Stress & Cognitive Function

Exploring the Impact of PTSD and Breast Cancer on Cognition and the Potential Benefit of Bright Light Therapy

by

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This Thesis is submitted to the Department of Psychology, School of Social Sciences, at Reykjavik University in partial fulfillment of the requirements for the degree of Doctor of Philosophy. The introductory part constitutes the formal Thesis which summarizes the accompanying papers that have either already been published or submitted for peer review.

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Abstract

Cognitive function—the ability to learn, solve problems, and effectively use stored information—is essential for everyday activities. While many factors contribute to cognitive impairment, this Thesis specifically examines the often-overlooked influence of stress. Major life stressors (e.g., war exposure, sexual violence, cancer diagnosis and treatment) can cause posttraumatic stress disorder (PTSD), and affect biological (e.g., cortisol) and psychological (e.g., depressive symptoms) stress markers known to impair cognitive function. Given the significant negative impact of cognitive impairment on individuals and society, the overarching goals of this Thesis were to a) further investigate the relationship between life stressors and cognitive impairment, b) identify potential moderators of this relationship and c) explore whether circadian-stimulating bright light therapy (BLT) can mitigate the negative effects of life stressors on stress markers, and cognitive function. The three papers listed below highlight the main aims and findings of this Thesis.

In Paper I, a multilevel random effect meta-analysis was conducted to investigate the relationship between PTSD and cognitive impairment, along with potential moderating factors. Literature search yielded 53 peer-reviewed relevant studies in which this relationship was examined. Age, study design, study population, neurocognitive outcome assessed, gender, study quality, type of PTSD measure, as well as the presence of comorbidities such as traumatic brain injury, depression, and substance use, were investigated as potential moderators. The results suggested that PTSD is associated with both cognitive impairment and neurocognitive disorder, compared to healthy controls (HC), demonstrating a consistent link that persisted across all examined moderators.

Paper II examined cancer-related cognitive impairment (CRCI) among women undergoing the life stressor of breast cancer (BC) diagnosis. Previous studies primarily examined chemotherapy's effect on CRCI, while this study aimed to assess CRCI in women with BC before any treatment and explore potential associations with stress. A population-based study with 112 treatment-naïve women with BC and 67 HC was conducted. Cognitive function was assessed via neuropsychological

assessment. Cognitive complaints and psychological stress markers (i.e., cancer-related stress (related to PTSD), depressive and anxiety symptoms) were measured with a self-report battery. Biological stress markers (i.e., cortisol and α-amylase) were collected from saliva. The findings revealed that treatment-naïve women with BC had greater impairments in processing speed and verbal memory, along with more frequent cognitive complaints than HC. Multilinear regressions showed that a) steeper α-amylase slope, younger age and lower overall cancer-related stress were associated with better overall cognitive performance, and b) greater depressive symptoms were associated with more frequent cognitive complaints. These findings indicate that CRCI can start before BC treatment and that stress could contribute to it.

Paper III builds on the findings from Papers I and II, indicating that life stressors may contribute to cognitive impairment by affecting stress markers. Since the cancer itself and surgery can trigger stress responses and disrupt circadian rhythms, further increasing the risk of CRCI, Paper III explored whether BLT could mitigate the negative effects associated with BC (including BC surgery) on cognitive function and stress. A double-blind, randomized controlled trial was conducted with the same participants and measurements as in Paper II. Participants were randomly allocated to receive circadian-stimulating bright white light (BWL, $N = 60$) or non-circadian-stimulating dim white light (DWL, $N = 57$) for four weeks post-BC surgery. Linear regression and path analyses indicated that the BWL group reported significantly fewer cognitive complaints. Additionally, there were non-significant trends, with small to medium effects, for faster reaction times and fewer intrusive thoughts in the BWL group compared to the DWL group.

Overall, the results of this Thesis emphasize the importance of monitoring cognitive function in individuals exposed to major life stressors and an early intervention when needed. Future studies should further investigate BLT's potential in ameliorating cognitive impairment and stress among individuals experiencing major life stressors and explore the underlying mechanisms.

Keywords: Cognitive function, stress, post-traumatic stress disorder, cancer-related cognitive impairment, light therapy

Ágrip

Hugræn virkni, þ.e. getan til að læra, leysa vandamál og beita upplýsingum á skilvirkan hátt, er nauðsynleg fyrir daglegt líf. Margir þættir geta leitt til hugrænnar skerðingar en í þessari doktorsrannsókn voru áhrif streitu á hugræna virkni rannsökuð sérstaklega. Streituvaldandi atburðir á lífsleiðinni (t.d. stríð, kynferðislegt ofbeldi, greining brjóstakrabbameins (BK) og krabbameinsmeðferð) geta valdið áfallastreituröskun (ÁSR), ásamt því að hafa áhrif á líffræðileg (t.d. kortisól) og sálræn (t.d. einkenni þunglyndis) streitumerki sem geta skert hugræna virkni. Þar sem hugræn skerðing getur haft umtalsverð neikvæð áhrif á einstaklinga og samfélagið í heild, var markmið þessarar doktorsrannsóknar að rannsaka nánar a) sambandið á milli streituvaldandi atburða og hugrænnar skerðingar, b) hvaða þættir geta haft áhrif á þetta samband og c) hvort ljósameðferð (LM) geti dregið úr áhrifum streituvaldandi atburða á líffræðileg og sálræn streitumerki og hugræna virkni. Doktorsrannsóknin var þríþætt og er rannsóknunum þremur lýst hér á eftir.

Fyrsta rannsóknin kannaði sambandið á milli ÁSR og hugrænnar virkni ásamt hugsanlegum mótunarþáttum þessa sambands með þriggja laga slembiáhrifa safngreiningu. Heimildaleit skilaði 54 ritrýndum vísindagreinum sem uppfylltu inntökuskilyrðin. Hugsanlegir mótunarþættir þessa sambands sem skoðaðir voru í þessari rannsókn voru aldur, rannsóknarsnið, tegund úrtaks, hugræn útkoma, kyn, gæði rannsókna, mælitæki ÁSR, heilahristingur, þunglyndi og notkun vímugjafa. Niðurstöðurnar gáfu til kynna tengsl milli ÁSR og þróunar á hugrænni skerðingu og einnig á milli ÁSR og heilabilunar, miðað við heilbrigða samanburðarhópinn (HS) og að auki, að þessi tengsl væru óháð þeim mótunarþáttum sem skoðaðir voru.

Önnur rannsóknin kannaði krabbameinstengda hugræna skerðingu (KHS) meðal kvenna sem greinst höfðu með BK. Fyrri rannsóknir á KHS hafa einkum kannað áhrif lyfjameðferðar á KHS en markmið þessarar rannsóknar var að meta hvort KHS meðal kvenna með BK geti komið fram áður en BK meðferð hefst og einnig hvort streita geti mögulega spilað þar hlutverk. Rannsóknin var lýðgrunduð með 112 þátttakendum með BK (fyrir BK meðferð) og 67 þátttakendum úr HS. Hugræn virkni var metin bæði með taugasálfræðiprófum og spurningalista. Sálræn streitumerki (þ.e.

krabbameinstengd streita (tengd ÁSR), þunglyndis- og kvíðaeinkenni) voru mæld með spurningalistum. Líffræðileg streitumerki (þ.e. kortisól og α-amýlasi) voru mæld í munnvatnssýnum. Niðurstöðurnar sýndu að þátttakendur með BK stóðu sig verr á taugasálfræðiprófum sem mældu vinnsluhraða og orðaminni og töldu hugræna virkni sína vera verri miðað við þátttakendur í HS. Marghliða línuleg aðhvarfsgreining sýndi að a) betri hugrænni virkni fylgdi hærri α-amýlasa-hallastuðull, yngri aldur og minni krabbameinstengd streita og að b) þátttakendur með alvarlegri þunglyndiseinkenni töldu hugræna virkni sína vera verri. Niðurstöðurnar benda til að KHS geti komið fram áður en meðferð við BK hefst og að streita getur átt sinn þátt í skerðingunni.

Þriðja rannsóknin byggir á niðurstöðum hinna tveggja sem gáfu til kynna að streituvaldandi atburðir á lífsleiðinni geti átt þátt í hugrænni skerðingu með áhrifum sínum á streitumerki. Þar sem bæði krabbameinið sjálft ásamt skurðaðgerð því tengd geta framkallað streituviðbrögð og einnig raskað dægursveiflum, og þar með enn frekar aukið hættuna á KHS, þá var í þriðju rannsókninni skoðað hvort LM geti dregið úr neikvæðum áhrifum tengdum BK (þar með skurðaðgerð við BK) á hugræna virkni og streitu. Til að skoða þetta nánar var tvíblind slembirannsókn framkvæmd á sama úrtaki og notað var í annarri rannsókninni. Þátttakendum var handahófskennt skipt í hópa þar sem íhlutunarhópurinn fékk dægursveiflu-örvandi bjart ljós (BL, $N = 60$) á meðan samanburðarhópurinn fékk dimmt ljós án dægursveiflu-örvunar (DL, $N = 57$). LM stóð yfir í fjórar vikur að skurðaðgerð lokinni. Línulegar aðhvarfsgreiningar og leiðargreiningar sýndu að BL hópurinn, í samanburði við DL hópinn, taldi hugræna virkni sína vera marktækt betri. Að auki var ómarktæk tilhneiging (með litlum til meðal áhrifastærðum) hjá BL hópnum til hraðari viðbragðstíma og færri uppáþrengjandi hugsana samanborið við DL hópinn.

Á heildina litið þá undirstrika niðurstöður þessarar doktorsrannsóknar nauðsyn þess að fylgjast með hugrænni virkni hjá einstaklingum sem hafa orðið fyrir meiriháttar streituvaldandi atburðum á lífsleiðinni en einnig mikilvægi snemmtækrar íhlutunar eftir þörfum. Framtíðarrannsóknir ættu að rannsaka nánar hvort LM geti dregið úr hugrænni skerðingu og streitu meðal einstaklinga sem hafa upplifað meiriháttar streitu á lífsleiðinni, ásamt því að skoða undirliggjandi þætti.

Lykilorð: Hugræn virkni, streita, áfallastreituröskun, krabbameinstengd hugræn skerðing, ljósameðferð

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This work is dedicated to my grandma, Erna Aspelund—who watched an entire research seminar in English to support me (one of many presenters)—even though she barely spoke a word of English.

List of Studies

This thesis is based on the following original publications, which are referred to in the text by their Roman numerals (I, II, III):

I. Aspelund, S. G., Lorange, H. L., Halldorsdottir, T., Baldursdottir, B., Valdimarsdottir, H. B., Valdimarsdottir, U. A., Hjördísar-Jónsdóttir, H. L. (n.d.). Assessing neurocognitive outcomes in PTSD: A multilevel meta-analytical approach. [*Manuscript under revision in the European Journal of Psychotraumatology*.]

II. Aspelund, S.G., Halldorsdottir, T., Agustsson, G., Tobin, H. R. S., Wu, L. M., Amidi, A., Johannsdottir, K. R., Lutgendorf, S., Telles, R., Daly, H. F., Sigurdardottir, K., Valdimarsdottir, H., Baldursdottir, B. (2024). Biological and psychological predictors of cognitive function in breast cancer patients before surgery. *Support Care Cancer* **32**, 88. https://doi.org/10.1007/s00520-023-08282-5

III. Aspelund, S. G., Halldorsdottir, T., Agustsson, G., Tobin, H. R. S., Wu, L. M., Amidi, A., Johannsdottir, K. R., Lutgendorf, S., Telles, R., Daly, H. F., Sigurdardottir, K., Figueiro, M. G., Redd, W. H., Valdimarsdottir, H., Baldursdottir, B. (n.d.). The effects of light therapy on cognitive function and stress in women with breast cancer before systemic treatment. [*Manuscript submitted*.]

Declaration of Contribution

The doctoral candidate, Snæfríður Guðmundsdóttir Aspelund (SGA), wrote this doctoral Thesis under the guidance of Heiðdís B. Valdimarsdóttir (HBV), and Birna Baldursdóttir (BB), supervisors, and the Thesis Committee, Þórhildur Halldórsdóttir (ÞH), Lisa Maria Wu (LMW) and Ali Amidi (AA). Further collaborations on the manuscripts were Harpa Lind Hjördísar Jónsdóttir (HLHJ), Hjördís Lilja Lorange (HLL), Unnur Anna Valdimarsdóttir (UAV), Guðjón Ágústsson (GÁ), Hannah Rós Sigurðardóttir Tobin (HRST), Kamilla Rún Jóhannsdóttir (KRJ), Susan Lutgendorf (SL), Rachel Telles (RT), Huldís Franksdóttir Daly (HFD), Kristín Sigurðardóttir (KS), Mariana G. Figueiro (MF), and William H. Redd (WHR). The contribution to each study was as follows:

I. SGA, HLL, TH, and HLHJ designed the study. SGA and HLL extracted the data. SGA, HLL, and HLHJ assessed the data quality. SGA, HLHJ, and TH did the data analysis. SGA, HLL, TH, and HLHJ drafted the manuscript. TH, HLL, BB, HBV, UAV, and HLHJ gave feedback on the manuscript. SGA incorporated comments and finalized the manuscript. All authors read and approved the final manuscript.

II. SGA, HBV, KRJ, HFD, TH, LMW, AA, and BB designed the study. SGA, GA, HRST, KS, and HFD conducted the study and collected data. HBV, BB, LMW, AA, TH, SL, HRST, and RT guided SGA with the data analysis. SGA analyzed the data, drafted the manuscript, incorporated comments, and finalized the manuscript. HBV, BB, LMW, AA, TH, SL, and KRJ discussed the results and commented on the manuscript. All authors read and approved the final manuscript.

III. SGA, HBV, KRJ, HFD, TH, LMW, AA, and BB designed the study. SGA, GA, HRST, KS, and HFD conducted the study and collected data. TH, HBV, BB, LMW, AA, SL, HRST, and RT guided SGA with the data analysis. SGA analyzed the data, wrote the manuscript, incorporated comments, and finalized the manuscript. HBV, BB, LMW, AA, TH, SL, MF, WHR, and KRJ gave feedback on the manuscript. All authors read and approved the final manuscript.

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List of Abbreviations

APOE	Apolipoprotein E
BC	Breast Cancer
BLT	Bright Light Therapy
BMI	Body Mass Index
BWL	Bright White light
CEQ	Credibility/Expectancy Questionnaire
CES-D	Center for Epidemiological Studies Depression Scale
COWAT	Controlled Oral Word Association Test
CR	Circadian Rhythms
CRCI	Cancer-Related Cognitive Impairment
DSM-IV-TR	The Diagnostic and Statistical Manual of Mental disorders, 4th Edition, Text revision
DWL	Dim White Light
FACIT-TS-G	Functional Assessment of Chronic Illness Therapy-Treatment Satisfaction-General
FDR	False Discovery Rate
GAD	Generalized Anxiety Disorder
GCS	Global Composite Score
HC	Healthy Controls
HER2	Human Epidermal Growth Factor Receptor 2
HPA axis	Hypothalamic Pituitary Adrenal axis
IES-R	Impact of Events Scale - Revised

IQR	Interquartile Range
ITT	Intention-To-Treat
MMSE	Mini-Mental State Examination
NCD	Neurocognitive Disorder
PROMIS	Patient-Reported Outcomes Measurement Information System
PTSD	Post-Traumatic Stress Disorder
PVT	Psychomotor Vigilance Test
RAVLT	Rey Auditory Verbal Learning Fluency Test
REDCap	Research Electronic Data Capture
SCN	Suprachiasmatic Nucleus
TMT	Trail Making Test
WAIS	Wechsler Adult Intelligence Scale

1 Introduction

Cognitive function—the ability to learn, solve problems, and effectively use stored information—plays a vital role in everyday activities such as decision-making and communication. It is essential for maintaining independence, fostering interpersonal relationships, self-confidence, occupational abilities, and promoting overall well-being (Morley et al., 2015; Von Ah et al., 2013). Major life stressors (such as war exposure, sexual violence, cancer diagnosis and treatment) have the potential to impact biological and psychological stress markers associated with cognitive impairment (McEwen, 2017). Diagnostic critieria for cognitive impairment vary depending on the condition but in short, they generally include a measurable decline (via neuropsychological assessment) that exceeds typical age-related changes in one or more cognitive domains, such as attention, processing speed, learning and memory, and executive functioning (American Psychiatric Association, 2013; Mills, 2017; Wefel et al., 2011; World Health Organization, 2018). The current Thesis will explore various types of cognitive impairment, and unless otherwise specified, the term "cognitive impairment" refers to sub-clinical levels. Although diagnostic criteria for cognitive impairment generally do not include self-reported cognitive complaints, they can provide clinically important information that complements objective measurements (i.e., neuropsychological assessment) since they capture the patients' personal experience (Kanaskie & Loeb, 2015). In fact, neuropsychological tests often fail to detect the cognitive impairments that patients themselves report (Hutchinson et al., 2012; Pullens et al., 2010). Possible reasons for this discrepancy include that the cognitive impairment may be too subtle for neuropsychological tests to detect (Lange et al., 2019) or because compensatory brain areas might sustain neuropsychological performance in a controlled test environment, as brain imaging studies have indicated (Apple et al., 2018; McDonald et al., 2012; Menning et al., 2017). However, cognitive complaints may be more closely related to psychological distress than to neuropsychological performance (Hutchinson et al., 2012).

Given the extensive impact of cognitive impairment on individuals and society, the need for uncovering underlying mechanisms, moderating factors, and appropriate interventions is clear.

One potential modifiable risk factor for cognitive impairment that needs to be studied further is stress (i.e., biological and psychological stress markers). Since major life stressors can affect stress markers which can contribute to cognitive impairment (McEwen, 2017), the current Thesis will examine the effects of posttraumatic stress disorder (PTSD) and breast cancer (BC) diagnosis on cognitive function. Additionally, it will investigate potential modifying factors and explore if a novel intervention mitigates the impact of life stressors on biological and psychological stress markers, and the resulting cognitive impairment.

First, the Thesis will examine the impact of PTSD, the most extreme spectrum of stress responses, where the effects of stress on the brain and cognitive function may be the most starkly evident, on cognitive function. As the forthcoming analysis shows, PTSD significantly impacts cognitive function, increasing the risk of cognitive impairment and neurocognitive disorder (NCD, which includes conditions formerly referred to as dementia in the DSM 4th edition text revision (DSM-IV-TR) (American Psychiatric Association, 2000, 2013)). With NCD rates projected to triple by 2050 due to longer life expectancy and increased exposure to cardiovascular risk factors (e.g., diabetes, midlife hypertension and obesity), addressing this issue is crucial (Livingston et al., 2017; Prince et al., 2013). Given that these previously mentioned risk factors for NCD can be modified throughout life, and evidence suggests that approximately a third of NCD cases can be prevented or delayed (Livingston et al., 2017; Salthouse, 2009), it is vital to identify potential predictors, such as PTSD, and explore modifying factors that may mitigate the impact of NCD on individuals and communities.

Second, the current Thesis will investigate the impact of a BC diagnosis (as well as the cancer itself), a major life stressor, on cognitive function. As cancer treatments continue to evolve with advancing technology, and the number of cancer survivors steadily increases, some side effects of cancer and its treatment persist, significantly

impacting the quality of life for cancer survivors over many years (Williams et al., 2022). One of these barriers to returning to normal functioning post treatment is cancer-related cognitive impairment (CRCI). For years, most studies on CRCI presumed it was solely due to the neurotoxic effects of chemotherapy (Collins et al., 2013), and even when baseline assessments were undertaken, they were often conducted after cancer surgery (Lange et al., 2014; Scherling et al., 2011, 2012). However, as this Thesis will demonstrate, by that point, the stress associated with the cancer diagnosis—along with other contributing factors—may already have impacted patients' cognitive function, rendering these assessments unreliable.

Building on the knowledge of the adverse effects of major life stressors on cognitive function (McEwen, 2017), as can be seen in individuals with PTSD, this Thesis will investigate the cognitive function of women with BC before undergoing treatment, focusing on the impact of the stress associated with a cancer diagnosis (and the cancer itself) on cognitive function. However, although this Thesis sheds a light on the often-overlooked role of stress in cognitive impairment, it is essential to clarify that cognitive function is influenced by a myriad of complex, interacting factors (including stress). The interplay among these factors makes it nearly impossible to isolate the effects of stress due to their intricate interconnections. Other factors contributing to cognitive impairment include behavioural risk factors such as smoking and heavy alcohol use, as well as individual vulnerabilities like low education and cognitive reserve (Ahles & Root, 2018; Lange, Joly, et al., 2019). When individuals exhibit symptoms of cognitive impairment, their cognitive reserve may further diminish as a result of avoiding daily life activities and social withdrawal (Aloni et al., 2018; Stern, 2012). Additionally, genetic factors (e.g., APOE-4, COMT, BDNF), inflammation markers (e.g., cytokines such as TNF-α and IL-6) and accelerated biological aging also play significant roles in cognitive impairment (Ahles & Root, 2018; Lange, Joly, et al., 2019).

Lastly, the third study in this Thesis will explore whether bright light therapy (BLT), using circadian-stimulating bright light shown to ameliorate cognitive impairment (Bersani et al., 2008; Killgore et al., 2020; Kim et al., 2021) and stress (Kawamura et al., 2019; Mårtensson et al., 2015; Valdimarsdottir et al., 2018), can mitigate the

negative effects of major life stressors (i.e., BC diagnosis, surgery and associated factors) on CRCI (assessed via neuropsychological assessments and self-reported cognitive complaints), as well as on biological (i.e., cortisol and α-amylase) and psychological stress markers (i.e., cancer-related stress and depressive symptoms). As Paper II delves into the cognitive function and stress among women with BC before treatment, Paper III will take this exploration further by examining these same factors post BC surgery and after a 4-week BLT. While most studies have focused on the effects of chemotherapy, the cancer disease itself as well as subsequent surgery can trigger biological stress and disrupt circadian rhythms (CR), both of which may increase the risk of CRCI. Given the limited research in this area, the current Thesis aims to address these knowledge gaps and contribute valuable insights to the field.

1.1 Stress and cognitive function

Although stress is a regular part of daily life, it can increase the risk of adverse health and cognitive outcomes. Both acute and prolonged stress can overstimulate and disrupt the stress reactivity systems, the hypothalamic pituitary adrenal (HPA) axis and the sympathetic nervous system, a component of the autonomic nervous system (McEwen, 2017).

The function of these stress systems can be assessed with secretion patterns of stress biomarkers, such as cortisol and α-amylase (Sultan et al., 2018). Cortisol is a glucocorticoid hormone regulated by the HPA axis while α-amylase is a salivary enzyme involved in digestion (Ali & Nater, 2020). While cortisol has a long history of being utilized as a stress biomarker in research (Kirschbaum & Hellhammer, 1989), α-amylase emerged more recently as a biomarker of autonomic nervous system activity (Ali & Nater, 2020; Nater & Rohleder, 2009).

The role of cortisol in cognitive function has been well established (Gaysina et al., 2014). For instance, one large population-based study found that individuals with elevated cortisol levels performed worse in tests measuring verbal memory, processing speed and other cognitive functions (Lee et al., 2007). Additionally, dysregulation in diurnal cortisol rhythms, or flatter diurnal cortisol (meaning there is less variation in cortisol levels throughout the day, explained in greater detail later),

has been associated with worse memory performance among healthy individuals (Abercrombie et al., 2004). One reason for such findings is that the hippocampus and prefrontal cortex—critical brain regions for cognitive functions such as memory, processing speed and executive function—are particularly vulnerable to the detrimental effects of stress since due to their high concentration of cortisol receptors (Lupien et al., 2009).

The role of α-amylase in cognitive function has been much less explored, but recent studies have begun to shed light on that area. For example, one study linked a steeper α-amylase response (i.e., immediate response to an acute stressor) to poorer memory performance among healthy adults (Becker & Rohleder, 2020). Other studies have associated elevated α-amylase levels to mild cognitive impairment in older adults (Yamane et al., 2022), as well as to poorer cognitive performance, including visual memory and sustained attention, in individuals at ultra-high risk for psychosis (Almstrup et al., 2023). Beyond its role as a stress biomarker, α-amylase has been located in the hippocampus, a brain area critical for memory, participating in glycogen metabolism within neurons (Byman et al., 2018, 2021). Glycogen, which the body breaks down into glucose when energy is needed, serves as an important energy source during memory formation. Impairments in glycogen metabolism can disrupt this energy supply, potentially impacting cognitive functions like memory (Duran et al., 2019). Given that impaired glycogen metabolism may contribute to cognitive impairment observed in conditions such as NCD (Byman et al., 2018, 2021), a deeper understanding of α-amylase's role could provide valuable insight into how stress and neurobiology influence cognitive function.

As discussed below, PTSD, representing the extreme end of the stress response, provides important insights into the adverse effects of stress on cognitive function and enhances our understanding of how life stressors, such as cancer diagnosis, can affect cognitive function.

1.2 PTSD and cognitive function

PTSD is a psychiatric disorder that can occur after exposure to traumatic life stressors, i.e., where the individual's (or someone else's) life is threatened (American

Psychiatric Association, 2013). The diagnostic criteria for PTSD include intrusive thoughts, hyperarousal, avoidance, negative alterations in mood, arousal and reactivity, as well as memory and concentration problems (American Psychiatric Association, 2013). In addition to memory and concentration problems, meta-analyses have found that individuals with PTSD demonstrate cognitive impairment that extends to attention, processing speed, working memory and executive functioning (Qureshi et al., 2011; Schuitevoerder et al., 2013; Scott et al., 2015). Cognitive impairment among individuals with PTSD is especially concerning as it can hinder the effectiveness of psychosocial treatments like cognitive behavioral therapy which rely on the ability to learn and apply new skills (Falconer et al., 2013; Samuelson, 2011; Wild & Gur, 2008). Additionally, cognitive performance among veterans with PTSD has been shown to be a strong predictor of their social and occupational functioning (Geuze et al., 2009).

PTSD symptoms have been linked to structural and functional brain changes resulting from extreme stress (Bremner, 2006). Key brain areas implicated in PTSD include the limbic system (i.e., the hippocampus, the amygdala and the cingulate cortex) and the prefrontal cortex (Campanella & Bremner, 2016).

Effective coping mechanisms when dealing with stress include both a rapid activation of the biological stress response when required and its adequate termination once the stressful situation is over (de Kloet et al., 2005). Conversely, when individuals with PTSD react to threats or emotionally arousing stimuli, their amygdala (the threat alarm of the brain) is overactivated, and their ventromedial prefrontal cortex (the threat alarm's "brake") is underactivated, rendering the prefrontal cortex unable to inhibit the amygdala fully. This kind of chronic stress can cause cortisol levels to remain elevated for prolonged periods (which can result in a flat diurnal slope), potentially damaging the previously mentioned brain regions (hippocampus and prefrontal cortex) critical for cognitive function (memory, processing speed and executive function) (Arnsten, 2009; McEwen et al., 2016). An example of such damage may be the shrinkage observed in the prefrontal cortex and hippocampus among individuals with PTSD (Chao et al., 2014; Nilaweera et al., 2020; Sapolsky, 2000).

Recurrent stress (such as in PTSD) has been shown to increase the risk of developing NCD later in life (Escher et al., 2019; Nilaweera et al., 2020). In line with this, PTSD has been recognized as a risk factor for developing NCD (Greenberg et al., 2014; Günak et al., 2020). NCD is defined as cognitive impairment with substantial impairment in one or more cognitive domains, resulting in difficulties with daily life activities (American Psychiatric Association, 2013). Over the years, much of the research on the effects of PTSD on cognitive function has focused on veterans, resulting in potential limitations due to the homogeneity of the study populations, since these studies primarily involve men who have experienced a unique type of trauma under special circumstances (Scott et al., 2015). In addition, veterans are more likely to have comorbidities such as traumatic brain injury, which itself is a risk factor for both cognitive impairment and NCD (Barman et al., 2016; Shively et al., 2012). Although women are underrepresented in the literature, they are twice as likely as men to develop PTSD (Pietrzak et al., 2012). One reason being that women are more likely than men to experience sexual assault (Tolin & Foa, 2006), which is strongly associated with PTSD (Resnick et al., 2007).

1.2.1 Stress and cognitive function in cancer

1.2.1.1 Cancer-related stress

PTSD symptoms, such as intrusive thoughts and avoidance, can also occur in women with BC (Dedert et al., 2012; Dupont et al., 2014; Lebel et al., 2008). BC is the most common cancer in women worldwide (Torre et al., 2017). Receiving a life-threatening diagnosis, such as cancer, and undergoing treatment can be a major life stressor, as these experiences can be highly stressful and even traumatic (Cordova et al., 2017; Swartzman et al., 2017). After receiving a cancer diagnosis, a period of heightened stress can follow, characterized by uncertainty about the cancer stage and the upcoming cancer treatment. Processing complex medical information and making important decisions regarding the cancer treatment can make this period especially overwhelming (Brocken et al., 2012; Cordova et al., 2017). However, whether cancer can be classified as trauma independently causing PTSD is controversial. This debate stems from a few considerations (Cordova et al., 2017; Swartzman et al., 2017).

Firstly, while PTSD manifests as a severe reaction to trauma which affects daily life (Iribarren et al., 2005), cancer can involve multiple and repeated traumatic events throughout its trajectory. Secondly, the most distressing aspect of cancer is a fear of a potential death in the future, while PTSD results from a single past event. Lastly, cancer stems from an internal threat as opposed to an external threat (such as suffering an attack or a natural disaster) (Cordova et al., 2017; Swartzman et al., 2017). Due to this, in the current Thesis, PTSD symptoms (i.e., intrusive thoughts, hyperarousal and avoidance) in cancer patients will henceforth be referred to as "cancer-related stress".

As is clear from the above discussion, the focus of this Thesis is on general biological and psychological aspects of stress. However, it is important to acknowledge that e.g., cognitive appraisal—the evaluation of the major life stressor, i.e., the cancer diagnosis, as a threat, challenge or harm—can influence cancer patients' stress levels and psychological outcomes (Poręba-Chabros et al., 2022). For example, cancer patients who view cancer primarily as a loss or unfairness (i.e., harm appraisal) may experience higher levels of cancer-related stress, compared to those who view the cancer diagnosis as a challenge to be overcome (Poręba-Chabros et al., 2022).

1.2.1.2 Cancer-related cognitive impairment (CRCI)

Just as in PTSD, cognitive impairment is common among women with BC. In fact, a recent study found that 75% of cancer survivors (of which >85% were women with BC) reported CRCI post-treatment, which influenced their occupational function (Lange et al., 2019). Thus, CRCI can act as a barrier when returning to daily life after cancer treatment (Schmidt et al., 2019). Not only is CRCI frequent, but can be long-lasting too, as it has been detected in women with BC even 10-20 years post-treatment (Koppelmans et al., 2012; Ruiter et al., 2011). Even though CRCI is one of the most common and feared side effects of BC (Ahles et al., 2012; Bower, 2008), it has only been fully acknowledged recently (Winocur et al., 2018) and remains understudied.

One of the limitations in the field of CRCI is that the focus has mostly been on the effects of chemotherapy on CRCI (Ahles & Saykin, 2007; Collins et al., 2013; Janelsins et al., 2018; Ono et al., 2015; Schagen & Wefel, 2013; van Dam et al., 1998; Wefel et al., 2010) in lieu of other BC treatments, e.g., surgery. In fact, CRCI used to

be called 'chemobrain' (Hurria et al., 2007). There is evidence for the neurotoxic effects of chemotherapy, but these effects do not account for all CRCI (Ono et al., 2015). Indeed, meta-analyses have shown that CRCI can be present in women with BC, irrespective of whether they underwent chemotherapy (Bernstein et al., 2017; Ono et al., 2015). Additionally, CRCI has even been found in 28% of women with BC before starting treatment, compared to HC (Lange et al., 2020). In line with this, a brain imaging study observed structural and functional brain changes in treatment-naïve women with BC (Kesler et al., 2017). Despite these findings, many previous studies lack baseline assessments prior to cancer treatment and instead conduct them post-BC surgery (Lange et al., 2014; Scherling et al., 2011, 2012). However, post-surgery, women with BC have been found to be 3-4 times more likely to experience cognitive impairment compared to HC (Debess et al., 2009). Additionally, a brain imaging study observed that after surgery, women with BC had structural changes in the thalamus accompanied by an attentional dysfunction, compared to HC (Sato et al., 2015). Considering these previously mentioned factors, e.g., post-operative cognitive impairment, and the stress associated with the cancer diagnosis and undergoing cancer treatment, conducting baseline assessments post-surgery may not be accurate (Hovens et al., 2012).

Despite vast literature illustrating how stress and trauma can influence the brain and cognitive function, surprisingly few studies have examined whether psychological and biological stress markers are associated with CRCI. Psychological stress markers, such as depressive and anxiety symptoms, both common among women with BC (Linden et al., 2012), have been linked to CRCI (Yang & Hendrix, 2018). Additionally, in one study, CRCI was associated with PTSD among treatment-naïve women with BC (Hermelink et al., 2015).

Cortisol is one of few biological stress markers currently linked to CRCI. Surgery may exacerbate CRCI, not only due to the psychological stress associated with a BC diagnosis and subsequent treatment but also by independently triggering the peri-operative cortisol stress response (Prete et al., 2018), or through the effects of anesthesia (Mandal et al., 2010). Supporting this, a study among post-operational testicular cancer patients found that elevated cortisol levels independently predicted

poorer neuropsychological performance (Amidi, Wu, Agerbæk, et al., 2015). Similarly, another study identified that cortisol dysregulation (i.e., cortisol slope) mediated the association between childhood trauma and cognitive complaints in BC survivors (Kamen et al., 2017). Despite the established associations between betewen cortisol and CRCI, as well as the link between α-amylase and cognitive function (as discussed above), no study to date has explored whether α-amylase is associated with CRCI.

When discussing the role of biological stress in cancer, is essential to note that tumors can also contribute to biological stress and induce inflammation, independently affecting cognitive function (Eckerling et al., 2021). This inflammation is mediated by cytokines produced in the tumor environment, which can enter the bloodstream and cross the blood-brain barrier, potentially activating glial cells and directly affect neuronal circuits involved in cognition (Olson & Marks, 2019).

1.3 Stress, circadian rhythms (CR) and cognitive function

Acute and chronic stress can impact cognitive function through its effects on biological and psychological markers, as discussed above. Additionally, another mechanism may be at play, given the bi-directional relationship between the stress response system and the circadian system (Amidi & Wu, 2022; Ancoli-Israel et al., 2022). These two fundamental systems work in tandem to optimize energy by anticipating and adapting the organism to daily cyclic challenges. The circadian system upregulates the stress response system before the active phase of the day and downregulates it for its resting phase (Gamble et al., 2014).

CR are approximately 24-hour biological and behavioral cycles that follow the rotation of the earth and are generated by neurons in the master circadian clock, located in the suprachiasmatic nucleus (SCN) of the hypothalamus (Moore & Eichler, 1972; Stephan & Zucker, 1972). These innate cycles can be found in virtually all living organisms and consist of cellular, biochemical and behavioral activities (Bell-Pedersen et al., 2005; Hastings, 1997). CR are entrained to the environment via environmental cues (zeitgebers), the strongest being light (Boivin et al., 1994; Küller, 2002). CR influence everything from sleep/wake cycles and arousal to cognitive

function (Fisk et al., 2018). In fact, CR have been found to independently predict cognitive function (Luik et al., 2015; Wu et al., 2018) and can impact cognitive function directly via circadian clocks found in brain areas involved in memory, e.g., the amygdala and lateral habenula (Abe et al., 2002; Guilding & Piggins, 2007).

Both cortisol and α-amylase follow a regular circadian pattern (Granger et al., 2007; Kirschbaum & Hellhammer, 1989). Cortisol peaks within 30-60 min after awakening and declines throughout the day (Edwards et al., 2001). Conversely, α-amylase declines 60 min after awakening, increases throughout the day and peaks in the afternoon (Nater et al., 2007). These contrasting diurnal fluctuations in cortisol and α-amylase activity reflect a circadian regulation (Marchand et al., 2016). However, among individuals with PTSD, α-amylase shows a response profile opposite to that of healthy individuals, with a sharp increase upon awakening (Thoma et al., 2012). In addition, the cortisol awakening response seems to be lower among individuals with PTSD, in comparison to HC (Wessa et al., 2006; Yehuda et al., 2005).

Similarly, among women with both early and advanced BC (in comparison to HC) flattened diurnal cortisol (indicative of chronic, uncontrollable and traumatic stress (Miller et al., 2007)) has been observed (Abercrombie et al., 2004; Dedert et al., 2012). Although few studies have examined α-amylase in women with BC, one study found that they tend to have higher levels of α-amylase compared to HC (Wan et al., 2016). As previously mentioned, a flat diurnal cortisol slope has been linked to poorer memory performance (Abercrombie et al., 2004), and elevated levels of α-amylase with mild cognitive impairment (Yamane et al., 2022).

1.3.1 The effects of bright light therapy on CR, stress and cognition

Given that CR are often disrupted in women with BC (Blakeman et al., 2016; Liu et al., 2013) and considering that cancer treatments—including surgery, anesthesia, sedatives and the intensive care unit environment—along with chemotherapy can exacerbate this disruption, the risk of CRCI is significantly increased (Ancoli-Israel et al., 2022; Brainard et al., 2015). Thus, there is a pressing need to address this issue.

As previously mentioned, light is the most potent zeitgeber for regulating CR (Boivin et al., 1994; Küller, 2002). Therefore, BLT, which effectively harnesses this natural

mechanism, may be a promising treatment option to mitigate CR disruption and thereby stress, and consequently, reduce the risk of CRCI. Indeed, evidence shows that BLT can improve the robustness and strength of CR (Ancoli-Israel et al., 2003; Ancoli-Israel et al., 2002) and even prevent CR from desynchronizing in women undergoing chemotherapy for BC (Neikrug et al., 2012).

BLT is a low-effort, low-cost treatment with minimal patient burden since it only consists of wearing BLT glasses for half an hour every day, and can show effects within two weeks (Johnson et al., 2018; Starreveld et al., 2018). In addition to synchronizing CR, BLT has been observed to regulate cortisol (Jung et al., 2010; Scheer & Buijs, 1999), decrease depressive (Mårtensson et al., 2015; Valdimarsdottir et al., 2018) and PTSD symptoms (Kawamura et al., 2019; Youngstedt et al., 2022; Zalta et al., 2019). Furthermore, BLT has been found to improve cognitive function in healthy individuals as well as in patients with NCD (Mitolo et al., 2018; Phipps-Nelson et al., 2003). However, while these studies found positive effects of BLT on cognitive function, they did not provide details about the effect sizes, limiting the ability to assess the clinical significance of the findings.

BLT can impact cognitive function indirectly and directly. Indirectly, by influencing cognitive function through synchronizing CR (Boivin et al., 1994; Küller, 2002), as has been suggested in studies on institutionalized individuals with major NCD (Lek et al., 2008; Rubiño et al., 2020; Yamadera et al., 2000). Directly, light activates the intrinsically photosensitive retinal ganglion cells (ipRGCs) which project to the SCN, dorsal raphe nucleus (Shen & Semba, 1994), VLPO (Gooley et al., 2003) and other brain areas involved in promoting wakefulness, sleep and arousal regulation (Chou et al., 2002; Deurveilher & Semba, 2005; Deurveilher & Semba, 2003; Vandewalle et al., 2009; Vandewalle & Dijk, 2013). These acute effects of BWL include enhanced alertness, vigilance, sustained attention and cognitive performance (Cajochen et al., 2005; Chellappa, Gordijn, et al., 2011; Chellappa, Steiner, et al., 2011; Lockley et al., 2006; Rahman et al., 2014; Vandewalle et al., 2009), such as in neuroimaging studies employing attentional and working memory tasks (Vandewalle et al., 2006, 2011). In one such study, a dose-response relationship was found between light intensity and ocular and EEG correlates of human alertness, in addition to the synchronization of

CR (Cajochen et al., 2000). Another study found that bright white light (BWL) compared to dim white light (DWL) improved reaction time assessed via Psychomotor Vigilance Task (PVT) performance (Phipps-Nelson et al., 2003).

Research on the the efficacy of BLT among cancer patients has been scarce and results inconsistent. One meta-analysis on the effects of BLT on sleep quality in cancer patients found a significant improvement in self-reported sleep quality with moderate effects (Yao et al., 2023). During chemotherapy for BC, studies have found that BWL can prevent fatigue, sleep quality, and quality of life from worsening, compared to dim red light (Ancoli-Israel et al., 2012; Jeste et al., 2013; Rissling et al., 2022). Additionally, as previously mentioned, BWL can prevent CR from deteriorating in women undergoing chemotherapy for BC, compared to dim red light (Neikrug et al., 2012). However (to our knowledge), no study has explored whether BLT can mitigate CRCI, or regulate biological and psychological stress markers, in post-operative women with BC.

Recent studies (Johnson et al., 2020; Wu et al., 2022) among cancer patients showed that post-BLT, both the experimental group receiving circadian-stimulating BWL and the comparison conditions receiving non circadian-stimulating dim red light demonstrated steeper cortisol slopes and improved cognitive function, respectively. However, it was not clear whether their cognitive function truly improved or whether these were placebo or practice effects (Wu et al., 2022). An explanation for why both groups improved might be, as the authors themselves argued (Wu et al., 2022), that the long wavelength red light may have enhanced the effects of subsequent light exposure (e.g., daylight) on cognitive function (Chellappa et al., 2014), although this hypothesis needs to be studied further. In an attempt to address this knowledge gap, other studies on cancer patients have tried administering a DWL comparison condition. One of them included programmed environmental illumination during hospitalization for autologous stem cell transplantation in patients with multiple myeloma and found that BWL reduced the severity of depressive symptoms compared to DWL (Valdimarsdottir et al., 2018). Another study (Starreveld et al., 2021) (using BLT glasses) found, similarly to the previously mentioned studies, improvements in depression, cancer-related fatigue, and more, across both groups.

However, as the authors explained (Starreveld et al., 2021), their DWL condition might not have been fully placebo as it involved exposure to a light intensity of 8 lux, which might have had some effect.

To summarize, while BLT has shown promising results regarding improving cognitive function, synchronizing CR, and decreasing biological (i.e., cortisol) as well as PTSD and psychological stress (i.e., depressive symptoms), the efficacy of BLT on CRCI among women with BC remains to be explored. The knowledge gap introduced by these previously mentioned recent studies (where both intervention groups showed improvements (Johnson et al., 2020; Starreveld et al., 2021; Wu et al., 2022)) could potentially be addressed by applying a DWL comparison condition with lower light intensity, thereby providing a more rigorous control and hopefully offering clearer insights into the efficacy of BWL.

2 Aims

As discussed above, major life stressors (such as war exposure, sexual violence, cancer diagnosis and treatment) can cause PTSD, and affect biological (e.g., cortisol and α-amylase) and psychological stress markers (e.g., depressive symptoms) known to impair cognitive function. Since cognitive impairment negatively impacts individuals and society at large, the overarching aim of this Thesis was to investigate this relationship between major life stressors and cognitive impairment further, and identify potential moderators that might affect this association. Furthermore, to explore whether BLT can mitigate the negative effects of life stressors on stress markers, and cognitive function. The aims of each paper included in this Thesis are outlined below.

2.1 Aim of Paper I

The aims of Paper I were to conduct a meta-analysis to (1) explore neurocognitive outcomes associated with PTSD and (2) examine potential moderating factors for cognitive impairment among individuals with PTSD. The moderating factors assessed included age (20-39, 40-59, 60+), study design (cross-sectional or longitudinal), study population (war-exposed populations/veterans or the general population), neurocognitive outcome assessed (i.e., a diagnosis of NCD or type of cognitive domain as classified according to A Compendium of Neuropsychological Tests (Strauss et al., 2006), i.e., attention, processing speed, executive function, memory, visuospatial ability, working memory, and general cognitive function)), gender (≥ 50% women or < 50% women), study quality (high vs low), type of PTSD measure (self-report or clinical diagnosis), as well as the presence of comorbidities such as traumatic brain injury (TBI), depression, and substance use (all coded as either present or absent). Previous research studied the association between PTSD and cognitive impairment either without including an NCD diagnosis (Schuitevoerder et al., 2013; Scott et al., 2015) or focused solely on individuals with an established NCD diagnosis (Günak et al., 2020). By

encompassing a wide spectrum of cognitive impairment, ranging from pre-clinical (cognitive impairment) to clinical (NCD) stages, as well as examining a broad range of clinically important moderators (as listed above), we aimed for a more comprehensive understanding of the long-term cognitive function among individuals with PTSD. Additionally, this meta-analysis is the first to employ a multilevel approach (with maximum likelihood estimation) to study the association between PTSD and cognitive impairment, which is less biased than traditional meta-analytic methods (Cheung, 2019).

2.2 Aim of Paper II

It has been well established that stress can influence the brain and cognitive function. In fact, the results of Paper I indicated that PTSD (representing the most severe spectrum of stress responses) was associated with cognitive impairment. Even so, previous studies on CRCI have mainly focused on how chemotherapy impacts cognitive function (Ahles & Saykin, 2007; Collins et al., 2013; Janelsins et al., 2018; Ono et al., 2015; Schagen & Wefel, 2013; van Dam et al., 1998; Wefel et al., 2010). Very few have examined whether the major life stressor of being diagnosed with cancer (as well as the tumor itself and other factors) can play a part in CRCI (Hermelink et al., 2015), and whether CRCI can emerge before any cancer treatment (Lange et al., 2020). To address this gap in the literature, we conducted a population-based study in Paper II, where all newly diagnosed women with BC in Iceland were invited to participate, to test whether 1) CRCI can begin before any BC treatment, by comparing the cognitive function of treatment-naïve women with BC to HC matched on age and education, and 2) investigate whether stress was linked to CRCI. To achieve the second aim, biological (i.e., cortisol and α-amylase) and/or psychological stress factors (i.e., depressive symptoms, anxiety and overall cancer-related stress) were tested for any potential associations.

2.3 Aim of Paper III

Collectively, the findings of Papers I and II suggest that PTSD, as well as psychological (i.e., cancer-related stress and depressive symptoms) and biological stress markers (i.e., α-amylase) can affect cognitive function, emphasizing the need

for effective interventions targeting cognitive impairment. As discussed above, there is a bidirectional relationship between biological stress markers and CR (Gamble et al., 2014). The fact that light is the strongest zeitgeber for CR (Boivin et al., 1994; Küller, 2002) raises the possibility that BLT may reduce the impact of life stressors (and associated factors) on cognitive function. Previous findings showing that BLT can synchronize CR (Ancoli-Israel et al., 2003; Ancoli-Israel et al., 2002), ameliorate stress (Kawamura et al., 2019; Mårtensson et al., 2015; Valdimarsdottir et al., 2018), and improve cognitive function (Bersani et al., 2008; Killgore et al., 2020; Kim et al., 2021), further supports this possibility. Cancer treatment, including surgery, can elevate stress and disrupt CR, further increasing the risk of CRCI (Brainard et al., 2015; Prete et al., 2018). Therefore, the aim of Paper III was to examine if BLT could mitigate the impact of BC surgery (and associated factors)—usually one of the first treatment (The Icelandic Cancer Society, 2023)—on cognitive function and stress markers (i.e., biological and psychological) in post-operative women with BC.

3 Materials and Methods

An overview of the methods used in Papers I, II and III in the current Thesis are presented in Table 1. The table provides an overview of research design, participants, measures, procedures, and statistical analyses for each study.

Table 1. Overview of the methods employed in Papers I, II and III.

	Paper I	Paper II	Paper III
Design	Three-level random effect meta-analysis using maximum likelihood estimation	Cross-sectional population-based study	Double-blind randomized controlled trial with repeated measures
Participants	Eligible studies comprised of a group with clinical levels of PTSD and a comparison group without clinical levels of PTSD. In total, eligible studies were 53, consisting of 376 analyses with a pooled sample size of 5,709,547.	112 treatment-naïve women with BC (mean age 61.8, SD: 10.7, age range: 25-81) scheduled to receive surgery and 67 HC (mean age: 60.9, SD: 9.5, age range: 37-82) matched on age and education.	Same participants post-surgery: 117 women with BC (mean age 61.8, SD: 10.7, age range: 25-81) randomly allocated to receive BWL, $N = 60$ or DWL, $N = 57$ for four weeks post-surgery.
Measures	Eligible studies needed to use validated methods to determine PTSD (e.g. diagnosis or clinical cutoff on well-established measure) and assess two or more cognitive domains via neuropsychological assessments or use a clinical diagnosis of neurocognitive disorder (e.g., medical records, clinical interview).	Neuropsychological test battery to assess cognitive function and a self-report battery to assess psychiatric symptoms. Cortisol and α-amylase were collected from saliva.	Same measures as in Paper II. Additionally, treatment credibility was assessed pre-BLT and treatment satisfaction post-BLT. BLT was conducted via glasses emitting light from LEDs, 120 lux for the BWL group and 1.16 lux for the DWL group.
Procedure	Peer-reviewed studies from PubMed and Web of Science were extracted using predetermined keywords and criteria.	Neuropsychological assessment and self-report assessment. Saliva collection after awakening and before bedtime for 3 consecutive days. Participants completed all assessments before surgery.	Same procedure as in Paper II was conducted after a 4-week BLT post BC surgery. Participants were randomly allocated to groups using a blocked randomized design. BLT started the day after surgery and continued for four consecutive weeks.
Data analysis	Effect sizes were calculated for each analysis. Moderator analyses were conducted on study design, age, study population, neurocognitive outcome, gender, study quality, type of PTSD measure, traumatic brain injury, depression, and substance use.	Multilinear regressions were conducted.	Path analysis and linear regression within structural equation modeling frameworks were conducted.

PTSD = post-traumatic stress disorder; BC = breast cancer; HC = healthy controls; BWL = bright white light, DWL = dim white light; BLT = bright light therapy

3.1 Paper I

3.1.1 Study eligibility

Studies were included in the meta-analysis if they met the following inclusion criteria: (1) examined the association between a diagnosis of PTSD and cognitive function in human adults aged 18 and older; (2) used validated methods to diagnose PTSD (e.g., diagnosis or clinical cutoff on well-established measure); (3) employed neuropsychological assessment to measure at least two different cognitive domains; (4) used a clinical diagnosis of NCD (e.g., from medical records, clinical interviews and neuropsychological assessment); (5) included a comparison group without PTSD; (6) provided enough data for calculating effect sizes; and (7) were published in a peer-reviewed journal in English.

3.1.2 Information sources and search strategy

In a comprehensive search, initially conducted in December 2019 and updated in April 2024, all studies meeting our inclusion criteria in PubMed/Medline and Web of Science were identified. The search terms included combinations of the following: PTSD, posttraumatic stress disorder, cognitive function, cognitive impairment, cognitive decline, cognitive dysfunction, neurocognitive disorder, Lewy Body dementia, vascular dementia, frontotemporal dementia, and Alzheimer's.

See Figure 1 for a PRISMA flow diagram of the review process and study selection the meta-analysis.

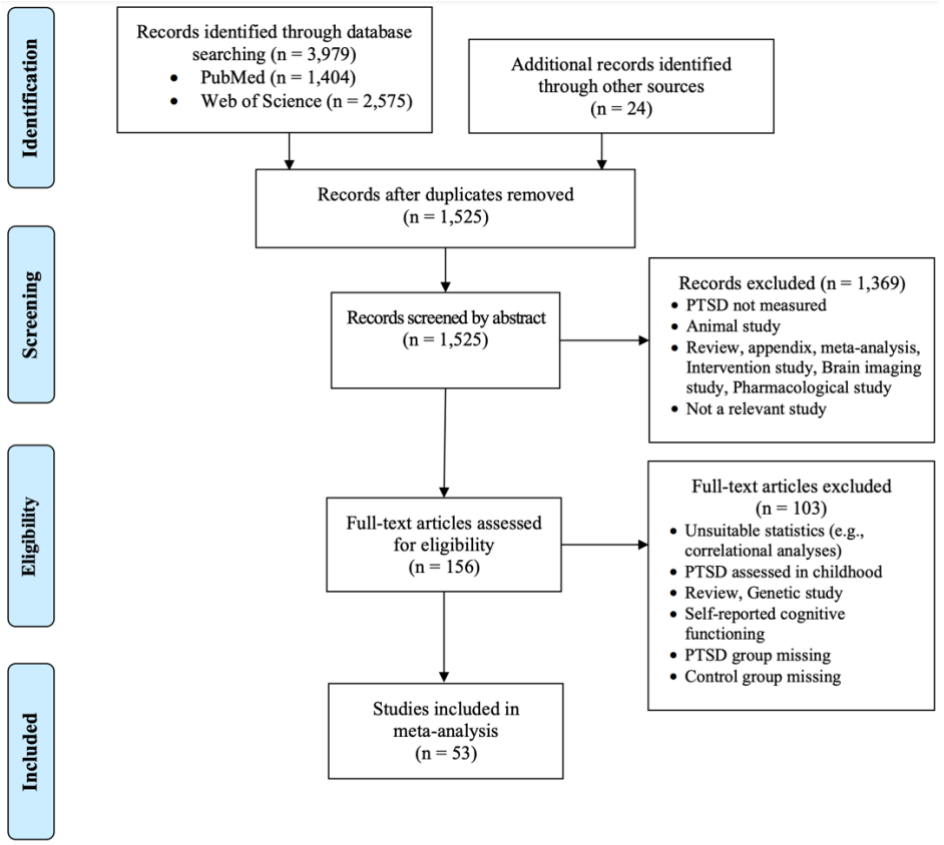

Figure 1. PRISMA flow diagram of the systematic search for applicable studies (Paper I).

3.1.3 Data extraction

Data from fully adjusted models were used to calculate effect sizes. Since either high or low scores on neuropsychological tests can indicate cognitive impairment, all analyses were adjusted such that positive effect sizes indicated greater cognitive impairment for the PTSD group compared to HC.

When two manuscripts presented findings from the same datasets, the study with a greater number of participants or a more rigorous methodology was included.

The Cochrane Handbook, Agency for Healthcare Research and Quality (Owens et al., 2010) and The Newcastle-Ottawa Scale (Wells et al., 2012) were used to assess the study quality of the included studies. Good reproducibility (76.7%) was found among the raters when assessing study quality.

3.1.4 Moderators

3.1.4.1 Age

Given the increased risk of cognitive impairment with age (Morovic et al., 2019), the included studies were classified into distinct chronological age groups based on the mean age of the samples: early adulthood (20-39 year olds), middle adulthood (40-59 year olds), and old age (60+ year olds) (Lachman, 2001).

3.1.4.2 Gender

Since women might be likelier to develop both PTSD and NCD (Christiansen & Berke, 2020; Günak et al., 2020), gender was coded based on the proportion of women in each study, ≥ 50% or < 50% women, and included as a moderator. As previously noted, women may be likelier to develop PTSD given their greater risk (compared to men) of experiencing sexual assault (Tolin & Foa, 2006), which is strongly associated with PTSD (Resnick et al., 2007).

3.1.4.3 Study design

To capture both short-term and long-term effects of PTSD on cognitive function (including the development of NCD), the included studies were coded based on their study design as cross-sectional or longitudinal. Longitudinal studies provide insights into whether cognitive function changes over time, while cross-sectional studies offer a snapshot of cognitive function at a single point in time. Examining study design as a moderator helps determine if the duration of data collection influences the strength or direction of the relationship between PTSD and cognitive function.

3.1.4.4 Study population

The study population included were categorized into war-exposed individuals/veterans and the general population. Most previous studies in the field have focused on veterans, who have higher prevalence rates of PTSD compared to many other subgroups. As previously mentioned, veterans are predominantly male and commonly affected by complications such as traumatic brain injury, which can increase the risk of cognitive impairment and NCD (Barman et al., 2016; Shively et al., 2012). Therefore, it is important to determine whether the association between

PTSD on cognitive function applies to the general public (which has various types of trauma exposures and clinical profiles), or if they are specific to veterans (Scott et al., 2015).

3.1.4.5 Traumatic Brain Injury

Given that traumatic brain injury (also called concussion), including head injuries, increases the risk of developing both cognitive impairment and NCD (Barman et al., 2016; Shively et al., 2012), it was included as a moderator (coded as either present or absent).

3.1.4.6 Depression

Depression was included as a moderator (coded as either present or absent) since it is a common comorbidity of PTSD and associated with both cognitive impairment and NCD (Cohn-Schwartz et al., 2024; Kuring et al., 2020).

3.1.4.7 Substance use

Since substance use (coded as either present or absent) is common among individuals with PTSD, as well as individually linked with cognitive impairment (Kutash et al., 2023), it was included as a moderator.

3.1.4.8 Study quality

To determine whether study quality impacted the association between PTSD and cognitive impairment, it was included as a moderator. Studies with a Newcastle-Ottowa Scale score of 7 or higher were initially classified as high quality. However, with only 11% of studies achieving this standard, the threshold was lowered to include studies with a score of 6 or higher, thereby encompassing 28% of the total studies.

3.1.4.9 Neurocognitive outcomes

Informed by previous research on how PTSD can affect various cognitive domains differently, as well as the risk of developing NCD (leading to varying degrees of cognitive impairment) (Günak et al., 2020; Qureshi et al., 2011; Schuitevoerder et al., 2013; Scott et al., 2015), the neurocognitive outcome assessed in the retrieved studies was included as a moderator in the meta-analysis.

The neurocognitive outcomes in the present study included an established diagnosis of NCD, and the cognitive domains assessed in the retrieved studies. The Compendium of Neuropsychological Tests (Strauss et al., 2006) was used to classify neuropsychological tests into their respective cognitive domain: General cognitive function (e.g. MMSE), Attention (e.g. Continuous Performance task), Working memory (e.g. Digit Span), Processing speed (e.g. Digit Symbol), Memory (e.g. Rey Auditory Verbal Learning Fluency Test (RAVLT)), Executive function (e.g. Stroop) or Visuospatial function (e.g. Block Design).

3.1.5 Statistical Analysis

Effect sizes were converted into Hedges g effect sizes using the *esc* R package (Lüdecke, 2019). Hedges' *g* correction formula was used to decrease small sample bias (Borenstein et al., 2009; Hedges, 1981).

Since the included studies used multiple neuropsychological tests assessing different cognitive domains, we conducted a three-level meta-analysis using the maximum likelihood estimation to assess heterogeneity and account for dependency between the effect sizes. This method is less biased than traditional meta-analytic procedures and allows for a broader scope of research questions (Cheung, 2019).

The *metafor* package in R (Viechtbauer, 2010) was used to perform the three-level random effect meta-analysis. It was assumed that individual effect sizes (random effect at level 2) were nested within studies (random effect at level 3). Heterogeneity of the variance between studies was calculated using I^2 (Thorlund et al., 2012). Since the fixed effects model analyses revealed high inter-study heterogeneity (I^2 = 86.42%), a random effects model was utilized. Egger's regression intercept (Egger et al., 1997), Duval and Tweedie's trim and fill analysis (Duval & Tweedie, 2000) and Rosenthal's fail-safe N (Rosenthal, 1979) were employed to assess publication bias. In this Thesis, all statistical analyses were performed in R.

3.2 Paper II

3.2.1 Participants

Participants were 112 newly diagnosed treatment-naïve women with BC (stages I-III) scheduled to receive surgery (mean age 61.8, SD: 10.7, age range: 25-81) and 67 HC (mean age: 60.9, SD: 9.5, age range: 37-82) matched on age and educational level. The HC group was selected from a large population-based study representative of the Icelandic population, called *Trauma, mental health and disclosures of sexual violence* (*N*=1,793), that studied whether participants had experienced trauma. Eligibility criterion for the HCs was that they had no history of cancer. Table 2 compares the women with BC and HC groups on sociodemographic, biological and psychological factors.

Table 2. Sociodemographic differences between women with breast cancer and healthy controls before any cancer treatment (Paper II).

	Women with breast cancer (*N*=112)	Healthy controls (*N*=67)	*p*
Age in years (mean, SD)	61.8 (10.7)	60.9 (9.5)	.57
Currently partnered, *N*(%)			1
Yes	74 (66.1%)	44 (65.7%)	
No	33 (29.5%)	19 (28.4%)	
Education level, *N*(%)			.55
Primary	18 (16.1%)	10 (14.9%)	
Secondary	36 (32.1%)	17 (25.4%)	
University	53 (47.3%)	37 (55.2%)	
BMI (mean, SD)	27.7 (5.0)	28.1 (4.8)	.61
Physical activity, *N*(%)			.48
None	17 (15.2%)	12 (17.9%)	
Once a week	10 (8.9%)	2 (3.0%)	
Twice a week	16 (14.3%)	10 (14.9%)	
≥3 times a week	64 (57.1%)	40 (59.7%)	
Menopause, yes %	88 (78.6%)	56 (83.6%)	.62
Cortisol (mean, SD)	5.1 (2.1)	-	-
α-amylase (mean, SD)	140.5 (94.8)	-	-
Depressive symptoms (mean, SD)	11.0 (8.5)	8.8 (7.3)	.08
Anxiety symptoms (mean, SD)	4.1 (3.8)	2.8 (3.3)	.02*
Overall cancer-related stress (mean, SD)	25.5 (14.6)	-	-
Average time since diagnosis (weeks)	3.0	-	-
Cancer stage, *N*(%)			
0	4 (3.6%)	-	-
I	49 (43.8%)	-	-
II	36 (32.1%)	-	-
III	10 (8.9%)	-	-
HER-2 positive, *N*(%)	8 (7.1%)	-	-
Estrogen positive, *N*(%)	101 (90.2%)	-	-
Progesterone positive, *N*(%)	80 (71.4%)	-	-

BMI = Body Mass Index; HER-2 = human epidermal growth factor receptor 2
* = $p < 0.05$ (two-sided). Two-sample t-tests were performed for continuous variables to compare means between groups, and chi-squared tests were used for categorical variables to test for group differences.

Since Papers II and III included the same sample, exclusion criteria included contraindications for BLT as well as a neurological condition that could influence neuropsychological functioning (i.e., autism diagnosis, epilepsy and traumatic brain

injury), age younger than 18 years, if their first BC treatment was another treatment than surgery (e.g., neoadjuvant), if they had other cancers or were currently undergoing treatment for other cancers, pregnancy, pre-existing anemia, currently employed in night shift work, confounding underlying medical illnesses which may cause fatigue, eye diseases which limit the ability to process light, severe sleep disorders (e.g., narcolepsy), severe psychological impairment (e.g., hospitalization for depressive episode the past year or history of bipolar disorder/mania), current use of light therapy, living abroad and being unable to understand or read Icelandic. See Figure 2 for the participant flow throughout Paper II.

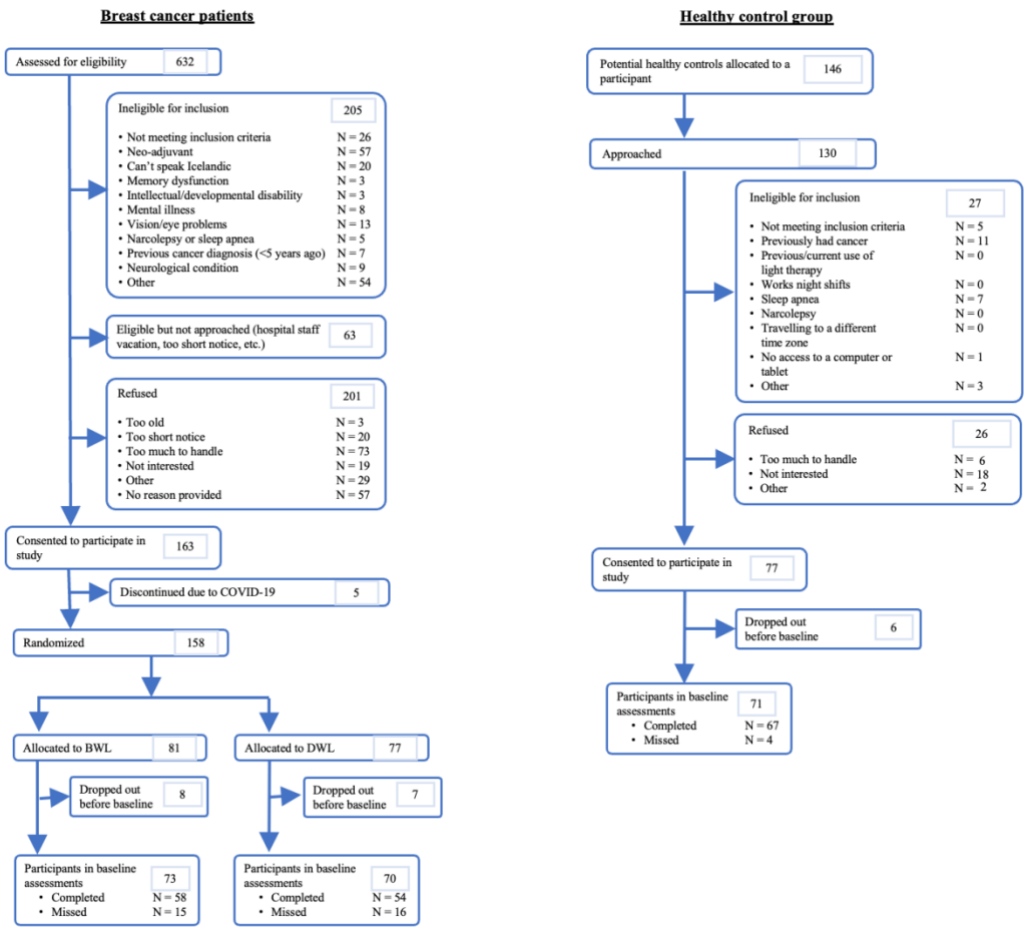

Figure 2. Participant flow through Paper II.

3.2.2 Measures

3.2.2.1 Neuropsychological assessment

The neuropsychological assessment was based on the recommendations of the International Cancer and Cognition Task Force (Wefel et al., 2011) and availability of translations.

Sustained attention and reaction time (RT) was measured with the 5-minute Psychomotor Vigilance Test (PVT) (Dinges & Powell, 1985). The participants were instructed to observe a red rectangular box on the computer screen, and to press a button as soon as possible after a yellow stimulus counter was presented inside the box. As soon as the participants responded, the counter stopped and displayed the reaction time in milliseconds (Basner & Dinges, 2011). The test has shown good psychometric properties, with test-retest reliability above 0.8 (Dorrian et al., 2004).

Processing speed was assessed with the computerized Trail Making Test-A (TMT-A) (Reitan, 1958; Woods et al., 2015) where the task of the participants was to tap 25 randomly arranged circles containing a number from 1-25 as fast and accurately as they could, in the correct ascending numerical sequence (1-2-3, etc.). See Woods et al. (2015) for more details about the computerized TMT. The computerized TMT taps into the same aspects of cognition as the paper-based TMT (r=0.98) (Dahmen et al., 2017) and a test-retest reliability of 0.87 (Woods et al., 2015).

Working memory and immediate auditory recall was measured with the Wechsler Adult Intelligence Scale-Fourth Edition (WAIS-IV) Digit Span subtest (Wechsler, 2008). This test consists of two subsections: Digits forwards and Digits backwards, each containing eight items. Participants were required to repeat the numbers read by the examiner either in the same order or in reverse order. Digit Span demonstrates good reliability and validity, with an internal consistency of 0.79, test-retest reliability of 0.77 and split-half reliability of 0.88 (Elwood, 1991; Kane et al., 2004).

Verbal memory and learning were assessed using the RAVLT (Rey, 1964). Participants listened to a series of 15 common words, which were read aloud five times. After each repition, they were asked to repeat as many as they could recall.

Afterwards, a second list of 15 unrelated words was read, participants were tasked with recalling as many words from the original list as possible. The RAVLT demonstrates good internal consistency (Cronbach's α = 0.80) and adequate convergent and divergent validity (Magalhães et al., 2012).

Verbal fluency was assessed with the Icelandic equivalent (translated by María K. Jónsdóttir, *unpublished*) of the Controlled Oral Word Association Test (COWAT) (Benton et al., 1994). The COWAT consists of two parts: the first part assesses phonemic fluency, where participants are required to generate as many words as possible that begin with a specific letter within one minute (F-A-S in the original test and H-S in Icelandic since they are the most frequent letters in Icelandic (Pind et al., 1991)). The second part evaluates semantic fluency (Delis et al., 2001), in which participants must name as many animals as they can within the same timeframe. A study reported good internal consistency for the F-A-S test (Cronbach's α = 0.83) and a test-retest reliability of 0.74 (Tombaugh et al., 1999).

Executive function was measured with the computerized TMT-B (Reitan, 1958; Woods et al., 2015), where participants were tasked with connecting randomly arranged encircled numbers from 1 to 13 and letters from A to L. Their task was to tap them in the correct ascending sequence while alternating between letters and numbers, as quickly and as accurately as possible (first number-first letter (1-A), second number-second letter (2-B), etc.). TMT-B has demonstrated a test-retest reliability of 0.85) (Woods et al., 2015).

3.2.2.2 Psychological assessment

Cognitive complaints were measured with the Patient-Reported Outcomes Measurement Information System (PROMIS®)-Cognitive Function 8a (Lai et al., 2014), with higher scores indicating fewer cognitive complaints. Depressive symptoms were measured with the Center for Epidemiological Studies Depression Scale (CES-D) (Radloff, 1977). Anxiety was assessed with Generalized Anxiety Disorder-7 (GAD-7) (Spitzer et al., 2006). These measures were administered to both the women with BC and HC. The Impact of Events Scale-Revised (IES-R) (Weiss & Marmar, 1997) was administered only to the women with BC to assess overall cancer-

related stress. Unless otherwise specified, higher scores on all measures reflected more severe psychiatric symptoms or traits. The internal consistency (Cronbach's α) of the measures ranged from .87 (GAD) to .96 (PROMIS-Cognitive Function).

3.2.2.3 Sociodemographic and clinical variables

Sociodemographic information regarding gender, age, education, relationship status, body mass index (BMI), physical activity and menopause were collected via self-report. Clinical variables were collected from the medical records of the women with BC, including cancer stage, type of surgery, human epidermal growth factor receptor 2 (HER2), estrogen and progesterone status.

3.2.2.4 Cortisol and α-amylase

Saliva samples were collected using Salivette tubes twice a day, upon awakening and <30 minutes from bedtime, for three consecutive days. The women with BC were instructed to refrigerate the saliva samples. After retrieving the saliva samples from participants, they were stored at -80°C and then batched and shipped on dry ice for analysis. There the saliva samples were frozen and stored at -20°C. After thawing, samples were centrifuged at 3,000 rpm for 5 minutes. The intra- and inter-assay coefficients of variance were below 9%.

3.2.3 General procedure

Due to COVID-19 social restrictions, all assessments were conducted remotely. Participants completed the psychological assessment online via Research Electronic Data Capture (REDCap) (Harris et al., 2009). The Digit Span, COWAT and RAVLT were administered over the phone by trained research staff members. Participants took part in the TMT and PVT remotely on a computer and were given instructions on how to extract the saliva samples at home for three consecutive days. They were instructed to extract the morning sample as soon as possible within half an hour after awakening and the evening sample within half an hour before bedtime. The women with BC completed all baseline measurements before any BC treatment.

3.2.4 Statistical analysis

Based on the recommendations of International Cancer and Cognition Task Force (Wefel et al., 2011), CRCI was categorized by having at least one neuropsychological

outcome with z-scores ≤ -1.5 in two or more cognitive domains. To evaluate overall cognitive performance, a global composite score (GCS) was derived by averaging the z-scores of all neuropsychological outcomes for participants with complete neuropsychological data (Amidi, Wu, Agerbæk, et al., 2015). Since the computerized neuropsychological tests were self-administered online without supervision (because of COVID-19), time values that were 1.5 * interquartile range (IQR) away from the mean were removed (20 from PVT and 6 from the TMT-A). Welch two-sample *t*-tests, chi-square or Fisher's tests were employed to test the differences between the women with BC and HC on neuropsychological outcomes. Listwise deletion was used in all analyses. Multiple linear regression analyses were performed to test whether the biological variables (cortisol and α-amylase) and psychological variables (depressive symptoms, anxiety and cancer-related stress), along with age and education predicted overall cognitive performance, cognitive impairment, and cognitive complaints. The standardized regression coefficient was used. Welch two-sample *t*-test was employed to test whether women with BC had more cognitive complaints than the HC. For all models, when the assumption of heteroscedasticity for linear regression was violated, the dependent variable was log-transformed. All other assumptions for the statistical analyses were met. Effect sizes were calculated using Partial η^2.

3.3 Paper III

The participants in Paper III consisted of 117 women with BC (age range: 25-81), who participated in baseline assessments before any BC treatment (Paper II) and again after undergoing a 4-week BLT post BC surgery (Paper III). To ensure the homogeneity of the sample in Paper III, four participants diagnosed with stage 0 BC (TisN0M0) were excluded, as accurate cancer staging can only be determined post-surgery. Additionally, exclusions included a participant who was subsequently diagnosed with lung cancer and another diagnosed with age-related macular degeneration. See Figure 3 for the participant flow throughout Paper III.

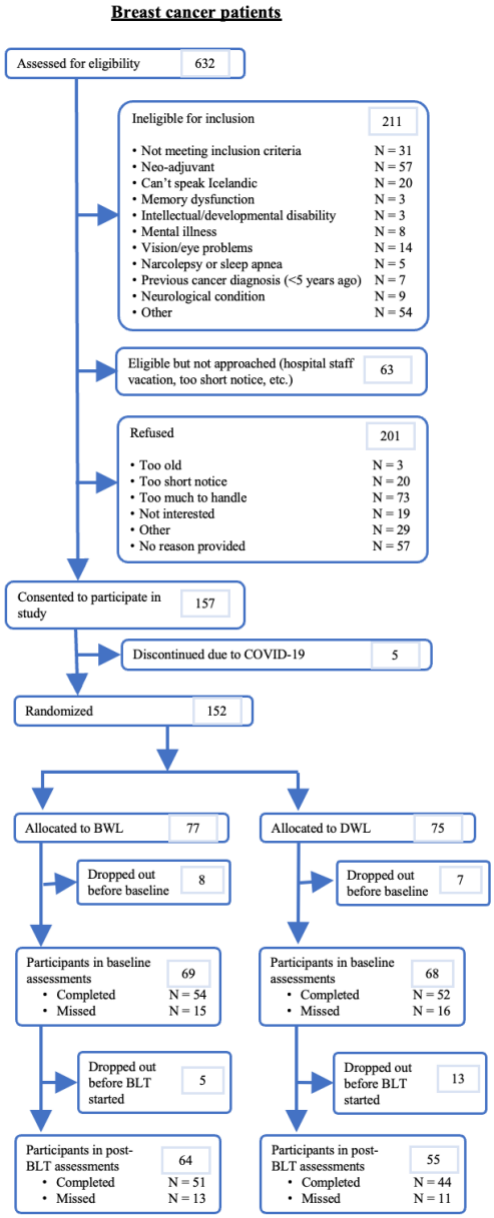

Figure 3. Participant flow through Paper III.

Note. The sample sizes reflect participants who completed either baseline or follow-up (or both).

These post-operative women with BC were randomly allocated to receive either a circadian-stimulating BWL (N=60) or non-circadian stimulating DWL (N=57). Table 3 summarizes the main participant characteristics and shows that the groups did not differ on any variable (i.e., sociodemographic, clinical, biological nor psychological), except in treatment credibility, p = .010 (see Table 3).

Table 3. Demographic and clinical characteristics of the groups, the post-operative women with breast cancer who were administered BWL, compared to the post-operative women with breast cancer who were administered DWL (Paper III).

	BWL (*N*=60)	**DWL** (*N*=57)	***p***
Age in years *(M, SD)*	61.5 (11.7)	61.5 (10.2)	.98
Currently partnered, *N*(%)			.28
Yes	38 (63.3)	32 (56.1)	
No	12 (20.0)	17 (29.8)	
Education level, *N*(%)			.68
Primary	9 (15.0)	7 (12.3)	
Secondary	17 (28.3)	14 (24.6)	
University	24 (40.0)	28 (49.1)	
BMI *(M, SD)*	27.5 (5.71)	28.5 (4.36)	.35
Physical activity, *N*(%)			.25
None	8 (13.3)	8 (14.0)	
Once a week	8 (13.3)	2 (3.5)	
Twice a week	6 (10.0)	9 (15.8)	
≥3 times a week	28 (46.7)	30 (52.6)	
Menopause, *yes %*	40 (66.7)	40 (70.2)	.06
Biological (M, SD)			
Cortisol	4.84 (1.85)	4.94 (2.08)	.76
α-amylase	144.99 (92.08)	125.88 (82.12)	.20
Psychological (M, SD)			
Depressive symptoms	12.0 (9.42)	9.46 (7.68)	.13
Anxiety symptoms	4.48 (4.32)	3.85 (3.70)	.41
Overall cancer-related stress	25.2 (14.7)	25.2 (14.6)	.99
Clinical (N, %)			
Cancer stage			
I	33 (55.0)	27 (47.4)	.23
II	20 (33.3)	27 (47.4)	
III	7 (11.7)	3 (5.3)	
Type of surgery			.42
Lumpectomy	39 (65.1)	33 (57.9)	
Mastectomy	17 (28.3)	21 (36.8)	
Subsequent BC treatment			0.69
No treatment	10 (16.7)	7 (12.3)	
Endocrine	31 (51.7)	28 (49.1)	
Radio/chemotherapy	19 (31.7)	22 (38.6)	
HER-2 positive	5 (8.3)	6 (10.5)	.76
Estrogen positive	54 (90.0)	52 (91.2)	.72
Progesterone positive	44 (73.3)	42 (73.7)	.83
Light Exposure (M, SDI)			
Light glasses use (days)	21.0 (8.87)	15.7 (6.85)	.29
Light glasses use (min.)	631 (266)	472 (205)	.29
Patient perception of BLT (M, SD)			
Treatment credibility (out of 10)	7.76 (1.45)	6.76 (2.21)	.010*
Treatment satisfaction (out of 5)	2.0 (1.00)	2.0 (1.41)	.10

Note. The sample size includes participants who completed either baseline or follow-up (or both).
M = Mean; SD = Standard deviation; BWL = Bright white light; DWL = Dim white light; BMI = Body Mass Index; HER-2 = human epidermal growth factor receptor 2; BLT = Bright light therapy
* = $p < .05$ (two-sided). Two-sample t-tests were performed for continuous variables and Fisher's exact test for categorical variables.

3.3.1 Blinding and randomization

Participants were randomly allocated to receive either BWL or DWL using a blocked randomized design. Participants and the research team members employing the neuropsychological assessments were blinded to the group allocation.

3.3.2 Light Therapy

Since previous research (Starreveld et al., 2021; Wu et al., 2022) may not have provided an optimal placebo condition (i.e., due to the long wavelength of dim red light and dim white light with higher-than-ideal intensity, as previously explained), the current study will build on their findings and address these concerns with a lower intensity DWL comparison condition.

Hence, AYO light glasses were utilized for emitting the BLT. These glasses safely emit LED lights 15 mm from the eye (Suls et al., 2022). The circadian-stimulating BWL of the experimental group consists of 470–475 nanometers (nm) blue light with an irradiance of 250 $\mu W/cm^2$ (120 lux), the most efficient wavelength to adjust the CR (Suls et al., 2022; Tosini et al., 2016). In comparison, the non-circadian stimulating DWL glasses have an irradiance of 2.5 $\mu W/cm^2$ (1.16 lux).

3.3.3 Measures

Paper III contained the same measures (both neuropsychological and psychological) as in Paper II. Since the HC were not utilized in Paper III, *T*-scores for cognitive complaints were calculated using Icelandic norms (*unpublished*). Higher PROMIS scores indicated less cognitive complaints. Since BLT could potentially influence the overall cancer-related stress symptoms (assessed with IES-R as in Paper II) differently, we conducted three separate path analyses for each of the three IES-R subscales: intrusive thoughts, hyperarousal, and avoidance. Treatment credibility of the BLT was measured at baseline with the first item of the Credibility/Expectancy Questionnaire (CEQ) (Devilly & Borkovec, 2000), "*How logical does the BLT offered to you seem?*" (Devilly & Borkovec, 2000) and post-BLT, treatment satisfaction was assessed with the item "*How do you rate this treatment overall?*" from the Functional Assessment of Chronic Illness Therapy-Treatment Satisfaction-General (FACIT-TS-G) (Peipert et al., 2014). The internal consistency (Cronbach's

α) of these measures ranged from .89 (CEQ, CES-D) to .96 (PROMIS-Cognitive Function).

3.3.4 Cortisol and α-amylase

Post-BLT, the women with BC were instructed to refrigerate the saliva samples and bring them to their next scheduled hospital appointment, if applicable. Thereafter, staff retrieved the samples either from the hospital, the home of the participants or from the post office if they lived outside the greater capital area.

3.3.5 Covariates

3.3.5.1 Sociodemographic variables

The same sociodemographic and clinical variables as in Paper II were utilized. In the path analysis models, age and education (commonly accounted for when testing cognitive function, e.g., in Amidi, Wu, Pedersen, et al., 2015) were examined for their association with overall cognitive performance, reaction time, processing speed, working memory and verbal memory. Since cortisol and α-amylase responses can differ with age, age was additionally controlled for in the biological path analysis models (Larsson et al., 2009; Strahler et al., 2010).

3.3.5.2 Clinical variables

Since BC stage (I, II or III) and subsequent BC treatments (no further BC treatment (0), endocrine therapy (1) or chemotherapy/radiotherapy (2)) may influence cognitive function (Hardy et al., 2018), as well as biological and psychological stress (Brown et al., 2020), we adjusted for their effects in the path analyses models.

3.3.6 General procedure

As previously stated, in Paper II, participants completed all baseline measurements before any BC treatment, and in Paper III, they were instructed to start the BLT on the day after their BC surgery while still at the hospital. The BLT session was initiated through a specialized mobile application so that its date and duration could be monitored. Participants were instructed to initiate the BLT session as soon as possible after awakening since BLT is most effective shortly after waking up (Gooley, 2008;

Scheer & Buijs, 1999). After completing the 4-week BLT, participants were instructed to take part in the post-BLT assessments (same as in the pre-BLT assessments in Paper II) as soon as possible within a week.

3.3.7 Statistical analysis

Descriptive statistics, independent samples T-tests and Fisher's tests were used to compare the BWL and DWL groups on sociodemographic, clinical and psychological variables. The post-BLT *z*-scores were calculated as follows (Wu et al., 2022):

$$Z\text{-}Score_{Post\text{-}BLT} = (Raw\ score_{Post\text{-}BLT} - \mu_{Baseline})/\sigma_{Baseline}$$

where μ represents the baseline mean and σ the baseline standard deviation. A post-BLT GCS score was calculated with the mean *z*-scores of all neuropsychological outcomes for participants with complete data. Time values exceeding 1.5 * IQR from the mean (28 from PVT and 7 from the TMT-A) were classified as outliers and treated accordingly. To control for multiple comparisons, False Discovery Rate (FDR) with the Benjamini-Hochberg procedure was employed.

Our analytical strategy tested the direct influence of treatment condition (BWL compared to DWL) on post-treatment function, while controlling for theoretically justified covariates. To achieve this, and handle missing data using maximum likelihood estimation (Larsen, 2011; Muthén et al., 1987), the *Lavaan* package was used to perform path analyses in R (Rosseel et al., 2023). The Yeo-Johnson transformation was employed on skewed data using the *caret* R package (Kuhn, 2008), since it is especially effective for variables consisting of both positive and negative values (i.e., diurnal slopes and *z*-scores of the neuropsychological tests). Since responses to cognitive complaints and treatment credibility were still skewed post-transformation (with participants predominantly rating their perceived cognitive function and treatment credibility highly), both were categorized into two groups (cognitive complaints based on a clinical cut-off score ≥ 45 being classified as being within normal limits vs. below normal limits) (Edelen et al., 2022; Rothrock et al., 2019) and treatment credibility (≥ 7 vs. others).

First, analyses were conducted on autoregressive models (containing only autoregressive paths from pre- to post-BLT), and fit indices analyzed. Second, the full model containing the treatment condition and covariates (included based on theoretical rationale and their relationship with key outcomes) was examined. Modification indices were used to identify potential paths or relationships to improve model fit. Third, to find the best fitting models, fit indices between the autoregressive and full models were compared using Likelihood ratio tests. Model fit was assessed with standard indices for path analyses, including a non-significant χ^2, Comparative Fit Index (CFI > 0.90), Tucker-Lewis Index (TLI < 0.95), Root Mean Square Error of Approximation (RMSEA < 0.05), and Standardized Root Mean Residual (SRMR < 0.08) (Hu & Bentler, 1999).

The models testing cognitive function (i.e., overall cognitive performance, reaction time, processing speed, working memory and verbal memory) included direct effects of treatment group and baseline cognitive function on post-treatment cognitive function, while controlling for age, education, BC stage, subsequent BC treatment and perceived treatment credibility (due to the significant differences between BWL and DWL groups, see Table 3). When comparing completers and non-completers in overall cognitive function and overall cancer-related stress, the groups significantly differed in cognitive complaints, depressive and anxiety symptoms. Therefore, these variables were additionally controlled for (i.e., cognitive complaints, depressive and anxiety symptoms in the overall cognitive function path analysis, and cognitive complaints in the overall cancer-related stress path analysis). Furthermore, since choice of BC treatment is often dependent on BC stage and the patient's age (age may influence BC treatment decisions through e.g., physiological tolerance, comorbidities, and risk tolerance), age and BC stage were allowed to correlate with subsequent BC treatment. Age was also allowed to correlate with education (e.g., since younger women may be more educated than older women). The biological and psychological stress models followed the same structure, except education was not included, and age was only included in the biological stress models.

All statistical analyses were based on an intention-to-treat (ITT) basis. Sensitivity analyses were conducted to test the robustness of the findings across different

conditions, i.e., among participants with minimum of 50% treatment adherence (N = 79), and those who participated during winter (N = 81), when daylight hours were under average globally (during October to March). A complete case analysis was conducted to evaluate the impact of maximum likelihood estimation in handling the missing data, and lastly, characteristics of completers and non-completers were compared (the only analysis not corrected for multiple testing).

3.4 Ethical considerations

3.4.1 Paper I

When conducting a meta-analysis, the analysis consists of already existing data from previously published studies, meaning it did not involve direct contact with human participants, and therefore, no informed consent or ethical approvals were needed.

3.4.2 Papers II and III

All participants in Papers II and III gave informed consent before participating in the studies. Additionally, the studies in Papers II and III were approved by the Icelandic Data Protection Authority, the chief medical officer at the National University Hospital and the National Bioethics Committee (VSN-18-199) of Iceland.

4 Results

This section presents the main results from the three Papers included in this Thesis. See each paper at the end of this Thesis for a more detailed description.

4.1 Paper I

To examine neurocognitive outcomes of PTSD, 53 applicable studies were analyzed, consisting of a pooled sample size of 5,709,547 participants and 376 analyses. The three-level model had a significantly better fit than the two-level model, (χ^2= 108.66, $p < .0001$). The pooled effect across the studies was $g = 0.30$, $p < .0001$, 95% CI [0.23 - 0.37], with small to medium effects (see Table 2), indicating greater cognitive impairment among individuals with PTSD compared to HC.

None of the moderators (i.e., study design, study population, age, gender, neurocognitive outcome, depression, TBI, type of PTSD assessment, or substance use) significantly moderated the association between PTSD and cognitive impairment. However, significant effects were found within all subgroups, with small to medium effects (see Table 4).

Table 4. Meta-analysis and moderators of the association between PTSD and cognitive impairment (Paper I).

Analysis	Number†	Effect sizes (95% CI)	Heterogeneity Q, I^2
Main analysis	53 (376)	30 (.23 - 37)	1998.24***, 86.6%
Study design			1491.50***, 86.8%
F(df1 = 1, df2 = 375) = 0.46, p = 0.50			
Cross-sectional [index]	36 (346)	0.28 (0.21 – 0.36)	
Longitudinal	17 (30)	0.35 (0.27 – 0.43)	
Neurocognitive outcomes			1258.12***, 87.1%
F(df1 = 6, df2 = 369) = 0.72, p = .63			
Diagnosis [index]	16 (26)	0.34 (0.21 – 0.47)	
Attention & processing speed	6 (63)	0.29 (0.17 - 0.42)	
Executive function	5 (84)	0.26 (0.13 - 0.38)	
General cognitive function	12 (42)	0.29 (0.17 - 0.42)	
Memory	7 (116)	0.31 (0.19 - 0.44)	
Visuospatial & perceptual ability	2 (9)	0.30 (0.17 - 0.42)	
Working memory	5 (36)	0.24 (0.11 - 0.37)	
Study population			1360.23***, 86.9%
F(df1 = 1, df2 = 374) = 0.00, p = .99			
General population [index]	24 (186)	0.30 (0.20 – 0.40)	
War exposure (including veterans)	29 (190)	0.30 (0.06 – 0.54)	
Age group			1043.19***, 86.6%
F(df1 = 2, df2 = 343) = 0.31, p = .74			
20 - 39 [index]	15 (191)	0.32 (0.20 - 0.44)	
40 - 59	18 (83)	0.27 (-0.03 - 0.56)	
60 +	17 (72)	0.33 (0.04 – 0.62)	
Traumatic Brain Injury			1698.88***, 86.7%
F(df1 = 1, df2 = 374) = 1.17, p = .28			
Without TBI [index]	45 (349)	0.32 (0.24 – 0.39)	
With TBI	8 (27)	0.22 (0.02 - 0.41)	
Depression			1760.61***, 98.1%
F(df1 = 1, df2 = 374) = 0.06, p = .81			
Depression absent [index]	42 (352)	0.30 (0.22 - 0.37)	
Depression present	11 (24)	0.32 (0.07 - 0.56)	
Proportion of women			1457.63***, 86.9%
F(df1 = 1, df2 = 374) = 0.01, p = .93			
< 50% women [index]	30 (202)	0.30 (0.21 - 0.39)	
≥ 50% women	23 (174)	0.30 (0.14 - 0.47)	

Type of PTSD measure			1297.28***, 86.8%
F(df1 = 1, df2 = 374) = 0.19, p = .66			
Self-report diagnosis [index]	15 (75)	0.27 (0.14 – 0.41)	
Clinical diagnosis	38 (301)	0.31 (0.02 – 0.59)	
Substance use			1712.29***, 86.9%
F(df1 = 1, df2 = 374) = 0.03, p = .87			
Absent [index]	43 (345)	0.30 (0.22 - 0.37)	
Present	10 (31)	0.31 (0.06 - 0.56)	
Study quality			1697.25***, 86.9%
F(df1 = 1, df2 = 374) = 0.00, p = .98			
Low quality (< 6) [index]	38 (243)	0.30 (0.22 - 0.38)	
High quality (≥ 6)	15 (133)	0.30 (0.22 - 0.38)	

Note. PTSD=Post-Traumatic Stress Disorder; TBI = Traumatic Brain Injury
†Number of studies (analyses included)
******* p < .0001

Egger's test revealed significant publication bias in the primary analysis for the association between PTSD and cognitive impairment (t[374] = 3.08, p = .002). To adjust for this bias, Duval and Tweedie's trim-and-fill procedure was applied, revising the initial effect size from g = 0.30 to g = 0.13, p < 0.0001, 95% CI (0.10 - 0.17), suggesting a small effect size. The robustness of the association between PTSD and cognitive impairment was further supported by Rosenthal's fail-safe N, which suggested that 9,531,366 null findings would be required to invalidate our finding, indicating a minimum risk of bias (Rosenthal, 1991; Shi et al., 2021).

4.2 Paper II

To explore whether CRCI can start before any cancer treatment, the cognitive function of treatment-naïve women with BC was compared with HC matched on age and education. Table 5 shows that women with BC had significantly slower processing speed (t[136.3]=2.6, p = .01, CI [.14,.98]) compared to HC. Additionally, Fisher's exact test showed that women with BC were more likely to score within the impaired range for processing speed (total time on TMT-A, p < .001) and verbal memory (RAVLT total score, p < .001). Women with BC and HC did not significantly differ on any other neuropsychological outcomes, including overall cognitive performance.

Table 5. A comparison of the treatment-naïve breast cancer patients and healthy controls on their neuropsychological performance and impairment (categorized as scoring $z \leq -1.5$) frequency in each outcome (Paper II).

Cognitive domain	NP test outcome measure†	Raw score, mean (SD) *N*		Z-score, mean (SD)‡	*p* – value Group differences (*z*-scores)	Impairment frequency by test ($z < -1.5$) *N* (%)		p-value ($\chi 2$ or Fisher's test)
		HC	BC	BC		HC	BC	
Reaction time (RT)	PVT Mean RT	424.2 (104.8) *N*=58	417.7 (113.5) *N*=67	.06§ (1.1)	.74	7 (12.1%)	6 (9.0%)	.46
Processing speed	TMT-A (s)	51.2 (15.2) *N*=61	59.7 (23.1) *N*=80	-.56 (1.5)	.01*	6 (7.5%)	20 (25.0%)	<.001**
Working memory	WAIS-IV Digit Span (correct)	17.3 (5.1) *N*=67	17.1 (4.6) *N*=112	-.05 (.9)	.75	1 (1.5%)	3 (2.7%)	.79
Verbal memory	RAVLT total score	46.2 (11.9) *N*=67	43.3 (10.8) *N*=103	-.24 (0.9)	.11	4 (6.0%)	10 (9.7%)	<.001**
	RAVLT delayed recall	9.8 (3.1) *N*=64	9.2 (3.4) *N*=102	-.21 (1.1)	.21	6 (9.4%)	15 (14.7%)	.95
Verbal fluency	COWAT-Letters (H,S)	13.7 (4.8) *N*=67	13.1 (4.3) *N*=112	-.13 (.9)	.39	4 (6.0%)	4 (3.6%)	.09
	COWAT-Category (Animals)	21.7 (5.5) *N*=67	20.6 (6.0) *N*=111	-.02 (.9)	.19	2 (3.0%)	4 (3.6%)	.84
Executive function	TMT-B (s)	103.3 (38.9) *N*=61	110.1 (48.7) *N*=80	-.17 (1.3)	.36	6 (9.8%)	10 (12.5%)	.46

†Neuropsychological test outcome measure; ‡Z-scores of women with BC compared with HC ($HC_z = 0$); BC = Breast cancer patients; HC = healthy controls; PVT = Psychomotor Vigilance Test; TMT = Trail Making Test; WAIS = Wechsler Adult Intelligence Scale; RAVLT = Rey Auditory Verbal Learning Test; COWAT = Controlled Oral Word Association Test

* = $p < 0.05$ (two-sided)

** = $p < 0.001$ (two-sided)

These findings showed that treatment-naïve women with BC had impairments in processing speed and verbal memory compared to HC. This indicates that CRCI is not solely due to chemotherapy-induced neurotoxicity, as previously believed, but may also be associated with the BC itself or associated factors (such as the stress associated with the BC diagnosis).

To test whether stress plays a role in CRCI, we regressed stress-related biological and psychological predictors on overall cognitive performance and the impaired cognitive domains, i.e., processing speed and verbal memory, in the treatment-naïve women with BC. Table 6 shows these findings, when controlling for age and education.

Table 6. Biological and psychological predictors of the impaired neuropsychological outcome (i.e., processing speed) and overall cognitive performance in treatment-naïve women with breast cancer (Paper II).

	Processing Speed				**Overall cognitive performance (GCS)†**			
	β	SE β	p	η^2	β	SE β	p	η^2
Biological	N=46				N=33			
Age	.64	0.00	<.001**	.32	-.44	0.01	.02*	.18
Education	.06	0.03	.69	.00	-.08	0.05	.67	.00
Cortisol slope	.26	0.14	.05	.09	.08	0.33	.60	.01
α-amylase slope	.02	0.01	.85	.00	.42	0.01	.02*	.19
Psychological	N=62				N=47			
Age	.52	0.28	<.001**	.22	-.42	0.01	.01*	.15
Education	.04	1.74	.73	.00	-.00	0.04	.98	.00
CES-D	.20	0.48	.24	.02	.38	0.01	.12	.02
GAD	-.22	1.11	.29	.01	-.01	0.03	.97	.00
IES-R	.34	0.31	.09	.05	-.52	0.01	.049*	.09

†GCS = Global Composite Score; CES-D = Center for Epidemiological Studies Depression Scale (CES-D); GAD = Generalized Anxiety Disorder; IES-R = Impact of Events Scale-Revised
* = $p < 0.05$ (two-sided)
** = $p < 0.01$ (two-sided)

The model assessing the biological predictors of the women with BC's overall cognitive performance accounted for 25% of its variance, ($F(4,28) = 3.6$, $p = .02$) with a steeper diurnal α-amylase slope ($\beta = .42$, $p = .02$) significantly predicting better overall cognitive performance. The model with the psychological predictors of overall cognitive performance accounted for 19% of its variance, ($F(5,41) = 3.1$, $p = .02$) with lower overall cancer-related stress ($\beta = -.52$, p = .049) significantly predicting better overall cognitive performance. Age significantly predicted overall

cognitive performance and processing speed in all analyses ($p < .05$). No other predictor significantly estimated processing speed. Both the models with the biological ($p = .15$) and psychological ($p = .18$) predictors of verbal memory were non-significant.

Women with BC reported significantly higher levels of cognitive complaints than HC, (t[164.3]=3.5, $p < .001$, CI [1.59,5.71]). The model assessing biological predictors of cognitive complaints was non-significant ($p = .73$).

Table 7. Biological and psychological predictors of cognitive complaints (assessed via PROMIS-Cognitive function) in treatment-naïve women with breast cancer (Paper II).

	Cognitive complaints			
	β	SE β	p	η^2
Biological	*N*=54			
Age	.18	0.11	.23	.02
Education	-.02	0.68	.89	.00
Cortisol slope	.09	3.62	.54	.00
α-amylase slope	.00	0.18	1	.00
Psychological	*N*=84			
Age	-.00	0.09	.96	.00
Education	-.18	0.50	.09	.04
CES-D	-.36	0.14	<.01*	.09
GAD	.11	0.34	.47	.00
IES-R	-.05	0.09	.73	.00

CES-D = Center for Epidemiological Studies Depression Scale (CES-D); GAD = Generalized Anxiety Disorder; IES-R = Impact of Events Scale-Revised
* = $p < 0.01$ (two-sided)

Table 7 shows that more severe depressive symptoms significantly predicted higher levels of cognitive complaints, (β = -.36, p = .01). The model with the psychological predictors accounted for 22% of the variance in cognitive complaints, (F(5,78) = 5.8, p < .001).

4.3 Paper III

To test whether BWL can mitigate the negative impact of life stressors (i.e., BC diagnosis, surgery and associated factors) on cognitive function and stress (i.e., biological and psychological stress markers) among post-operative women with BC, compared to DWL, path analyses were conducted. Specifically, to test the hypotheses that post-operative women with BC randomly allocated to receive the circadian-stimulating BWL would perform better in cognitive measures (i.e., overall cognitive

performance, reaction time, processing speed, working memory, as well as report fewer cognitive complaints) as well as demonstrate reduced biological (via steeper diurnal α-amylase and cortisol slopes) and psychological stress (i.e., depressive symptoms, overall cancer-related stress and its symptoms: hyperarousal, avoidance, and intrusion) compared to the post-operative women with BC administered the non-circadian stimulating DWL.

Table 8. Path analysis results highlighting group differences in cognitive function, cognitive complaints, and biological and psychological stress markers between post-operative women with breast cancer receiving circadian-stimulating bright white light (BWL, coded as 1) versus those receiving the non-circadian stimulating dim white light (DWL, coded as 0) (Paper III).

	β	SE	*z*	FDR *p*	*d*
Cognitive					
Overall cognitive performance	0.10	0.10	0.91	.53	-.03
Reaction Time	0.24	0.19	2.02	.08	.49
Processing speed	0.15	0.19	1.44	.24	.06
Working memory	0.04	0.12	0.51	.75	-.04
Verbal memory	-0.04	0.17	-0.55	.72	-.28
Cognitive complaints	0.22	0.07	2.84	.011*	.23
Biological stress					
Diurnal cortisol slope	–0.05	0.12	-0.27	.86	.12
Diurnal α-amylase slope	–0.21	2.49	-1.42	.26	-.29
Psychological stress					
Depressive symptoms	–0.11	0.21	-1.35	.29	-.11
Overall cancer-related stress	–0.11	0.38	-1.50	.22	-.27
Intrusive thoughts	–0.16	0.05	-2.08	.07	-.36
Hyperarousal	–0.10	0.04	-1.21	.35	-.16
Avoidance	–0.12	0.06	-1.54	.21	-.27

BWL = Bright white light; DWL = Dim white light
* = $p < 0.05$ (two-sided)

Table 8 compares post-BLT cognitive function, cognitive complaints, and psychological and biological stress markers following BLT between the BWL and DWL groups. No significant group differences were found in overall cognitive performance, processing speed, working memory, or verbal memory (FDR $p > .05$). However, the BWL group exhibited a non-significant trend for faster reaction times ($\beta = 0.24$, SE = 0.19, $z = 2.02$, FDR $p = .08$), indicating moderate effects ($d = .49$) compared to the DWL group. Additionally, the BWL group reported significantly

fewer cognitive complaints ($\beta = 0.22$, SE = 0.07, $z = 2.79$, FDR $p = .011$), with a small effect ($d = 0.23$). Regarding psychological stress markers, the BWL group showed a non-significant trend for fewer intrusive thoughts ($\beta = –0.16$, SE = 0.05, $z = -2.08$, FDR $p = .07$ with small to moderate effects ($d = -.36$). No significant group differences were observed for overall cancer-related stress, other cancer-related stress symptoms (i.e., hyperarousal or avoidance), or depressive symptoms. Lastly, there were no significant group differences in biological stress markers (i.e., diurnal α-amylase and cortisol slopes).

5 Discussion

Evidence about how major life stressors can cause PTSD, and affect biological (e.g., cortisol) and psychological (e.g., depressive symptoms) stress markers known to impair cognitive function is slowly accumulating. Given the substantial impact of cognitive impairment on individuals and society, the overarching goals of this Thesis were to a) further investigate the relationship between major life stressors and cognitive impairment, and b) identify potential factors influencing this association, and lastly c) explore whether BLT could mitigate the negative effects of life stressors (i.e., BC diagnosis, surgery and associated factors) on biological and psychological stress markers, and cognitive function.

Offering a broad overview, the findings of this Thesis further support the evidence that life stressors (and associated factors) can negatively impact cognitive function. Paper I established that PTSD was associated with cognitive impairment compared to HC, and contributes to the existing literature by employing a novel less biased multilevel meta-analytic approach and examining a broad range of clinically important moderators. The study conducted a large number of analyses across a broad spectrum of cognitive impairment, encompassing all age groups, as well as both the general population and veterans, thus enhancing the generalizability of the findings compared to some previous meta-analyses (Qureshi et al., 2011; Schuitevoerder et al., 2013). Paper II demonstrated that CRCI can occur among newly diagnosed women with BC even before any BC treatment, using a population-based sample of women with BC, and age- and education-matched HC. These findings emphasize the importance of early intervention in the cancer trajectory and inform future studies to conduct their baseline assessments before surgery. Additionally, Paper II is the first to investigate the potential role of α-amylase in relation to CRCI and one of few to show that stress contributes to CRCI (Hermelink et al., 2015). Paper III, using the same sample as in Paper II now post-surgery, employed a double-blind, randomized controlled design with a novel comparison condition. Paper III is the first to demonstrate that BLT may mitigate the impact of life stressors (i.e., BC diagnosis,

surgery, and associated factors) on cognitive complaints, as well as hinting towards faster reaction time and fewer intrusive thoughts (a symptom of overall cancer-related stress). This needs to be studied further since improvements this early in the cancer trajectory (i.e., post-surgery) may lead to better long-term outcomes, such as buffering the adverse outcomes of subsequent BC treatments (e.g., radio- or chemotherapy) or smoother transitions back to daily life post BC treatment.

To provide a clear understanding of the research focus of this Thesis, the discussion begins by reviewing its overarching aims, followed by a detailed examination of each study.

The first aim of this Thesis, to explore the relationship between major life stressors and cognitive impairment further, was fulfilled in the first two studies. Paper I revealed that individuals exposed to life stressors resulting in PTSD were at an increased risk of developing cognitive impairment compared to HC. Additionally, Paper II showed poorer performance in processing speed and verbal memory, as well as higher levels of cognitive complaints, among newly diagnosed women with BC compared to HC. Together, these findings provide further evidence that major life stressors (and associated factors) can negatively impact cognitive function.

The second aim of this Thesis was to identify potential moderators influencing the association between life stressors and cognitive impairment. Specifically, the study examined age, study design, study population, neurocognitive outcomes, gender, study quality, type of PTSD measure, traumatic brain injury, depression, and substance use as potential moderators. The link remained robust regardless of the explored moderators, i.e., individuals exposed to life stressors resulting in PTSD had increased risk of cognitive impairment compared to HC across all neurocognitive outcomes (both general cognitive impairment and established diagnoses of NCD). This indicates that PTSD had a general influence on cognitive function, independent of the explored moderators (Paper I). Among newly diagnosed women with BC, biological (i.e., cortisol and α-amylase), and psychological stress markers (i.e., depressive symptoms, anxiety and cancer-related stress), as well as age and education, were explored as potential factors influencing their cognitive function. The

findings revealed that younger age, steeper α-amylase slope, and less overall cancer-related stress were associated with better cognitive function, while more severe depressive symptoms were associated with higher levels of cognitive complaints (Paper II). Overall, the findings from Papers I and II further highlight the association between stress and cognitive impairment.

The third aim of this Thesis was to test whether BLT could mitigate the negative impact of life stressors (i.e., BC diagnosis, surgery and associated factors) on biological and psychological stress markers, and cognitive function. Promisingly, in Paper III, the BWL group (compared to the DWL group) reported significantly fewer cognitive complaints and demonstrated a non-significant trend for faster reaction time and fewer intrusive thoughts.

5.1 PTSD and cognitive function (Paper I)

In Paper I, a meta-analysis was conducted to investigate the association between PTSD and cognitive function, and explore potential moderating factors. Previous research studied the association between PTSD and cognitive impairment (Qureshi et al., 2011; Schuitevoerder et al., 2013; Scott et al., 2015) either without including an NCD diagnosis or focused solely on individuals with an established NCD diagnosis (Günak et al., 2020).

By incorporating both, the aim of the study was to provide a more comprehensive understanding of the long-term effects of PTSD on cognitive function, including pre-clinical (cognitive impairment) to clinical (NCD) stages, and examine a broader range of clinically important moderators—age, study design, study population, neurocognitive outcomes, type of PTSD measurement, gender, study quality, and comorbidities such as traumatic brain injury (TBI), substance use and depression—that may influence the association between PTSD and cognitive impairment. Furthermore, Paper I was the first to utilize a novel multilevel design with maximum likelihood estimation to study the association between PTSD and cognitive impairment, as this design is less susceptible to bias compared to traditional meta-analysis approaches (Cheung, 2019).

The findings implied that, in line with previous findings (Qureshi et al., 2011; Schuitevoerder et al., 2013; Scott et al., 2015), PTSD was associated with elevated risk of cognitive impairment, across all neurocognitive outcomes, compared to HC. The finding that PTSD increases the risk of developing NCD supports earlier conclusions (Günak et al., 2020). The association between PTSD and cognitive impairment remained robust regardless of the explored moderators (listed above).

Consistent with the findings of Scott and colleagues (Scott et al., 2015), neither the type of PTSD measurement, depression, TBI, or substance use, significantly moderated the association between PTSD and cognitive impairment. Furthermore, the results that neither age nor study population moderated the association between PTSD and cognitive impairment are in line with previous results (Günak et al., 2020; Scott et al., 2015). However, regarding gender differences, while Scott et al. (Scott et al., 2015) found that studies with a larger portion of men exhibited greater cognitive impairment, Günak et al. (Günak et al., 2020) found an increased risk of developing NCD among women. Perhaps, the inclusion of both cognitive impairment and NCD in the current meta-analysis may have contributed to the absence of significant gender differences in our results. Paper I is the first study (that we know of) to test study design as a possible moderator of this relationship. Since study design was not a significant moderator, our findings provide new insights that individuals with PTSD consistently exhibit cognitive impairment, regardless of whether a study collects data at a single timepoint or over an extended period. This, combined with our finding that PTSD increases the risk of developing NCD later in life, highlights the importance of early intervention and continuous monitoring of cognitive function in individuals with PTSD, as well as addressing risk factors for cognitive impairment and NCD.

5.2 Stress and cognitive function in cancer (Paper II)

Building on the findings from Paper I (that life stressors resulting in PTSD were associated with cognitive impairment), combined with the prevalence of CRCI (and cancer-related stress) among women with BC, Paper II examined whether stress plays a role in CRCI, focusing on the impact of the stress from the cancer diagnosis (and

associated factors, such as the cancer disease itself) on cognitive function. Very few have studied whether CRCI can start before any cancer treatment (Kesler et al., 2017; Lange et al., 2020; Patel et al., 2015) and whether stress is involved (Hermelink et al., 2015), as previous studies in the field mostly focused on the effects of chemotherapy on CRCI (Ahles & Saykin, 2007; Collins et al., 2013; Janelsins et al., 2018; Ono et al., 2015; Schagen & Wefel, 2013; van Dam et al., 1998; Wefel et al., 2010). To fill in these knowledge gaps, we compared the cognitive function of newly diagnosed treatment-naïve women with BC to that of HC matched on age and education. The results showed that women with BC were more frequently impaired in processing speed and verbal memory compared to HC. These findings imply that CRCI can start before any BC treatment and that other factors than chemotherapy-induced neurotoxicity can contribute to it. This finding is in line with the few studies examining CRCI before any BC treatment (Kesler et al., 2017; Lange et al., 2020; Patel et al., 2015). Further, consistent with previous conclusions (Hermelink et al., 2015), no differences were found between the women with BC and HC in other cognitive domains or overall cognitive performance. These findings, however, contradict those of Lange et al. (2020), who found group differences between women with BC and HC in overall cognitive performance, which is the only other study we know of employing a population-based sample of treatment-naïve women with BC and comparing them with HC. Differences in recruitment strategy may partly explain this discrepancy. Lange et al. (2020) recruited HC via local advertisements, potentially biased if those with greater impairment self-selected to participate. Our findings are also inconsistent with another study (Schilder et al., 2010), which found differences in overall cognitive performance when comparing treatment-naïve women with BC to HC. This discrepancy might again stem from recruitment differences, as the women with BC in their study selected the study's HC participants, leading to group differences in age, IQ, co-morbidities and health behaviour, which may have influenced their results.

Despite no measurable differences between the women with BC and HC in overall cognitive performance in Paper II, the women with BC reported more frequent cognitive complaints than HC, aligning with previous findings (Lange et al., 2020)

but contrasting others (Kesler et al., 2017). As previously explained, women with BC could experience CRCI in their daily lives but employ compensatory brain areas to sustain their neuropsychological performance (Apple et al., 2018) or CRCI could be too subtle for neuropsychological tests to detect (Lange, Joly, et al., 2019).

To explore whether stress was associated with pre-treatment CRCI among women with BC, both biological (cortisol and α-amylase) and psychological stress markers (depressive symptoms, anxiety, and overall cancer-related stress) were investigated. The results revealed, aligning with previous results, that lower overall cancer-related stress predicted better overall cognitive performance (Hermelink et al., 2015) among treatment-naïve women with BC. Additionally, steeper diurnal α-amylase and younger age similarly predicted better cognitive function. The association between steeper diurnal α-amylase slope and cognitive function suggests that more regulated CR (i.e., greater variability in α-amylase levels throughout the day) may also be linked to better cognitive outcomes. This suggestion, coupled with the finding that less cancer-related stress similarly predicted better cognitive function, implies that lower stress (both biological and psychological stress markers) is associated with better cognitive function. Notably, Paper II is the first study (that we know of) to explore α-amylase in relation to CRCI. Since most research has focused on the role of the HPA axis (and thereby cortisol) in cognitive function (including CRCI), these findings underscore the need for further research on the role of autonomic nervous system and α-amylase. Lastly, reflecting previous findings (Wu et al., 2019), depressive symptoms seem to be associated with cognitive complaints, such that greater severity of depressive symptoms could be related to more frequent cognitive complaints, further highlighting the potential link between stress and cognitive function.

To summarize, these findings imply that CRCI can indeed start before any BC treatment and that stress may contribute to its development. These results highlight the potential need for closely monitoring stress levels and CRCI, as well as implementing treatment early in the cancer trajectory. However, as previously discussed, CRCI is influenced by a complex interplay of factors, including the

underlying cancer biology, treatments effects, genetic predispositions, and inflammation markers (Ahles & Root, 2018; Lange, Joly, et al., 2019).

5.3 The effects of light therapy on cognitive impairment and stress (Paper III)

Combined, Papers I and II indicate that psychological and biological stress markers can play a role in cognitive function, and emphasize the necessity of effective interventions targeting cognitive impairment. As discussed above, there is a bidirectional relationship between biological stress markers and CR (Gamble et al., 2014). The fact that one of the strongest zeitgeber for CR is light (Boivin et al., 1994; Küller, 2002) raises the possibility that BLT might reduce the effects of life stressors (and associated factors) on cognitive function. The aim of Paper III was to examine if BLT could mitigate the impact of BC (including the stress associated with the diagnosis, surgery and the cancer disease itself), which increases stress and CR disruption (Brainard et al., 2015; Prete et al., 2018), on cognitive function and stress markers (i.e., biological and psychological stress) in post-operative women with BC. To accomplish this, a double-blind, randomized controlled trial was conducted to test the efficacy of a 4-week BLT intervention, where participants were randomly allocated to receive circadian-stimulating BWL or non-circadian stimulating DWL.

The hypothesis that BWL could mitigate the negative impact of BC surgery on cognitive performance compared to DWL was partially supported. While no significant group differences were found in overall cognitive function, processing speed, working memory, or verbal memory, the BWL group demonstrated a non-significant trend for faster reaction times, compared to the DWL group. The finding that BWL improves reaction time is well-established among the general population (Chellappa, Steiner, et al., 2011; Lockley et al., 2006; Rahman et al., 2014). In addition, the BWL group reported significantly fewer cognitive complaints (i.e., rated their own cognitive function better) compared to the comparison DWL group. Potential reasons as to why Paper III showed group differences while the study of Wu et al. (2022) found none could include a) our larger sample, and b) our use of DWL instead of dim red light. As previously explained, red light has a long wavelength, which may enhance the effects of subsequent light exposure on cognitive

function. Additionally, participants may more easily recognize dim red light as a more obvious placebo condition than DWL (Chellappa et al., 2014; Starreveld et al., 2021; Wu et al., 2022).

With regards to whether BLT can ameliorate stress, Paper III revealed a non-significant trend for fewer intrusive thoughts among the BWL group compared to the DWL group. These findings are in line with the scarce previous research (mostly pilot studies with small samples) which found that BWL improved combat-related PTSD symptoms among veterans and augmented exposure-based cognitive behavioral therapy among participants with panic disorder or PTSD (Kawamura et al., 2019; Youngstedt et al., 2022; Zalta et al., 2019). The findings that the BWL group reported fewer cognitive complaints and hinted towards less intrusive thoughts post-BLT are noteworthy and underscore the need for further research, since these symptoms have been associated with poorer functional outcomes and quality of life in women with BC (Dupont et al., 2014; Lycke et al., 2019; Reid-Arndt et al., 2010).

No group differences were observed in depressive symptoms, echoing previous results (Starreveld et al., 2021). These findings, however, contrast with another study (Valdimarsdottir et al., 2018) that reported effects of environmental BWL in hospitalized patients with multiple myeloma. However, our studies are not directly comparable: ours employed light glasses for half an hour with lower light intensity (due to the proximity to the eyes), while their study used environmental lighting for three hours with a higher light intensity. Moreover, participants in their study likely demonstrated greater treatment adherence, being hospitalized and thus having consistent access to the light source. While an environmental light source might be suitable for hospital settings, light glasses offer greater flexibility and portability, allowing participants to leave the room while continuing the intervention.

Although a sensitivity analysis (among participants with at least 50% treatment adherence) revealed flatter diurnal α-amylase slopes in the BWL group compared to the DWL group, this was neither observed in the main analysis nor other sensitivity analyses, and therefore, requires further investigation. The absence of group differences in cortisol are consistent with previous results (Johnson et al., 2020).

Other previous studies did not find effects of light on α-amylase either (Figueiro & Rea, 2010; Ivanova et al., 2016; Sahin et al., 2014). However, these previous studies were not directly comparable to ours since they examined acute effects of light on α-amylase, unlike our 4-week intervention. Long-term light exposure such as this may help shift or strengthen CR robustness that underlies α-amylase secretion, potentially improving participant outcomes (e.g., reducing stress and improving cognitive function).

In summary, it is uncommon to study interventions for cancer patients this early in the treatment trajectory (i.e., post-surgery, often the first BC treatment, as noted by the Icelandic Cancer Society, 2023). Early improvements could lead to better long-term patient outcomes, such as in upcoming BC treatments (e.g., radio- or chemotherapy) or when returning to daily life post-BC treatment. If replicated, BLT could be employed to improve cognitive function (i.e., cognitive complaints and reaction time) and cancer-related stress (i.e., intrusive thoughts) among women with BC, and should be tested among other cancer populations, as well as with other participant groups undergoing surgery.

5.4 Methodological limitations and strengths

5.4.1 Paper I

Limitations of Paper I include that studies assessing cognitive function may exclude participants with TBI, potentially leading to a selection bias that could affect the generalizability of the results in Paper I regarding the moderating role of TBI. Furthermore, the lack of relevant data limited our ability to control for several common comorbidities of PTSD that can also increase the risk of cognitive impairment. These include anxiety (Kuring et al., 2020), for which only two studies accounted for, pre-morbid intelligence, similarly controlled for in two studies, and attention-deficit hyperactivity disorder, included in just one study—a factor which Scott et al. (2015) found to influence their results. Additionally, we were not able to control for antipsychotic use (Roughead et al., 2017). Moreover, the lack of data on cognitive reserve (Seil et al., 2019) in the retrieved studies prevented its inclusion as a moderator, representing another limitation. However, even without controlling for

these potentially confounding factors, the link between PTSD and cognitive impairment (including NCD), remained significant, highlighting the robustness of this relationship. Another limitation is the considerable heterogeneity in our findings, the origins of which remain unclear and persisted despite conducting sensitivity analyses. Lastly, as previously noted, only 11% of the included studies in Paper I were categorized as having a low risk of bias (Newcastle-Ottowa Scale score ≥ 7) (Lo et al., 2014).

The strengths of Paper I lie in (1) employing a multilevel meta-analytic approach which is less biased than traditional meta-analytic methods, (2) comprising a large number of analyses, and (3) including a broad range of studies examining a wide spectrum of cognitive impairment. This broad approach allowed us to capture a wider range of cognitive impairments associated with PTSD, which may otherwise have been overlooked. Additionally, only studies with validated methods to determine clinically impairing levels of PTSD were included. Lastly, Paper I encompassed all age groups and a balanced representation of veterans and the general population. This inclusive approach enhances the generalizability of the findings to the broader population.

5.4.2 Papers II & III

The main limitation of Papers II and III is the small sample size, especially in the saliva sampling. Due to this small sample size, the findings should be interpreted cautiously. Another limitation is that saliva samples were limited to morning and evening collections. While this approach reduced patient burden, collecting samples four times daily would have offered a more accurate description of the diurnal cortisol and α-amylase slopes (Johnson et al., 2020). Furthermore, since participants collected saliva at home, it is uncertain whether they followed the instructions (such as refraining from consuming coffee or brushing their teeth prior to saliva sampling), which may have introduced noise to the biological data. Additionally, since the HC did not undergo the biological assessments, potential differences in cortisol and α-amylase between the women with BC and HC could not be explored.

The studies, described in Papers II and III, were mainly conducted during the COVID-19 pandemic, which could potentially have influenced the psychological and cognitive function of participants. Furthermore, in Paper III, only 79 participants (67.5%, out of $N = 117$) adhered to minimum of 50% of the BLT treatment protocol, which might have impacted the findings. This treatment adherence might have been influenced by COVID-19, which likely imposed unprecedented psychological and logistical challenges for these newly diagnosed women with BC undergoing cancer treatment. Additionally, recruiting participants before BC surgery is particularly challenging due to urgent treatment timelines and high anxiety levels related to the BC diagnosis and undergoing surgery (Jenkins et al., 2016). Despite these challenges with missing data and treatment adherence, it is noteworthy that the main findings generally aligned with the sensitivity analyses, reinforcing the reliability of our results. Furthermore, the inclusion criteria, which required surgery to be the first treatment for BC, likely excluded women with more aggresive forms of BC requiring neoadjuvant chemotherapy. Consequently, our sample may have disproportionately included women with estrogen receptor-positive tumors and/or early-stage BC, who generally have a more favorable prognosis. This potential selection bias may have limited the generalizability of the findings to the broader population of women with BC. Moreover, the predominance of early-stage BC in the sample could have led to milder stress-related disruptions of CR, potentially diminishing the observed efficacy of BLT due to ceiling effects.

Moreover, since two of the neuropsychological tests had to be computerized and conducted remotely due to COVID-19, it could potentially have created problems for participants who were not as technologically proficient. Moreover, due to the brevity of the questionnaire assessing cognitive complaints (comprising of only 10 items) and skewed participant responses (generally rating their cognitive function highly), we opted to code cognitive complaints as a binary variable since transformation attempts did not take to sufficiently address the skewness. This might not have been reflective enough of the participants' cognitive experiences or fully elucidated the effects of BLT on cognitive complaints. Another limitation is that since Paper II was an explorative study, there was no correction for multiple testing. Additionally, there

was no validity of test performance in Paper II (Larrabee, 2012), meaning participants may have scored within the impaired range on the neuropsychological assessments due to suboptimal effort which would then not be reflective of their cognitive function. Lastly, as previously explained, CRCI can result from (and be influenced by) a complex interplay of factors. Therefore, it is not possible to determine to what extent CRCI is due to stress, neither whether the stress itself is due to psychological reactions or biological processes related to the cancer itself (e.g., inflammatory cytokines produced in the tumor environment) (Olson & Marks, 2019).

The strengths include that the samples in Papers II & III were drawn from a population-based sample, where all newly diagnosed women with BC in Iceland were invited to participate. Furthermore, the HC were matched to the women with BC on age and education, and randomly invited to participate from a large population-based study representative of the population. Both studies tested cognitive function via neuropsychological assessment as well as self-report, and conducted analyses on biomarkers and psychological measures. Notably, Paper II marks the beginning of research into the role of α-amylase in CRCI. Additionally, Paper III employed an intention-to-treat approach, and is the first to study the effects of BLT on the negative effects of BC (including the stress associated with the diagnosis, surgery and associated factors) on psychological and biological stress markers, and CRCI, using a novel DWL as a comparison.

5.5 Future directions

Future studies examining the association between PTSD and cognitive impairment should include NCD in their analyses to provide a more comprehensive understanding of the long-term effects of PTSD on cognitive function. Further research in this field with a more balanced representation of both veterans and the general population, as well as all genders, is essential. Additionally, future meta-analyses should investigate additional moderators, such as cognitive reserve (Seil et al., 2019) and account for the potential confounding variables previously mentioned, if possible (i.e., depressive and anxiety symptoms, TBI, substance use and antipsychotic use). In addition, to address the considerable heterogeneity present in

this meta-analysis, and the fact that only 11% of the included studies were categorized as having a low risk of bias (Newcastle-Ottowa Scale score ≥ 7) (Lo et al., 2014), developing guidelines on key methodological aspects in the field—such as diagnostic criteria, control of confounders, and the inclusion of large, non-biased samples—is recommended to both enhance the quality and consistency of findings across studies. Lastly, the presence of publication bias in this meta-analysis highlights the need for pre-registering studies and disclosing all outcomes, including negative or null results, to provide a more balanced representation of the evidence.

Given the finding that self-reported cognitive complaints can predict developing NCD later in life among healthy individuals (Mitchell et al., 2014; Rönnlund et al., 2015), it is important for future studies to test whether similar predictive patterns exist among individuals with PTSD. The clinical implications of the findings from Paper I and II emphasize the importance of early intervention (or prevention) of PTSD (and cancer-related stress). They also highlight the need for ongoing monitoring of cognitive function in individuals exposed to major life stressors, addressing risk factors for cognitive impairment, and providing timely interventions when required. Recent studies indicate that interventions aimed to improve cognitive appraisals can reduce PTSD symptoms and predict better outcomes in PTSD treatments (Samuelson et al., 2021). Future studies should explore this further and test whether BWL can augment these kind of treatments, given that BWL have been found to augment cognitive behavioral therapy for panic disorder and PTSD (as previously noted) (Kawamura et al., 2019).

Future studies in the field might also consider using BLT, since CR (Agorastos & Olff, 2020) and the diurnal rhythms of biological stress markers (e.g., cortisol and α-amylase) are known to be disrupted in PTSD, as previously discussed (Thoma et al., 2012; Wessa et al., 2006; Yehuda et al., 2005). Indeed, recent studies support the efficacy of BLT in reducing PTSD symptoms (Kawamura et al., 2019; Youngstedt et al., 2022; Zalta et al., 2019). Additionally, our data hinted that the BWL group experienced fewer intrusive thoughts—a symptom of cancer-related stress, closely linked to PTSD—compared to the DWL group. Our finding that PTSD increases the

risk of developing cognitive impairment and NCD underscores the urgency of this line of research.

As previously mentioned, larger samples with greater power are needed to confirm the findings of Paper II and III. In addition, the association between CRCI and stress needs to be further clarified, especially the potential role of α-amylase. This emerging stress biomarker has been found to be a reliable stress marker in women with BC (Sultan et al., 2018) and can be collected in conjunction with cortisol (Ali & Nater, 2020). However, in both the current study and another recent study (Johnson et al., 2020), no group differences were observed in cortisol when comparing a BWL experimental group to a comparison condition. This may suggest that BWL has stronger effects on the autonomic nervous system (e.g., α-amylase) than the HPA axis (e.g., cortisol). Future studies should refine their research methodologies regarding cortisol with these recent findings in mind and consider incorporating α-amylase assessments into their saliva data collection. Furthermore, additional markers of CR (e.g., actigraphy, melatonin), as well as indicators of inflammation and accelerated aging should be studied as potential biological predictors of CRCI.

Future studies should address the previously mentioned limitations in Papers I-III. That includes testing the efficacy of BLT on cognitive complaints using a longer and more comprehensive scale, and employing performance validity measures to better ascertain that the neuropsychological performance scores are valid and representative of the participants' true cognitive abilities. Additionally, since the current sample consisted of women with BC, future studies should test whether the current findings extend to other cancer patient groups undergoing other cancer treatments. As noted earlier, it is possible that the participants predominantly had early-stage BC or a more favorable BC prognosis, which could have led to ceiling effects influencing the observed efficacy of BLT. To overcome such limitations, future studies should aim to include a more diverse cohort of women with BC, thus potentially mitigating these ceiling effects and provide a clearer understanding of how BLT affects cognitive function and stress.

Given the previous belief in the field that CRCI primarily resulted from cancer treatment, some studies conducted their baseline assessments post-surgery (Lange et al., 2014; Scherling et al., 2011, 2012). Our findings that CRCI can start before surgery highlight that future studies need to conduct their baseline assessments before the start of any cancer treatment, including surgery. However, as previously mentioned, this presents a methodological challenge, as urgent treatment is often neccessary following a cancer diagnosis (due to its life-threatening nature).

Since the most severe cognitive impairments may arise post-surgery, such as during chemotherapy, future research (incorporating a DWL comparison condition) could also investigate whether the effects of BLT are more pronounced during these later stages, where the potential for observable improvement may be greater. Additionally, the continuous use of BLT throughout extended cancer treatments, such as radiotherapy or chemotherapy, should be explored.

Research should also examine whether early interventions in the cancer trajectory, aimed at reducing the impact of BC surgery on CRCI and stress, lead to long-term improvements in patient outcomes—both during the remaining treatment, and when returning to daily life post-treatment. Furthermore, our findings in Paper II and III suggest that future research should study cognitive function and stress among treatment-naïve cancer patients further, as well as the effects of BC surgery. Since our findings indicated that BLT may mitigate some of the negative effects of surgery (including the stress associated with the BC diagnosis, and associated factors) on cognitive function as well as psychological stress markers, future studies may want to test whether environmental BWL lighting in operating and hospital rooms may mitigate some of the negative side effects of surgery, e.g., the surgical cortisol stress response and CR disruption (Brainard et al., 2015; Prete et al., 2018).

On average, the cancer patients in our study and that of Wu et al. (2022) rated their BLT treatment satisfaction on average as "fair", with an average score of 2 out of 5. The field might benefit from exploring BLT treatment satisfaction among cancer patients, identifying obstacles to treatment adherence, and finding ways to boost adherence.

Secondary analyses, which we could not conduct in Paper III due to the small sample size, are needed to ascertain whether BWL impacted cognitive function and intrusive thoughts through synchronizing CR, modulating the stress systems, and/or improving sleep quality (Ancoli-Israel et al., 2022). Should these analyses reveal no group differences in terms of CR or sleep quality, an alternative explanation might be that BWL enhanced attentional control by increasing alertness (Canazei et al., 2023), thereby reducing intrusive thoughts (via improved interference inhibition) (Kertzman et al., 2014). This would elucidate how BWL decreased cognitive complaints (with marginal improvements in reaction time, cancer-related stress and intrusive thoughts) without affecting depressive symptoms. If the findings of Paper III are replicated, future studies with larger sample sizes are needed to test the underlying mechanisms.

6 Conclusions

Taken together, the findings of this Thesis provide additional evidence for the association between exposure to major life stressors and cognitive impairment. In Paper I, individuals with PTSD had a greater risk of developing cognitive impairment, as well as NCD, compared to HC. This association between PTSD and cognitive impairment remained robust among individuals with PTSD across all neurocognitive outcomes, regardless of the explored moderators, i.e., age, study population, study design, gender, study quality, type of PTSD measure, as well as the presence of comorbidities such as traumatic brain injury, depression, and substance use.

Furthermore, Paper II showed that treatment-naïve women with BC performed worse on neuropsychological tests assessing processing speed and verbal memory, and reported more frequent cognitive complaints compared to HC matched on age and education. Among these newly diagnosed women with BC, younger age, lower overall cancer-related stress, and steeper diurnal α-amylase slope predicted better overall cognitive performance. Additionally, fewer depressive symptoms predicted fewer cognitive complaints. These findings underscore the potential role of stress in CRCI and inform future research to explore this further, as well as the potential role of α-amylase in CRCI. Moreover, these results inform future studies to conduct their baseline assessments before surgery, since CRCI may already have begun by then.

In Paper III, the findings indicated that BLT can mitigate the effect of major life stressors (i.e., BC diagnosis and surgery, as well as associated factors) on cognitive function (by significantly reducing cognitive complaints and hinting towards faster reaction time) and cancer-related stress (hinting towards fewer intrusive thoughts) among the post-operative women with BC. The current results are promising but further research with larger sample sizes is needed. If replicated, future studies should additionally explore the underlying mechanisms.

Improvements this early in the cancer trajectory (post-surgery) might result in better long-term patient outcomes, e.g., in upcoming BC treatments (e.g., radio- or chemotherapy) or when returning to daily life post BC treatment.

In sum, the findings of this Thesis emphasize the importance of monitoring stress, as well as mental and cognitive health among individuals experiencing life stressors, e.g., among individuals with PTSD and cancer. The finding that the simple act of wearing BLT glasses for half an hour daily may ameliorate cognitive impairment and cancer-related stress among women with BC is promising but needs to be studied further. Given its potential benefits, non-invasiveness, cost-effectiveness, and minimal side effects, BLT merits further investigation into its clinical and practical implications within the cancer patient population. Moreover, future studies should test the effectiveness of BLT among individuals with PTSD. Due to our findings that PTSD increases the risk of developing NCD, this future research is essential as well as time-sensitive, especially given the fact that NCD may possibly be prevented or delayed (Livingston et al., 2017; Salthouse, 2009).

To conclude, the findings of this Thesis highlight the importance of addressing risk factors for cognitive impairment and underscores the need for continuous monitoring of cognitive function among individuals exposed to major life stressors. Lastly, it emphasizes the necessity of implementing early interventions when needed.

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Original Publication

I. Aspelund, S. G., Lorange, H. L., Halldorsdottir, T., Baldursdottir, B., Valdimarsdottir, H. B., Valdimarsdottir, U. A., Hjördísar-Jónsdóttir, H. L. (n.d.). Assessing neurocognitive outcomes in PTSD: A multilevel meta-analytical approach. [*Manuscript under revision in the European Journal of Psychotraumatology*.]

II. Aspelund, S.G., Halldorsdottir, T., Agustsson, G., Tobin, H. R. S., Wu, L. M., Amidi, A., Johannsdottir, K. R., Lutgendorf, S., Telles, R., Daly, H. F., Sigurdardottir, K., Valdimarsdottir, H., Baldursdottir, B. (2024). Biological and psychological predictors of cognitive function in breast cancer patients before surgery. *Support Care Cancer* **32**, 88. https://doi.org/10.1007/s00520-023-08282-5

III. Aspelund, S. G., Halldorsdottir, T., Agustsson, G., Tobin, H. R. S., Wu, L. M., Amidi, A., Johannsdottir, K. R., Lutgendorf, S., Telles, R., Daly, H. F., Sigurdardottir, K., Figueiro, M. G., Redd, W. H., Valdimarsdottir, H., Baldursdottir, B. (n.d.). The effects of light therapy on cognitive function and stress in women with breast cancer before systemic treatment. [*Manuscript submitted*.]

Paper I

Paper II

Paper III