Neurocognitive Correlates and Psychological Group Treatments for Pathological Mental Fatigue

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To Annika, Blenda and Blanka:
You are the lights of my life

Abstract

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Pathological mental fatigue (PMF) is associated with many injuries and diseases in the brain, and is estimated to affect tens of millions of people worldwide every year. But despite its prevalence, knowledge remains limited as to the neurocognition of PMF and treatment options for alleviating it. Therefore, the aim of this doctoral thesis was to investigate neurocognitive correlates of PMF and evaluate psychological group treatments for alleviating it. In Study I, we wanted to investigate whether and how neurocognitive function differed between healthy individuals and individuals affected by PMF. The PMF group exhibited higher global efficiency and lower modularity during both resting state and the cognitive tasks Digit Symbol Coding and Symbol Search. Additionally, the groups differed in peak oxygenated hemoglobin levels during the BASE task, with the PMF group showing lower oxygenation. In addition, the results in Study I indicated that the PMF group was slower on Digit Symbol Coding, Symbol Search and Stroop compared to the control group. The psychological group treatment Mindfulness-Based Stress Reduction (MBSR) has been shown to alleviate PMF, but knowledge has been lacking as to why patients are helped by it. In Study III we sought to provide further knowledge regarding the effects of MBSR on PMF after acquired brain injury by interviewing individuals with PMF who had undergone MBSR treatment. Similarly, in Study II, we evaluated the novel treatment program Brain Fatigue and Mindfulness (BF-M) by interviewing participants with PMF after acquired brain injury or multiple sclerosis. Studies II and III provide insights into how participants experienced the programs as a place where they could meet people with PMF and exchange experiences, learn more about PMF, and gain tools and strategies for coping with PMF in everyday life. Study II also used a randomized design to examine the relationship between measures of PMF and anxiety before and after the intervention. Results indicated reduced PMF and anxiety associated with BF-M participation. Overall, this thesis has enhanced the understanding of the neurocognitive correlates and psychological treatment of PMF. With three small-scale feasibility studies, we have indicated that those who are affected by PMF may exhibit different neurocognitive functioning compared to healthy individuals (Study I) and that PMF may be alleviated through psychological group treatment (Studies II and III). The results presented in the thesis can be used to further develop the knowledge of how to identify and treat PMF.

Keywords: pathological mental fatigue, acquired brain injury, traumatic brain injury, multiple sclerosis, neuroimaging, functional Near Infrared Spectroscopy, psychological group treatment, mindfulness, mindfulness-based stress reduction

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Swedish Summary

Hjärntrötthet uppstår efter många skador och sjukdomar som påverkar hjärnan och bedöms drabba tiotals miljoner människor världen över varje år. Trots dess utbredning saknas diagnostik och behandlingsalternativ för hjärntrötthet. Syftet med denna doktorsavhandling är därför att utforska hur hjärntrötthet tar sig uttryck i hjärnan och kognitivt samt hur den kan behandlas. I Studie I ville vi undersöka om och hur hjärnans funktion skiljde sig mellan friska individer och individer som drabbats av hjärntrötthet. Grupperna uppvisade olika neurala mönster, både när det gäller neural konnektivitet och aktivitet under olika kognitiva uppgifter och i vila. Gruppen med hjärntrötthet presterade även långsammare än kontrollpersonerna på flera kognitionstest. I vissa av de beteendemässiga mätningarna och i vissa hjärnavbildningsmått kunde vi dock inte se några gruppskillnader. I Studie II utvärderade vi det nya behandlingsprogrammet Brain Fatigue and Mindfulness (BF-M) genom att intervjua personer som genomgått behandlingen. I studie II användes också en randomiserad design för att undersöka sambandet mellan mått på hjärntrötthet och ångest före och efter interventionen. Resultaten indikerade minskad hjärntrötthet och ångest efter BF-M-deltagande. Den psykologiska gruppbehandlingen Mindfulness-Baserad Stressreduktion (MBSR) har visat sig lindra hjärntrötthet, men det har saknats kunskap om varför hjärntrötta blir behjälpta av MBSR. I Studie III ville vi därför ge ytterligare kunskap om effekterna av MBSR på hjärntrötthet genom att intervjua deltagare som hade genomgått MBSR-behandling. Intervjuerna i Studie II och III ger en inblick i hur deltagarna upplevde programmen som en plats där de kunde träffa personer med hjärntrötthet och utbyta erfarenheter, lära sig mer om hjärntrötthet och få verktyg och strategier för att hantera hjärntrötthet i vardagen. Sammantaget har denna avhandling ökat förståelsen för hur hjärntrötthet kan bedömas och behandlas. Med tre småskaliga genomförbarhetsstudier har vi visat att de som är drabbade av hjärntrötthet kan uppvisa avvikande neurokognitiv funktion jämfört med friska individer (Studie I) och hur hjärntrötthet kan lindras med psykologisk gruppbehandling (Studie II och III). Resultaten från denna avhandling kan användas för att vidareutveckla kunskapen om hur man kan utreda och behandla hjärntrötthet.

List of Publications

This thesis consists of a frame for and summary of the following three papers, which are referred to in the text by their Roman numerals:

I. Glavå, G., Skau, S., Lövdén, M., & Johansson, B. (2025). Differences in Frontal Cortical Brain Function Between Individuals Suffering from Pathological Mental Fatigue Following Acquired Brain Injury and Healthy Individuals. *Accepted for Publication in Behavioural Brain Research.*

II. Glavå, G., Rönnbäck, L., & Johansson, B. (2025). A New Mindfulness and Psycho-Educative Program for Treatment of Brain Fatigue, Evaluated after an Acquired Brain Injury and Multiple Sclerosis. *Health Psychology and Behavioral Medicine.* https://doi.org/10.1080/21642850.2025.2502039

III. Glavå, G., & Johansson, B. (2025). Mindfulness-Based Stress Reduction as Perceived by Individuals with Pathological Mental Fatigue after an Acquired Brain Injury. *Scientific Reports.* https://doi.org./10.1038/s41598-025-90452-y

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Gustaf Glavå
Gothenburg, May 2025

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1. Introduction

Acquired brain injury and multiple sclerosis are neurological conditions that can have significant and lasting consequences for the affected person's psychological and physical functioning and well-being. Pathological mental fatigue (PMF) is a particularly debilitating condition for individuals living with acquired brain injury and multiple sclerosis. PMF is characterized by fatigability and/or a general sense of mental fatigue that is perceived to interfere with everyday life and cannot be explained by other medical conditions (Berginström, 2019; Rönnbäck et al., 2022; Skau et al., 2021). Therefore, generating treatment options for PMF in the context of acquired brain injury and multiple sclerosis is essential for improving the lives of those affected. But, since PMF is considered to be a trans-diagnostic condition that occurs and manifests with similar symptomatology after various diseases and injuries affecting the brain (Rönnbäck et al., 2022), reliable assessment methods and treatment may benefit many more clinical populations with PMF besides those with acquired brain injury and multiple sclerosis.

The prevalence of PMF is notably high in individuals with acquired brain injury and multiple sclerosis, with estimates from 36% to 77% after stroke, 45% to 73% after traumatic brain injury, and 38% to 83% in those with multiple sclerosis (Kluger et al., 2013). Considering these prevalence estimates for PMF along with the annual 15 million people suffering from stroke globally (WHO, 2023), 69 million suffering from traumatic brain injury globally (Dewan et al., 2018) and 2.8 million people suffering from multiple sclerosis globally (Walton et al., 2020), the number of people suffering from PMF after acquired brain injury and multiple sclerosis is counted in millions globally. Despite the prevalence of PMF, there are no cures, standardized treatments, or standardized diagnostic criteria for it. While different assessment and treatment options have been explored, further exploration and validation of such tools are called for (Berginström, 2019; Möller, 2013). This doctoral thesis seeks to investigate neurocognitive correlates of PMF (Study I), but also to evaluate whether and how the psychological group treatments Mindfulness-Based Stress Reduction (MBSR) (Study III) and the novel Brain Fatigue and Mindfulness Program (BF-M) (Study II) can alleviate PMF after acquired brain injury (Studies II & III) and multiple sclerosis (Study II). The overall aim of this thesis is to investigate neurocognitive correlates of PMF and evaluate psychological group treatments for alleviating it.

2. Empirical Background

In this section I will present previous research that is relevant to this thesis and describe how the thesis can contribute to the knowledge about treating PMF. I will begin by briefly describing the definitions, pathology, and symptomatology of acquired brain injury and multiple sclerosis. Thereafter I will define PMF and how it is characterized in relation to acquired brain injury and multiple sclerosis. I will continue by describing research on assessment and treatment options that have been explored for PMF. Finally, since the treatments evaluated in the thesis can be defined as mindfulness-based interventions, I will present previous research on mindfulness-based interventions in healthcare.

2.1. Acquired Brain Injury

Acquired brain injuries are neurological conditions that can affect psychological and physical functioning to various extents, and acquired brain injury is defined as any injury to the brain that has occurred after birth. Acquired brain injuries are roughly divided into traumatic and non-traumatic injuries to the brain. Traumatic brain injury is defined as an injury to the brain, with functional or structural expression, that is caused by an external force. This type of injury can be closed (non-penetrating) or open (penetrating). Falls, assaults, sport injuries, and traffic accidents are common causes of traumatic brain injury. Non-traumatic brain injuries are caused by damage to the brain by internal pathologies such as stroke, tumor, aneurysm, suffocation, central nervous system infections, cardiac arrest or other neurological diseases that affect the brain. Due to the wide range of brain injuries that fall under the umbrella term of acquired brain injury, the structural and functional expression of such injuries varies extensively. However, a common – trans-diagnostic – condition associated with acquired brain injuries is PMF, which will be further described below.

2.2. Multiple Sclerosis

Multiple sclerosis, also a neurological condition that can affect psychological and physical functioning to various extents, is a lifelong condition that can develop at any age. It is a neurological autoimmune disorder that can affect the whole central nervous system and cause a wide range of symptoms. In multiple sclerosis, the immune system attacks and causes damage to the myelin sheath surrounding the nerves. In turn, this damage causes slower or disrupted axonal communication between nerves, which is associated with a wide range of symptoms that depend on the location of the neuronal damage. It has been hypothesized that multiple sclerosis is caused by genetic and environmental factors, and at the time of writing there is no cure; but effective pharmaceutical treatments are available (Ransohoff et al., 2015). Multiple sclerosis can have many symptoms such as motor dysfunction, visual dysfunction, numbness, stiffness, spasms, and cognitive dysfunction. However, one of the main problems associated with the condition is PMF, which will be described in more detail next.

2.3. Pathological Mental Fatigue after Acquired Brain Injury and Multiple Sclerosis – Symptomatology and Definition

Fatigue as a consequence of various diseases is a common and often profoundly disabling condition (Möller, 2013; Rönnbäck et al., 2022). In this thesis, I will focus on pathological fatigue that affects mental abilities; in the remainder of the thesis, such fatigue will be referred to as PMF. In many studies investigating PMF, a clear terminological distinction is not made between physical and mental fatigue, and many studies with ambiguous terminology address both physical and mental pathological fatigue interchangeably with the term *fatigue* (Berginström, 2019). A related concern is that PMF is commonly described as a condition that relates to a specific disease or dysfunction, for example cancer fatigue, fatigue after traumatic brain injury or cognitive fatigue. The fact that operationalization and definitions of fatigue vary substantially between studies is problematic when trying to estimate prevalence and compare results (Kluger et al., 2013). That said, PMF is considered to be a trans-diagnostic condition that occurs and manifests with similar symptomatology after various diseases and injuries affecting the brain (Rönnbäck et al., 2022). For the thesis, I will focus on research on PMF concerning acquired brain injury and multiple sclerosis. The sample population in the thesis was partly motivated by the substantial impact of PMF in these groups, affecting quality of life and functional outcomes for millions worldwide, and is based on individuals seeking treatment and available for inclusion in the empirical studies.

PMF, a common condition among individuals with brain diseases, is characterized by rapid exhaustion and prolonged recovery time after cognitive or sensory stimuli (Rönnbäck & Johansson, 2022). The following symptoms are typical in PMF: decreased attention and concentration over time;

disproportionately long recovery time after mental exhaustion; subjective memory disturbance, noise sensitivity, light sensitivity, emotional lability, irritability, stress sensitivity; impaired simultaneous capacity; sleep disturbance; and headache after mental activity (Johansson & Rönnbäck, 2014). Slower processing speed is encountered on a group level, and common difficulties include distractibility, impaired automatic functions, sensitivity to impressions, reduced endurance, and decreased recall of memories (Berginström, 2019; Rönnbäck et al., 2022). Cantor et al. (2013 p. 876) provide descriptions of PMF by individuals suffering from it, who typically describe their condition as follows: "Anytime I have to focus…I'm fatigued." Another described a need for solitude, stating: "Like sometimes I feel that I need to be alone, I have to be alone, yes, no more stimulation." The overwhelming nature and vast consequences of PMF were described by another individual, who remarked: "If we are thinking in terms of words to describe fatigue – overwhelmed." Environmental stimuli also play a key role in the problem of PMF. One individual shared: "Responding to noise and light and people, in a restaurant, I know, I have to sit on the end of the table and face the wall. Otherwise, I know that I have to leave the restaurant." Furthermore, the cognitive effects of PMF were encapsulated by a participant who said: "Your brain gets full, so it is both a response but also what you can do…it's inaccuracy in things that you used to be able to do."

In contrast to non-PMF, or common fatigue, which can be relieved by resting, PMF interferes with daily life and cannot be alleviated by resting (Skau et al., 2021). This condition can have long-term negative effects on work ability, well-being, and overall health (Rönnbäck et al., 2022). The prevalence of PMF varies across different acquired brain injuries, multiple sclerosis, and other conditions. For instance, estimates range from 36% to 77% after stroke, 45% to 73% after traumatic brain injury, 38% to 83% in those with multiple sclerosis, and 28% to 58% in those with Parkinson's disease (Kluger et al., 2013). Moreover, PMF is associated with other conditions such as exhaustion disorder (Sandstrom et al., 2005; Krabbe et al., 2017), central nervous system infections (Morris et al., 2015) and hormonal imbalances (Johansson et al., 2023; Möller et al., 2014). PMF is not related to the severity of the injury/disease (Rönnbäck et al., 2022); even after a minor brain injury, PMF can be severe and long-term (Hiploylee et al., 2017; Pearce et al., 2019). While most of those who are affected experience relief from, or a cessation of, PMF when the injury or illness heals (Rönnbäck et al., 2022), for a smaller percentage PMF persists for months or even several years

(Cantor et al., 2013; Chaudhuri & Behan, 2004; Diaz-Arias et al., 2021; Kluger et al., 2013; Staub & Bogousslavsky, 2001).

Due to the condition's invisibility, individuals with PMF may face misjudgment by family members, friends, colleagues, and employers, which can result in social reclusiveness, depression, and anxiety (Berginström, 2019; Johansson, 2022). Along these lines, individuals suffering from PMF are often stigmatized and misunderstood (Berginström, 2019; Rönnbäck & Johansson, 2022). For example, PMF can be perceived as "laziness" by family and friends (Norrie et al., 2010). Indeed, PMF seems to be difficult to understand and accept, for both those affected and those around them (Berginström, 2019).

2.4. Assessing Pathological Mental Fatigue after Acquired Brain Injury and Multiple Sclerosis

Assessing PMF after acquired brain injury and multiple sclerosis presents a complex challenge. Due to the distinction between mental fatigue and mental fatigability, both subjective and objective mental fatigue and fatigability need to be considered. Concerning subjective measures, there are over 30 self-assessment scales for evaluating fatigue (Dittner et al., 2004). When assessing PMF, the task is to investigate whether and to what extent fatigue is a continuous part of an individual's everyday life, also known as trait fatigue (Genova et al., 2013). A frequently used measure with acceptable psychometric properties that investigates trait mental fatigue is the Mental Fatigue Scale (MFS) (Johansson et al., 2010). The MFS is a self-rating questionnaire that assesses trait mental fatigue by producing a score that can be used to evaluate the subjective trait aspect of PMF. That is, it is used to investigate how mental fatigue is perceived to impact the life of the person answering it. However, these measures have their limitations under conditions in which self-awareness can be compromised, such as traumatic brain injury (Berginström, 2019; Chiou et al., 2016). Therefore, the combination of self-assessed fatigue and more objectively measured fatigability assessed using neuropsychological tests and neuroimaging may produce more robust results, at least on a group level. Several studies utilizing neuropsychological tests to assess PMF after traumatic brain injury have indicated an association between PMF and reduced attention and information processing speed (Ashman et al., 2008; Azouvi et al., 2004; Belmont et al., 2009; Cicerone, 1996; Johansson et al., 2009; Johansson & Rönnbäck, 2015; Möller et al., 2014; Riese et al., 1999; Ziino &

Ponsford, 2006a, 2006b).

Another potential form of objective measure of PMF is neuroimaging assessment (Berginström, 2019). In general, two kinds of neuroimagery assessments are used to study brain function and pathology: neurofunctional, in terms of neural activity in specific brain areas during certain conditions; or functional connectivity, which measures the degree of connection between different brain regions. Several previous studies have investigated PMF after traumatic brain injury and other conditions using both of these functional measures. However, the findings from brain imaging studies on PMF display inconsistency; still, they reveal changes in activity and connectivity concerning PMF following traumatic brain injury (Johansson, 2021). Several neuroimaging studies on PMF have targeted brain regions such as the frontal cortex and the thalamus. The frontal cortex is involved in higher cognitive functions such as decision-making, problem-solving, and emotional regulation, while the thalamus acts as a relay station, transmitting sensory and motor signals to the cerebral cortex. Jointly, these structures are part of the cortico-striatal-thalamic circuits, which are involved in regulating motor control, cognitive functions, and emotional responses by integrating and relaying information between the cortex, striatum, and thalamus. PMF after traumatic brain injury has been found to be associated with increased activation in the caudate nucleus during a working memory task (Wylie et al., 2017). In resting state, PMF has been found to be associated with disrupted connectivity between the thalamus and middle frontal cortex (Liu et al., 2016; Möller et al., 2017; Nordin et al., 2016; Zhou et al., 2012). Similarly, other functional Magnetic Resonance Imaging (fMRI) studies have found dysfunction within cortico-striatal-thalamic circuits to be associated with fatigue after traumatic brain injury (Berginström et al., 2018; Kohl et al., 2009). However, these associations were not found in another study investigating white matter disruptions (Berginström et al., 2020). It has been suggested that individuals with traumatic brain injury, among whom PMF is common, exhibit lower and more widespread activation during the Stroop cognitive interference test (Chang et al., 2022). Concussion syndrome has also been found to be associated with reduced activation in the cortex during postural control (Helmich et al., 2020). In individuals with multiple sclerosis, PMF has been found to be associated with abbreviations in the cortico-striato-thalamic-cortical circuits during both cognitive tasks (Engström et al., 2013; Filippi et al., 2002; Rocca et al., 2016) and during resting state (Finke et al., 2015; Pravatà et al., 2016). Further, findings from neuroimaging studies using functional Near Infrared Spectroscopy (fNIRS) indicate that individuals with PMF after traumatic brain injury exhibit reduced frontal cortex recruitment associated with self-reported mental fatigue (Skau et al., 2019). fNIRS is a non-invasive neuroimaging technique that measures cortical brain activity by detecting changes in oxygenated and deoxygenated blood levels using near-infrared light. The technique offers several advantages, including non-invasiveness, portability, cost-effectiveness, and compatibility with other imaging modalities, making it a convenient tool for both clinical and research settings. However, unlike fMRI and many other neuroimaging tools, it is limited to measuring brain activity in the cortex and cannot detect activity in deeper brain structures.

Brain function can also be modeled as a functional network that may be more or less interconnected in terms of functional connectivity (Sporns, 2013). Modularity and global efficiency are two measures of functional connectivity (Rubinov & Sporns, 2010). High modularity indicates fewer connections between communities, suggesting higher segregation, whereas low modularity implies either low segregation or high integration within the overall network (Newman, 2006). Global efficiency measures connectivity within a network, with high global efficiency indicating a more interconnected network (Latora & Marchiori, 2001; Rubinov & Sporns, 2010). Therefore, global efficiency and modularity are inversely related: When global efficiency is high, modularity tends to be low. Of the various network measures, modularity is frequently utilized in the study of fatigue (Skau et al., 2022). Neuroimaging studies have examined the relationship between fatigue and functional connectivity, but results have been inconsistent (Skau et al., 2022). For example, concussion syndrome, which is common in traumatic brain injury, has been found to be associated with reduced functional connectivity during cognitive tasks (Hocke et al., 2018). Although these results do not apply directly to PMF, they are relevant in the context of PMF as it is a common condition after traumatic brain injury. Another study indicated differences in resting state connectivity between individuals suffering from chronic fatigue and healthy controls, differences that correlated with self-reported levels of fatigue (Gay et al., 2016). Kim et al. (2015) reported a decrease in network integration in the posterior cingulate cortex during resting state in people suffering from chronic fatigue syndrome. Conversely, Høgestøl et al. (2019) found that connectivity in the default mode network increased in people suffering from multiple sclerosis with high levels of depressive and fatigue symptoms. In studies with healthy adults, fatigue has been shown to lead to reduced segregation (Ben Simon et al., 2017), which means that the brain works in a less localized way. Another study indicated a decrease in functional connectivity between brain regions involved in sustained attention (Sun et al. 2014). Yet another study examined the functional connectivity of specific brain areas associated with fatigue; namely the striatum, dorsolateral prefrontal cortex (DLPFC), dorsal anterior cingulate cortex (dACC), ventro-medial prefrontal cortex (vmPFC), and anterior insula (Wylie et al., 2020). The study concluded that the functional connectivity within this specific network decreased as a function of becoming fatigued. The study also concluded that a decrease in functional connectivity occurred between the network and anterior brain regions while an increase occurred between the network and posterior brain regions. Another study focusing on frontal lobe functional connectivity measured using fNIRS showed that frontal lobe networks become more segregated over time in PMF compared to healthy individuals when performing cognitive tasks (Skau et al., 2022).

In summary, there is emerging evidence indicating that disruptions within the striato-thalamic-cortical pathways are associated with PMF after traumatic brain injury and multiple sclerosis. These results support theories on the causes of PMF, which I present below. In addition, altered activity and connectivity in the frontal cortex seem to be associated with PMF. However, the precise mechanisms responsible for these changes remain incompletely comprehended, as do their direct association with PMF. Overall, there are inconsistencies in the neuroimaging literature on PMF.

2.5. Treatment of Pathological Mental Fatigue after Acquired Brain Injury and Multiple Sclerosis

At the time of writing, there are no cures or standardized treatments for PMF. However, there are a few treatment options for trying to reduce it. Among pharmaceutical options, methylphenidate (Johansson et al., 2015; Johansson et al., 2020; Zhang & Wang, 2017) and OSU6162 (Berginström et al., 2017, Berginström et al., 2019; Johansson et al., 2012; Nilsson et al., 2020) have been evaluated in individuals with PMF after mild head injury or stroke. Both these drugs are associated with specific psychological functions: Methylphenidate improves cognitive focus and attention by increasing dopamine and norepinephrine activity, while OSU6162 helps regulate mood and behavior by stabilizing dopamine function and promoting balanced neurotransmission. In evaluations of methylphenidate, the treated groups showed less PMF as measured using the MFS, and also performed better on processing speed and attention tests (Johansson et al., 2015; Johansson et al., 2020; Zhang & Wang, 2017). The long-term effects of methylphenidate have also been studied, but the treatment effects appear to be reversible; that is, the positive effect on PMF is only observed during ongoing methylphenidate treatment (Johansson et al., 2020). In one study, OSU6162 did not have any noteworthy impact on PMF in individuals with traumatic brain injury in comparison to a placebo group (Berginström et al., 2017). In another study, fMRI findings demonstrated OSU6162-related treatment effects in both the right occipitotemporal cortex and the right orbitofrontal cortex. In these areas, the Blood-Oxygen-Level-Dependent (BOLD) response was brought back to a level comparable to that of healthy controls during the post-intervention fMRI session (Berginström et al., 2019). The BOLD response is a measure used in several functional neuroimaging techniques to detect brain activity by observing changes in blood flow and oxygenation associated with neuronal activity. Another study indicated that participants with a favorable response to OSU6162 reported clearer thinking, increased energy, and an easier time starting activities compared to a placebo control group. They also reported lower mental fatigue according to the MFS (Nilsson et al., 2020). An additional study on the effects of OSU6162 on PMF suggested a notable enhancement in mental endurance, as assessed using the MFS, and statistically non-significant effects concerning improvement in processing speed and attention (Johansson et al., 2012).

Non-pharmaceutical treatments for PMF have also been explored to a limited extent. A systematic review of non-pharmacological treatment for PMF after multiple sclerosis suggested that education in energy conservation and fatigue management was associated with reduced PMF (Miller & Soundy, 2017). Mindfulness programs have been found to alleviate depression, anxiety, and PMF after multiple sclerosis and acquired brain injury (Grossman et al., 2010; Ulrichsen et al., 2016). In addition, MBSR has been shown to reduce PMF after stroke and traumatic brain injury, improve attention, and alleviate symptoms related to depression and anxiety (Johansson et al., 2012; Johansson et al., 2015). These results raise further questions regarding how MBSR is perceived by individuals with PMF, since cognitive resources play a central role in mindfulness practices that are concerned with attention and concentration.

2.6. Mindfulness-Based Interventions as Medical Treatment

In this section, I will briefly present research on mindfulness-based interventions that is relevant to this thesis. Mindfulness-based interventions have been studied in other contexts than PMF, in both clinical and non-clinical populations. Among mindfulness-based interventions, MBSR and Mindfulness-Based Cognitive Therapy (MBCT) are considered to have the strongest evidence base (Carney et al., 2023; Querstret et al., 2020). The MBSR program is a structured, evidence-based approach designed to cultivate mindfulness and alleviate stress. Developed in the late 1970s, MBSR has become widely recognized and has been adopted in various settings, including healthcare and education (Kabat-Zinn, 1996; Querstret et al., 2020). MBSR typically consists of an eight-week program, comprising weekly sessions and a full-day retreat. The program incorporates various mindfulness meditation techniques, including body scans (in which the participant is guided by vocal instructions to introspectively scan their body to detect the sensations taking place throughout it) as well as sitting meditations and gentle yoga. Participants are guided through practices that aim to enhance awareness of the present moment, foster a non-judgmental attitude, and develop a more compassionate relationship with their thoughts and emotions (Kabat-Zinn, 1996). While pointing out considerable methodological limitations, another review suggested that MBSR has a significant impact on brain regions associated with attention, self-reflection, and emotional processing, aligning with the findings in the clinical literature (Hatchard et al., 2017). Yet another review investigating MBSR and MBCT in relation to depression also pointed out methodological concerns while reporting that seven of the ten included studies showed cognitive improvement in participants in the mindfulness-based treatments (Kraines et al., 2022).

Concerning non-clinical samples, a systematic review and meta-analysis suggested that mindfulness-based interventions are linked to improvements in health and overall well-being (Querstret et al., 2020). More specifically, in comparison to passive control groups, groups subjected to mindfulness-based interventions demonstrated a significant reduction in symptoms of rumination/worry (g= –1.13, [–2.17, –0.08]), stress/psychological distress (g= –0.52 [–0.68, –0.36]), depression (g= –0.45 [–0.64, –0.26]), and anxiety (g= –0.44 [–0.65, –0.23]), as well as significantly improved quality of life/well-being (g=0.32 [0.10, 0.54]) (Querstret et al., 2020). The study further concluded that MBSR and MBCT could be viable strategies for addressing subclinical mental health challenges and should be considered within the scope of public mental health initiatives.

Elucidating the cost effectiveness of mindfulness-based interventions, one systematic review suggested that MBSR was both more cost-effective and more efficient compared to standard cognitive-behavioral therapy in individuals dealing with symptoms associated with chronic lower back pain, fibromyalgia, and breast cancer (Zhang et al., 2022). MBSR also demonstrated cost reductions in healthcare for individuals with various physical and mental conditions. In addition, MBCT exhibited similar cost-effectiveness advantages over comparison groups in individuals with depression, medically unexplained symptoms, and multiple sclerosis. In summary, while reviews and meta-analyses of mindfulness-based interventions report methodological issues, they also suggest that such interventions can be cost-efficient and produce neural and psychological changes in participants that are beneficial in both clinical and non-clinical populations. However, there is a lack of research on patients' experiences of mindfulness-based interventions in general, and concerning acquired brain injury (Niraj et al., 2018) and PMF in particular. Insights into patients' experiences of such treatment are essential for understanding the benefits and challenges associated with it. That said, there are few studies available concerning how mindfulness-based interventions are perceived by participants.

A small category of research on mindfulness-based interventions has evaluated how they are perceived by participants within clinical samples. Such studies have pointed out that mindfulness-based interventions can help patients to become aware of and accept their challenges in order to deal with them (Bogosian et al., 2016; Malpass et al., 2015; Visser et al., 2015). Further, patients participating in mindfulness-based interventions have reported the importance of the group setting and the possibility to share their experiences with others who have similar ones (Cormack et al., 2018; Kvillemo & Bränström, 2011). While these studies on experiences of mindfulness-based interventions did not include individuals with PMF, similar results have been suggested for MBSR concerning PMF after acquired brain injury (Johansson, Bjuhr & Rönnbäck, 2015). Both in-person and live Internet MBSR groups reported similar post-program experiences, including increased energy levels, greater calmness, more positive thoughts, and enhanced hope and confidence for the future (Johansson & Bjuhr, 2016). However, the study also revealed challenges predominantly related to fatigue, with the weekly sessions being particularly demanding. Nevertheless, a sense of belonging to a group and the opportunity to share experiences with others were reported in both the live Internet and in-person groups (Johansson & Bjuhr, 2016).

Since the creation of MBSR, a range of different mindfulness-based programs have been developed, implemented, and researched. In parallel to this development, significant criticisms have been raised regarding such interventions and the associated research, which should be considered alongside the previous research on mindfulness-based interventions presented here. For example, criticism concerns poorly and diversely defined operationalizations of the concept of mindfulness, questionable research practices within mindfulness research, a lack of clarity concerning generalizability, and overexaggerated findings within neuroscience concerning mindfulness-based interventions (Van Dam et al., 2018). Criticism has also been raised regarding the lack of sufficiently trained mindfulness teachers and the associated risks of having poorly trained instructors teaching mindfulness within healthcare (Crane et al., 2012). In addition, potential shortcomings and suggestions for improvement have been put forward concerning the implementation of mindfulness-based interventions within healthcare systems (Andermo et al., 2021; Crane & Kuyken, 2013). One study explored perspectives on the implementation of mindfulness-based programs from providers, managers, and referrers, revealing factors that hinder or facilitate implementation (Andermo et al., 2021). Participants emphasized the need for national guidelines and teacher training pathways, along with improved training availability. The diverse participant viewpoints underscored the potential benefits of a stepped-care model for mindfulness-based program provision, addressing varying levels of severity and advocating for increased awareness to ensure targeted implementation; that is, to provide patients with the most effective yet least resource-intensive treatment for them. This might suggest the delivery of full programs for individuals with more severe conditions, requiring the establishment of thorough screening procedures to guarantee the safe provision of such programs, while shorter or less intensive programs may be advantageous for those with less severe conditions (Andermo et al., 2021). In addition to the concerns raised so far, there is a call for more attention to the question of risks and harm associated with mindfulness-based interventions (Baer et al., 2019). Indeed, researchers and clinicians are urged to carefully evaluate and incorporate precautions regarding the potential risks associated with mindfulness-based interventions, as highlighted by Jönhagen et al. (2024), Kuyken et al. (2012) and Van Dam et al. (2018). This caution is particularly crucial considering the heightened risks among vulnerable populations, including an elevated probability of suicidality, depression, negative emotions, and meditation-induced flashbacks for individuals with a history of trauma (Kuyken et al., 2012).

In summary, while mindfulness courses have proven helpful in enhancing psychological well-being and symptom management among individuals with PMF, the mechanisms behind their efficacy remain relatively unexplored. One way to study such mechanisms is to ask participants to share how they perceive and implement the treatment in everyday life. This approach was used in both treatment studies in this thesis. Having described the empirical background of the thesis, I will now move on to present the theoretical framework.

3. Theoretical Framework

In this section I will introduce the theoretical perspectives applicable to this thesis, beginning with theories on brain dysfunction associated with PMF, which are relevant to Study I. I will proceed by presenting a broad theory of patient empowerment. From there, I will narrow the theoretical scope by presenting theory that is particularly relevant concerning the treatments that were evaluated in Studies II and III; that is, theory on the psychological mechanisms of mindfulness. I will present specific developmental and theoretical concepts concerning the treatments and how these relate to the broader theory of patient empowerment.

3.1. Theories on the Brain Dysfunction in Pathological Mental Fatigue

Investigating the causes of PMF is beyond the scope of this thesis. However, I will describe a few theories on mechanisms behind and potential causes of PMF to provide context, point out the complexity of PMF and, later, discuss the results of the thesis in relation to the theories described here. While PMF is a common and disabling condition, its causes have not been determined (Berginström, 2019; Rönnbäck et al., 2022). As of yet there are no available biomarkers of PMF (Berginström, 2019). That said, several theories have been put forward to explain its causes from different perspectives. One theory on the cellular neurobiology of PMF suggests that various diseases in the brain cause neuroinflammation, affecting the astrocytes' ability to clear up glutamate from the extracellular space and the reuptake of glucose (Rönnbäck & Johansson, 2022). In turn, it is suggested that higher levels of glutamate lead to unspecific neuronal signaling, a sort of diffuse overactivation, which results in reduced cognitive functioning and a sense of fatigue associated with PMF. This theory has recently gained some empirical evidence from trials on healthy individuals who, after being fatigued due to cognitive workload in an experimental setting, exhibit glutamate increase in extracellular space in specific parts of the cortex (Wiehler et al., 2022). However, these results do not concern the neuroinflammation hypothesis or PMF per se.

Another neurobiological theory suggests that PMF is caused by structural, metabolic, or neurochemical dysfunction within the striato-thalamic-cortical circuits, which in turn reduces cortically driven motivational influence in these circuits (Chaudhuri & Behan, 2000, 2004). That is, neurological dysfunction generates a loss of motivation. This theory has been indirectly investigated in studies on dopamine and serotonin, which are neurotransmitters that are important within the striato-thalamic-cortical circuits (Hesse et al., 2014; Pavese et al., 2010). Similarly, a hypothesis has been put forward that builds on the notion that an imbalance in the levels of the neuromodulator dopamine within the central nervous system, whether too high or too low, is linked to reduced cognitive function and is the cause of PMF in various neurological disorders (Dobryakova et al., 2015). Therefore, there is an emphasis on the importance of maintaining a balanced dopaminergic neurotransmission for optimal cognitive performance. This hypothesis needs further evaluation, however. In addition to the neurobiological theories on PMF, others have theorized that psychosocial stress (Bay & Xie, 2009) and genetics (Sundström et al., 2007) can explain PMF after traumatic brain injury. These studies highlight potentially important aspects of the multidimensional concept of PMF, but need further confirmation.

Yet another theoretical approach to understanding PMF is to view it as a dysfunction in the neural connectivity of the affected person, which has been suggested in several empirical studies (Messé et al., 2013; Skau et al., 2022; Tessitore et al., 2019). This perspective does not attempt to explain the biological cause of the condition but can generate hypotheses on how those affected by the condition and healthy individuals may differ in terms of functional connectivity. Investigating the segregation and integration of brain networks – that is, how different regions of the brain interact – yields crucial information regarding cognitive ability, health, and age-related changes (Han et al., 2024). Integration and segregation refer to the degree of interconnectedness between subnetworks, also known as modules, of a network (Sporns, 2013; Sporns & Betzel, 2016; Han et al., 2024). In turn, modules can be used when generating the network measure modularity, which quantifies the degree to which a network is divided into distinct modules, whereby high modularity refers to more segregation between modules and low modularity to less segregation, or more connectivity, between modules (Wig, 2017). As subnetworks within the brain, modules exhibit dense connections and often correlate with specialized functions. However, the concept of modularity has been a topic of debate for decades among cognitive scientists and philosophers (Egeland, 2024). The massive modularity hypothesis posits that most cognitive processes are modular, meaning they function in isolation from one another. Understanding these modules helps in identifying how the brain has optimized its wiring to minimize redundancy while maximizing its functional capacities. By studying connectivity aspects of brain function, researchers can observe how large-scale patterns in brain networks change over time, across individuals, or in response to interventions (Wig, 2017). In practical settings, measures of network segregation and integration are often used in both basic research and applied clinical contexts. However, one of the key challenges in using these network measures is the variability in their reliability (Han et al., 2024). As pointed out, results concerning connectivity and fatigue are inconclusive, with studies focusing on different neuroanatomical structures and functions, examining these under different conditions and with different neuroimaging tools and measures of connectivity.

Findings from neuroimaging studies using fNIRS suggest that individuals with PMF after traumatic brain injury show reduced frontal cortex activity (Skau et al., 2019) and heightened segregation within the frontal cortex after prolonged cognitive tasks (Skau et al., 2022). These results prompt questions concerning whether PMF can be detected on a group level by assessing brain function in terms of neural activity and connectivity. Such questions are linked to the general notion that PMF is a consequence of some kind of brain pathology on either a structural or functional level. While the mentioned studies have begun the investigation of whether there is deviating brain function in PMF that may be detected through neuroimagery assessment of cortical brain function, more research is needed.

In sum, theories on the neurobiology of PMF have suggested that astrocytic and striato-thalamic-cortical circuitry dysfunction can cause PMF after diseases or injuries in the brain. As suggested, connectivity dysfunction may also explain the condition. While these theories are not the topic of this thesis, they are valuable for contextualization and for discussing potential explanations for the results in Studies I-III. Having discussed theory on brain dysfunction in PMF, I will now present the theoretical framework for Studies II and III.

3.2. Patient Empowerment Theory

Patient empowerment has been identified as a vague concept that has diverse operationalizations (Castro et al., 2016), and has been used for normative purposes (Aujoulat et al., 2007). Having acknowledged these concerns, I will put forward a theoretical framework based on the etymological root of the concept of empowerment. I suggest that this framework can be evaluated based on its utility when trying to understand the results in Studies II and III. Let me begin by defining empowerment as it is used here. For the purpose of this thesis, I propose a semantic definition of the concept; that is, a definition that relies on the word *empower* and is in line with its etymology. The word empower is formed from the prefix "em-" (meaning "in") and the word "power". The prefix "em-" is used to indicate putting something into or providing something with a particular quality or state, while "power" refers to the ability or capacity to do something or to act in a particular way, often associated with control, authority, or influence. So, when you put these components together, "empowerment" essentially means giving someone or something the authority, capacity, or ability to take control, make decisions, or act relatively independently in a particular context. It has come to be associated with the idea of enabling individuals or groups to have more control over their own lives or circumstances, often in the context of social, political, or personal development. In the thesis, empowerment refers to the ability to take control of one's medical condition. In line with this semantic definition, patient empowerment can refer to the provision of information and practical guidelines that can enhance a patient's ability to take control of their condition. Along these lines, I argue that psychoeducation and medical education in relation to a condition are potential options for enhancing patient empowerment. While patient empowerment commonly refers to several other aspects, such as the patient taking part in healthcare planning and choice of treatment, I will henceforth refer to patient empowerment with the psycho-educative aspect of it in mind.

In sum, patient empowerment, as referred to here, means that patients are provided with resources that enhance their ability to take control in relation to their condition. One way of providing such resources is through psycho-educative interventions in which patients are given information about their condition and suggestions for how they can deal with it. Next, I will describe the connection between empowerment and mindfulness.

3.3. The Role of Mindfulness in Patient Empowerment

Having defined empowerment and its theoretical basis, I will now suggest that mindfulness-based interventions are examples of psycho-educative tools that are used with the purpose of enhancing empowerment. In this thesis, mindfulness-based interventions are defined as a form of psychological group treatment since they aim to teach participants cognitive, affective, and behavioral skills in a group-based and interactive setting. It has been theorized that mindfulness-based interventions develop abilities in an individual that enhance psychological functioning (Carney et al., 2023). The core ability that is taught in mindfulness-based interventions is the ability to purposefully, inquisitively, and non-judgmentally witness internal and external experiences as they arise in the present moment (Kabat-Zinn, 1996). In other words, mindfulness teaches you to pay close attention to your thoughts, feelings, and surroundings without judgment. It helps you observe and understand what is happening inside and around you right now, curiously and intentionally. It has been theorized that this practice lessens the psychological burden associated with automatic negative thoughts (Kraines et al., 2022).

Theory on the mechanisms of mindfulness has gained empirical evidence within neuroimaging studies on clinical and non-clinical populations (Sezer et al., 2022). The neural basis for the theory of mindfulness has to do with changes in functional connectivity between neural networks that concern attention control, self-awareness, emotion regulation, and pain relief (Sezer et al., 2022). Thus, mindfulness can be viewed as a potential tool for functional plasticity when functional plasticity is defined as the altering of cognitive processes and their efficiency (Lövdén et al., 2010). If this is the case, mindfulness is empirically manifested as abilities that allow individuals to increase their ability to cope with their medical condition. That is, mindfulness can empower patients by enhancing their psychological functioning, which allows them to deal with their medical issues more efficiently.

In sum, patient empowerment implies providing patients with resources that enhance their ability to take control of their condition. I have argued that mindfulness-based interventions can constitute one such resource, as it has been theorized that they develop abilities in an individual that enhance psychological functioning (Carney et al., 2023). Mindfulness-based interventions are believed to induce functional plasticity associated with enhanced psychological functioning.

4. Summary of the Studies

The overall aim of this thesis is to investigate neurocognitive correlates of PMF and evaluate psychological group treatments for alleviating it. The overall aim is specified in each substudy. In Study I, we compared brain activity, connectivity, and cognitive measures between healthy individuals and individuals affected by PMF. Study II evaluated the new BF-M as a treatment option for PMF using a mixed-methods design. In the study's randomized component we investigated whether BF-M led to reduced PMF, and in its qualitative interview component we analyzed the participants' experiences of BF-M. Study III provided a qualitative evaluation of MBSR for PMF after acquired brain injury based on participants' perceptions of the treatment.

4.1. Ethical Procedures

The empirical studies that constitute the thesis were approved by the Regional Ethical Review Board in Gothenburg, Sweden, protocol numbers 2019-05177 and 2022-06702-02 (Study I), 2021-03125 (Study II), and 2021–000483 (Study III). All participants were assigned a number to ensure anonymity. All data were kept in secure research storage managed by the University of Gothenburg and only accessible to the researchers within the project and a research administrator. The participants' contact information was completely separated from the data to ensure that the data could not be connected to certain individuals. In Studies II and III, which draw on the interview data, any information in the quotes that could endanger participants' anonymity was removed or changed. All quoted participants were assigned pseudonyms. More information and reflections concerning ethical conduct are presented in the section on ethical considerations in the general discussion.

4.2. Study I

4.2.1. Aim

Study I aimed to investigate whether and how functional activity and connectivity differ during rest and cognitive tasks between individuals with PMF after acquired brain injury and healthy controls.

4.2.2. Method

Participants. Individuals suffering from PMF after acquired brain injury were recruited from a rehabilitation clinic for brain-injured patients. Inclusion criteria were: aged 18-65 years and suffering from lasting PMF after an acquired brain injury (stroke or traumatic brain injury), having a rating on the MFS above the cutoff, and having recovered from neurological symptoms. Exclusion criteria included severe psychiatric disorder, drug abuse, and not being able to follow instructions due to cognitive impairment. The final sample for the PMF group included 20 participants. Aiming to match age and educational level, 23 participants were convenience sampled to be part of the control group. With a score above the MFS cutoff being used as an exclusion criterion, four participants who exceeded the cutoff were excluded, leaving a final sample of 19 participants in the control group.

Measures. For Study I we collected questionnaire data including the MFS and the Workability Index (WAI). In the experimental session (see Figure 2 in Study I) we began by collecting behavioral data from the AX Continuous Performance Task (AX-CPT) (Braver et al., 2009), which measures reactive and proactive cognitive control. We then fitted the fNIRS cap, which covered regions of interest (ROIs) within the frontal cortex (see Figure 3 in Study I). After the cap was fitted, participants underwent a resting state session, which lasted five minutes. During resting state they were asked to close their eyes and avoid planning and thinking; to just relax and rest. After resting state, the participants performed a task called BASE, during which they were asked to press the space button on a computer keyboard when they heard a sound from the computer (11 times over the course of 135 seconds with a continuous interval between them). Thereafter, they performed the Symbol Search and Digit Symbol Coding tasks from the Wechsler Adult Intelligence Scale (WAIS-IV) (Wechsler, 2010). Finally, they performed an eight-minute Stroop task. All measures that were performed during the fNIRS recording allowed us to generate measures of peak oxygenation in hemoglobin in order to compare the groups' neurofunction. From the fNIRS recordings that were conducted throughout the resting state, Digit Symbol Coding, and Symbol Search, we generated connectivity measures of global efficiency and modularity that allowed us to compare the functional connectivity between the groups.

Data Analysis. We conducted a secondary data preregistration for the analyses in Study I (https://osf.io/5z7nr). A mixed analysis of variance (ANOVA) comparing global efficiency between groups concerning resting state, Digit Symbol Coding, and Symbol Search was conducted. Similarly, a mixed ANOVA comparing modularity between groups concerning resting state, Digit Symbol Coding, and Symbol Search was conducted. Peak oxygenation during the BASE task was compared between the groups using Mann Whitney U tests and, when suitable, independent T-test. In addition, we compared peak oxygenation during Stroop between the groups for each ROI by conducting multiple mixed ANOVAs. The groups were also compared behaviorally concerning work ability, AX-CPT, Digit Symbol Coding, Symbol Search, and Stroop.

4.2.3. Main Findings

The analyses of global efficiency indicated that the group with PMF and controls exhibited different connectivity patterns, with the group with PMF showing higher global efficiency during resting state, Digit Symbol Coding, and Symbol Search (η^2_p=0.138). Group differences were also found concerning connectivity in terms of modularity during resting state, Digit Symbol Coding, and Symbol Search, with controls exhibiting higher mean modularity (η^2_p=0.039). There were statistically significant differences between the groups in terms of peak oxygenation during the BASE task in several ROIs, with controls exhibiting higher mean peak oxygenation in hemoglobin. We did not detect any group differences in neural activity during Stroop or behaviorally during the AX-CPT task. However, the results indicated statistically significant behavioral differences between the groups during both Symbol Search as well as Neutral and Incongruent Stroop tasks. More specifically, the PMF group was statistically significantly slower than the controls on Symbol Search as well as during Neutral and Incongruent Stroop tasks. The groups also differed substantially in terms of their workability, with controls exhibiting excellent ability and the PMF group generally poor ability.

4.3. Study II

4.3.1. Aim

Study II aimed to evaluate the Brain Fatigue and Mindfulness program (BF-M) for participants suffering from long-term PMF after an acquired brain injury or multiple sclerosis. More specifically, the aim was to investigate the symptom relief effect of BF-M on PMF. The aim was also to evaluate BF-M qualitatively, based on the participants' experiences. Overall, Study II is a feasibility study evaluating BF-M's potential as a treatment for PMF.

4.3.2. Method

Participants. Participants with stroke, traumatic brain injury, brain tumor, brain inflammation, multiple sclerosis, and cardiac arrest were recruited via advertisement on the Swedish Neuro Association's website, a Facebook group for people suffering from PMF, and outpatient neuro- and rehabilitation clinics. For inclusion, interviews were conducted regarding the personal history (anamnestic) and assessment of PMF. Inclusion criteria were: aged 18-65 years and suffering from PMF for at least three months. Exclusion criteria were severe psychiatric disorder, drug abuse, and not able to follow the course instructions due to cognitive impairment. After inclusion, participants were randomized to a BF-M group or a waitlist control group with usual care (who were later offered BF-M). These were divided into two BF-M and two control groups, as we wanted to keep the number of group participants at a maximum of ten, with the intention of reducing impressions and keeping things calmer. The final randomized design comprised two groups: an intervention group with 16 participants and a waitlist control group with 16 participants.

Treatment. BF-M, a new treatment program for PMF that incorporates psychoeducation on PMF as well as practices that build on the MBSR curriculum, was developed by Birgitta Johansson (PhD, LP) at the Neurorehabilitation Clinic at Sahlgrenska University Hospital in Gothenburg, Sweden. The program is based on previous experience and research conducted with the MBSR program. Research on MBSR indicates that participants may find it strenuous to complete all tasks in the program, including meditations and homework assignments, within the weekly intervals between sessions. A less demanding program would arguably benefit individuals with PMF (Johansson & Dalheim, 2024). This has also been suggested for MBCT when used for fatigue, whereby the program can be provided without a full-day retreat and with fewer and spread-out sessions (McKechnie, 2023). This results in a program that spans a longer period, which can also be beneficial. The overall aim of BF-M was to create a less demanding course and include knowledge about PMF.

Study II is the first study to evaluate BF-M. BF-M spans six biweekly sessions, each lasting two hours, over the course of 11 weeks. Each session involves meditation practice and the dissemination of knowledge about PMF. The program begins by establishing an understanding of PMF and addressing common symptoms, with subsequent sessions delving into exploring emotions and reactions related to PMF and seeking a healthy balance between rest and activity in everyday life. Group discussions during sessions revolve around specific themes, fostering an environment for participants to share experiences and learn from one another. BF-M adopts a slower pace with repeated information, creating a flexible atmosphere with yoga mats, cushions, and chairs. Participants are provided pre-recorded meditations on a website, covering a 45-minute body scan, 20-minute sitting meditation, 45-minute sitting meditation, breathing space meditation, compassion meditation, and mountain meditation. Daily meditation practice between sessions is encouraged. Supplementary materials include videos on PMF and common symptoms (post-Session 1) and strategies for managing the condition (post-Session 4). Participants also receive a booklet outlining BF-M and containing short texts on key themes for each session.

Measures. In the quantitative component, questionnaires were answered before the randomization and the start of BF-M, and within one week after BF-M had ended. Participants answered the MFS (Johansson et al., 2010), the Comprehensive Psychopathological Rating Scale (CPRS) for depression and anxiety (Svanborg & Asberg, 1994), and the Brunnsviken Brief Quality of Life Scale (BBQ) (Lindner et al., 2016). In the qualitative component, participants took part in a semi-structured interview comprising questions concerning how they experienced BF-M and whether and how they utilized information from BF-M, as well as other questions concerning BF-M in relation to PMF. Follow-up questions were asked to encourage participants to elaborate on their answers. Interviews were conducted after the intervention.

Data Analysis. In the quantitative component, mixed ANOVA was used for comparing the MFS, CPRS, and BBQ between the BF-M group and the waitlist control group, followed by a post-hoc analysis using paired t-test. For background data, t-test or Chi-square was used. In the qualitative component, our analytic focus was on how participants experienced BF-M. For this purpose, we conducted an inductive semantic thematic analysis with a critical realist approach. That is, we viewed the participants' answers as descriptors of their actual experiences while also realizing that their descriptions are subject to contextual influences. In our analyses, extracts could be coded in multiple themes. We coded the interviews using ATLAS.ti (Version 23.0.1).

4.3.3. Main Findings

The results from the quantitative component showed that the BF-M group exhibited a statistically significant reduction in PMF and anxiety compared to the control group. More specifically, the repeated ANOVA revealed a statistically significant group by time interaction for PMF (MFS) (η^2_p= 0.184) and anxiety (CPRS) (η^2_p=0.160). The post-hoc test (paired t-test) showed a statistically significant reduction on the MFS with a large effect size (d=0.843) and a statistically significant reduction with a medium effect size (d=0.596) for anxiety (CPRS) for the BF-M group. No statistically significant change in depression (CPRS) or quality of life (BBQ) was detected in any of the groups, and no significant change in any of the variables was detected in the control group. Thematic analysis of interviews with 13 BF-M participants yielded these key findings: 1) BF-M facilitated the exchange and sharing of experiences related to PMF, 2) participants reported feeling understood and less isolated, and 3) they developed tools for managing and living with PMF. This study underscores BF-M's potential effectiveness in alleviating PMF and enhancing participants' ability to manage associated challenges, suggesting its potential as a rehabilitation option for those dealing with PMF.

4.4. Study III

4.4.1. Aim

The aim of Study III was to explore how people suffering from lasting PMF after an acquired brain injury experience the MBSR program in relation to their PMF.

4.4.2. Method

Participants. Seven participants were recruited from an outpatient medical rehabilitation clinic for acquired brain injuries. The group included two men and five women, with a mean age of 42 years and with a high school diploma or university degree. They had all suffered from PMF for more than one year (range 16-46 months) after an acquired brain injury such as mild traumatic brain injury, stroke, or benign brain tumor. They had recovered well cognitively and physically from their injury, and all were living independently, some with families and children. However, due to their PMF none of them had resumed work. They all reported a score on the MFS well above the cutoff, with a mean score of 20.2

(SD=4.8) and a range of 17 to 28.5 (Johansson & Rönnbäck, 2014). The MFS has been evaluated for people with acquired brain injury, and a value above 10.5 indicates a significant problem with PMF (Johansson & Rönnbäck, 2014; Johansson et al., 2010).

Treatment. The MBSR program spans eight weekly sessions, complemented by a full-day retreat between Sessions 6 and 7. Rooted in meditative practices, MBSR involves a structured approach for alleviating stress and enhancing awareness of the present moment. The meditations encompass a body scan, which systematically fosters awareness of different body regions; 20- and 45-minute sitting meditations emphasizing breath awareness and expanding awareness to include the body, feelings, mental states, and thoughts; breathing space exercises; and gentle Hatha yoga. During weekly sessions, participants engage in discussions centered on specific themes and share their experiences of the prescribed practices. The group dynamic facilitates the sharing of individual experiences. They are encouraged to perform daily 45-minute meditations, with weekly home assignments interspersed between sessions. While adhering to the MBSR curriculum's structure and standards, slight modifications, such as two-hour sessions and shorter discussions with brief breathing meditations due to a smaller group and participant preferences, were implemented. The course was led by a certified MBSR teacher and clinical neuropsychologist who was familiar with the participants from prior clinic encounters.

Measures. All participants took part in a semi-structured interview comprising questions involving how they experienced MBSR and whether and how they utilized information from MBSR, as well as other questions concerning MBSR in relation to PMF. Follow-up questions were asked to encourage participants to elaborate on their answers.

Data Analysis. Our aim with the analysis was to explore how participants had experienced the MBSR program in relation to their PMF. For this purpose, an inductive semantic thematic analysis was used (Braun & Clarke, 2020). That is, the participants' responses were viewed as descriptors of their actual experiences while also considering that their descriptions are subject to contextual influences. *Inductive* means that the analyst generated patterns from the data without using a predetermined theoretical approach or tool. *Thematic* refers to themes consisting of codes that are, in turn, descriptions of excerpts from the interviews and thus represent patterns or content within the interviews that can be used to answer the research question. The extracts were coded in multiple themes, with ATLAS.ti (Version 23.0.1) used for coding the interviews.

4.4.3. Main Findings

The thematic analysis revealed that the MBSR program helped the participants develop coping techniques for living with PMF, gain a deeper understanding of their condition, and be more self-compassionate, and gave them a forum to share their experiences with others with similar problems. More specifically, Theme 1 described *MBSR as a Coping Technique for PMF*. In our analysis, there were two kinds of techniques according to the participants' experiences: (1) intervening techniques and (2) preventive techniques. Theme 2 illustrated that participants gained *New Perspectives* through MBSR. Our analysis highlighted the following two aspects of *New Perspectives* based on the participants' experiences: (1) an understanding and acceptance of PMF through MBSR and (2) self-compassion. Theme 3 described *MBSR as a Forum for People with PMF* and included the following three aspects: (1) exchanging experiences, (2) having the chance to be normal and (3) social challenges.

5. General Discussion

The overall aim of this thesis was to investigate neurocognitive correlates of PMF and evaluate psychological group treatments for alleviating it. Study I indicated that the PMF group had different brain function compared to the control group. More specifically, the PMF group exhibited more network integration during rest and cognitive tasks, which may indicate a compensatory mechanism due to less efficient cognitively specialized regions. The results also demonstrated that for some behavioral and neurofunctional tests there seemed to be no meaningful differences between the groups. Mindfulness-based psychological group treatments were utilized in Studies II and III, MBSR in Study III, and the novel BF-M in Study II. From the participants' perspectives, both treatments showed promise as rehabilitation options for PMF when evaluated qualitatively. In Study II, the randomized design allowed for the investigation of post-treatment outcomes on PMF and indicated that BF-M significantly reduced PMF in the treatment group, relative to the control group. Jointly, Studies II and III provide support for MBSR and BF-M as possible rehabilitation treatments and symptom relief tools for PMF after acquired brain injury and multiple sclerosis. After summarizing the empirical studies, I will now discuss these findings in detail.

5.1. Neurocognitive Correlates of Pathological Mental Fatigue

Study I generated several results that indicate important differences in how the brain's function may be different in PMF. Discussing these results in light of previous research poses a challenge, due to the inconclusive results from previous studies as well as the methodological differences between them that make comparisons difficult. That said, there are several overlapping and contradictory findings in our study and previous studies that I will attempt to address. First, while most of our analyses were exploratory, we did preregister several working hypotheses informed by empirical knowledge from previous studies. We expected to see more segregation in terms of modularity in the individuals with PMF, since such patterns have been observed in similar previous studies (Skau et al., 2022). This hypothesis was not supported. Instead, our results indicated that the PMF group exhibited slightly less modularity during rest, Digit Symbol Coding, and Symbol Search. Further, exploratory results concerning connectivity indicated that controls exhibited lower global efficiency during resting state and cognitive tasks compared to the PMF group during the fNIRS assessment of functional connectivity in the frontal cortex. These results concerning modularity and global efficiency are consistent with each other as they reflect similar network properties, suggesting increased integration in the PMF group under the investigated conditions. These findings align with the inverse relationship between modularity and global efficiency: When global efficiency is high, modularity tends to be low. This consistency supports the internal validity of our findings, indicating that our results may reliably and accurately reflect the underlying neural network properties in the PMF group. These results may indicate a different kind of network organization in the brains of the individuals in the control group compared to those in the PMF group. More specifically, this result may indicate a pathological or redundant network integration in PMF. One interpretation of these results would be that controls have more segregation, meaning that the brain network of controls is more segregated into distinct, specialized communities or modules. This may indicate that the controls' frontal cortex is organized in such a way that functional regions work more independently or in specialized clusters. This interpretation is generally in line with the massive modularity hypothesis, which posits that most cognitive processes are modular, meaning they function in isolation from one another (Egeland, 2024). Further, this interpretation would allow us to talk about healthy segregation. That is, in a healthy brain, modularity or segregation may reflect the brain's ability to segregate cognitive processes into distinct subnetworks, potentially supporting better cognitive flexibility or specialized processing. Along these lines, we could also talk about these results in terms of adaptive versus maladaptive segregation. Controls may maintain better functional compartmentalization, whereas individuals with PMF might exhibit less distinct network segregation, which may reflect some degree of maladaptive integration. Such maladaptive integration could be the result of neuroinflammation, which affects the astrocytes' possibility to clear the extracellular space from glutamate and reuptake of glucose (Rönnbäck & Johansson, 2022). In turn, it is suggested that higher levels of glutamate lead to unspecific neuronal signaling, a sort of diffuse overactivation, resulting in the reduced cognitive functioning and sense of fatigue that are associated with PMF.

Lower global efficiency indicates that the information transfer across the whole frontal cortical brain network in controls is less correlated under the specific circumstances tested in our study. This could mean that controls may rely more on localized or modular processing than on rapid, large-scale integration of information across the entire frontal cortex. These results may have several explanations. For example, they could reflect controlled cognitive load; that is, lower global efficiency in healthy individuals might reflect the brain's natural tendency to prioritize specific subnetworks for particular cognitive tasks, possibly reducing the need for extensive global integration when not necessary. It may also have to do with being less reliant on global integration. The control group's lower global efficiency may indicate that they do not require the same level of cross-region communication for maintaining cognitive function, possibly because their brain is more specialized in task-specific regions.

The results indicated that the group with PMF exhibited higher global efficiency, meaning that their brain network may be more correlated under the examined conditions. In turn, this could reflect a compensatory mechanism or network integration due to diffuse, non-specific neural signaling that exhausts a person's possibility to maintain healthy cognitive function. One way to understand compensation in this instance would be that higher global efficiency in PMF may reflect compensatory neural mechanisms, whereby the brain is attempting to maintain cognitive function by increasing global integration due to deficits or dysfunction in more localized processing. Another possibility is that those who are affected by PMF may have reduced modularity and specialization, leading to an over-reliance on global communication – which might be less efficient for specific cognitive tasks – resulting in impaired performance despite higher overall connectivity. This reasoning is in line with the results of the behavioral tests during the fNIRS assessment of global efficiency, in which the PMF group was significantly slower on Symbol Search (M=31.7, SD=8.0) compared to controls (M=38.7, SD=6.5) and was also (non-significantly) slower on Digit Symbol Coding (M=62.6, SD=14) compared to controls (M=68.5, SD=8). Further, the PMF group was significantly slower on both Neutral and Incongruent Stroop tasks compared to the controls, with a larger Stroop interference. Jointly, these behavioral results are in line with previous findings concerning cognitive function on a group level between individuals suffering from PMF and healthy individuals (Ashman et al., 2008; Azouvi et al., 2004; Belmont et al., 2009; Johansson et al., 2009; Skau et al., 2019; Ziino & Ponsford, 2006). In addition, information processing speed correlates with the severity of PMF as measured with the MFS (Johansson et al., 2009). Overall, our results indicate that processing speed measures could be a potential tool for assessing PMF.

An unexpected result in Study I was that we found no support for the working hypothesis that the groups' neural activity would differ during the Stroop task, as previously indicated (Skau et al., 2019). However, the small sample size combined with a lack of signal quality limited our ability to investigate this hypothesis. The lack of statistically significant findings implies that the examined regions may not play a crucial role in the cognitive processes assessed through the Stroop task, or that the task may not effectively distinguish between the groups in this context due to the small sample size or other unknown factors. Interestingly, the PMF group exhibited reduced functional activity in their frontal cortex during the BASE task compared to the control group, suggesting altered neural activation during the simple task of pressing a button in response to a sound.

To summarize, concerning our results, lower global efficiency may reflect a more functionally specialized and segregated network, which could be optimal for balancing between task-specific processing and general cognitive demands. Higher global efficiency in the group with PMF might indicate a network that is less specialized and more reliant on widespread integration, potentially as a compensatory mechanism for some underlying dysfunction, but this might lead to less efficient cognitive processing overall. These results indicate that the brains of those with PMF may be attempting to compensate for deficits by increasing global integration, whereas the controls' brains are functioning with more specialized, compartmentalized networks that do not require high global efficiency for effective cognitive performance.

5.2. Treatment Options for Pathological Mental Fatigue

In both Studies II and III, participants had suffered from long-term PMF, most of them for several years. They were all of working age and a few were working part- or full-time, but most of them were not able to work due to their PMF. This is in accordance with previous reports showing the impact of PMF on work ability (Andersen et al., 2012; Balasooriya-Smeekens et al., 2016; Johansson, 2022; Norlander et al., 2021; Rutkowski et al., 2021). Furthermore, the participants had different diagnoses and the groups were mixed. It could be considered favorable not to mix diagnoses, instead having groups comprised of participants who have more in common with each other. However, in previous studies of PMF using the MFS, similar symptoms are reported among individuals with acquired brain injury and multiple sclerosis (Johansson et al., 2010) and, as PMF is the theme in BF-M, a mixture of diagnoses may be less important, especially since PMF is considered to be trans-diagnostic (Rönnbäck et al., 2022). Both MBSR and BF-M gave participants an opportunity to meet others with PMF and to share experiences associated with their condition. Sharing one's experiences with a group without having to explain shortcomings can be important; this is confirmed in previous studies (O'Dowd & Griffith, 2022). These qualitative results also correspond well with previous research findings highlighting the group-learning effect of mindfulness-based interventions (Kvillemo & Bränström, 2011; Malpass et al., 2015; Visser et al., 2015). In addition, sharing experiences can improve learning and may serve to enhance the mindfulness practice (Cormack et al., 2018). When the teacher builds a safe and supportive group environment, participants are able to benefit from their shared experiences (Cormack et al., 2018). While we did not study this directly, this is also what our results indicate.

Practicing mindfulness in a group can help participants choose more appropriate and beneficial solutions. As people with PMF commonly suffer from the "invisibility" of their condition and need to rest and withdraw, their needs can be misinterpreted as laziness or social reclusiveness, whereas they are in fact necessary means for coping with PMF. In the program, participants shared these experiences and were able to support each other in this. That said, the effectiveness of the group setting for different individuals may vary based on factors such as personality, psychological conditions, neurodevelopmental disorders, and other influences. While the group-based treatment seemed to work relatively well for the participants in Studies II and III, clinicians and researchers should consider potential challenges for individuals taking part in group treatments. Interestingly, the qualitative results of Study II showed some differences compared to the findings in Study III. Notably, participants in Study II did not emphasize the challenges of social interaction to the same extent as those in Study III did. One possible explanation for this discrepancy could be that BF-M was specifically tailored to fit the needs of those suffering from PMF. This adaptation may have influenced their experience and perception of the social interactions.

Studies II and III have added new knowledge by yielding specific qualitative insights into how the participants had come to better understand and live with PMF. This was achieved partly by learning about their needs associated with PMF and partly by gaining acceptance of their PMF, which could help them manage the condition. In addition, our studies have qualitatively revealed specific applied and strategic tools and coping strategies that the participants had come to use due to having taken part in MBSR and BF-M. For example, the participants were better able to adapt their activities to fit their abilities as well as their limitations. This did not entail avoiding activities but rather taking breaks and using short meditations, which allowed them to still take part in social activities but in new ways. Similarly, learning coping techniques through mindfulness-based interventions has been noted in other clinical groups (Bogosian et al., 2016; Malpass et al., 2015; Müller-Engelmann et al., 2017). Further, the coping techniques allowed the participants to gain a sense of agency, emotional control, and self-efficacy concerning their PMF. That is, these techniques enabled them to feel more in charge of their PMF. According to our qualitative analysis, one set of coping techniques concerned MBSR exercises used for intervening in activities involved in daily life. This could entail taking a short break for a breathing meditation or withdrawing from a noisy lunchroom. Arguably, these intervening techniques are also examples of how MBSR had led to a heightened self-efficacy among the participants. That is, the exercises allowed them to feel rooted in the present moment in order to gain mental control, thus serving as a protective mechanism for PMF. Similar results concerning mindfulness as a tool in everyday life have been reported in studies on primary healthcare patients who receive MBCT (Lilja, 2016).

In Study III, the MBSR program gave the participants new perspectives on PMF, as they gained more knowledge and became more attentive to their needs and reaction patterns. The theme *New Perspectives* illustrates how MBSR allowed participants to experience an increased awareness of their medical condition and how this in turn led to new perspectives on how to relate to and address these. Similar outcomes of group learning and new or altered insights into medical conditions have been shown in several qualitative studies on experiences of mindfulness-based interventions (Kvillemo & Bränström, 2011; Malpass et al., 2015; Visser et al., 2015). In addition to confirming these previous findings, this theme described several specifically relevant outcomes of MBSR concerning PMF as experienced by the participants. For example, it indicated that the MBSR program can raise awareness of behavior and cognitive patterns that are particularly negative when trying to cope with PMF, such as being mentally active too long, being in noisy environments, and rumination. In addition, the participants were able to find more kindness and self-compassion. This tendency can be viewed as being interconnected with gaining an understanding and acceptance of PMF; that is, understanding and accepting how PMF limits and sets boundaries on everyday life, and becoming more self-compassionate because of this greater awareness. PMF typically implies that the affected person can utilize cognitive resources for short periods and then need a longer rest than normal to recover from their exhaustion. This poses several challenges concerning day-to-day activities (Johansson & Rönnbäck, 2014). By utilizing the intervening techniques, the participants created cognitive relief for the brain and thereby allowed it to rest. In addition, preventive techniques explained how a mindful approach was utilized as a general coping technique, providing ways to organize one's life and ways to prevent exhaustion. This meant that participants made use of mindfulness in a more preventive way rather than using it as an intervening technique in a specific situation. This could involve scheduling rest or planning the day in a way that is sustainable in regard to PMF. Such experiences of a preventive use of mindfulness are in line with findings from previous studies on other clinical groups (Kvillemo & Bränström, 2011; Malpass et al., 2015).

MBSR is a structured program designed to promote mindfulness and alleviate stress and mental health issues. Similarly, BF-M is a structured program that shares aims with MBSR but more specifically utilizes a psycho-educative component that targets PMF. Arguments for the design of MBSR include that it has been proven effective in reducing stress and anxiety (Kabat-Zinn, 2003), incorporates a range of mindfulness practices that imply a holistic approach to fostering mindfulness, and often involves both group and individual practices to meet diverse needs among participants (Hofmann et al., 2010). Similar arguments can be made concerning the design of BF-M. The studies in this thesis confirm the efficacy of both treatment designs from the participants' perspectives. Study II also confirmed BF-M as a potential treatment for reducing PMF through a randomized design. That said, there are also several possibilities for how the treatment designs of MBSR and BF-M could be further improved in future research endeavors. For example, considering cultural adaptations and tailoring mindfulness programs to specific populations may enhance engagement and outcomes. BF-M already targets a specific population: people suffering from PMF. But other subgroups with different needs who are dependent on other factors could call for further adaptations, for example based on the severity of symptoms (Andermo et al., 2021). Additionally, exploring the integration of mindfulness programs with other therapeutic approaches to address specific mental health challenges may enhance effectiveness. Research and development focused on strategies for enhancing the long-term maintenance of mindfulness practices beyond the structured program duration could contribute to sustained benefits

(Teasdale et al., 2000). Furthermore, optimizing program delivery formats, for instance exploring flexible online or app-based formats, may accommodate diverse preferences and increase accessibility (Spijkerman et al., 2016). Online-provided MBSR has been proven feasible in relation to PMF (Johansson & Bjuhr, 2016; Johansson et al., 2015). Thus, exploring further delivery formats for BF-M is also a task for future studies.

In Study II, the results indicated that BF-M implied statistically significant reductions in PMF and anxiety, while no reduction was detected concerning depression or quality of life. The reason for not detecting a statistically significant reduction in depression or quality of life may simply be a consequence of our having had too few participants to detect such potential effects. However, the aim of Study II was not to detect significant differences in quantitative measures per se but rather to assess the overall feasibility of BF-M. Since Study II is a feasibility study, it might be appropriate to briefly discuss the trends regarding the non-significant results. It is worth noting that the non-significant trend in the mean scores for depression indicated that the BF-M group scored lower on depression after treatment (7.6) compared to before (8.1), and so did the controls (8.7 before, 8.3 after). The non-significant trends for quality of life indicated that the BF-M group exhibited a higher quality of life after the treatment (54.4) compared to before (50.8), as did the controls (43.9 before, 45.4 after). However, the standard deviations were relatively high for these non-significant results. Future studies with designs that are suitable for better investigating the effects of BF-M on such outcome measures could shed further light on whether these trends are present in other samples.

Since depression and anxiety are important differential diagnoses concerning PMF and are correlated with it (Rönnbäck et al., 2022), it might be expected that depression would have been reduced parallel to PMF – especially since mindfulness programs have been found to alleviate depression after multiple sclerosis and acquired brain injury (Grossman et al., 2010; Ulrichsen et al., 2016). Why this was not the case in Study II is a matter of speculation. Arguably, one reason for why no effects were found concerning depression might be that BF-M was not designed to reduce depression per se but rather to reduce PMF. In addition, the treatment group initially reported relatively low scores on depression, which is why the potential reduction effect on this was limited to a narrower span compared to if they had exhibited a high initial depression score. The reason for not finding a statistically significant reduction in quality of life is also subject to speculation. Since mindfulness treatments theoretically aim to reduce suffering and improve quality of life (Lilja, 2016), it would be expected that such effects would be found in Study II. As PMF can be severely debilitating and affect many aspects of an individual's life, a reduction in PMF would be expected to correlate with increased quality of life. The analyses in Study II cannot illuminate why these expected outcomes were not revealed. The reason for this might be that participants become aware of their medical condition and its consequences through the psycho-educative aspects of BF-M. In turn, this awareness could even out the potential reduction in depression and quality of life as the participants more fully realize the limitations associated with PMF, a potentially depressing insight that may imply an equilibrating effect on depression and quality of life. On the other hand, health awareness is arguably crucial to inducing behavioral change. That is, individuals with PMF need to understand their condition more fully in order to act on it. Whether the suggested equilibrating effect between mindfulness and psychoeducation in relation to quality of life and depression is the case in BF-M is a question for further investigation.

Jointly, the results in Studies II and III indicate that individuals suffering from PMF seem to benefit from education and knowledge about common symptoms related to PMF (Study II) and how to manage these (Studies II & III). Previous treatment studies report a reduction in PMF, but none have included a psycho-educative program specifically designed for PMF, such as in Study II. Pharmacological studies have reported reduced fatigue (Johansson et al., 2012, Johansson et al., 2015) or improved wakefulness, making the fatigue easier to manage (Kaiser et al., 2010; Stankoff et al., 2005). In addition, non-pharmacological studies have reported reduced mental fatigue (Grossman et al., 2010; Johansson, Bjuhr & Rönnbäck., 2012; Nguyen et al., 2017; Van Heest et al., 2017), while review reports offer few positive results (Ali et al., 2022; Hinkle et al., 2017; Su et al., 2020; Yang et al., 2017). In our experience of conducting this research, it was clear that participants benefitted from learning about PMF, learning useful strategies, and adapting new knowledge and tools to their capabilities. PMF needs to be addressed, and treatment options need to be implemented in healthcare, as well as being tailored to suit individual needs (Eng et al., 2019; McKevitt et al., 2010). BF-M and MBSR may be feasible symptom relief options for PMF.

5.3. Patient Empowerment and Treatment of Pathological Mental Fatigue

In this thesis, the theory of patient empowerment is retrospectively employed to analyze the findings from Studies II and III. In this context, mindfulness-based interventions are viewed as psychological group treatments that serve the purpose of invoking behavioral change in the participants.

Considering the results with regard to empowerment theory, the findings involving participants' experiences in Studies II and III can be understood in regard to the semantic interpretation of empowerment theory that I have proposed. That is, the participants' experiences indicate that they have gained the capacity to understand and deal with their condition, a capacity they lacked or had not developed before the treatments. These aspects of empowerment theory became empirically evident in both studies, with the analysis of the participants' experiences indicating a developmental process initiated in the treatment whereby they came to understand their condition and learn skills for dealing with it. In addition, the collective or social aspect of empowerment became evident as the participants stressed the social aspects of the treatments through which they came to better understand themselves and their needs by sharing experiences with others who live under similar conditions. Overall, I suggest that the evaluation of the mindfulness-based interventions in the current thesis indicates that the participants developed abilities that enhance psychological functioning, as previously theorized (Carney et al., 2023). Arguably, the mindfulness-based interventions evaluated in this thesis can be viewed as vessels for potential empowerment in individuals with PMF.

The resources provided to the participants and the skillsets they acquired were further indicated in the randomized quantitative assessment of BF-M in Study II. Interpreting the results involving reduced PMF after BF-M through the lens of empowerment theory suggests that the psycho-educative resources that were provided and the skillsets that were taught in BF-M implied a behavioral change that could explain the reduced PMF. Thus, the core idea of empowerment in terms of enabling individuals or groups to have more control over their own lives or circumstances became apparent in Studies II and III. Earlier I suggested that mindfulness-based interventions be defined as a form of psychological group treatment since they aim to teach participants cognitive, affective, and behavioral skills in a group-based and interactive setting. Whether effects and experiences associated with mindfulness-based interventions as demonstrated in this thesis can be linked to functional plasticity due to mindfulness (Sezer et al., 2022) is a question for future research. Interestingly, it has been indicated that default mode network (DMN) activity is disrupted in PMF after mild traumatic brain injury (Zhou et al., 2012) and multiple sclerosis (Høgestøl et al., 2019) but becomes more functionally interconnected with the salience network (SN) as a consequence of mindfulness practice in non-clinical populations (Rahrig et al., 2022). The DMN is involved in self-referential thinking, mind wandering, and introspection, while the SN detects important stimuli and helps shift attention between inner and outer focus. Thus, hypothetically, improvements in PMF after mindfulness-based interventions could be explained by restored DMN functionality induced by mindfulness practice. However, this potential association needs confirmation in clinical settings in investigations of mindfulness and PMF together. Even if other treatment options than psychoeducation and behavioral interventions seem crucial in addressing the complexity of PMF, empowering patients with psycho-educative resources can be a feasible component in a treatment regimen for PMF.

5.4. Ethical Considerations

The ethical considerations for all studies primarily involved the risk of evoking discomfort in the individuals with PMF. To address this, participants were informed several times that their participation was voluntary, and that if they chose to participate they could end their participation at any time without further explanation. We assured the participants of the confidentiality of their disclosures and informed them that they were free to skip questions or end their participation at any time without giving a reason. In Studies II and III the participants were asked several times during the interview if they wanted a break, and when the interviews took place in person they were also asked if they wanted the room's brightness to be adjusted. The interviews were conducted in a calm environment with as few distractions as possible. With PMF in mind, we aimed to keep the interviews as brief as possible without sacrificing the ability to ask the relevant questions concerning the studies' aims.

5.5. Methodological Considerations and Future Directions

The results in this thesis should be considered in the light of methodological considerations and limitations, and also invoke further questions for future research. First, Study II follows a pragmatic research design, focusing on real-world applicability and the practical execution of BF-M rather than being driven solely by statistical power or controlled experimental conditions. The primary goal was to explore meaningful insights into the feasibility of BF-M rather than to detect statistically significant differences between groups. That said, as part of assessing the feasibility of BF-M, we conducted statistical analyses of the outcome measures in order to provide indices of what outcome trends might be expected from the program. However, we want to stress that Study II is to be regarded as a feasibility study that needs to be followed up with confirmatory research that further evaluates the potential for BF-M as a treatment option for PMF.

There are no known cures or recommended treatment options for PMF. The challenge when trying to find a cure for it is to first understand the underlying pathology that causes the condition. The purpose of Studies II and III was not to evaluate curing effects of the treatments, and their designs did not allow such investigations. Instead, when we use the term *treatment* we refer to it as a tool for the relief of primary and secondary symptoms associated with the condition. For example, a lower score on the MFS would indicate primary symptom relief, and breaking social isolation and being more active would indicate secondary symptom relief. Until cures are discovered, future research needs to not only focus on symptom relief treatments but also find the causes of and cures for PMF.

In terms of the experiential results from interviews, both studies are limited to the specific population they examine, and the time span of eight sessions over seven weeks (MBSR) and six bi-weekly sessions over 11 weeks (BF-M). Other studies with follow-up interviews conducted later rather than alongside the treatments could imply variations such as frequency of continuous practice and other factors based on the amount of elapsed time. More closely examining the extent to which participants do the exercise tasks at home is also something that should be considered in future studies. Further, the interviews in both studies were conducted in conjunction with the program to avoid memory difficulties, which are common among individuals with acquired brain injury. This precautionary measure was reported in a previous interview study on individuals suffering from acquired brain injury (Niraj et al., 2018). A relatively small number of participants have been involved in the qualitative assessments in both studies. This implies that the analyses may have been altered and made more divergent if more experiences from additional interviews had been included. As previously highlighted, an attempt to extract deep and rich empirical data can be precarious when sample sizes are too small or too large (van Ravesteijn et al., 2014). Arguably, the sample sizes provided sufficient information power with a breadth of analysis while at the same time being small enough to allow a thorough analysis.

Study II is the first study to evaluate BF-M, and the number of participants is low for the quantitative randomized assessment. The goal was to evaluate the usefulness of BF-M in the context of PMF. Studies with more participants and other clinical groups are warranted in order to better assess the program's effects. We are also aware that Study II was not placebo-controlled. While future studies could design adequate control group situations for further evaluation of BF-M, a waitlist control group was regarded as a feasible option in Study II due to the limited number of participants. The recruitment of participants was not evenly divided between men and women; more women (74%) were represented. BF-M is inspired by the MBSR course, and the same problem with gender imbalance is reported in MBSR studies with women representing two-thirds of participants (Bodenlos et al., 2017). Thus, more research is needed in order to explore this, and modifications may be needed to better attract men with PMF to take part in mindfulness-based interventions. Unfortunately, we have no comments from those who dropped out since, according to the ethical rules, participants could cancel without providing any comments. Therefore, their reasons for not continuing can only be speculative. Further, the fact that the treatment group in Study II responded well to the treatment in terms of self-assessed PMF ratings might be explained by their being eager to find a solution to their PMF and thus indirectly overvaluing the treatments by scoring lower mental fatigue symptoms. The possible inclination among participants to overvalue or praise the assessed treatments, fueled by a keenness to pinpoint effective solutions, might underlie the lack of critical feedback and negative dispositions observed in interviews conducted in both Studies II and III. In other words, the qualitative assessments from these studies indicate an overall satisfaction among participants with the treatments, potentially indicating sample bias or inherent dispositions among the population. In future studies it is therefore advisable to use an active control group. It is also advisable to combine suitable subjective and objective measures of PMF and fatigability in order to compare these measures. It might also be advisable to actively recruit participants who are skeptical of mindfulness.

Ideally, the design of the randomized component in Study II would include neuroimaging assessments pre-, post-, and throughout the treatment to investigate neural correlates of the reduction in PMF. More precisely, such a design could utilize fMRI to investigate default mode alterations associated with mindfulness practice (Rahrig et al., 2022) as well as striato-thalamic-cortical correlates associated with PMF after traumatic brain injury (Berginström et al., 2018) and multiple sclerosis (Engström et al., 2013; Chaudhuri & Behan, 2000; Finke et al., 2015). fNIRS could be used to compare segregation between the control and treatment groups longitudinally (Skau et al., 2022). Further, such studies can test the potential association between neuronal changes due to mindfulness practice and reduction in PMF, an association that I have suggested could explain the results in this thesis as both PMF and mindfulness are associated with changes in the DMN. To investigate whether higher levels of glutamate are correlated with more severe PMF (Rönnbäck & Johansson, 2022), I would suggest a combination of several neuroimagery approaches to be applied before, during, and after treatments targeting PMF. Magnetic Resonance Spectroscopy (MRS) would allow us to directly measure the concentration of glutamate in specific brain regions (Wiehler et al., 2022).

Comparing glutamate levels between groups would allow us to assess whether there's an overload of glutamate correlated with more severe PMF. Novel studies on this topic indicate that the concentration of glutamate increases as a consequence of cognitive fatigue in healthy individuals (Wiehler et al., 2022). Positron Emission Tomography (PET) could be used with radiotracers that bind to glutamate receptors, providing information about glutamate receptor density and distribution within the control and treatment groups. Diffusion Tensor Imaging (DTI) could assess white matter integrity, which may be influenced by glutamate-induced excitotoxicity. Applying these neuroimagery approaches when assessing PMF and when evaluating treatments for it is therefore a task for future research. However, such methods and designs would imply a substantial cost for the neuroimagery assessments, as well as the workload of administrating such research designs. Due to the high prevalence of PMF and the suffering it causes, I sincerely hope that such research endeavors are funded and conducted despite the costs and workload involved.

In the qualitative components of Studies II and III, participants reported that they found the mindfulness-based interventions helpful to various extents. In Study II, these reports were also statistically confirmed in the evaluation of the MFS after BF-M through the randomized design. Even if the results in our studies pointed out the benefits of MBSR and BF-M among the participants, there are substantial criticisms of mindfulness-based interventions and research on them that should be considered alongside our results. Criticism has been voiced regarding methodological concerns in mindfulness research and aspects related to the fact that mindfulness is a relatively new field of study (Van Dam et al., 2018). This criticism extends to more specific issues, including how mindfulness is applied in practice. We have taken precautions in accordance with these suggestions in several ways. For example, we have aimed to be clear and concise regarding what we mean by mindfulness and how the interventions have been implemented in both studies. We have also pointed out that our results should be considered in their context, and that more research is needed in order to confirm and potentially extend the knowledge regarding their feasibility. All these precautions serve to lessen the risk of contributing to the 'mindfulness-hype' (Van Dam et al., 2018). In addition, we have considered and implemented suggestions concerning competence in teaching mindfulness (Crane et al., 2012), mainly by including a trained, senior mindfulness teacher in both interventions. Overall, our results highlight MBSR and BF-M as feasible treatments for the participants in our studies. That said, it is advised that researchers and clinicians carefully consider and implement precautions concerning participants' risks associated with mindfulness-based interventions (Kuyken et al., 2012; Van Dam et al., 2018); especially since risks for vulnerable groups can be severe, such as increased likelihood of suicidality, depression, negative emotions, and flashbacks during meditation for previously traumatized individuals (Kuyken et al., 2012).

The waitlist control design in Study II allowed us to investigate the effect of the BF-M treatment. That said, there are some key methodological issues with waitlist designs that are applicable concerning Study II. One such criticism concerns the absence of a placebo in the control group (Patterson et al., 2016). For example, in a pharmaceutical study using sugar pills as an active control, the experimental group experiences the effect=active ingredient+placebo, while the control group experiences the effect=placebo. This allows for an isolation of the effect of the active ingredient. However, this is not the case with a waitlist design, which carries the risk of overestimating the effect of the treatment. We cannot conclude whether such overestimation is the case in Study II, but as conveyed here, we are aware of this risk. While experimental designs with active control groups are preferred due to the presented criticism, they can be challenging to design due to costs and the difficulty involved with designing a reasonable active control treatment in relation to the treatment being tested (Patterson et al., 2016). It is difficult to assess what the active component of mindfulness is, how to eliminate it, or how to blind participants to the treatment. Future studies that further evaluate BF-M could consider designing and implementing an active control group that, for example, receives psychoeducation on PMF and/or attends a social support group while replacing or excluding the mindfulness-based exercises. Such a design could elucidate whether and to what extent the mindfulness components in BF-M play a specific role in the treatment, and by extension, in the psycho-educative aspects of the treatment. I recommend such endeavors in future research on BF-M.

Due to several key limitations, the results from Study I should be viewed with caution. First, the small sample size limits the results' generalizability and restricts conclusions about the clinical utility of these assessments, especially given conflicting findings from previous studies and the absence of standardized guidelines for assessing PMF via brain function. This lack of precedent meant we could not reliably predict expected effect sizes for the various measures. Nonetheless, our results do indicate that the group-level distinctions between individuals with PMF and healthy controls may be clinically meaningful. However, to validate measures that consistently differentiate those with PMF from healthy individuals, larger sample sizes and replication studies are essential in order to confirm the reliability of our findings. A second limitation in Study I was our lack of state fatigue measurements before and after experimental sessions, meaning we did not control for fluctuations in fatigue sensations. However, given that PMF typically involves an elevated baseline of fatigue, and since we did not aim to analyze changes in fatigue over time, this does not significantly impact our interpretation of the data. That said, given the prolonged recovery time associated with PMF, future studies could benefit from monitoring recovery over multiple time points following extended cognitive tasks, potentially offering deeper insights into how network properties stabilize or recover over time. When considering the results in Study I, it is important to recognize it as a small-sample feasibility study. Further confirmatory studies are needed in order to assess the feasibility of using cortical brain function as a biomarker for PMF, especially across diverse clinical populations beyond acquired brain injuries. Future research may also conduct comparative evaluations of different neuroimaging tools for PMF assessment. fNIRS is restricted to measuring brain activity and connectivity in the cortex, potentially overlooking crucial information about deeper brain structures. Furthermore, as the analyses in Study I concern group-level differences, additional research is required in order to investigate the potential that neuroimaging may hold for assessing PMF in individuals.

5.6. Practical Implications

Together with previous research, the findings in this thesis may be used by clinicians and policymakers to evaluate whether MBSR and BF-M could be implemented within primary healthcare and at rehabilitation clinics that see individuals with PMF. Given the high demand and limited treatment options for PMF, it may be advisable to implement the treatments evaluated in this study. These treatments appear to be relatively risk-free when administered to participants who are deemed suitable after anamnestic evaluation, as well as being cost-efficient and beneficial in helping those who are affected manage their PMF. However, implementation should be guided by the broader knowledge of psychological treatments for PMF, recognizing that the thesis is just one piece of the larger puzzle. Hopefully, future confirmatory research will enhance the treatment of PMF by expanding the understanding of the treatments evaluated in the thesis. Study I has provided yet another piece to the diagnostic puzzle of PMF. However, due to its exploratory findings and small-scale feasibility design, further confirmatory research is needed before its insights can be applied in clinical practice.

5.7. Conclusions

This thesis aimed to investigate neurocognitive correlates of PMF and evaluate psychological group treatments for alleviating it. Study I indicated that individuals with PMF exhibit more neural connectivity during rest and cognitive tasks, and less neural activity during an easy task, compared to healthy individuals. Study I also indicated cognitive differences between the control and PMF groups, with individuals in the PMF group performing more slowly on cognitive processing tasks. We evaluated the novel BF-M (Study II) and the perceived effect of MBSR (Study III) as psychological group treatments for PMF in individuals with acquired brain injury (Studies II & III) and multiple sclerosis (Study II). Participants experienced the programs as providing a place for them to meet others with PMF and share experiences, learn about PMF, and acquire tools and strategies for coping with PMF in everyday life. The results from the randomized experiment in Study II indicated reduced PMF and anxiety associated with BF-M participation. Overall, the thesis provides neurocognitive correlates of PMF and indicates that BF-M and MBSR show promise as symptom relief treatments for it in individuals with acquired brain injury and multiple sclerosis.

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