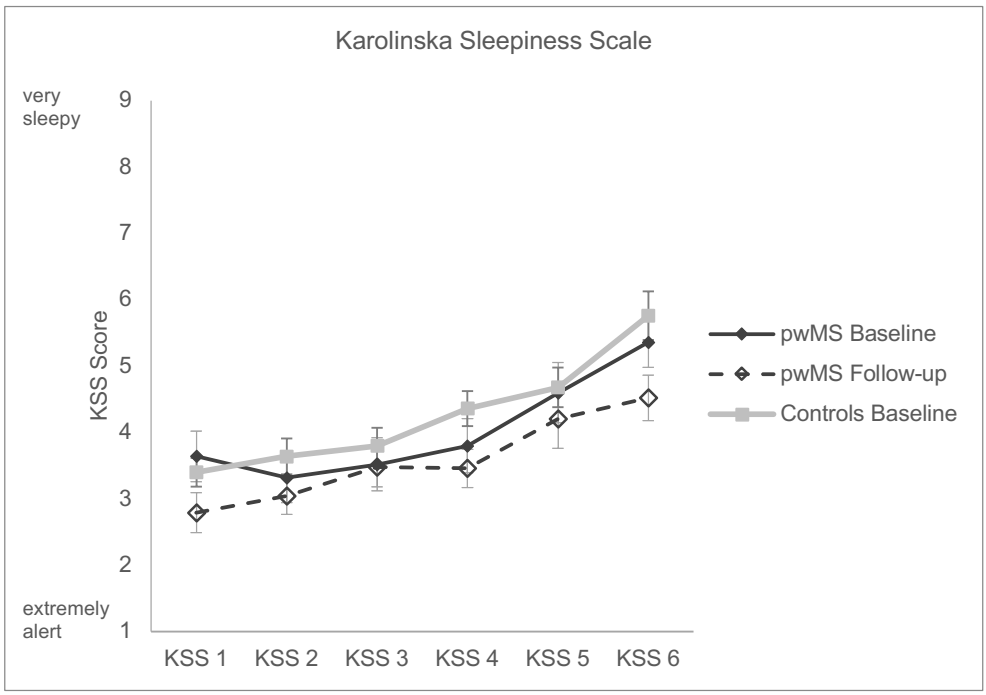
Table 1.3. Assessments of objective daytime sleepiness, alertness, and sustained attention.

	Descriptive statistics			***Statistical comparisons***			
	pwMS		**Controls**	**pwMS**		**Baseline**	
	baseline	follow-up	baseline	baseline vs. follow-up		pwMS vs. controls	
Measurements	*M (SD)*	*M (SD)*	*M (SD)*	*z/t*	*p*	*z/t*	*p*
Daytime sleepiness							
Pupillographic Sleepiness Test (PST)							
PUI	4,2 (3.0)	3.8 (1.5)	5.6 (2.1)	z = -0.426	.670	t(48) = 3.279	**.001***
Alertness and sustained attention							
Psychomotor Vigilance Task (PVT)							
Mean RT (ms)	273.2 (34.0)	277.6 (35.6)	263.9 (34.5)	z = -1.144	.253	z = -1.096	.273
Lapses	1.7 (2.7)	1.6 (2.1)	1.2 (2.0)	z = -1.701	.089	z = -1.009	.313
FRT (ms)	203.8 (19.2)	208.1 (22.5)	192.8 (15.9)	t(24) = -1.566	.130	t(48) = -2.225	.031
Mackworth Clock Test (MCT)							
Mean RT (ms)	484.2 (65.6)	489.5 (67.1)	501.4 (86.1)	t(24) = -0.480	.635	z = -0.582	.560
Correct	98.2 (2.2)	96.9 (4.1)	95.8 (6.5)	z = -1.529	.126	z = -0.748	.454
False starts	2.4 (1.9)	1.8 (1.6)	1.8 (1.7)	z = -1.455	.146	z = -1.589	.112

Note. pwMS, people with multiple sclerosis; *M*, mean; *SD*, standard deviation; PUI, pupillographic unrest index; RT: reaction time. FRT: 10% fastest reaction times. Descriptive statistics for pwMS at baseline and follow-up, and for controls at baseline. Statistical comparisons between pwMS at baseline and follow-up and between pwMS and controls at baseline. Statistical tests used for the within-participants comparisons were t-test (t[df]) for paired samples for normally distributed parameters, and Wilcoxon signed-rank test (z) for nonparametric variables. Between-participants comparisons were calculated using t-test for independent samples (t[df]) for normally distributed parameters, and Mann–Whitney U test (z) for nonparametric variables. **p*-Values adjusted using the Bonferroni correction with a significance level of. $\alpha < .014$

Figure 1.2 shows an increase in subjective sleepiness (KSS) throughout the alertness and fitness-to-drive assessments at baseline and follow-up. No significant differences were found at baseline between controls and pwMS nor at baseline and follow-up within pwMS.

Figure 1.2. Karolinska Sleepiness Scale scores of people with MS and controls throughout the fitness-to-drive assessment and alertness and sustained attention tests.



Note. Test times: KSS 1, before the fitness-to-drive assessment; KSS 2, during the fitness to drive assessment; KSS 3, between the fitness-to-drive assessment and the psychomotor vigilance task (PVT); KSS 4, after the PVT and before the pupillographic sleepiness test (PST); KSS 5, between the PVT and the Mackworth Clock Test (MCT); KSS 6, after the MCT; pwMS, people with multiple sclerosis.
For controls, only baseline measurements are depicted (additional display of control participants' follow-up values can be found in 6. Appendix, 6.1.4 Additional results for healthy control participants, Figure 6.1).

Objective and subjective sleep quality of recorded nights

PSG data at baseline showed no differences in any parameters between pwMS and controls. PwMS showed a significantly lower percentage of rapid eye movement (REM) sleep (% of sleep period time [SPT]) at follow-up (15.4 ± 5.3%) compared with baseline (17.7 ± 5.1%, p = 0.024; Table 1.4). Subjective sleep quality (SSA) at baseline was significantly better in controls (31.6 ± 6.5) than in pwMS (34.6 ± 7.4; p = 0.033).

However, with an adjusted *p*-value of $\alpha \leq 0.001$, these differences were non-significant after correction.

Table 1.4. Subjective and objective sleep quality of the polysomnography nights.

	Descriptive statistics			***Statistical comparisons***			
	pwMS		**Controls**	**pwMS**		**Baseline**	
	baseline	follow-up	baseline	baseline vs follow-up		pwMS vs. controls	
Measurements	*M (SD)*	*M (SD)*	*M (SD)*	*z (WSRT)*	*p (WSRT)*	*z (MWU)*	*p (MWU)*
Self-Assessment Scale for Sleep and Awakening Quality							
Overall Score	34.6 (7.4)	32.2 (5.4)	31.6 (6.5)	-1.635	.102	-2.131	.033
Polysomnography							
Main parameters							
Total sleep time (TST)	419.7 (34.4)	407.0 (44.6)	419.0 (47.9)	-1.652	.099	-0.600	.548
Sleep efficiency	87.5 (7.2)	84.7 (9.3)	87.9 (8.6)	-1.751	.080	-0.671	.502
Arousal index [/h TST]	16.6 (8.4)	16.7 (7.6)	15.4 (5.9)	0.000	1.000	-0.285	.776
Wake after sleep onset [min]	40.0 (28.2)	48.1 (36.2)	44.5 (38.8)	-0.870	.384	-0.288	.773
Sleep latency [min]	16.1 (13.4)	19.2 (19.1)	10.2 (7.2)	-1.767	.077	-1.883	.060
Distribution of sleep stages							
Wake [% sleep period time; SPT]	8.7 (6.1)	10.6 (8.0)	9.6 (8.3)	-0.990	.322	-0.298	.765
Sleep stage N1 [% SPT]	8.4 (5.5)	8.0 (4.9)	8.3 (2.9)	-0.786	.432	-1.340	.180
Sleep stage N2 [% SPT]	42.2 (8.8)	43.4 (11.2)	43.6 (7.9)	-0.647	.518	-1.386	.166
Sleep stage N3 [% SPT]	22.5 (9.1)	22.6 (13.1)	20.9 (6.8)	-0.149	.881	-0.252	.801
REM Sleep [% SPT]	17.7 (5.1)	15.4 (5.3)	17.6 (5.0)	-2.258	.024	-0.114	.909
Breathing and limb movements							
Apnoea-Hypopnea Index [/h TST]	1.7 (3.0)	2.0 (3.3)	2.5 (3.4)	-0.943	.346	-1.477	.140
Apnoea Arousal Index [/h TST]	1.1 (2.7)	0.8 (1.3)	1.0 (1.5)	-0.802	.423	-1.470	.142
Oxygen Desaturation Index [/h TST]	1.0 (1.5)	0.9 (1.2)	1.7 (2.7)	-0.672	.501	-0.883	.377
Mean saturation [%]	95.1 (1.5)	95.3 (1.5)	95.2 (1.5)	-0.378	.706	-1.026	.305
Minimum saturation [%]	90.1 (6.3)	90.2 (5.7)	89.3 (5.2)	-0.391	.696	-0.948	.343
PLMS Index [/h TST]	12.4 (18.6)	12.0 (19.2)	5.0 (7.9)	-0.429	.668	-1.234	.217
PLMS Arousal Index [/h TST]	3.3 (6.1)	2.6 (4.0)	1.3 (1.9)	-0.824	.410	-0.748	.454

Note. pwMS, people with multiple sclerosis; *M*, mean; *SD*, standard deviation; PSG, Polysomnography; SSA, Self-assessment Scale for Sleep and Awakening Quality; TST, total sleep time; SPT, sleep period time; REM, rapid eye movement; PLMS, periodic limb movement in sleep; WSRT, Wilcoxon signed-rank test; MWU, Mann–Whitney U test.

Wilcoxon signed-rank test was used for within-participant comparisons. Mann–Whitney U test was used for between-participants comparisons. *p*-Values adjusted using the Bonferroni correction with a significance level of $\alpha < .001$

Fitness to drive

Table 1.5 includes an overview of the fitness-to-drive results. At follow-up compared with baseline, pwMS performed better (follow-up: 257.3 ± 39.0; baseline: 243.0 ± 35.3; $p < 0.001$) and faster (follow-up: 755.6 ± 101.8 ms; baseline: 784.8 ± 99.1 ms; $p < 0.001$; Determination Test) and showed faster perceptual speed (follow-up: 10.4 ± 2.9; baseline: 13.1 ± 4.1; $p = 0.001$; Adaptive Tachistoscopic Traffic Perception Test). The readiness to take risks in pwMS was higher at follow-up (7.1 ± 1.5) compared to baseline (6.4 ± 1.4; $p = 0.001$; Vienna Risk-Taking Test Traffic). With an adjusted p-value of $\alpha < 0.0014$, pwMS and controls did not show significant differences in fitness-to-drive assessments at baseline.

At baseline, six pwMS (24%) and three control participants (12.5%) showed insufficient levels of fitness to drive. At follow-up, five pwMS (20%) were rated as unfit to drive; here, three pwMS remained stable, while five showed substantial changes (three improvement, two deterioration).

Mental health, quality of life

Table 1.6 shows the results of the statistical comparisons of questionnaire data regarding mental health, quality of life, daytime sleepiness, fatigue, and overall sleep quality. Mental health and quality of life did not change significantly in the first year after diagnosis (adjusted p-value of $\alpha < 0.002$). Comparing pwMS and controls at baseline, there were no differences regarding depression (SDS, Beck Depression Inventory-II [BDI-II]), anxiety levels (Self-rating Anxiety Scale), subjective health (Nottingham Health Profile), and quality of life (Multicultural Quality of Life Index).

Table 1.5. Psychological traffic test battery assessing fitness to drive.

		Descriptive statistics			***Statistical comparisons***			
		pwMS		**Controls**	**pwMS**		**Baseline**	
		baseline	follow-up	baseline	**baseline vs. follow-up**		**pwMS vs. Controls**	
Tests	**Measures**	*M (SD)*	*M (SD)*	*M (SD)*	*z/t*	*p*	*z/t*	*p*
AMT	IQ	94.2 (15.1)	94.4 (15.6)	99.6 (21.3)	z = -0.350	.726	t(24) = -0.988	.328
DT	correct	243.0 (35.3)	257.3 (39.0)	257.1 (33.0)	t(24) = -4.318	**< .001***	t(48) = -1.300	.200
	RT (ms)	784.8 (99.1)	755.6 (101.8)	762.7 (58.7)	t(24) = 5.554	**< .001***	t(48) = 0.831	.410
RTest	RT (ms)	445.4 (66.9)	458.0 (68.6)	458.0 (107.3)	t(24) = -1.004	.325	z = -0.371	.711
	motor time (ms)	177.1 (50.2)	170.3 (47.9)	167.0 (44.2)	t(24) = 0.874	.391	t(48) = 0.365	.717
COG	RT (s)	2.6 (0.6)	2.5 (0.5)	2.4 (0.5)	t(24) = 0.842	.418	t(48) = 1.468	.149
ATAVT	overview	13.1 (4.1)	10.4 (2.9)	11.7 (2.7)	z = -3.179	**.001***	z = -0.915	.360
PP	visual field	169.3 (11.9)	161.7 (19.0)	167.0 (13.8)	z = -1.600	.110	z = -0.691	.490
	tracking deviation	9.6 (1.9)	10.2 (3.6)	9.3 (1.9)	z = -0.186	.853	t(48) = 0.164	.871
LVT	Score	13.4 (4.1)	13.0 (4.4)	14.2 (4.4)	z = -0.595	.552	z = -1.291	.197
	Time (s)	68.0 (13.2)	68.9 (12.7)	65.4 (9.5)	z = -0.442	.658	z = -0.774	.439
WRBTV	Score	6.4 (1.4)	7.1 (1.5)	7.7 (1.4)	z = -3.377	**.001***	z = -2.763	**.**006
IVPE	Mental stability	2.4 (2.5)	2.3 (2.1)	2.4 (2.1)	z = -0.721	.471	z = -0.746	.456
	Responsibility	5.0 (2.5)	5.4 (2.5)	5.3 (2.7)	z = -0.547	.585	z = -0.239	.811
	Self-control	4.3 (1.8)	4.5 (1.3)	3.9 (1.5)	z = -0.390	.697	z = -0.304	.761
	Adventure	4.8 (2.3)	4.7 (2.0)	6.0 (2.0)	z = -0.097	.923	z = -1.657	.098
	Openness	2.8 (1.9)	2.6 (1.7)	2.5 (2.1)	z = -1.219	.223	z = -0.617	.537

Table 1.5, continued. Psychological traffic test battery assessing fitness to drive.

		Descriptive statistics		
		pwMS		**Controls**
		baseline	follow-up	baseline
Tests	**Measures**	*M (SD)*	*M (SD)*	*M (SD)*
Overall judgement of fitness to drive n [%]				
1. Inadequate		0 [0]	0 [0]	0 [0]
2. Non-compensable		5 [20]	3 [12]	2 [8]
3. Limited compensability		1 [4]	2 [8]	1 [4]
4. Adequate compensability		2 [8]	7 [28]	6 [24]
5. Adequate ability		17 [68]	12 [48]	15 [60]
Adequate overall (categories 4 and 5)		19 [76]	19 [76]	21 [84]
Unknown°		0 [0]	1 [4]	1 [4]

Note. pwMS, people with multiple sclerosis; *M*, mean; *SD*, standard deviation; AMT, Adaptive Matrices Test; DT, Determination Test; RT, reaction time; RTest, Reaction Test; COG, Cognitrone; ATAVT, Adaptive Tachistoscopic Traffic Perception Test; PP, Peripheral Perception; LVT, Visual Pursuit Test; WRBTV, Vienna Risk Taking Test Traffic; IVPE, Inventory of Driving-related Personality Traits.

Overall judgement of fitness to drive: 1. Inadequate, inadequate driving-specific ability; 2. Non-compensable, non-compensable performance deficits; 3. Limited compensability, performance deficits that can to a limited extend be compensated; 4. Adequate compensability, adequate driving-specific ability (performance deficits can be compensated); 5. Adequate ability, adequate driving-specific ability; Categories 4 and 5 indicate overall adequate driving-specific ability, categories 1 through 3 indicate inadequate driving-specific ability. ° In some cases, technical difficulties in some tests led to inconclusive assessment sessions of fitness to drive; The test system was then unable to give an overall judgement of fitness to drive.

Statistical comparisons between pwMS at baseline and follow-up; between pwMS and controls at baseline. Group sizes were n=24 for pwMS - controls baseline comparisons, n = 25 for pwMS baseline - follow-up comparisons. Statistical tests used for the within-participants comparisons were t-test (t[df]) for paired samples for normally distributed parameters, and Wilcoxon signed-rank test (z) for nonparametric variables. Between-participants comparisons were calculated using t-test for independent samples (t[df]) for normally distributed parameters, and Mann–Whitney U test (z) for nonparametric variables; *p*-Values adjusted using the Bonferroni correction with a significance level of $\alpha < .0014$

Table 1.6. Outcomes and statistical comparisons of psychological questionnaires with number (%) of participants showing critical values.

	Descriptive statistics						***Statistical comparisons***			
	pwMS				**Controls**		**pwMS**		**baseline**	
	baseline		follow-up		baseline		baseline vs. follow-up		pwMS vs. controls	
	M (SD)	n (%) critical	*M (SD)*	n (%) critical	*M (SD)*	n (%) critical	*z (WSRT)*	*p*	*z (MWU)*	*p*
Mental health, quality of life										
Nottingham Health Profile Score	46.9 (68.8)	NA	26.9 (51.8)	NA	29.0 (39.1)	NA	-1.287	.198	-0.181	.856
Multicultural Quality of Life Index	8.1 (1.6)	NA	8.5 (1.4)	NA	8.6 (1.1)	NA	-1.158	.247	-0.903	.366
Beck Depression Inventory II	6.2 (7.1)	5 (20)	4.4 (5.4)	4 (16)	4.4 (4.1)	6 (24)	-1.372	.170	-0.665	.506
Self-rating Depression Scale	31.6 (9.9)	4 (16)	28.4 (7.5)	3 (12)	29.2 (7.2)	2 (8)	-2.020	.043	-0.661	.509
Self-rating Anxiety Scale	30.4 (7.1)	5 (20)	28.1 (6.4)	5 (20)	29.0 (5.5)	3 (12)	-1.662	.096	-0.421	.674
Daytime sleepiness, fatigue, sleep quality										
Epworth Sleepiness Scale	6.5 (3.9)	3 (12)	6.0 (3.1)	1 (4)	7.6 (3.3)	4 (16)	-1.122	.262	-1.140	.254
Modified Fatigue Impact Scale	13.8 (13.3)	2 (8)	11.5 (11.4)	0 (0)	9.7 (10.2)	0 (0)	-1.112	.266	-0.866	.387
Fatigue Severity Scale	2.6 (1.5)	5 (20)	2.4 (1.2)	3 (12)	2.7 (1.5)	7 (28)	-0.985	.325	-0.146	.884
Pittsburgh Sleep Quality Inventory	4.8 (2.6)	9 (36)	4.8 (3.1)	7 (28)	3.7 (2.3)	4 (16)	-0.163	.871	-1.153	.249
Functional Outcomes of Sleep Questionnaire	18.2 (2.4)	NA	18.5 (1.8)	NA	18.5 (1.9)	NA	-0.329	.742	-0.039	.969
Regensburg Insomnia Scale	8.5 (4.6)	3 (12)	6.7 (4.2)	3 (12)	8.3 (4.4)	4 (16)	-2.311	.021	-0.010	.992

Note. pwMS, people with MS; M, mean; SD, standard deviation; n, number; WSRT, Wilcoxon signed-rank test; MWU, Mann–Whitney U test. n (%) critical refers to the number and percentage of participants within each group at each test time with questionnaire results above clinically suspicious levels; cut-offs for critical values: BDI-II, >8; SDS, >40; SAS, > 35; MFIS, > 38; FSS > 4; ESS >10; RIS > 12; PSQI > 5.

Wilcoxon signed-rank test (WSRT) was used for within-participants comparisons, whereas Mann–Whitney U test (MWU) was used for between-participants.

p-Values adjusted using the Bonferroni correction with a significance level of $\alpha < .002$.

Daytime sleepiness, fatigue, and general sleep quality

Regarding the comparison between baseline and follow-up within pwMS, no significant changes could be observed (adjusted p-value of $\alpha < 0.002$). At baseline, pwMS and controls showed no significant differences regarding daytime sleepiness (Epworth Sleepiness Scale), fatigue (Modified Fatigue Impact Scale, Fatigue Severity Scale), or sleep quality (Regensburg Insomnia Scale, Pittsburgh Sleep Quality Index, Functional Outcomes of Sleep Quality).

2.1.5 Discussion

The current study evaluated the development of alertness, sleep quality, fitness to drive, mental health, and fatigue in the first year after de novo MS diagnosis. To increase the strength of our study, we intentionally chose a rigorous analysis using multidimensional assessments as well as PSG data. The inclusion of PSG data provided a more thorough understanding of the main assessment test results and addressed the lack of PSG data from pwMS in the literature. Moreover, the prospective design of the study ensured meaningful comparisons. One main challenge was to include pwMS as early as possible after initial symptom appearance and diagnosis to longitudinally analyse the first year after disease onset; the mean (±standard deviation) disease duration was 0.5 (± 1.2) years at study inclusion. A follow-up period of one year was chosen in order to monitor any significant changes in MS symptoms at an early stage in the lifelong course of MS. In this early stage, de novo pwMS were comparable with matched healthy control participants in most assessment areas, and their condition did not deteriorate over the course of the first year.

Compared with other studies (Brass et al., 2014; Popp et al., 2017), a lower number of pwMS showed signs of daytime sleepiness (12% after diagnosis, 4% at follow-up). In the present sample, the fastest 10% of PVT reaction times in pwMS were significantly

slower than in controls at baseline, however this difference was not significant after correction for multiple comparisons. No other differences in alertness or sustained attention (assessed by the MCT) within or between groups were found. Research has shown that fatigue is a very common yet fluctuating MS symptom (Johansson et al., 2008; Palotai et al., 2020) that also impairs alertness and psychomotor vigilance (Rotstein et al., 2012). Fatigue was seen in 20% of pwMS after diagnosis and in 12% at follow-up, which was substantially lower than the prevalence rates as high as 60% found in the general MS population (Brass et al., 2014; van der Vuurst de Vries et al., 2018). Daytime sleepiness and fatigue levels were comparable between pwMS and controls. Controls even showed significantly higher PUI values; however, these values were within the normal range, indicating no increased sleepiness in controls (Eggert et al., 2012). In general, no fatigue- or sleepiness-related impairments were found, which is in line with the low number of pwMS reporting fatigue or daytime sleepiness in our study.

Objective sleep quality as assessed by PSG revealed no relevant differences between the study groups. Sleep efficiency, the most affected sleep parameter in pwMS (Tanioka et al., 2020), was normal at all test times in both groups. PwMS showed significantly, albeit mildly, reduced REM sleep percentages (~2% reduction) at the one-year follow-up compared with baseline; however, this was inconsistent with results showing no changes in REM sleep percentages in pwMS (Tanioka et al., 2020). Overall subjective sleep quality assessed using the Pittsburgh Sleep Quality Index was impaired in 36% of pwMS after diagnosis and in 28% after one year, which was comparable with control participants.

Tests on fitness to drive—a very relevant domain of cognitive functioning in everyday life—were comparable in both study groups, and no specific impairments were observed one year after diagnosis. On the contrary, pwMS showed improvements in accuracy and speed at follow-up (similar to the improvements observed in healthy

controls, see Appendix A4.2, Table A5), and more pwMS were judged to have adequate driving-specific abilities. Of the eight pwMS who were judged to have overall inadequate fitness to drive at one or both test times, five (62.5%) drove less than 8000 km per year. This indicated that external factors such as limited driving experience may explain poor fitness to drive performance in some pwMS. According to Siepman et al. (2008), recently diagnosed pwMS with increased disabilities (Expanded Disability Status Scale [EDSS] > 3) showed significantly more difficulty on cognitive tasks for which motor function was irrelevant. In comparison, the level of disability in the present clinical sample was low (EDSS scores of 0.7±0.8 at baseline, 0.70±0.91 at follow-up), which may explain why fitness to drive and alertness performance were not strongly affected.

PwMS and controls showed similar self-reported levels of mental health and quality of life. Around 20% of pwMS showed self-reported signs of anxiety and/or depression after diagnosis. Regarding anxiety, these numbers are in line with other studies (Boeschoten et al., 2016); however, higher depression rates have been reported among pwMS, even directly after diagnosis (Sullivan et al., 1995). One year after diagnosis, self-ratings of depressive states (SDS) were lower; however, no difference was seen here in BDI-II scores, which is internationally viewed as more valid measuring depression severity in a clinical setting (medium correlation between SDS and BDI-II: $r = 0.68$) (Tanaka-Matsumi & Kameoka, 1986).

While many of the tested outcomes did not show strong associations with MS in the current analysis, this could be related to the symptom severity in the present sample and relatively low levels of cognitive impairment. Compared to study samples with similar disease durations, the current sample primarily showed low levels of specific MS symptoms such as fatigue, assessed using internationally established rating scales such as the FSS or MFIS (Fisk, Ritvo, et al., 1994; Krupp et al., 1988). However, our inclusion and exclusion criteria as well as the drop-out and screening failure rates showed no signs

that our prospective recruitment was biased toward patients with mild cases of MS. Moreover, power analysis determined that the present sample size was sufficient to determine statistical differences.

Possibly due to the early diagnosis of the patients with clinically isolated syndrome or relapsing–remitting MS and early initiation of disease-modifying immunomodulatory treatments in our patient cohort, the observed fatigue and general symptom severity was rather low. Therefore, MS disease severity (as measured by the EDSS) may be less pronounced, and progression may be slower, in the present study sample than in more recent natural history studies (Cree et al., 2016; Sá et al., 2021).

2.1.6 Conclusions

Within the limitations of the present study (e.g., small sample size, relatively short longitudinal observation period), our findings indicated little change within the first year after diagnosis concerning alertness, sleep, fitness to drive, and fatigue. Future research should focus on these symptoms in long-term studies of pwMS (including different disease stages, disease activity, and pharmacological interventions) (Harding et al., 2019) combined with state-of-the-art pharmacological treatment early in the disease course (Harding et al., 2019; Hauser & Cree, 2020; Montalban et al., 2018; Rae-Grant et al., 2018). This could determine the extent to which early care and proper pharmacological treatment can alter these aspects, which strongly impair quality of life in people with this detrimental progressive disease.

2.2 STUDY 2

LIGHT THERAPY GLASSES DURING NIGHT SHIFT WORK:

A FIELD STUDY

Julia Ottersbach, Anna-Lena Eich, Katharina Ringeisen, Thomas C. Wetter, Roland F. J. Popp

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2.2.1 Abstract

Background: Night shift work leads to severe short- and long-term side effects, posing a risk to personal and occupational safety.

Objective: This study aimed to test the effects of blue-enriched light emitting glasses on sleepiness, alertness, and sustained attention during the early morning hours of night shift work.

Methods: To remedy the risks of reduced alertness, sustained attention, and increased sleepiness in a single-blind study design, Luminette® 3 (Lucimed SA, Wavre, Belgium) glasses emitting blue-enriched light (BL) were tested from 5:00 a.m. to 5:30 a.m. during night shift work in 21 participants at a sleep laboratory, and the effects were compared with those of glasses emitting sham dim red light (DRL). Sleepiness was rated hourly from 9:00 p.m. to 7:30 a.m. using the Karolinska Sleepiness Scale, while alertness was assessed using the PC-Psychomotor Vigilance Task before and after the intervention. At the end of the night shift, sustained attention (using the computerized Mackworth Clock Test), comfort ratings, and fatigue were measured. Statistical analyses were conducted using the Friedman and Wilcoxon signed-rank tests.

Results: Sleepiness increased significantly throughout the night and was not significantly reduced after the intervention, with a more prolonged reduction using BL. Compared with using DRL, using BL revealed no clear benefit in terms of alertness or sustained attention, yet comfort ratings were slightly better, without any negative side effects.

Conclusion: In the current study, BL glasses were not clearly superior to DRL glasses in ameliorating the negative side effects of night shift work. Despite some limitations, however, this field study showed high ecological validity and demonstrated the convenient use of an intervention that is easy to implement in a realistic workplace setting.

Keywords: Blue-enriched light emitting glasses, Shift work, Sleepiness, Alertness, Occupational safety

2.2.2 Introduction and background

Night shift work is a major contributor to economic value creation and myriad societal and economic benefits worldwide. According to the German Working Hours Act (Arbeitszeitgesetz; § 2 II, III, IV ArbZG), night shift work is defined as working longer than two hours between 11:00 p.m. and 6:00 a.m. (Bundesministerium der Justiz, 2023), which applies to 4.6% percent of employees in Germany (Statistisches Bundesamt, 2022). Despite its benefits for economies, night shift work poses severe risks to employees (Deutsche Gesellschaft für Arbeitsmedizin und Umweltmedizin, 2020). Humans are primarily diurnal, and night shift work creates a misalignment between natural circadian and wake/sleep rhythms (Pallesen et al., 2010). This leads to increased risk for cancer and reduced metabolic, cardiac, and mental health compared to non-night shift workers (James et al., 2017). Moreover, a considerable amount of shift workers suffers from shift work sleep disorder, which is characterized by severely disturbed sleep, fatigue, and daytime sleepiness (Rodenbeck & Mayer, 2023).

In addition to such long-term effects, sleep deprivation and night shift work increase the risk for work- and commute-related errors and accidents (Åkerstedt, 1998; Åkerstedt et al., 2005; de Cordova et al., 2016; D. Fischer et al., 2017). Sleep deprivation, a major effect of night shift work, negatively affects physiological sleepiness, performance, concentration, and sustained attention, as well as cognitive, motor, and memory function, which are all crucial for work safety, proficiency, and professionality (Caruso, 2014; Popp & Fulda, 2004; Schwarz et al., 2016). Torsvall et al. (1989) demonstrated that 20% of night shift workers were unable to maintain sufficient wakefulness at work, while Åkerstedt (2003) identified somnolence during night shift as one of the most troublesome symptoms of night shift work, which also causes impairments on subsequent days off. This can lead to substantially higher error rates and performance decrements (de Cordova et al., 2016). Lee et al. (2016) highlighted the

dangers of sleep-deprived driving following night shift work, revealing that 43.8% of drives on a closed driving track after night shift work had to be prematurely terminated for safety reasons.

Past research has examined various interventions to mitigate these risks (see Neil-Sztramko et al. [2014] and Slanger et al. [2016] for an overview), including caffeine supplementation, shown to be an effective countermeasure against sleepiness-induced errors (Valck & Cluydts, 2001), and napping, which can effectively reduce sleepiness and increase performance (Ruggiero & Redeker, 2014). Evidence on the effect of pharmacological interventions is sparse and rather inconclusive (Liira et al., 2014; Neil-Sztramko et al., 2014). Since some methods are difficult to implement in many work settings (i.e., naps), research on easily administrable and non-disruptive methods to increase alertness and wakefulness during night shift work is warranted. Interventions using light supplementation utilize the acute alerting effects of light at wavelengths of around 460 nm or illumination levels around 5,000 to 10,000 lux (Cajochen, 2007; Cajochen et al., 2005; Rodenbeck et al., 2019). To ensure convenient application in different work settings, light-supplementing eyeglasses that are wearable during low- to moderate-intensity work tasks may be a suitable choice. The use of such glasses has already been tested in different clinical (Formentin et al., 2020; Kirschbaum-Lesch et al., 2018; Langevin et al., 2014) and non-clinical settings (Comtet et al., 2019; Schmidt et al., 2018; Slama et al., 2015) as well as in the workplace during daytime work (Bragard & Coucke, 2013). Regarding night shift work, Aarts et al. (2020) demonstrated positive effects of using active light glasses in the middle of the night on sleepiness during the commute home. A second study conducted by van Woerkom (2021) compared napping at any time and/or using light therapy glasses between 2:00 a.m. and 4:00 a.m. during night shift work, with positive outcomes on fatigue and well-being. However, these studies did not include objective measures of alertness and sustained attention.

Additionally, using light therapy glasses during the early morning hours was not compared to a placebo/sham condition.

To the best of our knowledge, no studies have compared the effects of light supplementation glasses with those of sham glasses (i.e., using dim red, non-blue-enriched light) on subjective sleepiness, objective alertness, and sustained attention during the early morning hours of actual night shift work. We hypothesized that blue-enriched light supplementation, compared with a sham condition, can positively affect nighttime alertness and sleepiness as well as sustained attention at the end of the night.

2.2.3 Materials and methods

Study Design

The present study comprised a single-blind, randomized, placebo-controlled, within-subjects design. After an introduction and screening session, two test nights were conducted at the Center of Sleep Medicine of the University of Regensburg. All participants took part in both the active and the sham conditions in a randomized order. During the active condition (blue-enriched light, BL), genuine Luminette® 3 light glasses (Lucimed SA, Wavre, Belgium) were used at an illuminance level of 1500 lux for 30 min, emitting blue-enriched white light at 468 nm with a bandwidth of 70 nm. The sham condition (dim red light, DRL) included sham Luminette 3 glasses that emitted light at 660 nm with an illuminance level of 175 lux for 30 min. The study was conducted in accordance with the World Medical Association Declaration of Helsinki and was approved by the ethics committee of the University of Regensburg (reference number: 20-1835-101). All participants gave informed written consent.

Measurements and procedure

Table 2.1 shows an overview of all measurements included in the screening, baseline, and test nights.

A detailed description of all measurements included in the screening and descriptive and statistical analyses can be found in Appendix B1.

Screening. General information about sleep, sleep habits, chronotype, (mental) health, depression, quality of life, and sleep disorders such as increased daytime sleepiness, fatigue, restless legs syndrome, and obstructive sleep apnea syndrome were assessed during participant screening (see Table 2.1 and Appendix B1.1). We obtained baseline values for subjective sleepiness (Karolinska Sleepiness Scale [KSS]), alertness (Psychomotor Vigilance Task [PVT]), and sustained attention (Mackworth Clock Test [MCT]). During screening, participants received detailed information on the procedure during test nights, which were conducted unsupervised.

Test nights. Participants wore an actigraphy device (GENEActive, Activinsights Ltd, Huntingdon, UK) from 3 days prior to 3 days after the test nights to monitor activity and rest phases regarding study protocol adherence. Throughout the test nights, KSS and VAS ratings were completed hourly starting at 9:00 p.m. as well as before and after the alertness and sustained attention tests. Since the acute alerting effects of light are most effective when the circadian drive for sleep is at its peak between 2:00 a.m. and 6:00 a.m. (Cajochen, 2007), the intervention phase took place from 5:00 a.m. to 5:30 a.m. During this time, participants were instructed to follow their regular work schedule and to take note of any notable events (e.g., if a patient monitored in the sleep lab needed the worker's attention, the glasses' usage could be interrupted briefly). Before and after the intervention, participants completed the PVT. Ratings of comfort for the light glasses, fatigue during the night (Daily Fatigue Impact Scale [D-FIS]), and sustained attention were assessed once after completion of the night shift at 7:00 a.m. The average time between screening and the first test night was 18.9 ± 21.1 days (range 2–76 days), and that between the first and second test night was 8.7 ± 3.5 days (range 4–18 days)

Table 2.1. Subjective and objective measurements used throughout the study, along with the parameters measured and references

Assessment and time	*Measurements and measures*	References
Screening		
Sleep Disorders	• *Berlin questionnaire Sleep Apnoea*: obstructive sleep apnoea	Netzer et al. 1999
	• *Restless Legs Syndrome diagnostic criteria:* restless legs syndrome	Allen et al., 2014
	• *Regensburg Insomnia Scale* (RIS): psychophysiological insomnia	Crönlein et al. 2013
Daytime Sleepiness	• *Epworth Sleepiness Scale* (ESS): overall daytime sleepiness, sleep propensity	Johns, 1991
Fatigue	• *Fatigue Severity Scale* (FSS): fatigue severity	Krupp et al., 1989
	• *Modified Fatigue Impact Scale* (MFIS): fatigue impact	Fisk et al. 1994, Fischer et al., 1999
Sleep Quality	• *Pittsburgh Sleep Quality Index* (PSQI): overall subjective sleep quality	Buysse et al 1989
	• *Functional Outcomes of Sleep Questionnaire* (FOSQ): overall impact of sleep impairment	Weaver et al. 1997
Chronotype	• *Morningness–Eveningness Questionnaire* (D-MEQ)	Griefhahn et al., 2001
Mental health, quality of life	• *Beck Depression Inventory II* (BDI-II)*:* depressive symptoms	Beck et al. 1996
	• *Multicultural Quality of Life Index* (MQLI)*:* health and life quality	Mezzich et al. 2011
Baseline and test nights		
Sleep quality and quantity*	• *Sleep diary*: sleep times before and after test nights • *Actigraphy device GENEActiv*: activity and sleep times before and after test nights	ActivInsights, (Huntingdon, United Kingdom)
Sleepiness	• *Karolinska Sleepiness Scale* (KSS): acute levels of sleepiness	Åkerstedt & Gillberg 1990
Fatigue*	• *Fatigue Impact Scale for Daily Use (*D-FIS) German adaptation: fatigue	Fisk & Doble, 2002
Comfort ratings*	• *Comfort ratings* for sham and active light glasses	
Objective psychomotor vigilance, sustained attention	• *Psychomotor Vigilance Task* (PVT): Mean RT, refractional RT, lapses, fastest 10% of reaction times, slowest 10% of reaction times as measure for changes in vigilance	Khitrov et al. 2014
	• *VIGIL S1 - Computerized Mackworth Clock Test Vienna Test System*: Mean RT, number of false and true reactions as measure for sustained vigilance under monotonous conditions	Schuhfried GmbH, Mödling, Austria

Note. * Measurement not used during the baseline measurement.

Participants

Prior to study inclusion, 24 participants were screened who either worked irregular night shifts (once or twice per month) or shadowed night shifts in the sleep laboratory of the Center of Sleep Medicine Regensburg. A power analysis with an estimated effect size of d_z = 0.60, an α error of .05 and a power of 1-β = 0.80 provided a sample size of 19 participants for our within-subject design. The final sample consisted of 21 healthy participants aged 19–30 years (mean = 23.7 years; standard deviation = 3.1 years), of whom 20 (95.1%) were enrolled students and 16 (76.1%) were women. The inclusion and exclusion criteria for study participation are listed in Table 2.2. All participants received compensation for study participation. Table B1 in Appendix B2 provides an overview of participants' screening results and baseline PVT and MCT data, which were used descriptively to exclude any participants with deficient alertness and sustained attention.

Table 2.2. Inclusion and exclusion criteria for study participation

Inclusion criteria	Exclusion criteria
Aged 18–65 years	Distinct psychotic symptoms and/or other relevant cognitive disability
Night shift workers of the Center of Sleep Medicine Regensburg-Donaustauf or people shadowing at the Center of Sleep Medicine used to irregular night shifts	History of any neurologic and/or epileptic disorders
Sufficient cognitive and verbal ability to understand the study purposes, participant information documents, and all questionnaires and tests	Diagnosed psychological/psychiatric disorders according to the International Classification of Disorders 10th Edition
Compliance and willingness to adhere to the study protocol	Sleep disorders diagnosed according to the International Classification of Sleep Disorders 3rd Edition criteria (American Academy of Sleep Medicine, 2014)
Provided written informed consent to participate in the study	Inability to consent
	Intercontinental travel within 6 weeks prior to study participation
	Diseases of the eye, such as retinopathy, retinitis pigmentosa, diabetic retinopathy, macular degeneration, glaucoma
	Use of psychoactive substances within the prior week that could influence sleep or wakefulness
	History of or current substance use or substance use disorder according to the Diagnostic and Statistical Manual of Mental Disorders, 5th Edition criteria (alcohol, hypnotics, or other substances except nicotine)

Analyses

All data were pseudonymized before storage. Actigraphy and sleep diary data were only used to check for adherence to the study protocol. Four PVT values (three lapses, one mean RT) and four MCT values (two correct responses, two false starts) deviated more than three standard deviations from the group mean and were considered outliers. Of those, all PVT values and three MCT values were deemed systematic and retained in the dataset; one MCT outlier (correct response) was identified as unsystematic and replaced by the group mean. Means, standard deviations, and standard errors were calculated for descriptive analyses. The Shapiro–Wilk test was used to check for data normality. PVT and MCT data were not normally distributed; all other data were questionnaire data; therefore, only non-parametric tests were used for statistical analyses. PVT and KSS data were analysed using the Friedman test, and significant variables were entered into the post-hoc pairwise Dunn's test with Bonferroni correction. Data from the MCT, D-FIS, and comfort ratings were analysed using the Wilcoxon signed-rank test with Bonferroni correction for multiple comparisons. All analyses were performed in SPSS software (v29.0; IBM Corp., Armonk, NY, USA) and all tests were two-sided. The significance level was set to $\alpha = 0.05$.

2.2.4 Results

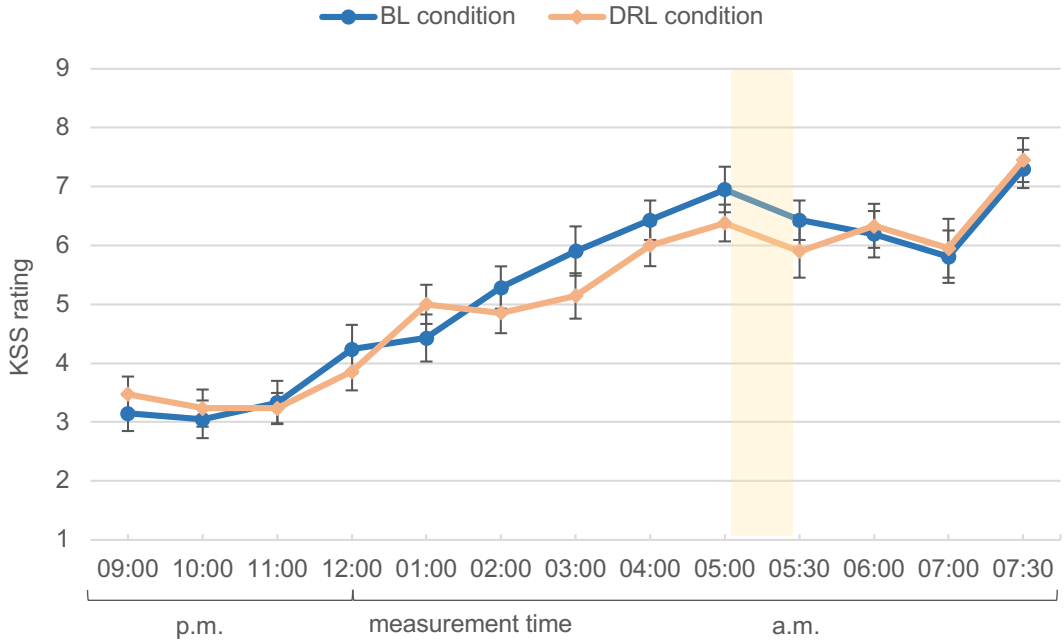
Subjective sleepiness and fatigue

Figure 2.1 shows participants' KSS ratings throughout the night from 9:00 p.m. to 7:30 a.m.

Before the intervention. The Friedman test was used to compare scores within and between the DRL and BL conditions. In one comparison, we analysed scores at 9:00 p.m., 12:00 a.m., 3:00 a.m., and 5:00 a.m. During this period, subjective sleepiness increased in both conditions, (X^2 [7, N=18] = 86.310, $p < 0.001$), with significant differences in the

DLR condition between 9:00 p.m. and 5:00 a.m. (z = -4.194, p < 0.001) and between 12:00 a.m. and 5:00 a.m. (z = -3.639, p < 0.001) as well as significant differences in the BL condition between 9:00 p.m. and 3:00 a.m. (z = -3.994, p < 0.001), between 9:00 p.m. and 5:00 a.m. (z = -4.778, p < 0.001), and between 12:00 a.m. and 3:00 a.m. (z = -2.750, p = 0.021). No significant differences were observed in the between-group comparisons (all p > 0.05).

Figure 2.1. Karolinska Sleepiness Scale (KSS) throughout the test nights



Note. Ratings on the Karolinska Sleepiness Scale (KSS) throughout the test nights in the BL (blue-enriched light, blue line) and DRL (dim red light, orange line) conditions. Participants' KSS scores ranging from 1 (*extremely alert*) to 9 (*extremely sleepy*) were measured hourly from 9:00 p.m. to 7:30 a.m. in the BL and DRL condition; yellow bar indicates the period (from 5:00 a.m. until 5:30 a.m.) in which the light intervention took place. Error bars indicate the standard error of the mean.

During the intervention. At 5:30 a.m., participants in both conditions rated their sleepiness to be slightly lower than before the intervention at 5:00 a.m. However, a second Friedman test revealed no significant differences between or within conditions (X^2 [3, N=20] = 4.113, p > 0.05).

After the intervention. In the early morning hours between 5:30 a.m. and 7:00 a.m., sleepiness increased in the DRL condition but decreased further in the BL condition. This

was, however, not significant within or between conditions (X^2 [5, N=21] = 2.799, p > 0.05). At the end of the night, sleepiness ratings differed significantly between 7:00 a.m. and 7:30 a.m. —before and after the MCT (X^2 [3, N=19] = 18.058, p < 0.001, Friedman test). Sleepiness was significantly higher after the MCT than before in the BL condition (z = -2.827, p = 0.028) and marginally higher in the DLR condition (p = 0.06).

At the end of the night, D-FIS ratings were non-significantly higher in the DLR (11.6 ± 7.4) compared with the BL condition (10.9 ± 7.9; z = -0.507, p > 0.05, Wilcoxon signed-rank test).

Objective alertness and sustained attention

Table 2.3 shows PVT data before and after the intervention and MCT data at the end of the night shift.

Table 2.3. Performance in the Psychomotor Vigilance Task and Mackworth Clock Test VIGIL S1

	Descriptive Statistics				***Inferential Statistics***	
	DRL condition		**BL condition**			
	pre intervention *M (SD)*	post intervention *M (SD)*	pre intervention *M (SD)*	post intervention *M (SD)*	*X2(df, N)*	*p*
Psychomotor Vigilance Task						
Lapses	5.00 (8.72)	7.38 (10.37)	4.48 (5.68)	6.67 (10.25)	3.018 (3, 21)	.389
Mean RT	311.97 (80.47)	329.77 (86.94)	315.58 (59.37)	331.00 (91.97)	4.257 (3, 21)	.235
FRT	219.22 (22.94)	227.00 (29.42)	222.83 (25.46)	227.00 (26.80)	3.514 (3, 21)	.319
Speed (1/RT)	3.53 (0.55)	3.41 (0.62)	3.47 (0.50)	3.41 (0.60)	6.736 (3, 21)	.081
Mackworth Clock Test					*z*	*p*
Correct Reactions	n.a.	91.62 (8.59)	n.a.	92.60 (6.91)	-0.589	.556
False Starts	n.a.	4.81 (6.49)	n.a.	3.05 (3.06)	-1.002	.316
Mean RT	n.a.	515.57 (74.13)	n.a.	510.38 (89.80)	-0.939	.348

Note. DRL, dim red light; BL, blue light; *M*, mean; *SD*, standard deviation; RT, reaction time in ms, FRT, fastest 10% of RT; n.a., not applicable.

Inferential statistics for comparisons between both conditions were calculated using the Friedman test and Wilcoxon signed-rank test.

PVT performance was worse after both interventions compared with before, with a higher number of lapses, mean RT, and fastest 10% of RTs, showing slightly fewer false starts and a faster mean RT in the MCT in the BL condition compared with the DRL condition. Significant differences were not, however, found within or between groups in either the PVT or the MCT (all p > 0.05).

Comfort ratings

Table 2.4 provides an overview of participants' comfort ratings regarding the light glasses in both conditions.

Table 2.4. Comfort ratings for the sham and active light glasses

	Descriptive Statistics				***Inferential Statistics***	
	DRL condition		**BL condition**			
	Mdn	*M (SD)*	*Mdn*	*M (SD)*	*z*	*p*
Rating for intervention (5-point Likert scale: 1 = not at all; 5 = very): The light glasses…						
…increased my fitness	2	2.1 (1.2)	3	2.7 (1.2)	-1.906	.057
…increased my well-being	2	2.5 (1.2)	2	2.5 (1.1)	-0.288	.773
…facilitated wakefulness	3	2.9 (1.2)	3	3.0 (1.0)	-0.453	.651
…had a positive effect on the morning	2	2.4 (1.0)	3	2.8 (1.2)	-1.072	.284
… positively influenced my concentration	2	2.7 (1.2)	3	2.7 (0.9)	-0.066	.948
…irritated me	3	2.9 (1.4)	3	2.9 (1.3)	-0.051	.959
…disturbed me	2	2.5 (1.3)	3	2.9 (1.3)	-1.257	.209
…irritated my eyes	2	2.3 (1.2)	2	2.5 (1.4)	-0.480	.631
…negatively affected my view	2	2.4 (1.4)	2	2.4 (1.4)	-0.045	.964
…disturbed my work	2	2.1 (1.1)	2	2.0 (1.1)	-0.551	.582
…generated disturbing reflections in the computer screen	1	1.8 (0.9)	1	1.9 (1.1)	-0.355	.722
Semantic Differential (7-point Likert scale: 1 = very…; 4 = neither nor; 7 = very…)						
pleasant - unpleasant	4	4.0 (1.5)	4	4.3 (1.2)	-0.717	.473
fitness increasing - fitness decreasing	4	3.8 (1.0)	4	3.7 (1.0)	-0.241	.809
drowsing - activating	5	4.8 (1.6)	5	4.8 (1.3)	0.000	> .999
not disturbing - disturbing	4	3.9 (2.1)	4	4.1 (1.8)	-0.288	.773
too short - too long	4	3.5 (0.8)	4	3.7 (0.8)	-1.040	.298
in the foreground - in the background	3	3.4 (1.5)	4	4.0 (1.3)	-1.547	.122
weak - strong	4	4.5 (1.2)	4	4.5 (0.9)	-0.480	.631
Overall rating for intervention (6-point Likert scale: 1 = not at all; 6 = absolutely)						
Recommendation	3	3.0 (1.5)	3	3.4 (1.1)	-1.331	.183
Evaluation of the intervention (6-point Likert scale: 1= very good; 6 = insufficient)						
Grade (i.e., school grade)	4	3.5 (1.2)	3	3.1 (1.0)	-1.253	.210

Note. DRL, dim red light; BL, blue-enriched light; *Mdn*, median; *M*, mean; *SD*, standard deviation
Inferential statistics were calculated using the Wilcoxon signed-rank test comparing ratings for the DRL (sham) and BL (active) condition.

Participant ratings showed that the BL glasses increased participants' fitness slightly more than the DRL glasses ($p = 0.057$). No negative side effects were reported, with similar ratings for BL and DRL glasses regarding negative aspects such as irritation

to the eyes, disturbances to eyesight or work, and reflections on the computer screen. Using a semantic differential scale with converse adjectives, both glasses were rated mostly neutral. The rating for "recommendation" and the school grade given by participants was slightly better for the BL glasses compared with the DRL glasses. However, none of these differences were statistically significant (all $p > 0.05$).

2.2.5 Discussion

To investigate mitigating the negative effects of night shift work on alertness and sleepiness during work hours as well as on sustained attention after work, we tested the effects of blue-enriched light therapy glasses during night shift work and compared these to sham glasses emitting dim red light without blue enrichment. Some well-known short-term negative effects of night shift work became apparent in the current study, such as increasing sleepiness throughout the night, reaction times, and error rates. However, compared to a sham condition, our results revealed no clearly significant benefit of using blue-enriched light glasses for 30 min from 5:00 a.m. to 5:30 a.m.

After a significant increase in sleepiness throughout the night, the BL intervention at 5:00 a.m. decreased sleepiness until 7:00 a.m. In the DRL condition, sleepiness increased again after a short decline at 5:30 a.m. These differences were not significant; however, they may indicate a slight superiority of the BL glasses to counteract sleepiness. Similar research conducted by Aarts et al. (2020) also showed no clear sleepiness-related benefit of using BL glasses compared with DRL glasses during night shift work, while van Woerkom (2021) showed a beneficial effect of light therapy glasses on fatigue during night shift work.

Performance in the PVT was worse after both interventions and MCT performance was similar between groups, without any significant differences. Inconclusive results have been reported from studies using light (specifically blue-enriched light) to increase alertness. In particular, objective outcomes of alertness and sustained attention failed to

show substantial effects (Canazei et al., 2021; Souman et al., 2018). Therefore, the results of the present study are not an exception.

Comfort ratings were similar for both the BL and DRL glasses. The BL glasses, however, were rated to improve fitness more than the DRL glasses. Importantly, no negative side effects were reported. Intervention methods to reduce sleepiness and improve alertness during night shift work should be effective, comfortable, and easy to use and implement. Therefore, the importance of positive comfort ratings should not be underestimated. To improve user comfort, further research should investigate allowing participants to determine the light intensity and duration of use.

In the context of treatment options, various studies have provided support for the beneficial effects of using light therapy glasses to treat mood disorders (Maruani & Geoffroy, 2019), seasonal affective disorders (Pjrek et al., 2020), and daytime sleepiness in Parkinson's disease (Raymackers et al., 2019; Smilowska et al., 2019). Regarding the alerting effects of light therapy glasses during night shift work, the available literature is much less clear, with inconclusive results reported by Aarts et al. (2020) and positive effects reported by van Woerkom (2021). The current study aimed to provide a clearly beneficial intervention for sleep-deprived night shift workers. Despite its comfortable, easy usage and easy implementation, the active light glasses, compared with sham glasses, were not proven to be an effective countermeasure to the short-term side effects of night shift work.

This may be explained by the following limitations of the present study. A final sample size of 21 participants may be too small to detect significant differences. However, based on our power analysis, our sample size should have been sufficient for this within-subjects design. Further research should include a larger sample size. The included participants were not typical night shift workers (i.e., not working several night shifts in a row). This may have influenced the results, considering that the first night shift

in particular can affect sustained attention (Santhi et al., 2007). We did not include a control group without an intervention. The goal of using a sham condition was to optimize consistency between test nights. However, this could have led to an expectation bias (Williams et al., 2012) or a placebo effect of the sham glasses, which has been reported in studies using similar sham conditions (Mateen et al., 2017; Voggenberger et al., 2022). Further research should include a control condition without light intervention to investigate the general effects of light supplementation during night shifts, similar to Comtet et al. (2019). During test nights, participants were not monitored. Some may have engaged in activities that affect sleepiness and alertness even further, such as studying. It was, however, the purpose of the current field study to investigate the usage of light glasses during night shift work in a workplace setting as realistically as possible, which is a major strength of our study.

2.2.6 Conclusions

Night shift workers experience short- and long-term side effects of sleep deprivation (Caruso, 2014) and circadian rhythm disruptions (Pallesen et al., 2010). Several interventions, including light supplementation, have been tested to reduce the short-term side effects (Aarts et al., 2020; van Woerkom, 2021) with often inconclusive results (Aarts et al., 2020; Souman et al., 2018). Our study is no exception, as no significant improvement in alertness was observed on the basis of objective outcome measures. However, our study demonstrated the feasibility of a convenient, easy-to-use light supplement in a real workplace setting without any negative side effects. As another relatively recent field study showed promising effects of bright light supplementation using a high proportion of blue light in industrial evening shifts (Rodenbeck et al., 2019), future research should focus on testing various aspects of light interventions (i.e., mode, duration, and timing of light application; light color or intensity; light use during different

shifts) to identify critical factors that may ameliorate the short-term negative effects of shift work without disturbing sleep.

2.3 Study 3

Efficacy and feasibility of light therapy glasses to mitigate fatigue in patients with multiple sclerosis: a randomised, placebo-controlled, crossover field study

Julia Ottersbach, Markus Canazei, Sophie K. Bauer, Celine Hfalek, Caren Berggold, Thomas C. Wetter, De-Hyung Lee, Ralf A. Linker, Roland F. J. Popp

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2.3.1 Abstract

Background: Fatigue is highly prevalent, clinically significant, and persistent in multiple sclerosis (MS), highlighting the need for effective countermeasures.

Objective: To evaluate the feasibility and efficacy of blue-enriched bright light (BL) therapy glasses in reducing MS-related fatigue.

Methods: This single-blind, randomized, placebo-controlled crossover study included 20 MS patients with significant fatigue (Fatigue Severity Scale [FSS] >36). Participants used active (BL) glasses or placebo dim red light (DRL) glasses for 20 minutes daily after waking. Each intervention lasted 1 week with 6 days washout in-between. Fatigue was the primary outcome (Visual Analogue Scale for Fatigue [VAS_F], immediately before, after each intervention, and at 13:00). Two additional fatigue measures and one quality of life measure were rated four times per week. Feasibility was evaluated using self-reported comfort, side effects, and sleep.

Results: Both interventions significantly reduced fatigue ratings (VAS_F) immediately after the intervention and at 13:00, with BL showing significantly more reduction compared to DRL. Both interventions significantly decreased FSS scores on the sixth and seventh intervention days. Patients reported greater comfort, improved well-being, and reduced fatigue with BL. Side effects were low and subjective sleep was unaffected.

Discussion: The present study provides initial evidence for BL glasses as a feasible, immediately effective intervention for MS-related fatigue.

Keywords: Fatigue; Multiple sclerosis; Light therapy; Blue-enriched bright light

2.3.2 Introduction

Fatigue, characterized by disproportionate tiredness and exhaustion, affects up to 90% of individuals with multiple sclerosis (MS), making it one of the most prevalent and disabling symptoms. The precise mechanisms underlying MS-related fatigue remain elusive, with studies discussing structural damage to white and grey matter, inflammatory processes, a maladaptive network recruitment, and metacognitive interpretations of brain states linked to helplessness (Manjaly et al., 2019). Fatigue can manifest in all stages of MS (Krupp et al., 1988) irrespective of neurological impairment (Fisk, Pontefract, et al., 1994). It affects social and professional life, severely impairs quality of life and compromises mental health. (Giovannoni, 2006; Krupp et al., 1988; Stuke et al., 2009) The consequences of this for the everyday life of patients with MS are severe, underscoring the urgent need for effective countermeasures.

Pharmacological treatments, including with amantadine, modafinil, and methylphenidate, have demonstrated no greater efficacy in reducing MS-related fatigue than placebo, and frequently induce adverse effects (Nourbakhsh et al., 2021). Non-pharmacological interventions, encompassing physical or psychological approaches, appear to hold greater promise (Tur, 2016). These include exercise therapy (Heine et al., 2015), resistance training (Englund et al., 2022), cognitive behavioural therapy (Vo et al., 2024), and mindfulness-based methods (Phyo et al., 2018).

Light therapy is an evidence-based treatment for seasonal affective disorder (SAD), typically involving exposure to polychromatic bright white light between 2,500 to 10,000 lx (Spitschan, 2024), In addition to its use in treating affective disorders, research has shown promising results for mitigating fatigue in patients with cancer (Johnson et al., 2018), Parkinson's disease (Raymackers et al., 2019), and after traumatic brain injury (Sinclair et al., 2014). There is also some evidence that blue-enriched light therapy with significantly lower illuminance levels (e.g., 750 lx) is effective in treating SAD (Meesters

et al., 2011) or mitigating sleepiness and sustained attentional lapses following sleep deprivation (Comtet et al., 2019).

Light therapy is commonly administered utilizing light boxes. The use of light therapy glasses, providing light via the frames of glasses, has recently gained some traction, as this approach can easily be integrated into daily life. Light therapy glasses have been shown to be effective in improving sleepiness and mood in medical inpatients (Formentin et al., 2020), in treating depression in adolescents (Legenbauer et al., 2024), and in reducing fatigue in patients with breast cancer (Bean et al., 2022) and patients with (non)Hodgkin lymphoma (Starreveld et al., 2021).

Two studies have examined the effects of light therapy on MS-related fatigue. Mateen et al. (2020) and Voggenberger et al. (2022) both compared the efficacy of bright light therapy (10,000 lx) to dim red light (DRL, < 300 lx) administered via light boxes. In the first study, patients were exposed twice daily for 1 hour over the course of 4 weeks (Mateen et al., 2020). In the study of Voggenberger et al. (2022), light therapy was applied once daily for 30 minutes in the morning (within 3 hours of awakening) over the course of 2 weeks. In both studies, exposure to both bright and dim light resulted in significant reductions in MS-related fatigue to the same extent.

To the best of our knowledge, no study has examined the effects of blue-enriched light therapy (BL) on MS-related fatigue or utilized light therapy glasses as an intervention in this context. To address this research gap, the present field study employed a randomized, placebo-controlled crossover study design, exposing patients with MS with significant fatigue to active (BL) and placebo (DRL) light therapy at home. Light therapy was administered daily via light glasses immediately after awakening for 1 week in each condition. We hypothesized that both interventions would improve MS-related fatigue after 1 week of usage, with stronger effects expected for BL compared to DRL within hours of exposure. Given that light exposure was conducted in the morning, we expected

no impact of the intervention on subjective sleep parameters during the nights following light exposure. As the blue-enriched light therapy in this study utilized an illuminance level of 1,500 lx, we further expected higher levels of reported side-effects profile than with DRL. As an exploratory analysis, we assessed comfort ratings for both light interventions as an additional measure of feasibility.

2.3.3 Methods

Study design and light interventions

Following a single-blind, placebo-controlled, crossover design, this study included two light interventions. For the active (BL) intervention, the Luminette® 3 glasses (Lucimed SA, Wavre, Belgium) with an illuminance of 1,500 lx and peak light emission at 468 nm were used for 20 minutes immediately upon awaking, which is a typical approach that has proven effective in prior research (Formentin et al., 2020; Legenbauer et al., 2024; Raymackers et al., 2019). The placebo (DRL) intervention also utilized Luminette® glasses with the same form factor, but with an illuminance of 150 lx and peak light emission at 660 nm, as utilized in prior studies (Langevin et al., 2014; Ottersbach et al., 2024; Raymackers et al., 2019). Both glasses switched off automatically after 20 minutes of exposure. At study inclusion, patients were randomly assigned to one of two study groups: group A first used DRL for 1 week, followed by a 6-day washout period and a second intervention week with BL; group B started with BL in week 1, followed by the 6-day washout period and the second intervention week using DRL. Participants were informed about testing two different light interventions and that both could aim to improve their MS-related fatigue. The study was conducted in accordance with the World Medical Association Declaration of Helsinki and approved by the ethics committee of the University of Regensburg (ID: 23-3307-101, date: 17 April 2023) The study was

registered with German Clinical Trials Register (ID: DRKS00036464). Participants received 100€ compensation for study participation.

Procedure and measurements

Recruiting was conducted using flyers that were disseminated to patients with MS at an outpatient clinic in the Department of Neurology (University of Regensburg) and patients of neurologists in private practice, and physiotherapists located in the Regensburg, Germany, area. Additionally, the study was promoted online in patient forums and on the study administration platform "Sona" of the University of Regensburg.

Study inclusion and screening. The first contact with potential participants took place via telephone and was aimed at checking inclusion and exclusion criteria as well as current MS-related fatigue levels.

Thereafter, a comprehensive screening took place at the Center of Sleep Medicine (University of Regensburg) or via video conference.

Following a description of the study and its interventions in detail, participants provided written informed consent for study participation and completed screening questionnaires (see Table 3.1 as well as Appendix C1) via the smartphone-based survey tool ExpiWell (West Lafayette, IN, USA). This survey instrument was also utilized to administer timed questionnaires throughout the 22-day study period. Participants were informed via push notifications in the smartphone tool about oncoming surveys and were sent reminders if there was a delay in receiving questionnaires responses.

Test weeks. Prior to each 7-day intervention period, a baseline assessment was conducted (on Friday; see Figure 3.1). Participants were administered the Visual Analogue Scale for Fatigue (VAS_F) three times (primary outcome) and the Fatigue Severity Scale (FSS), Daily Fatigue Impact Scale (D-FIS), and Multicultural Quality of Life Inventory (MQLI) once (secondary outcomes).

Table 3.1. Questionnaires used during the screening

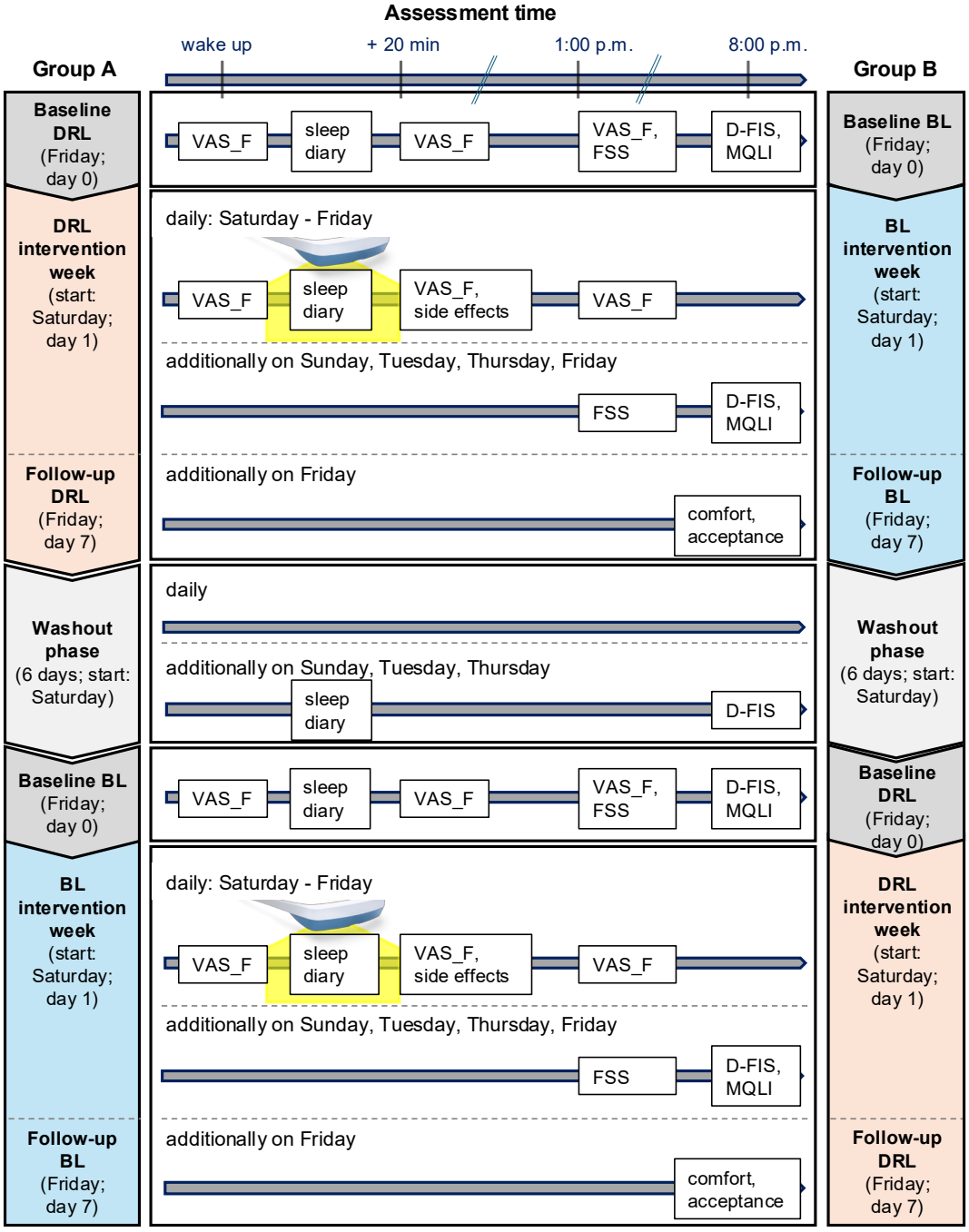
Assessment	Measurements and measures
General Questions	• Demographic data, disorders, medication • Expanded Disability Status Scale [a] score
Sleep Disorders	• *Berlin Questionnaire Sleep Apnoea* [b]: obstructive sleep apnoea • *Restless Legs Syndrome diagnostic criteria* [c]: restless legs syndrome • *Regensburg Insomnia Scale* [d]: psychophysiological insomnia
Daytime Sleepiness	• *Epworth Sleepiness Scale* [e]: overall daytime sleepiness, sleep propensity
Fatigue	• *Fatigue Severity Scale* [f]: fatigue severity • *Daily Fatigue Impact Scale* [g]: daily impact of fatigue • *Visual Analogue Scale for Fatigue:* fatigue level
Sleep Quality	• *Pittsburgh Sleep Quality Index* [h]: overall subjective sleep quality
Chronotype	• *Morningness–Eveningness Questionnaire* [i]
Mental health	• *Beck Depression Inventory II* [j]*:* depressive symptoms

Note: [a] (Kurtzke, 1983); [b] (Netzer et al., 1999); [c] (Allen et al., 2014); [d] (Crönlein et al., 2013); [e] (Johns, 1991); [f] (Krupp et al., 1989); [g] (Fisk & Doble, 2002), adapted; [h] (Buysse et al., 1989); [I] (Griefahn et al., 2001); [j] (Beck, Steer, Ball, et al., 1996)

Each 1-week intervention period started on Saturday (day 1), separated by a 6-day washout period (see Figure 3.1). During the intervention periods, participants were required to rate their level of fatigue daily on the VAS_F, immediately after awakening. The light exposure then began, during which participants filled in the sleep diary. The light glasses switched off automatically after 20 minutes, after which participants rated their fatigue levels on the VAS_F again and filled in the side effects questionnaire. At 1:00 p.m., fatigue was again rated on the VAS_F, and on days 2, 4, 6, and 7, participants additionally completed the FSS at 1:00 p.m. and the D-FIS and MQLI in the evening (8:00 p.m.). In addition, participants completed the comfort and acceptance questionnaire once at the conclusion of each intervention period (Friday, follow-up) at 8:00 p.m.

During the 6-day washout period, the sleep diary was filled in daily, and fatigue was rated every other evening using the D-FIS.

Figure 3.1. Study flow



Note. The yellow bars indicate the daily 20-minute light exposure during both intervention weeks starting on Saturday and ending on Friday; abbreviations: DRL, dim red light; BL, blue enriched bright light; VAS_F, Visual Analogue Scale for Fatigue; FSS, Fatigue Severity Scale; D-FIS, Daily Fatigue Impact Scale; MQLI, Multicultural Quality of Life Inventory

Outcome measures

Self-reported fatigue was measured as primary outcome using the VAS_F, ranging from 0 to 100, three times a day. Further measures included the FSS, D-FIS, and MQLI, which were completed four times during each intervention period. Comfort ratings were

recorded at the end of each intervention week. Side effects, their severity, and sleep logs were recorded daily during each intervention period (self-report). Adherence to the light intervention protocol was assessed by analysing the number and save-logs of the VAS_F questionnaires administered immediately before and after each light treatment.

Table 3.2 provides a list of all questionnaires and their specific assessment times along with the assessments and outcome measures for the questionnaires utilized. Additional information for each questionnaire can be found in Appendix C1.

Table 3.2. Measurements assessed during the two intervention weeks

Assessment	*Outcome*	Measurements and measures	Assessment time
Fatigue	*Efficacy, primary*	• *Visual Analogue Scale for Fatigue*: level of fatigue from 0-100%	Daily: before and after the intervention and at 1:00 p.m.
		• *Fatigue Severity Scale* [a]	At 1:00 p.m. on days 2, 4, 6, 7
		• *Daily Fatigue Impact Scale* [b]	At 8p.m. on days 2, 4, 6, 7
Quality of Life	*Efficacy, secondary*	• *Multicultural Quality of Life Index* [c]	At 8 p.m. on days 2, 4, 6, 7
Comfort ratings	*Feasibility, primary*	• *Comfort ratings, acceptance*	Last day of the intervention week (day 7, Friday)
Side effects	*Feasibility, secondary*	• *Asthenopic complaints* [d]*:* overexertion, headache, watering eyes, itchy eyes, stinging eyes, blurred vision, pain, glare, dizziness	Daily: post intervention
Sleep quality and quantity	*Feasibility, secondary*	• *Sleep diary*: sleep quality in %, time in bed, sleep time, wake-up time, naps during the day	Daily: during intervention

Note. [a] (Krupp et al., 1989); [b] (Fisk & Doble, 2002), adapted; [c] (Mezzich et al., 2011); [d] (Leichtfried et al., 2010), adapted.

Study population

Inclusion criteria. Consenting participants between 18 and 65 years, with a medical report of MS diagnosis and significant fatigue, defined as FSS scores >36 (Krupp et al., 1989), were included.

Exclusion criteria. The exclusion criteria included pregnant or breastfeeding women and participants with drug or alcohol use disorders, severe neurologic or somatic disorders (such as epilepsy or polyneuropathy), prevailing psychotic symptoms and/or relevant cognitive impairment, impairment in sensory or motor functions that could

compromise study participation, acute MS episode within the past 6 weeks prior to study participation, change in MS medication within the past 6 months of study participation, use of more than one psychoactive substance that impact wakefulness (such as amphetamines, sedatives, antidepressants, hypnotics, antihistamines, beta-blockers), excessive cigarette consumption (>15 cigarettes/day); eye diseases (such as retinopathy, retinitis pigmentosa, diabetic retinopathy, macular degeneration, and glaucoma), and intercontinental travel within 6 weeks prior to study participation.

Data analyses

We conducted a power analysis using G*Power v3.1 software (Faul et al., 2007) with estimated effect size of d = .60, as reported by light therapy research for cancer-related fatigue (Johnson et al., 2018); past research using light therapy for MS-related fatigue has not reported effect sizes (Mateen et al., 2020; Voggenberger et al., 2022). With a moderate effect size of d = .60, an α error of .05, and a power of 1-β = .80, a sample size of 19 participants was deemed sufficient for our within-subject design.

All data were examined for missing values and outliers (details in Appendix C2). The original dataset with missing data and the dataset with substituted data (intention-to-treat analysis) were both analysed using parametric and non-parametric statistical tests. All analyses yielded the same significant results. Thus, for VAS_F, FSS, D-FIS, MQLI, and sleep parameters, results from parametric statistical tests (repeated measures analyses of variance; ANOVA) with intention-to-treat analysis are reported.

To control for carry-over effects of the light interventions and the efficacy of the washout period, VAS_F, FSS, D-FIS, and MQLI scores from both baseline measurements were compared using the Student's t-test for dependent samples.

Baseline scores of the VAS_F (immediately after awaking, 20 minutes later, and at 1:00 p.m.), FSS, D-FIS, and MQLI were compared with values recorded on the last day of the 1-week intervention period (herein called the follow-up) using two-factorial

ANOVA with repeated measures with the factors of intervention (DRL, BL) and measurement day (baseline, follow-up).

Fatigue was measured with the VAS_F three times during each intervention day (immediately before and after the intervention and at 1:00 p.m.) on all seven intervention days (Saturday to Friday) during both interventions (BL, DRL). A three-factorial ANOVA with repeated measures including the factors of intervention (DRL, BL), measurement time (immediately before/after the intervention, and at 1:00 p.m.), and measurement day (day 1 to 7) revealed no significant effect of the factor measurement day. Thus, a two-factorial ANOVA with repeated measures was applied to VAS_F scores for the two factors of intervention (DRL, BL) and measurement time (immediately before/after the intervention and at 1:00 p.m.).

The FSS, D-FIS and MQLI were administered once (at 1:00 p.m. and in the evening, respectively) at baseline and on four intervention days (days 2, 4, 6, and 7) for both interventions. Thus, two-factor ANOVAs with repeated measures were run for FSS, D-FIS, and MQLI with the factors of intervention (DRL, BL) and measurement day (baseline and days 2, 4, 6, and 7). Moreover, FSS scores were analysed inter- and intraindividually regarding the minimally important difference of 4.05, which indicates a clinically significant difference of FSS-measured fatigue (Rooney et al., 2019). From the daily reported sleep diaries, the parameters of sleep quality (%), total sleep time (min), time in bed (min), sleep latency (min), and sleep efficiency (%) were extracted. Two-factor ANOVAs with repeated measures and the factors of intervention (DRL, BL) and measurement day (baseline to day 7) were run for each sleep parameter. Furthermore, the total number of naps were calculated for each intervention week and compared using the Student's *t*-test for dependent measures.

Comfort and side effects ratings were analysed using the Wilcoxon signed-rank test.

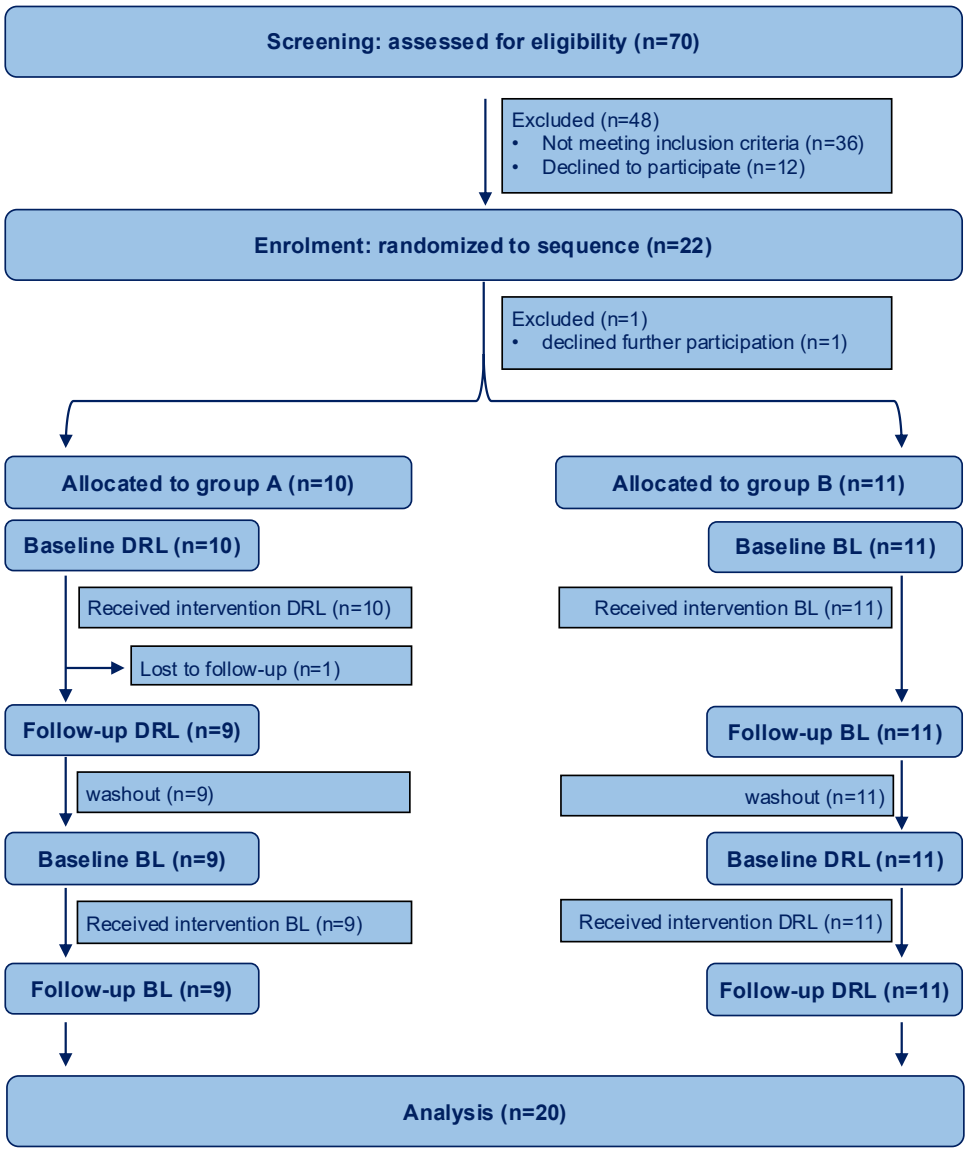
For descriptive analyses, mean, standard deviation, standard error, median, and interquartile range were calculated. All graphs show means and standard errors of the mean. For significant ANOVA findings, post-hoc pairwise comparisons were run using Bonferroni-corrected significance levels. In cases of sphericity violations, Greenhouse-Geisser correction was applied to the significance level. All analyses were performed in SPSS software (v29.0, IBM Corp., Armonk, NY, USA) with a significance level of 5% and two-sided testing.

2.3.4 Results

Study sample

A total of 70 patients diagnosed with MS were screened between December 2023 and May 2025, of whom 34 were eligible for participation. Most commonly, participants were excluded due to taking more than one psychoactive substance that can affect wakefulness. Of all eligible participants, 12 participants withdrew from the study prior to enrolment and 1 participant withdrew directly prior to the start of the first intervention week, leaving 21 participants who started the study, of which 20 participants completed it (one participant from group A dropped out during intervention week 1 [DRL condition]). Figure 3.2 shows the CONSORT study flow diagram.

Figure 3.2. Consort 2010 study flow diagram



Note. n, number; DRL, dim red light intervention; BL, blue-enriched light intervention

Reasons for exclusion were use of psychoactive substance that impairs wakefulness (n=30), severe smoking (n=3), severe alcohol intake (n=1), language barrier (n=1), and other severe disorders (n=1).

The final sample consisted of 20 participants aged 23 to 62 years (mean age ± standard deviation 40.5 ± 11.8 years) with 5 men and 15 women (Table 3.3). Sixteen patients had a diagnosis of relapsing–remitting MS, three were diagnosed with primary progressive MS and one was diagnosed with secondary progressive MS. Disease duration was most often more than 5 years (n=13). Sixteen patients reported poor levels of sleep (Pittsburgh Sleep Quality Inventory score > 5), 12 participants reported significant levels of insomnia symptoms (measured using Regensburg Insomnia Scale), and 10 participants

reported significant levels of depressive symptoms (measured using Beck Depression Inventory-II).

Table 3.3. Demographic and clinical characteristics of the study sample

Sample size (*n*)	20
Male (*n*)	5
Female (*n*)	15
Age in years (*M* ± *SD [range])*	40.5 ± 11.8 (23-62)
Occupation	
Student (*n*)	4
Working (*n*)	10
Stay-at-home (*n*)	1
Retired (*n*)	5
Diagnosis (McDonald criteria 2017)	
Relapsing-remitting MS (*n*)	16
Primary-progressive MS (*n*)	3
Secondary-progressive MS (*n*)	1
Disease duration	
1–3 years (*n*)	4
3–5 years (*n*)	3
More than 5 years (*n*)	13
EDSS Score [a] (*M* ± *SD*)	1.9 ± 1.8 (0-6)
Screening Questionnaires	
PSQI (*M* ± *SD [n poor sleep* [b]])	7.8 ± 3.2 (16)
D-MEQ (*M*±*SD*)	50.4 ± 13.6
Definite Evening (*n*)	2
Moderate Evening (*n*)	3
Neutral (*n*)	8
Moderate Morning (*n*)	6
Definite Morning (*n*)	1
OSAS (*n clinically suspicious* [c])	3
RLS (*n clinically suspicious* [d])	6
RIS (*M* ± *SD [n clinically suspicious* [e]])	14.6 ± 4.8 (12)
ESS (*M* ± *SD [n clinically suspicious* [f]])	10.6 ± 4.3 (8)
FSS (*M* ± *SD [n clinically suspicious* [g]])	52.3 ± 7.0 (20)
D-FIS (*M* ± *SD*)	19.9 ± 5.0
VAS_F (*M* ± *SD*)	56.5 ± 19.5
BDI-II (*M* ± *SD [n clinically suspicious* [h]])	14.35 ± 8.0 (10)

Note. n, number; *M,* mean, *SD,* standard deviation, MS, multiple sclerosis; EDSS, Expanded Disability Status Scale; PSQI, Pittsburgh Sleep Quality Index; D-MEQ, Morningness-Eveningness Questionnaire German version; OSAS, Berlin questionnaire Sleep Apnoea; RLS, Restless Legs Syndrome; RIS, Regensburg Insomnia Scale; ESS, Epworth Sleepiness Scale; FSS, Fatigue Severity Scale; D-FIS, Daily Fatigue Impact Scale; VAS_F, Visual Analogue Scale for Fatigue; BDI-II, Beck Depression Inventory – II. Revision.

[a] EDSS scores can range from 0 = "normal neurological exam, no disability in any functional system" in steps of 0.5 to 10 = "death due to MS".
Cut-off values for clinically suspicious scores:
[b] PSQI cut-off score > 5
[c] OSAS cut-off score of ≥ 2 in 2 or more out of 3 categories
[d] RLS cut-off score = 1 on all RLS criteria
[e] RIS cut-off sum score > 12
[f] ESS cut-off sum score > 10
[g] FSS cut-off sum score > 36
[h] BDI-II cut-off sum score > 14.

Adherence and control for carry-over effects

Adherence to the study protocol was indirectly monitored using the saved time stamps of the VAS_F questionnaires recorded before and after each light treatment. Of the maximum number of 280 interventions for the complete sample, 8 VAS_F ratings immediately before the start of the light exposure and 13 VAS_F ratings immediately after light exposure were missing, resulting in an adherence rate of 96.3%. Furthermore, the mean time difference between the two VAS_F ratings was 33 ± 13 min.

To control whether the washout period was effective to prevent carry-over effects of the first intervention week, baseline scores from both intervention weeks were compared using the Student's t-test for dependent variables. Patients' reported fatigue levels (VAS_F, FSS, D-FIS) and quality of life (MQLI) did not differ between the two baseline measurements (all $p > .05$, Table 3.4), demonstrating an effective wash-out.

Table 3.4. Baseline scores at the beginning of both intervention weeks

	DRL	BL		
	M ± *SD*	*M* ± *SD*	*t*(19)	*p*
VAS_F pre	51.3 ± 24.4	51.0 ± 25.5	0.036	.972
VAS_F post	43.3 ± 22.8	48.8 ± 21.5	-1.255	.225
VAS_F at 1:00 p.m.	51.0 ± 26.1	59.0 ± 22.0	-1.152	.264
FSS	48.8 ± 8.1	50.1 ± 8.0	-1.136	.270
D-FIS	18.4 ± 5.4	18.9 ± 8.4	-0.396	.697
MQLI	60.4 ± 17.2	65.2 ± 9.4	-1.349	.193

Note. DRL, dim red light intervention; BL, blue-enriched light intervention; *M*, mean, *SD*, standard deviation, VAS_F, Visual Analogue Scale for Fatigue; pre: before the intervention after awaking; post: after the intervention; FSS, Fatigue Severity Scale, D-FIS, Daily Fatigue Impact Scale, MQLI, Multicultural Quality of Life Inventory. Inferential statistics were calculated using Student's *t*-test for dependent measures

Efficacy

Comparison of baseline and follow-up scores. VAS_F scores immediately before the intervention were 3.5 points lower at follow-up than at baseline in the DRL intervention and 0.5 points higher in the BL intervention (Table 3.5). Immediately after the intervention, VAS_F scores were 3.8 points lower at follow-up with DRL and 10.8 points lower with BL. In the 1:00 p.m. measurements, VAS_F scores were 9.5 points lower at follow-up using DRL and 21.7 points lower using BL. A three-factor ANOVA including the factors of measurement time (immediately before and after the intervention, and at 1:00 p.m.), measurement day (baseline, follow-up), and intervention (BL, DRL) revealed a significant interaction effect between measurement time and measurement day ($F[2, 38] = 7.390$, $p = 0.002$, partial $\eta^2 = 0.280$). Post-hoc tests showed significantly lower VAS_F scores at follow-up immediately after the intervention (38.8 ± 20.6) than immediately before the intervention (50.1 ± 24.5 $p = 0.02$), but there were no other significant differences (all $p > 0.05$). Further, we found a significant main effect of measurement day ($F[1, 19] = 7.772$, $p = 0.012$, partial $\eta^2 = 0.290$), with significantly lower VAS_F scores at follow-up (42.8 ± 22.5) than at baseline (50.7 ± 23.7, $p = 0.012$). We found no interaction effects between measurement time and condition, measurement day and condition, or between measurement time, measurement day, and condition (all $p > 0.05$). Further, no main effect was found for condition ($p > 0.05$).

FSS scores were reduced by 2.7 points after 1 week of DRL and by 3.9 points after 1 week of BL (see Table 3.5). A two-factor repeated measures ANOVA revealed a significant main effect of measurement day ($F[1, 19] = 13.418$, $p = .002$, partial $\eta^2 = 0.414$), with significantly lower FSS scores at follow-up (46.2 ± 7.8) than at baseline (49.5 ± 8.1, $p = .002$), but no main effect for intervention and no interaction effect were seen (all $p > .05$).

Comparing D-FIS scores between baseline and follow-up, a reduction of 2.8 points was seen after 1 week of DRL, and a reduction of 2.9 points after 1 week of BL (Table 3.5). In a two-factor repeated measures ANOVA, no significant main effects or interaction effect were seen (all $p > .05$).

Quality of life scores, measured using the MQLI, were improved by 4.0 points after 1 week of DRL and remained stable at the same level as in the DRL condition after 1 week of BL (Table 3.5). No main effects or interaction effect were found in a two-factor ANOVA with repeated measures (all $p > .05$).

Table 3.5. Descriptive statistics of baseline and follow-up scores

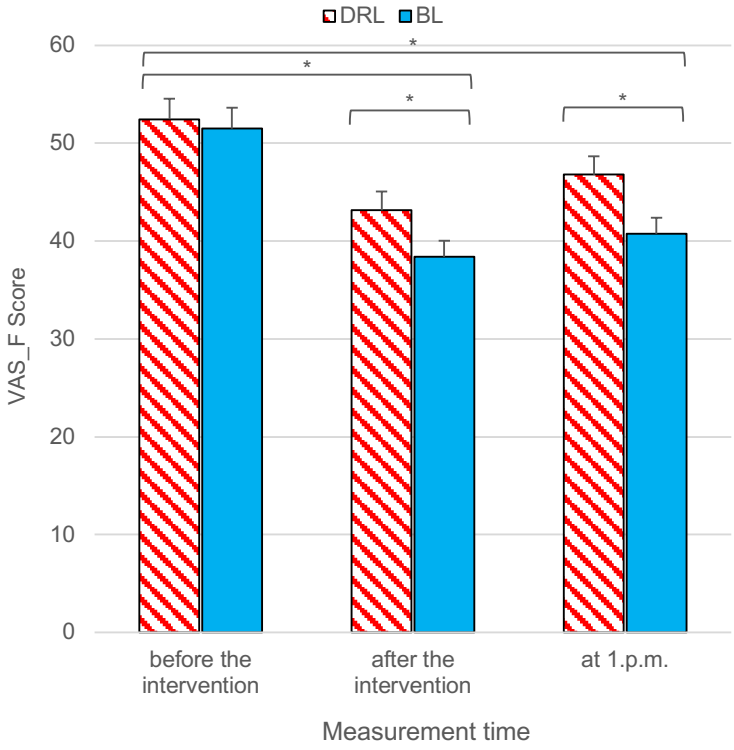
	DRL		**BL**	
	Baseline	Follow-up	Baseline	Follow-up
	M ± SD	*M ± SD*	*M ± SD*	*M ± SD*
VAS pre	52.3 ± 24.4	48.8± 25.8	51.0 ± 25.5	51.5 ± 23.7
VAS post	43.3 ± 22.8	39.5 ± 22.8	48.8 ± 21.5	38.0 ± 18.7
VAS 1:00 p.m.	51.0 ± 26.1	41.5 ± 22.5	59.0 ± 22.0	37.3 ± 20.0
FSS	48.8 ± 8.1	46.2 ± 8.8	50.1 ± 8.0	46.3 ± 7.0
D-FIS	18.4 ± 5.4	15.6 ± 6.6	18.9 ± 8.4	16.0 ± 4.9
MQLI	60.4 ± 17.2	64.4 ± 14.6	65.2 ± 9.4	65.3 ± 15.9

Note. DRL, dim red light intervention; BL, blue-enriched light intervention; *M*, mean, *SD*, standard deviation, VAS, Visual Analogue Scale for Fatigue, FSS, Fatigue Severity Scale, D-FIS, Daily Fatigue Impact Scale, MQLI, Multicultural Quality of Life Inventory

Fatigue throughout the intervention days. A two-factor repeated measures ANOVA including the factors intervention (DRL, BL) and measurement time (immediately before and after the intervention, and at 1:00 p.m.) showed a significant interaction effect between measurement time and intervention ($F[1.730, 240.492] = 3.513$, $p = 0.038$, partial $\eta^2 = 0.025$). Post-hoc comparisons revealed no significant differences of VAS_F scores in DRL and BL immediately before the intervention (DRL, 52.5 ± 24.7; BL. 51.5 ± 25.3, $p > 0.05$), but significantly lower VAS_F scores immediately after the intervention (DRL, 43.1 ± 22.8, BL, 38.4 ± 19.5, $p = 0.023$) and at 1:00 p.m. (DRL: 46.8 ± 22.3, BL, 40.8 ± 19.4, $p = 0.005$) in BL compared to DRL. Additionally, we observed a significant main effect for the factor intervention ($F[1, 139] = 5.384$, $p = 0.022$, partial $\eta^2 = 0.037$),

with significantly lower overall mean VAS_F scores with BL (overall: 42.8 ± 22.2) than with DRL (overall: 47.4 ± 23.2, $p = 0.022$; Figure 3.3). Further, we found a significant main effect for measurement time (F[1.535, 213.383] = 26.804, $p < 0.001$, partial $\eta^2 = 0.162$). Post-hoc comparisons revealed significantly lower VAS_F scores immediately after the intervention (39.8 ± 21.3, $p < 0.001$) and at 1:00 p.m. (44.4 ± 21.1, $p < 0.001$) than immediately before the intervention (51.1 ± 25.0), but no significant difference was found between measurements immediately after the intervention and at 1:00 p.m. ($p > 0.05$).

Figure 3.3. Visual Analogue Scale for Fatigue (VAS_F) scores



Note: Included are all measures from intervention days (day 1 until day 7 [follow-up]) in the placebo (dim red light [DRL], red shaded bar) and active intervention (blue-enriched light [BL], blue bar) immediately before and immediately after the intervention and at 1:00 p.m.
Error bars indicate the standard error of the mean.
* significant at $p < 0.05$

Fatigue throughout the intervention weeks. FSS values (Figure 3.4a) were included in a two-factorial repeated measures ANOVA with the factors intervention (DRL, BL) and measurement day (baseline, day 2, day 4, day 6, day 7), revealing a significant main effect for measurement day (F[4, 76] = 5.884, $p < 0.001$, partial $\eta^2 = 0.236$), with

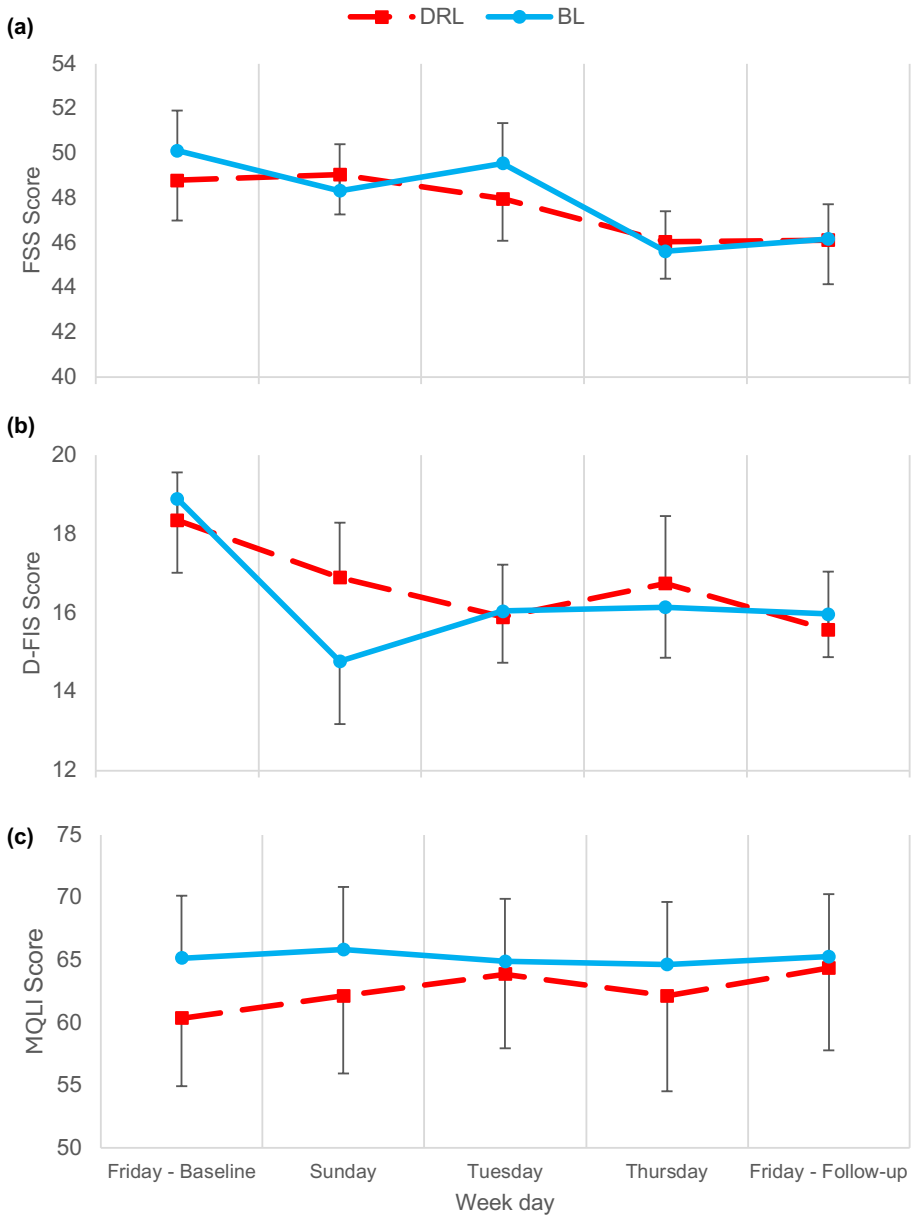
significantly lower FSS values on day 6 (Thursday, 45.9 ± 7.6, $p = 0.024$) and day 7 (Friday [follow-up], 46.2 ± 7.8, $p = 0.017$) than at baseline (Friday, 49.5 ± 8.0). Neither a main effect for intervention nor an interaction effect was found ($p > 0.05$). Regarding the minimally important difference of 4.05 on the FSS sum score, which would constitute a clinically significant difference in outcome measures according to Rooney et al. (2019), this was achieved for all patients using BL with a mean reduction in FSS scores from 50.13 at baseline (Friday) to 45.63 on day 6 (Thursday), but no reductions of 4.05 or more were seen on other intervention days. At follow-up, the minimally important difference was missed by 0.10, with a mean reduction in FSS scores of 3.95. In the DRL intervention, the group-based FSS baseline scores were not reduced by the minimally important difference on any intervention day.

When examining each patient's individual changes in FSS scores from baseline, a clinically significant difference was found in 11 patients with DRL (4 on day 4 [Tuesday], 7 on day 6 [Thursday], and 8 on day 7 [Friday, follow-up]) and in 15 patients with BL (6 on day 2 [Sunday], 3 on day 4 [Tuesday], 10 on day 6 [Thursday], and 6 on day 7 [Friday, follow-up]). Of these patients, three showed clinically significant differences only with DRL, and seven showed clinically significant differences only with BL.

D-FIS scores, depicted over the course of the week in Figure 3.4b, were compared in a repeated measures ANOVA with the factors of intervention (DRL, BL) and measurement day (baseline, day 2, day 4, day 6, day 7). No main effects or interaction effect were found ($p > 0.05$).

Quality of life throughout the intervention weeks. MQLI scores were included in a repeated measures ANOVA with the factors of intervention (DRL, BL) and measurement time (baseline, day 2, day 4, day 6, day 7) which yielded no significant main effects or interaction effect ($p > 0.05$). MQLI scores over the course of the week are depicted in Figure 3.4c.

Figure 3.4 Fatigue and quality of life scores over the course of the week



Note: (a) Fatigue Severity Scale (FSS); **(b)** Daily Fatigue Impact Scale (D-FIS); and **(c)** Multicultural Quality of Life Inventory (MQLI) for the placebo (dim red light [DRL], red dashed line) and active intervention (blue-enriched light [BL], blue line).
Error bars indicate the standard error of the mean.

Feasibility

Side effects and sleep parameters. The number of daily reported side effects and their severity rated on a 6-point Likert scale from 0 (not at all) to 5 (very strong) were low with no or hardly any notice of side effects in around 85.6% of ratings after BL and 89.1% of ratings after DRL. Glare was the most frequently reported side effect, with one report of strong glare and one report of very strong glare using DRL as well as six reports of strong

glare using BL. No other strong or very strong side effects were reported. When examining reported side effects per intervention day between DRL and BL, Wilcoxon signed-rank test revealed significantly more severe overexertion on day 1 (Saturday; DRL, 0.7 ± 1.0; BL, 1.2 ± 1.1, $z = –2.301$, $p = 0.021$, Cohen's $d = 0.51$) and day 2 (Sunday; DRL, 0.6 ± 0.8; BL, 1.0 ± 1.0, $z = –2.138$, $p = 0.033$, Cohen's $d = 0.48$), significantly more severe stinging eyes on day 3 (Monday; DRL, 0.3 ± 0.6; BL, 0.5 ± 0.7; $z = –2.000$, $p = 0.046$, Cohen's $d = 0.44$), and significantly more severe glare on day 1 (Saturday, DRL, 0.7 ± 1.2; BL, 1.7 ± 1.4; $z = –2.293$; $p = 0.022$, Cohen's $d = 0.51$), day 4 (Tuesday; DRL, 0.6 ± 0.9; BL, 1.4 ± 1.1; $z = –2.801$, $p = 0.005$, Cohen's $d = 0.63$), day 5 (Wednesday; DRL, 0.7 ± 0.9; BL, 1.4 ± 1.2; $z = –2.041$, $p = 0.041$, Cohen's $d = 0.46$), and day 6 (Thursday; DRL, 0.9 ± 1.0; BL, 1.5 ± 1.1; $z = –2.209$, $p = 0.027$, Cohen's $d = 0.49$) when using BL than with DRL. No differences were found on any other intervention day regarding these side effects, nor on any intervention day at all regarding headache, watering eyes, itchy eyes, blurred vision, pain in and around the eyes, and dizziness ($p > 0.05$). Table C1 and Figure C1 in Appendix C3 show the distribution of side effects severity between both study interventions. One participant discontinued study participation during the first week, after 3 days of DRL, due to severe glare. No other participant reported severe side effects that led to discontinuation of trials.

Comparing subjective sleep quality data, two-factor ANOVAs with repeated measures with the factors of measurement day (baseline to day 7 [follow-up]) and intervention (DRL, BL) were calculated for each parameter. A significant main effect of measurement day regarding sleep quality was found ($F[7, 133] = 2.466$, $p = 0.021$, partial $\eta^2 = 0.115$), with a significantly lower sleep quality reported on day 3 (Monday, 62.9 ± 19.4) compared to day 2 (Sunday, 73.3 ± 17.7, $p = 0.043$), but no main effect of intervention or interaction effect were observed. The remaining sleep parameters (sleep latency, time in bed, total sleep time, and sleep efficiency) yielded no significant main

effects nor interaction effect (all $p > 0.05$). Finally, the Student's *t*-test for dependent measures revealed significantly more naps on intervention days during the BL week (2.1 ± 2.3) than in the DRL week (1.3 ±1.4; $t = –2.223$, $p = 0.039$, $n = 20$, Cohen's $d = 0.45$).

Comfort ratings. Compared to the DRL intervention, participants rated the BL glasses significantly more positively regarding their ability to increase fitness (Cohen's $d = 0.64$) and well-being (Cohen's $d = 0.64$), have a positive effect on the morning (Cohen's $d = 0.52$), and to reduce fatigue (Cohen's $d = 0.66$), but also to negatively affect patients' view due to the brightness (Cohen's $d = 0.51$; Table 3.6). The BL intervention was also rated to be more fitness-increasing (Cohen's $d = 0.66$) and more activating (Cohen's $d = 0.61$) than DRL. Regarding the willingness to recommend the intervention and ratings using a "school grading" system both were higher for the BL than for the DRL intervention, but these differences were not significant.

Table 3.6 Comfort ratings for the placebo and active light glasses

	Descriptive Statistics				***Inferential Statistics***	
	DRL intervention		**BL intervention**			
	Mdn	*M (SD)*	*Mdn*	*M (SD)*	*z*	*p*
Rating for intervention (5-point Likert scale: 1 = not at all; 5 = very): The light glasses…						
…increased fitness	2	2.2 (1.1)	3	2.9 (1.1)	-2.636	.008
…increased well-being	3	2.5 (1.2)	4	3.6 (1.0)	-2.623	.009
…facilitated waking up	3	3.1 (1.2)	4	3.9 (1.2)	-1.951	.051
…facilitated wakefulness	3	2.7 (1.3)	3	3.5 (1.1)	-1.812	.070
…had a positive effect on the morning	3	3.0 (1.3)	4	4.0 (1.0)	-2.129	.033
… positively influenced concentration	3	2.7 (1.1)	3	3.3 (0.9)	-1.632	.103
…were irritating	1	1.5 (0.8)	1	1.3 (0.9)	0.000	>.999
…irritated the eyes	1	1.7 (0.9)	1	1.8 (1.0)	-0.577	.564
…brightness negatively affected the view	2	1.8 (0.9)	3	2.7 (1.1)	-2.095	.036
…disturbed reading	2	1.8 (0.8)	2	2.5 (1.0)	-1.930	.054
…generated disturbing reflections in the smartphone screen	2	1.9 (0.8)	2	2.0 (0.8)	-1.000	.317
…reduced fatigue	3	2.4 (1.0)	3	3.5 (0.9)	-2.658	.008
Semantic Differential (7-point Likert scale: 1 = very…; 4 = neither nor; 7 = very…)						
pleasant - unpleasant	4	3.5 (1.2)	3	2.9 (1.3)	-1.292	.196
fitness increasing - fitness decreasing	4	3.9 (1.3)	3	2.6 (1.1)	-2.641	.008
drowsing - activating	4.5	4.6 (1.4)	6	5.8 (1.1)	-2.448	.014
not disturbing - disturbing	3	2.9 (1.4)	2	2.7 (1.5)	-0.177	.859
too short - too long	4	3.7 (1.4)	4	3.4 (1.1)	-0.568	.570
weak - strong	4	4.3 (1.3)	4	4.6 (1.2)	-0.480	.631
Overall rating for intervention (6-point Likert scale: 1 = not at all; 6 = absolutely)						
Recommendation	4	4.2 (1.6)	5	4.9 (1.0)	-1.467	.143
Evaluation of the intervention (6-point Likert scale: 1= very good; 6 = insufficient)						
Grade (i.e., school grade)	3	3.1 (1.4)	2	2.4 (0.9)	-0.975	.330

Note: DRL, dim red light; BL, blue-enriched light; *Mdn*, median; *M*, mean; *SD*, standard deviation

Inferential statistics were calculated using the Wilcoxon signed-rank test comparing ratings for the DRL (placebo) and BL (active) intervention.

2.3.5 Discussion

In this field study, we evaluated the efficacy and feasibility of a novel light therapy method (blue-enriched light exposure immediately after awakening using light therapy glasses) to treat MS-related fatigue.

Our main findings indicated good efficacy of both light glasses in reducing fatigue levels immediately after light exposure and hours later (at 1:00 p.m.), with significantly higher effects with BL than with DRL on daily measured fatigue (VAS_F). In addition, 1 week of both light interventions significantly reduced fatigue levels measured using the VAS_F and FSS. Further, reduction in FSS fatigue levels with BL indicated clinically significant changes, which were not observed with DRL. The feasibility of our light treatment was high, and both light interventions were well tolerated. Patients reported a higher severity of side effects regarding overexertion (on two days), stinging eyes (on one day), and glare (on four days) using BL, but ratings for these glasses were significantly better than for the DRL glasses regarding items such as increasing fitness and well-being, positively influencing the morning, and, importantly, reducing fatigue. Subjectively assessed sleep parameters revealed no negative effects of the light interventions on sleep, but patients reported taking significantly more naps during the day when using the BL than with the DRL glasses.

A strength of the present study is the temporal resolution at which fatigue was assessed using the VAS_F. This allowed explorations of the effects of both interventions on the temporal dynamics of MS-related fatigue immediately after light treatment and hours later. Thus, this study provides first evidence for the superiority of BL, compared to DRL, in reducing fatigue levels immediately after light exposure as well as for a prolonged duration after light exposure. Comparing baseline with follow-up values, our results add to the findings of past research (Mateen et al., 2020; Voggenberger et al., 2022) by demonstrating a reduction of MS-related fatigue levels in both interventions

after only 1 week of usage. Further, we also found clinically significant changes in FSS scores, but only with BL. In contrast to past research, we further analysed each participants' individual changes in FSS scores throughout the intervention weeks and found variations between patients. Some patients responded only to BL, some responded only to DRL, some responded to both interventions, and some did not respond at all. This poses the question of whether there are responders and non-responders to light therapy among patients MS and fatigue, as observed in studies evaluating light therapy for SAD (Terman & Terman, 1999). Further, it highlights the need for examining individualized intervention methods for MS-related fatigue.

Another strength of our study is the daily assessment of side effects immediately after the light exposure, which also allowed a high temporal resolution in measurements of the severity of possible side effects as well as their development over the course of the intervention weeks. The reported side effects and their severity in our study were mild, and more severe side effects were observed early during the intervention weeks, potentially indicating that patients took a short time to adjust to the light exposure using glasses, as postulated in other research (Wirz-Justice & Bromundt, 2013). The differences in side effects and their severity observed between BL and DRL may in part be explained by the tenfold higher corneal illuminance in the BL intervention than in the DRL intervention. Further, the observed side effects and their severity in this study are negligible in comparison to those adverse effects experienced using pharmacological interventions for MS-related fatigue (Nourbakhsh et al., 2021; Tur, 2016). Along with the very low number of treatment discontinuations (1 patient during DRL) and the demonstrated reductions in fatigue levels, our results speak in favour of using light therapy to treat MS-related fatigue.

Within the framework of the study protocol, we focused on enabling patients to implement trial participation into their everyday lives. Interestingly, adherence rates were

high at 96%, and only one person discontinued participation due to severe side effects with DRL intervention.

Patients reported significantly more naps during the BL intervention week than the DRL week. This raises the question of if the light glasses' positive effects on fatigue levels during the morning led to increased sleepiness during the after 1:00 p.m. It may also put into perspective that the D-FIS results did not significantly change from baseline to follow-up: the D-FIS was administered in the evening and may have been affected by increased sleepiness following BL and, as reported in past research (Gabel et al., 2013), the possibility of an earlier melatonin onset following BL exposure. Since proper conduction and storage of melatonin samples is difficult in field studies such as this, a follow-up study using a laboratory study design could investigate this aspect.

In general, there are stark differences in how different measurements of fatigue operationalise fatigue, based on different definitions of this debilitating symptom (Manjaly et al., 2019). This offers another explanation on variations in fatigue results across different questionnaires, such as the VAS_F, D-FIS, and FSS in our study. Further, there is a history of strong placebo effects in the pharmacological (Nourbakhsh et al., 2021) and non-pharmacological treatment (Kos et al., 2007) of MS-related fatigue. Patients with MS often experience a strong placebo response, which would require a very large intervention effect to surpass. Studies on light interventions to treat MS-related fatigue are scarce, with our study being the third to have examined this method for MS-related fatigue. A review on light therapy for neurodegenerative disorders demonstrated that this treatment option offers attractive approaches for these types of diseases (Liu et al., 2021), highlighting the need for further research on the topic to refine light therapies for treating MS-related fatigue.

Our study comes with several limitations. Despite screening 70 interested patients, only 20 were included in the final analyses due to the exclusion criteria. This restricts the generalizability of our finding, and including a larger sample size with more advanced disease severity might produce more robust findings. Further, many of our included patients showed suspicious values regarding sleep disorders during screening. Past research has implemented a more vigorous exclusion of these patients as well as specific chronotypes (Voggenberger et al., 2022) and demonstrated that treating sleep disorders can significantly improve MS-related fatigue (Côté et al., 2013). The occurrence and underdiagnosis of sleep disorders is, however, relatively common in patients with MS (Kaminska et al., 2011; Tanioka et al., 2020; Veauthier, 2015), which is reflected in the screening results of our sample, since no patients reported pre-diagnosed sleep disorders. According to the manufacturer of the light therapy glasses, the effects of the light glasses should be noticeable within 4 to 6 days of usage (Lucimed SA, 2025). Therefore, we chose an intervention period of 7 days per intervention, since our study protocol was already rather intense, with 119 questionnaires required over the course of 22 days. For a symptom as severe as MS-related fatigue, regular usage over a longer period might be necessary to evoke more consistent and profound reductions in fatigue levels than our results showed, which could be queried in research including longer observation periods. Studies debate seasonal changes in MS-related fatigue in relation to the outdoor temperature, with increased fatigue severity linked to warmer months (Grothe et al., 2022), but findings remain inconclusive (Cordano et al., 2025). Further, increased exposure to sunlight was reportedly linked to reduced fatigue levels (Knippenberg et al., 2014). In our study, we did not monitor daily light exposure or temperature levels. However, our enrolment phase spanned from December 2023 to July 2025, and we included 12 patients who participated during winter and early spring (standard time) and 8 patients who participated during late spring and summer (daylight saving time),

covering the majority of seasons. Further research should consider monitoring outdoor temperature and illuminance levels to control for their effects on MS-related fatigue during light exposure trials.

2.3.6 Conclusions

The present study examined a novel light therapy method for MS-related fatigue, providing evidence for immediate beneficial effects of light therapy on MS-related fatigue, both within hours of usage (VAS_F) and over the course of the intervention week (VAS_F, FSS). Further, the active intervention using blue-enriched light proved superior to placebo in reducing fatigue immediately after usage as well as for a prolonged time. Our small sample size and the relatively short observation period of 1 week per intervention limited the generalizability of our results. Therefore, further research should include larger, less restricted samples of fatigued people with MS and fatigue for a longer duration. Importantly, using blue-enriched light-emitting glasses after waking up in the morning was well tolerated with high feasibility, providing evidence for a promising intervention method that could help patients with MS-related fatigue.

PART III: GENERAL DISCUSSION

3.1 Summary of findings

This dissertation consisted of three studies intended to achieve three major aims: i) to assess the development and progression of alertness, fatigue, mental health, sleep, and fitness to drive 1 year after de-novo MS diagnosis (Study 1); ii) to conduct and evaluate a novel light therapy-based intervention method by testing light therapy glasses in healthy control participants for effects on sleepiness and alertness levels during night shift work (Study 2); and iii) testing the same light therapy glasses' effects on fatigue levels throughout the morning and the intervention week in patients with MS (Study 3).

In Study 1, we chose an elaborate prospective multidimensional assessment design, including subjective questionnaires, objective computerized test batteries, multichannel PSG, and a psychological traffic test battery. Further, we compared results between patients with MS and matched healthy control participants. The findings demonstrated that, at the time of de-novo MS diagnosis, alertness, fatigue, mental health, sleep macrostructure, and fitness to drive were comparable between patients with MS and healthy controls and, within the first year after diagnosis, these did not significantly deteriorate in most assessed areas. Furthermore, this study attempted to increase our knowledge regarding PSG-assessed sleep macrostructure and fitness to drive at diagnosis and 1 year later. Fatigue levels were low in our sample of patients with MS, with clinically suspicious values (FSS sum score > 36) in 20% of patients after diagnosis and in 12% of patients 1 year later.

Study 2 included a randomized, placebo-controlled, crossover field study design, analysing the effects of using the light therapy glasses for 30 minutes during the early morning hours on alertness and sleepiness directly after the intervention, and on fatigue levels and sustained attention at the end of night shift work in healthy participants. Sleepiness levels increased significantly throughout night shifts. Thirty minutes of light

exposure decreased sleepiness levels in both interventions, yet there were no significant differences within or between the placebo and active light therapy conditions. Further, we found no effects on alertness levels, assessed immediately after light exposure, or on fatigue and sustained attention, assessed after the night shift. Importantly, no adverse effects were reported, and the light glasses in both conditions were well tolerated and received high acceptance levels ratings. Those levels were slightly but non-significantly higher for the blue-enriched light glasses. The findings from Study 2, we provided novel evidence for the feasibility of these glasses as an easy-to use, convenient light supplementation method in real-world workplace conditions.

In Study 3, patients with MS with clinically significant fatigue were recruited to wear the light therapy glasses for 20 minutes directly after awakening in the morning, testing the immediate and prolonged effects of light exposure on fatigue levels during the morning and during the intervention week. Further, quality of life, side effects of the glasses, and daily subjective sleep were reported. We found significantly reduced fatigue levels (measured with using a VAS_F ranging from 0-100%) after both interventions, with more profound and prolonged effects seen with the blue-enriched light intervention. The blue-enriched light intervention further led to clinically significant changes in FSS-measured fatigue levels on days 6 and 7 of the intervention weeks. Blue-enriched light therapy did not significantly improve quality of life or D-FIS measured fatigue. Side effects and their severity were reported to be low, and both interventions were well-tolerated and highly accepted. Importantly, no effects on subjectively reported sleep parameters were found. With a focus on assessing fatigue levels at a high temporal resolution, Study 3 is, to the best of our knowledge, the first study to provide evidence for the efficacy and feasibility of using blue-enriched light therapy to treat MS-related fatigue, applied in the form of portable light glasses.

Concerning the goals of this dissertation, we were i) able to add to the knowledge of the development of specific cognitive functions (alertness and fitness to drive), psychological symptoms, sleep, and fatigue at and 1 year after initial diagnosis with MS (Aim i). We further ii) provided evidence for the application of blue-enriched light therapy glasses to be feasible in the context of night shift work (Aim ii). Finally, iii), we demonstrated high immediate and prolonged efficacy of the blue-enriched light therapy glasses in mitigating MS-related fatigue during the morning and over the intervention week in addition to high feasibility and acceptance (Aim iii).

3.2 Progression of MS in the era of disease-modifying therapies

Regarding the variables examined in Study 1, patients with MS did not show much disease progression from diagnosis to follow-up 1 year later. This observation period is rather short, considering that MS is a lifelong disease. However, our findings do contribute to the existing knowledge about the initial development of the disease, as data on sleep, fitness to drive, alertness, and psychological symptoms in early disease stages are scarce. The approach of diagnosing MS as early as possible, also enabled by the inclusion of clinically isolated syndrome as a phenotype of MS in the 2013 revision of the MacDonald criteria (Lublin et al., 2014), in combination with prescribing disease-modifying therapies early after diagnosis, has altered the anticipated disease and disability course in MS (Cree et al., 2016, 2022; Harding et al., 2019; Sá et al., 2021). All patients included in our study were diagnosed early after the first onset of MS symptoms, followed by early intense disease-modifying therapy in almost all patients (23 patients received disease-modifying therapies at baseline shortly after diagnosis, 24 patients received such treatment between baseline and follow-up, and 22 patients received disease-modifying treatment at follow-up 1 year after diagnosis; see Table 1.2). During the 1-year period between both assessments included in our study, patients' EDSS scores

and levels of alertness, sustained attention, sleep, fitness to drive, and psychological health did not deteriorate; in fact, some variables such as levels of anxiety, insomnia, and fitness to drive even improved. Therefore, it appears that our data provide further evidence for the importance of the early application of intense disease-modifying therapy to control disease progression within the first year after diagnosis. Following up on the included patients now, roughly a decade after the first data collection period (recruitment and data collection for Study 1 was conducted between 2012 and 2018) would provide further insights into the progression of the assessed variables, especially in the context of the therapies provided since the last assessments.

Despite the large impact of the disease-modifying therapies on disease progression, monitoring symptoms and disease activity remains relevant throughout MS, even in cases of stable disease (Coerver et al., 2025). Further, fatigue remains a highly prevalent symptom in MS, and data on the effects of disease-modifying therapies on fatigue are incomplete and inconclusive (Penner & Schreiber, 2023). The presently described portable light therapy method is supported by past clinical light therapy-related research and may offer a promising intervention for mitigating fatigue in patients with MS. Its applications, however, do come with several challenges, such as the timing, duration, and dosage of therapy. The observations from Study 1 and Study 2 helped set the stage for examining whether portable light therapy glasses may also help alleviate fatigue in patients with MS in Study 3.

3.3 From Study 2 to Study 3: from night shift workers to patients with MS-related fatigue

Using light therapy glasses during night shift work demonstrated the practicality of this approach to light therapy in healthy participants. Testing the effects of the light therapy glasses on sleep-deprived night shift workers' sleepiness and alertness levels aimed to

address a research gap by including objective metrics. In the context of this dissertation, Study 2 played a role as an initial validation and exploration of using these portable light therapy glasses in a real-world setting. Thus, Study 3 was then planned and conducted. Examining the light therapy glasses in healthy participants with sleep deprivation allowed us to evaluate the feasibility and acceptance of the light therapy glasses and to refine the study design and protocol before proceeding with testing in patients with MS in Study 3.

In Study 2, the light therapy glasses were used at 1,500 lx for 30 minutes, while in Study 3, they were used at 1,500 lx for 20 minutes. Since the device turned off automatically after 20 minutes at 1,500 lux, participants in Study 2 were required to turn it back on for the remaining 10 minutes of usage. This proved impractical, which is why we decided to limit the usage time to 20 minutes at 1,500 lx in Study 3. Study 2 included actigraphy to assess activity and rest phases, which we deemed too burdensome for the patients with MS included in Study 3. Further, our initial idea to include objective measures of alertness in Study 3, such as the PVT used in Study 2, was discarded for the same reason: performing a 3- to 10-minute alertness test during the morning as an additional task after light therapy was reportedly too time-consuming for participants in Study 2. Thus, we considered this too burdensome for patients with MS and fatigue who integrated the use of light therapy glasses into their morning routine. Based on these decisions, the study protocol for Study 3 was adapted from Study 2's protocol, enabling the analysis of fatigue levels and adverse effects at a high temporal resolution while ensuring a relatively low and manageable workload for participants.

3.4 Light therapy: practical implications

Over the past 30 years, increasing evidence has shown the efficacy of light therapy in mitigating symptoms of psychiatric and neurological disorders as well as in improving well-being and alertness levels in healthy individuals (Canazei et al., 2021; Lam et al.,

2016; Partonen & Lönnqvist, 1996; Popp et al., 2024; Sinclair et al., 2014; van Woerkom, 2021). Technological advances have enabled the application of light therapy via portable glasses, and evidence comparing its effects to standard light therapy using light boxes has been provided over the past 10-20 years (Bragard & Coucke, 2013; Comtet et al., 2019). However, research on the effects of portable light therapy glasses on subjective sleepiness and objectively assessed alertness during night shift work has not been conducted. Further, studies including light therapy-based interventions to mitigate MS-related fatigue have only been reported within the past 5 years and have only used light boxes, demonstrating a large gap in light therapy research. With the results of Study 2 and Study 3, we were able to provide insights to fill these gaps.

3.4.1 Light therapy during night shift work

Not many studies have been conducted using light therapy glasses during night shift work, with Aarts et al. (2020) demonstrating positive effects of light therapy glasses during night shift work on sleepiness levels during the commute home and van Woerkom (van Woerkom, 2021) demonstrating reduced fatigue and increased well-being following glasses-based light therapy during night shift work. The novelty in our Study 2 was the inclusion of objective measures of alertness and sustained attention as well as comparisons of effects of active light therapy glasses to those of placebo glasses emitting dim red light. A methodological strength of this study was the inclusion of a washout period between both interventions. Further, the crossover design ensured that all participants underwent both interventions, serving as their own control participant and reducing inter-subject variability (Lim & In, 2021). Overall, the findings from Study 2 did not provide significant support for the efficacy of light therapy glasses to reduce subjective sleepiness and fatigue or to increase objective alertness levels during and sustained attention levels after night shift work. However, the findings did clearly demonstrate the feasibility and acceptance of using these glasses during night shift work

with no reports of side effects. We further gained insight into the use and application of light therapy glasses in the treatment of MS-related fatigue. With respect to Study 3, these insights proved invaluable.

3.4.2 Light therapy for MS-related fatigue

Study 3 provided evidence for the immediate and prolonged efficacy of light therapy glasses to reduce MS-related fatigue. Compared to levels measured before the intervention, fatigue was significantly reduced immediately after 20 minutes of blue-enriched bright light exposure applied directly after awakening in the morning and several hours after application at 1:00 p.m. (see Figure 3.3, p. 85) Further, fatigue levels measured using the FSS were reduced by a clinically significant level of 4.05, as defined by Rooney et al. (2019), after 1 week of light exposure in the blue-enriched light condition. Quality of life did not change over the courses of the intervention weeks, possibly because the intervention period was too short to show the significant effects on quality of life seen in prior related research (Mateen et al., 2020; Voggenberger et al., 2022). Unlike previous studies, we focused on assessing side effects after every intervention session to monitor their occurrence and severity with a high temporal resolution. This led to the discovery that the (low) number and severity of reported side effects decreased over the course of the intervention week. In addition, subjective sleep parameters assessed every morning during the intervention and washout weeks enabled us to control for carry-over effects of the light exposure on nighttime sleep. An interesting finding from these data was the increased need for naps during the active intervention week using blue-enriched bright light, allowing the hypothesis that this early morning light exposure, compared with dim red light used as placebo, might have led to increased feelings of sleepiness during the afternoon. Our study was conducted with a focus on rigorous methodology, including a 6-day washout period to control for carry-over effects and utilizing a placebo-controlled crossover design in which each patient served as their own control, again reducing inter-

subject variability in our comparisons (Lim & In, 2021). The findings add to the existing knowledge on the use of light therapy to treat MS-related fatigue by demonstrating that i) 1 week of light therapy was sufficient to achieve beneficial effects on MS-related fatigue, ii) blue-enriched light therapy was superior to dim red light in reducing MS-related fatigue, and iii) side effects and their severity were initially mild and decreased over time. The examined light therapy glasses, in contrast to standard light boxes, are compatible with many day-to-day activities and easy to use. Further research should focus on replicating our results with larger and more diverse samples. Based on the results of the studies herein, light therapy glasses offer a promising intervention method for patients with MS-related fatigue that can easily be integrated into the ongoing clinical treatments.

3.5 Limitations

Discussion on the specific limitations of each of the three studies can be found in the Discussion sections of each study. A discussion of the general limitations that apply to and all three studies is addressed in the following section.

3.5.1 Sample sizes

All three studies included small sample sizes, with several reasons for this. Study 1 included 25 patients with MS and 25 control participants, Study 2 included 21 healthy night shift workers, and Study 3 included 20 patients with MS with fatigue. In all three studies, a priori power analyses were conducted to calculate the required sample sizes, and all a priori calculated sample sizes were met. However, the achieved sample sizes were relatively small and do represent major limiting factors for these studies. With regards to Study 3, our power analyses were based on one-way ANOVAS. However, the results of Study 3 were calculated using two-factorial and three-factorial ANOVAs, which were therefore underpowered and would have required a bigger sample size to maintain a power of 1- β = .80. One major reason for the use of such small sample sizes

is that recruitment was difficult for all three studies. In Study 1, 26% of patients assessed during baseline measurements were lost to follow-up. Study 2 was planned and conducted during public health-related restrictions due to the outbreak of Coronavirus disease 2019, which delayed and impeded study recruitment and conduction. In Study 3, the exclusion criterion limiting the intake of psychoactive substances that could influence wakefulness (with the exception of one substance besides MS medication) led to the exclusion of about 67% of interested patients with MS. These patients presented with co-morbid mood disorders treated with antidepressant medication or coronary disorders that required the intake of betablockers. Both and further substances led to study exclusion. All three studies would have benefitted from larger sample sizes, which may have led to more definite findings, which should be addressed in future research.

3.5.2 Laboratory vs. field studies

Comparing the advantages and drawbacks of laboratory and field studies is often circular, as the advantages in one study setting are often drawbacks in the other. Within the framework of this dissertation, in which both field and laboratory settings were used, this debate is fruitful considering the way each setting limits the interpretation of each study's findings.

Study 1 was conducted as a laboratory study, where both healthy participants and patients with MS came to the clinic and all assessments were conducted in a quiet laboratory environment mostly lacking external distractors. This is not a representation of everyday life, with many surrounding distractions. Yet, it allowed a more controllable situation and allowed for an undisturbed collection of data to obtain a clear picture of the assessed variables (Aziz, 2017). Further, we included validated objective assessments, such as an internationally used psychological fitness to drive traffic test battery validated with real driving performance and widely used assessments for alertness and sustained attention.

Studies 2 and 3 were field studies; Study 2 was conducted in the participants' workplace, and Study 3 was conducted in patients with MS within their own homes and private environments. Both of these participant groups were not observed or closely monitored during the experiments and might, therefore, have violated the study protocol without our knowledge. Further, confounding variables such as the presence of colleagues (Study 2) or family members/cohabitants (Study 3), or other factors that might influence wakefulness (Study 2) or fatigue (Study 3) were not controlled for. These factors could have affected the reliability of the data. However, placing the experiments in real-life settings enabled the collection of data with high ecological validity, as field research offers greater generalizability compared to laboratory research (Aziz, 2017; Fisher & Wood, 2007). As a countermeasure to violations of the study protocol, participants in Study 2 were contacted by telephone in the morning after their study night. In Study 3, participants were contacted by telephone at pre-arranged times to inquire about their motivation to participate, side effects, and other factors that might negatively influence protocol adherence. Further, responses to the questionnaires used in Study 3 were time-stamped, ensuring indirect monitoring of adherence to the study protocol timing.

3.5.3 Placebo glasses as a control condition

Contrary to recommendations by Spitschan (2024), our placebo condition used as a control condition for evaluating the effects of the active intervention had both a different illumination level and a different spectral composition than the light from the active glasses instead of only modifying one of these factors. This was not an active decision but was limited by what the manufacturer provides for research purposes. An alternative would have been to include a control condition without any light-related intervention such as, for example, using an intervention method with a specific scent with alleged fatigue-reducing properties, as has been implemented in past research (Popp et al., 2024). We decided to use the placebo glasses as provided by the manufacturer to ensure maximum

comparability between the active (blue-enriched light) and the placebo (dim red light) interventions and to ensure better participant blinding. Further, dim red light is the most commonly used control condition in lighting research (Spitschan, 2024) and it can therefore be regarded as a valid control condition in our studies.

3.5.4 Generalizability

In line with the limited sample sizes, study designs, and study settings, the generalizability of each of the studies' findings may be considered low.

The patient sample from Study 1 had a mean disease duration of 0.5 years at study inclusion, at which point medication and disease activity were stable. Generally, the time between symptom onset and diagnosis of MS, followed by early intense disease-modifying therapy, has significantly decreased within recent years (Jakimovski et al., 2022). However, this may not be the case in more rural areas or where data on MS are incomplete or absent (The Multiple Sclerosis International Federation, 2020). Our data may therefore not represent patients with MS in countries with poor access to medical care.

Study 2 was conducted in a sleep laboratory, where monitoring PSG recordings commonly comprise the main task of night shift workers. Further, these night shift workers often have irregular shift schedules, working 1 or 2 night shifts per week, in contrast to the usual 3–5 night shifts worked in other fields. This working situation may not be comparable to other night shift work rotations and tasks, even though many of these occupations, such as flight operators, nurses, or factory workers, include monitoring activities. The relatively low level of interactions with others (night shift workers in the sleep lab generally work alone) in combination with a relatively low level of critical situations where immediate action is required may not reflect the typical requirement of other night shift situations. Therefore, the findings of Study 2 may not be reproducible in

other working occupations and environments during night shift work, which could be the focus of further research.

In Study 3, the strict exclusion criteria regarding medication use and disease activity were necessary to ensure a homogenous sample, generating relatively stable and reliable data. This, however, restricted the generalizability of the findings to all patients with MS who did not meet these criteria. As a proof of principle, this first study on blue-enriched bright light therapy in MS provided initial evidence for the efficacy and feasibility of these light glasses for mitigating MS-related fatigue. Future research could focus on a more tolerant approach regarding non-MS-specific medication as has been applied in past studies (Mateen et al., 2020; Voggenberger et al., 2022).

Despite these limitations, the three studies included in this dissertation were designed and conducted with great care, particularly considering the comfort of all participants. The findings from these studies add to the existing knowledge on MS-related fatigue and light therapy. Further research is required regarding all three studies to produce stronger, more stable, and more reliable results that can be interpreted more generally.

3.6 Future directions

There is still much to discover regarding the development, progression, and treatment of MS, as well as regarding light therapy-based interventions. In a next step, the results of the studies herein should be reproduced using larger sample sizes and more diverse populations. This would strengthen our findings and increase their reliability and generalizability.

Focusing on the initial development of symptoms related to alertness, fatigue, mental health, sleep, and fitness to drive, a follow-up study in the patients included in Study 1 could provide a broader and more longitudinal perspective on the progression of

these aspects within MS over a longer time after diagnosis. Currently, no study has examined fitness to drive in patients with MS with longer disease durations using a traffic test battery that has been validated using real driving. Further, a prospective, longitudinal study following patients with MS at different disease stages and with different disease activity over several years to assess alertness, fatigue, mental health, sleep, and fitness to drive at regular points could provide insights into the prolonged development of these factors, aiding the development of recommendations for clinical practice regarding timepoints after diagnosis when decrements in alertness, fatigue, mental health, sleep, and fitness to drive can be expected.

Regarding light therapy research, further studies focusing on different illumination levels at different application times during the night individually chosen by participants could shed light on the individualized application of light therapy that would suit each night shift worker best. The same approach could be tested including patients with MS with fatigue at different disease stages and with different levels of disease activities and medication backgrounds. Other devices such as Luminette Drive® (Lucimed SA, Wavre, Belgium) could also be tested during the morning drives to work, for example, to test the efficacy and feasibility of reducing fatigue levels while on the road. In addition, further research could include measuring melatonin levels throughout the day and night as well as before and after light exposure, as past studies have suggested a link between MS-related fatigue and a dysregulation of melatonin secretion (Melamud et al., 2012).

3.7 Conclusions

Fatigue remains a highly prevalent, clinically significant, disabling symptom of MS, even in the age of disease-modifying therapies. By including one prospective observational study and two intervention studies in this dissertation, three main aims were addressed: i) to prospectively assess alertness, fatigue, mental health, sleep, and fitness to drive after

de-novo MS diagnosis and 1 year later; ii) to assess the efficacy and feasibility of portable light therapy glasses to reduce sleepiness and fatigue as well as increase alertness and sustained attention in healthy night shift workers, and iii) to evaluate the light therapy glasses' usage directly after awakening to mitigate fatigue in patients with MS.

These studies demonstrated that, in the examined sample of patients with MS diagnosed very early after the first onset of MS symptoms, levels of fatigue, alertness, sleep, and fitness to drive were comparable to those in matched healthy control participants. Further, no progression in these symptoms and functional abilities was observed after 1 year (Aim i). Based on these findings, a follow-up study including the same patients could provide data over a longer period after diagnosis and provide insights into disease progression in patients that were diagnosed and treated with disease-modifying therapy at early disease stages.

Light therapy applied in healthy night shift workers did not show the expected results as defined in Aim ii). There was a reduction in sleepiness following light exposure in both the active and the placebo intervention, but the differences were not statistically significant. Further, fatigue, alertness, and sustained attention were unaffected by light therapy. Importantly, participants reported no negative side effects and good acceptance and feasibility of the glasses. Future research should include a more individualized approach to the usage of light therapy glasses during night shift to achieve Aim ii).

In contrast, Aim iii) was achieved by demonstrating that using blue-enriched bright light therapy glasses directly after awakening in the morning significantly decreased fatigue in patients with MS immediately after exposure and for a prolonged time. Further, fatigue levels were reduced by a clinically significant level after days 6 and 7 of active light intervention, with decreases seen in the few and mainly mild reported side effects over the course of the intervention week. We were, therefore, able to provide evidence for the efficacy and feasibility of blue-enriched light therapy glasses in mitigating MS-

related fatigue after a relatively short intervention period. A longer intervention period might be necessary to evoke effects on quality of life. In summary, this simple approach offered in the form of light does seem promising.

Within their limitations (small sample sizes, study design/settings, generalizability), all three studies contribute insightful data regarding MS progression shortly after diagnosis and the usage of light therapy glasses in two very different applications, adding to the knowledge in these fields and inspiring future research.

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APPENDIX

A Supplementary Materials for Study 1

A1 Detailed description of measurements used throughout the study

A1.1 Screening Questionnaires

- The **Berlin Questionnaire for sleep apnoea** (Netzer et al., 1999) is a self-administered 10-item questionnaire regarding three categories related to sleep apnoea (snoring, daytime sleepiness, obesity and hypertension). The outcomes define a high risk for obstructive sleep apnoea if a patient shows risk factors in at least two of the three categories. The Berlin Questionnaire shows sufficient internal consistency (Cronbach's α varies between 0.68 and 0.98) and test–retest reliability (Cohen's κ varies between 0.74 and 0.98).
- In the present study, the diagnosis of **Restless Legs Syndrome** (RLS) was based on the five essential diagnostic criteria defined by the International RLS Study Group (Allen et al., 2014). In addition, the symptoms of RLS were assessed in person by a somnologist.

A1.2 Questionnaires on general and mental health, quality of life

- The **Nottingham Health Profile** (Hunt et al., 1985) contains 38 questions assessing emotional, social, and physical health problems in six subareas (energy level, pain, emotional reaction, sleep, social isolation, and physical ability) based on the World Health Organization's definition of disability. Questions are answered to with "yes" or "no"; "yes" responses are weighted and added to obtain the subarea sum score ranging from 0–100. The total score is calculated by adding all subarea sum scores and ranges from 0–600, with higher numbers indicating poorer health. The internal consistency (Cronbach's α) of the Nottingham Health Profile ranges between 0.90 and 0.94 and the test–retest reliability ranges from

r=0.75 to 0.88 (Teixeira-Salmela, 2014). In the current study, the German version of the Nottingham Health Profile was used (Kohlmann et al., 1997).

- The **Multicultural Quality of Life Index** (Mezzich et al., 2011) assesses quality of life in 10 dimensions using 10 questions regarding physical well-being, psychological/emotional well-being, self-care and independent functioning, occupational functioning, interpersonal functioning, social emotional support, community and services support, personal fulfilment, spiritual fulfilment, and overall quality of life. Participants rate each domain from 1 = *poor* to 10 = *excellent*. The overall score consists of the added scores from all answered items and ranges from 10–100. The internal consistency (Cronbach's α) ranges from 0.90 to 0.92, test–retest reliability is reported at *r*=0.87 (Mezzich et al., 2011). The German version of the Multicultural Quality of Life Index was used in the current study (Saletu et al., 2003).
- The **Beck Depression Inventory-II** (BDI-II) (Beck, Steer, Ball, et al., 1996) is a 21-item questionnaire assessing the severity of depression symptoms such as sadness, self-harm, and loss of appetite in the two weeks prior to testing on a four-point scale from 0–3. The sum score ranges from 0–63, with values > 8 indicating depression. The BDI-II shows high internal consistency (Cronbach's α of 0.91) (Beck, Steer, Ball, et al., 1996) and good to excellent test–retest reliability (*r*=0.73–0.96) (Wang & Gorenstein, 2013). Participants were administered the German version of the BDI-II in the current study (Hautzinger et al., 2006).
- The **Self-rating Depression Scale** (Zung, 1965) contains 20 statements rated on a four-point scale from 1 = *a little of the time* to 4 = *most of the time* to measure depressive symptoms within seven days prior to testing. The overall score is the sum of all responses and indicates depressive symptoms at values > 50 (Dunstan

& Scott, 2019). The Self-rating Depression Scale shows good internal consistency (Cronbach's α = 0.81) (Tanaka-Matsumi & Kameoka, 1986).

- The 20-item **Self-rating Anxiety Scale** (Zung, 1971) measures signs of anxiety within one week prior to testing on a four-point scale from 1 = *a little of the time* to 4 = *most of the time*. Responses are added to produce an overall score, with values > 35 indicating anxiety (Dunstan & Scott, 2020). The Self-rating Anxiety Scale shows good internal consistency (Cronbach's α = 0.84) (Tanaka-Matsumi & Kameoka, 1986).

A1.3 Questionnaires on daytime sleepiness, fatigue

- The **Epworth Sleepiness Scale** (ESS) (Johns, 1991) is a self-administered questionnaire on subjective daytime sleepiness. The ESS contains eight questions about the probability of falling asleep or dozing off (i.e., subjective sleep propensity) while engaged in different daily activities. A global score is derived from adding the responses (each rated from 0–3; the global score ranges from 0–24). The ESS shows sufficient internal consistency (Cronbach's α=0.88) and test–retest reliability (r=0.82) (Johns, 1992). Participants in the present study were administered the German version of the ESS (Sauter et al., 2007). According to a German validation study, scores higher than 10 categorize a participant as "clinically suspicious", while scores < 12 define a participants' daytime sleepiness as "clinically relevant" (Sauter et al., 2007).
- The **Karolinska Sleepiness Scale** (KSS) (Åkerstedt & Gillberg, 1990) quantifies the current subjective state of sleepiness on a 9-point rating scale ranging from 1 = *extremely alert* to 9 = *very sleepy, great effort to keep awake, fighting sleep*. It was presented as a pen-and-paper versions six times throughout the alertness and fitness-to-drive assessments.

- The **Modified Fatigue Impact Scale** (MFIS) is a modified version of the Fatigue Impact Scale developed by Fisk et al. (Fisk, Ritvo, et al., 1994) that is included in the Multiple Sclerosis Quality of Life Inventory (J. S. Fischer et al., 1999). The MFIS includes 21 items regarding the effects of fatigue on the subscales of physical, cognitive, and psychosocial functioning rated on a 5-point scale from 0 = *never* to 4 = *almost always*. Scores are calculated for each subscale and summed to obtain the overall score (range 0–84) with values > 38 indicating fatigue (Flachenecker et al., 2002). The MFIS shows high internal consistency, with a Cronbach's α of 0.92, and sufficient test-retest-reliability, with an intraclass correlation coefficient of 0.91 (Kos et al., 2005).
- The **Fatigue Severity Scale** (FSS) (Krupp et al., 1988) is a 9-item questionnaire that assesses the severity of fatigue during the week prior to testing on a 7-point scale from 1 = *disagree* to 7 = *agree*. The sum score ranges from 9 to 63, with values > 36 indicating fatigue. The internal consistency of the FSS is high, with a Cronbach's α of 0.94. The German version of the FSS was used in the current study with test–retest reliability of the individual items ranging from r=0.63 to r=0.88 (Reske et al., 2006).

A1.4 Questionnaires on subjective sleep quality

- The **Pittsburgh Sleep Quality Index** (PSQI) (Buysse et al., 1989) is a self-administered questionnaire that assesses sleep quality and disturbances over a 1-month interval. The PSQI contains 19 items from which seven sleep component scores are derived (e.g., subjective sleep quality, sleep latency). A global sleep quality score can be calculated as the sum of the component scores with a minimum of 0 and a maximum of 21. This score can be used to group participants as good (score of 5 or lower) and bad sleepers (score above 5). The PSQI shows sufficient internal consistency with a Cronbach's α of 0.83, a sensitivity of 89.6%,

a specificity of 86.5%, and sufficient test–retest reliability of r=0.88 (Buysse et al., 1989). In the present study, a validated German version of the PSQI was used (Backhaus et al., 2002).

- The **Functional Outcomes of Sleep Questionnaire** (FOSQ) (Weaver et al., 1997) is a 30-item questionnaire that measures the influence of sleepiness on activities of daily living. It includes five subscales of activity level, vigilance, intimacy and sexual relationships, general productivity, and social outcome, for which sum scores are calculated. The overall score ranges from 5 to 20, with higher scores indicating a better functional outcome. The internal consistency of the FOSQ is high with a Cronbach's α of 0.95 (Omachi, 2011), while the test–retest reliability is high with r=0.90 (Weaver et al., 1997).
- The **Regensburg Insomnia Scale** (RIS) (Crönlein et al., 2013) is a 10-item self-administered questionnaire assessing cognitive, emotional, and behavioural aspects of psychophysiological insomnia. Participants respond by rating questions on a scale from 0 = *always* to 4 = *never*, which are added into a sum score of 0–40, with higher scores indicating higher levels of insomnia. Sum scores > 12 indicate symptoms of psychophysiological insomnia. The internal consistency of the RIS is good, with a Cronbach's α of 0.89.
- The **Self-Assessment-Scale for Sleep and Awakening Quality** (SSA) (Saletu et al., 1987) is a questionnaire administered in the morning to measure sleep quality, awakening quality, and somatic complaints of the prior night. In addition, an overall score describing sleep and awakening quality can be derived. The SSA contains 20 items, and the responses are summed to produce an overall score with a minimum of 20 and a maximum of 80. Scores closer to 20 indicate a high quality of sleeping and awakening, whereas scores closer to 80 indicate a low quality.

The SSA was completed in the mornings after nights of polysomnography recording.

A1.5 Objective sleep quality: cardiorespiratory polysomnography (PSG)

Polysomnography (PSG) is the physiological "gold standard" to record sleep parameters to evaluate both the quality and quantity of sleep. PSG recordings depict measures such as total sleep time, the percentage of sleep period time (SPT) spent in different sleep stages, oxygen levels, and movement. PSG measurements were recorded in the sleep laboratory at the Centrer for Sleep Medicine, University of Regensburg, Germany, according to the standards of the American Academy of Sleep Medicine (American Academy of Sleep Medicine, 2012). For the recordings, a digital PSG system (Nihon Kohden EEG 1200; Nihon Kohden, Tokyo, Japan) was used with the recording software Polysmith (v9.0; Nihon Kohden). The electrodes were placed as recommended by the American Academy of Sleep Medicine (American Academy of Sleep Medicine, 2012). PSG recordings included various physiological measurements, which are listed in Table A1. Sleep stage scoring was mostly based on electrooculography, electromyography, and electroencephalography. To evaluate objective sleep quality, standardized American Academy of Sleep Medicine outcome parameters were employed (e.g., total sleep time, sleep efficiency, arousal index, sleep onset latency, percentage of sleep period time spent in sleep stages N1–N3, and rapid eye movement sleep). PSG recordings were not monitored using video. After applying all electrodes and initializing the system, recording began after an impedance measurement and a biotest.

In the present study, all people with MS (pwMS) were monitored using PSG for two nights at baseline and two nights at follow-up. Participants in the control group underwent two nights of PSG at baseline. Of the 50 recorded baseline nights of pwMS, 49 were used for analyses, as one was excluded due to technical errors. Subsequently, the same night was excluded from follow-up analyses in pwMS as well as from baseline

analyses comparing pwMS and controls. All PSG recordings from control participants were usable. PSG recordings were analysed and categorized by a certified somnologist (RFJP). Included in the statistical analyses were the PSG measures total sleep time (TST [min]); sleep efficiency (%); arousal index (/h TST); wake after sleep onset (min); sleep latency to sleep stage N1; sleep stage distribution in percentage of sleep period time (SPT) spent awake (% awake) in sleep stages N1, N2, N3, and rapid eye movement sleep; breathing and limb movements, as measured by the apnoea-hypopnea index (/h TST), Apnoea Arousal Index (/h TST), Oxygen Desaturation Index (/h TST), mean saturation (%), minimum saturation (%), Periodic Limb Movement in Sleep (PLMS) index (/h TST), and PLMS arousal index (/h TST).

Table A1 Measurements of the first diagnostic polysomnography (PSG), along with their measures, channels, and electrodes

Measurement	***Measures***	***Number of channels***	***Electrodes***	***Reference electrode***
Electrooculography (EOG)	Horizontal and vertical eye movement	2	Pg1, Pg2	Fz
Electromyography (EMG)	Muscle tone at the chin	2	T1, T2, Pz	T2, Pz
	Leg movement	2	X1, X2	Gnd
Electroencephalography (EEG)	Brain activity	6	F3, F4, C3, C4, O1, O2	A1, A2
Nasal flow thermistor	Nasal air flow	1	X5	Gnd
Abdominal belt	Abdominal respiration	1	X7	Gnd
Snore microphone	Snoring	1	X4	Gnd
Oxygen clip	Pulse oximetry	1	Gnd	SpO2
Electrocardiography (ECG)	Heart rate, blood pressure	3	T3, T4	CZ

Note. Electrode names are according to the American Academy of Sleep Medicine (American Academy of Sleep Medicine, 2012)

A.1.6 Objective sleepiness, alertness, and sustained attention

- During the **Pupillographic Sleepiness Test** (PST; AMTech Pupilknowlogy GmbH, Dossenheim, Germany), participants sat in a darkened room with their head placed on a headrest and looked into a camera for 11 minutes. The infrared video camera recorded the participants eyes with a resolution of 0.05 mm at a sampling frequency of 25 Hz. A sleepy person shows more changes in pupil diameter, leading to a higher Pupillographic Unrest Index (PUI), showing fatigue waves in the PST output. The test–retest reliability of the PST is sufficient, with r=0.76 (Lüdtke et al., 2000).
- The **PC Psychomotor Vigilance Task (PVT)** (Khitrov et al., 2014) is a reaction time (RT) test that measures several reaction parameters to a series of visual stimuli presented on a computer screen. Although the task lasts only 10 minutes, it assesses alertness and sustained attention using a high stimulus-rate paradigm that is very sensitive to sleep loss and states of sleepiness (Basner & Dinges, 2011). The PVT stimulus is a red 4-digit number on a black screen counting upwards from zero in ms. The inter-stimulus interval had a random duration of 2–10 s. Participants were instructed to react as quickly as possible with a left mouse click (Logitech G 402-Hyperion-fury Gaming Mouse; Logitech International SA, Lausanne, Switzerland; sampling rate 1000 Hz) as soon as the digits appeared. Participants immediately received visual feedback about their RT after each reaction. Output measures were mean RT, lapses, and fastest 10% of RTs. Participants show stable performance across repeated PVT administrations, indicating no systematic repetition effects (Basner et al., 2017).
- The **Mackworth Clock Test** (MCT) measures sustained attention under monotonous conditions. On a computer screen, a dot jumps between adjacent positions along a circle in a clockwise direction. Participants are instructed to react with a button press when the dot skips one position when jumping along the circle.

We used the **VIGIL S1** (Schuhfried GmbH, Mödling, Austria), a computerized version of the MCT. Over the 26-min test duration, 100 skips occured. The output measures were mean RT (in ms), correct reactions, and false starts.

A1.7 Psychological traffic test battery – Vienna Test System TRAFFIC DRIVEPLS

The DRIVEPLS fitness-to-drive assessment of the Vienna Test System TRAFFIC (Schuhfried GmbH, Mödling, Austria) is an international standard tool used in traffic psychological testing. It consists of several subtests that provide a global assessment of fitness to drive.

- The **Adaptive Matrices Test** measures inductive reasoning. In this test, a computer screen shows a 3x3 matrix of squares with figures that follow a specific order. One square is left empty, and the participant is instructed to choose one of the eight squares below the matrix that follows the same rule as the matrix above. The test duration is 24 minutes and the test shows sufficient internal consistency (Cronbach's $\alpha = 0.83$)
- The **Determination Test** assesses reactive stress tolerance by providing five differently coloured visual stimuli, two different acoustic stimuli, and two signals for the foot pedals to which participants have to respond adequately and as quickly as possible. The test duration is 6 minutes and the test shows high internal consistency (Cronbach's $\alpha = 0.95$).
- The **Reaction Test** includes a simple choice reaction- time task with visual and acoustic stimuli. It measures reaction time and motor time throughout the 6-min test duration with sufficient internal consistency (Cronbach's $\alpha = 0.93$ for reaction time and Cronbach's $\alpha = 0.96$ for motor time).
- The **Cognitrone** measures concentration and selective attention by asking participants to compare figures in terms of congruency with a test duration of 5 minutes. It shows sufficient internal consistency with Cronbach's $\alpha = 0.95$.

- The **Adaptive Tachistoscopic Traffic Perception Task** measures the ability to obtain an overview in complex traffic situations. It quickly shows pictures of everyday traffic situations, which participants have to summarize after each picture. The test evaluates visual orientation, observational abilities, and perception speed. It has a duration of 14 min and shows sufficient internal consistency with Cronbach's $\alpha = 0.73$.
- The **Peripheral Perception** test provides divided attention conditions to measure peripheral visual information processing and tracking deviations. It includes peripheral visual stimuli to which participants respond by pressing the foot pedals while fixating on a moving ball on a computer screen. The test duration is 15 min; the peripheral perception test shows high internal consistency with Cronbach's $\alpha = 0.96$ for visual field and Cronbach's $\alpha = 0.98$ for tracking deviation.
- The **Visual Pursuit Test** measures visual orientation ability in a complex environment. In this test, random and disorderly lines are presented on a computer screen, and participants are asked to identify the end of a specific line as quickly as possible.
- The **Inventory of driving-related Personality Traits** assesses personality traits that are relevant for safe driving with subscales of emotional stability, sense of responsibility, self-control, and adventurousness and need for excitement. Participants evaluate how well statements about traffic, free time, and work apply to themselves. The test duration is 10 minutes.
- **Vienna Risk-Taking Test Traffic** assesses participants' readiness to take risks in everyday traffic situations. Participants are shown video clips of potentially dangerous traffic situations and then choose the moment in which certain traffic manoeuvres would be too dangerous to perform. The test duration is 18 minutes.

Results of the Visual Pursuit Test, the Inventory of driving-related Personality Traits, and the Vienna Risk-Taking Test Traffic are not taken into account for the overall judgement of fitness to drive provided by the DRIVEPLS assessment.

A2: Inclusion and exclusion criteria

A2.1 Inclusion criteria for control participants

- Aged 18–65 years
- Regular bedtimes (going to bed between 9:00 p.m. and 12:00 a.m.)
- Sufficient cognitive and verbal ability to understand the study purposes, participant information documents, and all questionnaires and tests
- Compliance and willingness to adhere to the study protocol
- Provided written informed consent to participate in the study

A2.2 Exclusion criteria for control participants

- Sleep disorders such as RLS, narcolepsy, or obstructive sleep apnoea diagnosed according to the International Classification of Sleep Disorders 3rd Edition criteria (American Academy of Sleep Medicine, 2014)
- Excessive smoking (more than 15 cigarettes/d)
- Excessive caffeine consumption (more than 5 servings of caffeinated beverages/d)
- Use of psychoactive substances within the prior week that could influence sleep and wakefulness (e.g., amphetamines, methylxanthines, sedatives, hypnotics, antidepressants, antihistamines, neuroleptics, beta blockers)
- History of or current substance use or substance use disorder according to the Diagnostic and Statistical Manual of Mental Disorders, 4th Edition criteria (alcohol, hypnotics, or other substances except nicotine)
- Any comorbid internal, neurologic, or psychiatric diseases or symptoms that could, assessed by the examiner, significantly influence sleep or wakefulness
- Severe disorders of the eyes (e.g., iridocyclitis)
- Chronic excessive daytime sleepiness (ESS score > 10)
- Impaired sleep quality (PSQI score > 5, except in older participants)

A2.3 Inclusion criteria for people with Multiple Sclerosis

- Women and men aged 18–65 years with the ability to provide consent

- Patients with de novo multiple sclerosis
- Compliance and willingness to adhere to the study protocol
- Provided written informed consent to participate in the study

A2.4 Exclusion criteria for people with Multiple Sclerosis

- Pregnant or breastfeeding participants
- History or current use of substances or substance use disorder according to DSM-IV criteria (alcohol, hypnotics, or other substances except nicotine)
- Severe comorbid neurologic or internal disorders that could confound the study results (e.g., Cushing's disease, diabetes)
- Use of psychoactive substances within the prior week that could influence sleep and wakefulness (e.g., amphetamine, methylxanthine, sedatives, hypnotics, antidepressants, antihistamines, neuroleptics, beta-blocker)
- Severe disorders of the eyes (e.g., iridocyclitis)
- Excessive smoking (more than 15 cigarettes/d)
- Excessive caffeine consumption (more than 5 servings of caffeinated beverages/d)
- Legal guardianship or inability to consent

A3. Additional patient information

A3.1 List of immunosuppressive medications that pwMS received throughout study inclusion

Table A2 Immunosuppressive medications taken by pwMS throughout study inclusion

Medication	***baseline (n)***	***between baseline and follow-up (n)***	***follow-up (n)***
Alemtuzumab (Lemtrada®) 12mg/day for 5 days	1	1	1
Dimethyl fumarate (Tecfidera®) 120 mg oral two times per day	0	0	1
Dimethyl fumarate (Tecfidera®) 240 mg oral two times per day	5	3	3
Fingolimod (Gilenya®) 0,5 mg oral once per day	0	0	1
Glatiramer acetate (Copaxone®) 40mg subcutaneous three times per week.	2	3	5
Interferon-beta-1a (Avonex®) 30 mg intramuscular once per week	4	3	3
Interferon beta-1 a (Plegridy®) 125µg subcutaneous every second week	5	3	3
Interferon beta-1b (Extavia®) 250µg subcutaneous every second day	1	1	1
Natalizumab (Tysabri®) 300mg intravenous every month	1	2	2
Teriflunomide (Aubagio®) 14mg oral once per day	1	2	2
Cortisone 1g (for acute therapy only, 3-5 days)	4	0	0
no relapse prophylaxis	1	2	3
Medication switch			
Interferon-beta-1a (Avonex®) 30mg intramuscular once per week, switch to Dimethylfumarate (Tecfidera®) 240mg oral twice per day.		1	
Interferon-beta-1a (Avonex®) 30mg intramuscular once per week; switch to Glatiramer acetate (Copaxone®) 40mg subcutaneous three times per week.		1	
Interferon beta 1b (Extavia®) 250µg subcutaneous every second day; switch to Interferon beta 1a (Pledridy®) 125µg subcutaneous every second week.		1	
Dimethylfumarate (Tecfidera R) 240 mg oral two times per day; switch to Interferon beta 1 a (Plegridy R) 125µg subcutaneous every second week; switch to Glatiramer acetate (Copaxone) 40mg subcutaneous three times per week.		1	
Glatirameracetat (Copaxone®) 40mg subcutaneous three times per week; switch to Dimethylfumarate (Tecfidera®) 240mg oral twice per day.		1	

Note. pwMS: people with Multiple Sclerosis; n=number.

A3.2 List of drop-out and excluded pwMS

Table A3. Drop-out and excluded pwMS throughout the study

#	Sex	Age	Diagnosis	EDSS	Medication	Time of study termination	Reason for study termination
01	Male	42	RRMS	2	None, planned (steroids, plasmapheresis)	after screening	personal reasons
02	Female	40	RRMS	2.5	Dimethylfumarate (Tecfidera®) 240mg oral, two times per day	after screening	exclusion; MS onset not shortly before diagnosis
03	Female	31	RRMS	2.5	Glatierameracetate (Copaxone®) 20mg subcutaneous, once per day	after baseline	personal reasons
04	Female	45	CIS	0	None, planned	after screening	personal reasons
05	Female	33	RRMS	2	None, planned	at baseline	personal reasons
06	Female	23	RRMS	0	Dimethylfumarate (Tecfidera®) 240mg oral, two times per day	at baseline	personal reasons
07	Female	28	RRMS	3	None, planned	at baseline	personal reasons
08	Male	36	RRMS	3	None, planned	at baseline	personal reasons
09	Female	29	RRMS	1	None, planned	after screening	personal reasons
10	Male	28	RRMS	0	Interferon-beta-1a (Avonex®) 30 mg intramuscular, once per week	after baseline	personal reasons
11	Female	48	RRMS	1	None, planned	after screening	personal reasons
12	Female	41	Susac's syndrome		None	after screening	Alternative disease, exclusion
13	Male	31	RRMS	1.5	None	after screening	personal reasons
14	Female	22	RRMS	2	Interferon-beta-1b (Betaferon®) 250µg subcutaneous. every second day	after screening	personal reasons
15	Female	27	RRMS	1.5	None, planned	at baseline	personal reasons
16	Male	35	RRMS	0	None, planned	after screening	personal reasons
17	Male	18	RRMS	1.0	Interferon beta 1 a (Plegridy®) 125µg subcutaneous, every second week	after baseline	personal reasons

Table A3, continued Drop-out and excluded pwMS throughout the study

#	Sex	Age	Diagnosis	EDSS	Medication	Time of study termination	Reason for study termination
18	Female	32	RRMS	0	Fingolimod (Gilenya®) 0,5mg oral, once per day	at baseline	personal reasons

Note. pwMS, people with Multiple Sclerosis; EDSS, expanded disability status scale; RRMS, relapsing-remitting multiple sclerosis; CIS, clinically isolated syndrome. EDSS scores can range from 0 = “normal neurological exam, no disability in any functional system” in steps of 0.5 to 10 = “death due to MS”; Patient scores ranged from 0 to 2 = “minimal disability in one functional system

A4 Additional results for healthy control participants

A4.1 Alertness and sustained attention, acute daytime sleepiness levels

Table A4 shows healthy control participants' additional results at follow-up, the statistical within-subject comparison of controls at baseline and follow-up, and the statistical between-subjects comparison of controls and pwMS at follow-up.

Measuring acute sleepiness on a physiological level using pupillography, PUI values were significantly higher in controls (baseline: 5.6±2.1; follow-up: 5.9±2.6) compared with those in pwMS (follow-up: 3.4±1.5; p=.003).

Table A4. Assessments of objective daytime sleepiness, alertness, and sustained attention, additional results for healthy controls.

	Descriptive statistics		***Statistical comparisons***			
	Controls		**Controls**		**Follow-up**	
	baseline	baseline	baseline vs. follow-up		pwMS vs. controls	
Measurements	*M (SD)*	*M (SD)*	*z/t*	*p*	*z/t*	*p*
Daytime sleepiness						
Pupillographic Sleepiness Test (PST)						
PUI	5.6 (2.1)	5.6 (2.1)	z = -0.061	.951	z = -2.969	**.003****
Alertness and sustained attention						
Psychomotor Vigilance Task (PVT)						
Mean RT (ms)	263.9 (34.5)	263.9 (34.5)	t(48) = -0.814	.419	t(48) = -0.814	.419
Lapses	1.2 (2.0)	1.2 (2.0)	z = -1.364	.173	z = -0.072	.942
FRT (ms)	192.8 (15.9)	192.8 (15.9)	t(48) = -1.640	.101	t(48) = -1.930	.060
Mackworth Clock Test (MCT)						
Mean RT (ms)	501.4 (86.1)	501.4 (86.1)	t(48) = 0.378	.707	t(48) = 0.378	.707
Correct	95.8 (6.5)	95.8 (6.5)	z = -.0.726	.468	z = -0.131	.896
False starts	1.8 (1.7)	1.8 (1.7)	z = -0.768	.442	z = -0.318	.751

Note. pwMS, people with multiple sclerosis; *M*, mean; *SD*, standard deviation; PUI, pupillographic unrest index; RT: reaction time. FRT: 10% fastest reaction times

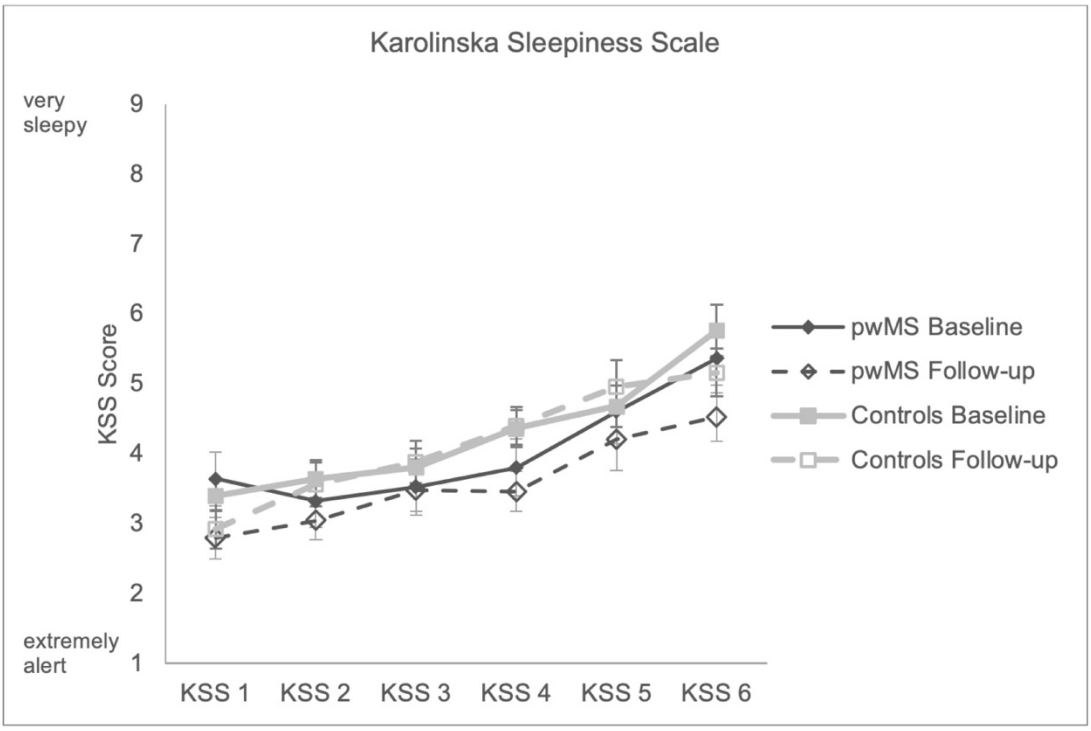
Descriptive statistics within pwMS and controls at baseline and follow-up, respectively.

Statistical comparisons between pwMS at baseline and follow-up; between pwMS and controls at baseline; and between pwMS and controls at follow-up.

Statistical tests used for the within-participants comparisons were t-test (t[df]) for paired samples for normally distributed parameters, and Wilcoxon signed-rank test (z) for nonparametric variables. Between-participants comparisons were calculated using t-test for independent samples (t[df]) for normally distributed parameters, and Mann–Whitney U test (z) for nonparametric variables. * *p*-Values adjusted using the Bonferroni correction with a significance level of $\alpha < .014$.

At follow-up between the MCT and PST tests (KSS 4), KSS scores were significantly higher in controls (4.4±1.4) than in pwMS (3.5±1.4; p=.015; see Figure A1).

Figure A1. Karolinska Sleepiness Scale scores throughout the assessment.



Note. Karolinska Sleepiness Scale scores of people with MS and controls throughout the fitness-to-drive assessment and alertness and sustained attention tests. Test times: KSS 1, before the fitness-to-drive assessment; KSS 2, during the fitness to drive assessment; KSS 3, between the fitness-to-drive assessment and the psychomotor vigilance task (PVT); KSS 4, after the PVT and before the pupillographic sleepiness test (PST); KSS 5, between the PVT and the Mackworth Clock Test (MCT); KSS 6, after the MCT; pwMS, people with multiple sclerosis. Error bars indicate the standard error of the mean.

A4.2 Fitness to drive

Table A5 shows additional results of healthy controls' fitness-to-drive assessment, comparing baseline with follow-up as well as comparing follow-up data between pwMS and controls. Compared to baseline within control subjects, performance at follow-up was better (follow-up: 275.5±22.2; baseline: 257.1±33.0; p<0.001) and faster (follow-up: 724.3±45.4 ms; baseline: 762.7±58.77 ms; p<0.001; Determination Test). At follow-up, two control participants (9%) showed insufficient driving abilities.

Table A5. Fitness-to-drive assessment results in healthy control participants and comparisons with pwMS

		Descriptive statistics		***Statistical comparisons***			
		Controls		**Controls**		**follow-up**	
		baseline	follow-up	**baseline vs. follow-up**		**pwMS vs. Controls**	
Tests	**Measures**	*M (SD)*	*M (SD)*	*z/t*	*p*	*z/t*	*p*
AMT	IQ	99.6 (21.3)	102.6 (21.7)	t(20) = -1.217	.238	z = -1.257	.209
DT	correct	257.1 (33.0)	275.5 (22.2)	t(20) = -4788	**.001***	t(32.52) = -1.527	.136
	RT (ms)	762.7 (58.7)	724.3 (45.4)	z =-3.743	**.001***	t(28.87) = 0.826	.416
RTest	RT (ms)	458.0 (107.3)	449.5 (69.8)	t(21) = 0.563	.579	t(42) = 0.000	1.000
	motor time (ms)	167.0 (44.2)	143.0 (38.7)	z = -2.387	.017	z = -2.125	.034
COG	RT (s)	2.4 (0.5)	2.3 (0.4)	t (20) = 1.505	.148	t(42) = 1.960	.057
ATAVT	overview	11.7 (2.7)	12.8 (4.4)	z = -0.950	.342	z = -1.475	.140
PP	visual field	167.0 (13.8)	168.2 (12.1)	z = -1.104	.269	z = -0.669	.503
	tracking deviation	9.3 (1.9)	9.7 (2.5)	t(21) = -1.351	.191	z = -0.317	.751
LVT	Score	14.2 (4.4)	14.6 (3.5)	z = 0.000	1.000	z = -0.958	.338
	Time (s)	65.4 (9.5)	64.8 (11.3)	z = -0.731	.465	z = -0.975	.329
WRBTV	Score	7.7 (1.4)	7.6 (1.5)	z = -0.162	.871	z = -1.021	.307
IVPE	Mental stability	2.4 (2.1)	2.6 (2.5)	z = -0.714	.457	z = -0.598	.550
	Responsibility	5.3 (2.7)	5.3 (2.8)	z = -0.361	.718	z = -0.426	.670
	Self-control	3.9 (1.5)	4.2 (1.7)	z = -1.012	.311	z = -0.576	.565
	Adventure	6.0 (2.0)	5.8 (1.9)	z = -0.136	.892	z = -1.467	.142
	Openness	2.5 (2.1)	2.2 (2.9)	z = -1.061	.289	z = -0.921	.357

Table A5, continued. Fitness-to-drive assessment results in healthy control participants and comparisons with pwMS

	Descriptive statistics	
	Controls	
	baseline	follow-up
Overall judgement of fitness to drive n [%]		
1. Inadequate	0 [0]	0 [0]
2. Non-compensable	2 [8]	1 [4]
3. Limited compensability	1 [4]	1 [4]
4. Adequate compensability	6 [24]	2 [8]
5. Adequate ability	15 [60]	17 [68]
Adequate overall (categories 4 and 5)	21 [84]	19 [76]
Unknown	1 [4]	4 [16]

Note pwMS, people with multiple sclerosis; *M*, mean; *SD*, standard deviation; AMT, Adaptive Matrices Test; DT, Determination Test; RT, reaction time; RTest, Reaction Test; COG, Cognitrone; ATAVT, Adaptive Tachistoscopic Traffic Perception Test; PP, Peripheral Perception; LVT, Visual Pursuit Test; WRBTV, Vienna Risk Taking Test Traffic; IVPE, Inventory of Driving-related Personality Traits.

Overall judgement of fitness to drive: 1. Inadequate, inadequate driving-specific ability; 2. Non-compensable, non-compensable performance deficits; 3. Limited compensability, performance deficits that can to a limited extend be compensated; 4. Adequate compensability, adequate driving-specific ability (performance deficits can be compensated); 5. Adequate ability, adequate driving-specific ability; Categories 4 and 5 indicate overall adequate driving-specific ability, categories 1 through 3 indicate inadequate driving-specific ability. ° In some cases, technical difficulties in some tests led to inconclusive assessment sessions of fitness to drive; The test system was then unable to give an overall judgement of fitness to drive

Statistical comparisons between between pwMS and controls at follow-up; and between controls at baseline and follow-up.

Group sizes were n = 22 for control baseline - follow-up comparisons and n = 22 for pwMS - controls follow-up comparisons.

Statistical tests used for the within-participants comparisons were t-test (t[df]) for paired samples for normally distributed parameters, and Wilcoxon signed-rank test (z) for nonparametric variables. Between-participants comparisons were calculated using t-test for independent samples (t[df]) for normally distributed parameters, and Mann–Whitney U test (z) for nonparametric variables; * *p*-Values adjusted using the Bonferroni correction with a significance level of $\alpha < .014$..

A4.3 Mental health, quality of life, daytime sleepiness, fatigue, and general sleep quality

Table A6 shows healthy controls' additional results regarding psychological symptoms. No significant differences were obtained, neither comparing baseline and follow-up within controls, nor comparing follow-up data of controls and pwMS.

Table A6. Outcomes and statistical comparisons of psychological questionnaires for healthy controls, with number (%) of participants showing critical values.

	Descriptive statistics				***Statistical comparisons***			
	Controls				**Controls**		**follow-up**	
	baseline		follow-up		baseline vs. follow-up		pwMS vs. controls	
	M (SD)	n (%) critical	*M (SD)*	n (%) critical	*z (WSRT)*	*p*	*z (MWU)*	*p*
Mental health, quality of life								
Nottingham Health Profile Score	29.0 (39.1)	NA	25.3 (44.7)	NA	-0.457	.647	-0.249	.804
Multicultural Quality of Life Index	8.6 (1.1)	NA	8.4 (1.1)	NA	-1.077	.281	-0.962	.336
Beck Depression Inventory II	4.4 (4.1)	6 (24)	5.0 (6.2)	5 (20)	-0.245	.806	-0.206	.837
Self-rating Depression Scale	29.2 (7.2)	2 (8)	29.3 (7.8)	2 (8)	-0.213	.831	-0.496	.620
Self-rating Anxiety Scale	29.0 (5.5)	3 (12)	28.8 (6.6)	2 (8)	-0.981	.326	-0.370	.712
Daytime sleepiness, fatigue, sleep quality								
Epworth Sleepiness Scale	7.6 (3.3)	4 (16)	7.0 (2.9)	2 (8)	-1.189	.234	-1.048	.295
Modified Fatigue Impact Scale	9.7 (10.2)	0 (0)	10.1 (11.4)	1 (4)	-0.163	.870	-0.272	.785
Fatigue Severity Scale	2.7 (1.5)	7 (28)	2.6 (1.3)	4 (16)	-0.114	.909	-0.992	.321
Pittsburgh Sleep Quality Inventory	3.7 (2.3)	4 (16)	4.0 (2.0)	7 (28)	-0.476	.634	-0.433	.665
Functional Outcomes of Sleep Questionnaire	18.5 (1.9)	NA	18.6 (1.8)	NA	-1.354	.176	-0.214	.831
Regensburg Insomnia Scale	8.3 (4.4)	4 (16)	7.5 (3.2)	2 (8)	-0.598	.550	-1.153	.249

Note. pwMS, people with MS; M, mean; SD, standard deviation; n, number; WSRT, Wilcoxon signed-rank test; MWU, Mann–Whitney U test.

n (%) critical refers to the number and percentage of participants within each group at each test time with questionnaire results above clinically suspicious levels; cut-offs for critical values: BDI-II, >8; SDS, >40; SAS, > 35; MFIS, > 38; FSS > 4; ESS >10; RIS > 12; PSQI > 5.

Wilcoxon signed-rank test (WSRT) was used for within-participants comparisons, whereas Mann–Whitney U test (MWU) was used for between-participants.

B Supplementary Material for Study 2

B1 Detailed description of measurements used throughout the study

B1.1 Screening Questionnaires

Sleep Disorders

- The **Berlin questionnaire for sleep apnoea** (Netzer et al., 1999) is a self-administered 10-item questionnaire regarding three categories related to sleep apnoea (snoring, daytime sleepiness, and obesity or hypertension). The outcomes define a high risk for obstructive sleep apnoea if a patient shows risk factors in at least two of the three categories. The Berlin questionnaire shows sufficient internal consistency (Cronbach's α varies between .68 and .98) and test–retest reliability (Cohen's κ varies between .74 and .98).
- In the present study, the diagnosis of **restless legs syndrome** (RLS) was based on the five essential diagnostic criteria defined by the International RLS Study Group (Allen et al., 2014).
- The **Regensburg Insomnia Scale** (RIS) (Crönlein et al., 2013) is a 10-item self-administered questionnaire assessing cognitive, emotional, and behavioural aspects of psychophysiological insomnia. Participants respond by rating questions on a scale from 0 (*always*) to 4 (*never*), which are summated for a score of 0–40, with higher scores indicating higher levels of insomnia. Total scores > 12 indicate symptoms of psychophysiological insomnia. The internal consistency of the RIS is good, with a Cronbach's α of .89.

Daytime Sleepiness

- The **Epworth Sleepiness Scale** (ESS) (Johns, 1991) is a self-administered questionnaire on subjective daytime sleepiness. The ESS contains eight questions about the probability of falling asleep or dozing off (i.e., subjective sleep

propensity) while engaged in different daily activities. A global score is derived from adding the responses (each rated from 0–3; the global score ranges from 0–24). The ESS shows sufficient internal consistency (Cronbach's α=.88) and test–retest reliability (r=.82) (Johns, 1992). Participants in the present study were administered the German version of the ESS (Sauter et al., 2007). According to a German validation study, scores higher than 10 categorize a participant's daytime sleepiness as 'clinically suspicious', while scores < 12 define it as 'clinically relevant' (Sauter et al., 2007).

Fatigue

- The **Fatigue Severity Scale** (FSS) (Krupp et al., 1988) is a nine-item questionnaire that assesses the severity of fatigue during the week prior to testing on a 7-point scale from 1 (*disagree*) to 7 (*agree*). The total score ranges from 9 to 63, with values > 36 indicating fatigue. The internal consistency of the FSS is high, with a Cronbach's α of .94. The German version of the FSS was used in the current study with test–retest reliability of the individual items ranging from *r*=.63 to *r*=.88 (Reske et al., 2006).
- The **Modified Fatigue Impact Scale** (MFIS) is a modified version of the Fatigue Impact Scale developed by Fisk et al. (1994) that is included in the Multiple Sclerosis Quality of Life Inventory (J. S. Fischer et al., 1999). The MFIS includes 21 items regarding the effects of fatigue on the subscales of physical, cognitive, and psychosocial functioning rated on a 5-point scale from 0 (*never*) to 4 (*almost always*). Scores are calculated for each subscale and summated to obtain the overall score (range 0–84) with values > 38 indicating fatigue (Flachenecker et al., 2002). The MFIS shows high internal consistency, with a Cronbach's α of .92,

and sufficient test–retest reliability, with an intraclass correlation coefficient of .91 (Kos et al., 2005).

Sleep Quality

- The **Pittsburgh Sleep Quality Index** (PSQI) (Buysse et al., 1989) is a self-administered questionnaire that assesses sleep quality and disturbances over a 1-month period. The PSQI contains 19 items from which seven sleep component scores are derived (e.g., subjective sleep quality, sleep latency). A global sleep quality score can be calculated as the sum of the component scores with a minimum of 0 and a maximum of 21. This score can be used to group participants as good (score of 5 or lower) and bad sleepers (score above 5). The PSQI shows sufficient internal consistency with a Cronbach's α of .83, a sensitivity of 89.6%, a specificity of 86.5%, and sufficient test–retest reliability of r=.88 (Buysse et al., 1989). In the present study, a validated German version of the PSQI was used (Backhaus et al., 2002).
- The **Functional Outcomes of Sleep Questionnaire** (FOSQ) (Weaver et al., 1997) is a 30-item questionnaire that measures the influence of sleepiness on activities of daily living. It includes five subscales of activity level, vigilance, intimacy and sexual relationships, general productivity, and social outcome, for which sum scores are calculated. The overall score ranges from 5 to 20, with higher scores indicating a better functional outcome. The internal consistency of the FOSQ is high with a Cronbach's α of .95 (Omachi, 2011), and the test–retest reliability is also high with r=.90 (Weaver et al., 1997).

Chronotype

- The **Morningness–Eveningness Questionnaire (MEQ)** subjectively assesses a person's chronobiological type. Responses to its 19 questions regarding

performance, sleep behaviour, and well-being within a 24-hour time frame are summated to provide a total score with a maximum of 86. This score indicates one of five chronotypes: definite evening (14–30), moderate evening (31–41), neutral (42–58), moderate morning (59–69), and definite morning type (70–86). In the present study, the German version of the MEQ, called the D-MEQ, was used, which shows high internal consistency with Cronbach's α = .82 (Griefahn et al., 2001).

Mental health, quality of life

- The **Beck Depression Inventory-II** (BDI-II) (Beck, Steer, Ball, et al., 1996) is a 21-item questionnaire assessing the severity of depression symptoms such as sadness, self-harm, and loss of appetite in the two weeks prior to testing on a four-point scale from 0–3. The total score ranges from 0–63, with values > 8 indicating depression. The BDI-II shows high internal consistency (Cronbach's α of 0.91) (Beck, Steer, Ball, et al., 1996) and good to excellent test–retest reliability (*r*=.73–.96) (Wang & Gorenstein, 2013). Participants were administered the German version of the BDI-II in the current study (Hautzinger et al., 2006).
- The **Multicultural Quality of Life Index** (Mezzich et al., 2011) assesses quality of life in 10 dimensions using 10 questions regarding physical well-being, psychological/emotional well-being, self-care and independent functioning, occupational functioning, interpersonal functioning, social emotional support, community and services support, personal fulfilment, spiritual fulfilment, and overall quality of life. Participants rate each domain from 1 (*poor*) to 10 (*excellent*). The total score consists of the summated scores from all answered items and ranges from 10 to 100. The internal consistency (Cronbach's α) ranges from .90 to .92, its test–retest reliability was reported at *r*=.87 (Mezzich et al.,

2011). The German version of the Multicultural Quality of Life Index was used in the current study (Saletu et al., 2003).

B1.2 Baseline and test night questionnaires

Sleepiness

The **Karolinska Sleepiness Scale** (KSS) (Åkerstedt & Gillberg, 1990) quantifies the current subjective state of sleepiness on a 9-point rating scale ranging from 1 (*extremely alert*) to 9 (*very sleepy, great effort to keep awake, fighting sleep*). It was presented hourly as a pen-and-paper version 13 times throughout the test nights.

Fatigue

The **Daily Fatigue Impact Scale** (D-FIS) (Fisk & Doble, 2002) is an eight-item questionnaire based on the Fatigue Impact Scale (Fisk, Ritvo, et al., 1994). Respondents rate the effects of fatigue on daily life on a five-point Likert scale from 0 (*no problem*) to 4 (*extreme problem*). The sum score ranges from 0 to 32, with higher scores indicating stronger effects of fatigue. For the current study, a non-validated German version of the D-FIS was created by the authors by means of forward-and-back translation.

Comfort ratings

Comfort ratings were used to assess and compare participants' acceptance of the interventions. Beneficial and visual side effects of the light intervention were evaluated on a five-point scale (1 [fully disagree]; 2 [rather disagree]; 3 [partly agree]; 4 [rather agree]; 5 [fully agree]). The beneficial effects questions included the items 'The light glasses increased my fitness', 'The light glasses increased my well-being', 'The light glasses facilitated wakefulness', 'The light glasses had a positive effect on the morning', and 'The light glasses positively influenced my

concentration'. The side effects questionnaire comprised six items: 'The light glasses irritated me', 'The light glasses disturbed me', 'The light glasses irritated my eyes', 'The light glasses negatively affected my view', 'The light glasses disturbed my work', and 'The light glasses generated disturbing reflections in the computer screen'. We used a seven-point semantic differential ranging from 1 (*very…*) via 4 (*neither nor*) to 7 (*very…*) with the following items: 'pleasant – unpleasant', 'fitness increasing - fitness decreasing', 'somniferous – activating', 'not disturbing – disturbing', 'too short – too long', 'in the foreground – in the background', and 'weak – strong'. Participants stated whether they would recommend the light glasses to other night shift workers on a scale from 1 (*not at all*) to 6 (*absolutely*) and gave the light glasses school grades from 1 (*very good*) to 6 (*insufficient*).

B1.3 Objective tests at baseline and during test nights

- The **PC Psychomotor Vigilance Task (PVT)** (Khitrov et al., 2014) is a reaction time (RT) test that measures several reaction parameters to a series of visual stimuli presented on a computer screen. Although the task lasts only 10 minutes, it assesses alertness and sustained attention using a high stimulus-rate paradigm that is very sensitive to sleep loss and states of sleepiness (Basner & Dinges, 2011). The PVT stimulus is a red four-digit number on a black screen counting upwards from zero in milliseconds. The inter-stimulus interval had a random duration of 2–10 s. Participants were instructed to react as quickly as possible with a left mouse click (Logitech G 402-Hyperion-fury Gaming Mouse; Logitech International SA, Lausanne, Switzerland; sampling rate 1000 Hz) as soon as the digits appeared. Participants immediately received visual feedback about their RT after each reaction. Output measures were mean RT, lapses, fastest 10% of RTs,

and speed (i.e., 1/RT). Participants show stable performance across repeated PVT administrations, indicating no systematic repetition effects (Basner et al., 2017).

- The **Mackworth Clock Test** (MCT) measures sustained attention under monotonous conditions. On a computer screen, a dot jumps between adjacent positions along a circle in a clockwise direction. Participants are instructed to react with a button press when the dot skips one position when jumping along the circle. We used the **VIGIL S1** (Schuhfried GmbH, Mödling, Austria), a computerized version of the MCT. Over the 26-minute test duration, 100 skips occurred. The output measures were mean RT (ms), correct reactions, and false starts.
- All computer-based tests were performed on a Latitude E5550 Laptop (Dell, Round Rock, TX, USA) running Microsoft Windows 10 (Microsoft Corp, Redmond, WA, USA) and a gaming mouse (G402 Hyperion Fury; Logitech International S.A., Lausanne, Switzerland) with a sampling rate of 1000 Hz. Blue light filters were installed on the laptop, all computers in the sleep lab necessary for patient monitoring, and personal smartphones to control for the effects of digital screens on alertness and sustained attention (Chang et al., 2015).

B2 Results of the screening and baseline measurements

Table B1. Screening questionnaires and baseline performance in the Psychomotor Vigilance Task and Mackworth Clock Test VIGIL S1

	M (SD)	*Mdn*
Screening		
Beck Depression Inventory-II	5.5 (6.0)	4.0
Multicultural Quality of Life Index	7.9 (1.2)	8.3
Epworth Sleepiness Scale	4.5 (3.2)	4.0
Regensburg Insomnia Scale	7.3 (2.8)	7.0
Restless Legs Syndrome Criteria	0.0 (0.0)	0.0
Berlin Questionnaire Obstructive Sleep Apnoea	0.0 (0.0)	0.0
Fatigue Severity Scale	2.7 (0.9)	2.8
Modified Fatigue Impact Scale	9.3 (7.6)	7.0
Functional Outcomes of Sleep Questionnaire	18.4 (1.5)	19.1
Pittsburgh Sleep Quality Index	3.8 (1.9)	4.0
Morningness-Eveningness Questionnaire	45.6 (12.2)	42.0
type		
definite morning n [%]	0 [0]	
moderate morning n [%]	10 [47.6]	
neutral n [%]	8 [38.1]	
moderate evening n [%]	1 [4.8]	
definite evening n [%]	2 [9.6]	
Baseline measurements		
Psychomotor Vigilance Task		
Lapses	0.4 (0.8)	n.a.
Mean RT	268.0 (24.3)	n.a.
FRT	208.6 (14.7)	n.a.
Speed (1/RT)	3.9 (0.3)	n.a.
Mackworth Clock Test VIGIL S1		
Correct Reactions	98.8 (1.9)	n.a.
False Starts	2.2 (2.2)	n.a.
Mean RT	465.8 (50.1)	n.a.
Karolinska Sleepiness Scale		
KSS 1: before PVT	3.8 (1.5)	4.0
KSS 2: after PVT	4.1 (1.8)	3.5
KSS 3: before MCT	4.0 (1.8)	3.5
KSS 4: after MCT	5.2 (1.7)	6.0

Note. *M*, mean; *SD*, standard deviation; *Mdn*, median; n.a., not applicable; RT, reaction time in ms; FRT, fastest 10% of reaction times; PVT, Psychomotor Vigilance Task; MCT, Mackworth Clock Test

C Supplementary Material for Study 3

C1 Detailed description of screening and outcome measures

C1.1 Screening for sleep disorders

- The **Berlin Questionnaire for sleep apnoea** (Netzer et al., 1999) is a self-administered 10-item questionnaire regarding three categories related to sleep apnoea (snoring, daytime sleepiness, and obesity or hypertension). The outcomes define a high risk for obstructive sleep apnoea if a patient shows risk factors in at least two of the three categories. The Berlin Questionnaire shows sufficient internal consistency (Cronbach's α varies between .68 and .98) and test–retest reliability (Cohen's κ varies between .74 and .98).
- Screening for **restless legs syndrome** (RLS) was based on the five essential diagnostic criteria defined by the International RLS Study Group (Allen et al., 2014).
- The **Regensburg Insomnia Scale** (RIS) (Crönlein et al., 2013) is a 10-item self-administered questionnaire assessing cognitive, emotional, and behavioural aspects of psychophysiological insomnia. Participants respond by rating questions on a scale from 0 (*always*) to 4 (*never*), which are summed to a total score of 0–40, with higher scores indicating higher levels of insomnia. Total scores >12 indicate symptoms of psychophysiological insomnia (Crönlein et al., 2013). The internal consistency of the RIS is good, with a Cronbach's α of .89.

C1.2 Screening for daytime sleepiness

- The **Epworth Sleepiness Scale** (ESS) (Johns, 1991) is a self-administered questionnaire on subjective daytime sleepiness. The ESS contains eight questions about the probability of falling asleep or dozing off (i.e., subjective sleep propensity) while engaged in different daily activities. A global score is derived

from adding the responses (each rated from 0–3; the global score ranges from 0–24). The ESS shows sufficient internal consistency (Cronbach's α = .88) and test–retest reliability (r = .82) (Johns, 1992). Participants in the present study were administered the German version of the ESS (Sauter et al., 2007). According to a German validation study, scores higher than 10 categorize a participant's daytime sleepiness as "clinically suspicious", while scores > 12 define it as "clinically relevant" (Sauter et al., 2007).

C1.3 Fatigue

The following three questionnaires were used to assess fatigue levels during screening and intervention weeks.

- Using a **Visual Analogue Scale for Fatigue** (VAS_F), participants rated their current fatigue levels from 0% (no fatigue) to 100 (very strong fatigue), serving as primary outcome measure.
- The **Fatigue Severity Scale** (FSS) (Krupp et al., 1989) is a nine-item questionnaire that assesses the severity of fatigue during the week prior to testing on a 7-point scale from 1 (*disagree*) to 7 (*agree*). The total score ranges from 9 to 63, with values >36 indicating fatigue (Andreasen et al., 2011; Learmonth et al., 2013; Lerdal et al., 2005). The internal consistency of the FSS is high, with a Cronbach's α of .94. The German version of the FSS was used in the current study with test–retest reliability of the individual items ranging from *r* = .63 to *r* = .88 (Reske et al., 2006).
- The **Daily Fatigue Impact Scale** (D-FIS) (Fisk & Doble, 2002), an eight-item questionnaire based on the Fatigue Impact Scale (Fisk et al., 1994), was used every other evening during participation. Respondents rate the effects of fatigue on daily life on a five-point Likert scale from 0 (*no problem*) to 4 (*extreme*

problem). The sum score ranges from 0 to 32, with higher scores indicating stronger effects of fatigue. For the current study, a non-validated German version of the D-FIS was created by the authors by means of forward-and-back translation.

C1.4 Screening for Sleep Quality

- The **Pittsburgh Sleep Quality Index** (PSQI) (Buysse et al., 1989) is a self-administered questionnaire that assesses sleep quality and disturbances over a 1-month period. The PSQI contains 19 items from which seven sleep component scores are derived (e.g., subjective sleep quality, sleep latency). A global sleep quality score can be calculated as the sum of the component scores with a minimum of 0 and a maximum of 21. This score can be used to group participants as having generally good (score of 5 or lower) or bad sleep (score above 5). The PSQI shows sufficient internal consistency with a Cronbach's α of .83, a sensitivity of 89.6%, a specificity of 86.5%, and sufficient test–retest reliability of r=.88 (Buysse et al., 1989). In the present study, a validated German version of the PSQI was used during screening (Backhaus et al., 2002).

C1.5 Screening for Chronotype

- The **Morningness–Eveningness Questionnaire (MEQ)** assesses the chronotype. Responses to its 19 questions regarding performance, sleep behaviour, and well-being within a 24-hour time frame are summed to provide a total score with a maximum of 86. This score indicates one of five chronotypes: definite evening (14–30), moderate evening (31–41), neutral (42–58), moderate morning (59–69), and definite morning type (70–86). In the present study, the German version of the MEQ, called the D-MEQ, was used during screening. It shows high internal consistency with Cronbach's α = .82 (Griefahn et al., 2001).

C1.6 Mental health, quality of life

- The **Beck Depression Inventory-II** (BDI-II) (Beck, Steer, Ball, et al., 1996) is a 21-item questionnaire assessing the severity of depression symptoms such as sadness, self-harm, and loss of appetite in the two weeks prior to testing on a four-point scale from 0–3. The total score ranges from 0–63 indicating mild (14–19), moderate (20–28), and severe depression (29–63) (Beck, Steer, & Brown, 1996; Smarr & Keefer, 2011). The BDI-II shows high internal consistency (Cronbach's α of .91) (Beck, Steer, Ball, et al., 1996) and good to excellent test–retest reliability (r = .73–.96) (Wang & Gorenstein, 2013). Participants were administered the German version of the BDI-II in the current study during screening (Hautzinger et al., 2006).
- The **Multicultural Quality of Life Index** (Mezzich et al., 2011) assesses quality of life in 10 dimensions using 10 questions regarding physical well-being, psychological/emotional well-being, self-care and independent functioning, occupational functioning, interpersonal functioning, social emotional support, community and services support, personal fulfilment, spiritual fulfilment, and overall quality of life. Participants rate each domain from 1 (*poor*) to 10 (*excellent*). The total score consists of the summated scores from all answered items and ranges from 10 to 100. The internal consistency (Cronbach's α) ranges from .90 to .92, its test–retest reliability was reported at r = .87 (Mezzich et al., 2011). The German version of the Multicultural Quality of Life Index was used in the current study on every second evening during intervention weeks (Saletu et al., 2003).

C1.7 Side effects

Assessing side effects from using the light glasses', a questionnaire on **Asthenopic Complaints** was used to query and rate the following side effects on a 6-pooint scale (0 [not at all noticeable]; 1 [hardly noticeable]; 2 [a little noticeable] 3 [noticeable]; 4 [strong]; 5 [very strong]): Overexertion of the eyes, headache, watery eyes, stinging eyes, burning eyes, blurred vision, pain in and around the eyes, glare, dizziness. The questionnaire used selected items of a long version of the questionnaire reported in Leichtfried et al. (2010) based on an article by Terman and Terman (1999). Side effects were assessed after usage of the light glasses on every intervention day.

C1.8 Sleep

A **sleep diary** was used to assess patients sleep throughout study participation. From patients' responses, sleep quality (%), total sleep time (min; calculated as the difference between reported time falling asleep and reported time waking up), time in bed (min; calculated as the difference between reported bed time and reported time waking up), sleep latency (min; calculated as the difference between reported bed time and reported time falling asleep), and sleep efficiency (%; calculated as the ratio between reported total sleep time and time in bed) were extracted for further analyses.

C1.9 Comfort ratings

Comfort ratings were used to assess and compare participants' acceptance of the interventions. Beneficial and visual side effects of the light intervention were evaluated on a five-point scale (1 [fully disagree]; 2 [rather disagree]; 3 [partly agree]; 4 [rather agree]; 5 [fully agree]). The beneficial effects questions included the items "The light glasses increased my fitness", "The light glasses increased

my well-being", "The light glasses facilitated wakefulness", "The light glasses had a positive effect on the morning", and "The light glasses positively influenced my concentration". The side effects questionnaire comprised six items: "The light glasses were irritating", "The light glasses disturbed me", 2The light glasses irritated my eyes", "The light glasses negatively affected my view", "The light glasses disturbed reading", and "The light glasses generated disturbing reflections in the smartphone screen". We used a seven-point semantic differential ranging from 1 (*very…*) via 4 (*neither nor*) to 7 (*very…*) with the following items: "pleasant – unpleasant", "fitness increasing - fitness decreasing", "somniferous – activating", "not disturbing – disturbing", "too short – too long", "in the foreground – in the background", and "weak – strong". Participants stated whether they would recommend the light glasses to other night shift workers on a scale from 1 (*not at all*) to 6 (*absolutely*) and gave the light glasses school grades from 1 (*very good*) to 6 (*insufficient*).

C2 Outlier and missing data replacement

One outlier (FSS score = 9) was identified and replaced by the mean of that person's previous and subsequent data in the same intervention week.

If baseline values were missing from one intervention week, these were replaced with that same person's baseline values from the other intervention week. Missing values during the test weeks were filled in with the mean value of that person's data recorded one measurement day before and after within the same intervention week (VAS_F, 58 missing values out of 960 values were substituted [7%]; FSS, 15 missing values out of 200 values were substituted [8%]; D-FIS, 8 missing values out of 260 values were substituted [2%]; MQLI, 8 missing values out of 200 values were substituted [4%]; Sleep protocol, 100 missing values out of 2.020 values were substituted [5%]; side effects, 144 missing values out of 2.520 values were substituted [6%]). Comfort questionnaires were administered once at the end of each intervention period. We had missing data from two patients in the placebo intervention and one in the active intervention. To run matched pairs analyses, data from 17 persons for whom comfort ratings were available for both interventions were included in the analyses.

C3 Vision-related side effects of the interventions

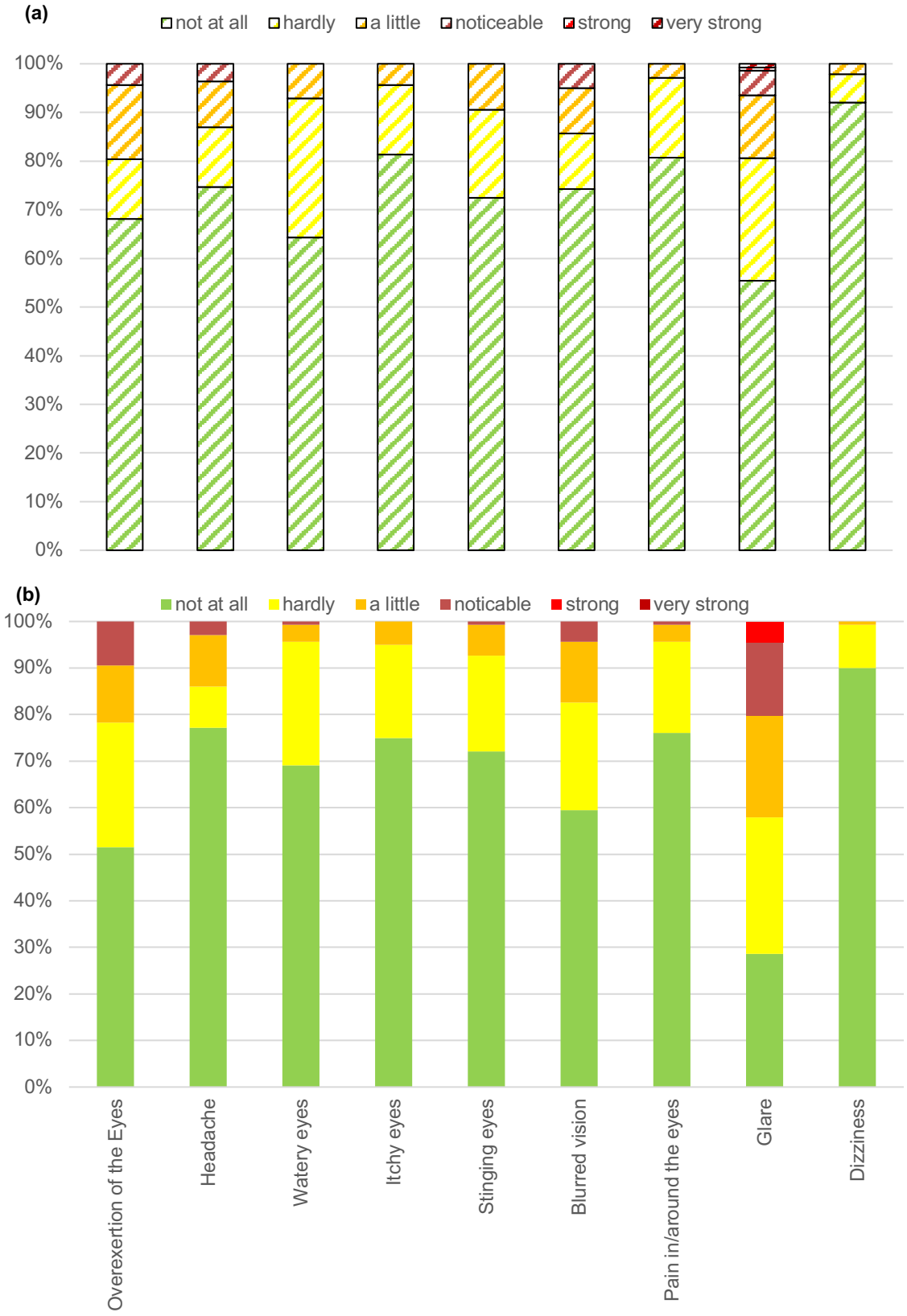
Table C1. Distribution of side effects' severity between the two study interventions

	Overexertion of the eyes	**Headache**	**Watering eyes**	**Itchy eyes**	**Stinging eyes**	**Blurred vision**	**Pain in and around the eyes**	**Glare**	**Dizziness**
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Dim red light intervention									
not at all	94 (67.1)	103 (73.6)	90 (64.3)	113 (80.7)	100 (71.4)	104 (74.3)	113 (80.7)	77 (55.0)	128 (91.4)
hardly	17 (12.1)	17 (12.1)	40 (28.6)	20 (14.3)	25 (17.9)	16 (11.4)	23 (16.4)	35 (25.0)	8 (5.7)
a little	21 (15.0)	13 (9.3)	10 (7.1)	6 (4.3)	13 (9.3)	13 (9.3)	4 (2.9)	18 (12.9)	3 (2.1)
noticeable	6 (4.3)	5 (3.6)	0 (0.0)	0 (0.0)	0 (0.0)	7 (5.0)	0 (0.0)	7 (5.0)	0 (0.0)
strong	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.7)	0 (0.0)
very strong	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.7)	0 (0.0)
Blue-enriched light intervention									
not at all	71 (50.7)	105 (75.0)	96 (68.6)	105 (75.0)	98 (70.0)	82 (58.6)	105 (75.0)	38 (27.1)	126 (90.0)
hardly	37 (26.4)	12 (8.6)	37 (26.4)	28 (20.0)	28 (20.0)	32 (22.9)	27 (19.3)	39 (27.9)	13 (9.3)
a little	17 (12.1)	15 (10.7)	5 (3.6)	9 (6.4)	9 (6.4)	18 (12.9)	5 (3.6)	29 (20.7)	1 (0.7)
noticeable	13 (9.3)	4 (2.9)	1 (0.7)	0 (0.0)	1 (0.7)	6 (4.3)	1 (0.7)	21 (15.0)	0 (0.0)
strong	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	6 (4.3)	0 (0.0)
very strong	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

Note. n, number.

A total of 280 questionnaires were included, 140 per intervention.

Figure C1. Side effects during the intervention sessions.



Note. Reported side effects severity during **(a) dim red light intervention** sessions and **(b) blue-enriched light intervention** sessions with ratings "not at all" (green), "hardly" (yellow), "a little" (light orange), "noticeable" (dark orange), "strong" (bright red), and "very strong" (dark red) noticeable.