Biopsychosocial Mechanisms in Fatigue –

Exploration of Factors Associated with the Occurrence and Maintenance of Fatigue in the General Population and Patients with Traumatic Brain Injury

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1 Acknowledgements

No scientist is ever an island, with scientific progress always being a collaborative process. This is especially true of the following thesis. My initial introduction to the potential impact of fatigue on chronic illness occurred during my initial years as a clinical psychologist working with patients with congenital, developmental and acquired brain injuries, as well as those suffering from chronic pain disorders. Each patient's story taught me about personal suffering and coping, which shaped my initial clinical curiosity towards seeking out knowledge about a symptom that has often been misunderstood and neglected in the field of chronic illness. For this, I would like to acknowledge those patients who suffer from fatigue in relation to various illnesses, and especially those patients with TBI who contributed their invaluable time and effort to this project. I hope that this thesis serves as a validation of your struggles while also illuminating hope and potential paths towards improved coping and future efficacious treatments.

In an extension of the many stories I heard from patients, we are lucky that user organisations such as Personskadeforbundet LTN exist. Not only do such organisations provide invaluable legal assistance and opportunities for sharing stories and connections between those living with the aftermath of injuries, but they also aid clinicians in identifying crucial problem areas and tailoring the dissemination of knowledge. I would like to thank Personskadeforbundet LTN for their invaluable support of our project and their collaborative efforts in attempting to make life worth living despite chronic ailments following injuries. Along these lines, I would also like to thank the user organisations LHL Hjerneslag, Landsforeningen for Slagrammede, Funksjonshemmedes Fellesorganisasjon, Hjernesvulstforeningen and the interest organisation Hjernerådet, for their continued interest in brain health, fatigue, and for contributing to the much-needed work that remains in providing equal rights to people living with chronic illness. I would also like to extend my gratitude to Stiftelsen Dam for their financial support of this project, and for the opportunity to conduct it.

A doctoral research fellowship has the potential to be a lonely project. If you add a global pandemic to this context, anyone can be brought to the brink of existential collapse. Neither the research project nor the retention of my mental health would have been possible without the help of my team of supervisors and collaborators. I would especially like to thank my main supervisor, Marianne Løvstad, who has provided support through the ups and downs of work, research and life in general. I would also like to thank Nada Andelic for sharing all

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We made it.

2 Abbreviations

ABI – Acquired Brain Injury
AIS-head – Head Abbreviated Injury Scale
ASA-PS – American Society of Anesthesiologists' Physical Status Classification
BIS – Behavioural Inhibition System
BAS – Behavioural Activation System
CFS – Chronic Fatigue Syndrome
CFQ – Chalder Fatigue Questionnaire
CoV – Coefficient of Variation
CPT-III – Conners Continuous Performance Test III
CT – Computed Tomography
CWIT – Color-Word Interference Test
D-KEFS – Delis-Kaplan Executive Function System
Dz – Dizygotic (fraternal twins)
FIML – Full Information Maximum Likelihood
FSS – Fatigue Severity Scale
GCS – Glasgow Coma Scale
GSCL – Giessen Subjective Complaints List
HISS – Head Injury Severity Scale
ICC – Intraclass Correlation Coefficient
ICF – International Classification of Functioning, Disability and Health
LOC – Loss of Consciousness
ME – Myalgic Encephalomyelitis
MLM – Multilevel Modelling
MRI – Magnetic Resonance Imaging
Mz – Monozygotic (identical twins)
NEO-FFI-3 – NEO Five Factor Inventory 3
NRS – Numerical Rating Scale
OUH – Oslo University Hospital
PROM – Patient-Reported Outcome Measure
REBW – Random Effects Between-Within Model
RPQ – Rivermead Post-Concussion Symptoms Questionnaire
RSA – Resilience Scale for Adults
SCL – Hopkins Symptoms Checklist
SD – Standard Deviation
T1 – Time Point 1
T2 – Time Point 2
TBI – Traumatic Brain Injury
TMT – Trail Making Test
WAIS-IV – Wechsler Adult Intelligence Scale IV
WASI – Wechsler Abbreviated Intelligence Scale

3 General Summary

Fatigue is a symptom characterised by a subjective experience of decreased capacity for activity and an increased need for rest, which is disproportionate to the effort expended. While fatigue is commonly observed in association with a wide range of chronic illnesses and interest in research on this symptom is steadily increasing, clear recommendations for its assessment, treatment and management remain lacking. Although research has identified several biopsychosocial mechanisms associated with fatigue, much remains to be identified in terms of the crucial mechanisms for fatigue treatment. Furthermore, potential confounders such as genetic and dispositional vulnerabilities may complicate our perception of the relationships between fatigue and other symptoms as being causal, while their co-occurrence may in fact only stem from shared vulnerabilities.

Patients with traumatic brain injury (TBI) often struggle with fatigue following injury. Fatigue is commonly reported in the early phases following injury and remains a troublesome symptom for many patients in the later phases of adaptation to life with the sequela of TBI.

While earlier research has established an abundance of associations between fatigue and various biological, psychological and social factors, much remains to be explored regarding the exact nature of these relationships. In relation to TBI, severe injuries are often associated with more severe cognitive, emotional and functional deficits. Despite this, associations are rarely found between injury severity and fatigue, or these are found to be marginal when significant associations have been documented. Similarly, no specific localisation of brain injury has been linked to an increased risk of fatigue, despite progress being made into neural underpinnings of the symptom. While cognitive dysfunction has been associated with fatigue in some studies, it has rarely accounted for much of the variation in fatigue. Self-reported biopsychosocial factors such as pain, depressive symptoms and trait neuroticism generally demonstrate more robust associations with fatigue than objective measures such as the severity of somatic illness and performance-based cognitive tests in TBI, other health conditions and the general population.

Much of the research into fatigue has revolved around examining cross-sectional hypotheses, with the primary aim of characterising those patients who develop persistent fatigue following injury, and those who do not. For the research field to move beyond mere correlation and towards verification or falsification of causal assumptions, studies need to

incorporate measures for dealing with confounding from shared vulnerabilities between fatigue and its correlates.

The overall aims of this thesis were to (1) explore the biopsychosocial correlates of fatigue using an improved and parsimonious characterisation of risk and protective factors and (2) identify the factors associated with fatigue over time. In the pursuit of a clearer understanding of how the mechanisms in this vast network of symptoms interact, this doctoral thesis has approached the problem from various angles in three scientific papers.

In **Paper I**, the primary aim was to examine (1) the behavioural genetic underpinnings of fatigue in a sample of mono- and dizygotic twins from the general population and (2) the degree of shared genetic and stable or time-varying environmental influences between fatigue, pain and psychological distress.

In **Paper II**, the primary aim was to explore potential parsimonious structures underlying the commonly implicated biopsychosocial mechanisms involved in the initiation, maintenance, and exacerbation of fatigue 6 months after TBI.

In **Paper III**, the aim was to better understand which factors contribute to the persistence and amelioration of fatigue from 6 to 12 months after TBI via an exploration of the between- and within-subject biopsychosocial correlates of fatigue.

The findings indicate that several biopsychosocial factors can be used to identify which individuals are at risk of developing fatigue following injury, while a smaller group of factors also covary with fatigue within subjects. Pain, somatic symptom burden, psychological distress and behavioural inhibition were implicated as the crucial factors to address within rehabilitation aimed at the amelioration of fatigue following injury. Combined, the studies described in these papers shed light on novel ways of understanding fatigue. As such, they may guide future research and clinical efforts aimed at managing fatigue through a parsimonious taxonomy of protective and vulnerability factors involved in the initiation, maintenance and exacerbation of fatigue following TBI.

4 List of Papers

This thesis is based on the following papers, which will be referred to by their respective numbers (i.e., I, II and III) throughout the text.

Paper I

Løke, D., Løvstad, M., Andelic, N., Andersson, S., Ystrom, E., & Vassend, O. (2022). The role of pain and psychological distress in fatigue: A co-twin and within-person analysis of confounding and causal relations. *Health Psychology and Behavioral Medicine*, *10*(1), 160–179.

Paper II

Løke, D., Andelic, N., Helseth, E., Vassend, O., Andersson, S., Ponsford, J. L., Tverdal, C., Brunborg, C., & Løvstad, M. (2022). Impact of somatic vulnerability, psychosocial robustness and injury-related factors on fatigue following traumatic brain injury—A cross-sectional study. *Journal of Clinical Medicine, 11*(6), 1733.

Paper III

Løke, D., Andelic, N., Helseth, E., Vassend, O., Andersson, S., Ponsford, J. L., Tverdal, C., Brunborg, C., & Løvstad, M. (2022). Stable and time-varying biopsychosocial mechanisms associated with fatigue in the first year following traumatic brain injury – An exploratory multilevel study. Submitted to the Journal of Head Trauma Rehabilitation.

5 Introduction

Daily life is characterised by a series of continuous demands on our ability to focus, perform and maintain vitality when faced with minor and major challenges in life. For most of us, our confrontation with this perpetual demand for our ability to sustain effort goes without saying, and little attention is paid to minor lapses in our abilities to remain aligned with our goals and ambitions. Our body and brain serve us well as instruments for our pursuit of desirable outcomes in life, while simultaneously being absent from our consciousness as they perform in line with our needs as we go about our business in an almost automated fashion. While our resources may become depleted through especially demanding and taxing times, rest and leisure nevertheless allow us to recuperate and mobilise once again. Evidently, this ability to remain energised and focused on our pursuits should not be taken for granted.

However, persistent and problematic fatigue is a common difficulty experienced by people suffering from several chronic illnesses and can affect function, activities of daily life and quality of life. While the scientific pursuit of precipitating, causal, maintaining and exacerbating factors has made significant progress, much effort remains in paving the way for explanatory models that could guide clinical practice and help patients better understand and cope with their persistent fatigue in various chronic illnesses. Despite evidence pointing towards commonalities in determinants of fatigue across diagnostic categories (e.g., pain, depression and sleep deficits), research into fatigue has been fragmented between diseases (Menting et al., 2018). Survivors of traumatic brain injuries (TBIs) frequently report persistent fatigue as one of the primary obstacles when returning to life following an injury. Injury characteristics do not account for much of the variation in fatigue experienced by survivors, and multifactorial approaches are necessary to gain a comprehensive understanding of potential influences on fatigue. Much remains to be identified in terms of the central mechanisms both unique to TBI and common to chronic illness in general, which can be targeted through individually tailored rehabilitation aimed at the amelioration of fatigue.

This thesis has an exploratory focus, and uses observational research to improve our understanding of which factors are crucial in the clinical management of fatigue in general, and in patients who have sustained a TBI in particular. It has been established that many patients with TBI suffer from persistent fatigue during the first year following injury and beyond (Mollayeva et al., 2014; Ponsford et al., 2014). Thus, an improved understanding of the crucial factors in determining which patients are at risk of fatigue following injury—and what characterises the development of fatigue—is the main aim of this thesis.

5.1 A Brief History of Fatigue

Although problems with fatigue, exhaustion and excessive tiredness have been documented for centuries, historian Rabinbach (1992) argued that the ubiquitously negative and medicalised connotations of fatigue first came about during the industrial revolution of the 18th to 19th century. Before this societal change of pace, fatigue was more often referred to as a natural consequence of overexertion and as a sign of one's limits of effort being reached—but rarely as a symptom of illness (p. 38). While people may have also suffered from persistent fatigue in pre-modern ages, there is little indication that it was a subject for medical inquiry. Hockey (2013) argued that as the gradual modernisation of Western societies from 1750 to 1880 led to the commodification of work and effort into a force to be harnessed in a standardised fashion for increased productivity gains, work itself took on a new form. While pre-industrial workers were unlikely to have worked less, the way people worked changed dramatically. Workers of the pre-modern era generally worked more task-oriented jobs rather than under strict time schedules, whilst the workflow and hours were generally more self-managed and under the control of the individual. Conversely, post-industrial work was—and, to some extent, remains—characterised by an increasing standardisation of the workplace and steadily increasing demands for productivity (Hockey, 2013). While the influence of socioeconomic shifts and modernisation on the perception and functional impact of fatigue can only be speculated upon in retrospect, these reflections nevertheless shed light on how health and disability never develop or operate in an isolated vacuum.

Throughout recent history, research into fatigue has taken several divergent paths, and fatigue has been conceptualised as being caused by a variety of factors. In the early 19th century, Austin Flint described chronic fatigue using the term ‘nervous exhaustion’. This concept was further elaborated by George Beard into the description of neurasthenia, or a weakness of the nerves that could be brought on by a variety of causes (Straus, 1991; Torres-Harding & Jason, 2005). While the concept of neurasthenia garnered much attention, it was abandoned as a diagnostic entity in the first half of the 20th century due to a lack of diagnostic precision and usefulness. Throughout the 20th century, several potential causal hypotheses paved the way for fatigue-related diagnoses such as DaCosta’s syndrome (thought to be brought on by exhaustion, an irritable heart, and later psychogenic causes), chronic brucellosis (bacterial infection thought to bring about fatigue in those with a latent psychogenic vulnerability) and other potential infectious or microbial aetiologies (Straus, 1991).

In recent decades, this field of research has taken on a broader perspective with regard to the potential causes and influences of fatigue. Persistent fatigue is a cardinal symptom of chronic fatigue syndrome (CFS)/myalgic encephalomyelitis (ME) (Rivera et al., 2019) and common comorbidity in other neurological illnesses (Penner & Paul, 2017), such as TBI (Mollayeva et al., 2014). With a growing body of knowledge concerning multiple potential initiating diseases and the broad spectrum of potential transdiagnostic mechanisms involved in its maintenance, our pursuit of explanatory models for fatigue must incorporate several potential paths to the same end state, which is commonly termed an equifinality (Wilshire et al., 2021).

5.2 Defining and Conceptualising Fatigue

5.2.1 Definitions and Classification

While fatigue has many definitions, the two cardinal signs that permeate most definitions are (1) the experienced disruption in one's ability to maintain focus and performance and (2) a subjective lack of energy. One often-cited definition of fatigue by Aaronson et al. (1999) holds that fatigue is 'an awareness of a decreased capacity for physical or mental activity due to an imbalance in the availability, utilisation or restoration of resources needed to perform activities'. This definition emphasises the subjective experience of fatigue and outlines three potential mechanisms through which we hypothesise the fatigue experience might arise. However, the subjective nature of fatigue makes it difficult to establish a clear-cut definition with the ability to distinguish normal fatigue from pathological fatigue since fatigue and fatigue interference seem to be rather normally distributed in the general population (Lerdal et al., 2005; Pawlikowska et al., 1994). As such, the literature on fatigue in association with medical illnesses lacks a unitary consensus on any particular definition, as discussed by Skau et al. (2021) along with their recently published proposal for unified definitions for fatigue and related terms. In their proposal, the sensation of fatigue was defined as being present 'if and only if there is a sensation of (i) feeling the need for rest, or (ii) mismatch between effort expended and actual performance' (p. 3). Incorporated into this definition is the acknowledgement of a mismatch between effort and performance, the proportion of which might be compared to the individual's premorbid standard or a more normatively based standard.

Fatigue can be distinguished depending on how we measure it, its experiential qualia, triggering activities and presumed causes. The subjective experience of fatigue can be distinguished from objective performance decrement during sustained physical or mental

exertion (i.e., fatigue and fatigability, respectively (Kluger et al., 2013)) since individuals may have a stable level of fatigue from which they might deviate from or fluctuate around (i.e., trait or state fatigue (Enoka & Duchateau, 2016; Malloy et al., 2021)). Also, fatigue can be differentiated by whether or not it interferes with function (i.e., pathological and non-pathological fatigue (Finsterer & Mahjoub, 2014; Jason et al., 2010)). Further elaboration of the definitions in the literature also incorporates modality-specific variations of fatigue based on the presumed cause and influence of fatigue on specific functions. In neurological illness, primary fatigue is considered to be brought on by acute injury- or disease-related activity, while fatigue maintained by other symptoms (e.g., depression and insomnia) is characterised as secondary fatigue (Cantor et al., 2013; Finsterer & Mahjoub, 2014). Similarly, a distinction is drawn between fatigue that is experienced as physical or cognitive/mental in nature and whether or not it is exacerbated by physical or mental exertion (Ezekiel et al., 2021; Finsterer & Mahjoub, 2014). A visual overview of potential dimensions for the classification of fatigue is presented in Figure 1.

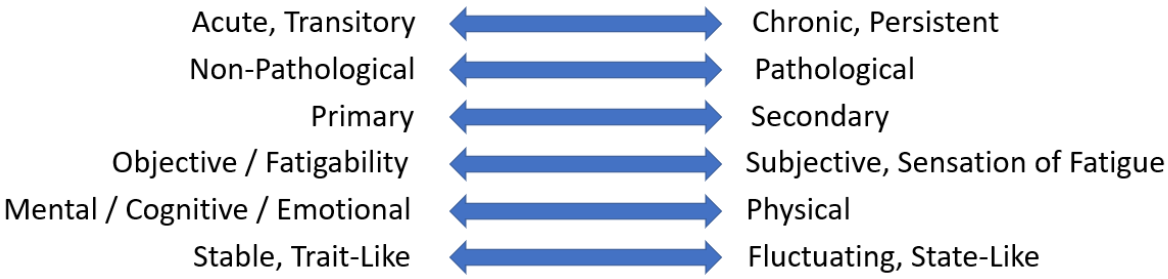

Figure 1. A simplified overview of various ways of classifying fatigue according to its temporal persistence (acute vs. chronic), functional interference (non-pathological vs. pathological), presumed aetiology in neurological illness (primary vs. secondary), how we measure it (objectively as performance decrement or subjectively as an experienced sensation), which functional domains it affects or is affected by (mental, cognitive, emotional and physical), and stable dispositional levels separated from fluctuations (trait-like vs. state-like). Whilst the figure simplifies these dimensions into diametrically opposed categories, an individual patient may experience a scenario such as both primary and secondary fatigue brought on by both mental and physical activity.

Transient, acute fatigue is commonly experienced in the general population, while chronic fatigue lasting beyond 6 months is rarer, with prevalence estimates ranging from 2–11% (Finsterer & Mahjoub, 2014)—or higher in cases of chronic illness (Finsterer & Mahjoub, 2014; Newland et al., 2016; Penner & Paul, 2017; Reyes-Gibby et al., 2006). The

term ‘pathological fatigue’ has been used to indicate fatigue with specific functional interference (Christodoulou, 2005, 2017; Finsterer & Mahjoub, 2014; Jason et al., 2010; Skau et al., 2021) in order to differentiate common, transitory fatigue from chronic fatigue associated with functional impairment and chronic illness. A qualitative meta-synthesis of patients with different chronic illnesses demonstrated a thematic pattern concerning the experience of fatigue in association with chronic illness as different from people’s experiences before injury or disease initiation (Jaime-Lara et al., 2020), indicating that pathologic fatigue is different from lay concepts such as tiredness or exhaustion, which is brought on by overexertion and easily ameliorated by rest. A comparative study of fatigue in cancer patients in contrast to the general population found differences in the distributions of fatigue and fatigue interference (Cella et al., 2002), indicating that while fatigue is commonly experienced in the general population, it might have different characteristics and functional consequences in association with illness.

While subjective, experiential fatigue and objective, measurable fatigability are conceptually linked, research has yet to demonstrate consistent associations between the subjective sensation of fatigue and performance decrement (DeLuca, 2005; Hockey, 2013; Kluger et al., 2013; Sandry et al., 2014). In clinical settings, this dissociation may be apparent when patients with ailments such as neurological illness present with apparent and objectively measurable deficits in their ability to sustain mental or physical effort, yet report no subjective experience of being or becoming exhausted while undergoing structured examinations. On the other hand, some patients will subjectively report problems with fatigue that interfere with their daily function and quality of life, while their performance during objective testing does not indicate a reduction in their ability to sustain effort. While it has been difficult to find consistent associations between objectively measured and subjectively experienced fatigue, both of these facets are commonly incorporated into models as conceptually and practically linked (e.g., Penner & Paul 2017).

Mental or cognitive, emotional and physical fatigue are often described as varieties of fatigue, depending on which activities seem to bring about fatigue in an individual and which functional domain it seems to affect (Cantor et al., 2013; Christodoulou, 2005; Ezekiel et al., 2021; Skau et al., 2021). For instance, fatigue brought on by mental exertion, sensory hypersensitivity and cognitively demanding tasks is quite common in neurological illnesses (Chaudhuri & Behan, 2004). However, fatigue can also be brought on by physical exertion, as with post-exertional malaise in ME (Brown & Jason, 2020).

Finally, people differ with regard to their general trait-like propensity for feeling fatigued, from which the momentary state-like fatigue might fluctuate due to exertion, stimulation, sleep deprivation or diurnal variations (Manierre et al., 2020; Wright et al., 2015).

5.2.2 Measurement of Fatigue

Since fatigue is characterised by subjective experiences, patient-reported outcome measures (PROMs) or structured interviews are necessary for the measurement of this phenomenon. However, the subjective nature of fatigue and our reliance on PROMs leads to an abundance of potential biases that might complicate the measurement of fatigue (Choi & Pak, 2005). For instance, fatigue PROMs may contain items relating to associated but separate constructs such as sleepiness and depression, thereby leading to inflated associations due to content overlap (Cantor et al., 2008). An abundance of PROMs has been developed to measure fatigue. For example, the Fatigue Severity Scale (FSS) (Krupp et al., 1989) is one of the most commonly used and psychometrically sound fatigue scales in chronic illness (Whitehead, 2009), including neurological illness (Penner & Paul, 2017) and TBI (Mollayeva et al., 2014).

As recently established in a recent study by Skogestad et al. (2019), who examined the content overlap between PROMs used in the literature on post-stroke fatigue, different fatigue PROMs tend to focus on different aspects of fatigue—such as the severity or characteristics of fatigue symptoms, functional interference and management—to varying degrees. Although all of these dimensions are relevant to our understanding of fatigue and its impact on chronic illness, no gold standard exists for its comprehensive measurement.

5.3 Frameworks for Understanding Fatigue

As emphasised in the brief historic review provided, the societal and medical understanding of fatigue has shifted throughout the last centuries, with interest previously aimed at identifying the specific causal factors thought to explain the presence of chronic fatigue in various patient groups. Today, chronic fatigue is generally accepted as a consequence of—and symptom associated with—many different diseases, while the specific mechanisms underlying the fatigue experience itself remain elusive. Although fatigue accompanies disease processes, considerable individual differences between patients with similar diagnoses and illnesses remain, while diagnoses, the biological severity of the injury,

and objective disease markers rarely explain a considerable proportion of variance in fatigue (Belmont et al., 2006; Landmark-Høyvik et al., 2010; Menting et al., 2018).

5.3.1 The Biopsychosocial Model

Most research conducted on fatigue across diagnostic categories is based on assumptions inherent to the biopsychosocial model by Engel (1977), which serves as a framework for understanding, communicating and researching complex health outcomes. Even diseases with clearly established biomarkers vary widely in their symptom burden, functional interference and impact on the individual's quality of life, which could exacerbate the initial medical condition. The biopsychosocial model posits that various hierarchical systems contribute to an individual's health, ranging from genetic to societal influences that could mutually interact with each other to influence the individual's health for better or worse. Since the biopsychosocial framework holds no specific assumptions regarding the primacy or sequencing of specific mechanisms or systems, it does not provide specific testable hypotheses regarding causal factors implicated in the initiation and maintenance of fatigue associated with illness. However, it does serve as a framework for health service providers, researchers and society to consider the complexity inherent to many health conditions and how biological disease might have wide ramifications for patients' abilities to function and thrive. Engel (1981) illustrated this through the use of hierarchical figures to demonstrate how even diseases with well-known biomedical causes are affected by psychological and social processes. In psychoeducation, the biopsychosocial framework is often used as a tool for communicating details regarding the complex interactions between biological, psychological and social factors which might exacerbate or ameliorate symptoms and functional impact (see Figure 2).

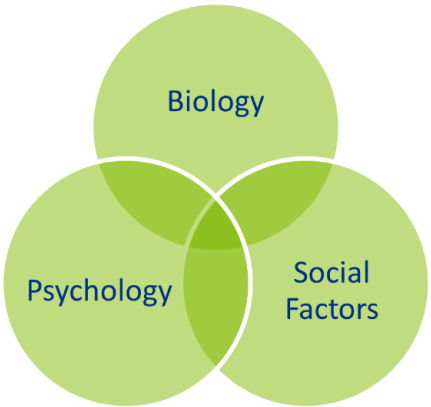

Figure 2. Simplified illustration of the biopsychosocial model often employed in patient education.

5.3.2 International Classification of Functioning, Disability and Health

The World Health Organization's (WHO) International Classification of Functioning, Disability and Health (ICF) (World Health Organization, 2001) is an implemented biopsychosocial framework. In addition to medical diagnoses, the ICF is commonly used in rehabilitation services to guide the integration of interdisciplinary assessment into a unitary case conceptualisation (see Figure 3 for a visual presentation of this model). The classification system categorises an individual's health information into (1) body functions and structures, (2) activities, (3) participation, (4) environmental factors and (5) personal factors. Furthermore, the model underlines that function and disability are determined through complex interactions between these components. Therefore, this model emphasises the need for interdisciplinary biopsychosocial assessment and treatment in patients with both acute and chronic illnesses. It also provides a practical framework for considering the potential pathways from illness to disability and reduced health-related quality of life. Recently, a core set of categories based on the ICF classification was proposed and evaluated in patients with CFS/ME, demonstrating the heterogeneity in how the diagnosis and severity of symptoms were associated with activities of daily living, participation, and personal and environmental factors (Bileviciute-Ljungar et al., 2020) whilst also highlighting the need to consider the broad spectrum of potential influences on health and disability in rehabilitation services.

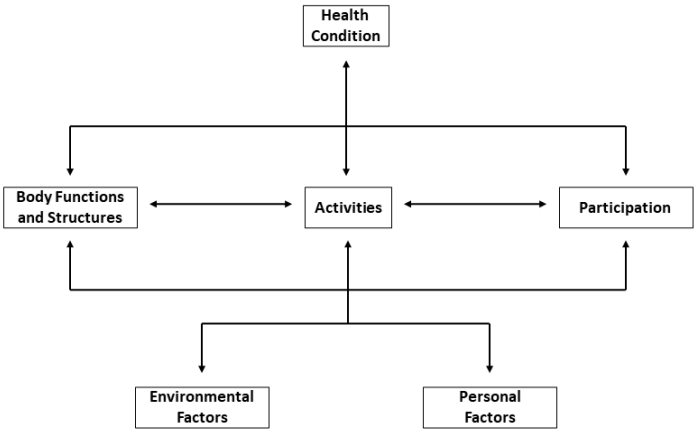

Figure 3. The International Classification of Functioning, Disability and Health, adapted from WHO (2001), encompassing the interactions between several domains in the conceptualisation of health, function and disability.

5.3.3 General Models of Fatigue

While disease processes unique to individual disorders such as TBI may contribute to the initiation and maintenance of fatigue, several factors have been implicated as almost universally linked to fatigue across aetiologies. Menting et al. (2018) examined fatigue in a study of patients with 15 different chronic diseases and found that the disease categories in themselves explained only minimal variance in fatigue, while generic, transdiagnostic symptoms such as pain, depressive symptoms, fatigue-related self-efficacy and sleep deficits explained a considerable proportion. Thus, several risks and protective factors associated with fatigue might contribute to the risk for fatigue, regardless of the specific disease.

The past decade has seen an increasing interest in understanding the adaptive function of fatigue (Enoka & Duchateau, 2016; Hockey, 2013) and the specific mechanisms that contribute to both pathological and non-pathological fatigue (Boksem & Tops, 2008; Pattyn et al., 2018). Fatigue was conceptualised by Hockey (2013) as an emotional/motivational state that guides us to reappraise our effort and energy expenditure in light of the perceived rewards gained from this exertion. Thus, fatigue serves as an adaptive signal that motivates us to shift perspectives and reconsider our effort in light of our perceived advancement towards our goals and pursuits. Similarly, Boksem and Tops (2008) proposed that fatigue acts as an adaptive signal when the currently employed behavioural strategy may no longer be suitable, which encourages the recalibration of our goals or strategies.

While several models have been proposed to explain the adaptive function of non-pathological fatigue and its disruption in chronic illness, several commonalities are shared between them. The models from Boksem and Tops (2008), Hockey (2013) and Pattyn et al. (2018) emphasise that subjective perceptions of effort or energetical costs in activity are crucial to the fatigue experience and counterbalanced by the perceived reward or gain for the individual. Pattyn et al. (2018) sought to bridge the gap between research on pathological and non-pathological fatigue and proposed a broad but flexible conceptual model for the different components that could contribute to fatigue in individuals (see Figure 4). Potential moderators of subjective fatigue include motivational factors and the decisional balance between the reward and cost of an activity, along with behavioural, cognitive, sensory and environmental factors acting in concert.

Although models such as these provide us with useful ways of thinking about the dynamics of fatigue, the models as a whole—and the relationships between their specific

components—still require further empirical validation. Additionally, the potential contributions to all of these components from disease activity and various implicated biopsychosocial mechanisms in fatigue must be considered. For instance, factors such as pain or depression might influence one or several of the components of the model, through which fatigue may be exacerbated or ameliorated.

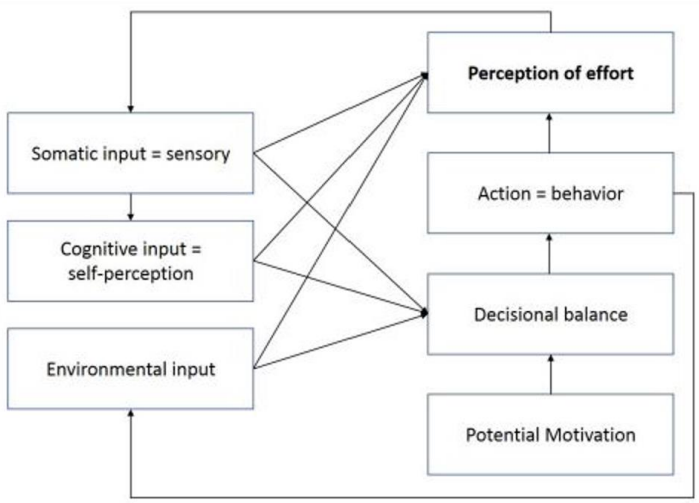

Figure 4. Proposal for a unified mechanistic model for both non-pathological and pathological fatigue by Pattyn et al. (2018). The perception of effort (i.e., subjective fatigue) is generated through cyclical interactions between intrinsic (sensory, cognitive, motivational and behavioural) and extrinsic, environmental input. Figure reproduced in line with the terms of the Creative Commons Attribution Licence (CC-BY).

5.3.4 Disease-Specific Models

Recent disease-specific conceptual models further highlight the biopsychosocial complexity of fatigue through the incorporation and integration of a vast network of biological, social and psychological mechanisms associated with fatigue; for instance, in patients with TBI (Mollayeva et al., 2014), stroke (Aarnes et al., 2020; Nadarajah & Goh, 2015), multiple sclerosis (Newland et al., 2016), heart failure (Pavlovic et al., 2021), cancer (Bower, 2019) and neurological illness in general (Penner & Paul, 2017). The model for fatigue following TBI by Mollayeva et al. (2014) is presented in Figure 5 to illustrate the conceptualisation of fatigue as determined by multiple disease-specific and generic factors.

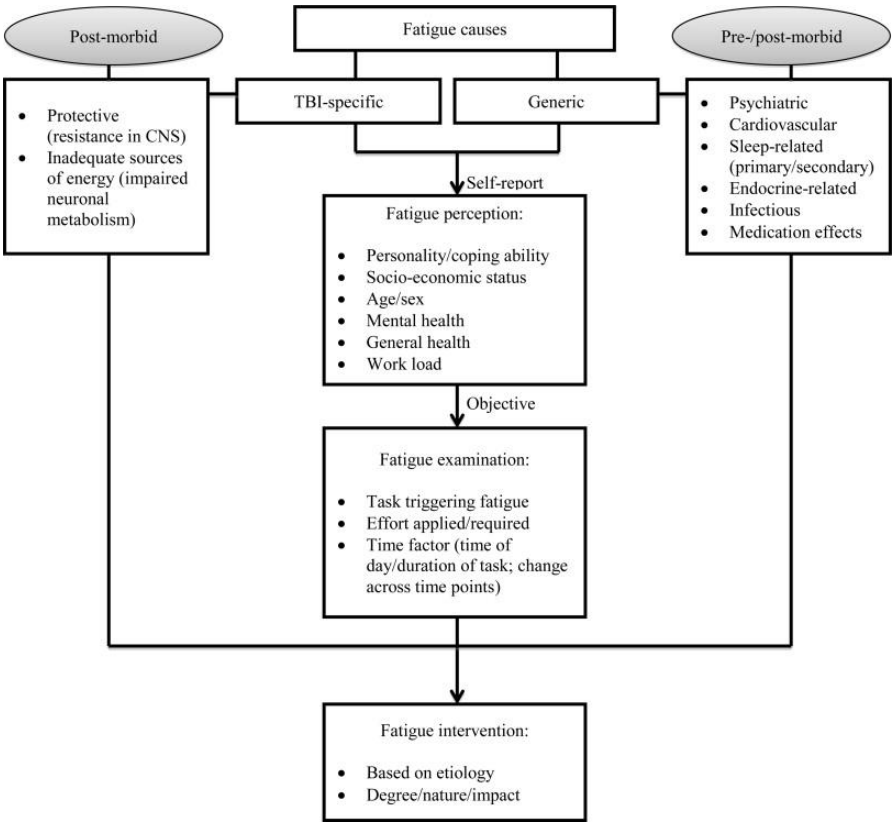

Figure 5. Model of fatigue following TBI by Mollayeva et al. (2014), which incorporates both TBI-specific and generic factors that can interact to bring about fatigue in individuals with TBI. The figure is reproduced with permission from the publisher.

5.4 Fatigue in TBI

5.4.1 Epidemiology, Severity and Socioeconomic Burden of TBI

TBI is a condition in which chronic fatigue often poses a considerable burden and obstacle in rehabilitation. TBI is defined as 'an alteration in brain function, or other evidence of brain pathology, caused by an external force' (Menon et al., 2010). Common causes of injury include head trauma resulting from falls and road traffic incidents. There is some sociodemographic variation in the most common causes of TBI, with elderly patients more often suffering fall injuries (Bruns Jr & Hauser, 2003; Peeters et al., 2015) and a general epidemiological shift in the population toward older median age upon injury (Maas et al., 2017). Males are generally overrepresented in the TBI population, with male/female ratios reaching up to 4.6:1 across studies conducted in Europe (Peeters et al., 2015). TBI is commonly characterised along an injury severity spectrum, from uncomplicated mild (commonly referred to as concussion) to complicated mild and moderate to severe injuries.

Injury severity is usually classified based on the impairment of consciousness, as determined using the Glasgow Coma Scale (GCS) (Teasdale et al., 2014), duration of loss of consciousness (LOC) and post-traumatic amnesia, and/or the presence of intracranial lesions as confirmed by computed tomography (CT) (Williams et al., 1990) or both CT and magnetic resonance imaging (MRI) (Voss et al., 2015).

The prevalence or percentage of the population living with the consequences of TBI, as well as the number of new patients injured with TBI each year, varies greatly from study to study due to the different inclusion criteria and injury severity categories examined. In their comprehensive summary of the international literature on TBI, Maas et al. (2017) presented incidence numbers ranging from 811–979 TBIs per 100 000 people when employing broad definitions of TBI, with incidence numbers ranging from 47.5–643.5 per 100 000 people when basing estimates on hospital discharge numbers alone. The global incidence has been estimated to range from 64–75 million per year, with mild TBIs being nearly 10 times more frequent than moderate-severe TBIs (Dewan et al., 2018; Maas et al., 2017). The prevalence or number of people living with the consequences of one or more sustained TBIs is even more difficult to estimate, since many who sustain milder injuries may not consult with their physician at all. A meta-analysis by Frost et al. (2013) incorporated studies examining the prevalence of TBI in developed countries and found that an estimated 12% of the general population may have sustained a TBI. For these reasons, TBI as a chronic condition has been characterised as ‘a silent epidemic’ since the high incidence and associated societal and individual costs of the sequelae of TBIs have wide-ranging societal consequences (Corrigan & Hammond, 2013; Rusnak, 2013). Globally, TBI is estimated to have a socioeconomic cost of approximately 500 billion USD (Maas et al., 2017), while the persistence of emotional, cognitive, behavioural and physical consequences associated with TBI can have long-term ramifications for the individuals who have sustained a TBI, and their families.

5.4.2 Impact and Outcome Following TBI

The survivors of TBI can experience many potential somatosensory and cognitive deficits in addition to emotional sequela, functional impairments, and reduced health-related quality of life, participation and work status (Jourdan et al., 2016; Ponsford, 2013). Common somatosensory deficits can include problems with balance, dizziness, headaches and impairments in sensory modalities (e.g., smell, taste, touch, seeing, hearing and proprioception) (Ponsford et al., 2014). Potential cognitive deficits include difficulties with concentration, processing speed, memory, communication skills and executive functions

(Ponsford, 2013; Rabinowitz & Levin, 2014). More severe injuries and a longer duration of reduced consciousness are generally accompanied by more severe and persistent cognitive deficits and functional impairments (Rnowitz & Levin, 2014). Problems with emotion regulation and emotional distress—such as symptoms of anxiety and depression, or post-traumatic stress disorder—are also commonly experienced consequences of TBI (Kennedy et al., 2007; Scholten et al., 2016; Sigurdardottir et al., 2013) due to both difficulties in psychological adjustment and the direct effects of brain injury. While medical advances have led to increased survival rates following TBI, sustaining a TBI is nevertheless associated with premature mortality due to the increased risk of suicide and the development of comorbid diseases over time (Fazel et al., 2014). Many survivors experience unmet rehabilitation needs in both the early and late phases following injury (Andelic et al., 2014; Andelic, Røe, Tenovuo, et al., 2021).

In keeping with the biopsychosocial model, TBI does not affect the individual living with the chronic effects of TBI in isolation. The family members and caregivers of those who have sustained a TBI have reported the continuous need for renavigation, renegotiation and the maintenance of balance within the familial ecosystem (Whiffin et al., 2021). Notably, these individuals are also at risk for psychological maladjustment and reduced quality of life due to the strains imposed by the consequences of injury (Manskow et al., 2017).

5.4.3 Fatigue Following TBI

As outlined in the previous section, TBI has the potential to influence a wide range of functions and abilities, with persistent fatigue being the sequela most commonly reported by patients in both earlier and chronic phases following complicated mild to severe TBI (Jourdan et al., 2016; Ponsford et al., 2014). Notably, estimates of fatigue prevalence are complicated by the use of different measures and cut-off values, as well as different time periods being examined, with values ranging from 7–80% (Andelic, Røe, Brunborg, et al., 2021; Mollayeva et al., 2014). Fatigue has been shown to contribute uniquely to disability in community-dwelling persons with TBI (Juengst et al., 2013). Moreover, it is associated with poorer health-related quality of life (Cantor et al., 2013). In a recent qualitative study of patients with fatigue after acquired brain injuries (including TBI), two themes that emerged from the study were the unpredictability of fatigue and its causes following injury, as well as the need to readjust activities and participation, which provide testimonial support to the differentiation between non-pathological and pathological fatigue in acquired brain injuries (Ezekiel et al., 2021).

Although some mechanisms may be unique to fatigue after TBI, many of the commonly implicated mechanisms have also been studied in other disorders and conditions. As illustrated by the conceptual model by Mollayeva et al. (2014), some generic risk and protective factors might predispose individuals to fatigue and contribute to secondary fatigue following injury, while some injury-specific factors might also contribute to both primary and secondary fatigue following TBI. In the following section, research into both the TBI-specific and generic correlates of fatigue is summarised.

4.4.3.1 TBI-Specific Correlates of Fatigue

One plausible explanation for why fatigue is commonly experienced by patients with TBI is the coping hypothesis by van Zomeren et al. (1984), which states that somatosensory and cognitive deficits might lead to a need for compensatory effort and strain during mental and physical activities. While there is little indication that objectively measurable declines in cognitive performance over time correlate with subjective increases in fatigue in general or in association with TBI in particular (Ashman et al., 2008; DeLuca, 2005), evidence for this hypothesis has nevertheless been demonstrated in several studies using various objective estimators of effort. Ziino and Ponsford (2006) found a significant association between increased diastolic blood pressure and subjective ratings of fatigue during a vigilance task. Increases in brain activity measured using functional magnetic resonance imaging (fMRI) in response to a cognitively demanding task have also been demonstrated in patients with TBI when compared to healthy controls (Kohl et al., 2009), with increased activity in areas including the basal ganglia, anterior cingulate and superior parietal cortex. Chaudhuri and Behan (2000) initially proposed a model for cognitive fatigue in neurological disorders, suggesting that alterations in the non-motor functions of the basal ganglia and striato-thalamo-cortical circuit may serve a central role in the initiation and maintenance of fatigue due to alterations in the processing of neural rewards, which is in line with the later model proposed by Boksem and Tops (2008). Interestingly, a recent experimental study by Dobryakova et al. (2020) found that monetary reward reduced the cognitive fatigue experienced by patients with TBI during a cognitively demanding task, and that the experimental reward condition was associated with higher activation in the left ventral striatum, which is central to reward processing. Brain injuries might also directly or indirectly interfere with the neural circuits involved in the processing and prediction of rewards; however, psychological factors such as depression might also interfere with the functioning of these regions (Admon & Pizzagalli, 2015; Bondy et al., 2021).

While the coping hypothesis and involvement of neural reward networks show some promise in explaining the underlying neurological processes that might contribute to fatigue in TBI, few or inconsistent associations have been found between fatigue and injury severity (Belmont et al., 2006; Mollayeva et al., 2014). In their review of the studies on fatigue following TBI, Mollayeva et al. (2014) found indications of a declining frequency of fatigue over time for patients who had sustained a mild TBI; however, the literature on moderate-severe TBI was scarce at the time of publication. A recent large-scale CENTER-TBI study involving assessments at 0, 3 and 6 months following mild to severe TBI found that injury severity—as measured by the Head Abbreviated Injury Scale (AIS-head)—was significantly associated with fatigue (Andelic, Røe, Brunborg, et al., 2021). Furthermore, a longitudinal study of patients with mild-severe TBI found injury severity-dependent differences in fatigue trajectories during the first year following injury, with follow-up sessions at 4, 8 and 12 months post-injury (Beaulieu-Bonneau & Ouellet, 2017). In this study, patients who had sustained a mild TBI initially reported more fatigue than patients with a severe TBI; however, they reported declining levels of fatigue across the study period. On the other hand, patients who had sustained a severe TBI initially reported lower levels of fatigue, with fatigue levels increasing over the study period. However, those who had sustained a moderate TBI reported relatively stable levels of fatigue across the first year post-injury. Beaulieu-Bonneau and Ouellet (2017) hypothesised that the difference in fatigue trajectories between mild and severe severities could be due to initially reduced self-awareness and problems with anosognosia in patients with severe TBI. They also hypothesised that the increase in fatigue in this cohort could be a result of the increasing awareness of fatigue as activity levels increased over time.

5.4.3.2 Generic Correlates of Fatigue

Although fatigue is inconsistently related to sociodemographic variables in the general population, female gender has been positively associated with fatigue in some epidemiological studies (Bensing et al., 1999; Evengård et al., 2005; Schwarz et al., 2003; Van't Leven et al., 2010). While sociodemographic variables might contribute to fatigue following TBI, such findings have been inconsistent. Minimal or non-significant associations have been found between fatigue, age and female gender in patients with TBI (Cantor et al., 2012; Mollayeva et al., 2014). Small—but positive—associations between fatigue, younger age and female gender were found in a recent CENTER-TBI study during the first 6 months post-injury (Andelic, Røe, Brunborg, et al., 2021). This study further demonstrated that higher education was associated with initially higher levels of fatigue following injury, with levels

stabilising at 3 and 6 months post-injury. In a study by Ziino and Ponsford (2005), higher education was also shown to be positively associated with fatigue in TBI.

Pain often co-occurs with fatigue in the general population, where it is commonly implicated as a central mechanism of fatigue regardless of the disease or condition (Menting et al., 2018), as is the case in TBI (Cantor et al., 2013). Pain and fatigue have been found to share genetic vulnerabilities (Burri et al., 2015; McBeth et al., 2015; Vassend et al., 2018) and there are indications that they overlap in their adaptive homeostatic functions (Wyller, 2019). Moreover, these factors might influence one another bidirectionally over time (Kratz et al., 2017; Lenaert et al., 2018). In their longitudinal study at 4, 8 and 12 months following TBI, Beaulieu-Bonneau and Ouellet (2017) found that pain was only associated with fatigue at the first two measurements, indicating that the relationship might vary depending on the time elapsed since injury.

Psychological distress (i.e., symptoms of depression and anxiety) is an established correlate of fatigue in the general population (Schwarz et al., 2003; Watt et al., 2000) and in TBI cases specifically (Cantor et al., 2013; Ponsford et al., 2012, 2015). Notably, fatigue seems to share genetic vulnerabilities with psychological distress (Hickie et al., 1999; Vassend et al., 2018). While fatigue is a common symptom of depression, it may nevertheless occur in isolation from depression in brain injury (Holmqvist et al., 2018). However, research on these associations is further complicated by content overlap between measures of fatigue and depression—and when eliminating overlapping items, the associations between them can be attenuated (Cantor et al., 2008). In their longitudinal study of the correlates of fatigue at 4, 8 and 12 months after TBI, Beaulieu-Bonneau and Ouellet (2017) established that depression was correlated with fatigue at all time points. Schönberger et al. (2014) examined temporal associations between fatigue, daytime sleepiness and depression in a cross-lagged panel model at 6 and 12 months following mild-severe TBI and found that depression and daytime sleepiness predicted later fatigue—and not the other way around. While psychological distress and symptoms of depression and anxiety may fluctuate as state-like influences on fatigue, people may differ with regard to their stable, trait-like propensity for psychological distress. Trait neuroticism has been implicated as a five-factor personality trait commonly associated with the risk of fatigue across aetiologies (Charles et al., 2008; Lau et al., 2017; Rosmalen et al., 2007; Stephan et al., 2022) and in patients with a sustained a mild TBI (Merz et al., 2019). As with psychological distress, trait neuroticism also shares a considerable proportion of genetic vulnerability with fatigue (Vassend et al., 2018).

While other personality traits have not generally been implicated as correlates of fatigue, Merz et al. (2019) also found significant negative associations between fatigue and trait extraversion, conscientiousness and agreeableness in their study on patients with mild TBI. These findings are strengthened by a recent large-scale meta-analysis of seven prospective studies, which found that trait extraversion, conscientiousness, agreeableness and openness were associated with less fatigue, albeit to varying degrees (Stephan et al., 2022).

Loneliness and feelings of isolation have previously been shown to be associated with and predict the future development of the symptom cluster fatigue, pain and depression in non-TBI samples (Jaremka et al., 2014; Powell et al., 2021). Loneliness as a potential contributor to fatigue following TBI has not been previously investigated. However, loneliness is commonly described by people living with TBI, and its relevance to fatigue following TBI remains to be explored (Kumar et al., 2020).

Psychosocial resilience, or characteristics that allow individuals to maintain psychological wellbeing and thrive despite adversity, has been shown to predict increased participation and improved outcomes after mild-severe TBI (Vos et al., 2019; Wardlaw et al., 2018), as well as longitudinal decreases in fatigue following mild TBI (Losoi et al., 2015). However, resilience has not been extensively studied in relation to fatigue following all injury severities of TBI.

Excessive daytime sleepiness is a common problem after TBI (Crichton et al., 2020) and in neurological illness in general (Happe, 2003). This symptom is associated with fatigue and predicts the later development of fatigue in TBI (Cantor et al., 2012; Ponsford et al., 2015; Schönberger et al., 2014). Insomnia, or subjective sleep deficits, has also been found to correlate with fatigue (Beaulieu-Bonneau & Ouellet, 2017; Bushnik et al., 2008; Ponsford & Sinclair, 2014). However, as Cantor et al. (2012) emphasised, fatigue may often also occur without the presence of insomnia. Interestingly, one study found that decreases in insomnia following a cognitive behavioural therapy (CBT) intervention were accompanied by decreases in fatigue, indicating an additional interplay between these factors within persons over time (Ouellet & Morin, 2007).

Of relevance to previously described models of neural reward circuits implicated in the development of fatigue, trait-like motivational propensities for behavioural inhibition and activation have garnered some attention in the research field. The behavioural inhibition system (BIS) is characterised by a propensity for being motivated by the avoidance of

unpleasant sensations, while the behavioural activation system (BAS) is characterised by a propensity for being motivated by the attainment of rewards and pleasant sensations. Based on prior research into the neuropsychology of learning, these two personality dimensions were first described by Gray (1981) and are commonly measured using self-report questionnaires (Carver & White, 1994). Furthermore, behavioural inhibition and a lower degree of reward responsiveness have been associated with fatigue in multiple sclerosis and other chronic illness (Bossola et al., 2020; Pardini et al., 2013); however, the impact of BIS/BAS-propensities on fatigue has not, to our knowledge, been examined in relation to TBI.

5.5 Causal Inference in Observational Research

How may we seek to explain fatigue when it ultimately cannot be measured objectively, keeping in mind the plethora of correlates of, potential pathways to, and consequences of fatigue, as well as the vast potential for confounders in research on potential causal mechanisms? Experimental designs with rigorous experimental control are the gold standard in research aimed at providing causal explanations. These designs have the potential to hold all conditions constant except for the variable thought to exert an effect on our outcome of interest, with randomisation dealing with the noise caused by variations between research subjects (Marinescu et al., 2018). While the efficacy of randomised, experimentally controlled designs is relatively undisputed, subjective phenomena such as fatigue partially remain outside of our experimental control since one cannot ethically or practically assign patients to many of the potential moderators and mediators of fatigue (e.g., disease, depression and pain). Since many of the potential influences on persistent fatigue remain outside of experimental control, observational research remains warranted.

However, there is no consensus on the most accurate ways of approaching confidence in our knowledge of the potential causal mechanisms involved in fatigue through observational research. *Triangulation* has been proposed as a possible approach, whereby different statistical methods and research designs are employed to examine the same relations with different strengths and limitations, which may provide incremental evidence for causal assumptions despite never reaching certainty in their veracity (Hammerton & Munafò, 2021). Cross-sectional studies may control for confounding variables that are measured in the relationship between, for example, fatigue and pain; however, they lack the potential to control for all possible confounders in the relations between them due to between-subject variability in a range of potential moderators or mediators of associations of interest.

Furthermore, group-level associations might distort or completely misrepresent effects when our research is interested in processes occurring within individuals (Fisher et al., 2018). Therefore, cross-sectional studies cannot implicate specific causal pathways and directional influences among mechanisms and outcomes. On the other hand, longitudinal studies provide the opportunity to evaluate changes in phenomena and associations with increases and decreases in fatigue over time. One additional benefit of longitudinal studies is that they allow us to control for potential confounders not measured directly by using each subject as his or her own control (Allison, 2009).

The use of genetically informed data from twins or families is another way of handling genetic and environmental confounders in the relationships between phenomena (McGue et al., 2010). These genetically informed designs are often used to calculate the degree to which genes and environmental factors shared between twins, siblings or family members can account for similarities in various phenotypes. These designs may provide control over confounding from factors that causally contribute to both fatigue and, for example, pain (e.g., genetics and environmental factors) through the use of counterfactuals: If two people with the same genetic makeup lived different lives, how would this affect an outcome or the relationship between two outcomes?

While no single observational design or statistical analysis can provide definite answers to causal hypotheses, attempts to control for potentially implicated confounders in the relationships between fatigue and other associated factors—either by design or statistical analyses—are nevertheless required if we are to move from the exploration of mere correlation towards the exploration of possible causation.

5.6 Thesis Aims

The primary aim of this study was to enhance our understanding of the nature of the relationships between fatigue and commonly implicated biopsychosocial factors such as pain, psychological distress, sleep deficits, sleepiness and personality traits. The secondary aims were to investigate whether the relationships between fatigue, pain and psychological distress are genetically or environmentally mediated in a sample of twins from the general population. Furthermore, we aimed to evaluate potential correlates of fatigue within persons, in order to inform us of the clinical relevance of these symptoms to the development and maintenance of fatigue. Furthermore, through an exploration of potential factors contributing to fatigue in patients with TBI, an aim was to seek a more parsimonious understanding of risk and

vulnerability factors, and more clearly define crucial factors for the maintenance and exacerbation of persistent fatigue during the first year following injury.

6 Materials and Methods

6.1 Study Design and Setting

This thesis includes studies conducted on two samples. Moreover, this section will accordingly present information pertinent to both samples and the data collection. For an overview of participant characteristics and design in Papers I–III, see Table 1.

Table 1. Design and sample characteristics. In Paper I, the measurement time points T1 and T2 correspond to 2011 and 2016, respectively. In Papers II and III, the measurement time points T1 and T2 correspond to approximately 6 and 12 months following TBI, respectively.

	Paper I	Paper II	Paper III
Design	Co-Twin and Within-Person Control	Cross-Sectional	Between- and Within-Person
Time Points	Twin Sample: T1 & T2	TBI Sample: T1	TBI Sample: T1 & T2
Participants	T1: n = 1482 T2: n = 1519	T1: n = 96	T1: n = 96 T2: n = 98 Total: n = 103
Percent Male / Female	T1: 35.5% / 64.5% T2: 41.8% / 58.2%	T1: 80.2% / 19.8%	T1: 80.2% / 19.8% T2: 80.6% / 19.4%
Mean Age in Years at T1 (±SD)	57.1 (4.5)	45.3 (13.9)	45.7 (13.9)

Abbreviations: T1, Time Point 1; T2, Time Point 2; TBI, Traumatic Brain Injury; SD, Standard Deviation.

6.1.1 Twin Sample

Paper I employed a co-twin control design with an added within-person component through the inclusion of two time points. The co-twin control design applied is a variant of the case-control design since each participant serves as a control for their own twin. The additional element of within-person control in the design adds another case-control condition, whereby each participant serves as his or her own control.

Data were sampled from the Norwegian Twin Registry (Nilsen et al., 2013) and collected at two time points (2011 and 2016). Participants were included if they on at least

one of the occasions had completed all of the included measures. All participants belonged to same-sex twin pairs. Dizygotic pairs with one male and one female twin were not included.

6.1.2 TBI Sample

The sub-study from which Papers II and III were derived took on a cross-sectional repeated measures design, wherein patients with TBI were examined approximately 6 (T1) and 12 (T2) months post-injury. The initial constraints on measurement time points for T1 and T2 were 6 ± 1 month and 12 ± 2 months, respectively; however, these constraints were modified due to external circumstances (see Section 6.2.2.1). All patients admitted to the Department of Neurosurgery, Oslo University Hospital (OUH), Ullevål with injury dates between January 2018 and April 2020 were screened by the Head Neurosurgeon (author EH in Papers II and III) for eligibility. The inclusion criteria for this study were patients (I) admitted with TBI (ICD-10 Diagnoses S06.1–S06.9) and with verified intracranial injury on either CT or MRI, (II) between 18 and 65 years of age, (III) who had survived until the first measurement. Exclusion criteria were (I) pre- or comorbid diagnoses of severe neurological or mental illness, or ongoing alcohol or substance abuse, (II) non-fluency in Norwegian or English languages, and (III) severe functional impairment hindering participation, such as disorders of consciousness, severe motor deficits and severe anosognosia. See Table 2 for an overview of injury characteristics of the included sample.

The neurosurgeon referred patients to routine follow-up consultations at the Department of Physical Medicine and Rehabilitation, OUH Ullevål, or Sunnaas Rehabilitation Hospital. Patients who did not appear at their later appointments, or who discharged themselves early from rehabilitation services, were mailed an invitation to participate and later contacted by telephone.

Table 2. Injury characteristics of patients in the TBI sample that were included in Papers II and III.

Participants	n = 103[1]
Injury Characteristics	
Months Since Injury, Mean (SD)	T1: 6.9 (1.0)
	T2: 14.0 (2.1)
Cause of Injury	
Fall, n (%)	47 (46%)
Traffic Related, n (%)	37 (36%)
Sports Related, n (%)	6 (6%)
Other or Unknown	13 (13%)
Acute Glasgow Coma Scale, Median (IQR)	13 (8–14)
Acute Head Injury Severity Scale	
Mild, n (%)	23 (22%)
Moderate, n (%)	51 (50%)
Severe, n (%)	29 (28%)
Head Abbreviated Injury Scale (AIS-head)	
Minor, n (%)	0 (0%)
Moderate, n (%)	3 (3%)
Serious, n (%)	16 (16%)
Severe, n (%)	32 (31%)
Critical, n (%)	52 (50%)

[1] N = 96 for Paper II.

6.2 Recruitment and Participants

6.2.1 Twin Sample

Data collection for this sample was already completed at the start of the project, and specific details on recruitment and data collection procedures for this sub-study can be found in Nilsen et al. (2013). The data was sampled from the Norwegian Twin Registry, which was established in 2009 as a merged register of three different databases of Norwegian twins. The registry is administrated by the Norwegian Institute of Public Health, with approximately 32 000 twins having contributed to the register as of 2018 (Folkehelseinstituttet, 2018). The

first measurement time point (T1) was collected in 2011, and the second measurement time point (T2) in 2016. Table 3 presents the overall contribution of each participant and their co-twins to the study, as presented in Paper I.

Table 3. Overview of the distribution of responders and level of completeness of their contribution to one or both time points, for one or both twins, separated by zygosity.

	Single Responder on a Single Occasion	Single Responder on Both Occasions	One Occasion with One Co-twin Occasion	One Occasion with Two Co-twin Occasions	Two Occasions with One Co-twin Occasion	Two Occasions with Two Co-twin Occasions	Total
Monozygotic	172	22	340	113	113	264	1024 (46.6%)
Dizygotic	297	49	326	143	143	214	1172 (53.4%)
Total	469 (21.4%)	71 (3.2%)	666 (30.3%)	256 (11.7%)	256 (11.7%)	478 (21.8%)	2196

6.2.2 TBI Sample

A total of 247 patients were identified through screening at the Neurosurgical Department, OUH Ullevål during the inclusion period from January 2018 until April 2020 (see Figure 6 for a flow chart of the recruitment and data collection process). During recruitment, 60 (24.3%) were excluded on the basis of severe comorbidities (n = 31), non-fluency in Norwegian or English languages (n = 18) or severe functional impairment 6 months post-injury (n = 11). A total of 187 patients were deemed eligible. Among these, 23 patients could not be reached during the inclusion stage, 52 declined to participate, 7 consented but did not show up at the scheduled time points and 2 patients dropped out during the baseline assessment since they did not return the questionnaires or respond following initial interview and assessment. Of the 103 patients who consented to participate, 96 were assessed at the first measurement point (T1), of which 5 were lost to follow-up at T2. A total of seven patients who had not completed the T1 assessment, but consented to participate, underwent the complete evaluation at T2 only. For the T2 measurement, 17 patients who had previously completed the T1 assessment requested only responding to the questionnaires (i.e., no neuropsychological reassessment), while 74 patients completed the entire protocol.

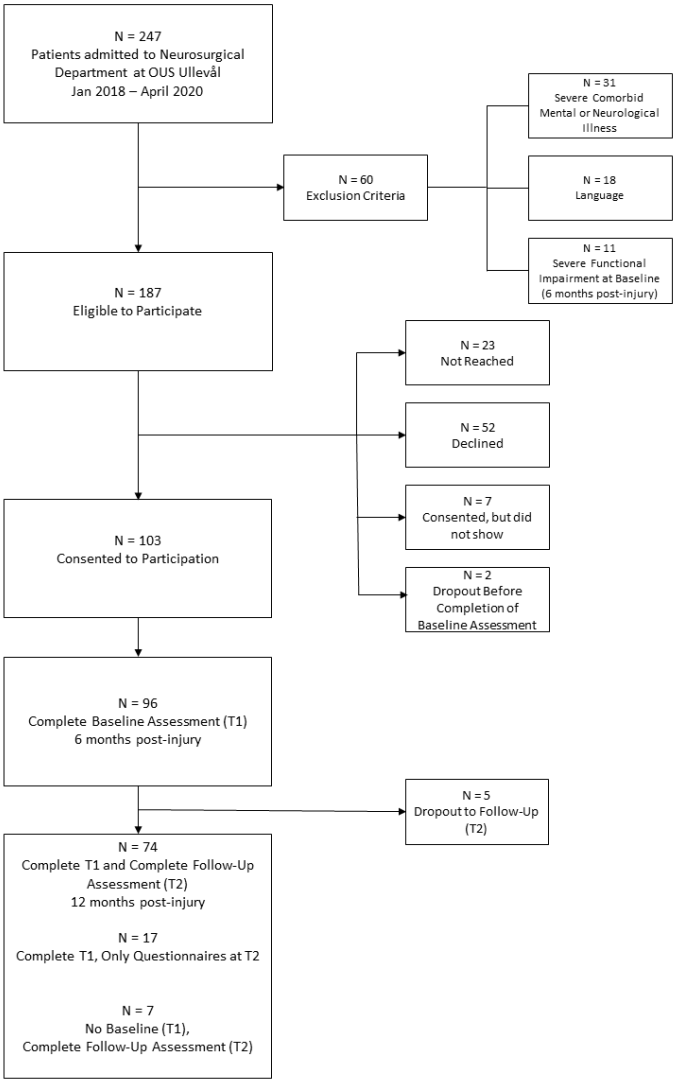

Figure 6. Flow chart of the recruitment, inclusion and data collection processes.

6.2.2.1 Delays Due to the COVID-19 Pandemic

Due to the COVID-19 pandemic and the restrictions imposed on Norwegian society and physical consultations in health services, there were some delays in the data collection process. Twenty-one patients were examined later than 15 months following injury for T2, for which the median measurement time in months since injury was 16.3 months (interquartile range = 15.9 – 17.2). Figure 7 presents the distribution of specific time points for both measurements (in months since injury). The average time between measurements was 7.4 months (SD = 2.0), i.e. close to the intended 6 month interval.

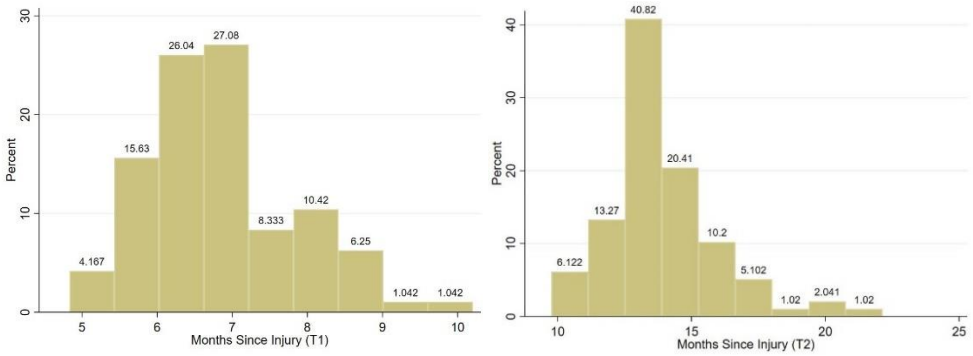

Figure 7. Distribution of measurement time points in months since injury for T1 and T2, respectively.

6.3 Data Collection and Procedures

6.3.1 Data Collection and Materials

All assessments were conducted by the PhD candidate Løke, with the exception of seven assessments at T2 conducted by a psychologist-in-training who had received training on the protocol. Most assessments were conducted at the outpatient clinic of the Department of Physical Medicine and Rehabilitation at OUH, Ullevål or during in-patient stays at Sunnaas Rehabilitation Hospital. Due to the travelling distance involved or scheduling issues, a few assessments were also conducted in the homes of patients if this was preferable for them. To ensure valid results, ample time was scheduled for breaks in between tests and questionnaires. All participants were allowed to bring the questionnaires home to respond at their own pace and return them by mail when completed.

All injury-related variables from the acute phase were extracted from the Oslo TBI Registry–Neurosurgery (Tverdal et al., 2020), with the exception of the Head Abbreviated Injury Scale (AIS-head) version 98, which was calculated by a medical doctor (co-author Nada Andelic) based on injury severity descriptions in the medical records. Age was measured and included at the first measurement occasion for each patient, along with years of education and gender.

For an overview of all included measures in Papers I–III, see Table 4.

Table 4. Complete overview of the instruments and variables included in Papers I to III.

Category	Scales/Instruments	Paper I	Paper II	Paper III
Injury-Related Variables	**Premorbid Health Status:** American Society of Anesthesiologists' Physical Status Classification (ASA-PS)		✓	✓
	Injury Severity Indices: 1. Glasgow Coma Scale (GCS) (1) at the injury site or upon admission to the hospital for pre-intubation, and (2) upon discharge from the acute hospital * 2. Rotterdam CT score * 3. Head Injury Severity Scale (HISS) * 4. Direct discharge to specialised rehabilitation services (0 / 1) * 5. Multitrauma - extracranial injury (0 / 1) * 6. The Head Abbreviated Injury Scale (AIS-head)		✓	✓
	Functional Outcome: **1.** Glasgow Outcome Scale (5-level) upon discharge * **2.** Glasgow Outcome Scale – Extended (8-level)		✓	
Fatigue	Fatigue Severity Scale (FSS)		✓	✓
	Chalder Fatigue Questionnaire (CFQ)		✓	✓
	Giessen Subjective Complaints List (GSCL) – Fatigue Subscale	✓	✓	✓
	Rivermead Post-Concussion Symptoms Questionnaire (RPQ) – Fatigue Item		✓	✓
Self-Report Questionnaires	**Psychological Distress (Anxiety & Depression):** The Hopkins Symptom Checklist (SCL-5, -8 and -10)	✓ (SCL-5 and -8)	✓ (SCL-10)	✓ (SCL-10)
	Somatic Symptom Burden: GSCL – Subscales for (1) musculoskeletal pain, (2) gastrointestinal symptoms, and (3) cardiovascular symptoms	✓ (Subscale 1)	✓	✓
	Resilience: Resilience Scale for Adults (RSA)		✓	✓
	Personality Traits: NEO Five-Factor Inventory-3 (NEO-FFI-3)		✓	✓
	Behavioural Inhibition & Activation Systems: The BIS/BAS Scale		✓	✓
	Trait Optimism: Life Orientation Test Revised: Optimism Subscale		✓	✓
	Loneliness: Three items from the UCLA Loneliness Scale – Version 3		✓	✓
	Daytime Sleepiness: Epworth Sleepiness Scale		✓	✓
	Insomnia Severity: Insomnia Severity Index		✓	✓
	Pain Severity: Numerical rating scales (0–10 within the last two weeks, where 10 is the most severe pain) of (1) strongest, (2) weakest, (3) average and (4) current severity of pain		✓	✓
	Pain Dispersion: Pain drawing		✓	✓
Neuropsychological Function	**Validity:** Rey 15-Item Memory Test		✓	✓
	General Intellectual Abilities: Vocabulary and matrix reasoning from Wechsler Abbreviated Intelligence Scale (WASI)		✓	✓
	Psychomotor Speed: The D-KEFS Color-Word Interference Test (CWIT)– Conditions 1–2 and the D-KEFS Trail Making Test (TMT) Conditions 1–3 and 5		✓	✓
	Attention Span/Working Memory: Digit Span from Wechsler Adult Intelligence Scale IV (WAIS-IV)		✓	✓
	Sustained and Focused Attention: Conners Continuous Performance Test III (CPT-III)		✓	✓
	Executive Function: D-KEFS CWIT – Conditions 3-4 & D-KEFS TMT Condition 4		✓	✓

* Variables extracted from the Oslo TBI Registry – Neurosurgery (Tverdal et al., 2020)

6.3.1.1 Injury-Related Variables Extracted From The Oslo TBI Registry–Neurosurgery

The **American Society of Anesthesiologists' Physical Status Classification (ASA-PS)** (Doyle & Garmon, 2018) was included as a measure of pre-injury physical health status. This was scaled from 1 to 6, with higher scores indicating more severe systematic disease premorbid to injury.

The **Glasgow Coma Scale (GCS)** (Teasdale et al., 2014), ranging from 3–15, was determined from the records of emergency personnel or the acute hospital prior to intubation, as well as upon discharge from the acute hospital.

Rotterdam CT score (Maas et al., 2005) is often used as a measure of prognostic classification based on findings from CT scans, and was included as an injury severity indicator. This score is rated based on the grade of compression of the basal cisterns, a midline shift, intraventricular blood or traumatic subarachnoid haemorrhage, and epidural mass lesions. Higher scores are indicative of greater brain injury severity.

The **Head Injury Severity Scale** (Stein & Spettell, 1995) was also included as a measure of injury severity. Injuries were classified according to the GCS score recorded between the time of injury and arrival at the acute hospital, or before intubation. Injuries were classified as either minimal (GCS = 15, with no amnesia or LOC), mild (GCS 14–15, with amnesia or brief (i.e., less than 5 minutes) LOC, or reduced alertness and memory), moderate (GCS 9–13, with LOC longer than 5 minutes or focal neurological deficits), or severe (GCS ≤ 8).

Direct Discharge to Specialised Rehabilitation Services (Tverdal et al., 2021) was recorded as a dichotomous variable (0 = discharged home or to a local hospital / 1 = discharged to a specialised rehabilitation service) for those patients who were directly discharged to in-patient specialised rehabilitation from the acute hospital.

Multitrauma was recorded as a dichotomous variable (0 / 1) to indicate the presence of other extracranial injuries.

The **Head Abbreviated Injury Scale (AIS-head), version 98** (Association for the Advancement of Automotive Medicine, 1998) was used to indicate the anatomical severity of the brain injury. Scores are rated on a scale from 1 to 6, where 1 indicates minor injuries, and 6 indicates fatal injuries. The AIS-head was scored retrospectively at a later time point than

the acute CTs and included the results from MRIs taken in the acute/post-acute phase. As such, this scale reflects higher severities than the CT scores.

6.3.1.2 Primary Outcome Measures

Several PROMs for fatigue were included in the studies.

The **FSS** (Krupp et al., 1989) is a questionnaire commonly used to assess fatigue, in which patients are primarily asked to indicate the level of interference from fatigue in various domains. The questionnaire consists of nine items with Likert-scale ratings from 1–7, where higher scores indicate greater functional interference from fatigue. This questionnaire is frequently used as a measure of fatigue in patients with TBI (Mollayeva et al., 2014). Norms adjusted for age, gender and education for the general population in Norway are available for comparison (Lerdal et al., 2005).

The **Chalder Fatigue Questionnaire (CFQ)** (Chalder et al., 1993) asks patients to indicate the presence of various symptoms of fatigue in comparison to the last time they were feeling well on a scale from 0 to 3, where 0 = 'less than usual', 1 = 'No more than usual', 2 = 'More than usual' and 3 = 'A lot more than usual'. The questionnaire consists of 11 items, of which the first 7 belong to the Physical Fatigue Subscale and the final 4 belong to the Mental Fatigue Subscale. Originally developed for use with CFS, some of the items may not be suited as a measure of fatigue in a neurological population, since the Mental Fatigue Subscale includes subjective cognitive symptoms that are common, yet separate, from the fatigue construct in the TBI population. Additionally, one item from the Physical Fatigue Subscale pertains to sleepiness rather than fatigue (Item #3), which is a related but separate problem that should be distinguished from fatigue (Shen et al., 2006). Norms adjusted for age and gender are available for the general Norwegian population on the CFQ for comparison (Loge et al., 1998).

The **Giessen Subjective Complaints List (GSCL) - Fatigue Subscale** (Brähler & Scheer, 1995) includes six questions asking the respondent to indicate the presence of various fatigue symptoms in general, on a scale from 0 ('not at all bothered') to 4 ('strongly bothered'). The GSCL has been used in epidemiological studies and has previously been validated in a Norwegian sample (Vassend et al., 1992). Two of the items specifically pertain to sleepiness rather than fatigue, whilst one of the items pertains to concentration difficulties, which might be somewhat problematic for a neurological sample.

The **Rivermead Post-Concussion Symptoms Questionnaire (RPQ) – Fatigue Item** (King et al., 1995) asks respondents to rate the presence of fatigue on a scale of 0–4, where 0 = 'not a problem', 1 = 'no longer a problem', 2 = 'a minor problem', 3 = 'a moderate problem' and 4 = 'a severe problem'. For the analyses conducted in Papers II and III, responses to the item as '1' were recoded as '0', so as to reflect currently experienced symptomatology. This item is often used in clinical screening for the presence of fatigue in patients with TBI and has also been used as a measure of fatigue in previous research (Andelic, Røe, Brunborg, et al., 2021; Norrie et al., 2010).

6.3.1.3 Self-Report Questionnaires

The **Hopkins Symptom Checklist (SCL-5, -8 and -10)** (Derogatis et al., 1974) was included as a measure of psychological distress or symptoms of depression and anxiety. The short versions (SCL-5 and -8) were used as single measures of psychological distress in Paper I, while SCL-10 was used in Papers II and III. On these measures, respondents are asked to indicate whether they are bothered by various symptoms of anxiety and depression. Notably, the short versions have been found to provide reliable measures of psychological distress (Strand et al., 2003).

The **GSCL** (Brähler & Scheer, 1995) subscales pertaining to (1) musculoskeletal pain, (2) cardiovascular symptoms and (3) gastrointestinal symptoms were included as measures of somatic symptom burden. As per the fatigue subscale described above, the patients were asked to rate the presence of symptoms in general on a scale from 0 ('not at all bothered') to 4 ('strongly bothered'), with six items per subscale. Sum scores were calculated for each subscale.

The **Resilience Scale for Adults (RSA)** (Hjemdal et al., 2011) was included as a measure of resilience. While the questionnaire has, to our knowledge, not been adopted in studies of patients with TBI, it has been recommended as a valid and reliable measure of resilience in various populations and nationalities (Windle et al., 2011). The questionnaire contains a total of 33 items, with patients being asked to indicate agreement with various statements indicative of intra- and interpersonal resilience. The questionnaire contains six subscales: (1) Perception of Self (six items), (2) Planned Future (four items), (3) Social Competence (six items), (4) Family Cohesion (six items), (5) Social Resources (seven items) and (6) Structured Style (four items). Sum scores were generated for each subscale.

NEO Five-Factor Inventory 3 (NEO-FFI-3) (McCrae & Costa, 2010) was used to assess five factor personality traits: (1) Neuroticism, (2) Extraversion, (3) Conscientiousness, (4) Openness and (5) Agreeableness. The questionnaire contains a total of 60 items (12 items per trait) rated on a scale from 0 = 'highly disagree' to 4 = 'highly agree'. Gender-adjusted T-scores were generated for each trait according to the official manual.

The **Behavioural Inhibition (BIS) / BAS Scale** (Carver & White, 1994) was included as a measure of behavioural inhibition or activation propensities. This scale includes 24 items on a rating scale from 0 = 'Very true for me' to 3 = 'Very false for me'. The questionnaire contains four subscales: (1) BIS (7 items), (2) BAS – Drive (4 items), (3) BAS – Reward Responsiveness (5 items) and (4) BAS – Fun-seeking (4 items). BIS and BAS are conceptualised as relatively stable motivational systems, with BIS providing a measure of motivation to avoid aversive outcomes and the BAS subscales providing measures of motivation to approach pleasurable or goal-directed outcomes. Sum scores were calculated for all subscales.

The **Life Orientation Test Revised – Optimism Subscale** (Scheier et al., 1994) was included as a measure of trait optimism. The questionnaire asks respondents to indicate their level of agreement with six items pertaining to hopefulness and optimism for the future in general, on a scale of 0 = 'Completely disagree' to 4 = 'Completely agree'. Negatively phrased questions were reversed and average scores were calculated.

Three items from the UCLA Loneliness Scale – Version 3 (Russell, 1996) were included as a measure of loneliness. The questions specifically ask respondents to report feelings of isolation, perceived lack of opportunities for socialisation, and feelings of being excluded, on a scale from 0 = 'Never' to 4 = 'Always'. Average scores were calculated from the three items.

Epworth Sleepiness Scale (Johns, 1991) was included as a measure of daytime sleepiness. This questionnaire asks respondents to rate the probability of falling asleep during eight different activities, on a scale from 0 = 'Would never fall asleep' to 3 = 'High likelihood of falling asleep'. Summed scores were calculated.

The **Insomnia Severity Index** (Bastien et al., 2001) was used to measure subjective sleep deficits. The questionnaire contains three items pertaining to specific difficulties with falling asleep, remaining asleep and early awakening, rated on a scale from 0 = 'None' to 4 = 'Very Severe'. It also includes four items rated on a scale from 0–4 pertaining to the

respondent's satisfaction with their sleep and the perceived functional impact of their sleep deficits. The score was calculated as the sum of all items.

The **Numerical Rating Scales (NRS) for Pain**, which are scored on a scale from 0 = 'No Pain' to 10 = 'Worst Possible Pain', were used to assess the (1) Strongest, (2) Weakest, (3) Average and (4) Current levels of pain. For the first three items, patients were asked to reflect the pain levels experienced within the last week.

A **Pain Drawing** (Kuorinka et al., 1987) was used as a measure of pain dispersion or localisation. Patients were asked to mark particular areas of their body where they had experienced pain within the last week. The drawing was scored using a standardised template, where each affected body region amounted to 1 point, for a combined maximum total of 10 points.

6.3.1.4 Neuropsychological Function

All patients were initially screened with the **Rey 15-Item Validity Test** to ensure the validity of subsequent neuropsychological assessments (Reznek, 2005). As measures of general intellectual abilities and domain-specific levels of abstraction, the subtests **Matrix Reasoning** and **Similarities** from **Wechsler Abbreviated Scale of Intelligence (WASI)** were included (Wechsler, 1999). As measures of psychomotor speed, subtests from the **Color-Word Interference Test (CWIT 1-2)** and **Trail Making Test (TMT 1-3 and 5)** from the **Delis-Kaplan Executive Functions System (D-KEFS)** were included (Delis et al., 2001). Executive functioning was measured with **CWIT 3-4** and **TMT 4** from the **D-KEFS**. Auditory digit span and working memory were measured using the **Digit Span Test** from **Wechsler Adult Intelligence Scale-IV (WAIS-IV)** (Wechsler, 2008). Finally, as a measure of sustained and focused attention, the **Conners Continuous Performance Test III (CPT-III)** was included (Conners, 2014). All tests were administered and scored according to their manuals. Scaled scores were used in the analyses conducted in this thesis. Additionally, for the CPT-III, variables were calculated for the coefficient of variation (CoV) (Flehmig et al., 2007) and for change in CoV in reaction times from the first to the second half of the sustained attention task.

6.3.1.5 Functional Outcome

Functional outcome was measured upon discharge from the acute hospital using the five-level Glasgow Outcome Scale (Wilson et al., 1998), which categorises functional impairment on a scale from 1–5, where 1 = Dead, 2 = Persistent Vegetative State, 3 = Severe

Disability, 4 = Moderate Disability and 5 = Good Recovery. Functional outcome was later assessed at T1 and T2 via the structured clinical interview for the eight-level Glasgow Outcome Scale – Extended (GOSE) (Wilson et al., 1998). GOSE rates functional outcome on a scale from 1–8, where 1 = Dead, 2 = Vegetative State, 3–4 = Lower-Upper Severe Disability, 5–6 = Lower-Upper Moderate Disability and 7–8 = Lower-Upper Good Recovery.

6.3.1.6 Measures Not Included in this Thesis

Although some additional measures were also collected as part of the study protocol, analyses of these measures are still pending. As such, these findings will be communicated in future papers. All participants underwent blood test screening at their first measurement to rule out other possible causes of fatigue, including kidney, liver, thyroidal, pituitary and adrenal cortex status, B-12 D-vitamins, haemoglobin and inflammatory marker CRP. The complete RPQ (King et al., 1995), and Quality of Life After Brain Injury (Truelle et al., 2010) were also administered at both measurement time points. List of Threatening Experiences Questionnaire (Brugha & Cragg, 1990) was also used to determine negative life events (1) in the last 12 months before injury, (2) in the months between injury and T1, and (3) in the months between T1 and T2. Finally, the Iowa Gambling Task II (Bechara, 2016) was included only at the second measurement.

6.4 Statistical Analyses

6.4.1 Paper I

All analyses in Paper I were conducted in Stata Statistical Software, Release 16 (StataCorp LLC, 2019). For this study, a multilevel regression approach was applied. Data were reconfigured from wide to long format, meaning that each participant had two rows in the data set, with each twin pair having four rows. Unique ID numbers were generated for each participant, zygote (for monozygotic, Mz twins) and twin pair (for Mz and dizygotic, Dz twins) for the identification of clusters within the regression models. This hierarchical compartmentalisation assumes that an individual measured on an outcome twice is more similar to him- or herself at another time point than to their monozygotic twin. It also assumes that two monozygotic twins are more similar to each other on the outcome than two dizygotic twins. Finally, it assumes that two dizygotic twins are more similar to each other on the outcome than two unrelated persons. Intraclass correlation coefficients (ICCs) were checked for clustering within individuals, Mz twins and Dz twins separately, to confirm the hierarchical structure of the data. The ICC for the primary outcome (fatigue) within subjects

was found to be 0.72, while that within Mz twin pairs was found to be 0.55 and that within Dz twin pairs was found to be 0.36, which supported this hierarchical parameterisation.

The use of multilevel modelling (MLM) for the estimation of behavioural genetic models has previously been outlined in detail by Rabe-Hesketh et al. (2008). The addition of a within-person dimension over time further allowed for the compartmentalisation of non-shared environmental variance into stable and time-varying components.

A four-level model was fitted as a multilevel mixed-effects generalised linear model, with time points (Level 1) nested within individuals (Level 2), nested within zygotes (for Mz twins, Level 3), and nested within twin pairs (for Mz and Dz twins, Level 4). To estimate the additive genetic variance component, a random slope for Levels 3 and 4 were constrained to be equal, meaning that the 50% additional shared genes in Mz twins were given an equal weight to the 50% shared genes in Dz twins in the estimation of the additive genetic effects. Although no random intercept was estimated for Levels 3 and 4 in the models presented in the final paper, a model with a random intercept was generated to evaluate the potential effects of the shared environment (i.e., residual effects of being clustered in a twin pair not explained by genetic covariance). Since no significant shared environmental component for fatigue was found, the subsequent modelling was conducted with only additive genetic familial variance.

Multilevel regression modelling was conducted block-wise, with a primary baseline model incorporating only gender. In the following three models, the contributions of psychological distress and musculoskeletal pain in isolation and combination were tested. In the final three models, controls were added to account for confounding in the relationships between fatigue, pain and distress. Using principles from Allison's (2009) hybrid fixed- and random-effects models, also called random effects between-within (REBW) models (Bell et al., 2019), independent variables (musculoskeletal pain and psychological distress) were parameterised into cluster means and deviations from cluster means in the same manner as the dependent variable. These were used to evaluate level-specific effects of pain and distress in the model, free from confounding from genetics and a stable non-shared environment. Explained variance (%) was calculated for each level for each modelling step. Model fit was evaluated using the log likelihood and Akaike information criterion.

6.4.2 Paper II

The analyses for Paper II were conducted in SPSS, Version 27 (IBM Corp, 2020). Bivariate correlations were inspected between fatigue and all included variables. Due to the

exploratory aims of the study, as well as the inclusion of variables with previously established associations with fatigue, the bivariate correlations used as criteria for variable selection in Paper II were not corrected for multiple comparisons. Thus, the significance level was set at $p < 0.05$, whilst also incorporating variables with nearly significant ($p < 0.08$) correlations with one or several fatigue measures. Since the Mental Fatigue Subscale from the CFQ mostly contains items pertaining to the presence of common cognitive sequela of brain injury not crucial to fatigue, variables only correlated with this measure were not selected for inclusion in subsequent analyses.

Dimension reduction was conducted with exploratory principal axis factor analyses. Items from all fatigue measures (pruned of non-crucial items relating to cognitive symptoms and sleepiness) were tested for underlying dimensionality. All variables significantly associated with fatigue measures were then tested for underlying dimensionality. Factor retention was determined based on critical thresholds (95%) from parallel analyses of 100 randomly generated samples (Patil et al., 2017). Oblimin rotation was conducted to allow for correlated factors. Variables not loading saliently on any factor (i.e., factor loadings below |0.40|) were removed, with analyses being reconducted without these variables. After the primary structural factor analysis, separate factor analyses were conducted for each factor whilst including only those variables with salient loadings. Cronbach's alpha was calculated for all factors to evaluate internal reliability.

Block-wise linear multiple regression was finally conducted on the fatigue factor from the previous step. To evaluate the robustness of the findings, the results were bootstrapped with 2000 random samples drawn from the sample. Effects were deemed significant at $p < 0.05$ and explained variance in the regression models were compared to a baseline model without any predictors. Post-hoc analyses were conducted to evaluate the individual contributions of each variable loading on each factor by replacing the factor with the individual variable in the final regression model, and evaluating the significance and change in explained variance.

6.4.3 Paper III

All analyses in Paper III were conducted in Stata Statistical Software, Release 16 (StataCorp LLC, 2019). Paper III used a multilevel approach similar to that employed in Paper I. MLM is an appropriate approach when data analysed is clustered hierarchically, as is the case in studies with repeated measures. For obvious reasons, genetic contributions to

intra-individual stability could not be estimated. In keeping with the methodology in Paper I, the between-subject variance component in Paper III was thus comprised of both genetic and stable environmental influences (including injury-related factors) that exert the same effects on each subject at both time points, thereby leading to stability in each subject's responses across time. While MLM is less commonly used in the field of rehabilitation, its applicability in rehabilitation research has previously been highlighted (Kwok et al., 2008).

For the primary outcome, a fatigue factor was extracted from the same items from the fatigue PROMs used in Paper II, with loadings constrained to be equal over time (i.e., an item loads uniformly on the factor regardless of measurement time point). Multilevel mixed-effects models without any predictors (variance component models) were initially estimated to evaluate ICCs for both the fatigue factor and all included time-varying variables. The ICC for subjects on the outcome (fatigue factor) in this study was found to be 0.78, thereby supporting the hierarchical compartmentalisation in the MLM.

Similar to the approach used in Paper I, all time-varying variables (including the fatigue factor) were segregated into means for each individual (Level 2: between-subject variables) and deviations from the mean at each time point (Level 1: within-subject variables). Bivariate correlations with fatigue were inspected separately at each level for variable selection for subsequent multilevel factor analyses. Thus, we identified significant correlations between the Level 2 between-subject aggregate scores of fatigue and other variables, along with time-invariant variables (e.g., injury severity indices) as a selection criterion for the subsequent Level 2 factor analysis. Additionally, we identified significant correlations between the Level 1 within-subject deviation scores of fatigue and other variables as a selection criterion for the subsequent Level 1 factor analysis. Thresholds for factor retention were set based on parallel analyses of 100 randomly generated samples (95%). Factor analyses were reconducted without variables with non-salient loadings on any of the resulting factors.

Finally, a multilevel mixed-effects model of fatigue was fitted with fatigue scores from each measurement (Level 1) clustered within individuals (Level 2). A hybrid fixed- and random-effects model/REBW was then run (Allison, 2009; Bell et al., 2019). Demographic variables were entered along with factors from the factor analyses of both Level 1 and 2 correlates of the fatigue factor, as well as time since injury. The variable for time elapsed since injury was calculated at both time points as $\frac{days\ since\ injury}{30}$ and thus varied within

individuals as a Level 1 variable. Gender, age (centred around the sample mean) and years of education (centred around the sample mean) were included as Level 2 variables, meaning that they do not change within individuals over time. Effect sizes were calculated as the percentage of explained variance at each level. Post-hoc analyses were conducted to evaluate the contributions of each variable to the model via the removal of each variable from the final model, and the calculation of changes in explained variance at each level with and without the variable included.

6.4.4 General Statistical Remarks

The regression analyses in Papers I and III were estimated with full information maximum likelihood (FIML). FIML allows for the inclusion of participants with only one measurement occasion for the estimation of higher-level variance components (i.e., no contributions to within-subject variance components or effects). To obtain the unbiased estimation of parameters and standard errors with FIML, occasions must be missing at random or missing completely at random, as opposed to missing not at random (Newman, 2014). In Paper III, two-group T-test comparisons of the fatigue factor between those who contributed to one occasion or both occasions revealed a nearly significant trend ($p = 0.075$) for the group with only one occasion to score lower on the fatigue factor (rather than higher). Therefore, attrition was likely not due to higher levels of fatigue despite the nearly significant trend potentially indicating a trend towards lower levels of fatigue in the patient sample with only one measurement time point.

6.5 Ethical Considerations

The studies were conducted according to the Helsinki Declaration. The study presented in Paper I was approved by the Regional Committee for Medical and Health Research Ethics, South-East Norway (project 2015/958). The TBI study presented in Papers II-III was also approved by the Regional Committee for Medical and Health Research Ethics, South-East Norway (project 2018/144). Written informed consent was obtained from all participants.

Since clinical research involving patients (Papers II and III) entails several dilemmas, much consideration was given to not unduly influence patients during the recruitment process. Some patients were first contacted during in-patient stays at Sunnaas Rehabilitation Hospital, with the primary investigator ensuring that the rehabilitation team and the treating neuropsychologist were aware of their potential inclusion. This collaboration was crucial to

avoid contacting patients during post-traumatic confusion or during particularly vulnerable life situations. All patients contacted during their primary in-patient rehabilitation were informed of the purpose of the study and the amount of time and effort it would require from them. Moreover, they were encouraged to think the decision through, and discuss it with their families and/or friends. All patients were reminded that declining to participate in the study would not at any point have negative consequences for them, and that they did not need to provide a reason for their decision.

In light of the extensive scopes of the evaluations that all patients underwent, the protocol was discussed with a user representative from the user organisation Personskadeforbundet LTN. Extra care was taken to ensure that patients did not experience unnecessary discomfort during or as a result of the examinations. Additionally, patients were given opportunities to respond to the questionnaires from home if they experienced fatigue and were in need for rest following the neuropsychological evaluation.

When presently unmet rehabilitation needs were uncovered as part of the study follow-up, the primary investigator discussed the case with supervisors, and referred patients to relevant services, or collaborated with already established health care providers when this was deemed necessary. The primary investigator also provided some guidance to a few patients in between the study assessments, primarily with regard to welfare rights and rehabilitation services. While the study had an observational aim and these points of contact may have influenced the trajectories of individual patients, these additional services were, however, of limited volume and deemed ethically necessary.

7 Summary of Findings

The findings outlined in Papers I–III converge on several findings relevant to our understanding of fatigue in general and in relation to TBI in particular. People differ in their proneness to fatigue symptoms, whilst several risk and protective factors were identified for determining the risk for fatigue following TBI. Despite the significant reduction in fatigue over time, one crucial finding of our studies was the tendency for trait-like stability since both the non-clinical sample in Paper I and the TBI sample in Paper III reported relatively consistent levels of fatigue across 5-year and 6-month intervals, respectively. When controlling for these stable factors, within-subject associations with fatigue could still be demonstrated for pain, depression, anxiety, somatic symptom burden and behavioural inhibition, thereby indicating their relevance to understanding changes in fatigue over time in persons with TBI and the general population.

Before arriving at these findings, a look at the comparability of fatigue symptom levels between the two independent samples, as well as the PROM-specific levels of fatigue in the TBI sample, is warranted.

7.1 Comparability of Symptom Levels Between Samples

The clinical TBI sample in Papers II and III reported median levels of musculoskeletal pain and psychological distress identical to the non-clinical twin sample in Paper I, with quite similar interquartile ranges (IQRs) (see Table 5). However, on the fatigue subscale, the TBI sample reported median levels above the IQR in the non-clinical sample. While no statistical between-group testing could be conducted, this nevertheless indicates that fatigue symptoms were elevated in the TBI sample.

Table 5. Median raw scores on the three measures included in both samples. In Paper I, the measurement time points T1 and T2 correspond to 2011 and 2016, respectively. In Papers II and III, the measurement time points T1 and T2 correspond to approximately 6 and 12 months following TBI, respectively.

Measure	Twin Sample (Paper I)	TBI Sample (Papers II and III)
GSCL Fatigue Subscale, Median (IQR)	T1: 0.3 (0.0 – 0.7) T2: 0.2 (0.0 – 0.5)	T1: 0.8 (0.2 – 1.7) T2: 0.8 (0.2 – 1.7)
GSCL Musculoskeletal Pain Subscale, Median (IQR)	T1: 0.5 (0.2 – 1.0) T2: 0.3 (0.2 – 0.7)	T1: 0.5 (0.2 – 1.0) T2: 0.5 (0.2 – 1.3)
SCL Total – Distress, Median (IQR)	T1: 1.2 (1.0 – 1.4) T2: 1.0 (1.0 – 1.3)	T1: 1.3 (1.0 – 1.5) T2: 1.3 (1.0 – 1.6)

Abbreviations: GSCL, Giessen Subjective Complaints List; IQR, Interquartile Range; SCL, Hopkins Symptoms Checklist.

7.2 Fatigue During the First Year Following TBI

Items from the different measures of fatigue (the FSS, CFQ and GSCL – Fatigue Subscale, as well as the fatigue item from the RPQ) were loaded on a single unidimensional fatigue factor as described in the exploratory factor analyses in Papers II and III, when items with confounding content (e.g., sleepiness and subjective cognitive deficits) were removed.

On the FSS, the overall average score was 3.7 (SD = 1.4) at the first measurement point (demographically adjusted average T-score: 48.9 (SD = 11.9)) and 3.8 (SD = 1.5) on the second measurement point (demographically adjusted average T-score: 49.1 (SD = 12.5)). Thus, the TBI sample reported quite similar levels of fatigue interference on both occasions, with levels of fatigue interference equivalent to those reported by the general population.

However, on the CFQ, the grand average total score was 16.2 (SD = 5.4) at the first measurement point (demographically adjusted average T-score: 60.8 (SD = 14.3)) and 15.5 (SD = 6.0) at the second measurement point (demographically adjusted T-score: 58.9 (SD = 15.9)). Due to the total score being comprised of several items pertaining to daytime sleepiness and common cognitive sequela not crucial to the fatigue construct, these scores could overestimate the levels of fatigue. As demonstrated by Kjeverud et al. (2021) in a sample of patients who had experienced a stroke, the overall questionnaire may seem to

overestimate levels of fatigue when compared to other measures, such as the FSS. However, on the first two items of the CFQ, patients were asked to rate whether they experienced increased tiredness or an increased need for rest, respectively, as compared to before their injury. At the first measurement point, 58 patients (60.4%) reported more or much more tiredness, whilst 59 patients (61.5%) reported an increased or much-increased need for rest. These single items therefore align with the demographically adjusted T-scores on CFQ, in indicating the presence of the central characteristics of fatigue in as many as 60% of patients at the first measurement point, At the second measurement point, 45 patients (45.9%) reported more or much more tiredness, whilst 47 patients (47.9%) reported more or much more need for rest. Similarly, on the RPQ fatigue item, 47 patients (49%) reported mild-severe problems with fatigue at the first measurement point compared to 44 patients (44.9%) at the second measurement point. These results indicate small decreases in the central characteristics of fatigue over time in our sample. Notably, this result is in line with the main findings from Paper III. However, the scores on the FSS and GSCL Fatigue Subscale showed no indication of a group-level change.

Finally, fatigue caseness was estimated across all fatigue PROMs according to the established cut-offs to assess differences in the classification of patients as fatigued or non-fatigued (see Figure 8 for an overview of fatigue caseness at both measurement points). However, items related to non-essential fatigue symptoms (e.g., cognitive deficits and sleepiness) were not pruned for this classification to provide a comparison of the PROMs when used in full.

To assess differences in the performance of the 7- and 9-item versions of the FSS, separate scores were calculated, and caseness was exploratively defined as an average score of ≥ 4 (mild-severe fatigue) or ≥ 5 (moderate-severe fatigue). For the CFQ, a categorical caseness scoring procedure was used to count every item response from 2–3 (‘more’ or ‘much more’) as 1, with the caseness criterion defined as a categorical score of 4 and above. For the fatigue subscale from the GSCL, an average score ≥ 1 was selected for fatigue caseness, indicating an average degree of ‘somewhat’ fatigued. Fatigue caseness on the RPQ fatigue item was defined by an item score of ≥ 2 (mild-severe fatigue) or ≥ 3 (moderate-severe fatigue).

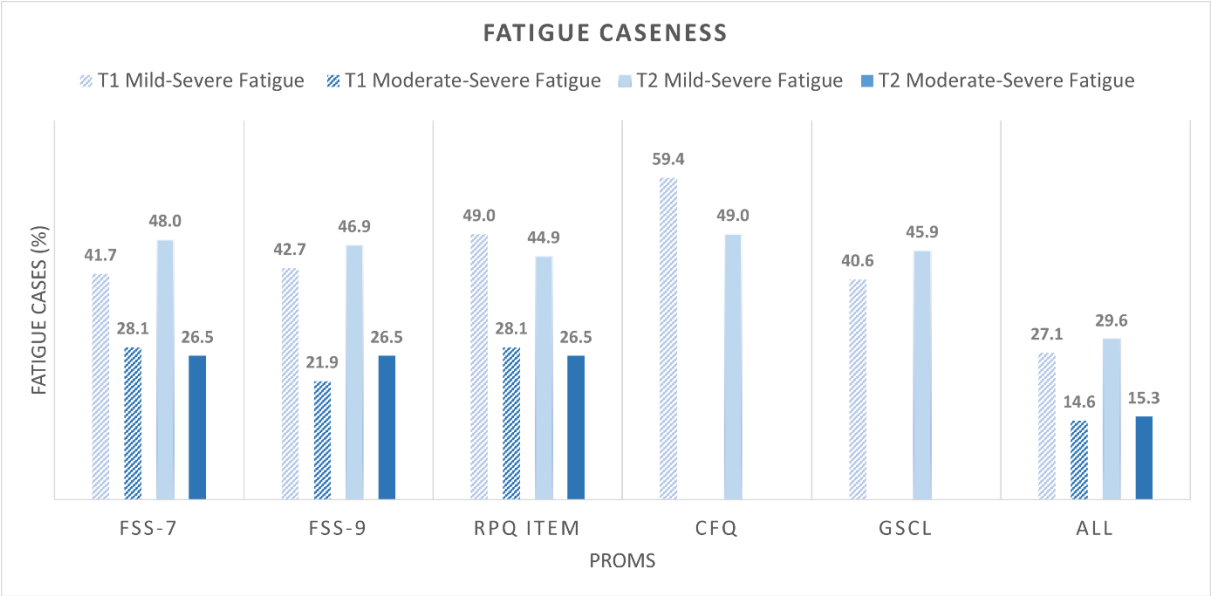

Figure 8. Caseness across included fatigue PROMs as the percentage of the total sample measured at T1 approximately 6 months following injury (n = 96) and T2 approximately 12 months following injury (n = 98).

As shown in Figure 8, caseness estimates vary between PROMs and across time points. Using the liberal mild-severe fatigue criteria, 27.1% of patients fulfilled the caseness criteria across all measures at the first time point, whilst 29.6% fulfilled it at the second time point. Using the more conservative moderate-severe fatigue criteria, 14.6% satisfied the caseness criteria on all PROMs at the first time point, whilst 15.3% did so at the second time point.

Although there were some deviations in fatigue scores between measures and across time points overall, the considerable stability in experienced levels of fatigue was the main finding in both the non-clinical and clinical TBI samples, which warranted an investigation of separate between- and within-subject contributions of correlates to fatigue, to distinguish confounding from direct and more viable causally implicated associations.

7.3 Between-Subject Covariation of Fatigue, Risk and Protective Factors

The stability of both fatigue and associated variables and factors in Papers I–III highlight the differences between people with regard to their vulnerability to fatigue. Paper I aimed to inform us of the hierarchy of contributions to within-person stability by using genetically informed data from a non-clinical sample of twins. This paper found that stability in fatigue, musculoskeletal pain and psychological distress (i.e., symptoms of anxiety and depression) could be compartmentalised into both genetic and acquired vulnerabilities from

life experiences. In essence, this meant that the same person measured twice was more similar to him- or herself than to his or her monozygotic twin, whilst two monozygotic twins reported more similar levels of fatigue than two dizygotic twins, who again reported more similar levels of fatigue than two random persons. Fatigue was estimated to have a heritability of 45%, while an additional 22% of the variance in fatigue could be attributed to stability within individuals not explained by genetics, with 27% of the variance being due to within-subject variability and measurement error. Note that gender was included in this baseline model, thus explaining some proportion of the variance. The stable components of fatigue were related to the stable components of pain and distress, indicating that they share genetic and accumulated lifetime vulnerabilities. Although controlling for the presence of comorbid somatic illness did not reduce the effects of pain and distress on fatigue, most comorbidity indicators were nevertheless significantly associated with fatigue in the study, including neurological illness and TBI.

Our studies on patients with TBI (Papers II and III) demonstrated that biopsychosocial variables commonly associated with fatigue align along three distinct cross-sectional and between-subject dimensions, which were termed somatic vulnerability, psychosocial robustness and injury severity. Somatic vulnerability, with positive loadings from several measures of pain severity and dispersion, somatic symptom burden, daytime sleepiness and insomnia severity, demonstrated the strongest and most consistent relationship with fatigue in cross-sectional analyses. Furthermore, psychosocial robustness demonstrated a smaller—yet significant—negative association with fatigue, with negative loadings from symptoms of anxiety and depression, trait neuroticism, behavioural inhibition and loneliness, as well as positive loadings from trait extraversion, conscientiousness and optimism, with facets of resilience related to self-efficacy and positive prospects for the future. Finally, the injury severity factor, with the most consistent positive loadings from the anatomical severity of head injury and the direct pathway to specialised rehabilitation services, demonstrated a small but significant association with fatigue. Neuropsychological measures of processing speed, sustained attention and mental flexibility were shown to overlap with the injury severity factor in its contribution to fatigue, indicating that these measures operate as proxies for injury severity. Notably, age did not demonstrate any significant association with fatigue.

The three-dimensional associative architecture underlying the assortment of variables previously highlighted by the literature as relevant to fatigue identifies theoretical umbrella terms in which biopsychosocial constructs seem to correlate with one another, which are

again associated with fatigue in TBI between subjects. The upper half of a figure from Paper III (reproduced here as Figure 9) may thus be used to identify the risk of fatigue. Somatic vulnerability, psychosocial robustness and injury severity, along with female gender and years of education, explained approximately 61% of the between-subject variance in fatigue. The relative stability of fatigue—and many of the associated variables—indicates the need for segregating these between-subject factors from potential within-subject effects.

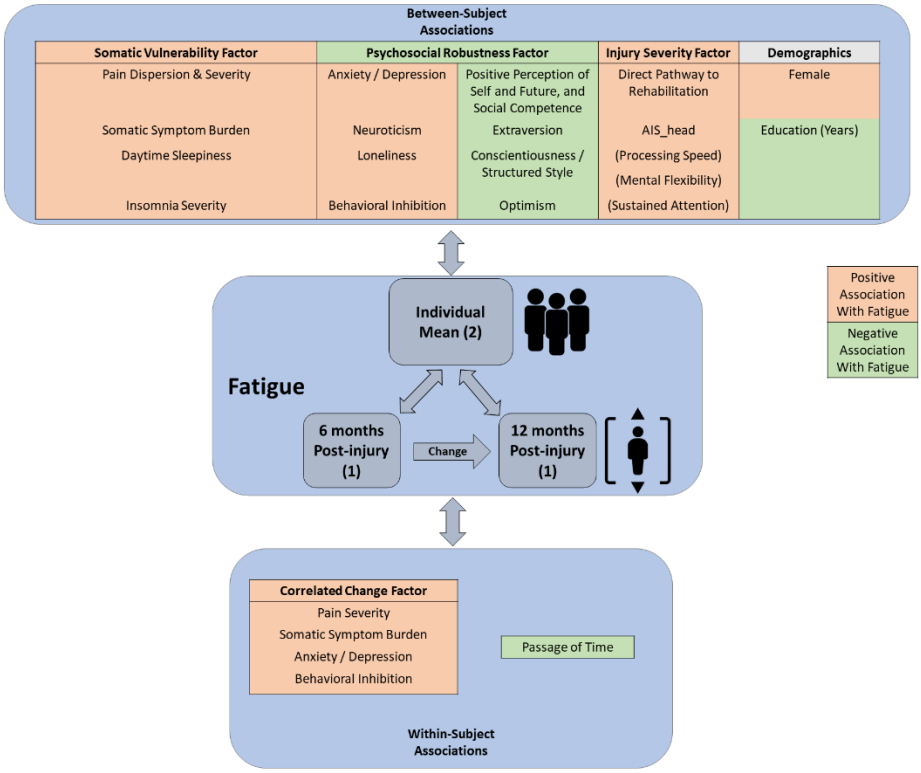

Figure 9. Graphical overview of between-subject (Level 2) and within-subject (Level 1) associations with fatigue. The upper half presents variables implicated as risk and protective factors, while the lower half presents variables additionally indicated as being correlated within subjects (i.e., associations free from between-subject confounding).

7.4 Within-Subject Covariation of Fatigue, Risk and Protective Factors

While considerable stability in fatigue and associated factors was documented, the studies aimed to examine any potential within-subject associations free from the influences of between-subject confounders from genetics and prior exposure to risk and protective factors. In Paper I, psychological distress and particularly pain demonstrated robust within-person associations with fatigue beyond the shared genetic and stable environmental vulnerabilities, implying synchronous changes among these symptoms, whilst also controlling for somatic comorbidity.

Paper III took on a broader view of potential within-subject associations with fatigue in patients with TBI and found a within-subject factor indicating that psychological distress, behavioural inhibition, somatic symptom burden and pain severity covary within persons across time (see the lower half of Figure 9). Essentially, this implies that if pain severity decreases or increases within a person, there is a significant tendency for overall somatic symptom burden, behavioural inhibition and psychological distress to also increase. This within-subject factor was significantly associated with fatigue, and explained 17.7% of the within-subject variance in fatigue in isolation. Along with the passage of time, however, it explained 21.7% of the within-subject variance in the complete model, thereby implying synchronous changes in fatigue. While changes in several neuropsychological performance measures were negatively and significantly bivariately associated with changes in fatigue, the neuropsychological within-subject variables did not load onto any single factor.

The passage of time (in months since injury) was negatively associated with fatigue within subjects, indicating a trend toward reporting less fatigue at the second measurement point than at the first. However, the dominant trend was stability in fatigue levels from the first to the second measurement, indicating that fatigue—for most individuals—seems to have stabilised 6 months post-injury. Differences between subjects in terms of changes in fatigue were, however, observed through the study period.

8 Discussion of the Main Findings

Fatigue remains a clinical enigma. While advances in scientific methodology continue to pave the way for potential new avenues for the exploration of this phenomenon, much research remains to be done before we can understand the precise mechanisms that bring about fatigue, and which targeted treatments should be implemented for those who suffer from persistent fatigue in association with chronic illness. This thesis has taken on an exploratory approach to examine the relationships between fatigue and various biopsychosocial mechanisms in both the general population and patients following TBI. The findings might serve to guide future research and clinical sense-making of a symptom that commonly interferes with rehabilitation efforts and has consequences for health-related quality of life and function in both TBI and other diagnoses.

The main findings of this thesis can be segregated based on the level at which they were investigated, specifically within-person stability or within-person variability. While changes in fatigue and correlates were evident in both samples over time, a primary finding was the relative within-person stability. Fatigue was considerably stable from the first to the second measurement in both the twin study and TBI study, as were all of the time-varying correlates of fatigue. As measured in our study, the stability of fatigue aligns with findings indicating that trait-like fatigue is distinguishable from state-like fluctuations in fatigue in TBI (Malloy et al., 2021), which highlights the importance of considering the stability of fatigue and its correlates when examining fluctuations from this baseline. Between- and within-subject correlates inform us of different possible relations between fatigue and associated variables. Notably, these findings have implications for future research and the clinical tailoring of individualised rehabilitation programmes.

8.1 Characteristics of the Trait-Like Stability of Fatigue

8.1.1 Stable Components of Fatigue

The cross-sectional dimensions of the biopsychosocial correlates of fatigue in patients with TBI are outlined in Paper II, whilst the between-subject dimensions that largely replicated these cross-sectional dimensions in Paper III inform us of what characteristics are associated with a person's relatively stable level of subjective fatigue. Also, the behavioural genetic twin study outlined in Paper I informed us that this stability can again be compartmentalised into genetic and environmental variation. The behavioural genetic design provided a way of examining the essential building blocks of fatigue and the proportion of variance attributable to genetic and environmental influences. Earlier studies of the genetic

components of fatigue have established heritability estimates between 0.30 and 0.53 (Corfield et al., 2017; Hickie et al., 1999; Sullivan et al., 2005; Vassend et al., 2018); thus, the heritability of fatigue estimated in Paper I is in line with previous findings.

Although the genetic and environmental components of fatigue cannot be segregated in the TBI sample, it is reasonable to assume that environmental influences might play a larger role in the TBI population since the injury itself would contribute to additional stable environmental influences on all measurements after injury. This is in line with findings indicating that heritability estimates may decline with age, when the longevity of life may provide opportunities for more environmental factors to influence health (Brommer & Class, 2015). Additionally, the directly comparable measures employed in both subsamples indicated that the median level of fatigue in the TBI sample exceeded the IQR of the non-clinical twin sample, whilst the medians and IQRs for psychological distress and musculoskeletal pain overlapped considerably. Thus, the TBI sample did seem to experience more fatigue symptoms, which poses the following question: Why?

8.1.2 Correlates of the Stable Components of Fatigue

The findings in Paper I demonstrated that psychological distress and musculoskeletal pain both share stable dispositions with fatigue. Two genetically matched twins are phenotypically similar to one another. The twin pair-specific tendency to report high or low levels of fatigue is correlated with the twin pair-specific tendency to report high or low levels of pain and distress, implying that some proportion of these relationships is due to genetics. However, shared influences on fatigue, pain and distress from the idiosyncratic life experiences experienced by each individual also lead to additional stability within individuals. Essentially, this implies that the individual-specific tendency for reporting high or low levels of fatigue when measured several times correlates with the individual-specific tendency for reporting high or low levels of distress and pain. Thus, pain and distress share both common genetic and environmental causes with fatigue. Being able to calculate these effects also allows us to better distinguish confounding from plausible causal relations. However, correlates of the stable components of fatigue are themselves informative of risk and protective factors with regard to an individual's relatively stable propensity for fatigue.

8.1.2.1 Stable Sociodemographic Correlates

Sociodemographic factors were inconsistently related to fatigue in the three papers, reflecting the heterogeneity also found in earlier studies (Bensing et al., 1999; Cantor et al.,

2012; Mollayeva et al., 2014; Van't Leven et al., 2010). In Papers I and III, female gender was univariately associated with a between-person tendency to report higher levels of fatigue. In the twin sample in Paper I, this association was no longer significant when controlling for musculoskeletal pain, while this association remained significant in the full model in the TBI sample in Paper III. Thus, gender may influence pathological fatigue in association with TBI differently than in the general population. Interestingly, gender was not significantly associated with fatigue in Paper II, which employed a cross-sectional analysis of the first measurement wave. Similarly, years of educational attainment was not significantly associated with fatigue in Paper II, yet higher education was associated with a between-person tendency to report more fatigue in Paper III.

These differences in findings between the cross-sectional and multilevel approaches may be due to several reasons. First, the multilevel approach incorporated both measurements, leading to an increase in statistical power. Secondly, the multilevel analysis examines a somewhat different relationship from the one examined in the cross-sectional study through the segregation of the between- and within-person components of fatigue. In the multilevel approach, gender and education were included as Level 2 variables, meaning that the relationship that was tested in the final multilevel model was the association with the between-person tendency to report more or less fatigue, rather than that between gender and individual measurements. Therefore, this contrast between the findings of Papers II and III could be due to the fact that within-person variability cannot be distinguished from between-person variability in cross-sectional studies, whilst these effects are segregated in a multilevel framework. As such, the person-specific risk of gender is analysed more clearly when using the multilevel approach, which is free from time-varying confounders.

8.1.2.2 Stable Psychosocial Correlates

Three cross-sectional and between-subject factors were found to underlie the included biopsychosocial correlates of fatigue in the TBI sample. The between-subject factor termed psychosocial robustness informs us that individual-specific, trait-like tendencies for reporting low levels of neuroticism are correlated with individual-specific, trait-like tendencies for reporting lower levels of distress, higher levels of resilience, less loneliness, more optimism, less behavioural inhibition and higher levels of extraversion and conscientiousness. Although people align differently across this dimension, the general tendency among these variables is significantly negatively correlated with the individual-specific, trait-like tendency to report fatigue. These findings support research previously implicating trait neuroticism as a risk

factor for and correlate with fatigue, as seen in stroke survivors (Lau et al., 2017) and the general population (Calderwood & Ackerman, 2011; Sørengaard et al., 2019; Stephan et al., 2022; Vassend et al., 2018). The relevance of considering personality traits, psychological distress, loneliness and resilience as risk and protective factors in TBI is also supported.

A recent study indicated that the risk posed by trait neuroticism for the development of psychological distress when faced with stressful life events may be mediated by reductions in the activation of ventral striatal cortical areas related to reward processing (Bondy et al., 2021)—areas which have similarly been implicated in neural models of fatigue (Chaudhuri & Behan, 2000; Dobryakova et al., 2013, 2020). Thus, whilst psychological distress (state) and neuroticism (trait) might both contribute to fatigue, a candidate mechanism through which they might affect fatigue, might be through the attenuation of reward associated with activity. In our study, the dimensional alignment of these factors with behavioural inhibition, or the trait-like propensity for being motived by the avoidance of unpleasant sensations rather than by the approach towards pleasant sensations and rewards, supports this reasoning.

The cross-sectional and between-subject factor termed somatic vulnerability once again shows that there is considerable overlap in individual-specific, trait-like tendencies for reporting pain, other somatic symptoms, daytime sleepiness and sleep deficits. Again, this general tendency is highly positively correlated with the individual-specific trait-like tendency to report fatigue. Trait-like dispositions for pain and somatic symptoms have previously been established (Davis & Cheng, 2019). Moreover, the relevance of pain and other somatic symptoms to fatigue has been demonstrated in various populations (Vassend et al., 2018; Wyller, 2019). Our findings once again underline the relevance of pain and other somatic symptoms to the comprehensive understanding of fatigue in TBI and the general population.

Finally, the cross-sectional and between-subject factor termed injury severity, demonstrated that some individual-specific injury severity markers were also associated with fatigue beyond the effects of the sociodemographic variables and other biopsychosocial factors. The dummy variable for having been discharged directly to rehabilitation services, as well as the anatomical severity of head injury measured with the AIS-head, were consistently related to fatigue in both the cross-sectional and between-person analyses, while the associations with other injury severity indicators and neuropsychological measures were inconsistent across analyses. While the findings on associations between injury severity and fatigue have been highly inconsistent, a recent CENTER-TBI study did find associations

between fatigue and several injury severity indices, including the AIS-head (Andelic, Røe, Brunborg, et al., 2021). Since the AIS-head incorporated neuroradiological findings from post-acute phases, it might have provided a more accurate reflection of injury severity than acute severity indicators. The AIS-head has previously been shown to predict functional outcomes slightly better than the GCS; however, injury severity does not generally explain much of the variance in functional outcomes (Foreman et al., 2007). Neuropsychological measures of processing speed, intra-individual stability in reaction times, and mental flexibility were variously associated with fatigue in the cross-sectional and between-subject analyses and overlapped with injury severity indices in their contributions to the models of fatigue. The association between information processing speed and fatigue has also been demonstrated in previous studies on TBI and acquired brain injuries (Johansson et al., 2009; Jonasson et al., 2018; Zgaljardic et al., 2014); however, the contributions of neuropsychological measures to the regression models were generally small.

8.2 Characteristics of State-Like Fluctuations in Fatigue

The examination of within-subject correlates of fatigue over time is an approach that is increasingly being used in the literature since it allows for control over the confounders unique to each individual. Several potential confounders could essentially explain the co-occurrence of fatigue and its correlates. This would be the case if, for instance, trait neuroticism—a relatively stable risk factor for many negative health outcomes (Charles et al., 2008)—was the sole underlying cause of the observed relationship between fatigue and depression. If this were the case, it is doubtful that interventions aimed at reducing depression could directly influence fatigue, which would have implications for clinical management. Statistical methods that consider the relative stability of fatigue and correlate with individual-specific random effects, such as those employed in these studies, enable us to control for many of the problematic confounders in these associations (Allison, 2009; Hamaker et al., 2015; Hamaker & Muthén, 2020).

Our findings indicated a cluster of variables that covary within persons, specifically pain and other somatic symptoms (musculoskeletal, cardiovascular and gastrointestinal), psychological distress (anxiety and depression) and behavioural inhibition. The tendency to worsen or improve on this within-person dimension was again correlated with a tendency to worsen or improve with regard to fatigue. These findings are in line with those from Rakers et al. (2021), who recently examined classes of trajectories in fatigue, psychological distress and coping styles during the first 6 months following mild TBI. Four distinct trajectories were

identified, two of which were characterised by good recovery from fatigue and two by the persistence of fatigue. The latter two clusters were characterised by either low or high levels of distress, respectively, and the increasing use of passive coping over the study period. Furthermore, the latter two clusters of patients generally reported significantly more pain and had significantly lower levels of education than the two former clusters. Age and injury severity indices were not correlated with any specific cluster. The clustering of the persistence of fatigue with the persistence or worsening of psychological distress and passive coping aligns well with our within-subject findings of within-subject associations between fatigue, pain, psychological distress and behavioural inhibition. While there is a shortage of TBI studies employing multilevel modelling with separate between- and within-effects, studies on other diagnoses have found similar results. For instance, anxiety and depression have been found to correlate with fatigue within subjects in patients with HIV (Barroso et al., 2010) and multiple sclerosis (Greeke et al., 2017), which is in line with our findings.

However, within-person changes in subjective sleep deficits were not significantly associated with within-person changes in fatigue. Given that an earlier intervention study found that the alleviation of insomnia was accompanied by reductions in general and physical fatigue in TBI (Ouellet & Morin, 2007), this finding was somewhat surprising. However, the lack of a within-person association might indicate that reductions or increases in insomnia are not directly associated with changes in fatigue, yet could be associated through interactions with other direct effects (e.g., depression and pain). Indeed, post-hoc analyses to assess this hypothesis revealed significant bivariate within-person associations between changes in insomnia and changes in depression (Pearson's $r = 0.39$, $p < 0.001$), anxiety (Pearson's $r = 0.26$, $p < 0.001$), behavioural inhibition (Pearson's $r = 0.28$, $p < 0.001$), and NRS scores of strongest (Spearman's rho = 0.28, $p < 0.001$) and average pain (Spearman's rho = 0.21, $p < 0.01$). Thus, it is possible that change in subjective sleep deficits is indirectly related to changes in fatigue through an association with directly influencing variables such as depression, or that sleep deficits exert influences on fatigue more distally rather than synchronously. This is in line with the findings from Cantor et al. (2012), who suggested that emotional distress might mediate associations between fatigue and insomnia, rather than insomnia being a considerable contributor to fatigue.

Despite identifying variables with potential causal relevance to changes in fatigue, our findings did not inform us of the directionality of effects between fatigue and these within-subject correlates. Using a cross-lagged panel model, Schönberger et al. (2014) found that

early levels of depression and daytime sleepiness following mild-severe TBI predicted fatigue 6 months following injury, but not the other way around. This finding, while not accounting for between- and within-components of the respective variables, indicates the potential influence of early depression on later fatigue. However, some caution is warranted in the conclusion of the unidirectional effect of early depression on later fatigue, as other studies examining these relations using the between- and within-separation of effects have found results indicating significant effects of early fatigue on later depression in diseases such as multiple sclerosis (Greeke et al., 2017).

8.3 Methodological Considerations

The methodological approaches adopted in the included studies warrant some discussion and elaboration since all observation studies carry the potential for bias due to threats against internal and external validity (Grimes & Schulz, 2002).

8.3.1 Study Design

Our decision to conduct the first measurement of participants approximately 6 months following their TBI had some ramifications that should be considered. The decision to first evaluate the patients in this post-acute phase was informed by our intent to include more severely injured patients, many of whom would not have been able to consent to participation or undergo examination at an earlier time point. Secondly, several patients who did not report significant levels of fatigue 6 months after injury, did, however, anecdotally report that they had initially suffered from severe fatigue in earlier phases of recovery but had recuperated by the time of our first assessment. Thus, some aspects of the primary, injury-related fatigue may have been lost as a result of this decision. However, we do not believe that this posed a threat to the validity of our findings since our primary aim was to gain an improved understanding of persistent fatigue in later phases of recovery following TBI.

8.3.2 External Validity

The generalizability of findings from our studies warrants some discussion. One strength of the design of our TBI study was the collaboration with the Neurosurgical Department at Ullevål, OUH, which allowed us to recruit a broader range of patients with TBI than studies that recruited primarily from rehabilitation cohorts (e.g., Cantor et al., (2012) and Schönberger et al. (2014)). Thus, our sample encompasses both patients who required lengthy rehabilitation following injury as well as those who recuperated during early phases, which commonly do not come into contact with rehabilitation services. This ensured that—while

perhaps not directly comparable to samples recruited from rehabilitation facilities—the sample has broader generalizability with regard to the overall TBI population.

Notably, the limited incidence of TBI in Norway resulted in a relatively small overall sample size for the TBI study. A total of 450 patients were admitted with intracranial injuries to the Neurosurgical Department during our inclusion period, of which 55% were assessed for eligibility and 22.8% were included in the final sample in Paper III. While we cannot directly compare the included sample with the total TBI population in terms of sensitive health measures, the gender ratio and mean age of our sample were similar to the total population of patients with TBI from the recruitment period. However, there was an indication that moderate and severe injuries (as measured using the Head Injury Severity Scale) were slightly overrepresented in our final sample (78%) when compared to the total population of patients with intracranial injuries admitted during the inclusion period, wherein moderate and severe injuries comprised only 57% of injuries (numbers extracted from the Oslo TBI Registry–Neurosurgery (Tverdal et al., 2020)

The twin sample was recruited from the Norwegian Twin Registry, and there are no indications of systematic differences between the twins in this registry and the general Norwegian population (Nilsen et al., 2013). This ensures that the findings should also be generalisable beyond the studied sample. Notably, the limited age range (50–65 in 2011) of the sample might have influenced the heritability estimates since these may vary based on the studied age cohort (Brommer & Class, 2015).

8.3.3 Internal Validity

The studies presented in this thesis employed several PROMs in the examination of fatigue and implicated correlates. While the subjective nature of fatigue necessitates patient-reported outcomes, PROMs do have certain limitations and a potential for bias that could influence the findings. As outlined in Choi and Pak's (2005) review of biases in the application of questionnaires in research, bias may influence questionnaires due to unclear item phrasing, the questionnaire's overall design and aspects of the setting for administration. Considering the abundance of PROMs employed, response fatigue could have potentially influenced the responses of participants; however, countermeasures were taken to reduce the potential impact of this source of bias. Furthermore, although not all of the employed questionnaires have been extensively validated in the TBI population, all PROMs have nevertheless been validated in other populations.

With regard to the twin study in Paper I, violations of the equal environments assumption—which states that the shared environment does not exert stronger influences in making monozygotic twins more similar to one another than dizygotic twins—could lead to inflated heritability estimates. While we could not control for potential violations in this assumption in our studies, potential violations have not generally been shown to bias the results from twin studies to a considerable degree (Felson, 2014).

8.3.4 Corrections for Multiple Testing

The studies presented in Papers II and III contained a vast array of variables with which fatigue could potentially be associated. Due to the exploratory aims of these studies and the inclusion of variables with previously established associations with fatigue, the bivariate correlations used as criteria for variable selection in subsequent factor analyses within Papers II and III were not corrected for multiple comparisons. Adjusting significance levels for multiple comparisons is essential in confirmatory studies to avoid erroneously rejecting the null hypothesis when there is no effect (i.e., type I-error) (Bender & Lange, 2001). However, these corrections increase the risk of erroneously accepting the null hypothesis when there is an effect (i.e., type II-error) (Rothman, 2014), which we deemed as a more critical error to make when the aim of the study was exploratory.

8.3.5 Multilevel Methodology – Strengths and Limitations

Traditionally, group-level statistical methods have been predominantly used in the analysis of both cross-sectional and longitudinal associations, including linear regression modelling, path modelling and cross-lagged panel modelling. These methods use group-level data from one or several measurement points to explain or predict some group-level associations or changes in outcomes of interest, lack the possibility to control for stability and simultaneously examine changes in outcomes of interest (Hamaker et al., 2015). This may lead to the misrepresentation or distortion of within-subject change processes (Fisher et al., 2018). Hamaker (2012) exemplified this error with the intuitive example of the relationship between keyboard typing speed and typing errors. Keyboard typing speed is negatively correlated with typing errors at the group level (between subjects); however, within-subject effects point in the other direction, suggesting that relative to themselves, most people make more errors the faster they type. Similarly, many between-subject correlates of fatigue might lead us to assume the causal relevance of these correlates when they provide no information on the within-subject processes we are interested in. The multilevel methodology employed in Papers I and III, in which between- and within-subject variance for both fatigue and correlates

could be segregated, allows us to improve our understanding of individual differences in risk for fatigue while also examining correlates of changes in fatigue within individuals (Hoffman, 2007).

The multilevel modelling strategies employed in Papers I and III also have certain limitations that are closely linked to the chosen design. Two-wave studies such as these do not provide the opportunity to examine fatigue trajectories, nor the possibility to evaluate the predictive value of earlier changes in correlates (e.g., pain) to later subsequent changes in fatigue, as with time-lagged multilevel models. More time points are required if trajectories are to be examined. Moreover, the temporal measurement sequence must be planned to consider the temporal intervals at which causes would be most likely to exert influence on the outcome (Grimes & Schulz, 2002). Due to the limitations imposed by having two time points, our study examined synchronous, simultaneous changes between fatigue and correlates, rather than earlier predictors of subsequent changes in fatigue. An earlier longitudinal study in patients with rheumatoid arthritis did find support for synchronous associations rather than sequential associations between fatigue and pain over a 12-month period (van Dartel et al., 2013), indicating that the evaluation of synchronous changes might capture effects more proximal in time than is possible with long measurement intervals.

9 Implications for Clinical Practice

Fatigue remains a symptom that is difficult to measure, understand and manage in clinical practice and rehabilitation. While some fatigue measures have proved to be psychometrically sound for research and clinical purposes, the vast potential for bias in responses to PROMs necessitates a more comprehensive clinical approach to dealing with individual patients suffering from fatigue. The clinical interview—informed by the current knowledge base, structured interview guides and case definitions such as the Lynch interview for stroke patients (Lynch et al., 2007) and the Clinical Interview for Fatigue Following Traumatic Brain Injury (Ouellet et al., 2019)—remains a necessary tool in determining the presence of pathological fatigue, its characteristics and its functional implications. Furthermore, the identification of potential modifiers of fatigue is likely best conducted through evidence-based clinical investigation of each patient's idiosyncratic experiences with fatigue, since one treatment alternative such as physical exercise might exacerbate fatigue for one person, and ameliorate it for another (Ezekiel et al., 2021).

The studies outlined have emphasised the relevance of pain, psychological distress, behavioural inhibition and somatic symptom burden as potential modifiers and within-subject covariates of fatigue, which should be addressed in treatment planning for patients with fatigue following TBI. Notably, these can be considered potentially viable targets for treatment in individually tailored rehabilitation. Between-subject correlates, such as trait neuroticism, may inform us about the risk for fatigue, but are not directly implicated in the exacerbation or amelioration of fatigue.

Furthermore, the findings of our studies may be used to inform clinical communication concerning fatigue, and remind us not to 'psychologise' the phenomenon any more or less than is beneficial to the treatment and outcome of individual patients. Fatigue has a considerable genetic component and some factors are associated with fatigue beyond shared genetic vulnerabilities, regardless of somatic comorbidity or—in the case of TBI—injury severity. While the injury severity indices in our study demonstrated significant associations with fatigue, the effects in question were minor. A comprehensive clinical evaluation should therefore incorporate premorbid experiences with fatigue and its management, considering the considerable contributions of genetic and lifetime vulnerabilities to fatigue. Pathological fatigue, however, which can be initiated by injury or disease, is influenced by an abundance of potentially modifiable biopsychosocial factors in acquired brain injury (Aarnes et al., 2020), which provides hope for future endeavours into exploring avenues for efficacious

treatments and methods for symptom alleviation. The relative stability of fatigue from 6 to 12 months following injury, however, indicates a need for interventions in the early phases following injury, before the pathological fatigue stabilises as a chronic, persistent symptom.

This thesis has illuminated several potential paths for clinicians aiming to improve the individualisation of treatment and rehabilitation and help people suffering from pathological fatigue in conjunction with TBI and other chronic illnesses. While earlier models for fatigue following TBI—such as the conceptual model by Mollayeva et al. (2014) and the empirically-based path model by Ponsford et al. (2015)—have clinical and research utility, our findings indicate a need for the development of multifactorial models with testable and potentially reciprocal influences between fatigue and its correlates. Although some factors are implicated as risk factors for fatigue, these might not inform us of why individual patients experience the amelioration or exacerbation of fatigue. Therefore, future clinically informative models should incorporate the possible complex interactions between within-person mechanisms if we aim to make these models applicable to the individually tailored rehabilitation of individual patients. Furthermore, our findings support the use of multimodal interventions for fatigue, since the demonstrated complexity of variables associated with the between-subject risk of fatigue and within-subject amelioration or exacerbation of fatigue necessitates an interdisciplinary approach to its assessment and management.

10 Conclusions and Future Directions

This thesis has illuminated several potential ways of understanding the relationships between fatigue and commonly implicated biopsychosocial variables. Through research design and statistical analyses we have attempted to control for many potential confounders in these relationships, to gain a more concise understanding of the development of fatigue. However, the exploratory nature of this study warrants scientific caution in extrapolating certainty regarding the relationships established in our study without the replication of these findings in other settings. The finding from Paper I that pain and psychological distress—two widely implicated correlates in the literature—were related to fatigue at both stable and time-varying levels, was, however, replicated in the clinical sample of patients with TBI in Paper III. As such, the potential causal relevance of pain and distress to fatigue should not be understated. However, the finding that behavioural inhibition and other somatic symptoms also covary with fatigue over time should be interpreted with greater caution, as these within-subject effects warrant further replication.

Furthermore, the use of multilevel methodology—which allows for the compartmentalisation of variance into between- and within-subject components—may improve our inferences on the nature of the crucial relations, with the potential to control for many sources of confounding in observational research. However, no design or methodology is without its caveats or limitations. Scientific triangulation using different methodological approaches might improve our pursuit of convergence towards certainty in our scientific findings regarding crucial mechanisms in fatigue (Hammerton & Munafò, 2021).

While our multifactorial approach to fatigue encompassed many correlates of fatigue, the abundance of measures involved may not always be practical or possible to measure in longitudinal studies of vulnerable patient groups. Therefore, this approach could be difficult to replicate in full. However, the segregation of stable and time-varying components of fatigue and its correlates can inform future studies, depending on the research questions posed. Studies aimed at characterising and better understanding those individuals at risk for fatigue would be well served by measuring or controlling for the established between-subject correlates of fatigue, such as trait neuroticism (a strong negative indicator of psychosocial robustness) and pain (a strong indicator of somatic vulnerability). However, studies aimed at characterising and understanding changes in fatigue across time would be well informed by also monitoring time-varying levels of pain, psychological distress, behavioural inhibition and somatic symptom burden. Together, these levels inform us of the characteristics of stability

and fluctuations in fatigue—both of which warrant further scientific scrutiny if a comprehensive understanding of fatigue is to be attained.

Through employing similar methodological approaches in two independent non-clinical and clinical samples, the findings indicate the clustering of common correlates of fatigue, and have informed us of the aetiological levels at which various biopsychosocial variables are associated with fatigue. Genetic factors contribute to fatigue and the associations commonly seen between fatigue and correlates such as psychological distress and pain; however, life experiences, disease and injuries might also uniquely contribute to the development of these factors irrespective of any potential influences between them. If we are to gain a more precise understanding of which biopsychosocial correlates are relevant to the amelioration and exacerbation of fatigue in TBI, other chronic illnesses and the general population, these genetic and lifetime vulnerabilities must be considered to understand which factors actually covary with—and could potentially influence—fatigue trajectories over time. This thesis has taken some steps towards disentangling direct effects from those due to mere confounding. However, much research remains in identifying all crucial factors with potential moderating or mediating effects on fatigue.

While this thesis has illustrated the use of multilevel methods when applied to two time points, future research monitoring fatigue and crucial time-varying correlates across several time points is also warranted. These findings should be replicated in further studies and improved and expanded upon through the inclusion of more measurements with different temporal sequencing (e.g., within days, or across days, weeks and months) to gain an understanding of the temporal dynamics of the crucial correlates of fatigue. Longitudinal studies with three—or preferably more—time points adopting similar approaches can also delineate either the uni- or bidirectional effects of within-subject correlates of fatigue through the use of time-lagged predictors within a multilevel framework to approach an improved understanding of causal paths underlying these relationships.

The segregation of between- and within-subject components of fatigue and correlates also has relevance for future intervention studies since the target outcome of fatigue interventions is within-subject improvements in fatigue rather than between-subject, group-level effects. The use of multilevel methods to control for the stable difference between subjects is thus a worthwhile endeavour with the potential to improve future clinical trials (Hilbert et al., 2019). Furthermore, our study has identified crucial within-subject correlates of

changes in fatigue in TBI towards which interventions might be targeted. This is in line with the concluding remarks in a recent review of intervention studies for fatigue in chronic illness (Hulme et al., 2018), where the need to identify transdiagnostic targets for fatigue interventions is emphasised.

In conclusion, individuals with TBI and other chronic illnesses carry unique strengths, vulnerabilities, values, goals and life stories. The recognition of this heterogeneity is crucial in improving future research. The use of methods that allow us to acknowledge, measure and control for this heterogeneity between individuals is essential if we are to better understand how and why fatigue fluctuates and develops within individuals over time. This thesis has demonstrated the usefulness of such an approach in the study of fatigue in patients with TBI and a sample of twins from the general population. Moreover, it has provided some novel ways of approaching and understanding fatigue for both future clinical and research endeavours.

11 References

Aarnes, R., Stubberud, J., & Lerdal, A. (2020). A literature review of factors associated with fatigue after stroke and a proposal for a framework for clinical utility. *Neuropsychological Rehabilitation, 30*(8), 1449–1476. https://doi.org/10.1080/09602011.2019.1589530

Aaronson, L. S., Teel, C. S., Cassmeyer, V., Neuberger, G. B., Pallikkathayil, L., Pierce, J., Press, A. N., Williams, P. D., & Wingate, A. (1999). Defining and measuring fatigue. *Journal of Nursing Scholarship, 31*(1), 45–50. https://doi.org/10.1111/j.1547-5069.1999.tb00420.x

Admon, R., & Pizzagalli, D. A. (2015). Dysfunctional reward processing in depression. *Current Opinion in Psychology, 4*(1), 114–118. https://doi.org/10.1016/j.copsyc.2014.12.011

Allison, P. D. (2009). *Fixed effects regression models*. California, USA: SAGE Publications.

Andelic, N., Røe, C., Brunborg, C., Zeldovich, M., Løvstad, M., Løke, D., Borgen, I. M., Voormolen, D. C., Howe, E. I., & Forslund, M. V. (2021). Frequency of fatigue and its changes in the first 6 months after traumatic brain injury: Results from the CENTER-TBI study. *Journal of Neurology, 268*(1), 61–73. https://doi.org/10.1089/neu.2013.3292

Andelic, N., Røe, C., Tenovuo, O., Azouvi, P., Dawes, H., Majdan, M., Ranta, J., Howe, E. I., Wiegers, E. J. A., & Tverdal, C. (2021). Unmet rehabilitation needs after traumatic brain injury across Europe: Results from the CENTER-TBI study. *Journal of Clinical Medicine, 10*(5), 1-18. https://doi.org/10.3390/jcm10051035

Andelic, N., Soberg, H. L., Berntsen, S., Sigurdardottir, S., & Roe, C. (2014). Self-perceived health care needs and delivery of health care services 5 years after moderate-to-severe traumatic brain injury. *Physical Medicine & Rehabilitation (PM&R), 6*(11), 1013–1021. https://doi.org/10.1016/j.pmrj.2014.05.005

Ashman, T. A., Cantor, J. B., Gordon, W. A., Spielman, L., Egan, M., Ginsberg, A., Engmann, C., Dijkers, M., & Flanagan, S. (2008). Objective measurement of fatigue following traumatic brain injury. *The Journal of Head Trauma Rehabilitation*, 23(1), 33–40. https://doi.org/10.1097/01.HTR.0000308719.70288.22

Association for the Advancement of Automotive Medicine. (1998). *Abbreviated injury scale; 1990 revision: Update 98 [Manual]*. Barrington, IL, USA: Association for the Advancement of Automotive Medicine.

Barroso, J., Hammill, B. G., Leserman, J., Salahuddin, N., Harmon, J. L., & Pence, B. W. (2010). Physiological and psychosocial factors that predict HIV-related fatigue. *AIDS and Behavior, 14*(6), 1415–1427. https://doi.org/10.1007/s10461-010-9691-2

Bastien, C. H., Vallières, A., & Morin, C. M. (2001). Validation of the Insomnia Severity Index as an outcome measure for insomnia research. *Sleep Medicine, 2*(4), 297–307. https://doi.org/10.1016/S1389-9457(00)00065-4

Beaulieu-Bonneau, S., & Ouellet, M. C. (2017). Fatigue in the first year after traumatic brain injury: Course, relationship with injury severity, and correlates. *Neuropsychological Rehabilitation*, *27*(7), 983–1001. https://doi.org/10.1080/09602011.2016.1162176

Bechara, A. (2016). *Iowa gambling task professional manual. Version 2*. Psychological Assessment Resources, Inc.

Bell, A., Fairbrother, M., & Jones, K. (2019). Fixed and random effects models: Making an informed choice. *Quality & Quantity*, *53*(2), 1051–1074. https://doi.org/10.1007/s11135-018-0802-x

Belmont, A., Agar, N., Hugeron, C., Gallais, B., & Azouvi, P. (2006). Fatigue and traumatic brain injury. *Annales de Readaptation et de Medecine Physique*, *49*(6), 370–374. https://doi.org/10.1016/j.annrmp.2006.04.018

Bender, R., & Lange, S. (2001). Adjusting for multiple testing—when and how? *Journal of Clinical Epidemiology*, *54*(4), 343–349. https://doi.org/10.1016/S0895-4356(00)00314-0

Bensing, J. M., Hulsman, R. L., & Schreurs, K. M. G. (1999). Gender differences in fatigue: Biopsychosocial factors relating to fatigue in men and women. *Medical Care*, 1078–1083. https://doi.org/10.1097/00005650-199910000-00011

Bileviciute-Ljungar, I., Schult, M.-L., Borg, K., & Ekholm, J. (2020). Preliminary ICF core set for patients with myalgic encephalomyelitis/chronic fatigue syndrome in rehabilitation medicine. *Journal of Rehabilitation Medicine*, *52*(6), jrm00074.

Boksem, M. A. S., & Tops, M. (2008). Mental fatigue: Costs and benefits. *Brain Research Reviews*, 59(1), 125–139. https://doi.org/10.1016/j.brainresrev.2008.07.001

Bondy, E., Baranger, D. A. A., Balbona, J., Sputo, K., Paul, S. E., Oltmanns, T. F., & Bogdan, R. (2021). Neuroticism and reward-related ventral striatum activity: Probing vulnerability to stress-related depression. *Journal of Abnormal Psychology*, *130*(3), 223-235. https://doi.org/10.1037/abn0000618

Bossola, M., Angioletti, L., di Stasio, E., Vulpio, C., de Filippis, D., & Balconi, M. (2020). Reward (BIS/BAS) mechanisms and fatigue in patients on chronic hemodialysis. *Psychology, Health & Medicine*, *25*(6), 710–718. https://doi.org/10.1080/13548506.2019.1653477

Bower, J. E. (2019). The role of neuro-immune interactions in cancer-related fatigue: Biobehavioral risk factors and mechanisms. *Cancer*, *125*(3), 353–364. https://doi.org/10.1002/cncr.31790

Brähler, E., & Scheer, J. W. (1995). *Der gießener beschwerdebogen:(GBB)*. Bern, Switzerland: Huber.

Brommer, J. E., & Class, B. (2015). The importance of genotype-by-age interactions for the development of repeatable behavior and correlated behaviors over lifetime. *Frontiers in Zoology*, *12*(1), 1–13. https://doi.org/10.1186/1742-9994-12-S1-S2

Brown, A., & Jason, L. A. (2020). Meta-analysis investigating post-exertional malaise between patients and controls. *Journal of Health Psychology*, *25*(13–14), 2053–2071. https://doi.org/10.1177/1359105318784161

Brugha, T. S., & Cragg, D. (1990). The list of threatening experiences: the reliability and validity of a brief life events questionnaire. *Acta Psychiatrica Scandinavica*, *82*(1), 77–81. https://doi.org/10.1111/j.1600-0447.1990.tb01360.x

Bruns Jr, J., & Hauser, W. A. (2003). The epidemiology of traumatic brain injury: a review. *Epilepsia*, *44(Suppl. 10)*, 2–10. https://doi.org/10.1046/j.1528-1157.44.s10.3.x

Burri, A., Ogata, S., Livshits, G., & Williams, F. (2015). The association between chronic widespread musculoskeletal pain, depression and fatigue is genetically mediated. *PLoS ONE*, *10*(11). https://doi.org/10.1371/journal.pone.0140289

Bushnik, T., Englander, J., & Wright, J. (2008). Patterns of fatigue and its correlates over the first 2 years after traumatic brain injury. *The Journal of Head Trauma Rehabilitation*, *23*(1), 25–32. https://doi.org/10.1097/01.HTR.0000308718.88214.bb

Calderwood, C., & Ackerman, P. L. (2011). The relative impact of trait and temporal determinants of subjective fatigue. *Personality and Individual Differences*, *50*(4), 441–445. https://doi.org/10.1016/j.paid.2010.10.030

Cantor, J. B., Ashman, T., Gordon, W., Ginsberg, A., Engmann, C., Egan, M., Spielman, L., Dijkers, M., & Flanagan, S. (2008). Fatigue after traumatic brain injury and its impact on participation and quality of life. *The Journal of Head Trauma Rehabilitation*, *23*(1), 41–51. https://doi.org/10.1097/01.HTR.0000308720.70288.af

Cantor, J. B., Bushnik, T., Cicerone, K., Dijkers, M. P., Gordon, W., Hammond, F. M., Kolakowsky-Hayner, S. A., Lequerica, A., Nguyen, M., & Spielman, L. A. (2012). Insomnia, fatigue, and sleepiness in the first 2 years after traumatic brain injury: An NIDRR TBI model system module study. *Journal of Head Trauma Rehabilitation*, *27*(6), E1-E14. https://doi.org/10.1097/HTR.0b013e318270f91e

Cantor, J. B., Gordon, W., & Gumber, S. (2013). What is post TBI fatigue? *NeuroRehabilitation*, *32*(4), 875–883. https://doi.org/10.3233/NRE-130912

Carver, C. S., & White, T. L. (1994). Behavioral Inhibition, Behavioral Activation, and Affective Responses to Impending Reward and Punishment: The BIS/BAS Scales. *Journal of Personality and Social Psychology*, 67(2), 319–333. https://doi.org/10.1037/0022-3514.67.2.319

Cella, D., Lai, J., Chang, C., Peterman, A., & Slavin, M. (2002). Fatigue in cancer patients compared with fatigue in the general United States population. *Cancer*, *94*(2), 528–538. https://doi.org/10.1002/cncr.10245

Chalder, T., Berelowitz, G., Pawlikowska, T., Watts, L., Wessely, S., Wright, D., & Wallace, E. P. (1993). Development of a fatigue scale. *Journal of Psychosomatic Research*, *37*(2), 147–153. https://doi.org/10.1016/0022-3999(93)90081-P

Charles, S. T., Gatz, M., Kato, K., & Pedersen, N. L. (2008). Physical health 25 years later: The predictive ability of neuroticism. *Health Psychology*, *27*(3), 369–378. https://doi.org/10.1037/0278-6133.27.3.369

Chaudhuri, A., & Behan, P. O. (2000). Fatigue and basal ganglia. *Journal of the Neurological Sciences*, 179(1-2), 34-42. https://doi.org/10.1016/S0022-510X(00)00411-1

Chaudhuri, A., & Behan, P. O. (2004). Fatigue in neurological disorders. *The Lancet*, *363*(9413), 978–988. https://doi.org/10.1016/S0140-6736(04)15794-2

Choi, B. C. K., & Pak, A. W. P. (2005). A catalog of biases in questionnaires. *Preventing Chronic Disease*, *2*(1), 1-13. Retrieved from https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1323316/

Christodoulou, C. (2005). The assessment and measurement of fatigue. In J. Deluca (Ed.), *Fatigue as a Window to the Brain* (p. 19–35). Cambridge, USA: MIT Press

Christodoulou, C. (2017). Approaches to the measurement of fatigue. In G. Matthews, P. A. Desmond, C. Neubauer & P. A. Hancock (Eds.), *The Handbook of Operator Fatigue* (p. 125–138). London, UK: CRC Press.

Conners, C. K. (2014). *Conners continuous performance test 3rd edition, technical manual*. Toronto, Canada: Multi-Health Systems Inc.

Corfield, E. C., Martin, N. G., & Nyholt, D. R. (2017). Familiality and heritability of fatigue in an Australian twin sample. *Twin Research and Human Genetics*, *20*(3), 208–215. https://doi.org/10.1017/thg.2017.22

Corrigan, J. D., & Hammond, F. M. (2013). Traumatic brain injury as a chronic health condition. *Archives of Physical Medicine and Rehabilitation*, *94*(6), 1199–1201. https://doi.org/10.1016/j.apmr.2013.01.023

Crichton, T., Singh, R., Abosi-Appeadu, K., & Dennis, G. (2020). Excessive daytime sleepiness after traumatic brain injury. *Brain Injury*, *34*(11), 1525–1531. https://doi.org/10.1080/02699052.2020.1810316

Davis, K. D., & Cheng, J. C. (2019). Differentiating trait pain from state pain: A window into brain mechanisms underlying how we experience and cope with pain. *Pain Reports*, *4*(4), 1-6. https://doi.org/10.1097/PR9.0000000000000735

Delis, D. C., Kaplan, E., & Kramer, J. H. (2001). *Delis-Kaplan executive function system*. [Database record]. APA PsycTests. https://doi.org/10.1037/t15082-000

DeLuca, J. E. (2005). *Fatigue as a Window to the Brain.* Camrbdige, USA: MIT press.

Derogatis, L. R., Lipman, R. S., Rickels, K., Uhlenhuth, E. H., & Covi, L. (1974). The Hopkins Symptom Checklist (HSCL): A self-report symptom inventory. *Behavioral Science*, *19*(1), 1–15. https://doi.org/10.1002/bs.3830190102

Dewan, M. C., Rattani, A., Gupta, S., Baticulon, R. E., Hung, Y.-C., Punchak, M., Agrawal, A., Adeleye, A. O., Shrime, M. G., & Rubiano, A. M. (2018). Estimating

the global incidence of traumatic brain injury. *Journal of Neurosurgery*, *130*(4), 1080–1097. https://doi.org/10.3171/2017.10.JNS17352

Dobryakova, E., DeLuca, J., Genova, H. M., & Wylie, G. R. (2013). Neural correlates of cognitive fatigue: Cortico-striatal circuitry and effort–reward imbalance. *Journal of the International Neuropsychological Society*, *19*(8), 849–853. https://doi.org/10.1017/S1355617713000684

Dobryakova, E., Genova, H., Schneider, V., Chiaravalloti, N. D., Spirou, A., Wylie, G. R., & DeLuca, J. (2020). Reward presentation reduces on-task fatigue in traumatic brain injury. *Cortex*, *126*, 16–25. https://doi.org/10.1016/j.cortex.2020.01.003

Doyle, D. J., & Garmon, E. H. (2018). American Society of Anesthesiologists Classification (ASA Class). Treasure Island FL, USA: StatPearls Publishing LLC.

Engel, G. L. (1977). The need for a new medical model: A challenge for biomedicine. *Science*, *196*(4286), 129–136. https://doi.org/10.1126/science.847460

Engel, G. L. (1981). The clinical application of the biopsychosocial model. *The Journal of Medicine and Philosophy: A Forum for Bioethics and Philosophy of Medicine*, *6*(2), 101–124. https://doi.org/10.1093/jmp/6.2.101

Enoka, R. M., & Duchateau, J. (2016). Translating fatigue to human performance. *Medicine and Science in Sports and Exercise*, *48*(11), 2228. https://doi.org/10.1249/MSS.0000000000000929

Evengård, B., Jacks, A., Pedersen, N. L., & Sullivan, P. F. (2005). The epidemiology of chronic fatigue in the Swedish Twin Registry. *Psychological Medicine*, *35*(9), 1317–1326. https://doi.org/10.1017/S0033291705005052

Ezekiel, L., Field, L., Collett, J., Dawes, H., & Boulton, M. (2021). Experiences of fatigue in daily life of people with acquired brain injury: A qualitative study. *Disability and Rehabilitation*, *43*(20), 2866–2874. https://doi.org/10.1080/09638288.2020.1720318

Fazel, S., Wolf, A., Pillas, D., Lichtenstein, P., & Långström, N. (2014). Suicide, fatal injuries, and other causes of premature mortality in patients with traumatic brain injury: a 41-year Swedish population study. *JAMA Psychiatry*, *71*(3), 326–333. https://doi.org/10.1001/jamapsychiatry.2013.3935

Felson, J. (2014). What can we learn from twin studies? A comprehensive evaluation of the equal environments assumption. *Social Science Research*, *43*, 184–199. https://doi.org/10.1016/j.ssresearch.2013.10.004

Finsterer, J., & Mahjoub, S. Z. (2014). Fatigue in healthy and diseased individuals. *American Journal of Hospice and Palliative Medicine*, *31*(5), 562–575. https://doi.org/10.1177/1049909113494748

Fisher, A. J., Medaglia, J. D., & Jeronimus, B. F. (2018). Lack of group-to-individual generalizability is a threat to human subjects research. *Proceedings of the National Academy of Sciences*, *115*(27), E6106–E6115. https://doi.org/10.1073/pnas.1711978115

Flehmig, H. C., Steinborn, M., Langner, R., Scholz, A., & Westhoff, K. (2007). Assessing intraindividual variability in sustained attention: Reliability, relation to speed and accuracy, and practice effects. *Psychology Science*, *49*(2), 132-149.

Folkehelseinstituttet. (2018). *Om Nasjonalt tvillingregister*. Retrieved from https://www.fhi.no/div/helseundersokelser/tvilling/om-nasjonalt-tvillingregister/

Foreman, B. P., Caesar, R. R., Parks, J., Madden, C., Gentilello, L. M., Shafi, S., Carlile, M. C., Harper, C. R., & Diaz-Arrastia, R. R. (2007). Usefulness of the abbreviated injury score and the injury severity score in comparison to the Glasgow Coma Scale in predicting outcome after traumatic brain injury. *Journal of Trauma and Acute Care Surgery*, *62*(4), 946–950. https//doi.org/10.1097/01.ta.0000229796.14717.3a

Frost, R. B., Farrer, T. J., Primosch, M., & Hedges, D. W. (2013). Prevalence of traumatic brain injury in the general adult population: A meta-analysis. *Neuroepidemiology*, *40*(3), 154–159. https://doi.org/10.1159/000343275

Gray, J. A. (1981). A critique of Eysenck's theory of personality. In H. J. Eysenck (Ed.), *A model for personality* (p. 246–276). New York, USA: Springer.

Greeke, E. E., Chua, A. S., Healy, B. C., Rintell, D. J., Chitnis, T., & Glanz, B. I. (2017). Depression and fatigue in patients with multiple sclerosis. *Journal of the Neurological Sciences*, *380*, 236–241. https://doi.org/10.1016/j.jns.2017.07.047

Grimes, D. A., & Schulz, K. F. (2002). Bias and causal associations in observational research. *The Lancet*, *359*(9302), 248–252. https://doi.org/10.1016/S0140-6736(02)07451-2

Hamaker, E. L. (2012). Why researchers should think" within-person": A paradigmatic rationale. In M. R. Mehl & T. S. Conner (Eds.), *Handbook of Research Methods for Studying Daily Life* (p. 43–61). New York, USA: The Guilford Press.

Hamaker, E. L., Kuiper, R. M., & Grasman, R. P. P. P. (2015). A critique of the cross-lagged panel model. *Psychological Methods*, *20*(1), 102-116. https://doi.org/10.1037/a0038889

Hamaker, E. L., & Muthén, B. (2020). The fixed versus random effects debate and how it relates to centering in multilevel modeling. *Psychological Methods*, *25*(3), 365-379. https://doi.org/10.1037/met0000239

Hammerton, G., & Munafò, M. R. (2021). Causal inference with observational data: The need for triangulation of evidence. *Psychological Medicine*, *51*(4), 563–578. https://doi.org/10.1017/S0033291720005127

Happe, S. (2003). Excessive daytime sleepiness and sleep disturbances in patients with neurological diseases. *Drugs*, *63*(24), 2725–2737. https://doi.org/10.2165/00003495-200363240-00003

Hickie, I., Kirk, K., & Martin, N. (1999). Unique genetic and environmental determinants of prolonged fatigue: A twin study. *Psychological Medicine*, *29*(2), 259–268. https://doi.org/10.1017/S0033291798007934

Hilbert, S., Stadler, M., Lindl, A., Naumann, F., & Bühner, M. (2019). Analyzing longitudinal intervention studies with linear mixed models. *TPM: Testing, Psychometrics, Methodology in Applied Psychology, 26*(1), 101-119. https://doi.org/10.4473/TPM26.1.6

Hjemdal, O., Friborg, O., Braun, S., Kempenaers, C., Linkowski, P., & Fossion, P. (2011). The Resilience Scale for Adults: Construct validity and measurement in a Belgian sample. *International Journal of Testing*, *11*(1), 53–70. https://doi.org/10.1080/15305058.2010.508570

Hockey, R. (2013). *The psychology of fatigue: Work, effort and control*. Cambridge, UK: Cambridge University Press.

Hoffman, L. (2007). Multilevel models for examining individual differences in within-person variation and covariation over time. *Multivariate Behavioral Research*, *42*(4), 609–629. https://doi.org/10.1080/00273170701710072

Holmqvist, A., Lindstedt, M. B., & Möller, M. C. (2018). Relationship between fatigue after acquired brain injury and depression, injury localization and aetiology: an explorative study in a rehabilitation setting. *Journal of Rehabilitation Medicine*, *50*(8), 725–731. https://doi.org/10.2340/16501977-2365

Hulme, K., Safari, R., Thomas, S., Mercer, T., White, C., van der Linden, M., & Moss-Morris, R. (2018). Fatigue interventions in long term, physical health conditions: A scoping review of systematic reviews. *PloS One*, *13*(10), 1-12. https://doi.org/10.1371/journal.pone.0203367

IBM Corp. (2020). *IBM SPSS Statistics for Windows* (Version 27). New York: IBM Corp.

Jaime-Lara, R. B., Koons, B. C., Matura, L. A., Hodgson, N. A., & Riegel, B. (2020). A qualitative metasynthesis of the experience of fatigue across five chronic Conditions. *Journal of Pain and Symptom Management*, 59(6), 1320–1343. https://doi.org/10.1016/j.jpainsymman.2019.12.358

Jaremka, L. M., Andridge, R. R., Fagundes, C. P., Alfano, C. M., Povoski, S. P., Lipari, A. M., Agnese, D. M., Arnold, M. W., Farrar, W. B., & Yee, L. D. (2014). Pain, depression, and fatigue: Loneliness as a longitudinal risk factor. *Health Psychology*, *33*(9), 948-957. https://doi.org/10.1037/a0034012

Jason, L. A., Evans, M., Brown, M., & Porter, N. (2010). What is fatigue? Pathological and nonpathological fatigue. *Physical Medicine and Rehabilitation (PM&R)*, *2*(5), 327–331. https://doi.org/10.1016/j.pmrj.2010.03.028

Johansson, B., Berglund, P., & Rönnbäck, L. (2009). Mental fatigue and impaired information processing after mild and moderate traumatic brain injury. *Brain Injury*, *23*(13–14), 1027–1040. https://doi.org/10.3109/02699050903421099

Johns, M. W. (1991). A new method for measuring daytime sleepiness: The Epworth sleepiness scale. *Sleep*, *14*(6), 540–545. https://doi.org/10.1093/sleep/14.6.540

Jonasson, A., Levin, C., Renfors, M., Strandberg, S., & Johansson, B. (2018). Mental fatigue and impaired cognitive function after an acquired brain injury. *Brain and Behavior*, *8*(8), 1-7. https://doi.org/10.1002/brb3.1056

Jourdan, C., Bayen, E., Pradat-Diehl, P., Ghout, I., Darnoux, E., Azerad, S., Vallat-Azouvi, C., Charanton, J., Aegerter, P., Ruet, A., & Azouvi, P. (2016). A comprehensive picture of 4-year outcome of severe brain injuries. Results from the PariS-TBI study. *Annals of Physical and Rehabilitation Medicine*, *59*(2), 100–106. https://doi.org/10.1016/j.rehab.2015.10.009

Juengst, S., Skidmore, E., Arenth, P. M., Niyonkuru, C., & Raina, K. D. (2013). Unique contribution of fatigue to disability in community-dwelling adults with traumatic brain injury. *Archives of Physical Medicine and Rehabilitation*, *94*(1), 74–79. https://doi.org/10.1016/j.apmr.2012.07.025

Kennedy, J. E., Jaffee, M. S., Leskin, G. A., Stokes, J. W., Leal, F. O., & Fitzpatrick, P. J. (2007). Posttraumatic stress disorder and posttraumatic stress disorder-like symptoms and mild traumatic brain injury. *Journal of Rehabilitation Research and Development*, *44*(7), 895-919. https://doi.org/10.1682/JRRD.2006.12.0166

King, N. S., Crawford, S., Wenden, F. J., Moss, N. E. G., & Wade, D. T. (1995). The Rivermead Post Concussion Symptoms Questionnaire: A measure of symptoms commonly experienced after head injury and its reliability. *Journal of Neurology*, *242*(9), 587–592. https://doi.org/10.1007/BF00868811

Kjeverud, A., Andersson, S., Lerdal, A., Schanke, A.-K., & Østlie, K. (2021). A cross-sectional study exploring overlap in post-stroke fatigue caseness using three fatigue instruments: Fatigue Severity Scale, Fatigue Questionnaire and the Lynch's Clinical Interview. *Journal of Psychosomatic Research*, *150*, 1-7. https://doi.org/10.1016/j.jpsychores.2021.110605

Kluger, B. M., Krupp, L. B., & Enoka, R. M. (2013). Fatigue and fatigability in neurologic illnesses: Proposal for a unified taxonomy. *Neurology*, *80*(4), 409–416. https://doi.org/10.1212/WNL.0b013e31827f07be

Kohl, A. D., Wylie, G. R., Genova, H. M., Hillary, F. G., & DeLuca, J. (2009). The neural correlates of cognitive fatigue in traumatic brain injury using functional MRI. *Brain Injury*, *23*(5), 420–432. https://doi.org/10.1080/02699050902788519

Kratz, A. L., Murphy, S. L., & Braley, T. J. (2017). Pain, fatigue, and cognitive symptoms are temporally associated within but not across days in multiple Sclerosis. *Archives of Physical Medicine and Rehabilitation*, *98*(11), 2151–2159. https://doi.org/10.1016/j.apmr.2017.07.003

Krupp, L. B., LaRocca, N. G., Muir-Nash, J., & Steinberg, A. D. (1989). The fatigue severity scale: Application to patients with multiple sclerosis and systemic lupus erythematosus. *Archives of Neurology*, *46*(10), 1121–1123.

Kumar, R. G., Ornstein, K. A., Bollens-Lund, E., Watson, E. M., Ankuda, C. K., Kelley, A. S., & Dams-O'Connor, K. (2020). Lifetime history of traumatic brain injury is associated with increased loneliness in adults: A US nationally representative study.

International Journal of Geriatric Psychiatry, *35*(5), 553–563. https://doi.org/10.1002/gps.5271

Kuorinka, I., Jonsson, B., Kilbom, A., Vinterberg, H., Biering-Sørensen, F., Andersson, G., & Jørgensen, K. (1987). Standardised Nordic questionnaires for the analysis of musculoskeletal symptoms. *Applied Ergonomics*, *18*(3), 233–237. https://doi.org/10.1016/0003-6870(87)90010-X

Kwok, O.-M., Underhill, A. T., Berry, J. W., Luo, W., Elliott, T. R., & Yoon, M. (2008). Analyzing longitudinal data with multilevel models: An example with individuals living with lower extremity intra-articular fractures. *Rehabilitation Psychology*, *53*(3), 370-386. https://doi.org/10.1037/a0012765

Landmark-Høyvik, H., Reinertsen, K. v., Loge, J. H., Kristensen, V. N., Dumeaux, V., Fosså, S. D., Børresen-Dale, A. L., & Edvardsen, H. (2010). The genetics and epigenetics of fatigue. *Physical Medicine and Rehabilitation (PM&R)*, *2*(5), 456–465. https://doi.org/10.1016/j.pmrj.2010.04.003

Lau, C. G., Tang, W. K., Liu, X. X., Liang, H. J., Liang, Y., Mok, V., Wong, A., Ungvari, G. S., Kutlubaev, M. A., & Wong, K. S. (2017). Neuroticism and fatigue 3 months after ischemic stroke: a cross-sectional study. *Archives of Physical Medicine and Rehabilitation*, *98*(4), 716–721. https://doi.org/10.1016/j.apmr.2016.08.480

Lenaert, B., Meulders, A., & van Heugten, C. M. (2018). Tired of pain or painfully tired? A reciprocal relationship between chronic pain and fatigue. *Pain*, *159*(6), 1178–1179. https://doi.org/10.1097/j.pain.0000000000001194

Lerdal, A., Moum, T., Wahl, A. K., Rustøen, T., & Hanestad, B. R. (2005). Fatigue in the general population: A translation and test of the psychometric properties of the Norwegian version of the Fatigue Severity Scale. *Scandinavian Journal of Public Health*, *33*(2), 123–130. https://doi.org/10.1080/14034940410028406

Loge, J. H., Ekeberg, Ø., & Kaasa, S. (1998). Fatigue in the general Norwegian population: Normative data and associations. *Journal of Psychosomatic Research*, *45*(1), 53–65. https://doi.org/10.1016/S0022-3999(97)00291-2

Losoi, H., Wäljas, M., Turunen, S., Brander, A., Helminen, M., Luoto, T. M., Rosti-Otajärvi, E., Julkunen, J., & Öhman, J. (2015). Resilience is associated with fatigue after mild traumatic brain injury. *The Journal of Head Trauma Rehabilitation*, *30*(3), E24–E32. https://doi.org/10.1097/HTR.0000000000000055

Lynch, J., Mead, G., Greig, C., Young, A., Lewis, S., & Sharpe, M. (2007). Fatigue after stroke: the development and evaluation of a case definition. *Journal of Psychosomatic Research*, *63*(5), 539–544. https://doi.org/10.1016/j.jpsychores.2007.08.004

Maas, A. I. R., Hukkelhoven, C. W. P. M., Marshall, L. F., & Steyerberg, E. W. (2005). Prediction of outcome in traumatic brain injury with computed tomographic characteristics: A comparison between the computed tomographic classification and

combinations of computed tomographic predictors. *Neurosurgery, 57*(6), 1173–1182. https://doi.org/10.1227/01.neu.0000186013.63046.6b

Maas, A. I. R., Menon, D. K., Adelson, P. D., Andelic, N., Bell, M. J., Belli, A., Bragge, P., Brazinova, A., Büki, A., & Chesnut, R. M. (2017). Traumatic brain injury: Integrated approaches to improve prevention, clinical care, and research. *The Lancet Neurology, 16*(12), 987–1048. https://doi.org/0.1016/S1474-4422(17)30371-X

Malloy, S., Genova, H., Chiaravalloti, N., DeLuca, J., Holtzheimer, P., & Wylie, G. R. (2021). Cognitive fatigue in traumatic brain injury: A pilot study comparing state and trait fatigue. *Brain Injury, 35*(10), 1254–1258. https://doi.org/10.1080/02699052.2021.1972144

Manierre, M., Jansen, E., & Boolani, A. (2020). Sleep quality and sex modify the relationships between trait energy and fatigue on state energy and fatigue. *PloS One, 15*(1), 1-14. https://doi.org/10.1371/journal.pone.0227511

Manskow, U. S., Friborg, O., Røe, C., Braine, M., Damsgard, E., & Anke, A. (2017). Patterns of change and stability in caregiver burden and life satisfaction from 1 to 2 years after severe traumatic brain injury: A Norwegian longitudinal study. *NeuroRehabilitation, 40*(2), 211–222. https://doi.org/10.3233/NRE-161406

Marinescu, I. E., Lawlor, P. N., & Kording, K. P. (2018). Quasi-experimental causality in neuroscience and behavioural research. *Nature Human Behaviour, 2*(12), 891–898. https://doi.org/10.1038/s41562-018-0466-5

McBeth, J., Tomenson, B., Chew-Graham, C. A., Macfarlane, G. J., Jackson, J., Littlewood, A., & Creed, F. H. (2015). Common and unique associated factors for medically unexplained chronic widespread pain and chronic fatigue. *Journal of Psychosomatic Research, 79*(6), 484–491. https://doi.org/10.1016/j.jpsychores.2015.10.004

McCrae, R. R., & Costa, P. T. (2010). *NEO inventories for the NEO personality inventory-3 (NEO-PI-3), NEO five-factor inventory-3 (NEO-FFI-3), NEO personality inventory-revised (NEO PI-R): Professional manual*. Lutz, USA: Psychological Assessment Resources.

McGue, M., Osler, M., & Christensen, K. (2010). Causal inference and observational research: The utility of twins. *Perspectives on Psychological Science*, 5(5), 546–556. https://doi.org/10.1177/1745691610383511

Menon, D. K., Schwab, K., Wright, D. W., & Maas, A. I. (2010). Position statement: Definition of traumatic brain injury. *Archives of Physical Medicine and Rehabilitation*, 91(11), 1637–1640. https://doi.org/10.1016/j.apmr.2010.05.017

Menting, J., Tack, C. J., Bleijenberg, G., Donders, R., Fortuyn, H. A. D., Fransen, J., Goedendorp, M. M., Kalkman, J. S., Strik-Albers, R., van Alfen, N., van der Werf, S. P., Voermans, N. C., van Engelen, B. G., & Knoop, H. (2018). Is fatigue a disease-specific or generic symptom in chronic medical conditions? *Health Psychology, 37*(6), 530–543. https://doi.org/10.1037/hea0000598

Merz, Z. C., Zane, K., Emmert, N. A., Lace, J., & Grant, A. (2019). Examining the relationship between neuroticism and post-concussion syndrome in mild traumatic brain injury. *Brain Injury*, *33*(8), 1003–1011. https://doi.org/10.1080/02699052.2019.1581949

Mollayeva, T., Kendzerska, T., Mollayeva, S., Shapiro, C. M., Colantonio, A., & Cassidy, J. D. (2014). A systematic review of fatigue in patients with traumatic brain injury: the course, predictors and consequences. *Neuroscience & Biobehavioral Reviews*, *47*, 684–716. https://doi.org/10.1016/j.neubiorev.2014.10.024

Nadarajah, M., & Goh, H. T. (2015). Post-stroke fatigue: A review on prevalence, correlates, measurement, and management. *Topics in Stroke Rehabilitation,* 22(3), 208–220. https://doi.org/10.1179/1074935714Z.0000000015

Newland, P., Starkweather, A., & Sorenson, M. (2016). Central fatigue in multiple sclerosis: A review of the literature. *The Journal of Spinal Cord Medicine*, *39*(4), 386–399. https://doi.org/10.1080/10790268.2016.1168587

Newman, D. A. (2014). Missing data: Five practical guidelines. *Organizational Research Methods*, *17*(4), 372–411. https://doi.org/10.1177/1094428114548590

Nilsen, T. S., Knudsen, G. P., Gervin, K., Brandt, I., Roysamb, E., Tambs, K., Orstavik, R., Lyle, R., Reichborn-Kjennerud, T., Magnus, P., & Harris, J. R. (2013). The Norwegian Twin Registry from a public health perspective: A research update. *Twin Research and Human Genetics*, *16*(1), 285–295. https://doi.org/10.1017/thg.2012.117

Norrie, J., Heitger, M., Leathem, J., Anderson, T., Jones, R., & Flett, R. (2010). Mild traumatic brain injury and fatigue: A prospective longitudinal study. *Brain Injury*, *24*(13–14), 1528–1538. https://doi.org/10.3109/02699052.2010.531687

Ouellet, M.-C., Beaulieu-Bonneau, S., Savard, J., & Morin, C. M. (2019). *Insomnia and Fatigue After Traumatic Brain Injury: A CBT Approach to Assessment and Treatment*. Cambridge, USA: Academic Press.

Ouellet, M.-C., & Morin, C. M. (2007). Efficacy of cognitive-behavioral therapy for insomnia associated with traumatic brain injury: a single-case experimental design. *Archives of Physical Medicine and Rehabilitation*, *88*(12), 1581–1592. https://doi.org/10.1016/j.apmr.2007.09.006

Pardini, M., Capello, E., Krueger, F., Mancardi, G., & Uccelli, A. (2013). Reward responsiveness and fatigue in multiple sclerosis. *Multiple Sclerosis Journal*, *19*(2), 233–240. https://doi.org/10.1177/1352458512451509

Patil, V. H., Singh, S. N., Mishra, S., & Donavan, D. T. (2017). *Parallel analysis engine to aid in determining number of factors to retain using R [Computer software]*. Gonzaga University, School of Business Administration Spokane, WA. Accessed at https://analytics.gonzaga.edu/parallelengine/

Pattyn, N., van Cutsem, J., Dessy, E., & Mairesse, O. (2018). Bridging exercise science, cognitive psychology, and medical practice: Is “cognitive fatigue” a remake of “the

emperor's new clothes"? *Frontiers in Psychology*, *9*, 1-13. https://doi.org/10.3389/fpsyg.2018.01246

Pavlovic, N. V, Gilotra, N. A., Lee, C. S., Ndumele, C., Mammos, D., Dennisonhimmelfarb, C., & AbshireSaylor, M. (2021). Fatigue in persons with heart failure: A systematic literature review and meta-synthesis using the biopsychosocial model of health. *Journal of Cardiac Failure,* 28(2), 283-315. https://doi.org/10.1016/j.cardfail.2021.07.005

Pawlikowska, T., Chalder, T., Hirsch, S. R., Wallace, P., Wright, D. J. M., & Wessely, S. C. (1994). Population based study of fatigue and psychological distress. *British Medical Journal (BMJ)*, *308*(6931), 763–766. https://doi.org/10.1136/bmj.308.6931.763

Peeters, W., van den Brande, R., Polinder, S., Brazinova, A., Steyerberg, E. W., Lingsma, H. F., & Maas, A. I. R. (2015). Epidemiology of traumatic brain injury in Europe. *Acta Neurochirurgica*, *157*(10), 1683–1696. https://doi.org/10.1007/s00701-015-2512-7

Penner, I. K., & Paul, F. (2017). Fatigue as a symptom or comorbidity of neurological diseases. *Nature Reviews Neurology*, 13(11), 662–675. https://doi.org/10.1038/nrneurol.2017.117

Ponsford, J. L. (2013). Factors contributing to outcome following traumatic brain injury. *NeuroRehabilitation*, *32*(4), 803–815. https://doi.org/10.3233/NRE-130904

Ponsford, J. L., Downing, M. G., Olver, J., Ponsford, M., Acher, R., Carty, M., & Spitz, G. (2014). Longitudinal follow-up of patients with traumatic brain injury: Outcome at two, five, and ten years post-injury. *Journal of Neurotrauma*, *31*(1), 64–77. https://doi.org/10.1089/neu.2013.2997

Ponsford, J. L., & Sinclair, K. L. (2014). Sleep and fatigue following traumatic brain injury. *Psychiatric Clinics*, *37*(1), 77–89. https://doi.org/10.1016/j.psc.2013.10.001

Ponsford, J. L., Ziino, C., Parcell, D. L., Shekleton, J. A., Roper, M., Redman, J. R., Phipps-Nelson, J., & Rajaratnam, S. M. W. (2012). Fatigue and sleep disturbance following traumatic brain injury—their nature, causes, and potential treatments. *The Journal of Head Trauma Rehabilitation*, *27*(3), 224–233. https://doi.org/10.1097/HTR.0b013e31824ee1a8

Ponsford, J., Schönberger, M., & Rajaratnam, S. M. W. (2015). A model of fatigue following traumatic brain injury. *Journal of Head Trauma Rehabilitation*, *30*(4), 277–282. https://doi.org/10.1097/HTR.0000000000000049

Powell, V. D., Abedini, N. C., Galecki, A. T., Kabeto, M., Kumar, N., & Silveira, M. J. (2021). Unwelcome companions: Loneliness associates with the cluster of pain, fatigue, and depression in older adults. *Gerontology and Geriatric Medicine, 7,* 1-10. https://doi.org/10.1177/2333721421997620

Rabe-Hesketh, S., Skrondal, A., & Gjessing, H. K. (2008). Biometrical modeling of twin and family data using standard mixed model software. *Biometrics*, *64*(1), 280–288. https://doi.org/10.1111/j.1541-0420.2007.00803.x

Rabinbach, A. (1992). *The human motor: Energy, fatigue, and the origins of modernity*. California, USA: University of California Press.

Rabinowitz, A. R., & Levin, H. S. (2014). Cognitive sequelae of traumatic brain injury. *Psychiatric Clinics*, *37*(1), 1–11. https://doi.org/10.1016/j.psc.2013.11.004

Rakers, S. E., Timmerman, M. E., Scheenen, M. E., de Koning, M. E., van der Horn, H. J., van der Naalt, J., & Spikman, J. M. (2021). Trajectories of fatigue, psychological distress, and coping styles after mild traumatic brain injury: A 6-month prospective cohort study. *Archives of Physical Medicine and Rehabilitation*, *102*(10), 1965–1971. https://doi.org/10.1016/j.apmr.2021.06.004

Reyes-Gibby, C. C., Aday, L. A., Anderson, K. O., Mendoza, T. R., & Cleeland, C. S. (2006). Pain, depression, and fatigue in community-dwelling adults with and without a history of cancer. *Journal of Pain and Symptom Management*, *32*(2), 118–128. https://doi.org/10.1016/j.jpainsymman.2006.01.008

Reznek, L. (2005). The Rey 15-item memory test for malingering: A meta-analysis. *Brain Injury*, *19*(7), 539–543. https://doi.org/10.1080/02699050400005242

Rivera, M. C., Mastronardi, C., Silva-Aldana, C. T., Arcos-Burgos, M., & Lidbury, B. A. (2019). Myalgic encephalomyelitis/chronic fatigue syndrome: A comprehensive review. *Diagnostics*, 9(3), 1-34. https://doi.org/10.3390/diagnostics9030091

Rosmalen, J. G. M., Neeleman, J., Gans, R. O. B., & de Jonge, P. (2007). The association between neuroticism and self-reported common somatic symptoms in a population cohort. *Journal of Psychosomatic Research*, *62*(3), 305–311. https://doi.org/10.1016/j.jpsychores.2006.10.014

Rothman, K. J. (2014). Six persistent research misconceptions. *Journal of General Internal Medicine*, *29*(7), 1060–1064. https://doi.org/10.1007/s11606-013-2755-z

Rusnak, M. (2013). Giving voice to a silent epidemic. *Nature Reviews Neurology*, *9*(4), 186–187. https://doi.org/10.1038/nrneurol.2013.38

Russell, D. W. (1996). UCLA Loneliness Scale (Version 3): Reliability, validity, and factor structure. *Journal of Personality Assessment, 66*(1), 20–40. https://doi.org/10.1207/s15327752jpa6601_2

Sandry, J., Genova, H. M., Dobryakova, E., DeLuca, J., & Wylie, G. (2014). Subjective cognitive fatigue in multiple sclerosis depends on task length. *Frontiers in Neurology*, *5*, 1-7. https://doi.org/10.3389/fneur.2014.00214

Scheier, M. F., Carver, C. S., & Bridges, M. W. (1994). Distinguishing optimism from neuroticism (and trait anxiety, self-mastery, and self-esteem): A reevaluation of the Life Orientation Test. *Journal of Personality and Social Psychology*, *67*(6), 1063–1078. https://doi.org/10.1037/0022-3514.67.6.1063

Scholten, A. C., Haagsma, J. A., Cnossen, M. C., Olff, M., van Beeck, E. F., & Polinder, S. (2016). Prevalence of and risk factors for anxiety and depressive disorders after traumatic brain injury: a systematic review. *Journal of Neurotrauma, 33*(22), 1969–1994. https://doi.org/10.1089/neu.2015.4252

Schönberger, M., Herrberg, M., & Ponsford, J. (2014). Fatigue as a cause, not a consequence of depression and daytime sleepiness: A cross-lagged analysis. *Journal of Head Trauma Rehabilitation*, *29*(5), 427–431. https://doi.org/10.1097/HTR.0b013e31829ddd08

Schwarz, R., Krauss, O., & Hinz, A. (2003). Fatigue in the general population. *Oncology Research and Treatment*, *26*(2), 140–144. https://doi.org/10.1159/000069834

Shen, J., Barbera, J., & Shapiro, C. M. (2006). Distinguishing sleepiness and fatigue: Focus on definition and measurement. *Sleep Medicine Reviews*, 10(1), 63–76. https://doi.org/10.1016/j.smrv.2005.05.004

Sigurdardottir, S., Andelic, N., Røe, C., & Schanke, A. K. (2013). Depressive symptoms and psychological distress during the first five years after traumatic brain injury: Relationship with psychosocial stressors, fatigue and pain. *Journal of Rehabilitation Medicine*, *45*(8), 808–814. https://doi.org/10.2340/16501977-1156

Skau, S., Sundberg, K., & Kuhn, H.-G. (2021). A proposal for a unifying set of definitions of fatigue. *Frontiers in Psychology*, *12*, 1-10. https://doi.org/10.3389/fpsyg.2021.739764

Skogestad, I. J., Kirkevold, M., Indredavik, B., Gay, C. L., & Lerdal, A. (2019). Lack of content overlap and essential dimensions–A review of measures used for post-stroke fatigue. *Journal of Psychosomatic Research*, *124*, https://doi.org/10.1016/j.jpsychores.2019.109759

Sørengaard, T. A., Saksvik-Lehouillier, I., & Langvik, E. (2019). Longitudinal and cross-sectional examination of the relationship between personality and fatigue among shift workers. *Cogent Psychology*, *6*(1), 1-13. https://doi.org/10.1080/23311908.2019.1574095

StataCorp LLC. (2019). Stata statistical software: Release 16. Texas, USA: StataCorp LLC.

Stein, S. C., & Spettell, C. (1995). The Head Injury Severity Scale (HISS): A practical classification of closed-head injury. *Brain Injury*, *9*(5), 437–444. https://doi.org/10.3109/02699059509008203

Stephan, Y., Sutin, A. R., Luchetti, M., Canada, B., & Terracciano, A. (2022). Personality and fatigue: meta-analysis of seven prospective studies. *Scientific Reports*, *12*(1), 1–8. https://doi.org/10.1038/s41598-022-12707-2

Strand, B. H., Dalgard, O. S., Tambs, K., & Rognerud, M. (2003). Measuring the mental health status of the Norwegian population: A comparison of the instruments SCL-25, SCL-10, SCL-5 and MHI-5 (SF-36). *Nordic Journal of Psychiatry*, *57*(2), 113–118. https://doi.org/10.1080/08039480310000932

Straus, S. E. (1991). History of chronic fatigue syndrome. *Reviews of Infectious Diseases*, *13*(Suppl. 1), S2–S7. https://doi.org/10.1093/clinids/13.Supplement_1.S2

Sullivan, P. F., Evengård, B., Jacks, A., & Pedersen, N. L. (2005). Twin analyses of chronic fatigue in a Swedish national sample. *Psychological Medicine*, *35*(9), 1327–1336. https://doi.org/10.1017/S0033291705005222

Teasdale, G., Maas, A., Lecky, F., Manley, G., Stocchetti, N., & Murray, G. (2014). The Glasgow Coma Scale at 40 years: Standing the test of time. *The Lancet Neurology*, *13*(8), 844–854. https://doi.org/10.1016/S1474-4422(14)70120-6

Torres-Harding, S., & Jason, L. A. (2005). What is fatigue? History and epidemiology. In J. DeLuca (Ed.), *Fatigue as a window to the brain* (pp. 3–17). Cambridge, USA: MIT Press.

Truelle, J.-L., Koskinen, S., Hawthorne, G., Sarajuuri, J., Formisano, R., von Wild, K., Neugebauer, E., Wilson, L., Gibbons, H., & Powell, J. (2010). Quality of life after traumatic brain injury: The clinical use of the QOLIBRI, a novel disease-specific instrument. *Brain Injury*, *24*(11), 1272–1291. https://doi.org/10.3109/02699052.2010.506865

Tverdal, C., Aarhus, M., Andelic, N., Skaansar, O., Skogen, K., & Helseth, E. (2020). Characteristics of traumatic brain injury patients with abnormal neuroimaging in Southeast Norway. *Injury Epidemiology*, *7*(1), 1–13. https://doi.org/10.1186/s40621-020-00269-8

Tverdal, C., Andelic, N., Helseth, E., Brunborg, C., Rønning, P., Hellstrøm, T., Røe, C., & Aarhus, M. (2021). In the aftermath of acute hospitalization for traumatic brain injury: Factors associated with the direct pathway into specialized rehabilitation. *Journal of Clinical Medicine*, *10*(16), 1-14. https://doi.org/10.3390/jcm10163577

van Dartel, S. A. A., Repping-Wuts, J. W. J., van Hoogmoed, D., Bleijenberg, G., van Riel, P., & Fransen, J. (2013). Association between fatigue and pain in rheumatoid arthritis: Does pain precede fatigue or does fatigue precede pain? *Arthritis Care & Research*, *65*(6), 862–869. https://doi.org/10.1002/acr.21932

van Zomeren, A. H., Brouwer, W. H., & Deelman, B. G. (1984). Attentional deficits: The riddles of selectivity, speed and alertness. In N. Brooks (Ed.), *Closed Head Injury: Psychological, Social, and Family Consequences* (pp. 74–107). Oxford, UK: Oxford University Press.

Van't Leven, M., Zielhuis, G. A., van der Meer, J. W., Verbeek, A. L., & Bleijenberg, G. (2010). Fatigue and chronic fatigue syndrome-like complaints in the general population. *European Journal of Public Health*, *20*(3), 251–257. https://doi.org/10.1093/eurpub/ckp113

Vassend, O., Lian, L., & Andersen, H. T. (1992). Norske versjoner av NEO-Personality Inventory, Symptom Checklist 90 Revised og Giessen Subjective Complaints List. Del I. *Tidsskrift for Norsk Psykologforening*, 29(29), 1150–1160.

Vassend, O., Røysamb, E., Nielsen, C. S., & Czajkowski, N. O. (2018). Fatigue symptoms in relation to neuroticism, anxiety-depression, and musculoskeletal pain. A longitudinal twin study. *PLoS One*, *13*(6), 1-21. https://doi.org/10.1371/journal.pone.0198594

Vos, L., Poritz, J. M. P., Ngan, E., Leon-Novelo, L., & Sherer, M. (2019). The relationship between resilience, emotional distress, and community participation outcomes following traumatic brain injury. *Brain Injury*, *33*(13–14), 1615–1623. https://doi.org/10.1080/02699052.2019.1658132

Voss, J. D., Connolly, J., Schwab, K. A., & Scher, A. I. (2015). Update on the epidemiology of concussion/mild traumatic brain injury. *Current Pain and Headache Reports*, *19*(7), 1–8. https://doi.org/10.1007/s11916-015-0506-z

Wardlaw, C., Hicks, A. J., Sherer, M., & Ponsford, J. L. (2018). Psychological resilience is associated with participation outcomes following mild to severe traumatic brain injury. *Frontiers in Neurology, 9*, 1-10. https://doi.org/10.3389/fneur.2018.00563

Watt, T., Groenvold, M., Bjorner, J. B., Noerholm, V., Rasmussen, N.-A., & Bech, P. (2000). Fatigue in the Danish general population. Influence of sociodemographic factors and disease. *Journal of Epidemiology & Community Health*, *54*(11), 827–833. http://doi.org/10.1136/jech.54.11.827

Wechsler, D. (1999). *Wechsler abbreviated scale of intelligence* [Database Record]. APA Psyctests. https://doi.org/10.1037/t15170-000

Wechsler, D. (2008). Wechsler adult intelligence scale–Fourth Edition (WAIS–IV). San Antonio, TX: NCS Pearson.

Whiffin, C. J., Gracey, F., & Ellis-Hill, C. (2021). The experience of families following traumatic brain injury in adult populations: A meta-synthesis of narrative structures. *International Journal of Nursing Studies*, *123*, 1-20. https://doi.org/10.1016/j.ijnurstu.2021.104043

Whitehead, L. (2009). The Measurement of Fatigue in Chronic Illness: A Systematic Review of Unidimensional and Multidimensional Fatigue Measures. *Journal of Pain and Symptom Management*, 37(1), 107–128. https://doi.org/10.1016/j.jpainsymman.2007.08.019

Williams, D. H., Levin, H. S., & Eisenberg, H. M. (1990). Mild head injury classification. *Neurosurgery*, *27*(3), 422–428. https://doi.org/10.1097/00006123-199009000-00014

Wilshire, C. E., Ward, T., & Clack, S. (2021). Symptom descriptions in psychopathology: How well are they working for us? *Clinical Psychological Science*, *9*(3), 323–339. https://doi.org/10.1177/2167702620969215

Wilson, J. T. L., Pettigrew, L. E. L., & Teasdale, G. M. (1998). Structured interviews for the Glasgow Outcome Scale and the extended Glasgow Outcome Scale: Guidelines for their use. *Journal of Neurotrauma*, *15*(8), 573–585. https://doi.org/10.1089/neu.1998.15.573

Windle, G., Bennett, K. M., & Noyes, J. (2011). A methodological review of resilience measurement scales. *Health and Quality of Life Outcomes*, *9*(1), 1–18. https://doi.org/10.1186/1477-7525-9-8

World Health Organization. (2001). *International classification of functioning, disability and health : ICF*. Retrieved from https://apps.who.int/iris/handle/10665/42407.

Wright, F., Melkus, G. D., Hammer, M., Schmidt, B. L., Knobf, M. T., Paul, S. M., Cartwright, F., Mastick, J., Cooper, B. A., & Chen, L.-M. (2015). Predictors and trajectories of morning fatigue are distinct from evening fatigue. *Journal of Pain and Symptom Management*, *50*(2), 176–189. https://doi.org/10.1016/j.jpainsymman.2015.02.016

Wyller, V. B. B. (2019). Pain is common in chronic fatigue syndrome–current knowledge and future perspectives. *Scandinavian Journal of Pain*, *19*(1), 5–8. https://doi.org/10.1515/sjpain-2018-2007

Zgaljardic, D. J., Durham, W. J., Mossberg, K. A., Foreman, J., Joshipura, K., Masel, B. E., Urban, R., & Sheffield-Moore, M. (2014). Neuropsychological and physiological correlates of fatigue following traumatic brain injury. *Brain Injury*, 28(4), 389–397. https://doi.org/10.3109/02699052.2014.884242

Ziino, C., & Ponsford, J. L. (2005). Measurement and prediction of subjective fatigue following traumatic brain injury. *Journal of the International Neuropsychological Society*, 11(4), 416-425. https://doi.org/10.1017/S1355617705050472

Ziino, C., & Ponsford, J. L. (2006). Vigilance and fatigue following traumatic brain injury. *Journal of the International Neuropsychological Society*, 12(1), 100-110. https://doi.org/10.1017/S1355617706060139

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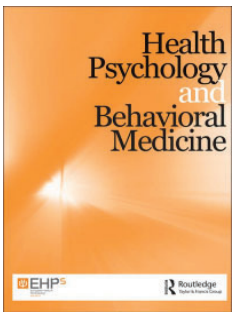

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RESEARCH ARTICLE

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The role of pain and psychological distress in fatigue: a co-twin and within-person analysis of confounding and causal relations

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ABSTRACT

Objective: Fatigue is a common symptom in somatic and mental illness. Musculoskeletal pain and psychological distress have in turn frequently been shown to be associated with fatigue across clinical conditions and in the general population. The study aims to disentangle direct effects from those due to mere confounding from shared etiologies.

Design: The study used genetically informative longitudinal twin data, through a co-twin control design with an additional within-person dimension.

Methods: Data on fatigue, pain and distress from 2196 mono – and dizygotic twins from the Norwegian Twin Registry examined at two time points five years apart was analyzed using multilevel generalized linear regression modeling. Fatigue was regressed on pain and distress, with further controls added for confounding from genetic and stable non-shared environmental sources.

Results: Pain and distress had a significant impact on fatigue at genetic, stable non-shared environmental and time-varying levels, even when controlling for somatic comorbidity.

Conclusion: The findings indicate that a significant proportion of the association between fatigue, pain and distress is due to genetic and environmental confounding. Pain and distress exert significant, albeit smaller effects on fatigue even when controlling for genetic and stable environmental contributions, indicating direct effects. Potential etiological pathways and underlying mechanisms are discussed.

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Abbreviations: AIC: Akaike Information Criterion; CFS: Chronic Fatigue Syndrome; Dz: Dizygotic; GSCL: Giessen Subjective Complaints List; ME: Myalgic Encephalomyelitis; Mz: Monozygotic; NSE: Non-Shared Environment; SCL: Symptoms Checklist

The experience of fatigue involves strong sensations of mental and physical tiredness, weakness, exhaustion, and difficulty with concentration. One definition conceptualizes fatigue as an awareness of a decreased capacity for physical or mental activity due to an imbalance in the availability, utilization or restoration of resources needed to perform an activity (Aaronson et al., 1999). Life stressors and homeostatic factors (i.e. overexertion) may contribute to acute fatigue in otherwise healthy individuals (Finsterer & Mahjoub, 2014). For some, however, the symptom may linger and take on a persistent, chronic form (Duncan, Wu, & Mead, 2012; Mollayeva et al., 2014), which is the case in, e.g. Chronic Fatigue Syndrome (CFS) (also denoted Myalgic Encephalomyelitis (ME)) (Cortes Rivera, Mastronardi, Silva-Aldana, Arcos-Burgos, & Lidbury, 2019). Fatigue is frequently reported in general primary care and community studies, and the exact threshold between common fatigue (e.g. 'feeling tired and weak') and diagnosable CFS can be arbitrary. Fatigue is therefore presumably best conceptualized as a continuously distributed symptom in the general population (Bültmann, Kant, Kasl, Beurskens, & van den Brandt, 2002; Loge, Ekeberg, & Kaasa, 1998).

While the exact pathogenesis of acute and chronic fatigue conditions remains unexplained, several biomedical, psychological, and social risk factors are associated with fatigue onset and maintenance (Cortes Rivera et al., 2019; Penner & Paul, 2017). Associations have, e.g. previously been established with symptoms of depression and anxiety (Bültmann et al., 2002; Hickie, Bennett, Lloyd, Heath, & Martin, 1999; Vassend, Røysamb, Nielsen, & Czajkowski, 2018), pain (Reyes-Gibby, Mendoza, Wang, Anderson, & Cleeland, 2003; Vassend et al., 2018), inflammatory processes (Matura, Malone, Jaime-Lara, & Riegel, 2018; Patejdl, Penner, Noack, & Zettl, 2016), metabolic dysfunction (Freidin et al., 2018; Manjaly et al., 2019) and personality (Henderson & Tannock, 2004; Nater et al., 2010; Poeschla, Strachan, Dansie, Buchwald, & Afari, 2013; Vassend et al., 2018). However, biomedical markers and processes such as viral infection, mitochondrial or metabolic dysfunction, and fatigue-related cytokines are only weakly related (or unrelated) to subjective symptom levels, and studies have often been inconclusive when appropriate controls were included (Kristiansen et al., 2019). While disease-specific processes might contribute to fatigue, there are strong indications of the existence of transdiagnostic mechanisms which may overlap in their associations with fatigue across disorders (Menting et al., 2018).

Musculoskeletal pain is one subjective complaint most commonly co-occurring with fatigue in both clinical and non-clinical populations (Van Damme, Becker, & Van der Linden, 2018). One study conducted in a large community sample revealed that as many as 60% of those who reported chronic widespread pain, also reported persistent fatigue (Creavin, Dunn, Mallen, Nijrolder, & van der Windt, 2010). Furthermore, psychological distress (i.e. symptoms of depression and anxiety) has been established as a significant risk factor for fatigue in both medical disorders and the general population (Bower, 2014; Corfield, Martin, & Nyholt, 2016a; Lamers, Hickie, & Merikangas,

2013; Menting et al., 2018; Ormstad & Eilertsen, 2015; Penner & Paul, 2017; Schreiber, Lang, Kiltz, & Lang, 2015).

While associative studies allow for the examination of covariation between fatigue, pain and psychological distress, causality or direct effects can rarely be inferred from conventional observational research, due to potential unmeasured confounding factors and lack of experimental control. Shared genetic etiology between phenotypes, also known as pleiotropy, is one such potential confounder in observational studies (McAdams, Rijsdijk, Zavos, & Pingault, 2020). The relatively few published twin studies of the genetic susceptibility for fatigue, based on both continuous and dichotomous (CFS/CFS-like) phenotype definitions, have generally found best fit for models incorporating additive genetic and non-shared environmental effects, with heritability estimates between 0.30 and 0.53, indicating moderate genetic and non-shared environmental effects underlying fatigue (Corfield, Martin, & Nyholt, 2017; Hickie, Kirk, & Martin, 1999; Sullivan, Evengård, Jacks, & Pedersen, 2005; Vassend et al., 2018). A twin study conducted with data from a Sri Lankan twin sample provides incremental support for the generalizability of the heritability of fatigue also within a non-western culture (Ball et al., 2010), as heritability estimates of 30% were found for continuous fatigue severity, and 39% for severe, abnormal fatigue in their best-fitting models including only additive genetic and non-shared environmental effects . Interestingly, Ball et al. (2010) investigated specific life exposures which might underlie environmental influences on fatigue, and found that leaving school early, poor standards of living, negative life events and poor parental care mediated fatigue through non-shared, but primarily shared environmental influences. Thus, while the shared environment generally does not explain a significant proportion of phenotype fatigue, there might exist some slight cultural variations. Furthermore, previous studies have revealed a considerable overlap in genetic and non-shared environmental dispositions for pain and fatigue (Hickie et al., 1999; Vassend et al., 2018), and likewise between fatigue and psychological distress (Ball et al., 2010; Corfield, Martin, & Nyholt, 2016b; Vassend et al., 2018). Pain and psychological distress thus seem to be interrelated with fatigue at both a phenotypic, genetic and environmental level, yet the causal nature of these relationships remain largely unknown. Twin studies allow for some control over genetic contributions to phenotypic associations, through the use of a genetically matched co-twin control condition (McGue, Osler, & Christensen, 2010), with the ability to measure within-pair effects of predictors when genetic and shared environmental factors are held constant. In twin studies, this can be evaluated by centering each twin's phenotype scores (e.g. pain and fatigue) around a twin pair average, and test for correlations between the centered scores. See Figure 1(a) for a simplified illustration of this process. As noted above, pain and distress are correlated with fatigue in the population. Should, however, the within-pair correlation in monozygotic twins be zero, this would indicate complete genetic confounding, because there would be no residual correlation when the effects of genes have been controlled for. Specifically, this would mean that there would be no pattern indicating that the twin with higher levels of pain and distress also tends to report higher levels of fatigue, given their completely shared genetic makeup. If, however, there is a within-pair tendency for a correlation between these symptoms within the monozygotic twin pair, this would indicate either direct effects, or effects attributable to some confounding from the non-shared environment (McGue et al., 2010).

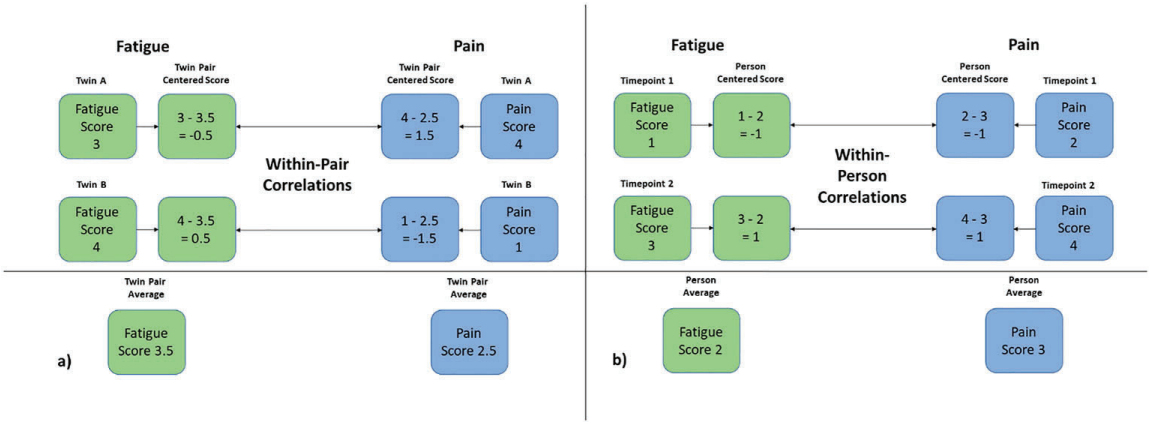

Figure 1. (a & b). A visual illustration of the co-twin and within-person procedures. The demonstrated procedures are simplified for ease of comprehension, and we refer to the Supplemental data for a review of the specific centering techniques applied in our study. Figure 1(a) demonstrates how within-pair correlations are calculated, by subtracting the twin pair average phenotype scores from the score of each twin. The resulting centered score provides a measure of each twin's distance from the twin pair average, which is then free from genetic influences. Likewise, Figure 1(b) demonstrates the application of the same procedure to two measurement timepoints within one individual. The within-person correlations are calculated by subtracting the person average phenotype scores from the phenotype scores at each timepoint. The resulting person centered scores provides a measure of each timepoint's distance from the person average, which is then free from influences from the stable non-shared environment.

While twin studies do allow for control over genetic confounding and environment shared by siblings, they still cannot account for potential confounding from the non-shared environment. Life experiences, educational attainment, spousal influences, somatic illness, and stochastic biological processes unique to the individual's life course may be common causal factors underlying associations. Such individual-specific events and processes pose as major causal and confounding factors in epidemiology and behavioral genetics (Smith, 2011; Tikhodeyev & Shcherbakova, 2019). Smith (2011) emphasized confounding from the non-shared environment, such as gene-by-environment interactions and stochastic events ranging across the sub-cellular and cellular levels, as particularly problematic in epidemiology and behavioral genetics, in that they are generally neither epidemiologically tractable nor available for intervention.

One way of dealing with the problem of the non-shared environment, is to consider that it has both stable and time-varying components. When examining adults who have lived long lives full of unique experiences, it is difficult to measure all specific life events and stochastic biological processes that have occurred throughout their lives unique to them. Indeed, as Tikhodeyev and Shcherbakova (2019) emphasize, attempts at identifying the specific contents of the non-shared environment have been futile. One conceptual way to capture the effects of the unique life experiences thus far, is to introduce a longitudinal element to co-twin models, and use the stability within individuals to capture stability in phenotypes not otherwise explained by genetic factors. By applying the same procedure as that applied within co-twin studies describes above, but instead using each person as their own control, within-person correlation can be calculated to evaluate if there remains a residual effect across time within individuals. See Figure 1

(b) for a simplified visual presentation of this procedure. If pain and distress are correlated with fatigue within twin pairs, but the within-person correlation across time is zero, this would indicate additional confounding from stable environmental influences not shared between twins, but exerting equal influences on all within-person measurements. Specifically, this would be the case if there was no pattern indicating that the timepoint with higher levels of pain and distress also coincides with the timepoint with higher levels of fatigue. If, however, there remains a significant within-person correlation across time, this would indicate direct associations free from genetic and stable non-shared environmental contributions.

Such dispositional stability within individuals could thus be conceptually construed as caused by factors in the *stable non-shared environment*, containing the effects of all the unique life events experienced by the individual prior to our measurements. Genetically informative longitudinal research is one way of examining the underlying genetic, stable and time-varying architecture of risk factors and their potentially causal relationships to fatigue symptoms. Ascertaining whether fatigue is causally linked with psychological distress and pain over time, or merely associated through genetic and environmental confounding, is essential to our understanding of fatigue, and contribute to future attempts at developing etiological models.

Aims

The present study aims to examine the contribution of psychological distress and musculoskeletal pain to fatigue, controlling for genetic confounding through the utilization of a co-twin control condition. The longitudinal dimension of the data allows for additional control over stable non-shared environmental confounding through a within-person control condition. Based on previous research, we expect to find strong pleiotropic effects between fatigue and pain, as well as between fatigue and distress, indicative of shared genetic susceptibility between them. Furthermore, if there exists additional environmental factors contributing to a stable risk for fatigue and pain, and fatigue and distress, we expect to find significant effects also at the stable non-shared environmental level. Finally, if pain and distress contribute significantly to fatigue even when controlling for genetic and environmental factors shared between these constructs, we expect to find significant effects at the time-varying non-shared environmental level.

Methods

Study design

The following study employed a co-twin control design, with an additional within-person dimension through the inclusion of two time points. The standard co-twin control design is a variant of the case–control design, where each participant is matched with their own twin. The addition of the within-person dimension to the design adds another case–control condition, whereby each participant is matched with themselves across time.

Sample

The study was approved by the Regional Committee for Medical and Health Research Ethics, South-East Norway (project 2015/958), and informed consent was obtained from all participants. Data was sampled from a subset of the Norwegian Twin Registry (Nilsen et al., 2013), collected at two time points (in 2011 and 2016). To be included in our study, one of the twins had to have responded to the questionnaires regarding both fatigue, pain and distress on at least one occasion. Zygosity was determined by response to a questionnaire item at earlier timepoints, which has previously been shown to identify approximately 98% correctly as either di – or monozygotic (Magnus, Berg, & Nance, 1983). The age range of the cohort was between 50–65 at the first measurement point, with a mean age of 57.1 (SD = 4.5). The sample consisted of 40.7% male and 59.3% female same-sex twin pairs. The sample included 2196 participants belonging to 609 monozygotic (Mz) and 759 dizygotic (Dz) twin pairs. For a complete overview of responders sorted by their own and their co-twin's contribution to the study, see Table 1.

Procedure

Two subscales from the self-report questionnaire Giessen Subjective Complaints List (GSCL) were used as a measure of fatigue and pain. The GSCL has been used extensively in epidemiological research, and has been validated in a Norwegian sample (Vassend, Lian, & Andersen, 1992). The fatigue subscale includes the following six items: 1. Physical weakness; 2. Excessive need for sleep; 3. Rapid exhaustion; 4. Tiredness or drowsiness; 5. Feeling distant and difficulty concentrating; 6. Feeling of listlessness. The respondents are asked to rate the degree to which they 'generally' suffer from the symptoms on a scale from 0 (not at all) to 4 (strongly). The fatigue subscale demonstrated good internal consistency when measured both in 2011 (Cronbach's alpha = 0.88) and in 2016 (Cronbach's alpha = 0.90). Included in the subscale for musculoskeletal pain are the following six items: 1. Pain in joints or limbs; 2. Backache; 3. Neck and shoulder pain; 4. Headache; 5. Heaviness in legs; 6. Feeling of pressure in the head. The pain subscale also showed good internal consistency both in 2011 (Cronbach's alpha = 0.79) and in 2016 (Cronbach's alpha = 0.78). Psychological distress was measured using two abbreviated versions

Table 1. The distribution of responders organized by their own contribution to the study as well as their co-twins', separated by zygosity.

	Single responder, single occasion	Single responder, both occasions	One occasion with one co-twin occasion	One occasion with two co-twin occasions	Two occasions with one co-twin occasion	Two occasions with two co-twin occasions	Total
Monozygotic	172	22	340	113	113	264	1024 (46.6%)
Dizygotic	297	49	326	143	143	214	1172 (53.4%)
Total	469 (21.4%)	71 (3.2%)	666 (30.3%)	256 (11.7%)	256 (11.7%)	478 (21.8%)	2196 (100%)

The lowest degree of contribution to the study is represented by the leftmost column, showing participants who only responded to one occasion (either 2011 or 2016), without a co-twin observation. The highest degree of contribution to the study is represented by the rightmost column, showing participants who responded at both occasions, and whose co-twin also responded at both occasions.

of the Symptoms Checklist (Derogatis, Lipman, Rickels, Uhlenhuth, & Covi, 1974). In 2011, a five item version (SCL-5) was used, asking the participants whether they over the last two weeks had experienced: 1. Feeling fearful; 2. Feelings of nervousness or inner turmoil; 3. Feeling hopeless about the future; 4. Feeling blue; and 5. Worrying too much about things. In 2016, the three following items were added to the scale (SCL-8): 6. Feeling that everything is an effort; 7. Feeling tense or keyed up; and 8. Feeling suddenly fearful without a reason. Each item was rated on a 4-point scale ranging from 1 (not at all) to 4 (extremely). Internal consistency was deemed acceptable for both the 5-item version (Cronbach's alpha = 0.87) and the 8-item version (Cronbach's alpha = 0.90). Short versions of this questionnaire have been shown to have good psychometric properties in the general Norwegian population (Strand, Dalgard, Tambs, & Rognerud, 2003). Comorbidity indicators were generated through the summation of dichotomous responses (yes / no) to questions regarding various disease categories in 2011 (see Supplemental data for details).

Statistical analyses

All statistical analyses were conducted using Stata Statistical Package: Release 16 (StataCorp, 2019). Preliminary bivariate phenotypic correlation analyses were conducted between distress, pain and fatigue, separated by timepoints. For the multilevel generalized modeling, data was structured in a long format with hierarchical leveling of timepoints (Level 1) nested within individuals (Level 2), within zygote (Level 3), within twin pairs (Level 4). The theoretical basis for application of multilevel modeling to biometrical analyses of twin data has been previously established, and the parameterization of such an approach within a multilevel framework is described in further detail in Rabe-Hesketh, Skrondal & Gjessing (Rabe-Hesketh, Skrondal, & Gjessing, 2008). Figure 2 illustrates the hierarchical structure of the data. The multilevel approach considers that there are dependent observations in the data, and a structure inherent in the degree of dependency. Fatigue reported on two occasions (level 1) by the same individual (nested at level 2) should be more correlated than between two individual Mz-twins, and two observations in Mz-twins (nested at level 3) should correlate more than two observations in Dz-twins (nested at level 4).

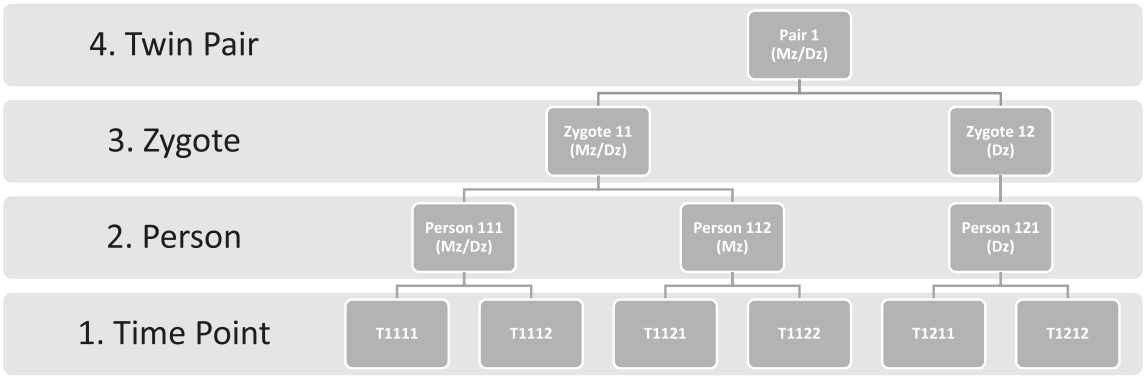

Figure 2. The hierarchical data structure to which the multilevel modeling was adapted. The numbering at the various levels indicate allocation of timepoints within persons within zygotes within twin pairs. Monozygotic (Mz) twins are nested together at both level 3 & 4, while dizygotic twins (Dz) are nested together only at level 4.

The use of multilevel generalized linear regression models using the 'meglm' command in Stata allows for variance compartmentalization into variance components at separate nested levels (Rabe-Hesketh & Skrondal, 2012). Variance components at level 3 and 4 were constrained to be equal, meaning that the 50% shared genes in Dz-twins must exert the same effect as the additional 50% shared genes in Mz-twins. The Supplemental data provides further details on the specific variable and model parameterization employed, along with explanations of the multilevel approach for the uninitiated. Models with an additional component for the effects of the shared environment (i.e. residual variance at the twin pair level) was estimated to evaluate the best fit of models incorporating either (1) additive genetic; or (2) additive genetic & shared environmental familial components. Aggregate variables were generated to control the time-varying effect from confounding from genetic and stable non-shared environment. Aggregate variables are essentially averaged scores within the nested level. For clarity, this means that a level 1 variable varies with each measurement point, a level 2 variable is constant within the individual (e.g. the average of reported pain across both time points), and that level 3 & 4 variables are constant within the twin pair (e.g. the average of reported pain across both time points in both twins). Cluster mean centering was performed to allow for non-dependency in the hierarchical variables (see Supplemental data for exact centering strategy). The inclusion of such aggregate variables in the fixed part of the regression model, allows us to control for and single out the confounding effects of genetics and stable non-shared environment.

A blockwise approach was applied during the estimation of the multilevel model, beginning from a baseline model including the fixed effect of female gender (Model 1). Further modeling was performed by adding fixed effects of (2) psychological distress (Level 1); (3) musculoskeletal pain (Level 1); (4) distress and pain (Level 1); (5) aggregate variables for pain and distress at the zygote and twin pair level (3 & 4) with co-twin control constraints, with level 1 variables centered around the zygote/pair aggregate variables; (6) aggregate variable for the individual (level 2) centered around the zygote/pair aggregate variables (level 3 & 4), with level 1 variables centered around the initial aggregate variable for the individual (level 2), to control for within-person stability, and (7) comorbidity indicators as observed covariates. The rationale for the final three model adjustments is demonstrated visually in Figure 3.

Missing observations at either timepoint or in a person's co-twin were modeled as missing-at-random, and the estimation was performed using full information maximum likelihood to allow for the utilization of data from participants without complete data in the likelihood estimation. Full information maximum likelihood has been shown to estimate unbiased parameter estimates and standard errors when data is missing-completely-at-random or missing-at-random (Newman, 2014).

Results

Phenotypic correlations

Bivariate correlation analyses were conducted to ascertain phenotypic correlations between the included phenotypes (see Table 2). As expected, fatigue shows a strong and significant positive association with musculoskeletal pain ($r = .58$ to .71 depending

Model: / Controlling for confounding effects of:	4. Unadjusted	5. Co-Twin Control	6. Within-Person Control	7. Covariates
• Factors shared between twins e.g. genetic effects, shared environmental influences, maternal health during pregnancy	No control	Controlled	Controlled	Controlled
• Stable non-shared environment e.g. unique life experiences, dispositional traits, stochastic biological processes.	No control	No control	Controlled	Controlled
• Somatic comorbidity Self-reported disorders (neurological, endocrine, autoimmune, oncological, cardiological or insomnia)	No control	No control	No control	Controlled
• Time-varying individual factors e.g. other life events or health issues between measurements	No control	No control	No control	No control

Figure 3. Adjustments made in the final four models estimated, showing each incremental control condition. Model 5 adjusts the main effects with a co-twin condition, while model 6 adjusts the main effects through a within-person control condition. Model 7 includes comorbidity indicators as observed covariates, to evaluate confounding from somatic illness. While the model adjustsments allow for a comprehensive control, they do not, however, allow for the control of potential confounding by unmeasured time-varying factors such as the effects of life events in between measurements.

on time point) and psychological distress ($r = .46$ to .62 depending on time point). These correlations within individuals across time indicate considerable intra-individual stability in the three phenotypes across time.

Variance component models

Multilevel variance component models with a fixed effect of female gender were constructed for all included phenotypes. Preliminary analyses confirmed best fit for models not incorporating the shared environment as an isolated component, and any potential effects of the shared environment is thus included in the additive genetic components. Due to the standardization of all variables, the variance components can be interpreted as percentages, although the inclusion of gender as a baseline covariate explains some variance in all three phenotypes, resulting in some variation in variance compositions. Table 3 lists the variance components for fatigue, pain and distress.

Table 2. Phenotypic correlations between included variables at both time points, T1 = 2011 and T2 = 2016.

	1	2	3	4	5	6
1. Fatigue T1	1					
2. Fatigue T2	**.74****	1				
3. Musculoskeletal Pain T1	.69 **	.58 **	1			
4. Musculoskeletal Pain T2	.61 **	.71 **	**.73 ****	1		
5. Psychological Distress T1	.50 **	.46 **	.38 **	.39 **	1	
6. Psychological Distress T2	.49 **	.62 **	.36 **	.47 **	**.65 ****	1

Note: Correlations marked in bold indicate within-phenotype correlation across timepoints. ** = $p < .001$.

Table 3. Variance component models of all included variables, with variance compartmentalized into levels of additive genetic variance, stable non-shared environmental variance and varying non-shared environmental variance, with 95% confidence intervals (95% CI).

Variance component models	Additive genetics (95% CI)	Stable non-shared environment (*95% CI*)	Varying non-shared environment (95% CI)
Fatigue	0.45 (.39 - .53)	0.22 (.17 - .28)	0.27 (.25 - .30)
Psychological Distress	0.36 (.29 – .44)	0.27 (.20 - .35)	0.38 (.35 - .42)
Musculoskeletal Pain	0.47 (.41 – .54)	0.14 (.10 - .20)	0.28 (.26 - .31)

Note: Due to best fit for models excluding the shared environment as a separate component, potential effects of environmental influences shared between twins are included within the additive genetic component. The additive genetic component nevertheless provides an estimate of the heritability (h^2) of the constructs, while the stable non-shared environmental components provide an estimate of stability within individuals not otherwise accounted for by additive genetics. The time-varying environment component includes variance not otherwise explained, i.e fluctuations in phenotype within individuals, and measurement error.

Fatigue had a heritability (h^2) of 45%. Furthermore, 22% of the variance in phenotype fatigue was attributable to stable non-shared environment. Finally, 27% of the variance was estimated as time-varying, residual variance. Female gender was significantly associated with fatigue ($\beta = 0.17$, $p < 0.001$). All predictor variables included show a moderate degree of heritability. Musculoskeletal pain had a heritability of 47%, while 14% of the variance was attributable to the stable non-shared environment, and 28% of the variance was estimated as time-varying, residual variance. Female gender had a significant effect on pain ($\beta = 0.28$, $p < 0.001$). Psychological distress was estimated with a heritability of 36%, a stable non-shared environmental component of 27%, and a time-varying, residual component of 38%. Female gender showed a significant positive association with distress ($\beta = 0.19$, $p < 0.001$).

Multilevel model fitting

Each modeling step led to an increase in model fit according to Log Likelihood in comparison to the previous one. Models 5–7 apply control conditions for confounding and lose some model fit in the process, which is to be expected given data loss when centering level 1 predictor variables. The fixed effects of musculoskeletal pain and psychological distress at all included levels across the models estimated are shown in Table 4 along with residual variance components and model fit indicators (log likelihood and Akaike Information Criterion (AIC)). A visual aid for the interpretation of the various level-specific coefficients is presented in Figure 4.

Firstly, model 2 includes distress as a predictor at each timepoint. Distress shows a significant effect on fatigue, and explains 46% of the additive genetic variance, 28% of the variance attributable to stable non-shared environment and 2% of the variance in varying non-shared environment. Model 3 includes solely musculoskeletal pain as a predictor at each timepoint. Pain has a strong effect on fatigue, and explains 74% of the additive genetic variance, 40% of the variance in fatigue due to stable non-shared environment, and 13% of the variance in fatigue due time-varying non-shared environment. Model 4 includes both musculoskeletal pain and distress (level 1), and in combination they explain 80% of the additive genetic variance, 56% of the variance due to stable non-shared environment, and 17% of the residual variance. The subsequent model steps are aimed at controlling the effects of pain and distress for confounding from genetic and

Table 4. Fixed effects with (95% Confidence Intervals) of level-specific coefficients for psychological distress and musculoskeletal pain, and residual variance components for each incremental modeling step with percentages of explained variance.

Fixed effects	1. Baseline	2. Distress	3. MS-pain	4. Distress & MS-Pain	5. Co-twin control	6. Within-person control	7. Observed covariates
Female Gender (95% CI)	0.17 (0.08–0.26)	0.09 (0.01–0.16)	−0.03 (−0.07–0.05)	−0.03 (−0.08–0.02)	−0.02 (−0.08–0.04)	−0.02 (−0-09 - 0.03)	−0.02 (−0.08–0.03)
Psychological Distress (Varying Non-Shared Environment) (95% CI)	–	0.46 (0.43–0.49)	–	0.28 (0.25–0.31)	0.14 (0.11–0.18)	0.08 (0.03–0.14)	0.09 (0.03–0.14)
Psychological Distress (Additive Genetics) (95% CI)	–	–	–	–	0.38 (0.33–0.43)	0.39 (0.34–0.44)	0.37 (0.32–0.42)
Psychological Distress (Stable Non– Shared Environment) (95% CI)	–	–	–	–	–	0.30 (0.26–0.35)	0.29 (0.25–0.34)
Musculoskeletal Pain (Varying Non–Shared Environment) (95% CI)	–	–	0.67 (0.64–0.70)	0.55 (0.53–0.58)	0.28 (0.24–0.32)	0.21 (0.15–0.27)	0.22 (0.16–0.28)
Musculoskeletal Pain (Additive Genetics) (95% CI)	–	–	–	–	0.70 (0.65–0.75)	0.72 (0.67–0.77)	0.67 (0.62–0.72)
Musculoskeletal Pain (Stable Non-Shared Environment) (95% CI)	–	–	–	–	–	0.53 (0.48–0.59)	0.50 (0.44–0.55)
Residual Variance Component (% explained variance)							
Additive Genetics	0.45	0.24 (46%)	0.12 (74%)	0.09 (80%)	0.11 (75%)	0.11 (72%)	0.10 (75%)
Stable Environmental	0.22	0.16 (28%)	0.13 (40%)	0.10 (56%)	0.12 (47%)	0.09 (54%)	0.11 (58%)
Residual	0.27	0.27 (2%)	0.24 (13%)	0.23 (17%)	0.22 (19%)	0.22 (20%)	0.22 (20%)
Model Fit Indicators	*Obs.* 3001. *df = 5*	*Obs.* 3001. *df = 6*	*Obs.* 3001. *df = 6*	*Obs.* 3001. *df = 7*	*Obs.* 3001. *df = 9*	*Obs.* 3001. *df = 11*	*Obs.* 3001. *df = 17*
Log Likelihood	−3804.03	−3416.83	−3029.52	−2822.46	−2915.14	−2887,774	−2823,923
Akaike Information Criterion	7618.06	6845.663	6071.042	5658.915	5848.283	5797.547	5681.847

Note: Each modeling step from 1–4 led to an increase in model fit (higher Log Likelihood and lower AIC) and explained variance, while models 5–7 aim primarily to add incremental control for confounders rather than increase model fit.

non-shared environment. Model 5 adds a co-twin control to isolate the effects of shared genetics from the main effects. This leads to a reduction in the main effects of pain and distress, due to the compartmentalization of the main effect into genetic and time-varying effects. Model 6 finally adds a within-person control for stable non-shared environment, leading again to a decrease in the time-varying effects of distress and pain. Model 7 adds comorbidity indicators as observed covariates to control for confounding from somatic illness burden, which might underlie shared genetic variance, with resulting slight reductions in the additive genetic and stable non-shared environment effects of pain and distress. In the final adjusted model, both musculoskeletal

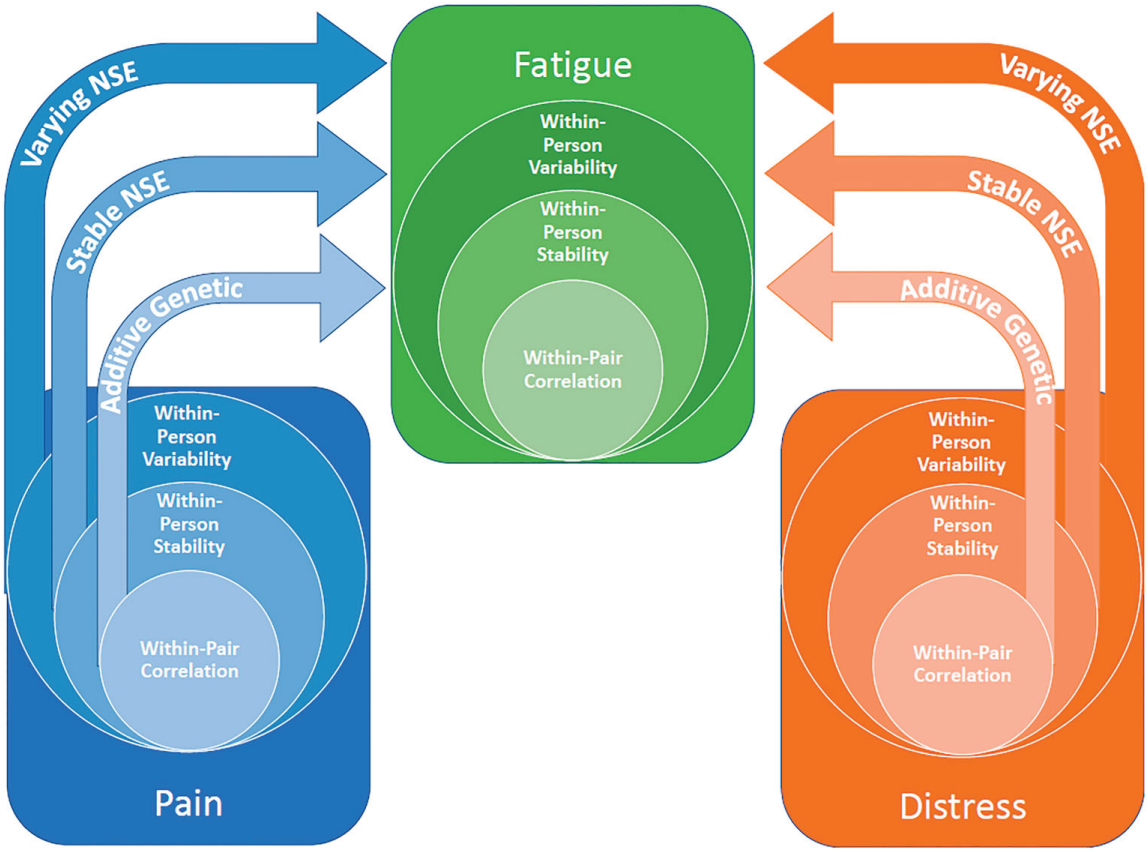

Figure 4. The multilevel regression model separates the additive genetic, stable non-shared environmental (Stable NSE) and varying non-shared environmental (varying NSE) components of the included phenotypes, and provides level-specific coefficients of distress and pain on fatigue. This is estimated through genetically weighted within-pair correlation, within-person stability and within-person variability. The model is strictly illustrative, and it should be noted that other possible models of the relationships between fatigue, pain and distress cannot be eliminated based on our findings.

pain and psychological distress (Level 1) show significant effects on fatigue even when controlling for confounding from shared genetic effects and stable non-shared environment, with pain showing a more robust effect than distress. The time-varying effect size of pain has been reduced from 0.55 in model 4 (controlling for distress) to 0.22 in model 7 (controlling for genetic and stable non-shared environmental confounding as well as comorbidity). Likewise, the time-varying effect size of distress has been reduced from 0.28 in model 4 (controlling for pain) to 0.09 in model 7 (controlling for genetic and dispositional confounding as well as comorbidity). For other fixed effects included in the final model, see Table 5.

Due to the potential construct overlap between item #6 on the depression scale (*feeling that everything is an effort*) and fatigue, all analyses were also repeated with this item removed from the depression scale. There were minimal changes in explained variance and fixed coefficients across all modeling steps, with discrepancy of maximum 0.01 in fixed effects of distress at all levels. The item was thus retained in the reported analyses.

Table 5. Fixed effects for the final model with observed comorbidity covariates (Model 7), with estimated regression coefficients (β), standard errors of the estimates (S.E.) and *p*-values generated from Wald-tests of significance.

Fixed effects	Psychological distress			Musculoskeletal pain			Intercept
	Varying NSE	Stable NSE	Additive Genetic	Varying NSE	Stable NSE	Additive Genetic	
β	0.09	0.29	0.37	0.22	0.49	0.67	−0.05
S.E.	0.03	0.02	0.03	0.03	0.03	0.03	0.02
$p > \|Z\|$	0.002	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001	0.024
Comorbidity indicators							Female gender
	Neurological	Endocrine	Autoimmune	Sleep Disorders	Cancer	Coronary	
β	0.23	0.08	0.15	0.43	0.27	0.17	−0.03
S.E.	0.06	0.04	0.06	0.06	0.05	0.09	0.03
$p > \|Z\|$	< 0.001	0.030	0.008	< 0.001	< 0.001	0.064	0.374

Note: Psychological distress and musculoskeletal pain have level-specific regression coefficients for varying non-shared environment (NSE), stable NSE and additive genetics, while regression coefficients of comorbidity indicators are included as level 2 variables (i.e. stable within each individual across timepoints).

Discussion

Through this study, we found that pain and psychological distress are associated with fatigue due to a considerable common genetic and stable non-shared environmental susceptibility, but also through direct within-person effects across time. The findings demonstrate the considerable relevance of pain and distress for a comprehensive understanding of the fatigue phenomenon, and may inform research on etiological and symptom-maintaining mechanisms. The empirical demonstration of direct within-person effects, untangled from genetic and stable environmental confounders, provides support for the necessity of addressing pain and distress as comorbidities in the management of fatigue, and may inform further research into clinical treatment options. While the exact pathogenesis and the comprehensive understanding of potential causal mechanisms of fatigue remains elusive, and the relationships with pain and distress remain outside of experimental control, our findings nevertheless suggest a complex causal structure underlying these associations.

Phenotype fatigue was shown to have a considerable heritable component of 45%, in line with earlier estimates (Hickie et al., 1999; Vassend et al., 2018), with a stable non-shared environmental component of 22%, and a time-varying component of 27%. The non-shared environmental component demonstrates that there is additional stability within individuals not attributable to additive genetic effects. Pain and distress showed moderate heritable components within the range of heritability estimates from earlier studies on pain (Williams, Spector, & MacGregor, 2010) and distress (Agrawal, Jacobson, Gardner, Prescott, & Kendler, 2004; Rijsdijk et al., 2003), but also considerable stable non-shared environmental components, albeit to a lesser degree for pain (14%) than for distress (27%).

The regression models indicate that both musculoskeletal pain and psychological distress have significant effects on fatigue through shared genetic causes, in line with previous research, which has shown that an abundance of the covariance between these phenotypes can be attributed to pleiotropic effects (i.e. shared genetic susceptibility)

(Corfield et al., 2016b; Vassend et al., 2018). An epistemic challenge in understanding these relationships has, however, been to control for the effects of additional environmental confounders which might mediate or moderate these associations. By using a within-person control condition, we isolated the effects of the non-shared environment, and pain and distress showed significant and strong effects on fatigue also at this level. This, in turn, indicates that intra-individual stability in pain and distress is associated with fatigue, beyond the effects of having the same genetic material. Following these control conditions, comorbidity indicators were employed to control for somatic illness burden, which could potentially explain some of the genetic or environmental covariance between these phenomena. Most illness categories showed significant effects, but did not reduce the time-varying effects of distress and pain considerably. This indicates that while there are evidently shared etiological influences underlying these phenotypes, these associations are not merely due to shared genetic and environmental causes, or due to somatic illness. Of interest to future studies that do not contain genetically informed data, the mere inclusion of pain as a time-varying predictor explains 74% of the additive genetic variance in fatigue, and this could conceptually entail that controlling for pain in models of fatigue could serve to eliminate a great deal of genetic confounding, and serve as a quasi-co-twin-control method.

While the longitudinal co-twin design employed in this study provides opportunities for inference of effects free from genetic and dispositional confounding, the effects may, however, be bidirectional (McAdams et al., 2020; McGue et al., 2010), and the exact direction of the relationships between pain, distress and fatigue cannot be inferred from our results. An earlier review of studies examining the associations between pain and fatigue, found that there was ample evidence for an etiological association between them (Fishbain et al., 2003), but as later pointed out by Lenaert, Meulders, and van Heugten (2018), there was at that time insufficient evidence to establish unidirectional causality. More recent studies have attempted to investigate directional influences between these symptoms. One recent study investigated the temporal patterns of fatigue, pain and depression in multiple sclerosis, and found a strong bidirectional influence between pain and fatigue, while depression showed no significant temporal association with fatigue (Kratz, Murphy, & Braley, 2017). A study on patients with traumatic brain injury found that pain was linked to fatigue only in the first months following injury, whereas depression remained a strong correlate of fatigue across the first year post-injury (Beaulieu-Bonneau & Ouellet, 2017). A longitudinal study of primary care patients presenting with fatigue examined the temporal relation between fatigue and pain, and found best support for a model of synchronous changes in fatigue and pain across time (Nijrolder, van der Windt, Twisk, & van der Horst, 2010). The results from our study establishes similar and robust synchronous changes in pain and fatigue across time, and furthermore provides a hierarchical overview of stable genetic and environmental contributions to susceptibility for fatigue and pain in general. When examining the impact of pain on fatigued versus non-fatigued adolescents with Epstein–Barr infection, both the number of pain symptoms and pain severity were elevated in the fatigued group, and pain had a significant negative impact on quality of life for those suffering from chronic fatigue following infection (Brodwall, Pedersen, Asprusten, & Wyller, 2020). The authors concluded that pain in chronic fatigue is essential to clinical management and further research into interventions for fatigue. The findings from our

study illustrate that a considerable degree of the co-occurrence of pain and fatigue is due to genetic and stable environmental influences contributing to vulnerability for both, but additionally that there is also a relationship between them over time. This strengthens the proposal from Brodwall et al. (2020) that pain should be construed as a candidate for treatment in conjunction with chronic fatigue.

These studies, along with our findings, seem to converge towards an understanding of pain and fatigue as particularly intertwined symptoms across time in a variety of clinical conditions, even though our findings does indicate overlap in genetic and environmental causes for both. This is in line with more recent proposals for understanding pain and fatigue as expressions of similar systems with overlapping biological, psychological and social mechanisms with bidirectional influences (Lenaert et al., 2018; Van Damme et al., 2018; Wyller, 2019).

Mechanisms of underlying associations

Earlier studies of the genetic contributions to fatigue have primarily focused on biological mechanisms, and according to a review by Landmark-Høyvik et al. (2010) the progress has been hindered by a lack of statistical power and inconsistent phenotype definitions. A recent review of studies examining specific genetic polymorphisms underlying chronic fatigue conditions, implicates single nucleotide polymorphisms related to HPA-axis regulation, immune-mediated inflammatory processes and various neurotransmitter regulation (Wang, Yin, Miller, & Xiao, 2017). Interestingly, HPA axis dysregulation and inflammatory processes have also been pathophysiologically linked to depression and chronic pain disorders (Pariante & Lightman, 2008; Woda, Picard, & Dutheil, 2016), which might explain the shared genetic vulnerability between pain, distress and fatigue. Boksem and Tops (2008) proposed a model for fatigue as an initially adaptive response to unconscious evaluations of reward and energetical costs in activity, with reward circuits including such neural structures as nucleus accumbens, orbitofrontal cortex, amygdala, insula and anterior cingulate cortex. Within this theoretical framework, HPA axis dysregulation, inflammatory processes and neurotransmitter imbalances (dopamine systems in particular) are hypothesized to contribute to chronification of fatigue. Later proposals for understanding the role of pain in fatigue build upon this conceptualization of fatigue as a homeostatic signal, and suggest that pain may interfere with the balance between perceived rewards and energetical costs (Van Damme et al., 2018; Wyller, 2019). Furthermore, biological underpinnings of central sensitization may be implied as a common genetic basis for fatigue, pain and distress, and has been increasingly implicated as a candidate mechanism for the chronification of pain, including in CFS (Meeus & Nijs, 2007). Central sensitization has been closely linked with stress dysregulation and psychological distress (Yunus, 2007), although it is unlikely that central sensitization in isolation can explain the development and exacerbation of fatigue (Yunus, 2015).

When considering stable (dispositional) environmental factors which might underlie the associations between pain, distress and fatigue, neuroticism or trait negative affectivity warrants some attention. Previous twin studies have found evidence for a common heritable factor underlying both neuroticism and psychological distress (Kendler et al., 2019), through an individual tendency for experiencing negative affectivity. Trait neuroticism is also associated with catastrophizing and avoidance in pain disorders, two

widely implicated mechanisms in the chronification of pain (Goubert, Crombez, & Van Damme, 2004; Leeuw et al., 2007).

Lastly, the current results indicate that pain and distress exert significant time-varying effects on fatigue. Through controlling for genetic and stable environmental confounding between them, these findings are highly suggestive of direct effects within time, with a particularly robust effect of pain. This establishes that changes in distress and particularly pain are associated with changes in fatigue within individuals, beyond that attributable to genetic or stable environmental predispositions.

Conclusions: implications for clinical understanding of fatigue

This study provides incremental evidence for the genetic, environmental and time-varying architecture underlying the relationship between musculoskeletal pain, psychological distress and fatigue. More research is needed to disentangle the exact genetic, epigenetic, and environmental mechanisms in the development of fatigue, and translational research is warranted to better understand the implications of these causal relations. While genetic and stable non-shared environmental factors may not be viable targets for treatment as of yet, due to their relatively stable nature, the demonstration that pain and distress are causally linked with fatigue indicates that comorbid complaints of pain and distress should be construed as important and viable targets for clinical interventions in persons with clinical levels of fatigue. Pain showed particularly robust time-varying effects, and should always be assessed and addressed in the presence of fatigue complaints. Furthermore, somatic comorbidity also showed significant effects on fatigue, but did not reduce the effects of pain and distress, supporting the notion that pain and distress may represent transdiagnostic mechanisms for maintenance and exacerbation of fatigue (Menting et al., 2018). Further research is warranted to examine the disease-specific relevance of these factors, and other potential factors contributing to the both phenotypically and etiologically heterogenous fatigue symptom.

Limitations

One underlying assumption for valid estimation of heritability and heritability-based statistics is the equal environments assumption. This assumption holds that monozygotic and dizygotic twins are influenced in a similar manner by their shared environment. While the assumption may not hold as universally valid, violations from the assumption are unlikely to bias the result considerably (Felson, 2014). Specific directional paths between distress, pain and fatigue cannot be isolated based on our findings, but the confounding-free effects evidently show covariation across time, supportive of presumably bidirectional or synchronous effects, in line with earlier research. One limitation, however, is that our design does not eliminate all confounding from the non-shared environment (see Figure 3), and that life events in between measurement timepoints might exert influences on fatigue, distress and pain that explain some proportion of the time-varying association between them. Further longitudinal studies with closer spaced measurement intervals and control over other

potential moderators and mediators might contribute to a better understanding of this dynamic.

Data availability statement

The relevant estimates and data for this study have been made available in this manuscript. Due to restrictions from the Norwegian Twin Registry (organized by the Norwegian Institute of Public Health) and privacy restrictions, individual twin data is unavailable for the public. Information on applications for data access can be found here: https://www.fhi.no/en/more/health-studies/norwegian-twin-registry/

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References

Aaronson, L. S., Teel, C. S., Cassmeyer, V., Neuberger, G. B., Pallikkathayil, L., Pierce, J., … Wingate, A. (1999). Defining and measuring fatigue. *Image--the Journal of Nursing Scholarship*, *31*(1), 45–50.

Agrawal, A., Jacobson, K. C., Gardner, C. O., Prescott, C. A., & Kendler, K. S. (2004). A population based twin study of sex differences in depressive symptoms. *Twin Research and Human Genetics*, *7*(2), 176–181.

Ball, H. A., Siribaddana, S. H., Sumathipala, A., Kovas, Y., Glozier, N., McGuffin, P., & Hotopf, M. (2010a). Environmental exposures and their genetic or environmental contribution to depression and fatigue: A twin study in Sri Lanka. *BMC Psychiatry*, *10*(1), 1–10.

Ball, H. A., Sumathipala, A., Siribaddana, S. H., Kovas, Y., Glozier, N., McGuffin, P., & Hotopf, M. (2010b). Aetiology of fatigue in Sri Lanka and its overlap with depression. *The British Journal of Psychiatry*, *197*(2), 106–113.

Beaulieu-Bonneau, S., & Ouellet, M.-C. (2017). Fatigue in the first year after traumatic brain injury: Course, relationship with injury severity, and correlates. *Neuropsychological Rehabilitation*, *27*(7), 983–1001.

Boksem, M. A., & Tops, M. (2008). Mental fatigue: Costs and benefits. *Brain Research Reviews*, *59*(1), 125–139. doi:10.1016/j.brainresrev.2008.07.001

Bower, J. E. (2014). Cancer-related fatigue—mechanisms, risk factors, and treatments. *Nature Reviews Clinical Oncology*, *11*(10), 597.

Brodwall, E. M., Pedersen, M., Asprusten, T. T., & Wyller, V. B. B. (2020). Pain in adolescent chronic fatigue following Epstein-Barr virus infection. *Scandinavian Journal of Pain*, *20*(4), 765–773.

Bültmann, U., Kant, I., Kasl, S. V., Beurskens, A. J., & van den Brandt, P. A. (2002). Fatigue and psychological distress in the working population: Psychometrics, prevalence, and correlates. *Journal of Psychosomatic Research*, *52*(6), 445–452.

Corfield, E. C., Martin, N. G., & Nyholt, D. R. (2016a). Co-occurrence and symptomatology of fatigue and depression. *Comprehensive Psychiatry*, *71*, 1–10.

Corfield, E. C., Martin, N. G., & Nyholt, D. R. (2016b). Shared genetic factors in the co-occurrence of depression and fatigue. *Twin Research and Human Genetics*, *19*(6), 610–618.

Corfield, E. C., Martin, N. G., & Nyholt, D. R. (2017). Familiality and heritability of fatigue in an Australian twin sample. *Twin Research and Human Genetics*, *20*(3), 208–215.

Cortes Rivera, M., Mastronardi, C., Silva-Aldana, C. T., Arcos-Burgos, M., & Lidbury, B. A. (2019). Myalgic encephalomyelitis/chronic fatigue syndrome: A comprehensive review. *Diagnostics*, *9*(3), 91.

Creavin, S. T., Dunn, K. M., Mallen, C. D., Nijrolder, I., & van der Windt, D. A. (2010). Co-occurrence and associations of pain and fatigue in a community sample of Dutch adults. *European Journal of Pain*, *14*(3), 327–334.

Derogatis, L. R., Lipman, R. S., Rickels, K., Uhlenhuth, E. H., & Covi, L. (1974). The hopkins symptom checklist (HSCL): a self-report symptom inventory. *Behavioral Science*, *19*(1), 1–15.

Duncan, F., Wu, S., & Mead, G. E. (2012). Frequency and natural history of fatigue after stroke: A systematic review of longitudinal studies. *Journal of Psychosomatic Research*, *73*(1), 18–27.

Felson, J. (2014). What can we learn from twin studies? A comprehensive evaluation of the equal environments assumption. *Social Science Research*, *43*, 184–199.

Finsterer, J., & Mahjoub, S. Z. (2014). Fatigue in healthy and diseased individuals. *American Journal of Hospice and Palliative Medicine*, *31*(5), 562–575.

Fishbain, D. A., Cole, B., Cutler, R. B., Lewis, J., Rosomoff, H. L., & Fosomoff, R. S. (2003). Is pain fatiguing? A structured evidence-based review. *Pain Medicine*, *4*(1), 51–62.

Freidin, M. B., Wells, H. R., Potter, T., Livshits, G., Menni, C., & Williams, F. M. (2018). Metabolomic markers of fatigue: Association between circulating metabolome and fatigue in women with chronic widespread pain. *Biochimica et Biophysica Acta (BBA)-Molecular Basis of Disease*, *1864*(2), 601–606.

Goubert, L., Crombez, G., & Van Damme, S. (2004). The role of neuroticism, pain catastrophizing and pain-related fear in vigilance to pain: A structural equations approach. *Pain*, *107*(3), 234–241.

Henderson, M., & Tannock, C. (2004). Objective assessment of personality disorder in chronic fatigue syndrome. *Journal of Psychosomatic Research*, *56*(2), 251–254. doi:10.1016/S0022-3999(03)00571-3

Hickie, I., Bennett, B., Lloyd, A., Heath, A., & Martin, N. (1999a). Complex genetic and environmental relationships between psychological distress, fatigue and immune functioning: A twin study. *Psychological Medicine*, *29*(2), 269–277.

Hickie, I., Kirk, K., & Martin, N. (1999b). Unique genetic and environmental determinants of prolonged fatigue: A twin study. *Psychological Medicine*, *29*(2), 259–268.

Kendler, K. S., Gardner, C. O., Neale, M. C., Aggen, S., Heath, A., Colodro-Conde, L., … Gillespie, N. A. (2019). Shared and specific genetic risk factors for lifetime major depression, depressive symptoms and neuroticism in three population-based twin samples. *Psychological Medicine*, *49*(16), 2745–2753.

Kratz, A. L., Murphy, S. L., & Braley, T. J. (2017). Pain, fatigue, and cognitive symptoms are temporally associated within but not across days in multiple sclerosis. *Archives of Physical Medicine and Rehabilitation*, *98*(11), 2151–2159.

Kristiansen, M. S., Stabursvik, J., O'Leary, E. C., Pedersen, M., Asprusten, T. T., Leegaard, T., … Godang, K. (2019). Clinical symptoms and markers of disease mechanisms in adolescent chronic fatigue following Epstein-Barr virus infection: An exploratory cross-sectional study. *Brain, Behavior, and Immunity*, *80*, 551–563.

Lamers, F., Hickie, I., & Merikangas, K. R. (2013). Prevalence and correlates of prolonged fatigue in a U.S. sample of adolescents. *American Journal of Psychiatry*, *170*(5), 502–510. doi:10.1176/appi.ajp.2012.12040454

Landmark-Høyvik, H., Reinertsen, K. V., Loge, J. H., Kristensen, V. N., Dumeaux, V., Fosså, S. D., … Edvardsen, H. (2010). The genetics and epigenetics of fatigue. *PM&R*, *2*(5), 456–465.

Leeuw, M., Goossens, M. E., Linton, S. J., Crombez, G., Boersma, K., & Vlaeyen, J. W. (2007). The fear-avoidance model of musculoskeletal pain: Current state of scientific evidence. *Journal of Behavioral Medicine*, *30*(1), 77–94.

Lenaert, B., Meulders, A., & van Heugten, C. M. (2018). Tired of pain or painfully tired? A reciprocal relationship between chronic pain and fatigue. *Pain*, *159*(6), 1178–1179.

Loge, J. H., Ekeberg, Ø, & Kaasa, S. (1998). Fatigue in the general Norwegian population: Normative data and associations. *Journal of Psychosomatic Research*, *45*(1), 53–65.

Magnus, P., Berg, K., & Nance, W. E. (1983). Predicting zygosity in Norwegian twin pairs born 1915-1960. *Clinical Genetics*, *24*(2), 103–112. <Go to ISI>://WOS:A1983RF13100004.

Manjaly, Z. M., Harrison, N. A., Critchley, H. D., Do, C. T., Stefanics, G., Wenderoth, N., … Stephan, K. E. (2019). Pathophysiological and cognitive mechanisms of fatigue in multiple sclerosis. *Journal of Neurology Neurosurgery & Psychiatry*, *90*(6), 642–651. doi:10.1136/jnnp-2018-320050

Matura, L. A., Malone, S., Jaime-Lara, R., & Riegel, B. (2018). A systematic review of biological mechanisms of fatigue in chronic illness. *Biological Research for Nursing*, doi:10.1177/1099800418764326

McAdams, T. A., Rijsdijk, F. V., Zavos, H. M., & Pingault, J.-B. (2020). Twins and causal inference: Leveraging nature's experiment. *Cold Spring Harbor Perspectives in Medicine*, *11*(6), Article a039552.

McGue, M., Osler, M., & Christensen, K. (2010). Causal inference and observational research: The utility of twins. *Perspectives on Psychological Science*, *5*(5), 546–556.

Meeus, M., & Nijs, J. (2007). Central sensitization: A biopsychosocial explanation for chronic widespread pain in patients with fibromyalgia and chronic fatigue syndrome. *Clinical Rheumatology*, *26*(4), 465–473.

Menting, J., Tack, C. J., Bleijenberg, G., Donders, R., Droogleever Fortuyn, H. A., Fransen, J., … van der Werf, S. P. (2018). Is fatigue a disease-specific or generic symptom in chronic medical conditions? *Health Psychology*, *37*(6), 530–543.

Mollayeva, T., Kendzerska, T., Mollayeva, S., Shapiro, C. M., Colantonio, A., & Cassidy, J. D. (2014). A systematic review of fatigue in patients with traumatic brain injury: The course, predictors and consequences. *Neuroscience & Biobehavioral Reviews*, *47*, 684–716. doi:10.1016/j.neubiorev.2014.10.024

Nater, U. M., Jones, J. F., Lin, J. M., Maloney, E., Reeves, W. C., & Heim, C. (2010). Personality features and personality disorders in chronic fatigue syndrome: A population-based study. *Psychotherapy and Psychosomatics*, *79*(5), 312–318. doi:10.1159/000319312

Newman, D. A. (2014). Missing data: Five practical guidelines. *Organizational Research Methods*, *17*(4), 372–411.

Nijrolder, I., van der Windt, D. A., Twisk, J. W., & van der Horst, H. E. (2010). Fatigue in primary care: Longitudinal associations with pain. *Pain*, *150*(2), 351–357.

Nilsen, T. S., Knudsen, G. P., Gervin, K., Brandt, I., Røysamb, E., Tambs, K., … Magnus, P. (2013). The Norwegian twin registry from a public health perspective: A research update. *Twin Research and Human Genetics*, *16*(1), 285–295.

Ormstad, H., & Eilertsen, G. (2015). A biopsychosocial model of fatigue and depression following stroke. *Medical Hypotheses*, *85*(6), 835–841.

Pariante, C. M., & Lightman, S. L. (2008). The HPA axis in major depression: Classical theories and new developments. *Trends in Neurosciences*, *31*(9), 464–468.

Patejdl, R., Penner, I. K., Noack, T. K., & Zettl, U. K. (2016). Multiple sclerosis and fatigue: A review on the contribution of inflammation and immune-mediated neurodegeneration. *Autoimmunity Reviews*, *15*(3), 210–220.

Penner, I. K., & Paul, F. (2017). Fatigue as a symptom or comorbidity of neurological diseases. *Nature Reviews Neurology*, *13*(11), 662–675.
Poeschla, B., Strachan, E., Dansie, E., Buchwald, D. S., & Afari, N. (2013). Chronic fatigue and personality: A twin study of causal pathways and shared liabilities. *Annals of Behavioral Medicine*, *45*(3), 289–298.
Rabe-Hesketh, S., & Skrondal, A. (2012). *Multilevel and longitudinal modeling using stata* (3rd ed.). College Station, TX: STATA press.
Rabe-Hesketh, S., Skrondal, A., & Gjessing, H. K. (2008). Biometrical modeling of twin and family data using standard mixed model software. *Biometrics*, *64*(1), 280–288.
Reyes-Gibby, C. C., Mendoza, T. R., Wang, S., Anderson, K. O., & Cleeland, C. S. (2003). Pain and fatigue in community-dwelling adults. *Pain Medicine*, *4*(3), 231–237.
Rijsdijk, F., Snieder, H., Ormel, J., Sham, P., Goldberg, D., & Spector, T. (2003). Genetic and environmental influences on psychological distress in the population: General health questionnaire analyses in UK twins. *Psychological Medicine*, *33*(5), 793–801.
Schreiber, H., Lang, M., Kiltz, K., & Lang, C. (2015). Is personality profile a relevant determinant of fatigue in multiple sclerosis? *Frontiers in Neurology*, *6*, 2. doi:10.3389/fneur.2015.00002
Smith, G. D. (2011). Epidemiology, epigenetics and the 'gloomy prospect': Embracing randomness in population health research and practice. *International Journal of Epidemiology*, *40*(3), 537–562.
StataCorp. (2019). *Stata Statistical software: Release 16*. College Station, TX: StataCorp LLC.
Strand, B. H., Dalgard, O. S., Tambs, K., & Rognerud, M. (2003). Measuring the mental health status of the Norwegian population: A comparison of the instruments SCL-25, SCL-10, SCL-5 and MHI-5 (SF-36). *Nordic Journal of Psychiatry*, *57*(2), 113–118.
Sullivan, P. F., Evengård, B., Jacks, A., & Pedersen, N. L. (2005). Twin analyses of chronic fatigue in a Swedish national sample. *Psychological Medicine*, *35*(9), 1327–1336.
Tikhodeyev, O. N., & Shcherbakova, OV. (2019). The problem of non-shared environment in behavioral genetics. *Behavior Genetics*, *49*(3), 259–269.
Van Damme, S., Becker, S., & Van der Linden, D. (2018). Tired of pain? Toward a better understanding of fatigue in chronic pain. *Pain*, *159*(1), 7–10.
Vassend, O., Lian, L., & Andersen, H. T. (1992). Norske versjoner av NEO-personality inventory, Symptom Checklist 90 revised og Giessen subjective complaints list. Del I. *Tidsskrift for Norsk Psykologforening*, *29*(12), 1150–1160.
Vassend, O., Røysamb, E., Nielsen, C. S., & Czajkowski, N. O. (2018). Fatigue symptoms in relation to neuroticism, anxiety-depression, and musculoskeletal pain. A longitudinal twin study. *Plos One*, *13*(6), e0198594.
Wang, T., Yin, J., Miller, A. H., & Xiao, C. (2017). A systematic review of the association between fatigue and genetic polymorphisms. *Brain, Behavior, and Immunity*, *62*, 230–244.
Williams, F. M., Spector, T. D., & MacGregor, A. J. (2010). Pain reporting at different body sites is explained by a single underlying genetic factor. *Rheumatology*, *49*(9), 1753–1755.
Woda, A., Picard, P., & Dutheil, F. (2016). Dysfunctional stress responses in chronic pain. *Psychoneuroendocrinology*, *71*, 127–135.
Wyller, V. B. B. (2019). Pain is common in chronic fatigue syndrome–current knowledge and future perspectives. *Scandinavian Journal of Pain*, *19*(1), 5–8.
Yunus, M. B. (2007). Fibromyalgia and overlapping disorders: The unifying concept of central sensitivity syndromes. *Seminars in Arthritis and Rheumatism*, *36*(6), 339–356.
Yunus, M. B. (2015). Editorial review (thematic issue: An update on central sensitivity syndromes and the issues of nosology and psychobiology). *Current Rheumatology Reviews*, *11*(2), 70–85.

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Impact of Somatic Vulnerability, Psychosocial Robustness and Injury-Related Factors on Fatigue following Traumatic Brain Injury—A Cross-Sectional Study

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Abstract: Fatigue is a common symptom after traumatic brain injuries (TBI) and a crucial target of rehabilitation. The subjective and multifactorial nature of fatigue necessitates a biopsychosocial approach in understanding the mechanisms involved in its development. The aim of this study is to provide a comprehensive exploration of factors relevant to identification and rehabilitation of fatigue following TBI. Ninety-six patients with TBI and confirmed intracranial injuries were assessed on average 200 days post-injury with regard to injury-related factors, several patient-reported outcome measures (PROMS) of fatigue, neuropsychological measures, and PROMS of implicated biopsychosocial mechanisms. Factor analytic approaches yielded three underlying factors, termed Psychosocial Robustness, Somatic Vulnerability and Injury Severity. All three dimensions were significantly associated with fatigue in multiple regression analyses and explained 44.2% of variance in fatigue. Post hoc analyses examined univariate contributions of the associations between the factors and fatigue to illuminate the relative contributions of each biopsychosocial variable. Implications for clinical practice and future research are discussed.

Keywords: fatigue; rehabilitation; traumatic brain injury; neuropsychological function; PROMS

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1. Introduction

Fatigue is a common symptom following traumatic brain injury (TBI) [1], with potentially severe impact on participation and quality of life [2], even when controlling for injury severity [3]. TBI is defined as "an alteration in brain function, or other evidence of brain pathology, caused by an external force" [4]. TBI is associated with increased mortality [5], and survivors may suffer from severe functional impairment, of which fatigue is often reported as a persistent problem in sub-acute and chronic phases following injury [6].

Fatigue is often defined as "an awareness of a decreased capacity for physical or mental activity, due to a perceived imbalance in the availability, utilization or restoration of energy that is needed to perform activities" [7]. A large number of heterogenous patient-reported outcome measures (PROMS) have been developed to evaluate subjectively experienced severity, characteristics and consequences of fatigue [8]. PROMS are, however, vulnerable to an assortment of potential biases [9], and there is currently no consensus for a single gold standard measure. A recent study evaluated the content overlap between items included in various fatigue PROMS often used in patients with stroke [10], showing that items from different PROMS may measure severity, characteristics, management or consequences of fatigue to varying degrees. Items from the Fatigue Severity Scale (FSS) [11], which is commonly used in patients with TBI, pertain primarily to the perceived consequences of fatigue. For a comprehensive measurement of fatigue, it is therefore necessary to expand the measurement using other PROMS and to establish whether fatigue can be construed as a unidimensional phenomenon across measures.

Conceptual models for the development and maintenance of fatigue after TBI and in other neurological disorders emphasize the heterogeneity in associated factors, spanning from premorbid characteristics, through primary injury-related factors, to secondary exacerbating factors [1,8]. The complex nature of fatigue and the abundance of implicated biopsychosocial factors necessitates an investigation of potential unifying mechanisms underlying the relationships between fatigue and associated constructs.

1.1. Mechanisms Associated with Fatigue

Demographic factors play an uncertain role in fatigue following TBI. Earlier studies have shown minimal or nonsignificant associations between fatigue, age and female gender [1,12–14], and a recent larger cohort study showed small but positive associations between fatigue, younger age, and female gender through the first six months post-injury [15]. This study further demonstrated an interaction between age and fatigue trajectory, with patients above 48 years of age reporting increasing, and younger patients decreasing, rates over the first 6 months. Of interest, injury severity does not seem to be consistently related to fatigue [1], with the caveat that most studies include a majority of patients with mild TBI. Cognitive deficits such as slowed information processing and attentional deficits have however been shown to be associated with increased levels of fatigue [16,17]. The coping hypothesis put forward by van Zomeren et al. [18] is one plausible explanation, in that cognitive deficits might result in increased energy expenditure during mental and physical exertion, which in turn may contribute to fatigue.

Beyond the direct effect of cognitive and other injury-related factors, an abundance of biopsychosocial mechanisms are implicated in onset and maintenance of fatigue. A conceptual model by Mollayeva et al. [1] emphasized the role of both TBI-specific as well as generic, non-injury-related mechanisms. A recent review [19] likewise established that there are several common risk factors for fatigue across neurological disorders, such as pre- and comorbid psychiatric symptoms, pain, sleep problems, and genetics.

Pain commonly co-occurs with fatigue after TBI [20,21] and is implicated as a central mechanism in fatigue across etiologies [22]. Beaulieu-Bonneau and Ouellet [23] found that pain was associated with fatigue 4 and 8 but not 12 months post TBI, indicating that this relationship may vary as an effect of time since injury.

Psychological distress (i.e., symptoms of depression and anxiety) is also related to fatigue following TBI [24–28]. While fatigue may by itself be a depressive symptom, fatigue may occur in isolation from depression in TBI and acquired brain injury [26], suggesting that the two are related, but distinguishable. Beaulieu-Bonneau and Ouellet [23] found depression to be associated with fatigue at 4, 8 and 12 months post-injury, indicating that these symptoms are intertwined over time. Symptoms of anxiety have also been linked with fatigue in isolation, although anxiety and depression frequently co-occur [27,29].

In addition to symptoms that may vary over time, people differ in their stable proneness for negative affect. Trait neuroticism as a five-factor personality trait has been ex-

tensively implicated as a possible precipitating mechanism in relation to fatigue in other populations, in epidemiological studies [30–33] and in mild TBI [34]. Merz et al. [34] also found negative associations between fatigue and trait agreeableness, conscientiousness and extraversion in patients with mild TBI. The role of neuroticism and other personality traits have, however, not been examined in relation to fatigue following more severe TBI. Trait optimism, furthermore, has been linked to better cognitive functioning after TBI [35], but has, to the best of our knowledge, not been examined in relation to post-TBI fatigue.

Daytime sleepiness and insomnia have been extensively studied in relation to fatigue following TBI [27,36,37]. For instance, Cantor et al. [14] demonstrated that fatigue and insomnia frequently co-occur, but that post-TBI fatigue may also occur without insomnia. Insomnia without post-TBI fatigue, however, was rare. As expected, daytime sleepiness was reported more frequently in patients with fatigue.

Motivational propensities for reward and punishment might additionally contribute to the development of fatigue. Behavioral inhibition (i.e., a tendency to be motivated by avoidance of unpleasant stimuli) and behavioral activation (i.e., a tendency to be motivated by the attainment of pleasure and reward) systems (BIS/BAS) were initially described by Carver and White [38]. A greater propensity for being motivated by avoidance of aversive stimuli and lower degree of reward responsiveness has been linked to fatigue in, e.g., multiple sclerosis [39]. The impact of BIS/BAS-propensities on fatigue has not, to the best of our knowledge, been examined in TBI.

Feelings of loneliness and isolation predict later development of both fatigue, pain and depression in non-TBI populations [40]. While loneliness has not been examined specifically as a risk factor for fatigue after TBI, loneliness is a common issue for people living with the chronic effects of TBI [41], leaving this factor of interest to explore.

Psychosocial resilience has been shown to predict increased participation following mild-severe TBI [42], and to predict longitudinal decreases in fatigue following mild TBI [43] but has not been studied extensively with regard to post-TBI fatigue.

1.2. Clinical Complexity

In summary, fatigue following TBI has a demonstrable impact on quality of life and functional recovery, and an abundance of mechanisms could potentially be implicated in the precipitation, initiation and maintenance of fatigue following TBI. The factors involved may act in isolation, their effects may be summed, and they may interact with each other in dynamic ways. An obstacle in studies involving vulnerability and protective factors is that inferences drawn from models incorporating only a few factors may not provide a comprehensive understanding of possible underlying constructs. A clearer picture of the underlying clustering of vulnerability and protective factors, however, may inform further research in selection of the most essential constructs in fatigue models, and inform clinical decision making.

1.3. Study Aims

The primary aim of this study was to enhance our theoretical understanding of the relationship between fatigue and injury-related, cognitive and self-reported biopsychosocial factors. A factor analytic approach was used to (1) examine if fatigue could be construed as one single outcome across several measures, and (2) examine potential underlying dimensionality of several injury-related, cognitive and psychosocial measures commonly associated with fatigue. Finally, we aimed to (3) explore the relevance of these dimensions to fatigue 6 months after TBI.

2. Materials and Methods

2.1. Recruitment

The study includes the first wave from a prospective observational study of patients with TBI conducted from 2018–2021. Included patients were injured between January 2018 and April 2020 and admitted to the Neurosurgery department at Oslo University Hospital

(OUH). OUH is the only Level I trauma center with neurosurgical services in the south-eastern region of Norway with a population base of more than half of the Norwegian population (i.e., 2.9 million).

Injury characteristics and clinical data from the acute hospital stay were retrieved from the Oslo TBI Registry—Neurosurgery, a quality database at OUH [44]. The remaining variables were measured approximately 6 months post-injury. Inclusion criteria were patients between 18–65 years of age, admitted with TBI (ICD-10 diagnoses S06.1–S06.9), herein defined as patients presenting with intracranial injury (as confirmed by computed tomography (CT) or magnetic resonance imaging (MRI)) during the acute phase, and who have survived until six months post-injury. Exclusion criteria were pre- and comorbid diagnoses of severe mental illness or neurological disorders, ongoing substance or alcohol abuse, non-fluency in Norwegian or English, and severe functional impairment hindering completion of the study protocol (i.e., disorders of consciousness, persistent severe anosognosia and severe motor deficits). Patients were identified prospectively after admission to the Neurosurgical department at OUH. Patients were recruited through clinical follow-up consultations at Sunnaas Rehabilitation Hospital and the Department of Physical Medicine and Rehabilitation at OUH. Patients not followed up at these institutions received an invitation to participate by mail.

2.2. Injury Characteristics

Pre-injury physical health status was scored using the American Society of Anesthesiologists' physical status classification (ASA-PS), with scores ranging from 1 to 6 depending on the absence or presence of various severities of systemic disease premorbid to injury [45], with increasing scores indicating more severe disease.

Several indicators of injury severity were included. Lowest Glasgow Coma Scale (GSC) score ranged from 3–15 registered at injury site, or admission to hospital pre-intubation was registered, as well as GCS upon discharge from the acute hospital. Rotterdam CT score is a prognostic classification of traumatic brain injuries scored on the basis of grade of compression of the basal cisterns, the presence of a midline shift, epidural mass lesion, and intraventricular blood or tSAH [46], with higher scores indicating more severe injuries. The Head Abbreviated Injury Scale (AIS_head) version 1998 [47] was used to describe the anatomical severity of injury. AIS classifies injuries to various body regions ranging from minor (1) to fatal (6). We dichotomized AIS_head scores into AIS < 4 (less severe) and AIS ≥ 4 (very severe injury) for descriptive analyses but used the ordinal scale scores in subsequent analyses. Finally, discharge destination from the acute hospital was registered. For this study, a dichotomous dummy variable was generated for those who were referred through a direct pathway into rehabilitation units.

2.3. Measures

2.3.1. Fatigue

The Fatigue Severity Scale (FSS) [11] contains 9 items and asks the participants to rate the degree of interference from fatigue in various functional domains on a Likert scale from 1 to 7, with higher scores indicating higher degree of fatigue interference. Norwegian norms adjusted for age, gender and education are available [48]. The FSS has good psychometric qualities [48].

Chalder Fatigue Scale (CFQ) [49], has been applied primarily in research into chronic fatigue syndrome (CFS) and myalgic encephalomyelitis (ME), but also in neurological populations such as stroke [50]. Patients are asked to rate 11 items pertaining to physical and cognitive/mental symptoms of fatigue within the last month. The CFQ uses a four-point response scale where 0 = "less than usual", 1 = "no more than usual", 2 = "more than usual" and 3 = "much more than usual". Normative data from the general population exist, grouped by age and gender [51].

The fatigue subscale of Giessen Subjective Complaints List (GSCL) [52] has been used within psychosomatic and epidemiological studies. The fatigue subscale includes 6 items,

rating the presence of fatigue symptoms in general on a five-point scale from 0 = "not at all" to 4 = "strongly".

Finally, one item from the Rivermead Post-Concussion Symptoms Questionnaire (RPQ) [53] asks the participants to rate the presence of fatigue on a scale from 0 to 4, where 0 = "not a problem", 1 = "no longer a problem", 2 = "a mild problem", 3 = "a moderate problem", and 4 = "a severe problem". This single item is often used to assess fatigue in patients with concussion and TBI in clinical settings, and a recent multicenter TBI study employed it as a primary outcome measure of fatigue [15].

2.3.2. Neuropsychological Tests

Cognitive functioning was assessed with the following neuropsychological measures:

The Matrix Reasoning and Similarities subtests from Wechsler's Abbreviated Scale of Intelligence (WASI) [54] were included as measures of abstract reasoning abilities. Auditory attention and working memory were assessed with Digit Span from Wechsler's Adult Intelligence Scale IV (WAIS-IV) [55]. Psychomotor speed was assessed with Trail Making Test (TMT) subtests 2–3 and Color-Word Interference Test (CWIT) subtests 1–2 from Delis–Kaplan Executive Function System (D-KEFS) [56]. Subtest 4 from the TMT and subtests 3–4 from the CWIT furthermore provide measures of executive function/mental flexibility. The Conners Continuous Performance Test III (CPT-III) [57] was included as a measure of sustained and focused attention. The change in coefficient of variation (CoV), a measure of increase in intraindividual variability in reaction times from the first to the second half of the test, was computed. CoV is calculated by dividing the standard deviation of reaction times (RT) by the average RT within the individual [58], and the measure of change in CoV was calculated by subtracting the CoV for the first three blocks from the last three blocks (CoV block change).

2.3.3. Secondary PROMS

Psychological distress over the last two weeks was measured using a 10-item short version of Hopkins Symptom Checklist [59,60], with subscales for (1) depressive and (2) anxiety symptoms.

Five-factor personality traits were measured using the NEO Five Factor Inventory 3 (NEO-FFI-3) [61], which provides gender-corrected normative scores on trait neuroticism, conscientiousness, extroversion, agreeableness and openness to experience. The inventory contains 60 items, with 12 items pertaining to each personality trait.

Behavioral inhibition and activation tendencies were measured using The Behavioral Inhibition System/Behavioral Activation System (BIS/BAS) Scale [38], which contains one subscale for BIS, and three subscales for the BAS, namely (1) reward responsiveness, (2) drive, and (3) fun seeking.

Loneliness was measured using three items from the UCLA Loneliness Scale, Version 3 [62].

Trait optimism was measured with six items from the optimism subscale of the Life Orientation Test Revised (LOT-R) [63].

Resilience was measured with the Resilience Scale for Adults (RSA) [64], with subscales for facets of resilience, namely (1) planned future, (2) social competence, (3) family cohesion, (4) perception of self, (5) social resources, and (6) structured style.

Somatic symptom burden was assessed with subscales from Giessen Subjective Complaints List (GSCL) [52], regarding the presence of (1) gastrointestinal symptoms, (2) musculoskeletal symptoms, and (3) cardiovascular symptoms. Pain localization was assessed using a pain drawing [65], with higher scores indicating generalized pain dispersed across several bodily regions. Pain severity across the last two weeks was assessed with Numerical Rating Scales (0–10, where 10 indicates most severe pain) [66], asking the participants to rate (1) the lowest pain severity, (2) the highest pain severity, (3) the average pain severity, and (4) the current pain severity.

Daytime sleepiness was measured with the Epworth Sleepiness Scale [67], which asks respondents to rate the probability of falling asleep throughout a range of daily activities. Subjective sleep deficits were measured with the Insomnia Severity Index [68], which rates the presence of difficulties with falling asleep, staying asleep, early awakening, and the functional impact of sleep problems.

2.3.4. Functional Outcome

Global functional impairment upon discharge from the acute hospital stay was estimated with the five-level Glasgow Outcome Scale (GOS) [69], while functional outcome 6 months post-injury was assessed with the eight-level Glasgow Outcome Scale Extended (GOSE) [70], which categorizes patients based on their degree of return to work, vocational and leisure activities, social and emotional symptoms and a variety of other persistent complaints following injury. Lower scores indicate greater functional impairment.

2.4. Analyses

All analyses were conducted in SPSS, version 27 [71]. Preliminary Pearson correlation analyses were conducted to evaluate bivariate relations between the various measures of fatigue, sociodemographic variables, injury-related factors, neuropsychological measures and self-reported psychosocial constructs.

2.4.1. Dimension Reduction

In order to ascertain a fatigue factor possibly reflecting a unidimensional phenomenon in our TBI sample, a factor analysis was conducted on FSS, CFQ, the fatigue subscale from GSCL, and the fatigue item from RPQ. Items pertaining specifically to cognitive complaints (CFQ items 8–11 and GSCL item 15) and daytime sleepiness (CFQ item 3 and GSCL item 4 and 14) were excluded from these analyses to avoid item overlap between fatigue and independent variables.

Furthermore, an exploratory factor analysis was conducted on all variables (PROMS, neuropsychological and injury-related) with significant ($p < 0.05$) bivariate associations with either one or several of the fatigue measures. Due to the exploratory aim of the study, variables approaching significance (i.e., $p < 0.08$) were also included. Factors with eigenvalues above 1 were first generated in line with the Kaiser Guttman criterium. A scree plot was generated and inspected according to Cattell's criterium [72]. Parallel analyses were performed to generate significant eigenvalues for factor retention [73], which has been shown to be a more consistently accurate method for factor retention decisions [74]. Oblimin oblique rotation was conducted to allow factors to correlate. Saliency of factor loadings was evaluated for significance ($p < 0.05$) according to the formula proposed by Norman and Streiner (2014), providing a cut-off for salient loadings at 0.40. Variables not loading significantly on any of the factors were removed, and the analyses were repeated without them. In the case of cross-loading variables, variables were selected on the basis of the strength of their loadings, as well as their conceptual alignment with the factor on the whole. New factor analyses were then conducted for each factor, including only those variables saliently loading on the factor. Factor scores were generated through regression.

Factor reliability was assessed for all resulting factors, through the calculation of Cronbach's alpha with standardized variables, with negatively loading variables reversed. Alpha values of 0.70 or higher were deemed acceptable, and values of 0.90 or higher were considered excellent.

2.4.2. Multiple Regression

In order to evaluate the relations between fatigue and the factors derived from the previous step, the fatigue factor was regressed on the factor scores from associated constructs. Variables were entered into the linear regression model blockwise. Sociodemographic variables were entered first, with age (centered around the sample mean of 45), educational attainment (centered around the sample mean of 13 years), and gender (female) as baseline

covariates. The factors from the previous step were then added to examine if they contributed significantly to the model. Changes in F-scores were evaluated for significance in model improvement across each block. Bootstrapping was conducted to evaluate the robustness of the regression coefficients, and a 95% confidence interval (CI) was produced based on 2000 random draws from the sample. The results from linear regression analyses are reported with unstandardized regression coefficients (B) with bootstrapped standard errors (SE), 95% confidence intervals (CI), standardized regression coefficients (β) and explained variance (adjusted R^2).

Partial regression plots were generated to evaluate the impact of potential outliers. Residual plots were also inspected to evaluate deviance from assumptions of normality, homoscedasticity and linearity. Residual scores were finally checked for associations with variables not included in previous factor analyses, to evaluate potential residual effects not captured by this model. Post hoc analyses were then conducted to evaluate the potential additional explanatory value of these variables. Finally, univariate regression analyses were conducted post hoc to evaluate the associations between individual variables contained within each factor, and the fatigue factor.

3. Results

3.1. Sample Characteristics

A total of 96 patients were included. See Figure 1 for an overview of the exclusion and inclusion process.

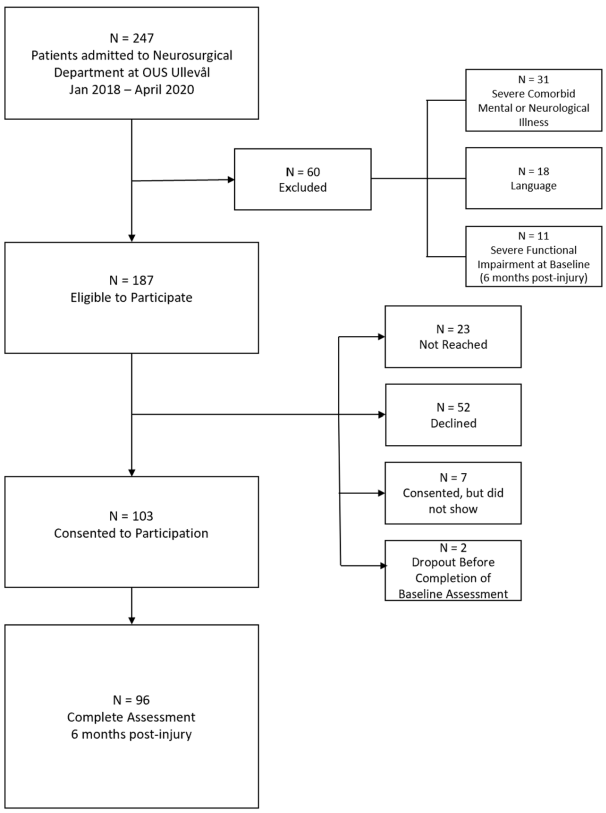

Figure 1. Flow chart of the inclusion and exclusion process. From a sample of 187 eligible patients, 103 participants (55%) consented to participate, and 96 ended up with a complete dataset.

The average age was 45.3 (SD = 13.9), with a mean educational attainment of 13.5 years (SD = 2.3). The sample consisted of 77 (80.2%) males and 19 (19.8%) females.

On the ASA-PS, 69 patients (71.9%) were classified as healthy prior to injury, 19 (19.8%) as having moderate organic disease not impairing function, and eight patients (8.3%) as having severe organic disease.

The sample mean of GCS registered at injury site or at admission to the hospital pre-intubation was 10.7 (SD = 3.6), while GCS registered upon discharge from the acute hospital was 14.4 (SD = 0.9). The sample mean Rotterdam CT score was 2.8 (SD = 0.9). Using the dichotomized AIS_head classification, 18 patients (18.8%) were classified within the less severe category, and 78 (81.3%) within the very severe category. Upon discharge from the acute hospital, GOS ratings based on medical records classified 39 patients (40.6%) with moderate disability, 56 (58.3%) with severe disability, and one patient (1.1%) as being in a vegetative state.

Fifteen patients (15.6%) were discharged directly to their homes, 32 (33.3%) to a local hospital, and 49 (51%) were referred to a rehabilitation unit.

The study assessment was conducted on average 205 days (SD = 28) since injury.

3.2. Fatigue PROMS

The FSS demonstrated good internal consistency ($\alpha = 0.91$). The average score was 3.7, corresponding to a demographically corrected T-score of 48.8 (SD = 11.9).

CFQ demonstrated good internal consistency ($\alpha = 0.89$). The mean sum score for the total scale was 16.2, corresponding to a demographically corrected T-score of 60.8 (SD = 14.2), with comparable results on the mental/cognitive and physical subscales. Items 1 and 2 on the CFQ ask the patients to rate whether they experience increased tiredness or an increased need for rest within the last month compared to their habitual function, and 58 (60.4%) and 59 (61.5%) patients, respectively, endorsed the presence of these problems as compared to their habitual function.

The GSCL subscale demonstrated good internal consistency ($\alpha = 0.89$). On the GSCL fatigue subscale, the mean score was approximately 1 (SD = 0.9), corresponding to the response category "somewhat a problem".

On the RPQ fatigue item, 47 patients (49%) reported at least mild problems with fatigue, and 27 (28.1%) reported moderate-severe problems. For an overview over bivariate correlations between fatigue PROMS, see the Supplementary Materials (Table S1).

3.3. Fatigue and Associated Factors

Overall, fatigue as measured with several PROMS was consistently associated with several biopsychosocial PROMS and functional outcome, while the associative patterns were less consistent for injury-related and neuropsychological variables. There were no bivariate associations between demographic variables (age, gender, education) and any of the fatigue measures. The Head Abbreviated Injury Scale (AIS_head), length of acute hospital stay, GOS at discharge from acute hospital, and having a direct pathway to rehabilitation were associated with higher Physical Fatigue on CFQ. GCS at discharge trended toward significance ($p < 0.08$) in its relationship with the Physical Fatigue subscale from CFQ. No other measure of fatigue was significantly associated with variables from the acute phase.

Fatigue scores (FSS, CFQ, GSCL and RPQ) were positively associated with depression, anxiety, trait neuroticism, daytime sleepiness, insomnia, behavioral inhibition (BIS), all measures of pain, loneliness, and somatic (musculoskeletal/gastrointestinal/cardiovascular) symptom burden, albeit with some variation across measures. Trait openness was positively associated with the RPQ fatigue item only.

Fatigue was negatively associated with two resilience subscales (perception of self and planned future) on most fatigue PROMS, and trending toward significance ($p < 0.08$) for trait optimism in association with the FSS. Trait extraversion was negatively associated with the GSCL fatigue subscale only, and trait conscientiousness was trending toward significance ($p < 0.08$) for a negative association with the FSS.

Fatigue was negatively associated with performance on the CWIT 4—Switching Condition (a measure of mental flexibility) for the FSS and CFQ, and FSS was negatively associated with performance on measure of intraindividual stability of sustained reaction times on the CPT-III. The mental fatigue subscale on the CFQ was negatively associated

with performance on several neuropsychological measures. However, this subscale probes about subjective cognitive complaints such as memory and word-finding difficulties, and these associations are not taken into account in the following analyses.

All measures of fatigue were negatively associated with functional outcome 6 months post-injury as measured by GOSE.

For a complete overview of bivariate associations between fatigue and included variables, see the Supplementary Materials (Tables S2–S4).

3.4. Dimension Reduction

In the factor analysis of the items from the included fatigue outcome measures, three factors were initially generated with an eigenvalue above 1. Both an inspection of the scree plot and parallel analysis of critical threshold for significant eigenvalues provided support for a one-component solution. Items 1 and 2 from the FSS were excluded following the primary factor analysis due to non-salient loadings on the generated factor. All remaining items loaded saliently on the single component (see Table 1). The factor demonstrated excellent reliability (Cronbach's alpha = 0.95) and thus provided an opportunity to examine relationships between the other variables and one single and robust fatigue measure.

Table 1. Factor loadings of items from fatigue measures. All items load saliently on the component at significance level of $p < 0.05$, i.e., loadings above 0.40.

	Fatigue
	Component
FSS Item 3	0.80
FSS Item 4	0.44
FSS Item 5	0.76
FSS Item 6	0.73
FSS Item 7	0.80
FSS Item 8	0.78
FSS Item 9	0.82
CFQ Item 1	0.81
CFQ Item 2	0.70
CFQ Item 4	0.63
CFQ Item 5	0.80
CFQ Item 6	0.56
CFQ Item 7	0.54
GSCL Item 1	0.61
GSCL Item 12	0.85
GSCL Item 17	0.69
RPQ Item 6	0.81
Extraction Sum of Squared Loadings (% of variance)	8.9 (52.4%)
Cronbach's alpha	0.95

For the factor analysis of all associated constructs, seven components were initially generated with an eigenvalue above 1. While the inspection of the scree plot of eigenvalues might suggest retention of either three or four components according to Cattell's criterium, the thresholds from the parallel analysis supported the retention of only the first three components. The component matrix was obliquely rotated using Oblimin rotation, which allows for correlated components. The neuropsychological measures (CWIT-4 and CPT-III CoV Block Change) and trait openness did not load saliently on any of the three factors, and the analysis was repeated without these variables included.

Based on the salient positive loadings from resilience subscales, trait optimism, trait extraversion and trait conscientiousness on Factor 1, this component was designated as a Psychosocial Robustness factor. Factor 1 also has salient negative loadings from trait neuroticism, behavioral inhibition, symptoms of depression and anxiety, loneliness, and

gastrointestinal and cardiovascular symptoms, confirming that robustness is a combination of presence of positive protective factors, but is also an absence of risk factors. Factor 2 had salient loadings from all measures of pain, somatic symptom burden (musculoskeletal, cardiovascular and gastrointestinal), daytime sleepiness, subjective sleep complaints, as well as symptoms of depression and anxiety. This factor was thus designated as a somatic vulnerability factor. Factor 3 had salient loadings from all five variables from the acute phase, with negative loadings from GCS and GOS at discharge from the acute hospital, and positive loadings from length of ICU stay, AIS_head and a direct pathway to rehabilitation. This factor was designated as an injury severity factor.

New factor analyses were conducted, one for each factor. Anxiety and depression were cross-loaded on factors 1 and 2 and were selected for inclusion in the psychosocial robustness factor due to stronger loadings. Likewise, the GSCL subscales for gastrointestinal and cardiovascular symptoms were cross-loaded on factors 1 and 2 and were selected for inclusion in the somatic vulnerability factor due to higher loadings and more conceptual overlap. The final factor analyses supported the unidimensionality of the three factors, and the factors demonstrated good to adequate factor reliability. See Table 2 for final factor loadings and reliability indicators.

Table 2. Factor loadings for the final unidimensional factor analyses of self-reported independent variables (N = 96). Squared loadings and explained variance therefore refer to only those variables included in each of the three factor analyses. For an overview of the primary factor analyses, see the Supplementary Materials (Table S5).

	Factors		
	Psychosocial Robustness	**Somatic Vulnerability**	**Injury Severity**
Behavioral Inhibition	−0.55		
Trait Neuroticism	−0.90		
Trait Extraversion	0.63		
Trait Conscientiousness	0.56		
Trait Optimism	0.69		
Loneliness	−0.70		
Anxiety Symptoms	−0.64		
Depressive Symptoms	−0.76		
Resilience–Perception of Self	0.84		
Resilience–Planned Future	0.64		
Daytime Sleepiness		0.48	
Insomnia Severity Index		0.48	
Pain–Affected Regions		0.74	
Strongest Pain		0.84	
Weakest Pain		0.64	
Average Pain		0.88	
Current Pain		0.73	
Gastrointestinal Symptoms		0.61	
Musculoskeletal Symptoms		0.84	
Cardiovascular Symptoms		0.53	
AIS_head			0.58
Length of ICU Stay (days)			0.58
GCS at Discharge			−0.67
GOS at Discharge			−0.77
Direct Pathway to Rehabilitation			0.71
Extraction Sums of Squared Loadings (% of variance in included variables)	4.9 (49.0%)	4.8 (48.0%)	2.2 (44.4%)
Cronbach's alpha	0.91	0.89	0.80

3.5. Multiple Regression

Results from the blockwise multiple linear regression of fatigue in the sample with complete data are shown in Table 3. Age, education and gender had no significant associations with the fatigue factor (Model 1), and the model explains a non-significant amount of variance in fatigue. The injury severity factor did not in isolation contribute significantly to the model in the second regression block.

Table 3. Blockwise multiple linear regression (N = 96). Unstandardized (B) and standardized coefficients (β) are reported. Adjusted R^2 shows the model-explained variance, and the F change-statistic is a test of the improvement from the previous model. Standard errors (SE) shown are calculated from bootstrapping. The final column shows the 95% confidence interval for the unstandardized coefficients (B) in Model 3. ^{ns} not significant, * $p < 0.05$, *** $p < 0.001$.

	Model 1		Model 2		Model 3		95% CI	
	β	B (SE)	β	B (SE)	β	B (SE)	Lower	Upper
Constant		−0.08 (0.14)		−0.08 (0.11)		−0.08 (0.09)	(−0.25	0.09)
Age (Centered)	0.01	0.00 (0.01)	0.00	0.00 (0.01)	−0.01	−0.00 (0.01)	(−0.01	0.01)
Education (Centered)	0.00	0.00 (0.04)	0.01	0.00 (0.01)	0.10	0.05 (0.04)	(−0.02	0.13)
Female	0.17	0.41 (0.26)	0.17	0.40 (0.27)	0.12	0.29 (0.18)	(−0.08	0.65)
Injury Severity			0.13	0.14 (0.11)	0.16 *	0.18 (0.08)	(0.01	0.34)
Psychosocial Robustness					−0.17 *	−0.17 (0.09)	(−0.34	−0.01)
Somatic Vulnerability					0.59 ***	0.60 (0.08)	(0.46	75)
Adjusted R^2	0.001		0.001		0.442			
F Change	0.89 ^{ns}		1.65 ^{ns}		36.8 ***			

In Model 3, psychosocial robustness was significantly negatively associated with fatigue, and somatic vulnerability showed a strong positive association with fatigue. The injury severity factor entered in the previous block now showed a barely statistically significant effect. While the effects for the psychosocial robustness factor and the injury severity factor were significant, the confidence intervals bootstrapped for their coefficients border on zero, and as such, demonstrate less robust effects than the somatic vulnerability factor. This final model explains 44.2% of the variance in the fatigue factor.

3.6. Post Hoc Analyses

Due to the non-inclusion of the neuropsychological measures in the factors derived from earlier steps, correlations between the residuals of the regression analysis and the neuropsychological measures were inspected. The residual from the final regression model was negatively associated with mental flexibility (CWIT-4, n = 90, r = −0.27) and sustained attention (CPT-III CoV block change, n = 95, r = −0.20). For exploratory purposes, a composite score of these two measures was added in a final block in the blockwise regression (n = 89). The results overlapped considerably with those from the primary regression model. The addition of the neuropsychological composite variable in the final block led to a significant increase in explained variance up to 51.6%. However, the neuropsychological composite score was negatively associated with the injury severity factor (n = 89, r = −0.23), and its inclusion suppressed the association of the injury severity factor below significance (see Table S6 in the Supplementary Materials).

Finally, the relative importance of each variable loading upon the three factors was explored in univariate regression models, with the fatigue factor as the dependent variable. For univariate regression coefficients and explained variance, see Tables S7–S9 in the Supplementary Materials. The anxiety, depression and the resilience subscale, planned future, had the strongest univariate impact on fatigue in the psychosocial robustness factor. In the somatic vulnerability factor, all variables explained a significant amount of variance in fatigue, but the GSCL musculoskeletal symptoms subscale demonstrated the strongest positive association. Finally, for the injury severity factor, effects were in general weak,

and only the Direct Pathway to Rehabilitation and AIS_head demonstrated significant univariate associations with fatigue.

4. Discussion

The present study aimed to explore dimensions underlying various biopsychosocial constructs commonly associated with fatigue six months following TBI. In line with the notion of fatigue as being influenced by both injury-specific and general risk factors, this study examined the relationship between a multitude of variables that have previously been associated with fatigue after TBI, and several fatigue outcome measures. The results highlight that three underlying factors related to psychosocial robustness, somatic vulnerability and injury severity can be identified, providing a clearer picture of the somewhat fragmented literature on protective and risk factors for post-TBI fatigue.

4.1. Unidimensionality of Post-TBI Fatigue

Regarding fatigue levels, our findings confirm variations between measures. On the FSS, the patients reported similar levels of fatigue interference as those seen in the general population [48]. On the CFQ, however, the sample reported fatigue symptoms approximately one standard deviation above the normative average [51], and on specific items, 60% reported increases in tiredness and their need for rest. Our findings support the notion that the majority of patients with TBI experience increased levels of fatigue, while many, despite their symptoms, report little to no interference from fatigue during the first 6 months. This aligns with the findings by Kjeverud et al. [38] in stroke patients, which were interpreted as a dissociation between fatigue severity and fatigue interference. Some patients may experience more fatigue following injury but are able to compensate successfully such that it does not interfere with the roles and activities pertinent to their daily life. Additionally, many patients were still on sick leave at the time of measurement, which could contribute to a low degree of functional interference due to decreased environmental demands.

Despite these variations, the items from the included fatigue PROMS demonstrated good reliability and considerable unidimensionality in our factor analytic approach, indicating that the measures seem to measure a uniform concept. The single fatigue item from the RPQ also demonstrated good correspondence with the other measures, which support the utility of this single item in clinical practice, and items from the GSCL fatigue subscale also aligned well along the unidimensional fatigue factor. Items 1 and 2 from the FSS did not load saliently on the fatigue factor, in line with previous studies of the FSS in patients with, e.g., stroke [75], and were thus not included.

4.2. Biopsychosocial Dimensions-Relevance for Fatigue

Through factor analyses, we evaluated overlap and underlying dimensionality among self-reported PROMS of biopsychosocial constructs often associated with fatigue. Two salient factors were extracted, which we termed psychosocial robustness and somatic vulnerability. These factors showed some overlap with regard to anxiety and depression, as well as gastrointestinal and cardiovascular symptoms, showing that there are some commonalities between them despite the parsimonious structure selected. A third factor was found, termed as an injury severity factor based on strong loadings from injury-related severity indices from an acute hospital stay. In the subsequent multivariate regression analyses, somatic vulnerability, psychosocial robustness and injury severity factors all demonstrated significant associations with fatigue, explaining 44.2% of variance in fatigue 6 months after TBI.

Somatic vulnerability demonstrated a particularly strong and robust association with fatigue, in line with the literature linking pain and fatigue as central comorbidities [22,76], and earlier studies in the TBI population [23,25]. This factor explained 39% of the variance in fatigue in isolation, in essence contributing most of the explained variance in the multivariate regression models. Subsequent univariate post hoc regression analyses showed that all the variables underlying this dimension contributed significantly to the association

between somatic vulnerability and fatigue. Notably, the GSCL subscale for musculoskeletal symptoms explained more variance in fatigue than the somatic vulnerability factor in large, indicating that nonspecific musculoskeletal pains are particularly crucial markers for somatic vulnerability and the factor's association with fatigue in this sample.

The association between psychosocial robustness and fatigue supports earlier findings linking resilience with less fatigue after TBI [77]. Trait extraversion, conscientiousness and optimism seemed to align with resilience factors in this protective dimension, while trait neuroticism, loneliness, behavioral inhibition and psychological distress were placed on the opposite side of this dimension, confirming that absence of negative emotionality is a prominent feature of psychosocial robustness. Associations between high neuroticism, low extraversion and low conscientiousness and fatigue have been demonstrated in mild TBI [34] and other populations [78]; thus, these findings are in line with previous findings. While trait extraversion, trait conscientiousness and trait optimism did load heavily on this protective dimension, they were not significantly associated with fatigue 6 months post-injury in isolation. Conversely, measures of state and trait negative affectivity (state depression and anxiety, and trait neuroticism to a lesser degree) and resilience (planned future, and to a lesser degree perception of self) were essential to the relevance of psychosocial robustness for fatigue in our sample. The resilience subscale for planned future pertains to the perception of the future as manageable and predictable through goal-directedness and structure, while the subscale for perception of self relates to self-efficacy and potential for growth through adversity. These constructs thus align well as opposites to anxiety and depression.

The association between fatigue and injury severity became significant when controlling for psychosocial robustness and somatic vulnerability. Among the underlying injury-related variables, only the direct pathway to rehabilitation and the AIS_head demonstrated significant univariate associations with fatigue in post hoc regression analyses, indicating that anatomical brain injury severity combined with early functional status are particularly relevant. Post hoc analyses furthermore demonstrated that a measure of mental flexibility suppressed the association between the injury severity factor and fatigue, indicating that the injury severity factor from the acute phase and the resulting cognitive deficits in mental flexibility after six months overlap in their contributions to fatigue.

A visual representation of the findings is provided in Figure 2.

4.3. Implications for Rehabilitation

The fact that fatigue was strongly associated with functional status 6 months post-injury is in line with earlier findings. The results illustrate that fatigue is associated with everyday functioning and point to the importance of addressing fatigue in rehabilitation [2]. While fatigue is a severe problem for many patients with TBI, there is nevertheless considerable heterogeneity, with some patients reporting little to no fatigue interference in everyday life. Understanding which patients are at risk of developing persistent fatigue and functional interference from fatigue, and why, is crucial in improving our care for this patient group.

While more severe injuries are accompanied by greater sensory-motor and cognitive deficits, and accordingly might necessitate greater compensatory efforts in returning to mental and cognitive activities, initial injury severity indices were inconsistently associated with fatigue in our study. Our findings showed that some brain injury severity indices and having a direct pathway to rehabilitation were weakly associated with fatigue. The latter finding may likely be interpreted as a proxy for functional status, as patients with severe symptoms were more likely to be transferred to rehabilitation, irrespective of injury severity measures. The injury severity factor was only associated with fatigue when controlling for robustness and vulnerability, confirming that other risk factors for fatigue are intertwined with injury severity initially, but can be disentangled when adjusted for. For instance, patients with relatively mild injuries, but who suffer from co- or premorbid pain or depression, may be at high risk for fatigue despite mild injuries. While having

a high degree of somatic vulnerability and low degree of psychosocial robustness might contribute to an increased risk of fatigue in isolation, injury characteristics serve as an independent risk as well, although these associations are less robust.

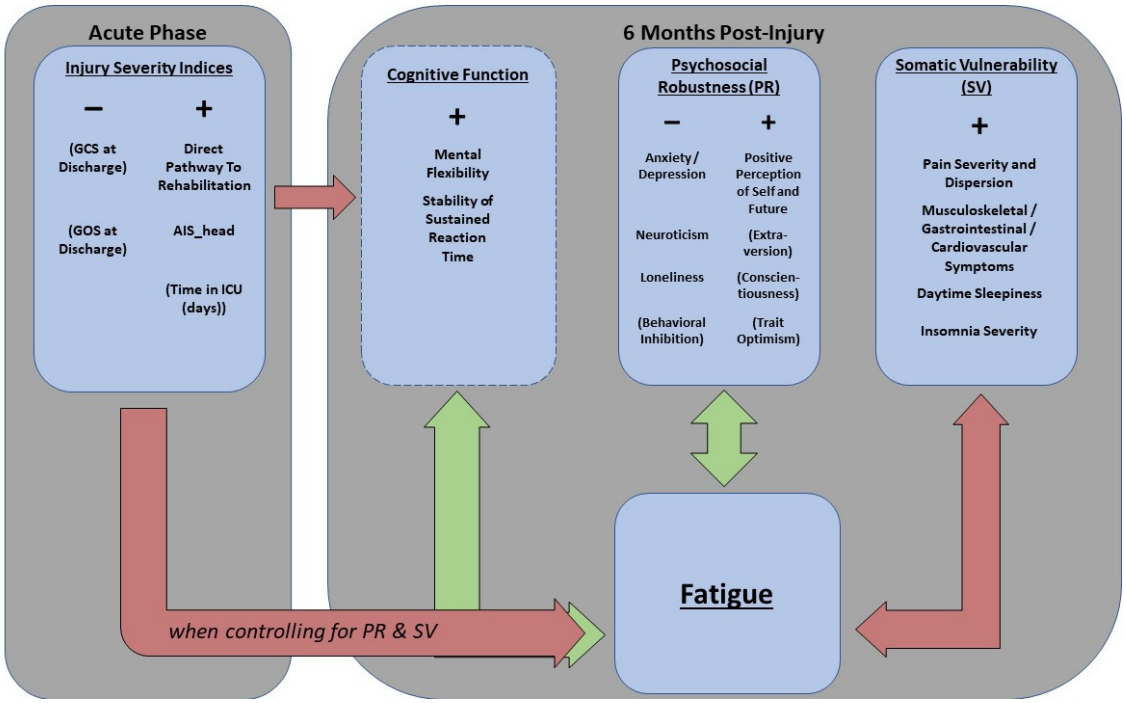

Figure 2. A visual representation of the findings from our study. Note that cognitive function is marked by a dotted box, so as to illustrate that these effects were found in post hoc analyses with a slightly smaller sample due to missing data. Double-sided arrows imply within-time associations, while one-sided arrows imply unidirectional influences. Green arrows imply positive correlations, and red arrows imply negative correlations. Parentheses signify variables with significant loadings on the factor, but with no significant contribution to fatigue when inspected in isolation.

Our findings also underline the importance of the contribution of various biopsychosocial protective and vulnerability factors. Somatic symptom burden and especially pain emerge as important associated factors with fatigue following TBI, which should be considered as central targets for rehabilitation. The exact nature of the relationship between fatigue and pain cannot be deduced based on our cross-sectional design, but until further longitudinal research sheds more light on these relationships, the possibility of temporal and bidirectional influences should be considered. Rehabilitation efforts addressing fatigue should therefore also address concurrent risk factors for fatigue. This can be achieved through holistic rehabilitation programs. New methods such as virtual reality have shown promising results in the treatment of pain, emotional symptoms, and fatigue, and should be explored [79,80].

This study furthermore demonstrates the importance of taking into account protective factors which might buffer against fatigue. Aspects of resilience such as perceiving the future as manageable and predictable, and self-efficacy in the face of adversity, were negatively associated with fatigue. On the opposite side of the same dimension, lower levels of loneliness and negative effects are positively associated with fatigue. The findings indicate that rehabilitation efforts aimed at helping patients re-establish a coherent sense of self and their future, and to reconnect with social resources, might lessen their risk of fatigue in the early stages of rehabilitation. This latter point was supported in a recent qualitative study [81], in which the use of social support was identified as a promising treatment angle for breaking vicious cycles for perpetuation and exacerbation of fatigue after brain injury.

4.4. Limitations

This study examined cross-sectional associations between fatigue and related constructs but did not allow for inferences regarding directional influences. Furthermore, while dimensions derived from factor analyses provide a parsimonious structure to the relations between various predictors of fatigue, one cannot eliminate possible within- and between-factor dynamics, such as premorbid trait neuroticism influencing the post-injury development of anxiety and depression, which could again influence fatigue. Our post hoc analyses furthermore demonstrated that the variable loading on each factor contributed to different degrees of fatigue when viewed in isolation. Finally, our study has a relatively modest sample size, and generalizations of the results to other cohorts should be made with caution. Of 450 patients with intracranial injury admitted to the Neurosurgery department in the study period, we assessed 55% for eligibility and included 21.3% of the total population. The mean age and the gender ratio included are in line with the TBI population included in the quality database [44]. However, our sample is weighted toward moderate and severe injuries (77%) compared with those included in the quality database (57%). Thus, the results may not be generalizable to those with milder intracranial injuries.

Ideally, a somewhat larger sample would have to be investigated to provide better estimates of essential parameters (particularly factor loadings and regression coefficients) in the population in question. However, while the parameter estimates could be more accurate, and small sample sizes tend to increase the liability to Type II errors, and we see no reason to doubt the general pattern of findings from the study.

5. Conclusions

Through the exploration of factors associated with fatigue following TBI, this study has demonstrated that factors related to fatigue after TBI might be described along three dimensions, i.e., psychosocial robustness, somatic vulnerability and injury-related factors. Within these factors, somatic symptom burden (especially pain), depression, anxiety, positive perceived prospects for the future, loneliness daytime sleepiness, subjective insomnia, anatomical severity of injury and being referred directly to rehabilitation services all demonstrated relevance for fatigue 6 months post-injury. These factors, while having varying importance, illustrate the breadth of biopsychosocial underpinnings for fatigue following TBI.

The findings illuminate potential tangible treatment targets in rehabilitation of fatigue after TBI and may guide future research aimed at establishing evidence-based treatment options. More research is needed to understand potential dynamic interactions between fatigue and the associated vulnerability and protective factors, and to understand how these may develop over time.

Supplementary Materials: The following supporting information can be downloaded at: https://www.mdpi.com/article/10.3390/jcm11061733/s1, Table S1: Bivariate correlations between PROMS of fatigue. Table S2: Bivariate associations between fatigue PROMS, sociodemographic variables and injury-related factors. Table S3: Bivariate correlations between fatigue PROMS and neuropsychological measures. Table S4: Bivariate correlations between fatigue PROMS and PROMS of related constructs. Table S5: Structure matrix with variable loadings for the primay factor analysis after oblique rotation (Oblimin), with factor correlations. Table S6: Post-Hoc Blockwise multiple regression. Table S7: Coefficients and explained variance in the fatigue factor (outcome variable) from univariate regression models with the Psychosocial Robustness factor and the individual variables loading onto this factor. Table S8: Coefficients and explained variance in the fatigue factor (outcome variable) from univariate regression models with the Somatic Vulnerability factor and the individual variables loading onto this factor. Table S9: Coefficients and explained variance in the fatigue factor (outcome variable) from univariate regression models with the Injury Severity factor and the individual variables loading onto this factor, as well as the neuropsychological measures and their composite.

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References

1. Mollayeva, T.; Kendzerska, T.; Mollayeva, S.; Shapiro, C.M.; Colantonio, A.; Cassidy, J.D. A systematic review of fatigue in patients with traumatic brain injury: The course, predictors and consequences. *Neurosci. Biobehav. Rev.* **2014**, *47*, 684–716. [CrossRef] [PubMed]
2. Cantor, J.B.; Ashman, T.; Gordon, W.; Ginsberg, A.; Engmann, C.; Egan, M.; Spielman, L.; Dijkers, M.; Flanagan, S. Fatigue after traumatic brain injury and its impact on participation and quality of life. *J. Head Trauma Rehabil.* **2008**, *23*, 41–51. [CrossRef] [PubMed]
3. Juengst, S.; Skidmore, E.; Arenth, P.M.; Niyonkuru, C.; Raina, K.D. Unique contribution of fatigue to disability in community-dwelling adults with traumatic brain injury. *Arch. Phys. Med. Rehabil.* **2013**, *94*, 74–79. [CrossRef] [PubMed]
4. Menon, D.K.; Schwab, K.; Wright, D.W.; Maas, A.I. Position statement: Definition of traumatic brain injury. *Arch. Phys. Med. Rehabil.* **2010**, *91*, 1637–1640. [CrossRef] [PubMed]
5. Fazel, S.; Wolf, A.; Pillas, D.; Lichtenstein, P.; Långström, N. Suicide, fatal injuries, and other causes of premature mortality in patients with traumatic brain injury: A 41-year Swedish population study. *JAMA Psychiatry* **2014**, *71*, 326–333. [CrossRef]
6. Ponsford, J.L.; Downing, M.G.; Olver, J.; Ponsford, M.; Acher, R.; Carty, M.; Spitz, G. Longitudinal follow-up of patients with traumatic brain injury: Outcome at two, five, and ten years post-injury. *J. Neurotrauma* **2014**, *31*, 64–77. [CrossRef] [PubMed]
7. Aaronson, L.S.; Teel, C.S.; Cassmeyer, V.; Neuberger, G.B.; Pallikkathayil, L.; Pierce, J.; Press, A.N.; Williams, P.D.; Wingate, A. Defining and measuring fatigue. *Image J. Nurs. Scholarsh.* **1999**, *31*, 45–50. [CrossRef]
8. Hjollund, N.H.; Andersen, J.H.; Bech, P. Assessment of fatigue in chronic disease: A bibliographic study of fatigue measurement scales. *Health Qual. Life Outcomes* **2007**, *5*, 12. [CrossRef] [PubMed]
9. Choi, B.C.; Pak, A.W. Peer reviewed: A catalog of biases in questionnaires. *Prev. Chronic Dis.* **2005**, *2*, A13.
10. Skogestad, I.J.; Kirkevold, M.; Indredavik, B.; Gay, C.L.; Lerdal, A. Lack of content overlap and essential dimensions–A review of measures used for post-stroke fatigue. *J. Psychosom. Res.* **2019**, *124*, 109759. [CrossRef]
11. Krupp, L.B.; LaRocca, N.G.; Muir-Nash, J.; Steinberg, A.D. The fatigue severity scale: Application to patients with multiple sclerosis and systemic lupus erythematosus. *Arch. Neurol.* **1989**, *46*, 1121–1123. [CrossRef] [PubMed]
12. Norup, A.; Svendsen, S.W.; Doser, K.B.; Ryttersgaard, T.O.; Frandsen, N.; Gade, L.; Forchhammer, H.B. Prevalence and severity of fatigue in adolescents and young adults with acquired brain injury: A nationwide study. *Neuropsychol. Rehabil.* **2017**, *29*, 1113–1128. [CrossRef] [PubMed]
13. Ziino, C.; Ponsford, J. Measurement and prediction of subjective fatigue following traumatic brain injury. *J. Int. Neuropsychol. Soc.* **2005**, *11*, 416–425. [CrossRef] [PubMed]
14. Cantor, J.B.; Bushnik, T.; Cicerone, K.; Dijkers, M.P.; Gordon, W.; Hammond, F.M.; Kolakowsky-Hayner, S.A.; Lequerica, A.; Nguyen, M.; Spielman, L.A. Insomnia, fatigue, and sleepiness in the first 2 years after traumatic brain injury: An NIDRR TBI model system module study. *J. Head Trauma Rehabil.* **2012**, *27*, E1–E14. [CrossRef]
15. Andelic, N.; Røe, C.; Brunborg, C.; Zeldovich, M.; Løvstad, M.; Løke, D.; Borgen, I.M.; Voormolen, D.C.; Howe, E.I.; Forslund, M.V.; et al. Frequency of fatigue and its changes in the first 6 months after traumatic brain injury: Results from the CENTER-TBI study. *J. Neurol.* **2021**, *268*, 61–73. [CrossRef]
16. Johansson, B.; Berglund, P.; Rönnbäck, L. Mental fatigue and impaired information processing after mild and moderate traumatic brain injury. *Brain Inj.* **2009**, *23*, 1027–1040. [CrossRef]

17. Ziino, C.; Ponsford, J. Selective attention deficits and subjective fatigue following traumatic brain injury. *Neuropsychology* **2006**, *20*, 383. [CrossRef]
18. van Zomeren, A.H.; Brouwer, W.H.; Deelman, B.G. Attentional deficits: The riddles of selectivity, speed and alertness. In *Closed Head Injury: Psychological, Social, and Family Consequences*; Brooks, N., Ed.; Oxford University Press: Oxford, UK, 1984; pp. 74–107.
19. Penner, I.-K.; Paul, F. Fatigue as a symptom or comorbidity of neurological diseases. *Nat. Rev. Neurol.* **2017**, *13*, 662–675. [CrossRef]
20. Bushnik, T.; Englander, J.; Katznelson, L. Fatigue after TBI: Association with neuroendocrine abnormalities. *Brain Inj.* **2007**, *21*, 559–566. [CrossRef]
21. Cantor, J.B.; Gordon, W.; Gumber, S. What is post TBI fatigue? *NeuroRehabilitation* **2013**, *32*, 875–883. [CrossRef]
22. Wyller, V.B.B. Pain is common in chronic fatigue syndrome–current knowledge and future perspectives. *Scand. J. Pain* **2019**, *19*, 5–8. [CrossRef] [PubMed]
23. Beaulieu-Bonneau, S.; Ouellet, M.-C. Fatigue in the first year after traumatic brain injury: Course, relationship with injury severity, and correlates. *Neuropsychol. Rehabil.* **2017**, *27*, 983–1001. [CrossRef] [PubMed]
24. Sigurdardottir, S.; Andelic, N.; Roe, C.; Schanke, A. Depressive symptoms and psychological distress during the first five years after traumatic brain injury: Relationship with psychosocial stressors, fatigue and pain. *J. Rehabil. Med.* **2013**, *45*, 808–814. [CrossRef]
25. Ponsford, J.L.; Ziino, C.; Parcell, D.L.; Shekleton, J.A.; Roper, M.; Redman, J.R.; Phipps-Nelson, J.; Rajaratnam, S.M.W. Fatigue and sleep disturbance following traumatic brain injury—their nature, causes, and potential treatments. *J. Head Trauma Rehabil.* **2012**, *27*, 224–233. [CrossRef]
26. Holmqvist, A.; Lindstedt, M.; Möller, M. Relationship between fatigue after acquired brain injury and depression, injury localization and aetiology: An explorative study in a rehabilitation setting. *J. Rehabil. Med.* **2018**, *50*, 725–731. [CrossRef] [PubMed]
27. Ponsford, J.; Schönberger, M.; Rajaratnam, S.M.W. A Model of Fatigue Following Traumatic Brain Injury. *J. Head Trauma Rehabil.* **2015**, *30*, 277–282. [CrossRef]
28. Englander, J.; Bushnik, T.; Oggins, J.; Katznelson, L. Fatigue after traumatic brain injury: Association with neuroendocrine, sleep, depression and other factors. *Brain Inj.* **2010**, *24*, 1379–1388. [CrossRef]
29. Ouellet, M.C.; Morin, C.M. Fatigue following traumatic brain injury: Frequency, characteristics, and associated factors. *Rehabil. Psychol.* **2006**, *51*, 140. [CrossRef]
30. Sindermann, C.; Saliger, J.; Nielsen, J.; Karbe, H.; Markett, S.; Stavrou, M.; Montag, C. Personality and primary emotional traits: Disentangling multiple sclerosis related fatigue and depression. *Arch. Clin. Neuropsychol.* **2018**, *33*, 552–561. [CrossRef]
31. Vassend, O.; Roysamb, E.; Nielsen, C.S.; Czajkowski, N.O. Fatigue symptoms in relation to neuroticism, anxiety-depression, and musculoskeletal pain. A longitudinal twin study. *PLoS ONE* **2018**, *13*, e0198594. [CrossRef]
32. Charles, S.T.; Gatz, M.; Kato, K.; Pedersen, N.L. Physical Health 25 Years Later: The Predictive Ability of Neuroticism. *Health Psychol.* **2008**, *27*, 369–378. [CrossRef] [PubMed]
33. Lau, C.G.; Tang, W.K.; Liu, X.X.; Liang, H.J.; Liang, Y.; Mok, V.; MSocSc, A.W.; Ungvari, G.S.; Kutlubaev, M.A.; Wong, K.S. Neuroticism and fatigue 3 months after ischemic stroke: A cross-sectional study. *Arch. Phys. Med. Rehabil.* **2017**, *98*, 716–721. [CrossRef]
34. Merz, Z.C.; Zane, K.; Emmert, N.A.; Lace, J.; Grant, A. Examining the relationship between neuroticism and post-concussion syndrome in mild traumatic brain injury. *Brain Inj.* **2019**, *33*, 1003–1011. [CrossRef]
35. Lee, E.; Jayasinghe, N.; Swenson, C.; Dams-O'Connor, K. Dispositional optimism and cognitive functioning following traumatic brain injury. *Brain Inj.* **2019**, *33*, 985–990. [CrossRef] [PubMed]
36. Schönberger, M.; Herrberg, M.; Ponsford, J. Fatigue as a cause, not a consequence of depression and daytime sleepiness: A cross-lagged analysis. *J. Head Trauma Rehabil.* **2014**, *29*, 427–431. [CrossRef] [PubMed]
37. Ouellet, M.-C.; Beaulieu-Bonneau, S.; Morin, C.M. Sleep-wake disturbances after traumatic brain injury. *Lancet Neurol.* **2015**, *14*, 746–757. [CrossRef]
38. Carver, C.S.; White, T.L. Behavioral Inhibition, Behavioral Activation, and Affective Responses to Impending Reward and Punishment: The BIS/BAS Scales. *J. Personal. Soc. Psychol.* **1994**, *67*, 319–333. [CrossRef]
39. Pardini, M.; Capello, E.; Krueger, F.; Mancardi, G.L.; Uccelli, A. Reward responsiveness and fatigue in multiple sclerosis. *Mult. Scler. J.* **2013**, *19*, 233–240. [CrossRef]
40. Jaremka, L.M.; Andridge, R.R.; Fagundes, C.P.; Alfano, C.M.; Povoski, S.P.; Lipari, A.M.; Agnese, D.; Arnold, M.; Farrar, W.B.; Yee, L.D.; et al. Pain, depression, and fatigue: Loneliness as a longitudinal risk factor. *Health Psychol.* **2014**, *33*, 948–957. [CrossRef]
41. Jumisko, E.; Lexell, J.; Söderberg, S. The meaning of living with traumatic brain injury in people with moderate or severe traumatic brain injury. *J. Neurosci. Nurs.* **2005**, *37*, 42–50. [CrossRef]
42. Wardlaw, C.; Hicks, A.J.; Sherer, M.; Ponsford, J.L. Psychological resilience is associated with participation outcomes following mild to severe traumatic brain injury. *Front. Neurol.* **2018**, *9*, 563. [CrossRef]
43. Losoi, H.; Wäljas, M.; Turunen, S.; Brander, A.; Helminen, M.; Luoto, T.M.; Rosti-Otajärvi, E.; Julkunen, J.; Öhman, J. Resilience is associated with fatigue after mild traumatic brain injury. *J. Head Trauma Rehabil.* **2015**, *30*, E24–E32. [CrossRef] [PubMed]
44. Tverdal, C.; Aarhus, M.; Andelic, N.; Skaansar, O.; Skogen, K.; Helseth, E. Characteristics of traumatic brain injury patients with abnormal neuroimaging in Southeast Norway. *Inj. Epidemiol.* **2020**, *7*, 45. [CrossRef]

45. Doyle, D.J.; Garmon, E.H. American Society of Anesthesiologists classification (ASA class). In *StatPearls [Internet]*; StatPearls Publishing: Treasure Island, FL, USA, 2021. Available online: https://www.ncbi.nlm.nih.gov/books/NBK441940 (accessed on 17 March 2022).
46. Maas, A.I.; Hukkelhoven, C.W.; Marshall, L.F.; Steyerberg, E.W. Prediction of outcome in traumatic brain injury with computed tomographic characteristics: A comparison between the computed tomographic classification and combinations of computed tomographic predictors. *Neurosurgery* **2005**, *57*, 1173–1182. [CrossRef] [PubMed]
47. Association for the Advancement of Automotive Medicine. *Abbreviated Injury Scale*; 1990 Revision: Update 98 [Manual]; Association for the Advancement of Automotive Medicine: Barrington, IL, USA, 1998.
48. Lerdal, A.; Wahl, A.K.; Rustoen, T.; Hanestad, B.R.; Moum, T. Fatigue in the general population: A translation and test of the psychometric properties of the Norwegian version of the fatigue severity scale. *Scand. J. Public Health* **2005**, *33*, 123–130. [CrossRef]
49. Chalder, T.; Berelowitz, G.; Pawlikowska, T.; Watts, L.; Wessely, S.; Wright, D.; Wallace, E.P. Development of a Fatigue Scale. *J. Psychosom. Res.* **1993**, *37*, 147–153. [CrossRef]
50. Kjeverud, A.; Andersson, S.; Lerdal, A.; Schanke, A.K.; Østlie, K. A cross-sectional study exploring overlap in post-stroke fatigue caseness using three fatigue instruments: Fatigue Severity Scale, Fatigue Questionnaire and the Lynch's Clinical Interview. *J. Psychosom. Res.* **2021**, *150*, 110605. [CrossRef]
51. Loge, J.H.; Ekeberg, Ø.; Kaasa, S. Fatigue in the general Norwegian population: Normative data and associations. *J. Psychosom. Res.* **1998**, *45*, 53–65. [CrossRef]
52. Brähler, E.; Scheer, J.W. *Der Gießener Beschwerdebogen: (GBB)*; Huber: Bern, Switzerland, 1983.
53. King, N.S.; Crawford, S.; Wenden, F.J.; Moss, N.E.G.; Wade, D.T. The Rivermead Post Concussion Symptoms Questionnaire: A measure of symptoms commonly experienced after head injury and its reliability. *J. Neurol.* **1995**, *242*, 587–592. [CrossRef]
54. Wechsler, D. *Wechsler Abbreviated Scale of Intelligence*; The Psychological Corporation: Harcourt Brace & Company: New York, NY, USA, 1999.
55. Wechsler, D. *Wechsler Adult Intelligence Scale–Fourth Edition (WAIS–IV)*; NCS Pearson: San Antonio, TX, USA, 2008.
56. Delis, D.C.; Kaplan, E.; Kramer, J.H. Delis-Kaplan executive function system. *APA PsycTests* **2001**. [CrossRef]
57. Conners, C.K. *Conners Continuous Performance Test 3rd Edition, Technical Manual*; Multi-Health Systems Inc.: Toronto, ON, Canada, 2014.
58. Flehmig, H.C.; Steinborn, M.; Langner, R.; Scholz, A.; Westhoff, K. Assessing intraindividual variability in sustained attention: Reliability, relation to speed and accuracy, and practice effects. *Psychol. Sci.* **2007**, *49*, 132.
59. Derogatis, L.R.; Lipman, R.S.; Rickels, K.; Uhlenhuth, E.H.; Covi, L. The Hopkins Symptom Checklist (HSCL): A self-report symptom inventory. *Behav. Sci.* **1974**, *19*, 1–15. [CrossRef]
60. Strand, B.H.; Dalgard, O.S.; Tambs, K.; Rognerud, M. Measuring the mental health status of the Norwegian population: A comparison of the instruments SCL-25, SCL-10, SCL-5 and MHI-5 (SF-36). *Nord. J. Psychiatry* **2003**, *57*, 113–118. [CrossRef] [PubMed]
61. McCrae, R.R.; Costa, P.T. *NEO Inventories for the NEO Personality Inventory-3 (NEO-PI-3), NEO Five-Factor Inventory-3 (NEO-FFI-3), NEO Personality Inventory-Revised (NEO PI-R): Professional Manual*; Psychological Assessment Resources: Lutz, FL, USA, 2010.
62. Russell, D.W. UCLA Loneliness Scale (Version 3): Reliability, validity, and factor structure. *J. Personal. Assess.* **1996**, *66*, 20–40. [CrossRef]
63. Scheier, M.F.; Carver, C.S.; Bridges, M.W. Distinguishing Optimism from Neuroticism (and Trait Anxiety, Self-Mastery, and Self-Esteem): A Reevaluation of the Life Orientation Test. *J. Personal. Soc. Psychol.* **1994**, *67*, 1063–1078. [CrossRef]
64. Hjemdal, O.; Friborg, O.; Braun, S.; Kempenaers, C.; Linkowski, P.; Fossion, P. The Resilience Scale for Adults: Construct validity and measurement in a Belgian sample. *Int. J. Test.* **2011**, *11*, 53–70. [CrossRef]
65. Kuorinka, I.; Jonsson, B.; Kilbom, A.; Vinterberg, H.; Biering-Sørensen, F.; Andersson, G.; Jørgensen, K. Standardised Nordic questionnaires for the analysis of musculoskeletal symptoms. *Appl. Ergon.* **1987**, *18*, 233–237. [CrossRef]
66. Williamson, A.; Hoggart, B. Pain: A review of three commonly used pain rating scales. *J. Clin. Nurs.* **2005**, *14*, 798–804. [CrossRef]
67. Johns, M.W. A new method for measuring daytime sleepiness: The Epworth sleepiness scale. *Sleep* **1991**, *14*, 540–545. [CrossRef] [PubMed]
68. Bastien, C.H.; Vallières, A.; Morin, C.M. Validation of the Insomnia Severity Index as an outcome measure for insomnia research. *Sleep Med.* **2001**, *2*, 297–307. [CrossRef]
69. Teasdale, G.M.; Pettigrew, L.E.; Wilson, J.L.; Murray, G.; Jennett, B. Analyzing outcome of treatment of severe head injury: A review and update on advancing the use of the Glasgow Outcome Scale. *J. Neurotrauma* **1998**, *15*, 587–597. [CrossRef] [PubMed]
70. Wilson, J.L.; Pettigrew, L.E.; Teasdale, G.M. Structured interviews for the Glasgow Outcome Scale and the extended Glasgow Outcome Scale: Guidelines for their use. *J. Neurotrauma* **1998**, *15*, 573–585. [CrossRef]
71. IBM Corp. *IBM SPSS Statistics for Windows*; IBM Corp: Armonk, NY, USA, 2020.
72. Cattell, R.B. The scree test for the number of factors. *Multivar. Behav. Res.* **1966**, *1*, 245–276. [CrossRef] [PubMed]
73. Patil, V.H.; Singh, S.N.; Mishra, S.; Donavan, D.T. *Parallel Analysis Engine to Aid in Determining Number of Factors to Retain Using R [Computer Software]*; School of Business Administration Spokane, Gonzaga University: Spokane, WA, USA, 2017; Available online: https://analytics.gonzaga.edu/parallelengine/ (accessed on 25 October 2021).
74. Norman, G.R.; Streiner, D.L. *Streiner, Biostatistics: The Bare Essentials*, 4th ed.; People's Medical Publishing House: Shelton, CO, USA, 2014.
75. Lerdal, A.; Kottorp, A. Psychometric properties of the Fatigue Severity Scale—Rasch analyses of individual responses in a Norwegian stroke cohort. *Int. J. Nurs. Stud.* **2011**, *48*, 1258–1265. [CrossRef] [PubMed]

76. van Damme, S.; Becker, S.; Van Der Linden, D. Tired of pain? Toward a better understanding of fatigue in chronic pain. *Pain* **2018**, *159*, 7–10. [CrossRef]
77. Neils-Strunjas, J.; Paul, D.; Clark, A.N.; Mudar, R.; Duff, M.C.; Waldron-Perrine, B.; Bechtold, K.T. Role of resilience in the rehabilitation of adults with acquired brain injury. *Brain Inj.* **2017**, *31*, 131–139. [CrossRef] [PubMed]
78. De Vries, J.; Van Heck, G.L. Fatigue: Relationships with basic personality and temperament dimensions. *Personal. Individ. Differ.* **2002**, *33*, 1311–1324. [CrossRef]
79. Ioannou, A.; Papastavrou, E.; Avraamides, M.N.; Charalambous, A. Virtual reality and symptoms management of anxiety, depression, fatigue, and pain: A systematic review. *SAGE Open Nurs.* **2020**, *6*, 2377960820936163. [CrossRef]
80. Aida, J.; Chau, B.; Dunn, J. Immersive virtual reality in traumatic brain injury rehabilitation: A literature review. *NeuroRehabilitation* **2018**, *42*, 441–448. [CrossRef]
81. Ezekiel, L.; Field, L.; Collett, J.; Dawes, H.; Boulton, M. Experiences of fatigue in daily life of people with acquired brain injury: A qualitative study. *Disabil. Rehabil.* **2021**, *43*, 2866–2874. [CrossRef]

III

Stability and change in biopsychosocial factors associated with fatigue 6 and 12 months after traumatic brain injury – an exploratory multilevel study

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Abstract

Objective:

To explore factors associated with stability and change in fatigue from 6 to 12 months following traumatic brain injury (TBI).

Setting:

Combined in- and outpatient acute care and post-acute rehabilitation settings.

Participants:

A total of 103 patients with confirmed intracranial injury were assessed 6 and/or 12 months following traumatic brain injury.

Design:

A prospective observational study with repeated measures at two time points, analyzed with a hybrid mixed effects model.

Main Measures:

Primary Outcome: Fatigue factor derived from items from several fatigue PROMS (Fatigue Severity Scale, Chalder Fatigue Scale, Giessen Subjective Complaints List – fatigue subscale, and Rivermead Post-Concussion Symptoms Questionnaire – fatigue item)

Secondary outcomes were PROMS relating to pain, somatic and psychological distress, insomnia, sleepiness, personality traits, optimism, resilience, behavioral activation and inhibition, and loneliness, as well as neuropsychological measures. Demographic variables and injury severity characteristics were included as covariates.

Results:

In multilevel regression, female gender, years of education, and three factors related to injury severity, somatic vulnerability, and psychosocial robustness were all significantly associated with variation in fatigue between subjects, and explained 61% of the variance in fatigue that was due to stable between-subject differences.

Fatigue levels declined significantly over time. Changes in pain severity, somatic symptom burden, psychological distress, and behavioral inhibition were positively associated with changes in fatigue, explaining 22% of the variance in fatigue within subjects.

Conclusion:

The study demonstrated that several previously implicated factors show robust effects in distinguishing individuals with TBI on levels of fatigue, but only a few show additional within-subject associations across time. Pain severity, somatic symptom burden, psychological distress, and behavioral inhibition correlated with fatigue across time, implicating these factors as crucial targets for rehabilitation of patients with TBI who suffer from persistent fatigue.

Introduction

Persistent fatigue is common after traumatic brain injury (TBI)[1,2], and is associated with functional impairment and reduced quality of life even when controlling for injury severity[3]. Estimates of prevalence vary between 7-80%, dependent on injury severity, the patient-reported outcome measure (PROM) employed, cut-off values applied, and post-injury time interval investigated[2,4]. Fatigue remains one of the most troublesome symptoms in the chronic phase following TBI[5], and there is a need for improved interventions to ameliorate fatigue in earlier phases[6]. Although some TBI-specific mechanisms have been suggested, such as injury-related cognitive impairment[7–10] and post-TBI endocrine disturbances[10], fatigue is common in many chronic illnesses, and relatively normally distributed in the general population[11,12]. There is also overlap in several predisposing and exacerbating factors for fatigue across disorders[13,14], such as pre- or comorbid pain, sleep disorders and psychological distress. The biopsychosocial nature of fatigue necessitates a multifactorial approach in studying changes in fatigue and related factors across time.

In a previous cross-sectional analysis on the first wave of the current study[15], we found three factors underlying biopsychosocial correlates of fatigue in patients with TBI 6 months post-injury. Pain, somatic symptoms, daytime sleepiness and insomnia, were related to fatigue through a factor termed Somatic Vulnerability. Psychological distress, personality traits (neuroticism, extraversion, conscientiousness, optimism), behavioral inhibition and loneliness were associated with fatigue through a factor termed Psychosocial Robustness. Thirdly, we demonstrated injury severity and neuropsychological variables to be associated with fatigue, although the effects were small. Together, these factors explained 44.2% of variance in fatigue 6 months after injury. Cross-sectional designs, however, do not inform us regarding directional influences and potential confounders in the relationships between fatigue and associated factors.

There is currently a scarcity of longitudinal TBI-studies examining temporal dynamics between fatigue and associated biopsychosocial variables. In a study of 88 patients with complicated mild to severe TBI, Schönberger et al.[16] found that early fatigue predicted more depression 6 months post-

injury, but that early depression and daytime sleepiness did not predict later fatigue. Beaulieu-Bonneau & Ouellet[17] found injury severity-dependent trajectories of fatigue 4, 8 and 12 months following TBI, and found that depression and insomnia were associated with fatigue in linear regression models at all time points, while pain was associated with fatigue only 4 and 8 months post-injury. More recently, Rakers et al.[18] examined symptom clusters implicated in trajectories of fatigue following mild TBI with latent class growth models throughout the first six months following injury. The two clusters with persistent levels of fatigue were characterized by an overrepresentation of female patients, the presence of pain, pre- and comorbid sleep complaints, and consistent passive coping compared to the clusters of patients experiencing decreases in fatigue.

Studies focusing on identifying changes in fatigue over time, seldom investigate the relationship with changes in other variables, as the aim is typically to predict which individuals develop persistent fatigue, and do not take into account that there may be considerable stability in both fatigue outcome and its predictors[19]. However, in order to ascertain whether associated variables are related to changes in fatigue across time, within-subject associations must be examined. For example, shared genetic susceptibility for both fatigue and several of the implicated factors such as pain and psychological distress has been demonstrated[20], which may complicate our understanding of their relationships. Exposure to risk factors prior to the brain injury, such as premorbid mental or physical illness, might predispose someone to both fatigue and depression following TBI, and explain their co-occurrence. Confounders such as these cannot be controlled for when examining only between-subject variability. Studying within-subject change and associations across variables over time provides a reliable method for identifying relevant and crucial targets for intervention, by taking into account stable trait-like propensities for fatigue and related factors[19].

Aims

The aim of this study was to investigate characteristics of stable between-subject levels of fatigue 6 and 12 months following TBI, and to evaluate synchronous changes in fatigue and associated factors within-subjects.

Methods

Sample Recruitment

Participants were identified prospectively between January 2018 through March 2020 from the Neurosurgical Department Oslo University Hospital (OUH), Ullevål, and underwent assessments approximately 6 and 12 months post-injury. Inclusion criteria were patients between 18-65 years, admitted with traumatic brain injury (ICD-10 diagnoses S06.1-S06.9) with intracranial injuries (verified by CT or MRI). Exclusion criteria were severe pre- or comorbid mental illness, ongoing substance or alcohol abuse, and severe physical and/or cognitive functional impairment hindering the completion of the study protocol at the first measurement point. Patients were identified following admission to the acute hospital and recruited through routine follow-up hospital consultations or by invitations through mail. Injury severity indices were retrieved from the Oslo TBI Registry – Neurosurgery, a quality database at OUH[21].

Primary Outcome Measures

Our study employed several fatigue measures, and in an earlier study we found a single, reliable factor underlying items from these Patient-Reported Outcome Measures (PROMS) in our sample[15]. Fatigue was therefore measured with a factor analytic regression score, with factor loadings constrained across time (i.e. assuming no time-related measurement invariance), using items from several fatigue PROMS. The Fatigue Severity Scale (FSS)[22] has been extensively used in the measurement of fatigue following TBI, and consists of 9 items pertaining to perceived impact of fatigue on various functional domains, of which only items 3-9 were included in the factor due to

non-salient loadings from items 1 & 2. Chalder Fatigue Questionnaire (CFQ) has been used in studies of Chronic Fatigue Syndrome / Myalgic Encephalomyelitis and other neurological illness[23], with 11 questions of various fatigue symptoms related to habitual functioning. Items relating to daytime sleepiness and common cognitive symptoms were not included in the fatigue factor due to overlap with independent variables in the study. Giessen Subjective Complaints List measures somatic symptom burden, with one subscale pertaining specifically to fatigue[24]. The subscale consists of 6 items, of which 3 were not included in the fatigue factor due to overlap with independent variables. Finally, one fatigue item from Rivermead Post-Concussion Symptoms Questionnaire (RPQ)[25] was included in the factor.

Secondary Outcome Measures

The study included several PROMS of secondary factors potentially associated with fatigue, such as pain severity and dispersion, somatic symptom burden, psychological distress, daytime sleepiness, and insomnia severity, Five-Factor Personality Traits (Neuroticism, Extraversion, Conscientiousness, Agreeableness and Openness), trait Optimism, behavioral inhibition, loneliness, and facets of resilience. Furthermore, several injury severity indices from the acute phase were included. Abbreviated Injury Scale – Head (AIS_head)[26]. A variable was calculated for those patients discharged directly to rehabilitation from the neurosurgical department (Direct Pathway to Rehabilitation), and was associated with fatigue in an earlier cross-sectional study on data from the first measurement[15]. Finally, performance-based assessment with neuropsychological subtests from Delis-Kaplan Executive Function System (D-KEFS[27]; Trail Making Test & Color Word Interference Test), Wechsler's Adult Intelligence Scale IV (WAIS-IV[28]; Digit Span), Wechsler's Abbreviated Scale of Intelligence (WASI[29]; Matrix Reasoning & Similarities), & Conners Continuous Performance Task III (CPT-III) were included. Further details on specific instruments and measures used can be found in the Supplemental Digital Content (Table S1.1).

Analyses

All analyses were conducted in Stata, Version 16[30]. Multilevel modelling is one way of investigating within-subject associations, as the within-subject stability (i.e. between-subject variance) in fatigue and its correlates are segregated from within-subject changes, and can be investigated separately. To assess the data for clustering effects, all time-varying variables (i.e. measured at both occasions) were assessed for intraclass-correlations within individuals.

Using principles from the hybrid fixed-random effects model proposed by Allison[31], all time-varying secondary outcome variables were segregated into person-mean variables, and within-subject deviations from the person-mean at each time point. Mean scores averaged across both time-points within individuals were thus generated for all time-varying variables to create between-subject components for all independent variables, and change scores were generated as each observation's deviation from the individual's mean to create within-subject components for all independent variables (see Figure 1 and Supplemental Digital Content, Section S3). Person-mean centering is a commonly employed technique in multilevel modelling for segregation of between- and within-subjects effects[32].

Correlation matrices were generated between individual mean scores (level 2) for fatigue and all level 2 variables. Next, correlation matrices between the change scores (centered level 1) for fatigue and other time-varying variables. Pearson correlations were used for associatiosn with continuous variables, and Spearman correlations for dichotomous variables.

Exploratory multilevel factor analysis was conducted by performing separate principal axis factor analyses on 1) all associated between-subject variables (including mean scores of time-varying variables), and 2) all associated within-subject variables (change scores from individual mean), respectively. The first analysis aimed to identify clustering of variables between patients, while the second analysis aimed to identify clustering of *changes* in variables across time. Factor retention was decided on the basis of eigenvalue thresholds from parallel analyses of 100 random correlation

matrices (95% threshold values)[33], and oblimin rotations were performed so as to allow factors to correlate. Loadings were deemed salient above |0.40|, and factor scores were generated through regression.

Finally, linear multilevel regression was performed with the fatigue factor as primary outcome variable, to evaluate the relative contributions to fatigue by multilevel factors derived from secondary outcome variables, demographics and time since injury. Observations (level 1) were parameterized as clustered within individuals (level 2). See figure 1 for an illustration of how multilevel models compartmentalize variance components based on clustering.

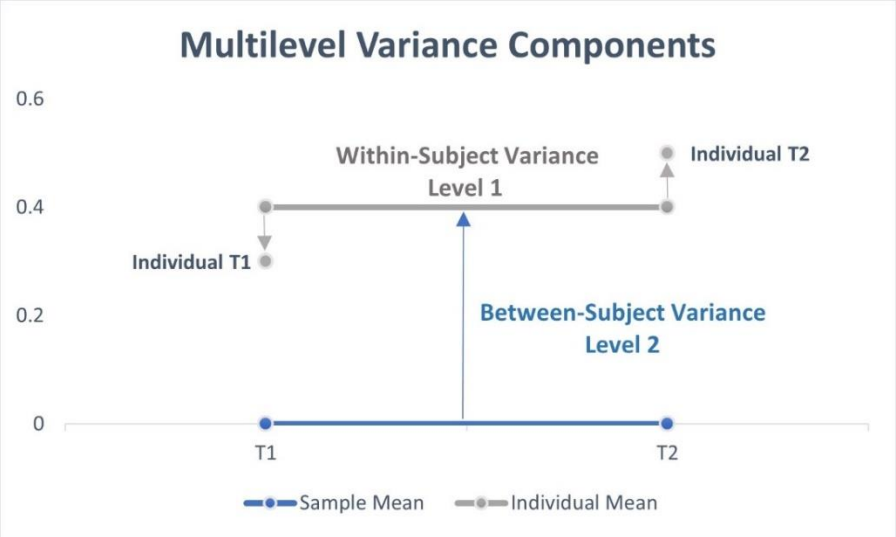

Figure 1. A visual illustration of the variance compartmentalization, for ease of comprehension of the multilevel approach. Rather than calculating variance as the deviation of each measurement from the total sample mean as in traditional regression analyses, the multilevel approach separates variance components into deviations of each individual's mean from the total sample mean (Between-Subject Variance), and the deviations of each measurement from the individual's mean (Within-Subject Variance). The Between-Subject Variance provides an estimate of the degree of total variance due to differences between individuals rather than between measurements, while the Within-Subject Variance provides an estimate of the degree of total variance due to differences in measurements within individuals. The hybrid mixed model uses the same approach on independent variables, to evaluate separate between- and within-subject effects of time-varying predictors.

The baseline variance component model included no fixed effects. For the final regression model, time-invariant variables were added, i.e. demographics and resulting factors from the Level 2-factor analyses, along with time-varying variables, i.e. time and variables and factors from the Level 1-factor analyses. Akaike's Information Criterion (AIC) and Bayesian Information Criterion (BIC) for the models were reported to determine model fit and parsimony. Changes in variance at both levels were calculated to determine to what degree the model predicted between-subject variance and within-subject variance in fatigue, and effect sizes were calculated as the explained variance contributed to the model at each level by each variable. See the Supplemental Digital Content (section S5) for further details on analyses, including a script with explanations of the procedures (section S3).

Results

Sample Demographics and Injury Severity

A schematic presentation of eligible and included patients is shown in figure 2. A total of 103 patients were included, with some variation in their contribution to either one or both time points. See Table 1 for an overview of sample characteristics. Ninety-six patients were assessed at the first assessment (T1), and ninety-eight patients for the second assessment (T2), with an average interval between measurements of 220 days (SD = 59.0). There was greater variability in the time point for the second measurement due to restrictions imposed by Covid-19 (see Supplemental Digital Content section S2 for an overview of measurement time points). In multilevel modelling this issue is handled by allowing time since injury to vary within individuals, and the effects of time can be evaluated despite differing measurement intervals.

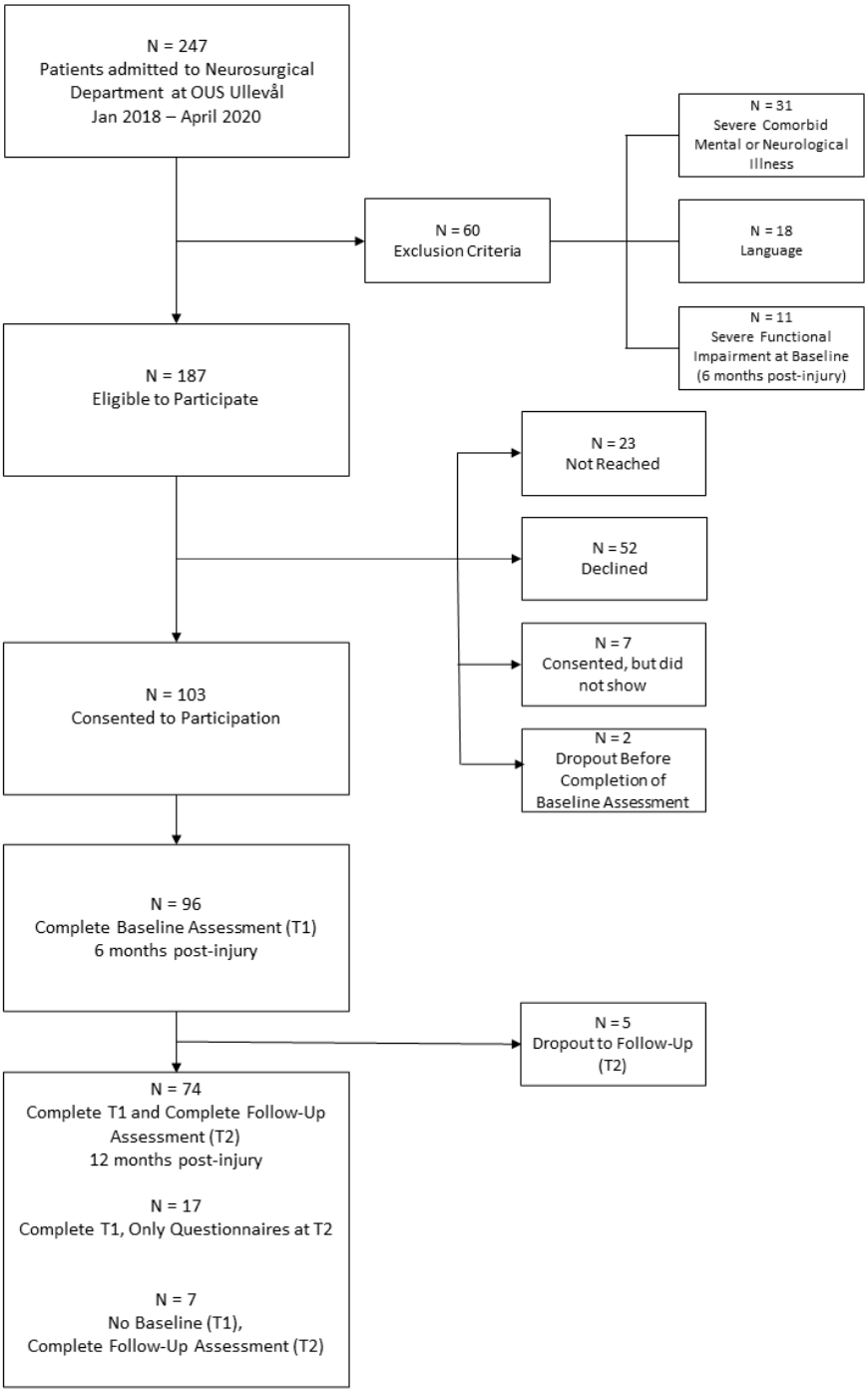

Figure 2. Flow chart outlining the inclusion and recruitment process, along with an overview of the contribution of each patient to either one or both of the time points.

Table 1. Distribution of central sample characteristics and the various measures of fatigue at both time points (T1 and T2).

Variable	n (%) (Level 2)	T1 (Level 1)	T2 (Level 1)
Total N	103	96	98
Head Injury Severity (HISS)			
Mild	23 (22.3)		
Moderate	51 (48.5)		
Severe	29 (28.2)		
Anatomical Injury Severity (AIS – head)			
2 - Moderate	3 (2.9)		
3 – Serious	16 (15.5)		
4 – Severe	32 (31.1)		
5 – Critical	52 (50.5)		
Cause of Injury			
Falls	47 (45.6)		
Traffic (including Bicycle)	37 (35.9)		
Sports-Related	6 (5.8)		
Violent Crime	5 (4.9)		
Other or Unknown	8 (7.8)		
Direct Discharge to Rehabilitation Services	61 (49.5)		
Age, median (IQR)	48 (34, 58)		
Male	83 (80.6)		
Education (Years), mean (SD)	13.6 (2.4)		
Months Since Injury, mean (SD)		6.9 (1.0)	14.0 (2.1)
FSS, mean (SD)	3.7 (1.5)	3.7 (1.4)	3.8 (1.5)
CFQ, mean (SD)	15.9 (5.7)	16.2 (5.4)	15.5 (6.0)
GSCL Fatigue, mean (SD)	1.0 (0.9)	1.0 (0.9)	1.0 (0.9)
RPQ Fatigue Item		n (%)	n (%)
0 = Not a problem		38 (39.6)	38 (38.8)
1 = No longer a problem		11 (11.5)	16 (16.3)
2 = A mild problem		20 (20.8)	18 (18.4)
3 = A moderate problem		20 (20.8)	17 (17.4)
4 = A severe problem		7 (7.3)	9 (9.2)

Abbreviations: HISS, Head Injury Severity Scale; AIS, Abbreviated Injury Scale; IQR, interquartile range; SD, standard deviation; FSS, Fatigue Severity Scale; CFQ, Chalder Fatigue Questionnaire; GSCL, Giessen Subjective Complaints List; RPQ, Rivermead Post-Concussion Symptoms Questionnaire.

Preliminary Analyses

Fatigue demonstrated a considerable within-subject stability (ICC) of 0.78, indicating that most of the variance in fatigue was due to differences between people, rather than changes within people. Similar patterns indicating trait-like stability were observed for all of the included predictors, supporting the use of a hybrid mixed effects model which deconstructs variables into between- and within-subject-components.

Multilevel Factor Analysis (MFA)

Level 2 MFA – Between-Subject Variables

Factor analysis of level 2 between-subject variables confirmed the three factors that were found in our previous publication from the first wave only[15]. Factor 1 was termed Psychosocial Robustness, with positive loadings from facets of resilience, trait Extraversion, Conscientiousness and Optimism, and negative loadings from anxiety, depression, loneliness, behavioral inhibition, and trait neuroticism. Factor 2 was termed Somatic Vulnerability, with positive loadings from all measures of pain and somatic symptom burden, as well as daytime sleepiness and insomnia severity. Factor 3 was termed Injury Severity, with positive loadings from AIS – head, direct discharge to rehabilitation, and three neuropsychological measures of processing speed, mental flexibility and intraindividual variability of reaction times / sustained attention (CPT-III Coefficient of Variation). For an overview of variables included in these factors, see Figure 3. Due to missing neuropsychological data in five participants at both time points due to color-blindness on subtests in the Injury Severity Factor (Color-Word Interference Test Subtests 2 and 4), the analyses presented in this paper were conducted with an Injury Severity factor comprised of only the AIS_head and the Direct Pathway to Rehabilitation variables. The same sequence of analyses was conducted in the complete case sample with an Injury Severity factor incorporating the three neuropsychological measures as a sensitivity analysis, with minimal increases in the factor's contributions to later regression models (data not shown).

Level 1 MFA – Within-Subject Variables

Factor analysis of level 1 within-subject change variables supported only one factor, indicating correlated change between several of the independent variables, specifically numerical rating scales of strongest and average pain within the last week, somatic symptom burden, anxiety, depression, and behavioral inhibition. While changes in performance on several neuropsychological measures were correlated with changes in fatigue, these changes did not load saliently on any single factor, indicating that there was no common factor underlying neuropsychological improvement. See figure 3 for an overview of included variables. Factor loadings from both level 1- and 2-analyses can be inspected in the Supplemental Digital Content (Section S4).

Linear Multilevel Regression

Results from the linear multilevel regression are shown in Table 2, and the proportion of explained variance for each variable in the model can be inspected in the Supplemental Digital Content (Table S5.1). Female gender and education were significantly positively associated with fatigue, each contributing approximately 2% explained variance to the between-subject level in the final regression model. All level 2-factors (i.e. Somatic Vulnerability, Psychosocial Robustness and Injury Severity) were significantly associated with fatigue. Somatic Vulnerability uniquely explained 36% of the variance in random intercepts for fatigue, while Psychosocial Robustness and Injury Severity uniquely explained 4.5% and 3.9%, respectively. Months since injury explained 6.4% of variance within-subjects, while the Correlated Change factor uniquely explained 17.7% of variance within-subjects. In total, the final regression model explained 61.1% of variance between-subjects in fatigue, and 21.7% of the variance within-subjects, summing up to 52.3% variance in total. See the Supplemental Digital Content (Section S6) for comments on post-hoc analyses.

Table 2. Fixed regression coefficients with Standard Errors SE, 95% confidence intervals, along with random effects at baseline and for the complete model, with level-wise percentage of explained variance, and fit indices. * = p < 0.05, ** = p < 0.01, *** = p < 0.001 for significance of fixed effects.

			95% Confidence Interval	
Fixed Effects (Level)	Coefficient	SE	Lowest	Highest
Constant	-0.63	0.28	-1.17	-0.08
Age – Centered (2)	0.00	0.00	-0.01	0.00
Gender (2)	0.35*	0.16	0.05	0.66
Years of Education - Centered (2)	-0.06*	0.03	-0.11	-0.00
Psychosocial Robustness (2)	-0.21**	0.07	-0.34	-0.08
Somatic Vulnerability (2)	0.58***	0.07	0.44	0.72
Injury Severity (2)	0.34**	0.12	0.10	0.57
Correlated Change Factor (1)	0.15***	0.03	0.08	0.21
Months Since Injury (1)	-0.02*	0.00	-0.04	-0.01
Random Effects (Level)	Baseline Model	Full Model	% explained	
Between Subject Variance (2)	0.75	0.30	61.1	
Within-Subject Variance (1)	0.21	0.17	21.7	
Total Variance	0.96	0.46	52.3	
Fit indices				
Log Likelihood	-228.89	-175.21		
AIC	463.78	372.42		
BIC	473.58	408.31		
Observations	193	193		
Groups	102	102		
df	3	11		

Discussion

Fatigue is associated with a wide range of biopsychosocial factors in the first year following TBI, and the present study examined between-subject associations with fatigue, and furthermore evaluated within-subject changes associated with changes in fatigue from 6 to 12 months. The findings highlight several biopsychosocial determinants for identifying patients at high risk for developing fatigue following TBI, and also factors associated with increases or decreases in fatigue within individuals.

Between-Subject Effects

Factor analyses replicated similar underlying dimensions in trait-like stability of predictors as previously reported in a cross-sectional analysis of the first wave of this study[15]. However, these between-subject factors demonstrated more robust effects in multilevel regressions than in our previous cross-sectional design, now explaining 61% of the variance in fatigue between individuals. Female gender also demonstrated a small, but significant positive association with fatigue, along with a slight negative association between years of education and fatigue.

These findings emphasize that through the first year post-injury, knowing the gender of the patient, their educational level, their degree of somatic vulnerability and psychosocial robustness, and initial injury severity, allowed us to distinguish significantly between individuals regarding their risk for fatigue after TBI.

Between-subject effects are, however, prone to confounding from potentially shared causes. Shared genetic susceptibility for fatigue, pain and psychological distress has been demonstrated earlier[20,34,35], and shared risk for and resilience to fatigue and associated factors might additionally be accumulated through an individual's idiosyncratic life experiences prior to and following injury. Thus, while demonstrating that individuals with higher psychosocial robustness (i.e. lower levels of trait neuroticism, behavioral inhibition, loneliness and psychological distress, and higher levels of conscientiousness, extraversion, resilient coping and optimism) have significantly lower levels of fatigue, this does not automatically imply any of these factors as crucial to the within-subject process of increasing or decreasing fatigue across time. For this, an evaluation of longitudinal within-subject effects is necessary.

Within-Subject Effects

Within-subject changes from 6 to 12 months in pain and somatic symptom burden, depression, anxiety and behavioral inhibition were correlated with one another, and loaded on a single factor which was positively associated with changes in fatigue. Thus, increases or decreases in fatigue from

6 to 12 months demonstrate significant synchronous changes in pain, somatic symptoms, psychological distress and behavioral inhibition. These within-subject changes, along with the time-dependent decrease in fatigue, explained approximately 22% of within-subject variance in fatigue. This is in line with the findings by Rakers et al.[18], linking persistence and recovery of fatigue with the presence or absence of emotional distress, pain and active or passive coping styles. Behavioral inhibition, which demonstrated a significant within-subject association with fatigue in our study, can be conceptualized as a trait-like propensity for avoidance of unpleasant and novel sensations, and is linked with passive coping. The correlated change between behavioral inhibition and fatigue thus aligns well with the results from Rakers et al.[18], in demonstrating that increases or decreases in behavioral inhibition is associated with increases or decreases in fatigue, respectively, which could imply compensatory changes in coping strategies for the management of fatigue.

Implications for Research and Rehabilitation

The findings support the notion of fatigue following TBI as a multifactorial phenomenon, associated with a wide range of biopsychosocial factors 6 to 12 months following injury. While there is a significant reduction in fatigue in this period, our study demonstrates that some factors only help to distinguish levels of fatigue between individuals, while others inform us of characteristics of those who experience reductions or increases in fatigue from 6 to 12 months. The two levels of analyses inform us of different, but clinically important ways to understand the development of fatigue following injury. See figure 3 for a graphical overview of the results, for ease of comprehension in the following discussion.

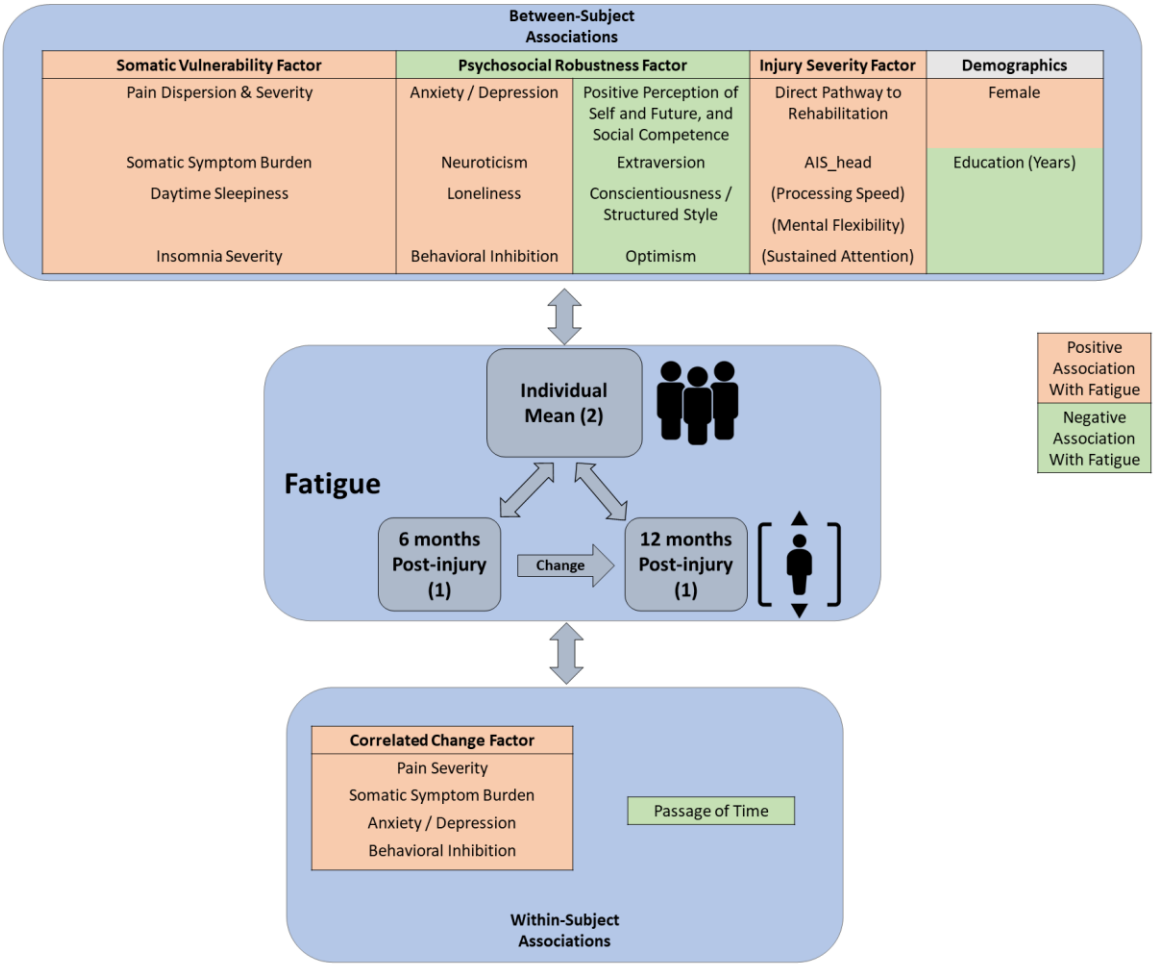

Figure 3. A graphical presentation of the findings, with separate between-subjects effects (Level 2) and within-subjects effects (Level 1).

Between-subject factors are important for clinicians and researchers preoccupied with the question of *which patients* might be at risk for experiencing fatigue. Thus, if a female patient with severe TBI initially reports complaints with pain and daytime sleepiness (indicators of somatic vulnerability), depressive symptoms and high levels of trait neuroticism (negative indicators of psychosocial robustness), there is a considerable likelihood that she will also experience fatigue. The underlying cause for the co-occurrence between fatigue and these factors cannot be delineated in this study, but one may presume that their co-occurrence may be due to shared genetic, injury-related and environmental causes[35], as well as potential reciprocal pathways between them over time.

Within-subject factors are important for clinicians and researchers preoccupied with the question of *which mechanisms drive* changes in fatigue. Therefore, if the aforementioned patient did suffer from fatigue, a reduction or increase in fatigue to a follow-up consultation 6 months later would in part be dictated by synchronous changes in pain and psychological distress, but not daytime sleepiness or trait neuroticism, according to our findings. Thus, individualized rehabilitation aimed at ameliorating fatigue should especially focus on the simultaneous treatment of pain and psychological distress, as their development is correlated with changes in fatigue. For instance, self-reported personality traits would not be expected to change significantly over a six month interval due to their relatively stable nature[36], but they are nevertheless linked with fatigue between-subjects. Pain, somatic symptoms, behavioral inhibition and psychological distress, on the other hand, fluctuate within individuals in association with fatigue. Further studies examining the development of fatigue would be well served in also tracking changes in these associated factors, to unravel potential causal pathways among them.

Limitations

The study has some limitations which should be noted. While the large battery of instruments employed allow for an exploration of overlap between variables commonly associated with fatigue, the exploratory approach combined with a relatively small sample size might affect generalizability. As with all dimension reduction techniques, a parsimonious structure is sought at the cost of complexity. There is, however, reason to trust the general pattern of findings, and the within-subject associations found in our study partially replicate previous findings from an unrelated, non-clinical sample[35]. Directional causality cannot, however, be concluded, as the synchronous changes might imply several potential directional pathways between fatigue and associated factors. Finally, longitudinal studies with more than two measurements could potentially capture more within-

subject variability and map individual differences in trajectories across time, and further studies investigating within-subject associations are warranted.

Conclusions

The study used a multilevel approach to explore the stable and time-varying relationships between fatigue and commonly implicated biopsychosocial factors in the literature. While gender, pre-injury educational attainment, injury severity indices and neuropsychological function explained significant variance in fatigue following TBI, the vast majority of explained variance was due to self-reported biopsychosocial constructs. Furthermore, the multilevel approach allowed us to disentangle between-subject risk and protective factors, and to single out within-subject factors crucial to changes in fatigue from 6 to 12 months following injury.

References

1. Cantor JB, Gordon W, Gumber S. What is post TBI fatigue? *NeuroRehabilitation*. 2013;32(4):875-883. https://doi.org/10.3233/NRE-130912

2. Mollayeva T, Kendzerska T, Mollayeva S, Shapiro CM, Colantonio A, Cassidy JD. A systematic review of fatigue in patients with traumatic brain injury: the course, predictors and consequences. *Neuroscience & Biobehavioral Reviews*. 2014;47:684-716. https://doi.org/10.1016/j.neubiorev.2014.10.024

3. Juengst S, Skidmore E, Arenth PM, Niyonkuru C, Raina KD. Unique contribution of fatigue to disability in community-dwelling adults with traumatic brain injury. *Archives of Physical Medicine and Rehabilitation*. 2013;94(1):74-79. https://doi.org/10.1016/j.apmr.2012.07.025

4. Andelic N, Røe C, Brunborg C, et al. Frequency of fatigue and its changes in the first 6 months after traumatic brain injury: results from the CENTER-TBI study. *J Neurol*. 2021;268(1):61-73. https://doi.org/10.1007/s00415-020-10022-2

5. Ponsford JL, Downing MG, Olver J, et al. Longitudinal follow-up of patients with traumatic brain injury: outcome at two, five, and ten years post-injury. *J Neurotrauma*. 2014;31(1):64-77. https://doi.org/10.1089/neu.2013.2997

6. Ali A, Morfin J, Mills J, et al. Fatigue After Traumatic Brain Injury: A Systematic Review. *The Journal of Head Trauma Rehabilitation*. 2021; 37(4):E249-E257. https://doi.org/10.1097/htr.0000000000000710

7. Johansson B, Berglund P, Rönnbäck L. Mental fatigue and impaired information processing after mild and moderate traumatic brain injury. *Brain Injury*. 2009;23(13-14):1027-1040. https://doi.org/10.3109/02699050903421099

8. Belmont A, Agar N, Hugeron C, Gallais B, Azouvi P. Fatigue and traumatic brain injury. *Annales de Readaptation et de Medecine Physique*. 2006;49(6):370-374. https://doi.org/10.1016/j.annrmp.2006.04.018

9. Ziino C, Ponsford JL. Selective attention deficits and subjective fatigue following traumatic brain injury. *Neuropsychology*. 2006;20(3):383-390. https://doi.org/10.1037/0894-4105.20.3.383

10. Zgaljardic DJ, Durham WJ, Mossberg KA, et al. Neuropsychological and physiological correlates of fatigue following traumatic brain injury. *Brain Injury*. 2014;28(4):389-397. https://doi.org/10.3109/02699052.2014.884242

11. Bültmann U, Kant I, Kasl S v, Beurskens AJHM, van den Brandt PA. Fatigue and psychological distress in the working population Psychometrics, prevalence, and correlates. *Journal of Psychosomatic Research*. 2002;52(6):445-452. https://doi.org/10.1016/S0022-3999(01)00228-8

12. Lerdal A, Moum T, Wahl AK, Rustøen T, Hanestad BR. Fatigue in the general population: A translation and test of the psychometric properties of the Norwegian version of the fatigue severity scale. *Scandinavian Journal of Public Health*. 2005;33(2):123-130. https://doi.org/10.1080/14034940410028406

13. Penner IK, Paul F. Fatigue as a symptom or comorbidity of neurological diseases. *Nature Reviews Neurology*. 2017;13(11):662-675. https://doi.org/10.1038/nrneurol.2017.117

14. Menting J, Tack CJ, Bleijenberg G, et al. Is fatigue a disease-specific or generic symptom in chronic medical conditions? *Health Psychology*. 2018;37(6):530-543. https://doi.org/10.1037/hea0000598

15. Løke D, Andelic N, Helseth E, et al. Impact of Somatic Vulnerability, Psychosocial Robustness and Injury-Related Factors on Fatigue following Traumatic Brain Injury—A Cross-Sectional Study. *J Clin Med*. 2022;11(6):1-19. https://doi.org/10.3390/jcm11061733

16. Schönberger M, Herrberg M, Ponsford J. Fatigue as a cause, not a consequence of depression and daytime sleepiness: A cross-lagged analysis. *Journal of Head Trauma Rehabilitation*. 2014;29(5):427-431. https://doi.org/10.1097/HTR.0b013e31829ddd08

17. Beaulieu-Bonneau S, Ouellet MC. Fatigue in the first year after traumatic brain injury: course, relationship with injury severity, and correlates. *Neuropsychological Rehabilitation*. 2017;27(7):983-1001. https://doi.org/10.1080/09602011.2016.1162176

18. Rakers SE, Timmerman ME, Scheenen ME, et al. Trajectories of Fatigue, Psychological Distress, and Coping Styles After Mild Traumatic Brain Injury: A 6-Month Prospective Cohort Study. *Archives of Physical Medicine and Rehabilitation*. 2021;102(10):1965-1971. https://doi.org/10.1016/j.apmr.2021.06.004

19. Yamada K, Adams H, Ellis T, et al. The temporal relation between pain and fatigue in individuals receiving treatment for chronic musculoskeletal pain. *BMC Musculoskeletal Disorders*. 2022;23(1):1-10. https://doi.org/10.1186/s12891-022-05162-7

20. Vassend O, Røysamb E, Nielsen CS, Czajkowski NO. Fatigue symptoms in relation to neuroticism, anxiety-depression, and musculoskeletal pain. A longitudinal twin study. *PLoS One*. 2018;13(6):1-21. https://doi.org/10.1371/journal.pone.0198594

21. Tverdal C, Aarhus M, Andelic N, Skaansar O, Skogen K, Helseth E. Characteristics of traumatic brain injury patients with abnormal neuroimaging in Southeast Norway. *Injury Epidemiology*. 2020;7(1):1-13. https://doi.org/10.1186/s40621-020-00269-8

22. Krupp LB, LaRocca NG, Muir-Nash J, Steinberg AD. The fatigue severity scale: application to patients with multiple sclerosis and systemic lupus erythematosus. *Arch Neurol*. 1989;46(10):1121-1123. https://doi.org/10.1001/archneur.1989.00520460115022

23. Chalder T, Berelowitz G, Pawlikowska T, et al. Development of a Fatigue Scale. *Journal of Psychosom Research*. 1993;37(2):147-153. https://doi.org/10.1016/0022-3999(93)90081-P

24. Brähler E, Scheer JW. *Der Gießener Beschwerdebogen:(GBB)*. Huber; 1995.

25. King NS, Crawford S, Wenden FJ, Moss NEG, Wade DT. The Rivermead Post Concussion Symptoms Questionnaire: a measure of symptoms commonly experienced after head injury and its reliability. *Journal of Neurology*. 1995;242(9):587-592. https://doi.org/10.1007/BF00868811

26. Association for the Advancement of Automotive Medicine. *Abbreviated Injury Scale; 1990 Revision: Update 98*. Association for the Advancement of Automotive Medicine; 1998.

27. Delis DC, Kaplan E, Kramer JH. *Delis-Kaplan executive function system [Database Record]*. APA PsycTests; 2001. https://doi.org/10.1037/t15082-000

28. Wechsler D. *Wechsler Adult Intelligence Scale–Fourth Edition (WAIS–IV)*. NCS Pearson; 2008.

29. Wechsler D. *Wechsler Abbreviated Scale of Intelligence*. APA PsycTests; 1999. https://doi.org/10.1037/t15170-000

30. StataCorp LLC. Stata statistical software: Release 16. *StataCorp LLC*; 2019.

31. Allison PD. *Fixed Effects Regression Models*. SAGE Publications; 2009.

32. Hamaker EL, Muthén B. The fixed versus random effects debate and how it relates to centering in multilevel modeling. *Psychological Methods*. 2020;25(3):365-379. https://doi.org/10.1037/met0000239

33. Patil VH, Singh SN, Mishra S, Donavan DT. Parallel analysis engine to aid in determining number of factors to retain using R [Computer software]. Published online 2017. Accessed May 30th, 2022. https://analytics.gonzaga.edu/parallelengine/

34. Burri A, Ogata S, Livshits G, Williams F. The association between chronic widespread musculoskeletal pain, depression and fatigue is genetically mediated. *PLoS One*. 2015;10(11). https://doi.org/10.1371/journal.pone.0140289

35. Løke D, Løvstad M, Andelic N, Andersson S, Ystrom E, Vassend O. The role of pain and psychological distress in fatigue: a co-twin and within-person analysis of confounding and causal relations. *Health Psychol Behav Med*. 2022;10(1):160-179. https://doi.org/10.1080/21642850.2022.2033121

36. Rush BK, Malec JF, Brown AW, Moessner AM. Personality and functional outcome following traumatic brain injury. *Rehabilitation Psychology*. 2006;51(3):257-264. https://doi.org/10.1037/0090-5550.51.3.257

Supplemental Digital Content – Appendices

Løke, Andelic, Helseth, Vassend, Andersson, Ponsford, Tverdal, Brunborg & Løvstad (2022). Stability and change in biopsychosocial factors associated with fatigue 6 and 12 months after traumatic brain injury – an exploratory multilevel study

Contents

S1. Overview of Included Measures

Table S1.1 provides a more detailed overview of all included variables in the study, with level indicators describing at which level the variable is situated. (II) indicates a level 2-variable, meaning that both time points within the individual share the same value on the variable. (I) indicates a level 1-variable, meaning that the variable was measured at both time points, and varies within individuals.

Table S1.1. An overview of all preimary and secondary outcome measures used in our study.

Constructs	**Measure**
Fatigue (Primary Outcome)	Fatigue Severity Scale (FSS) (Krupp et al., 1989) (I) Rivermead Post-Concussion Symptoms Questionnaire (RPQ) Fatigue Item (King et al., 1995) (I) Giessen Subjective Complaints List – Fatigue Subscale(Brähler & Scheer, 1995) (I) Chalder Fatigue Questionnaire (CFQ) (Chalder et al., 1993) with subscales for 1) Physical Fatigue (I) 2) Mental Fatigue (I) 3) Total Fatigue (I) Fatigue Factor – estimated with Principal Axis Factoring from items from all fatigue measures (I)
Demographic Variables	Age – centered around the sample mean (II) Sex (Female / Male) (II) Years of Education – centered around the sample mean (II)
Injury Severity Indices	Lowest Glasgow Coma Scale score (G. Teasdale et al., 2014) at injury site or upon admission to the hospital pre-intubation (II) Rotterdam CT Score (Maas et al., 2005) (II) Abbreviated Injury Scale – Head (AIS_head) (Association for the Advancement of Automotive Medicine, 1998) (II) Head Injury Severity Scale (HISS) (Stein & Spettell, 1995) (II) Direct Pathway to Rehabilitation (0/1) (II) Glasgow Outcome Scale (5-level version)(G. M. Teasdale et al., 1998) Upon Discharge from the Acute Hospital (II)

Cognitive Function (Scaled Scores)	WAIS-IV (Wechsler, 2008) Digit Span, with subscale scores for 1) Digit Span Forward Recall (I) 2) Digit Span Backward Recall (I) 3) Digit Span Sequencing Recall (I)
	Delis-Kaplan Executive Function System (D-KEFS) (Delis et al., 2001) – Trail Making Test (TMT) with subscales 1) Visual Scanning (I) 2) Number Sequencing (I) 3) Letter Sequencing (I) 4) Number-Letter Sequencing (I) 5) Motor Speed (I) & Color-Word Interference Test (CWIT) with subscales 1) Color Naming (I) 2) Color Reading (I) 3) Color-Word Interference (+ Error Measure) (I) 4) Color-Word Interference – Switching (+ Error Measure) (I)
	WASI (Wechsler, 1999) subscales 1) Similarities (I) 2) Matrix Reasoning (I)
	Conners' Continuous Performance Task (CPT-III) (Conners, 2014) with scaled scores for 1) Hit Reaction Time (HRT) (I) 2) Hit Reaction Time Standard Deviation (HRT SD) (I) 3) Variability (I) 4) Commissions (I) 5) Omissions (I) 6) HRT Block Change (I)

	7) HRT Inter-Stimulus-Interval Change (I) 8) Coefficient of Variation (CoV) (calculated independently, raw score) (I) 9) 8) Coefficient of Variation (CoV) Block Change (calculated independently, raw score) (I)
Pain Severity	Numerical Rating Scales (0-10) concerning (within the last two weeks) the 1) Strongest (I) 2) Weakest (I) 3) Average (I) 4) Current Pain Severity (I)
Pain Dispersion	Pain Drawing (# of Body Regions) (Kuorinka et al., 1987)(I)
Somatic Symptom Burden	Giessen Subjective Complaints List (Brähler & Scheer, 1995)with symptom subscales for 1) Musculoskeletal Symptoms (I) 2) Gastrointestinal Symptoms (I) 3) Cardiovascular Symptoms (I)
Behavioral Inhibition (BIS) & Activation (BAS) Systems	The BIS/BAS Scales (Carver & White, 1994) with subscales scores for 1) BAS – Drive (I) 2) BAS – Reward Responsiveness (I) 3) BAS – Fun Seeking (I) 4) Behavioral Inhibiton (BIS) (I)
Daytime Sleepiness	Epworth Sleepiness Scale (ESS) (Johns, 1991) (I)
Insomnia Severity	Insomnia Severity Index (ISI) (Bastien et al., 2001) (I)
Psychological Distress	Hopkins Symptoms Checklist (SCL-10) (Derogatis et al., 1974; Strand et al., 2003), with subscales for 1) Anxiety (I) 2) Depression (I)
Resilience	Resilience Scale for Adults (RSA) (Hjemdal et al., 2011), with subscale scores for 1) Planned Future (I) 2) Social Competence (I) 3) Social Resources (I)

	4) Perception of Self (I) 5) Structured Style (I)
Five-Factor Personality Traits	NEO Five Factor Inventory 3 (NEO-FFI-3) (McCrae & Costa, 2010) with scaled scores for 1) Neuroticism (I) 2) Extraversion (I) 3) Conscientiousness (I) 4) Agreeableness (I) 5) Openness (I)
Trait Optimism	Life Orientation Test – Revised, Optimism Subscale (LOT-R) (Scheier et al., 1994) (I)
Loneliness	Three items from UCLA Loneliness Scale 3 (UCLA-LA) (Russell, 1996) (I)

S2. Distributions of Measurement Occasions

As remarked in the main manuscript, restrictions posed by the Covid-19 pandemic meant that some measurements had to be postponed, which led to a higher degree of variability in time between measurements for some patients. For the sake of transparency, histograms are presented here that show the distributions of measurements by months since injury ($\frac{Days\ Since\ Injury}{30}$). In figure S2.1, the time points for all measurements in the first (T1) and second (T2) wave is presented, and finally the time between measurements within subjects is presented in figure S2.2.

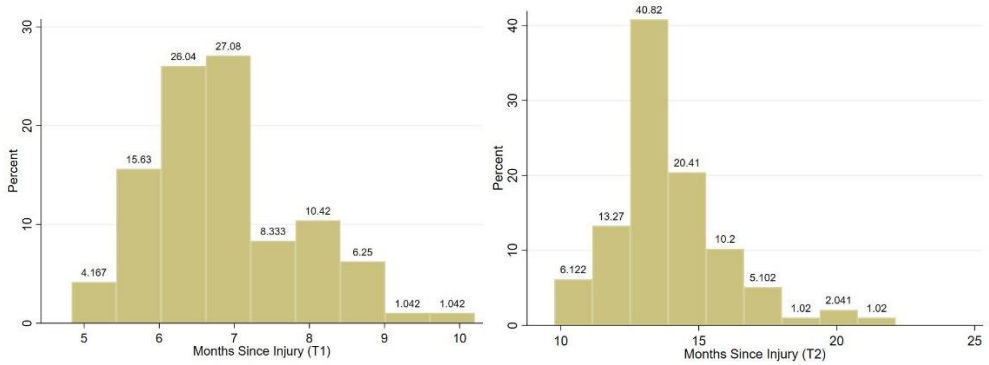

Figure S2.1. The distribution of time since injury (in months) for the first (T1) and second (T2) measurement occasions for all participants. As shown in the latter figure, approximately 20 patients were examined 15 months or more following injury.

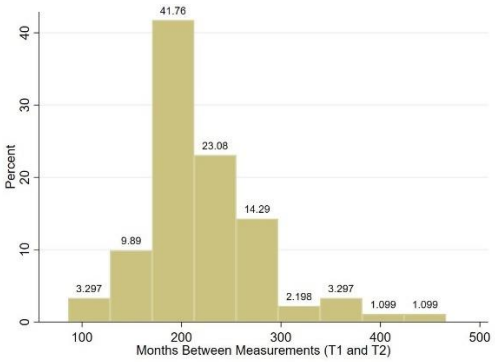

Figure S2.2. Histogram of intervals between measurement occasions for all participants who completed both measurements (in months). Seven patients were examined for their second measurement more than 300 days following their first measurement.

S3. Analyses – Stata Script (with explanatory remarks)

The specific steps of the analyses used in this study is presented in Table S3.1, with additional explanatory comments for the ease of comprehension. Prior to analyses, the data file was transformed from wide format (one row per subject) to long format (two rows per subject). The fatigue factor (primary outcome) was estimated prior to these analyses.

Table S3.1. Overview of specific commands performed both during preliminary exploratory analyses, multilevel factor analyses, and final multilevel regression modelling.

Command	**Comment**
bysort ID: egen Variable_im = mean(Variable_)	Generate individual aggregate scores within subjects (ID) across both time points for primary outcome and all time-varying associated factors (_im = Individual Mean).
gen Variable_imc = Variable_ - Variable_im	Generate new level 1 scores centered around the individual's mean (_imc = Individual Mean Centered)
pwcorr Fatigue_factor_im Varible_im …, sig star(.025)	Bivariate correlations between the individual mean scores (Level 2 aggregate) of fatigue and all included variables, with p < 0.025 due to the long format of the data.
pwcorr Fatigue_factor_imc Varible_imc …, sig star(.025)	Bivariate correlations between the scores centered around the individual's mean of fatigue and all included variables, with p < 0.025 due to the long format of the data.
factor Variable_im …., mineigen(1) blanks(.40) factor Variable_im …., factors(3) blanks(.40) rotate, oblimin blanks(.40) factor Variable_im … (factor 1-3), mineigen(1) blanks(.40) predict (factor 1-3) alpha Variable_im … (factor 1-3), std	Factor analyses of all significant level 2-variables from prior correlation analyses (individual mean scores). Three factors supported by parallell analyses. Oblimin oblique rotation applied which allows for correlated factors. Three separate factor analyses are conducted for each factor. Reliability (Cronbach's alpha) checked for each factor.
factor Variable_imc …., mineigen(1) blanks(.40) factor Variable_imc …., factors(1) blanks(.40) predict Change_factor_imc alpha Variable_imc … , std	Factor analyses of all significant centered level 1-variables from prior correlation analyses (deviation from individual's mean score). One factor supported by parallell analyses.
Mixed Fatigue_factor || ID:	Baseline multilevel regression model (variance components model), with Fatigue_factor scores nested within individual subjects.
Mixed Fatigue_factor Age_centered Education_centered Gender Factor_im1 Factor_im2 Factor_im3 Change_factor_imc time_months || ID:	Full multilevel regression model with factor scores, demographic variables and time as predictors.

S4. Between- and Within-Subject Factor Loadings

In this section, factor loadings from multilevel factor analyses are presented. Table S4.1 presents the results from the final one-factor between-subject factors (level 2). Note that an initial factor analysis was conducted to evaluate dimensionality and salient loadings, and that the presented loadings are from the resulting one-factor solutions incorporating only variables with salient loadings. Loadings from the level 1 factor is presented in Table S4.2.

Table S4.1. Factor loadings for the final unidimensional factor analyses of between-subject variables associated with fatigue, with reliability estimated with Cronbach's alpha. Factor correlations are presented in the bottom rows. Note that the Injury Severity factor was generated using polychoric factor analysis to allow for adequate calculation of a factor from the ordinal and binary variables. For factor correlations, $^{n.s.}$ = not significant, *** = $p < 0.001$.

	Factors		
	Psychosocial Robustness	Somatic Vulnerability	Injury Severity
Behavioral Inhibition	**-0.52**		
Trait Neuroticism	**-0.86**		
Trait Extraversion	**0.76**		
Trait Conscientiousness	**0.68**		
Trait Optimism	**0.76**		
Loneliness	**-0.74**		
Anxiety Symptoms	**-0.59**		
Depressive Symptoms	**-0.72**		
Resilience – Perception of Self	**0.88**		
Resilience – Planned Future	**0.73**		
Resilience – Social Competence	**0.70**		
Resilience – Structured Style	**0.62**		
Daytime Sleepiness		**0.43**	
Insomnia Severity Index		**0.59**	
Pain – Affected Regions		**0.77**	
Strongest Pain		**0.80**	
Weakest Pain		**0.74**	
Average Pain		**0.92**	
Current Pain		**0.84**	
Gastrointestinal Symptoms		**0.57**	
Musculoskeletal Symptoms		**0.90**	
Cardiovascular Symptoms		**0.61**	
AIS_head			**0.74**
Direct Pathway to Rehabilitation			**0.74**
Cronbach's alpha	0.92	0.91	0.69
Factor Correlations	1	2	3
1. Psychosocial Robustness	-		
2. Somatic Vulnerability	-0.35^{***}	-	
3. Injury Severity	$0.05^{n.s.}$	$0.05^{n.s.}$	-

Table S4.2. Factor loadings for the final unidimensional factor analyses of within-subject variables associated with within-subject variance in fatigue. Factor reliability was calculated with Cronbach's alpha.

	Correlated Change Factor
Behavioral Inhibition	**0.51**
Anxiety Symptoms	**0.60**
Depressive Symptoms	**0.68**
Strongest Pain	**0.49**
Average Pain	**0.56**
Gastrointestinal Symptoms	**0.45**
Musculoskeletal Symptoms	**0.53**
Cardiovascular Symptoms	**0.54**
Cronbach's alpha	0.80

S5. Unique Contributions to Final Regression Model

In order to evaluate the unique contributions to the final regression model with fatigue as primary outcome, post-hoc analyses were conducted. Separate regression models were ran without each significant fixed effect, and estimates were calculated as the difference in explained variance from the final model, as a proportion of baseline variance. Table S5.1 shows the proportion of explained variance by each variable to the final regression model, separated by levels.

Table S5.1. Estimated proportions of variance explained (Quasi- R^2) in fatigue by each variable, separated by levels.

	Variance Explained (Quasi-R^2)		
Variable (Level)	Level 2 Between Subjects (%)	Level 1 Within Subjects (%)	Total (%)
Gender (2)	2.6	0.1	2.0
Education (2)	1.9	0.4	1.5
Psychosocial Robustness (2)	4.5	0.6	3.6
Somatic Vulnerability (2)	35.9	-0.7	27.8
Injury Severity (2)	3.9	0.0	3.0
Change Factor (1)	-2.9	17.7	1.7
Months Since Injury (1)	-1.5	6.4	0.2

S6. Post-Hoc Analyses

No common factor could be found to underlie neuropsychological change scores, which may be due to the relatively modest sample size. Post-hoc analyses were conducted to evaluate additional contributions to the final model by changes in performance on single neuropsychological measures. While improvement in several individual measures of neuropsychological functions were univariately associated with decreases in fatigue, models incorporating these variables did not demonstrate significant improvements in model fit, likely due to significant positive correlations between neuropsychological change and time, suppressing the effects of both in the regression model.

S7. References

Association for the Advancement of Automotive Medicine. *Abbreviated Injury Scale; 1990 Revision: Update 98*. Association for the Advancement of Automotive Medicine; 1998.

Bastien, C. H., Vallières, A., & Morin, C. M. (2001). Validation of the Insomnia Severity Index as an outcome measure for insomnia research. *Sleep Medicine*, *2*(4), 297–307. https://doi.org/10.1016/S1389-9457(00)00065-4

Brähler, E., & Scheer, J. W. (1995). *Der gießener beschwerdebogen:(GBB)*. Bern, Switzerland: Huber.

Carver, C. S., & White, T. L. (1994). Behavioral Inhibition, Behavioral Activation, and Affective Responses to Impending Reward and Punishment: The BIS/BAS Scales. Journal of Personality and Social Psychology, 67(2), 319–333. https://doi.org/10.1037/0022-3514.67.2.319

Chalder, T., Berelowitz, G., Pawlikowska, T., Watts, L., Wessely, S., Wright, D., & Wallace, E. P. (1993). Development of a fatigue scale. Journal of Psychosomatic Research, 37(2), 147–153. https://doi.org/10.1016/0022-3999(93)90081-P

Conners, C. K. (2014). Conners continuous performance test 3rd edition, technical manual. Toronto, Canada: Multi-Health Systems Inc.

Delis, D. C., Kaplan, E., & Kramer, J. H. (2001). Delis-Kaplan executive function system. [Database record]. APA PsycTests. https://doi.org/10.1037/t15082-000

Derogatis, L. R., Lipman, R. S., Rickels, K., Uhlenhuth, E. H., & Covi, L. (1974). The Hopkins Symptom Checklist (HSCL): A self-report symptom inventory. Behavioral Science, 19(1), 1–15. https://doi.org/10.1002/bs.3830190102

Hjemdal, O., Friborg, O., Braun, S., Kempenaers, C., Linkowski, P., & Fossion, P. (2011). The Resilience Scale for Adults: Construct validity and measurement in a Belgian sample. International Journal of Testing, 11(1), 53–70. https://doi.org/10.1080/15305058.2010.508570

Johns, M. W. (1991). A new method for measuring daytime sleepiness: The Epworth sleepiness scale. Sleep, 14(6), 540–545. https://doi.org/10.1093/sleep/14.6.540

King, N. S., Crawford, S., Wenden, F. J., Moss, N. E. G., & Wade, D. T. (1995). The Rivermead Post Concussion Symptoms Questionnaire: A measure of symptoms commonly experienced after head injury and its reliability. Journal of Neurology, 242(9), 587–592. https://doi.org/10.1007/BF00868811

Krupp, L. B., LaRocca, N. G., Muir-Nash, J., & Steinberg, A. D. (1989). The fatigue severity scale: Application to patients with multiple sclerosis and systemic lupus erythematosus. Archives of Neurology, 46(10), 1121–1123.

Kuorinka, I., Jonsson, B., Kilbom, A., Vinterberg, H., Biering-Sørensen, F., Andersson, G., & Jørgensen, K. (1987). Standardised Nordic questionnaires for the analysis of musculoskeletal symptoms. Applied Ergonomics, 18(3), 233–237. https://doi.org/10.1016/0003-6870(87)90010-X

Maas, A. I. R., Hukkelhoven, C. W. P. M., Marshall, L. F., & Steyerberg, E. W. (2005). Prediction of outcome in traumatic brain injury with computed tomographic characteristics: A comparison between the computed tomographic classification and

combinations of computed tomographic predictors. Neurosurgery, 57(6), 1173–1182. https://doi.org/10.1227/01.neu.0000186013.63046.6b

McCrae, R. R., & Costa, P. T. (2010). NEO inventories for the NEO personality inventory-3 (NEO-PI-3), NEO five-factor inventory-3 (NEO-FFI-3), NEO personality inventory-revised (NEO PI-R): Professional manual. Lutz, USA: Psychological Assessment Resources.

Russell, D. W. (1996). UCLA Loneliness Scale (Version 3): Reliability, validity, and factor structure. Journal of Personality Assessment, 66(1), 20–40. https://doi.org/10.1207/s15327752jpa6601_2

Scheier, M. F., Carver, C. S., & Bridges, M. W. (1994). Distinguishing optimism from neuroticism (and trait anxiety, self-mastery, and self-esteem): A reevaluation of the Life Orientation Test. Journal of Personality and Social Psychology, 67(6), 1063–1078. https://doi.org/10.1037/0022-3514.67.6.1063

Stein, S. C., & Spettell, C. (1995). The Head Injury Severity Scale (HISS): A practical classification of closed-head injury. Brain Injury, 9(5), 437–444. https://doi.org/10.3109/02699059509008203

Strand, B. H., Dalgard, O. S., Tambs, K., & Rognerud, M. (2003). Measuring the mental health status of the Norwegian population: A comparison of the instruments SCL-25, SCL-10, SCL-5 and MHI-5 (SF-36). Nordic Journal of Psychiatry, 57(2), 113–118. https://doi.org/10.1080/08039480310000932

Teasdale, G. M., Pettigrew, L. E. L., Wilson, J. T. L., Murray, G., & JENNETT, B. (1998). Analyzing outcome of treatment of severe head injury: a review and update on advancing the use of the Glasgow Outcome Scale. *Journal of Neurotrauma*, *15*(8), 587–597. https://doi.org/10.1089/neu.1998.15.587

Teasdale, G., Maas, A., Lecky, F., Manley, G., Stocchetti, N., & Murray, G. (2014). The Glasgow Coma Scale at 40 years: Standing the test of time. The Lancet Neurology, 13(8), 844–854. https://doi.org/10.1016/S1474-4422(14)70120-6

Wechsler, D. (1999). Wechsler abbreviated scale of intelligence [Database Record]. APA Psyctests. https://doi.org/10.1037/t15170-000

Wechsler, D. (2008). Wechsler adult intelligence scale–Fourth Edition (WAIS–IV). San Antonio, TX: NCS Pearson.