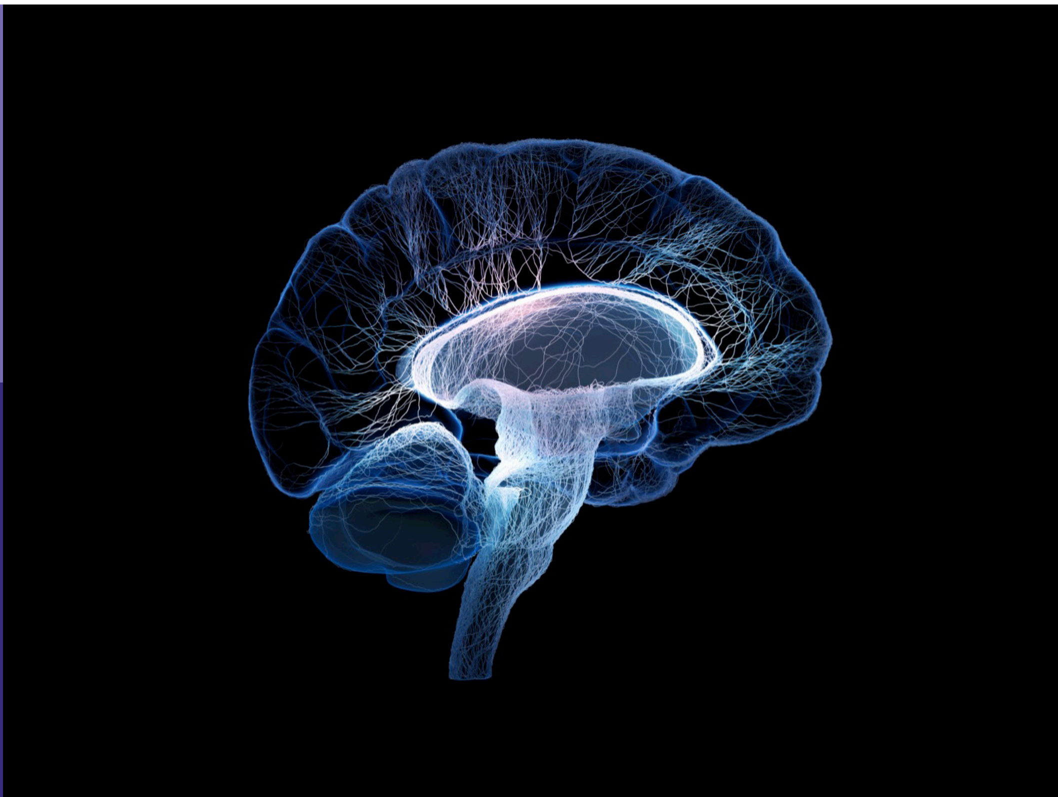
frontiers | Research Topics

Fatigue: Physiology and pathology

Edited by
Sławomir Kujawski, Pawel Zalewski, Lynette Hodges,
Jo Nijs and Julia Newton

Published in
Frontiers in Neuroscience
Frontiers in Physiology
Frontiers in Public Health
Frontiers in Psychology



ISSN 1664-8714
ISBN 978-2-8325-4471-6
DOI 10.3389/978-2-8325-4471-6

About Frontiers

Frontiers is more than just an open access publisher of scholarly articles: it is a pioneering approach to the world of academia, radically improving the way scholarly research is managed. The grand vision of Frontiers is a world where all people have an equal opportunity to seek, share and generate knowledge. Frontiers provides immediate and permanent online open access to all its publications, but this alone is not enough to realize our grand goals.

Frontiers journal series

The Frontiers journal series is a multi-tier and interdisciplinary set of open-access, online journals, promising a paradigm shift from the current review, selection and dissemination processes in academic publishing. All Frontiers journals are driven by researchers for researchers; therefore, they constitute a service to the scholarly community. At the same time, the *Frontiers journal series* operates on a revolutionary invention, the tiered publishing system, initially addressing specific communities of scholars, and gradually climbing up to broader public understanding, thus serving the interests of the lay society, too.

Dedication to quality

Each Frontiers article is a landmark of the highest quality, thanks to genuinely collaborative interactions between authors and review editors, who include some of the world's best academicians. Research must be certified by peers before entering a stream of knowledge that may eventually reach the public - and shape society; therefore, Frontiers only applies the most rigorous and unbiased reviews. Frontiers revolutionizes research publishing by freely delivering the most outstanding research, evaluated with no bias from both the academic and social point of view. By applying the most advanced information technologies, Frontiers is catapulting scholarly publishing into a new generation.

What are Frontiers Research Topics?

Frontiers Research Topics are very popular trademarks of the *Frontiers journals series*: they are collections of at least ten articles, all centered on a particular subject. With their unique mix of varied contributions from Original Research to Review Articles, Frontiers Research Topics unify the most influential researchers, the latest key findings and historical advances in a hot research area.

Find out more on how to host your own Frontiers Research Topic or contribute to one as an author by contacting the Frontiers editorial office: frontiersin.org/about/contact

Fatigue: Physiology and pathology

Topic editors
Sławomir Kujawski — Ludwik Rydygier Collegium Medicum in Bydgoszcz Nicolaus Copernicus University in Toruń, Poland
Pawel Zalewski — Nicolaus Copernicus University in Toruń, Poland
Lynette Hodges — Massey University Palmerston North, New Zealand
Jo Nijs — Vrije University Brussels, Belgium
Julia Newton — Newcastle University, United Kingdom

Citation
Kujawski, S., Zalewski, P., Hodges, L., Nijs, J., Newton, J., eds. (2024).
Fatigue: Physiology and pathology. Lausanne: Frontiers Media SA.
doi: 10.3389/978-2-8325-4471-6

Table of contents

frontiers | Frontiers in Neuroscience

TYPE Editorial
PUBLISHED 02 February 2024
DOI 10.3389/fnins.2024.1368897

OPEN ACCESS

EDITED AND REVIEWED BY
Joel C. Bornstein,
The University of Melbourne, Australia

*CORRESPONDENCE
Sławomir Kujawski
✉ skujawski@cm.umk.pl

RECEIVED 11 January 2024
ACCEPTED 23 January 2024
PUBLISHED 02 February 2024

CITATION
Kujawski S, Zalewski P, Hodges L, Nijs J and Newton JL (2024) Editorial: Fatigue: physiology and pathology.
Front. Neurosci. 18:1368897.
doi: 10.3389/fnins.2024.1368897

Editorial: Fatigue: physiology and pathology

Sławomir Kujawski[1]*, Paweł Zalewski[1,2], Lynette Hodges[3], Jo Nijs[4,5,6] and Julia L. Newton[7]

[1]Department of Exercise Physiology and Functional Anatomy, Ludwik Rydygier Collegium Medicum in Bydgoszcz Nicolaus Copernicus University in Toruń, Bydgoszcz, Poland, [2]Laboratory of Centre for Preclinical Research, Department of Experimental and Clinical Physiology, Warsaw Medical University, Warsaw, Poland, [3]School of Sport, Exercise and Nutrition, Massey University, Palmerston North, New Zealand, [4]Pain in Motion International Research Group, Department of Physiotherapy, Human Physiology and Anatomy, Faculty of Physical Education and Physiotherapy, Vrije Universiteit Brussel, Ixelles, Belgium, [5]Chronic Pain Rehabilitation, Department of Physical Medicine and Physiotherapy, University Hospital Brussels, Brussels, Belgium, [6]Department of Neuroscience and Physiology, University of Gothenburg, Gothenburg, Sweden, [7]Retired, Newcastle upon Tyne, United Kingdom

KEYWORDS

ME/CFS, chronic fatigue, Multiple Sclerosis, fatigue, long COVID, PACS

Editorial on the Research Topic
Fatigue: physiology and pathology

Introduction

Most of us perceive a rich amount of mind states throughout our lives. A qualia could be a derivate of an amalgamation of multiple qualities at a given moment. The severity of fatigue is like a wool coat that is worn by the mind. When the severity of fatigue is low, most healthy people are unaware of its presence. However, when fatigue severity increases, the wool coat gets wet and its presence becomes more and more unpleasant and overwhelming. In pathological conditions, the heaviness of the coat of the fatigue can significantly limit a patient's functionality.

A clear distinction between mind and body appears to be abandoned by the neuroscience paradigm of today at the expense of the underlying interconnection between those two dimensions (Glannon, 2020). Nevertheless, even with the clear advancement of nervous system imaging tools in recent decades, there are potent barriers to translating neural system activity to mental states and experiences, including fatigue (Gonzalez-Castillo et al., 2021). We hope that the current Research Topic provided a closer inspection of one of the fabrics making up the mind.

Fatigue physiology: prevalence, assessment, stigma

In the review on global fatigue prevalence in the general population included in the Research Topic, ninety-one studies involving 623,624 participants were taken into account (Yoon et al.). Authors observed that 6% of minors and 15% of adults worldwide report fatigue, with a tendency to higher rates in women vs. in men (Yoon et al.). Ten percent of adults and one-and-a-half percent of minors experience chronic fatigue. In addition to having a frequency that is greater in women than in men, medically unexplained exhaustion is also 2.7 times more common than explained fatigue (Yoon et al.).

von dem Knesebeck and Barbek reported data gathered from one thousand two hundred and nine responders regarding public stigma toward individuals with fatigue. Results showed that a significant amount of responders are prone to apply stereotypical labels to people with fatigue, such as being "hypersensitive" or characterized by "weak will" (von dem Knesebeck and Barbek).

Modern brain imaging techniques offer an opportunity to gather huge amounts of data. It seems that neural correlates of fatigue are highly complex (Sun et al., 2014). Therefore, one can facilitate the process of finding patterns in data by applying mathematical models. Yuan et al. applied a variety of methods including the attention mechanism and the gated recurrent unit for fatigue detection using electroencephalography (EEG).

Fatigue pathology: MS, ME/CFS, long COVID

It should be noted that in some circumstances, acute fatigue seems to be a physiological response to a higher workload. In healthy people, fatigue can be alleviated by rest in a rather short matter of time. However, in patients with Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS), an increase in symptom severity can be caused by relatively low intensity physical, emotional, or psychological stressors. Post-exertional malaise (PEM) is a crucial source of suffering in the majority of ME/CFS patients. PEM is comprehensively described in the paper by Vøllestad and Mengshoel.

Core symptoms of ME/CFS also often occur in long COVID (otherwise known as post-acute sequelae of COVID-19) patients, and may include fatigue, pain, post-exertional malaise, breathing difficulties, and cognitive dysfunction (Davis et al., 2021; Komaroff and Bateman, 2021). In the current main paradigm of science, it is assumed that symptoms perceived by patients are output products of the nervous system. However, there is still much to explore and the study of Thapaliya et al. seems to be a very important step in this direction. "Pain" and "breathing difficulty" perceived by patients were related to multiple brain regions, including pons, midbrain, and whole brainstem volumes (Thapaliya et al.).

The last decades of research in human neuroscience have produced an appreciation of bidirectional cooperation between the nervous system and its effectors. In this line, Day et al. have provided a study on the relationship between changes in the cardiovascular system response to changing position from prone to supine with cognitive dysfunction in patients suffering from ME/CFS and long COVID.

Fatigue is a non-specific symptom, occurring in multiple chronic disorders. In addition, to the description of fatigue in Multiple Sclerosis (MS), Pinarello et al. described modes of treatment of MS both pharmacological and non-pharmacological including telemedicine approach.

Fatigue management: breathing exercises and integrative care

In skeletal muscle physiology, peripheral fatigue refers to a group of changes occurring in response to prolonged muscle activity, while central fatigue is the inability of the nervous system to produce and transmit the signal to contract to the effectors (Dotan et al., 2021). This distinction is somewhat controversial, as there seems to be no clear barrier between "peripheral" vs. "central" (Dotan et al., 2021). Nevertheless, in keeping with this distinction, Amiri and Zemková suggested study protocol for the application of a breathing exercise program in decreasing fatigue of postural skeletal muscles.

By taking a whole picture of all manuscripts published on the above Research Topic, one can appreciate the multidimensionality of research on fatigue. Because of the innate complexity of physiology and pathology in various conditions, and interaction with the ambient world, it is worth looking at the current medical system in Western countries from various perspectives. A piece of this approach has been implemented in the paper by Araja et al..

In conclusion, the Research Topic includes several important scientific contributions to the field of fatigue physiology and pathology. This includes work addressing the prevalence, assessment, stigma, and fatigue pathology in patients with MS, ME/CFS, and long COVID, as well as reports on fatigue management. Although the field of fatigue physiology and pathology is a growing field, many research gaps remain. Therefore, the guest editors call for more cutting-edge research to advance this field of research, especially to improve care for millions of people suffering from severely debilitating ME/CFS.

Author contributions

SK: Writing—original draft, Writing—review & editing. PZ: Writing—original draft, Writing—review & editing. LH: Writing—original draft, Writing—review & editing. JN: Writing—original draft, Writing—review & editing. JLN: Writing— original draft, Writing—review & editing.

Funding

The author(s) declare that no financial support was received for the research, authorship, and/or publication of this article.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

References

Davis, H. E., Assaf, G. S., McCorkell, L., Wei, H., Low, R. J., Re'em, Y., et al. (2021). Characterizing long COVID in an international cohort: 7 months of symptoms and their impact. *eClinicalMedicine* 1:101019. doi: 10.1016/j.eclinm.2021.101019

Dotan, R., Woods, S., and Contessa, P. (2021). On the reliability and validity of central fatigue determination. *Eur. J. Appl. Physiol.* 121, 2393–2411. doi: 10.1007/s00421-021-04700-w

Glannon, W. (2020). Mind-brain dualism in psychiatry: ethical implications. *Front. Psychiatry* 3:85. doi: 10.3389/fpsyt.2020.00085

Gonzalez-Castillo, J., Kam, J. W., Hoy, C. W., and Bandettini, P. A. (2021). How to interpret resting-state fMRI: ask your participants. *J. Neurosci.* 41, 1130–1141. doi: 10.1523/JNEUROSCI.1786-20.2020

Komaroff, A. L., and Bateman, L. (2021). Will COVID-19 lead to myalgic encephalomyelitis/chronic fatigue syndrome? *Front. Med.* 18:606824. doi: 10.3389/fmed.2020.606824

Sun, Y., Lim, J., Kwok, K., and Bezerianos, A. (2014). Functional cortical connectivity analysis of mental fatigue unmasks hemispheric asymmetry and changes in small-world networks. *Brain Cogn.* 1, 220–230. doi: 10.1016/j.bandc.2013.12.011

frontiers | Frontiers in Neuroscience

TYPE Original Research
PUBLISHED 02 March 2023
DOI 10.3389/fnins.2023.1125208

OPEN ACCESS

EDITED BY
Pawel Zalewski,
Nicolaus Copernicus University in Toruń,
Poland

REVIEWED BY
Davide Ferrazzoli,
Hospital of Vipiteno, Italy
Karl Morten,
University of Oxford, United Kingdom

*CORRESPONDENCE
Kiran Thapaliya
✉ k.thapaliya@griffith.edu.au

SPECIALTY SECTION
This article was submitted to
Autonomic Neuroscience,
a section of the journal
Frontiers in Neuroscience

RECEIVED 16 December 2022
ACCEPTED 17 February 2023
PUBLISHED 02 March 2023

CITATION
Thapaliya K, Marshall-Gradisnik S, Barth M, Eaton-Fitch N and Barnden L (2023) Brainstem volume changes in myalgic encephalomyelitis/chronic fatigue syndrome and long COVID patients.
Front. Neurosci. 17:1125208.
doi: 10.3389/fnins.2023.1125208

Brainstem volume changes in myalgic encephalomyelitis/chronic fatigue syndrome and long COVID patients

Kiran Thapaliya[1,2]*, Sonya Marshall-Gradisnik[1], Markus Barth[2,3], Natalie Eaton-Fitch[1] and Leighton Barnden[1]

[1]National Centre for Neuroimmunology and Emerging Diseases, Menzies Health Institute Queensland, Griffith University, Gold Coast, QLD, Australia, [2]Centre for Advanced Imaging, The University of Queensland, Brisbane, QLD, Australia, [3]School of Information Technology and Electrical Engineering, The University of Queensland, Brisbane, QLD, Australia

Myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) and long COVID patients have overlapping neurological, autonomic, pain, and post-exertional symptoms. We compared volumes of brainstem regions for 10 ME/CFS (CCC or ICC criteria), 8 long COVID (WHO Delphi consensus), and 10 healthy control (HC) subjects on 3D, T1-weighted MRI images acquired using sub-millimeter isotropic resolution using an ultra-high field strength of 7 Tesla. Group comparisons with HC detected significantly larger volumes in ME/CFS for pons (p = 0.004) and whole brainstem (p = 0.01), and in long COVID for pons (p = 0.003), superior cerebellar peduncle (p = 0.009), and whole brainstem (p = 0.005). No significant differences were found between ME/CFS and long COVID volumes. In ME/CFS, we detected positive correlations between the pons and whole brainstem volumes with "pain" and negative correlations between the midbrain and whole brainstem volumes with "breathing difficulty." In long COVID patients a strong negative relationship was detected between midbrain volume and "breathing difficulty." Our study demonstrated an abnormal brainstem volume in both ME/CFS and long COVID consistent with the overlapping symptoms.

KEYWORDS

myalgic encephalomyelitis/chronic fatigue syndrome, brainstem, magnetic resonance imaging (MRI), pain, breathing difficulty, long COVID

Introduction

Myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) is a complex illness that affects multiple body systems and is characterized by a range of symptoms including post-exertional neuroimmune exhaustion (PENE), fatigue, pain, breathing difficulties, and difficulties with concentration and cognitive function (Baker and Shaw, 2007; Carruthers et al., 2011; Stussman et al., 2020). ME/CFS affects 17 to 24 million people worldwide (Lim et al., 2020). There is an absence of a laboratory diagnostic test for ME/CFS, instead diagnosis follows clinical case criteria and exclusion of other illnesses that may account for the symptoms. Over three decades, up to 30 case definitions have been published; however, the three more commonly recognized definitions include Fukuda criteria (Fukuda, 1994), Canadian Consensus Criteria (CCC) (Carruthers et al., 2003), and International Consensus Criteria (ICC) (Carruthers et al., 2011).

Recently, coronavirus 2019 (COVID-19) caused by the novel Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) has infected more than 600 million and caused the deaths of over six million people worldwide (World Health Organization [WHO], 2022). Studies show that up to 43% of people infected by SARS-CoV-2 do not recover fully and develop post-COVID conditions, also known as long COVID (Davis et al., 2021; Chen et al., 2022). Long COVID is defined by the World Health Organisation (WHO) as the continuation or development of new symptoms 3 months after the initial SARS-COV-2 infection, with these symptoms lasting for at least 2 months with no other explanation (World Health Organization [WHO], 2021). The most frequently reported symptoms in the long COVID patients are fatigue, pain, post-exertional malaise, breathing difficulties, and cognitive dysfunction ("brain fog") (Davis et al., 2021; Komaroff and Bateman, 2021; Mantovani et al., 2021; Nalbandian et al., 2021) that are all common core symptoms of ME/CFS (Davis et al., 2021). Recent studies showed that 13–58% of long COVID patients met ME/CFS criteria (González-Hermosillo et al., 2021; Jason and Islam, 2022; Twomey et al., 2022) and symptoms like fatigue and disability score, autonomic dysfunction, and hand grip strength are similar in ME/CFS and long COVID patients (Kedor et al., 2022). A systematic review of long COVID and ME/CFS has shown that there is a high degree of similarity of fatigue, reduced daily activity, and post-exertional malaise between long COVID and ME/CFS (Wong and Weitzer, 2021). Furthermore, 36.4% of hospitalized COVID-19 patients presented neurological symptoms such as impaired consciousness, dizziness, and headache (Mao et al., 2020). This has stimulated researchers to investigate the effect of SARS-CoV-2 on the central nervous system in long COVID patients.

Magnetic resonance imaging (MRI) is non-invasive, can detect subtle changes in brain structure, and has been used to study brain dysfunction in ME/CFS and COVID patients. Recently, an ME/CFS study demonstrated increased hippocampal subfield volumes (Thapaliya et al., 2022b) and reduced caudal middle frontal volume and precuneus thickness (Thapaliya et al., 2022a). Global differences in gray and white matter volume were observed in ME/CFS (de Lange et al., 2005), although not in all studies (Barnden et al., 2011). Voxel-based morphometry (VBM) reported a decrease in the pons and midbrain volume and an increase in the amygdala and insula volumes in ME/CFS patients (Finkelmeyer et al., 2018). An MRI study in COVID-19 patients showed reduced gray matter thickness in the para-hippocampal gyrus, anterior cingulate cortex, and temporal lobe (Douaud et al., 2022). COVID-19 patients also have higher gray matter volume in the left Rolandic operculum, bilateral olfactory cortices, bilateral insulas, bilateral hippocampi, and right cingulate gyrus (Lu et al., 2020) and lower mean diffusivity in the left insula, cingulate gyri, right precuneus, right thalamus, and superior frontal-occipital fasciculus (Lu et al., 2020). MRI scans before and after COVID-19 infection showed an increased volume in the putamen, temporal cortex, fusiform and para-hippocampal gyrus (Salomon et al., 2021).

Recent studies have shown that COVID-19 survivors will develop symptoms of long COVID in all cohorts, even in young adults, students, children (Greenhalgh et al., 2020; Yelin et al., 2021; Yong, 2021a). Progression from COVID infection into long COVID may result from tissue damage, viral persistence, and/or chronic inflammation that remains unresolved after acute COVID-19 (Baig, 2020; Greenhalgh et al., 2020; Yelin et al., 2021; Yong, 2021a). Another potential cause could be persistent brainstem dysfunction (Yong, 2021b). Autopsy studies in the brainstem of deceased COVID-19 patients have shown shrunken neurons and inflammation (Al-Dalahmah et al., 2020), hemorrhages (Bradley et al., 2020), positive SARS-CoV-2 RNA (Deigendesch et al., 2020; Fabbri et al., 2021), and perivascular and interstitial encephalitis and neurodegeneration (von Weyhern et al., 2020). Notably long COVID symptoms overlap with ME/CFS in which brainstem dysfunction has been reported. The symptom severity of ME/CFS was associated with brainstem dysfunction (Barnden et al., 2016). MRI studies showed lower mean diffusivity (Thapaliya et al., 2021), higher signal intensity (Barnden et al., 2018; Thapaliya et al., 2020), and impaired brainstem connectivity (Barnden et al., 2019) in the brainstem regions of ME/CFS patients. The brainstem regulates respiratory, cardiovascular, gastrointestinal, and neurological processes and its impairment can explain the overlapping symptoms of ME/CFS and long COVID. Brainstem invasion by viruses (Deigendesch et al., 2020; Fabbri et al., 2021), pathological immune, or vascular activation (Al-Dalahmah et al., 2020; Fabbri et al., 2021) might lead to brainstem dysfunction in ME/CFS and long COVID.

Despite several studies showing a similar symptom presentation between ME/CFS and long COVID, structural change in the brainstem using MRI is yet to be investigated. The specific aims of this pilot study were to (a) quantify volumes of brainstem subregions and the whole brainstem in ME/CFS and long COVID and compare them to healthy controls (HC), and (b) explore the relationship between brainstem volumes and clinical symptom severity in ME/CFS and long COVID patients.

Materials and methods

Participant recruitment

The study was approved by the Griffith University Human Research Ethics Committee (ID: 2022/666) and written informed consent was obtained from all individuals. This cross-sectional investigation was conducted at the National Centre for Neuroimmunology and Emerging Diseases (NCNED) on the Gold Coast, Queensland, Australia. Eligible participants were contacted using the NCNED research registry database. ME/CFS patients were considered eligible if they fulfilled the CCC and/or ICC definitions for diagnosis, had received a formal diagnosis of ME/CFS by a physician, and did not report a history of COVID-19 infection. Participants with long COVID reported symptoms persisting for at least 3 months following COVID-19 infection according to the WHO working case definition. HC reported no diagnosis of a chronic health condition or evidence of underlying illness and had no current or prior COVID-19 infection. Participants were aged between 18- and 65-years. Medical history was requested to identify comorbid manifestations or exclusionary diagnoses including mental illness, malignancies, autoimmune, neurological, or cardiovascular diseases. Female participants were excluded if they were pregnant and/or breastfeeding. Finally, 10 ME/CFS patients fulfilling the CCC and ICC criteria (Carruthers et al., 2011), eight long COVID as defined by the WHO clinical case definition (World Health Organization [WHO], 2021) and 10 age-matched HC subjects were included in this study (see **Table 1** for demographic information).

Symptom presentation and clinical measures

Symptom presentation was collected using the NCNED Research Registry questionnaire developed by NCNED with the Centres for Disease Control and Prevention (CDC) Symptom Inventory Questionnaire distributed online through LimeSurvey. The presence and severity of each symptom was assessed on a five-point scale: (1) very mild; (2) mild; (3) moderate; (4) severe; and (5) very severe. Validated patient-reported outcome measures were used to determine participant quality of life (QoL) and functional capacity. The 36-item short form health survey (SF-36) (Alonso et al., 1995) has been frequently employed in previous observational studies to assess QoL among people with ME/CFS (Eaton-Fitch et al., 2020), as well as, more recently, among people with the long COVID condition (O'Kelly et al., 2022). Eight QoL domains were assessed including physical functioning, role limitations due to physical health problems, bodily pain, general health perceptions, vitality, social functioning, role limitations due to personal or emotional health, and emotional wellbeing/mental health. Survey item scores were assigned a value between 0 and 100, before scores were averaged for each domain.

For subsequent correlation analysis, the severity measure of "pain" was extracted from SF36v2, while breathing scores were obtained *via* the NCNED Research Registry questionnaire. Symptom severity of 10 ME/CFS and eight long COVID patients have been provided as a **Supplementary material**.

MRI scans and data processing

Magnetic resonance imaging was performed on a 7 T whole-body MRI research scanner (Siemens Healthcare, Erlangen, Germany) with a 32-channel head coil (Nova Medical Wilmington, Wilmington, NC, USA). We acquired T1-weighted data using a Magnetization prepared 2 rapid acquisition gradient echo sequence (MP2RAGE) as in Thapaliya et al. (2019). In brief, MP2RAGE data were acquired sagittally using the following parameters: repetition time (TR) = 4,300 ms, echo time (TE) = 2.45 ms, first inversion time (TI1) = 840 ms, TI2 = 2,370 ms, first flip angle (FA1) = 5°, FA2 = 6° and resolution = 0.75 mm^3 with matrix size = 256 × 300 × 320.

MP2RAGE data were processed similarly to our previous publications (Thapaliya et al., 2022a,b). In brief, MP2RAGE images were anatomically segmented using FreeSurfer version 7.1.1 (Fischl, 2012) [1]using the default FreeSurfer command "recon-all" on a Macintosh computer (Operating system: Catalina, RAM = 36GB, and core: 8). The "recon-all" processing includes motion correction, non-linear spatial normalization to Talairach space, intensity normalization, removal of non-brain tissue, cortical percolation, sub-cortical segmentation, gray and white matter boundary tessellation, automated topology correction, and surface deformation. Detailed information about the pipeline can be found at.[2]

Brainstem subregions were segmented using the FreeSurfer 7.1.1 brainstem module (Iglesias et al., 2015) as shown in **Figure 1**. Using this module, the brainstem was segmented into the midbrain, pons, superior cerebellar peduncle (SCP), and medulla oblongata. Brainstem subregions for all participants were visually checked for distortion-free segmentation.

Statistical analysis

Multivariate general linear model (GLM) statistical analysis was performed to test brainstem subregions and whole brainstem volume differences between ME/CFS, long COVID patients, and HC using SPSS version 28. After confirmation of homogeneity using Levene's test, the multivariate GLM was used to test for three group differences. Correction for multiple group comparisons was implemented using the Bonferroni method. Then Spearman correlations were performed between brainstem subregion and whole brainstem volumes and clinical severity measures for ME/CFS and long COVID patients. The normality condition for data was checked using the Shapiro-Wilk method available in SPSS before the correlation. Age and sex were included as covariates for group comparisons and correlation analysis.

---

[1] https://surfer.nmr.mgh.harvard.edu/

[2] https://surfer.nmr.mgh.harvard.edu/fswiki/recon-all

TABLE 1 Demographic and clinical characteristics of patients with ME/CFS, long COVID, and HC.

	ME/CFS (n = 10)	Long COVID (n = 8)	HC (n = 10)	P-value
Age	46.4 ± 15.2	43.2 ± 10.7	42.3 ± 14	0.53^a, 0.29^b, 0.69^c,
F/M	6/4	5/3	7/3	N/A
Pain	38 ± 20.4	37.8 ± 16.4	87 ± 19.7	$<0.001^a$, $<0.001^b$, 0.98^c
Breathing difficulty	0.8 ± 1.13	1.8 ± 1.6	N/A	0.15^c

Superscripts a, b, and c are the p-values for ME/CFS vs. HC, long COVID vs. HC, and ME/CFS vs. long COVID, respectively.

FIGURE 1
Demonstrates brainstem subregions of a healthy participant. Subregions are color coded.

Results

Group comparison: ME/CFS vs. HC

The brainstem subregion volumes were *larger* in ME/CFS patients compared with HC (see Table 2). After adjusting for multiple comparisons, volumes remained significantly *larger* in the pons ($p = 0.004$) and whole brainstem ($p = 0.01$) (see Figure 2 and Table 2).

Group comparison: Long COVID vs. HC

In long COVID patients, after adjusting for multiple comparisons, we observed significantly *larger* volumes in the pons ($p = 0.003$), SCP ($p = 0.009$), and whole brainstem ($p = 0.005$) (see Figure 2 and Table 3). The medulla ($p = 0.042$) and midbrain ($p = 0.026$) volumes were not significantly larger compared with HC (see Table 3) after adjusting for multiple comparisons.

Group comparison: ME/CFS vs. long COVID

Although brainstem subregion volumes were smaller in ME/CFS patients compared with long COVID (see Table 4), these differences were not statistically significant ($p < 0.05$).

Brainstem subregion volume correlations with pain and breathing

We demonstrated that subregion and whole brainstem volumes in ME/CFS and long COVID patients are significantly associated with clinical measures of "pain," and "breathing difficulty" (see Figure 3 and Table 5). We observed a significantly strong positive relationship between "pain" and volume of pons ($r = 0.83$, $p = 0.011$) and whole brainstem ($r = 0.85$, $p = 0.008$) (see Table 5). There was also a strong negative relationship between "breathing difficulty" and midbrain ($r = -0.78$, $p = 0.023$) and whole brainstem ($r = -0.78$, $p = 0.022$) volumes in ME/CFS patients (see Figure 3). Furthermore, we found a very strong negative relationship between "breathing difficulty" and midbrain volume ($r = -0.91$, $p = 0.03$) in long COVID patients (see Figure 3 and Table 5).

Discussion

This study reports volumetric differences in the whole brainstem and four subregions in ME/CFS, long COVID, and HC. We showed that pons, SCP, and whole brainstem volumes were significantly larger in long COVID patients compared with HC. Similarly, pons and whole brainstem volumes were significantly larger in ME/CFS patients compared with HC. Interestingly, no brainstem subregion volumes were significantly different between ME/CFS and long COVID patients between ME/CFS and long COVID patients. To the authors' knowledge this is the first investigation to demonstrate the overlap between ME/CFS and long COVID metrics using MRI. We also demonstrated that "pain" and "breathing difficulty" are strongly associated with brainstem volumes in ME/CFS and long COVID.

Group comparisons

Our study found significantly *larger* volumes for whole brainstem, pons, and SCP in ME/CFS and long COVID patients. The brainstem contains multiple small and dispersed neuron structures in the midbrain, pons, and medulla (Naidich et al., 2009) which together they constitute the reticular activation system (RAS). RAS nuclei connect with each other and to the body and subcortical and cortical structures (Guyton and Hall, 2011). RAS neurons influence cortical function *via* two different pathways. Firstly, RAS neuron projections deliver neurotransmitters directly or indirectly (e.g., *via* hypothalamus, basal forebrain) to the cortex (Saper and Fuller, 2017), and secondly RAS neurons generate oscillatory electrical signals that facilitate the coherence of cortical oscillations necessary for attention, sensory perception, problem solving, and memory (Garcia-Rill et al., 2013). Excitatory midbrain nuclei and inhibitory medulla nuclei constitute a circuit that controls both cortical arousal levels (cognition, wake/sleep, pain, respiration) and gait selection (e.g., walking or running) in response to inputs from multiple brain centers (Stornetta, 2008; Nicholls and Paton, 2009). Therefore, structural changes in the brainstem of ME/CFS and long COVID patients could result in severe and varied deficits in brain function.

ME/CFS vs. HC group comparison

We observed a larger volume for the whole brainstem and pons in ME/CFS patients compared with HC. Previous studies

TABLE 2 For ME/CFS, and HC, the mean and standard deviation of volumes for the brainstem subfields.

	Volume in mm^3		*P*-value	95% confidence interval	
				Lower	Upper
Regions					
	ME/CFS	HC			
Medulla	3110.3 ± 155.7 ↑	2756.1 ± 440.6	0.166	−238.7	830.8
Pons	13889.5 ± 333.5 ↑	11461.3 ± 1776.9	**0.004***	444.1	4227.1
Midbrain	5331.6 ± 295.5 ↑	4792.1 ± 507.1	0.056	−151.5	1220.1
SCP	270.01 ± 83.81 ↑	217.10 ± 42.25	0.054	−13.2	110.0
Whole brainstem	22601.4 ± 488.7 ↑	19226.7 ± 2644.3	**0.01***	261.7	6167.0

↑ Indicates a larger volume in ME/CFS than in HC. *Represents difference from HC statistically significant ($p < 0.05$) after adjusting for multiple comparisons. SCP, superior cerebral peduncle.

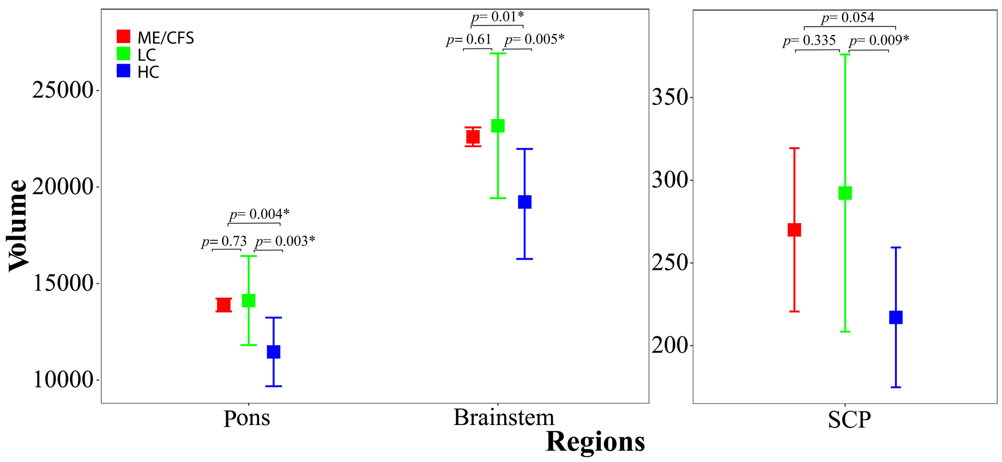


FIGURE 2
Shows the estimated mean volumes and their standard deviations (bars) for the pons and whole brainstem regions **(left)** and SCP **(right)** across ME/CFS (red), long COVID (green), and HC (blue) participants. ME/CFS and long COVID mean volumes were both significantly larger than HC ($p < 0.05$) in the pons and whole brainstem region. SCP volumes were only significantly larger than HC in long COVID. Error bars indicate one standard deviation. SCP, superior cerebellar peduncle.

TABLE 3 Volume means and standard deviations for long COVID and HC for the brainstem subregions and the whole brainstem.

	Volume in mm^3		*P*-value	95% confidence interval	
				Lower	Upper
Regions					
	Long COVID	HC			
Medulla	3302.4 ± 696.7 ↑	2756.1 ± 440.6	0.042	−95.0	1052.9
Pons	14120.3 ± 2305.8 ↑	11461.3 ± 1776.9	**0.003***	569.0	4629.6
Midbrain	5456.1 ± 889.2 ↑	4792.1 ± 507.1	0.026	−55.4	1416.7
SCP	292.27 ± 83.81 ↑	217.10 ± 42.25	**0.009***	6.8	139.1
Whole brainstem	23171.1 ± 3750.7 ↑	19226.7 ± 2644.3	**0.005***	662.5	7001.1

Long COVID volumes were statistically different from HC ($p < 0.05$). ↑ Indicates a larger volume in long COVID than HC. SCP, superior cerebral peduncle, *represents statistical significance after adjusting for multiple comparisons with the Bonferroni method.

in ME/CFS patients have reported lower mean diffusivity in the pons (Thapaliya et al., 2021), and higher T1/T2 signal intensity in the medial lemniscus and cortical spinal tract (Thapaliya et al., 2020) that is sensitive to the level of myelination or iron. A functional MRI study reported impaired connectivity within the brainstem and to the hippocampus and thalamus of ME/CFS patients (Barnden et al., 2019). In ME/CFS patients, decreased myelin-sensitive T1-weighted spin echo signals were detected in the brainstem (Barnden et al., 2018) and the brainstem perfusion ratios were reduced (Costa et al., 1995). The brainstem contains the nuclei of the reticular activation system which control arousal, the sleep/wake cycle, gait, and memory *via* cortical connections and cardio-respiratory function (Costa et al., 1995; Garcia-Rill et al., 2013, 2016). Therefore, brainstem dysfunction is consistent

TABLE 4 Volume means and standard deviations volumes for ME/CFS and long COVID for the brainstem subfields and whole brainstem and their statistical inference.

	Volume in mm^3		*P*-value	95% confidence interval	
				Lower	Upper
Regions					
	ME/CFS	Long COVID			
Medulla	3110.3 ± 155.7 ↓	3302.4 ± 696.7	0.407	−741.6	375.9
Pons	13889.5 ± 333.5 ↓	14120.3 ± 2305.8	0.734	−2240.2	1712.7
Midbrain	5331.6 ± 295.5 ↓	5456.1 ± 889.2	0.603	−862.9	570.2
SCP	270.01 ± 83.81 ↓	292.27 ± 83.81	0.335	−88.9	39.8
Whole brainstem	22601.4 ± 488.7 ↓	23171.1 ± 3750.7	0.610	−3702.7	2467.8

↓ Indicates a smaller volume in ME/CFS patients than long COVID. No significant volumetric differences were obtained between ME/CFS and long COVID. SCP, superior cerebral peduncle.

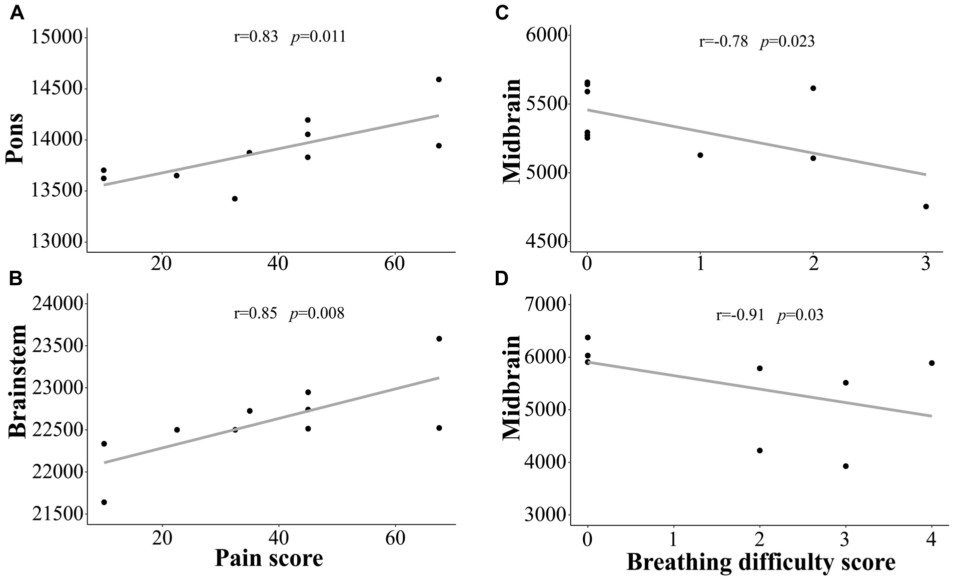


FIGURE 3
Shows the strong correlation between brainstem region volumes and clinical measures for ME/CFS and long COVID patients. We observed statistically significant relationship between the pons, brainstem volumes and "pain" score in ME/CFS patients **(A,B)**. We also found statistically significant relationship between midbrain volume and "Breathing difficulty" score in ME/CFS **(C)** and long COVID **(D)** patients. *Y*-axis is the volume and *x*-axis are the clinical scores.

with the symptoms experienced by ME/CFS patients including cognitive dysfunction, sleep disturbance, orthostatic intolerance, and dyspnea.

Long COVID vs. HC group comparison

We also found larger volumes of the whole brainstem, pons, and SCP in long COVID patients compared with HC. Such volume increases may reflect edema of inflammatory responses, neurodegeneration, and/or viral invasion (Yong, 2021b). Autopsy studies of the brain have detected SARS-CoV-2 RNA and proteins in the brainstem of COVID-19 patients (Deigendesch et al., 2020; Matschke et al., 2020). Higher concentrations of SARS-CoV-2 are consistent with the high expression of Angiotensin-converting enzyme 2 which is the receptor SARS-CoV-2 uses to infect host cells in the brainstem (Letko et al., 2020; Zhou et al., 2020). Other autopsy studies showed inflammation, neuronal cell loss, and axonal degeneration in the brainstem of COVID-19 patients (Matschke et al., 2020; von Weyhern et al., 2020). Activated microglia and astrocytes, leukocyte infiltration, and micro-thrombosis have also been reported in the brainstem of COVID-19 patients (Deigendesch et al., 2020; Schurink et al., 2020; Meinhardt et al., 2021; Mukerji and Solomon, 2021). A microscopy study showed more tissue damage in the pons in COVID-19 patients than in controls (Bulfamante et al., 2021), and MRI also showed severe damage to the brainstem in two COVID-19 patients (Manganelli et al., 2020). Abnormal diffusion (lower fractional anisotropy) was reported in the SCP for multiple sclerosis patients with cerebellar symptoms and this correlated with cognitive performance (Nicoletti et al., 2017). The SCP has large sensory and motor nerve tracts that connect the cortex and pons and facilitate refined motor movements, learning of new motor skills, and balance (Khonsary, 2022). However, the function of

TABLE 5 Correlation between brainstem region volumes and clinical measures in ME/CFS and long COVID.

Brainstem region	Clinical measure	*r*	*P*
ME/CFS			
Pons	Pain	0.83	0.011
Brainstem	Pain	0.85	0.008
Midbrain	Breathing difficulty	−0.78	0.023
Brainstem	Breathing difficulty	−0.78	0.022
Long COVID			
Midbrain	Breathing difficulty	−0.91	0.03

r, correlation coefficient. The Spearman correlation test was used to perform correlation analysis using SPSS software version 28.

this region needs to be investigated in different diseases. Damage to the brainstem, in particular the respiratory neurons of the dorsal medulla, could cause respiratory failure which is a key symptom of COVID-19 patients (Boutou et al., 2021a,b; Huang et al., 2021). Brainstem dysfunction has been demonstrated in chronic migraine headache (Aurora and Brin, 2017; Chong et al., 2017) which also occurs in long COVID (Membrilla et al., 2021). Therefore, structural changes in the brainstem are associated with the heterogeneous changes in brain function that correspond to the key symptoms of long COVID.

ME/CFS vs. long COVID group comparison

We did not find significant differences in the brainstem volumes of ME/CFS and long COVID patients which is consistent with the overlapping presentation of both cohorts (Sukocheva et al., 2021; Marshall-Gradisnik and Eaton-Fitch, 2022). Cardiovascular and respiratory symptoms of ME/CFS and long COVID are controlled by neuronal circuits between the hypothalamus and the brainstem (Benarroch, 2018). The symptom overlap between ME/CFS and long COVID patients is consistent with by our current findings of similar abnormalities in the brainstem. Further, a recent investigation demonstrated the biological overlap of ME/CFS and long COVID through transient receptor potential melastatin 3 (TRPM3) ion channel dysfunction (Sasso et al., 2022). TRPM3 ion channel dysfunction in the pathology of both ME/CFS and long COVID suggests further research is required to determine whether the illnesses are separate. TRPM3 channels are widely expressed through multiple cell and tissue types and are highly expressed in the brainstem, thus may account for a common pathology in ME/CFS and long COVID (Held and Tóth, 2021; Ragozzino et al., 2021).

Correlations with clinical measures

We detected significant correlations between clinical measures (pain and breathing difficulty) and volumes of the whole brainstem and its subregions in ME/CFS and long COVID patients. Pain is regarded as one of the major symptoms of ME/CFS (Bourke et al., 2014). Our study shows a significantly strong positive correlation between "pain" and pons and whole brainstem volumes in ME/CFS patients (see **Figure 3** and **Table 5**) indicating that larger brainstem volumes are associated with higher pain severity. The brainstem regions have several nuclei that receive ascending and descending signal pathways that inhibit or facilitate pain by upward or downward regulation of neurotransmission (Mills et al., 2021). Several brainstem nuclei including periaqueductal gray in the midbrain, dorsal and median raphe nuclei, parabrachial nucleus, and locus coeruleus in the pons region are involved in pain processing (Napadow et al., 2019). Functional connectivity differences were observed between brainstem nuclei in fibromyalgia patients (Ioachim et al., 2022). Recently, a study showed that the hippocampal subfield volumes were associated with pain levels in ME/CFS patients (Thapaliya et al., 2022b).

Breathing difficulty is another common symptom experienced by ME/CFS and long COVID patients (Ravindran et al., 2013), (Mancini et al., 2021). It has been reported that 30–50% of COVID-19 patients experience breathing difficulty (Mandal et al., 2021; Shah et al., 2021). We showed that smaller midbrain and whole brainstem volumes were associated with more severe "breathing difficulty" in both ME/CFS and long COVID patients (see **Figure 3** and **Table 5**). Breathing difficulties in ME/CFS and long COVID are associated with brainstem volume changes that may reflect changes to the respiratory and cardiovascular neuronal circuits in the brainstem (Benarroch, 2018). The brainstem has a ventral respiratory column that controls rhythmic breathing (Smith et al., 1991; Moreira et al., 2011), a pontine respiratory group that controls the transition between expiration and inspiration (Stornetta, 2008), and the caudal ventrolateral medulla that controls inspiration (Nicholls and Paton, 2009). Therefore, brainstem dysfunction may contribute to the respiratory-related symptoms in ME/CFS and long COVID.

Limitations

This study does have some limitations. This is a pilot study with a relatively small sample size that will affect the power of the study to detect brainstem volume differences and their association with clinical measures. Another limitation is that pain and breathing scores were obtained using self-reported questionnaires, which by their subjective nature may limit the interpretation of our findings. This study was a cross-sectional study; therefore, further investigations with a larger cohort and longitudinal studies are recommended to test progressive changes in the brainstem volume in ME/CFS and long COVID patients.

Conclusion

In this pilot study, volumetric differences in brainstem regions were detected in ME/CFS and long COVID patients relative to HC. Clinical measures for "pain" and "breathing difficulty" showed a strong relationship with pons, midbrain, and whole brainstem volumes in ME/CFS and long COVID patients. Interestingly, volumes of the whole brainstem and its subregions were not significantly different between ME/CFS and long COVID patients. This is consistent with ME/CFS and long COVID having similar brainstem abnormalities which will contribute to their neurological and cardio-respiratory symptoms.

Data availability statement

The original contributions presented in this study are included in this article/Supplementary material, further inquiries can be directed to the corresponding author.

Ethics statement

The studies involving human participants were reviewed and approved by Griffith University. The patients/participants provided their written informed consent to participate in this study.

Author contributions

KT: conceptualization, formal analysis, and writing – original draft. KT and LB: methodology. KT, LB, NE-F, MB, and SM-G: writing – review and editing. LB and SM-G: supervision. All authors contributed to the article and approved the submitted version.

Funding

This research is funded by ME Research UK (SCIO Charity Number SC036942) with the financial support of The Fred and Joan Davies Bequest. Other funding bodies include: The Stafford Fox Medical Research Foundation (489798), the National Health and Medical Research Council (1199502), McCusker Charitable Foundation (49979), Ian and Talei Stewart, Buxton Foundation (4676), Henty Community (4879), Henty Lions Club (4880), Mason Foundation (47107), Mr. Douglas Stutt, Blake Beckett Trust Foundation (4579), Alison Hunter Memorial Foundation (4570), and the Change for ME Charity (4575).

Acknowledgments

We are thankful to Ms. Tania Manning and Kay Schwarz for recruiting participants for this study, radiographers (Nicole Atcheson, Aiman Al-Najjar, Jillian Richardson, and Sarah Daniel) at the Centre for Advanced Imaging, The University of Queensland for helping us to acquire MRI data and all the patients and healthy controls who donated their time and effort to participate in this study.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fnins.2023.1125208/full#supplementary-material

References

Al-Dalahmah, O., Thakur, K. T., and Nordvig, A. S. (2020). Neuronophagia and microglial nodules in a SARS-CoV-2 patient with cerebellar hemorrhage. *Acta Neuropathol. Commun.* 8:147. doi: 10.1186/s40478-020-01024-2

Alonso, J., Prieto, L., and Anto, J. M. (1995). The Spanish version of the SF-36 Health Survey (the SF-36 health questionnaire): an instrument for measuring clinical results. *Med. Clín.* 104, 771–776.

Aurora, S. K., and Brin, M. F. (2017). Chronic migraine: an update on physiology, imaging, and the mechanism of action of two available pharmacologic therapies. *Headache* 57, 109–125. doi: 10.1111/head.12999

Baig, A. M. (2020). Deleterious outcomes in long-hauler COVID-19: the effects of SARS-CoV-2 on the CNS in chronic COVID syndrome. *ACS Chem. Neurosci.* 11, 4017–4020. doi: 10.1021/acschemneuro.0c00725

Baker, R., and Shaw, E. J. (2007). Diagnosis and management of chronic fatigue syndrome or myalgic encephalomyelitis (or encephalopathy): summary of NICE guidance. *BMJ* 335, 446–448. doi: 10.1136/bmj.39302.509005.AE

Barnden, L. R., Crouch, B., Kwiatek, R., Burnet, R., Mernone, A., Chryssidis, S., et al. (2011). A brain MRI study of chronic fatigue syndrome: evidence of brainstem dysfunction and altered homeostasis. *NMR Biomed.* 24, 1302–1312. doi: 10.1002/nbm.1692

Barnden, L. R., Kwiatek, R., Crouch, B., Burnet, R., and Del Fante, P. (2016). Autonomic correlations with MRI are abnormal in the brainstem vasomotor centre in Chronic Fatigue Syndrome. *NeuroImage* 11, 530–537. doi: 10.1016/j.nicl.2016.03.017

Barnden, L. R., Shan, Z., Staines, D., Marshall-Gradisnik, S., Finegan, K., Ireland, T., et al. (2018). Hyperintense sensorimotor T1 spin echo MRI is associated with brainstem abnormality in chronic fatigue syndrome. *Neuroimage Clin.* 20, 102–109. doi: 10.1016/j.nicl.2018.07.011

Barnden, L. R., Shan, Z., Staines, D., Marshall-Gradisnik, S., Finegan, K., Ireland, T., et al. (2019). Intra brainstem connectivity is impaired in chronic fatigue syndrome. *NeuroImage* 24:102045. doi: 10.1016/j.nicl.2019.102045

Benarroch, E. E. (2018). Brainstem integration of arousal, sleep, cardiovascular, and respiratory control. *Neurology* 91, 958–966. doi: 10.1212/WNL.0000000000006537

Bourke, J. H., Johnson, A. L., Sharpe, M., Chalder, T., and White, D. (2014). Pain in chronic fatigue syndrome: response to rehabilitative treatments in the PACE trial. *Psychol. Med.* 44, 1545–1552. doi: 10.1017/S0033291713002201

Boutou, A. K., Asimakos, A., Kortianou, E., Vogiatzis, I., and Tzouvelekis, A. (2021a). Long COVID-19 pulmonary sequelae and management considerations. *J. Pers. Med.* 11:838. doi: 10.3390/jpm11090838

Boutou, A. K., Georgopoulou, A., Pitsiou, G., Stanopoulos, I., Kontakiotis, T., and Kioumis, I. (2021b). Changes in the respiratory function of COVID-19 survivors during follow-up: a novel respiratory disorder on the rise? *Int. J. Clin. Pract.* 75:e14301. doi: 10.1111/ijcp.14301

Bradley, B. T., Maioli, H., Johnston, R., Chaudhry, I., Fink, S., Xu, H., et al. (2020). Histopathology and ultrastructural findings of fatal COVID-19 infections in Washington State: a case series. *Lancet* 396, 320–332. doi: 10.1016/S0140-6736(20)31305-2

Bulfamante, G., Bocci, T., Falleni, M., Campiglio, L., Coppola, S., Tosi, D., et al. (2021). Brainstem neuropathology in two cases of COVID-19: SARS-CoV-2 trafficking between brain and lung. *J. Neurol.* 268, 4486–4491. doi: 10.1007/s00415-021-10604-8

Carruthers, B. M., Jain, A., De Meirleir, K., Peterson, D. L., Klimas, N. G., and Lerner, A. M. (2003). Myalgic encephalomyelitis/chronic fatigue syndrome: clinical working case definition, diagnostic and treatment protocols. *J. Chronic Fatigue Syndr.* 11, 7–115.

Carruthers, B. M., van de Sande, M., De Meirleir, K., Klimas, N., Broderick, G., Mitchell, T., et al. (2011). Myalgic encephalomyelitis: international consensus criteria. *J. Internal Med.* 270, 327–338. doi: 10.1111/j.1365-2796.2011.02428.x

Chen, C., Haupert, S. R., Zimmermann, L., Shi, X., Fritsche, L. G., and Mukherjee, B. (2022). Global prevalence of post COVID-19 condition or long COVID: a meta-analysis and systematic review. *J. Infect. Dis.* 226, 1593–1607. doi: 10.1093/infdis/jiac136

Chong, C. D., Plasencia, J. D., Frakes, D. H., and Schwedt, T. J. (2017). Structural alterations of the brainstem in migraine. *Neuroimage Clin.* 13, 223–227. doi: 10.1016/j.nicl.2016.10.023

Costa, D. C., Tannock, C., and Brostoff, J. (1995). Brainstem perfusion is impaired in chronic fatigue syndrome. *QJM* 88, 767–773.

Davis, H. E., Assaf, G., McCorkell, L., Wei, H., Low, R., Redfield, S., et al. (2021). Characterizing long COVID in an international cohort: 7 months of symptoms and their impact. *eClinicalMedicine* 38:101019. doi: 10.1016/j.eclinm.2021.101019

de Lange, F., Kalkman, J. S., Bleijenberg, G., Hagoort, P., van der Meer, J. W. M., and Toni, I. (2005). Gray matter volume reduction in the chronic fatigue syndrome. *Neuroimage* 26, 777–781. doi: 10.1016/j.neuroimage.2005.02.037

Deigendesch, N., Sironi, L., Kutza, M., Wischnewski, S., Fuchs, V., Hench, J., et al. (2020). Correlates of critical illness-related encephalopathy predominate postmortem COVID-19 neuropathology. *Acta Neuropathol.* 140, 583–586. doi: 10.1007/s00401-020-02213-y

Douaud, G., Lee, S., Alfaro-Almagro, F., Arthofer, C., Wang, C., McCarthy, P., et al. (2022). SARS-CoV-2 is associated with changes in brain structure in UK Biobank. *Nature* 604, 697–707. doi: 10.1038/s41586-022-04569-5

Eaton-Fitch, N., Johnston, S. C., Zalewski, P., Staines, D., and Marshall-Gradisnik, S. (2020). Health-related quality of life in patients with myalgic encephalomyelitis/chronic fatigue syndrome: an Australian cross-sectional study. *Qual. Life Res.* 29, 1521–1531. doi: 10.1007/s11136-019-02411-6

Fabbri, V., Foschini, M., Lazzarotto, T., Gabrielli, L., Cenacchi, G., Gallo, C., et al. (2021). Brain ischemic injury in COVID-19-infected patients: a series of 10 post-mortem cases. *Brain Pathol.* 31, 205–210. doi: 10.1111/bpa.12901

Finkelmeyer, A., He, J., Maclachlan, L., Watson, S., Gallagher, P., Newton, J., et al. (2018). Grey and white matter differences in chronic fatigue syndrome - a voxel-based morphometry study. *Neuroimage Clin.* 17, 24–30. doi: 10.1016/j.nicl.2017.09.024

Fischl, B. (2012). FreeSurfer. *NeuroImage* 62, 774–781. doi: 10.1016/j.neuroimage.2012.01.021

Fukuda, K. (1994). The chronic fatigue syndrome: a comprehensive approach to its definition and study. *Ann. Intern. Med.* 121:953. doi: 10.7326/0003-4819-121-12-199412150-00009

Garcia-Rill, E., Kezunovic, N., Hyde, J., Simon, C., Beck, P., and Urbano, F. J. (2013). Coherence and frequency in the reticular activating system (RAS). *Sleep Med. Rev.* 17, 227–238. doi: 10.1016/j.smrv.2012.06.002

Garcia-Rill, E., Virmani, T., Hyde, J. R., D'Onofrio, S., and Mahaffey, S. (2016). Arousal and the control of perception and movement. *Curr. Trends Neurol.* 10, 53–64.

González-Hermosillo, J. A., Martínez-López, J., Carrillo-Lampón, S., Ruiz-Ojeda, D., Herrera-Ramírez, S., Amezcua-Guerra, L., et al. (2021). Post-Acute COVID-19 symptoms, a potential link with myalgic encephalomyelitis/chronic fatigue syndrome: a 6-month survey in a Mexican cohort. *Brain Sci.* 11:760. doi: 10.3390/brainsci11060760

Greenhalgh, T., Knight, M., A'Court, C., Buxton, M., and Husain, L. (2020). Management of post-acute covid-19 in primary care. *BMJ* 370:m3026. doi: 10.1136/bmj.m3026

Guyton, A. C., and Hall, J. E. (2011). *Guyton and Hall Textbook of Medical Physiology*. Amsterdam: Elsevier.

Held, K., and Tóth, B. I. (2021). TRPM3 in brain (patho)physiology. *Front. Cell Dev. Biol.* 9:635659. doi: 10.3389/fcell.2021.635659

Huang, C., Huang, L., Wang, Y., Li, X., Ren, L., Gu, X., et al. (2021). 6-month consequences of COVID-19 in patients discharged from hospital: a cohort study. *Lancet* 397, 220–232. doi: 10.1016/S0140-6736(20)32656-8

Iglesias, J. E., Van Leemput, K., Bhatt, P., Casillas, C., Dutt, S., Schuff, N., et al., (2015). Bayesian segmentation of brainstem structures in MRI. *Neuroimage* 113, 184–195. doi: 10.1016/j.neuroimage.2015.02.065

Ioachim, G., Warren, H. J. M., Powers, J. M., Staud, R., Pukall, C. F., and Stroman, W. (2022). Altered pain in the brainstem and spinal cord of fibromyalgia patients during the anticipation and experience of experimental pain. *Front. Neurol.* 13:862976. doi: 10.3389/fneur.2022.862976

Jason, L. A., and Islam, M. F. (2022). A classification system for post-acute sequelae of SARS CoV-2 infection. *Central Asian J. Med. Hypoth. Ethics* 3, 38–51. doi: 10.47316/cajmhe.2022.3.1.04

Kedor, C., Freitag, H., Meyer-Arndt, L., Wittke, K., Hanitsch, L., Zoller, T., et al. (2022). A prospective observational study of post-COVID-19 chronic fatigue syndrome following the first pandemic wave in Germany and biomarkers associated with symptom severity. *Nat. Commun.* 13:5104. doi: 10.1038/s41467-022-32507-6

Khonsary, S. A. (2022). Atlas of functional neuroanatomy. *Surg. Neurol. Int.* 13:238. doi: 10.25259/SNI_424_2022

Komaroff, A. L., and Bateman, L. (2021). Will COVID-19 lead to myalgic encephalomyelitis/chronic fatigue syndrome? *Front. Med.* 7:606824. doi: 10.3389/fmed.2020.606824

Letko, M., Marzi, A., and Munster, V. (2020). Functional assessment of cell entry and receptor usage for SARS-CoV-2 and other lineage B betacoronaviruses. *Nat. Microbiol.* 5, 562–569. doi: 10.1038/s41564-020-0688-y

Lim, E.-J., Ahn, Y.-C., Jang, E.-S., Lee, S.-W., Lee, S.-H., and Son, C.-G. (2020). Systematic review and meta-analysis of the prevalence of chronic fatigue syndrome/myalgic encephalomyelitis (CFS/ME). *J. Transl. Med.* 18:100. doi: 10.1186/s12967-020-02269-0

Lu, Y., Li, X., Geng, D., Mei, N., Wu, P., Huang, C., et al. (2020). Cerebral micro-structural changes in COVID-19 patients – an MRI-based 3-month follow-up study. *EClinicalMedicine* 25:100484. doi: 10.1016/j.eclinm.2020.100484

Mancini, D. M., Brunjes, D. L., Lala, A., Trivieri, M. G., Contreras, J., and Natelson, B. H. (2021). Use of cardiopulmonary stress testing for patients with unexplained dyspnea post–coronavirus disease. *JACC* 9, 927–937. doi: 10.1016/j.jchf.2021.10.002

Mandal, S., Barnett, J., Brill, S., Brown, J., Denneny, E., Hare, S., et al. (2021). "Long-COVID": a cross-sectional study of persisting symptoms, biomarker and imaging abnormalities following hospitalisation for COVID-19. *Thorax* 76, 396–398. doi: 10.1136/thoraxjnl-2020-215818

Manganelli, F., Vargas, M., Iovino, A., Iacovazzo, C., Santoro, L., and Servillo, G. (2020). Brainstem involvement and respiratory failure in COVID-19. *Neurol. Sci.* 41, 1663–1665. doi: 10.1007/s10072-020-04487-2

Mantovani, E., Mariotto, S., Gabbiani, D., Dorelli, G., Bozzetti, S., Federico, A., et al. (2021). Chronic fatigue syndrome: an emerging sequela in COVID-19 survivors? *J. Neurovirol.* 27, 631–637. doi: 10.1007/s13365-021-01002-x

Mao, L., Jin, H., Wang, M., Hu, Y., Chen, S., He, Q., et al. (2020). Neurologic manifestations of hospitalized patients with coronavirus disease 2019 in Wuhan, China. *JAMA Neurol.* 77, 1–9. doi: 10.1001/jamaneurol.2020.1127

Marshall-Gradisnik, S., and Eaton-Fitch, N. (2022). Understanding myalgic encephalomyelitis. *Science* 377, 1150–1151. doi: 10.1126/science.abo1261

Matschke, J., Lütgehetmann, M., Hagel, C., Sperhake, J., Schröder, A., Edler, C., et al. (2020). Neuropathology of patients with COVID-19 in Germany: a post-mortem case series. *Lancet Neurol.* 19, 919–929. doi: 10.1016/S1474-4422(20)30308-2

Meinhardt, J., Radke, J., Dittmayer, C., Franz, J., Thomas, C., Mothes, R., et al. (2021). Olfactory transmucosal SARS-CoV-2 invasion as a port of central nervous system entry in individuals with COVID-19. *Nat. Neurosci.* 24, 168–175. doi: 10.1038/s41593-020-00758-5

Membrilla, J. A., Caronna, E., Trigo-López, J., González-Martínez, A., Layos-Romero, A., Pozo-Rosich, P., et al. (2021). Persistent headache after COVID-19: pathophysioloy, clinic and treatment. *Neurol Perspect.* 1, S31–S36. doi: 10.1016/j.neurop.2021.10.003

Mills, E., Keay, K. A., and Henderson, L. A. (2021). Brainstem pain-modulation circuitry and its plasticity in neuropathic pain: insights from human brain imaging investigations. *Front. Pain Res.* 2:705345. doi: 10.3389/fpain.2021.705345

Moreira, T. S., Takakura, A., Damasceno, R., Falquetto, B., Totola, L., Sobrinho, C., et al. (2011). Central chemoreceptors and neural mechanisms of cardiorespiratory control. *Braz. J. Med. Biol. Res.* 44, 883–889. doi: 10.1590/s0100-879x2011007500094

Mukerji, S. S., and Solomon, I. H. (2021). What can we learn from brain autopsies in COVID-19? *Neurosci. Lett.* 742:135528. doi: 10.1016/j.neulet.2020.135528

Naidich, T., Duvernoy, H. M., Delman, B. N., Sorensen, A. G., Kollias, S. S., and Haacke, E. M. (2009). *Duvernoy's Atlas of the Human Brain Stem and Cerebellum: High-Field MRI, Surface Anatomy, Internal Structure, Vascularization and 3 D Sectional Anatomy*. Berlin: Springer Science & Business Media.

Nalbandian, A., Sehgal, K., Gupta, A., Madhavan, M., McGroder, C., Stevens, J., et al. (2021). Post-acute COVID-19 syndrome. *Nat. Med.* 27, 601–615. doi: 10.1038/s41591-021-01283-z

Napadow, V., Sclocco, R., and Henderson, L. A. (2019). Brainstem neuroimaging of nociception and pain circuitries. *PAIN Rep.* 4:e745. doi: 10.1097/PR9.0000000000000745

Nicholls, J. G., and Paton, J. F. R. (2009). Brainstem: neural networks vital for life. *Philos. Trans. R Soc. Lond. B Biol. Sci.* 364, 2447–2451. doi: 10.1098/rstb.2009.0064

Nicoletti, G., Valentino, P., Chiriaco, C., Granata, A., Barone, S., Filippelli, E., et al. (2017). Superior cerebellar peduncle atrophy predicts cognitive impairment in relapsing remitting multiple sclerosis patients with cerebellar symptoms: a DTI study. *J. Multiple Scler.* 4, 1–6.

O'Kelly, B., Vidal, L., Avramovic, G., Broughan, J., Connolly, S., Cotter, A., et al. (2022). Assessing the impact of COVID-19 at 1-year using the SF-12 questionnaire: data from the Anticipate longitudinal cohort study. *Int. J. Infect. Dis.* 118, 236–243. doi: 10.1016/j.ijid.2022.03.013

Ragozzino, F. J., Arnold, R., Fenwick, A., Riley, T., Lindberg, J., Peterson, B., et al. (2021). TRPM3 expression and control of glutamate release from primary vagal afferent neurons. *J. Neurophysiol.* 125, 199–210. doi: 10.1152/jn.00229.2020

Ravindran, M. K., Adewuyi, O., Zheng, Y., Rayhan, R., Le, U., Timbol, C., et al. (2013). Dyspnea in Chronic Fatigue Syndrome (CFS): comparison of two prospective cross-sectional studies. *Glob. J. Health Sci.* 5, 94–110. doi: 10.5539/gjhs.v5n2p94

Salomon, T, Cohen, A, Barazany, D, Ben-Zvi, G, Botvinik-Nezer, R, Gera, R, et al. (2021). Brain volumetric changes in the general population following the COVID-19 outbreak and lockdown. *NeuroImage* 239:118311. doi: 10.1016/j.neuroimage.2021.118311

Saper, C. B., and Fuller, M. (2017). Wake-sleep circuitry: an overview. *Curr. Opin. Neurobiol.* 44, 186–192. doi: 10.1016/j.conb.2017.03.021

Sasso, E. M., Muraki, K., Eaton-Fitch, N., Smith, P., Lesslar, O., Deed, G., et al. (2022). Transient receptor potential melastatin 3 dysfunction in post COVID-19 condition and myalgic encephalomyelitis/chronic fatigue syndrome patients. *Mol. Med.* 28:98. doi: 10.1186/s10020-022-00528-y

Schurink, B., Roos, E., Radonic, T., Barbe, E., Bouman, C., de Boer, H. H., et al. (2020). Viral presence and immunopathology in patients with lethal COVID-19: a prospective autopsy cohort study. *Lancet Microbe* 1, e290–e299. doi: 10.1016/S2666-5247(20)30144-0

Shah, A. S., Wong, A., Hague, C., Murphy, D., Johnston, J., Ryerson, C., et al. (2021). A prospective study of 12-week respiratory outcomes in COVID-19-related hospitalisations. *Thorax* 76, 402–404. doi: 10.1136/thoraxjnl-2020-216308

Smith, J. C., Ellenberger, H. H., Ballanyi, K., Richter, D. W., and Feldman, J. L. (1991). Pre-Bötzinger complex: a brainstem region that may generate respiratory rhythm in mammals. *Science* 254, 726–729. doi: 10.1126/science.1683005

Stornetta, R. L. (2008). Identification of neurotransmitters and co-localization of transmitters in brainstem respiratory neurons. *Respir. Physiol. Neurobiol.* 164, 18–27. doi: 10.1016/j.resp.2008.07.024

Stussman, B., Williams, A., Snow, J., Gavin, A., Scott, R., Nath, A., et al. (2020). Characterization of post–exertional malaise in patients with myalgic encephalomyelitis/chronic fatigue syndrome. *Front. Neurol.* 11:1025. doi: 10.3389/fneur.2020.01025

Sukocheva, O. A., Maksoud, R., Beeraka, N., Madhunapantula, S., Sinelnikov, M., Nikolenko, V., et al. (2021). Analysis of post COVID-19 condition and its overlap with myalgic encephalomyelitis/chronic fatigue syndrome. *J. Adv. Res.* 40, 179–196. doi: 10.1016/j.jare.2021.11.013

Thapaliya, K., Marshall-Gradisnik, S., Staines, D., and Barnden, L. (2020). Mapping of pathological change in chronic fatigue syndrome using the ratio of T1- and T2-weighted MRI scans. *NeuroImage* 28:102366. doi: 10.1016/j.nicl.2020.102366

Thapaliya, K., Marshall-Gradisnik, S., Staines, D., and Barnden, L. (2021). Diffusion tensor imaging reveals neuronal microstructural changes in myalgic encephalomyelitis/chronic fatigue syndrome. *Eur. J. Neurosci.* 54, 6214–6228. doi: 10.1111/ejn.15413

Thapaliya, K., Marshall-Gradisnik, S., Staines, D., Su, J., and Barnden, L. (2022a). Alteration of cortical volume and thickness in myalgic encephalomyelitis/chronic fatigue syndrome. *Front. Neurosci.* 16:848730. doi: 10.3389/fnins.2022.848730

Thapaliya, K., Staines, D., Marshall-Gradisnik, S., Su, J., and Barnden, L. (2022b). Volumetric differences in hippocampal subfields and associations with clinical measures in myalgic encephalomyelitis/chronic fatigue syndrome. *J. Neurosci. Res.* 100, 1476–1486. doi: 10.1002/jnr.25048

Thapaliya, K., Urriola, J., Barth, M., Reutens, D. C., Bollmann, S., and Vegh, V. (2019). 7T GRE-MRI signal compartments are sensitive to dysplastic tissue in focal epilepsy. *Magn. Resonan. Imaging* 61, 1–8. doi: 10.1016/j.mri.2019.05.011

Twomey, R., DeMars, J., Franklin, K., Culos-Reed, S. N., Weatherald, J., and Wrightson, J. G. (2022). Chronic fatigue and postexertional malaise in people living with long COVID: an observational study. *Phys. Ther.* 102:zac005. doi: 10.1093/ptj/pzac005

von Weyhern, C. H., Kaufmann, I., Neff, F., and Kremer, M. (2020). Early evidence of pronounced brain involvement in fatal COVID-19 outcomes. *Lancet* 395:e109. doi: 10.1016/S0140-6736(20)31282-4

Wong, T. L., and Weitzer, D. J. (2021). Long COVID and myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS)—a systemic review and comparison of clinical presentation and symptomatology. *Medicina* 57:418. doi: 10.3390/medicina57050418

World Health Organization [WHO] (2021). *A Clinical Case Definition of Post COVID-19 Condition by a Delphi Consensus*. Available online at: https://www.who.int/publications-detail-redirect/WHO-2019-nCoV-Post_COVID-19_condition-Clinical_case_definition-2021.1 (accessed September 29, 2022).

World Health Organization [WHO] (2022). *WHO Coronavirus (COVID-19) Dashboard*. Available online at: https://covid19.who.int (accessed September 29, 2022).

Yelin, D., Margalit, I., Yahav, D., Runold, M., and Bruchfeld, J. (2021). Long COVID-19—it's not over until? *Clin. Microbiol. Infect.* 27, 506–508. doi: 10.1016/j.cmi.2020.12.001

Yong, S. J. (2021a). Long COVID or post-COVID-19 syndrome: putative pathophysiology, risk factors, and treatments. *Infect. Dis.* 53, 737–754. doi: 10.1080/23744235.2021.1924397

Yong, S. J. (2021b). Persistent brainstem dysfunction in long-COVID: a hypothesis. *ACS Chem. Neurosci.* 12, 573–580. doi: 10.1021/acschemneuro.0c00793

Zhou, P., Yang, X., Wang, X., Hu, B., Zhang, L., Zhang, W., et al. (2020). A pneumonia outbreak associated with a new coronavirus of probable bat origin. *Nature* 579, 270–273. doi: 10.1038/s41586-020-2012-7

frontiers | Frontiers in Physiology

TYPE Original Research
PUBLISHED 30 May 2023
DOI 10.3389/fphys.2023.1196919

EDITED BY
Jo Nijs,
Vrije University Brussels, Belgium

REVIEWED BY
Aijing Lin,
Beijing Jiaotong University, China
Rishi Raj Sharma,
Defence Institute of Advanced Technology (DIAT), India

*CORRESPONDENCE
Peng Zan,
✉ zanpeng@shu.edu.cn
Chunyong Li,
✉ lcy07@tsinghua.org.cn

†These authors have contributed equally to this work and share first authorship

RECEIVED 30 March 2023
ACCEPTED 17 May 2023
PUBLISHED 30 May 2023

CITATION
Yuan D, Yue J, Xiong X, Jiang Y, Zan P and Li C (2023), A regression method for EEG-based cross-dataset fatigue detection.
Front. Physiol. 14:1196919.
doi: 10.3389/fphys.2023.1196919

A regression method for EEG-based cross-dataset fatigue detection

Duanyang Yuan[1†], Jingwei Yue[2†], Xuefeng Xiong[1], Yibi Jiang[1], Peng Zan[1*] and Chunyong Li[2*]

[1]Shanghai Key Laboratory of Power Station Automation, School of Mechatronics Engineering and Automation, Shanghai University, Shanghai, China, [2]Beijing Institute of Radiation Medicine, Academy of Military Medical Sciences (AMMS), Beijing, China

Introduction: Fatigue is dangerous for certain jobs requiring continuous concentration. When faced with new datasets, the existing fatigue detection model needs a large amount of electroencephalogram (EEG) data for training, which is resource-consuming and impractical. Although the cross-dataset fatigue detection model does not need to be retrained, no one has studied this problem previously. Therefore, this study will focus on the design of the cross-dataset fatigue detection model.

Methods: This study proposes a regression method for EEG-based cross-dataset fatigue detection. This method is similar to self-supervised learning and can be divided into two steps: pre-training and the domain-specific adaptive step. To extract specific features for different datasets, a pretext task is proposed to distinguish data on different datasets in the pre-training step. Then, in the domain-specific adaptation stage, these specific features are projected into a shared subspace. Moreover, the maximum mean discrepancy (MMD) is exploited to continuously narrow the differences in the subspace so that an inherent connection can be built between datasets. In addition, the attention mechanism is introduced to extract continuous information on spatial features, and the gated recurrent unit (GRU) is used to capture time series information.

Results: The accuracy and root mean square error (RMSE) achieved by the proposed method are 59.10% and 0.27, respectively, which significantly outperforms state-of-the-art domain adaptation methods.

Discussion: In addition, this study discusses the effect of labeled samples. When the number of labeled samples is 10% of the total number, the accuracy of the proposed model can reach 66.21%. This study fills a vacancy in the field of fatigue detection. In addition, the EEG-based cross-dataset fatigue detection method can be used for reference by other EEG-based deep learning research practices.

KEYWORDS

fatigue detection, cross-dataset, EEG, regression method, self-supervised learning

1 Introduction

Fatigue is one of the major factors leading to human errors, which is accompanied by impaired attentional control, decreased individual alertness, and poor performance in tasks (Liu et al., 2020). These are dangerous for certain jobs requiring continuous concentration, such as pilots, vehicle drivers, and helmsmen (Liu W. et al., 2019). To avoid failures caused by fatigue, researchers are working on ways to detect/monitor fatigue using different types of signals. The first is based on individual behavior, including physiological responses, such as eyelid-related parameters (Hu and Zheng, 2009), facial expressions (Liu Y. et al., 2019), head movement (SMITH et al., 2016), percentage of eye closure (PERCLOS) (Zheng and Lu, 2017), and the performance observed during the execution of specific tasks, such as reaction time (RT) and response accuracy (Huang et al., 2016; Liu et al., 2020; Zeng et al., 2020). The second is based on psychological surveys, such as the Karolinska Sleepiness Scale, Stanford Sleepiness Scale, and Chalder Fatigue Scale (Foong et al., 2019; Qin et al., 2020; Krigolson et al., 2021; Zeng et al., 2021). The third is based on physiological signals, such as electroencephalogram (EEG) (Gao et al., 2019; Peng et al., 2021), electrooculogram (Bulling et al., 2011), electrocardiogram (Murugan et al., 2020), or a combination of signals (Qi et al., 2018; Du et al., 2022). Precisely, EEG measures the potential difference produced from the electrical signals generated by the synaptic excitation of neurons to the scalp, and it can directly reflect the activities of nerve cells in the brain (Kostas et al., 2021; Liqiang et al., 2022). Therefore, it is considered to be the most effective method to detect fatigue.

At present, the fatigue detection method of within-subject and cross-subject has achieved outstanding performance. For the within-subject fatigue recognition, Yang et al. (2021a) proposed a complex network (CN)-based broad learning system (CNBLS) to realize fatigue detection based on EEG. The classification accuracy of CNBLS was 99.58%. Wang H. et al. (2021) introduced a new attention-based multiscale convolutional neural network–dynamical graph convolutional network model for driving fatigue detection. The two-class accuracy was 95.65%. For cross-subject fatigue recognition, Zeng et al. (2020) used the InstanceEasyTL method to detect driver fatigue, and the two-class accuracy was 88.02%. Liu et al. (2020) proposed a transfer learning-based algorithm using maximum independence domain adaption (MIDA), and it achieved an accuracy of 73.01% with all 30 channels for the two-class mental fatigue recognition. Wei et al. (2018) developed a subject-transfer framework for obviating inter- and intra-subject variability in drowsiness detection, and this framework remarkably reduced the required calibration time for a new user. In addition, in the emotion recognition field, Iyer et al. (2023) proposed the ensemble learning-based EEG emotion recognition system, and the ensemble model outperforms the compared methodologies with 97.16% accuracy for EEG-based emotion recognition on the SEED dataset. In the sleep stage classification, Sharma et al. (2021) used a discrete wavelet transform and discrete entropy to analyze EEG signals, studied the wavelet sub-band of EEG sleep records and its performance based on wave dispersion entropy, and finally obtained EEG features suitable for sleep stage classification.

However, when faced with new users under different datasets, the model of within-subject and cross-subject fatigue detection still needs a large amount of EEG data for training. It has poor applicability. The cross-dataset fatigue detection model has a strong practical application value because it does not need to be retrained, and it can directly detect fatigue states of new datasets. In order to get a general cross-dataset fatigue detection model, this study considers different sets in BCIs. In other words, different datasets have different label spaces (He and Wu, 2020). For fatigue detection, this means that the subjects of different datasets perform different fatigue-induced tasks. Different tasks have different feature spaces. Thus, the very effort of selecting different features for different tasks is a critical challenge for cross-dataset fatigue detection. However, the within-subject and cross-subject fatigue detection models are difficult to generalize knowledge to new datasets because they suffer the drawbacks of fully supervised learning and large-scale labeled datasets for training (Ye et al., 2022), and the label work process is prone to human bias and may also result in ambiguous annotations. In particular, each dataset has multiple subjects, so cross-dataset fatigue detection is a multi-source to multi-target domain problem.

Up to now, the methods of fatigue detection are mainly judged from facial expressions, physiological signals, and questionnaire surveys, but it is difficult to have a general fatigue detection model to adapt to various fatigue-induced tasks. To the best of our knowledge, no one has studied this problem previously. However, the idea of a cross-dataset has gained widespread attention in other fields, such as emotion recognition, sleep staging, and personal identification. Ni et al. (2021) used a domain adaptation sparse representation classifier to minimize the data distribution difference between datasets and then classify emotions for EEG collected from different subjects, different periods, and different devices. Eldele et al. (2022) used the adversarial learning framework called ADAST for automatic sleep staging. The framework can tackle the domain shift problem in the unlabeled target domain, which is a limitation to domain adaptation in sleep staging. Kong et al. (2018) proposed a method for cross-dataset personal identification based on a brain network of EEG signals. The method used brain functional networks and linear discriminant analysis (LDA) to classify personal identification. As can be seen from the aforementioned fields, domain adaptation is one of the main methods to solve cross-dataset problems (Chen et al., 2021; Ding et al., 2021). In addition, the method proposed in this study can also be applied to these fields.

In real life, there is a coherent sequence of changes in EEG variables during the transition from normal driving, high mental workload, and eventual mental fatigue and drowsiness, so fatigue detection should be a regression problem. However, current fatigue evaluation methods are mostly classification methods, aiming to divide the brain states into two or more alert and fatigue states (Yang et al., 2021b). This is a simplified version of regression analysis. To develop a model that can adapt to different fatigue-induced tasks, this study focuses on the following four points to carry out the specific content of this study.

(a) A regression method for EEG-based cross-dataset fatigue detection is proposed to detect the fatigue states of the new datasets collected for different fatigue-induced tasks. The method includes two steps: pre-training and the domain-specific adaptive step. The purpose of pre-training is mainly to extract specific features for different datasets. The domain-specific adaptive step is mainly to align specific features extracted from the pre-training step and mine the internal relationship between features. To validate the proposed method, a large number of experiments were conducted to compare the proposed method with state-of-the-art domain adaptation methods.
(b) In the pre-training step, this study designs a pretext task to distinguish data from the source or target domains. In this

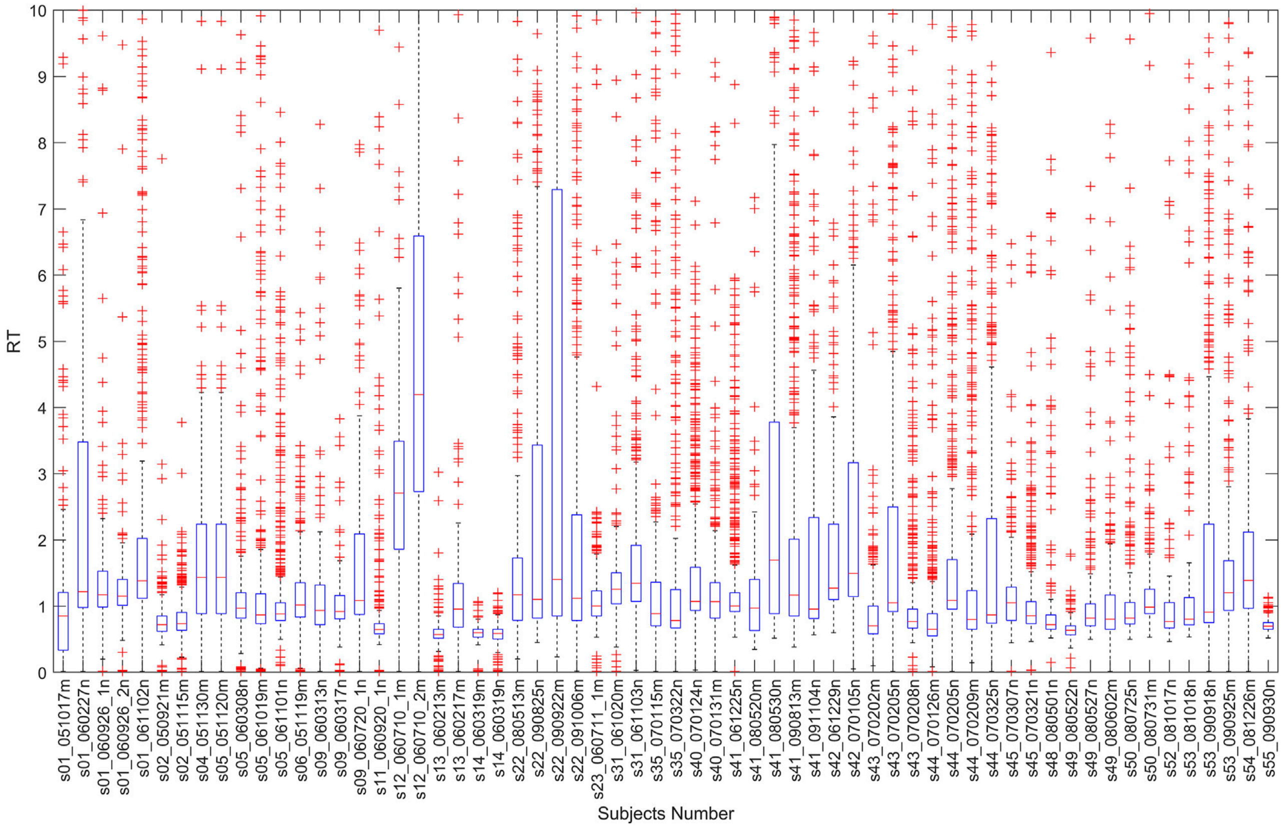


FIGURE 1
All trails' reaction times.

way, the specific features of different fatigue-induced tasks can be obtained. The pre-training step includes a common feature extractor and a domain discriminator. In this study, we have performed a lot of experiments to verify that the accuracy of pre-training steps is better than that of no pre-training steps, which proves the contribution of pre-training.

(c) In the domain-specific adaptive step, this study proposes an EEG-based domain-adaptive fatigue detection network. In addition, it includes a domain-specific feature extractor, domain distribution alignment network, and regression multilayer perceptron. Maximum mean discrepancy (MMD) is used to optimize the network parameters in the domain-specific adaptive step, which can minimize differences between the source and target domains.

(d) The attention mechanism is introduced to extract continuous information on spatial features, and the gated recurrent unit (GRU) is introduced to capture information on time series. This study also conducts experiments to verify the effectiveness of the attention mechanism and GRU.

The rest of this paper is organized as follows: Section 2 describes the proposed method. Section 3 presents the experiment and results. Section 4 discusses the results, and Section 5 concludes the paper.

2 Materials and methods

2.1 Problem statement

It is difficult to obtain a general model that is suitable for datasets because of different tasks. Therefore, if the model trained by one dataset is applied to another dataset directly, it will lead to performance degradation. When faced with a new dataset, the conventional method needs to undergo the calibration process, that is, to collect lots of new labeled data and train a new model for these data (Wang Y. et al., 2021). This is time-consuming and not economical.

Suppose we have labeled EEG samples from one dataset $\{X_s, Y_s\} = \left\{(x_{s_i}, y_{s_i})\right\}_{i=1}^{N_s}$, denoted as the multi-source domain D_s, and unlabeled EEG samples from the another dataset $\{X_t\} = \left\{x_{t_j}\right\}_{j=1}^{N_t}$, denoted as the multi-target domain D_t, where $X_s \in R^{d \times N_s}$, $X_t \in R^{d \times N_t}$, $Y_s \in R^{C \times N_s}$, $x_{s_i}, x_{t_j} \in R^d$, and $y_{s_i} \in R^C$ is a one-hot vector, d is the feature dimensionality, C is the fatigue index, and N_s and N_t are the number of samples in multi-source and multi-target domains, respectively. However, the marginal distributions and conditional distributions of the feature space, and the fatigue index space of both domains are different due to the domain shift: $P_s(X_s) \neq P_t(X_t)$ and $P_s(Y_s|X_s) \neq P_t(Y_t|X_t)$. Domain adaptation solves this problem by mapping the multi-source and multi-target domains to a new space R and then

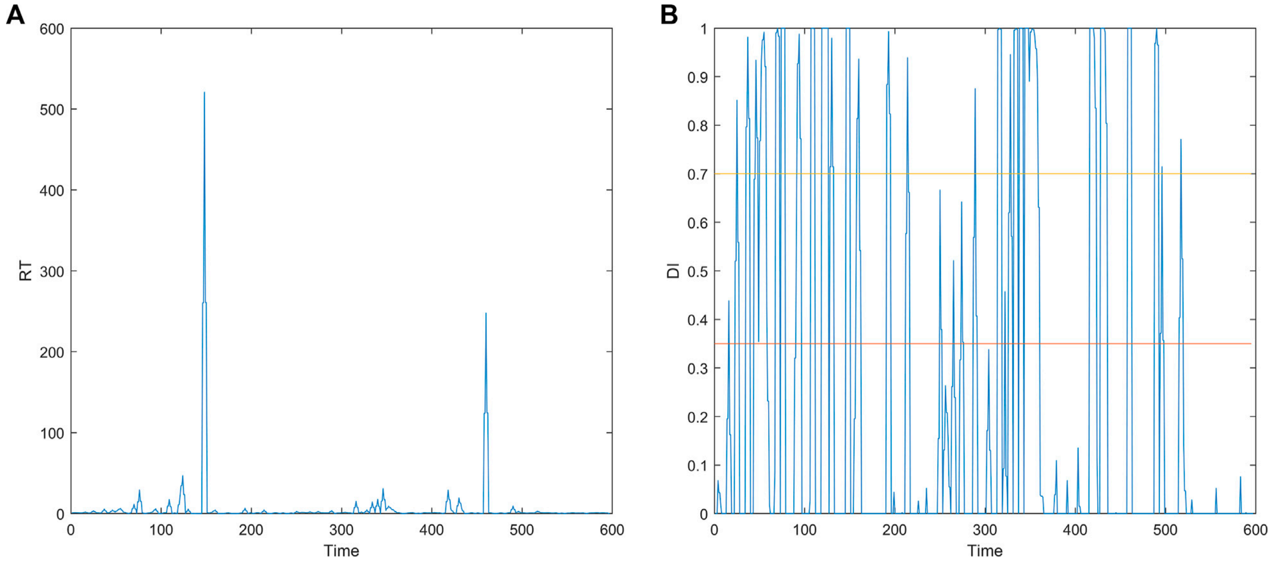


FIGURE 2
Curves before and after the transformation. **(A)** RT curve. **(B)** DI curve.

minimizing the distance D_{s-t} between the multi-source mapping distributions R_{X_s} and multi-target mapping distributions R_{X_t}.

2.2 Datasets

2.2.1 SEED dataset

The data were collected by Zheng and Lu (2017). A total of 23 subjects participated in the experiments. The experimental data collection scenario was a virtual-reality-based simulated driving scene. A four-lane highway scene is shown on a large LCD screen in front of a real vehicle without the unnecessary engine and other components. The vehicle movements in the software application are controlled by the steering wheel and gas pedal. During the experiments, the subjects were asked to drive the car using the steering wheel and gas pedal, and the scenes were simultaneously updated according to the participants' operations. The 12-channel EEG signals from the hindbrain (CP1, CPZ, CP2, P1, PZ, P2, PO3, POZ, PO4, O1, OZ, and O2) and 6-channel EEG signals from the temporal lobe (FT7, FT8, T7, T8, TP7, and TP8) were recorded. The author of the dataset used independent component analysis filtering to remove noise, such as the artifact of eye movement, electromyography, and baseline drift. In this study, we filtered the dataset with 1-Hz high-pass and 50-Hz low-pass finite impulse response (FIR) filters. The processed data were finally downsampled to 128 Hz. The vigilance annotation method of the dataset used PERCLOS, which refers to the percentage of eye closure. Specifically, eye movements were simultaneously recorded using SMI ETG eye tracking glasses.

Data labels were defined in a way that classifies EEG data into three fatigue states (awake, fatigue, and drowsy) with two thresholds (0.35 and 0.7) based on the PERCLOS index. In addition, in the following study, this study uses "SEED_0" for awake, "SEED_1" for fatigue, and "SEED_2" for drowsy in the SEED dataset.

2.2.2 Multi-channel dataset

The dataset consists of EEG signals collected by Cao et al. (2019). In the experiment, 27 participants were invited to the experiment. Fatigue and drowsy states were induced by a 90-min sustained-attention night-time driving task in an immersive driving simulator. The participants were tasked to drive and maintain the car in the center of the lane. Lane-departure events were randomly induced, which made the car drift to the left or right from the lane, and participants were asked to move back as quickly as possible by steering the wheel. In addition, their reactions were timed. The vigilance annotation method of the dataset used the RT, which provides a gauge of the subjects' fatigue level. The preprocessed version of the dataset was used in this study. As described by the authors, the raw EEG signals were filtered by 1-Hz high-pass and 50-Hz low-pass FIR filters. Apparent eye blinks that contaminate the EEG signals were manually removed through visual inspection by the authors of the dataset. Ocular and muscular artifacts were removed by the automatic artifact removal plug-in of EEGLAB. The processed data were finally downsampled to 128 Hz.

The RT is the time difference between the lane-departure event onset and the subject's response onset. This study calculated all trails' RT, and the boxplot of these is shown in Figure 1. As can be seen from Figure 1, each person's RT is different, and it has a long-tail effect. Therefore, the RT τ is transformed into the drowsiness index (DI) (Yang et al., 2021a) by the following Equation 1 in this study. The RT has been proved to have a strong correlation with the drowsiness level, while the DI is positively correlated with the RT. Therefore, the DI can be used to indicate the drowsiness level. The curves before and after the transformation are shown in Figures 2A, B (take s01_051017m.set as an example). As can be seen from Figure 2B, the fatigue curve determined according to the performance observed during the execution of specific tasks fluctuates greatly.

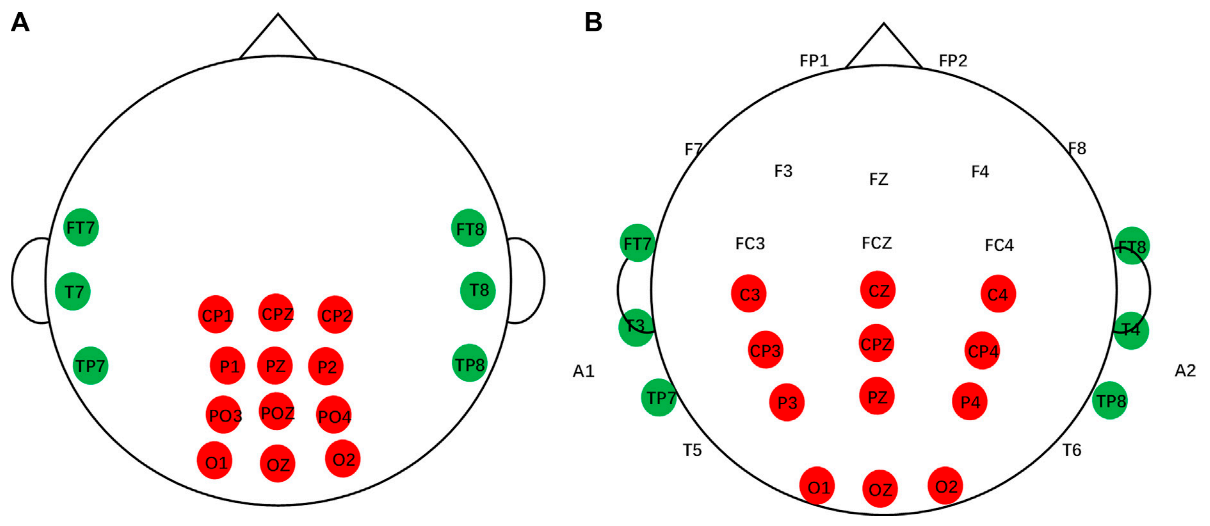


FIGURE 3
Channels of the SEED dataset and multi-channel dataset. **(A)** SEED dataset. **(B)** Multi-channel dataset.

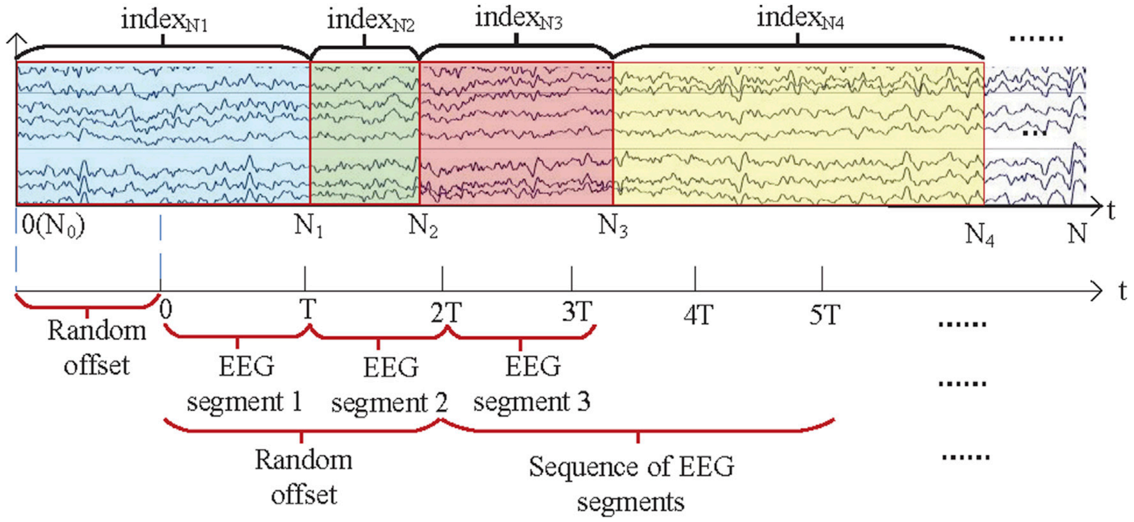


FIGURE 4
Random sampling method.

$$DI = \max\left(0, \frac{1-e^{-(\tau-\tau_0)}}{1+e^{-(\tau-\tau_0)}}\right), \tag{1}$$

where τ_0 was set to 1.

The transformation can normalize the RT to the interval [0,1] and overcome the long-tail effect. Like the SEED dataset, the data labels are defined in such a way that the EEG data are classified into three fatigue states (awake, fatigue, and drowsy) based on the DI index with two thresholds (0.35 and 0.7). Specifically, in the following study, this study uses "multi-channel_0" for awake, "multi-channel_1" for fatigue, and "multi-channel_2" for drowsy in the multi-channel dataset.

2.2.3 Channel selection

For the EEG setup, the SEED dataset recorded 12-channel EEG signals from the posterior site (CP1, CPZ, CP2, P1, PZ, P2, PO3, POZ, PO4, O1, OZ, and O2) and 6-channel EEG signals from the temporal site (FT7, FT8, T7, T8, TP7, and TP8) according to the International 10–20 electrode system, as shown in Figure 3A.

The multi-channel dataset included 32 EEG signals and one signal for vehicle position. The first 32 signals were from the Fp1, Fp2, F7, F3, Fz, F4, F8, FT7, FC3, FCZ, FC4, FT8, T3, C3, Cz, C4, T4, TP7, CP3, CPz, CP4, TP8, A1, T5, P3, PZ, P4, T6, A2, O1, Oz, and O2 electrodes. Two electrodes (A1 and A2) were references placed on the mastoid bones. The next signal was used to describe the

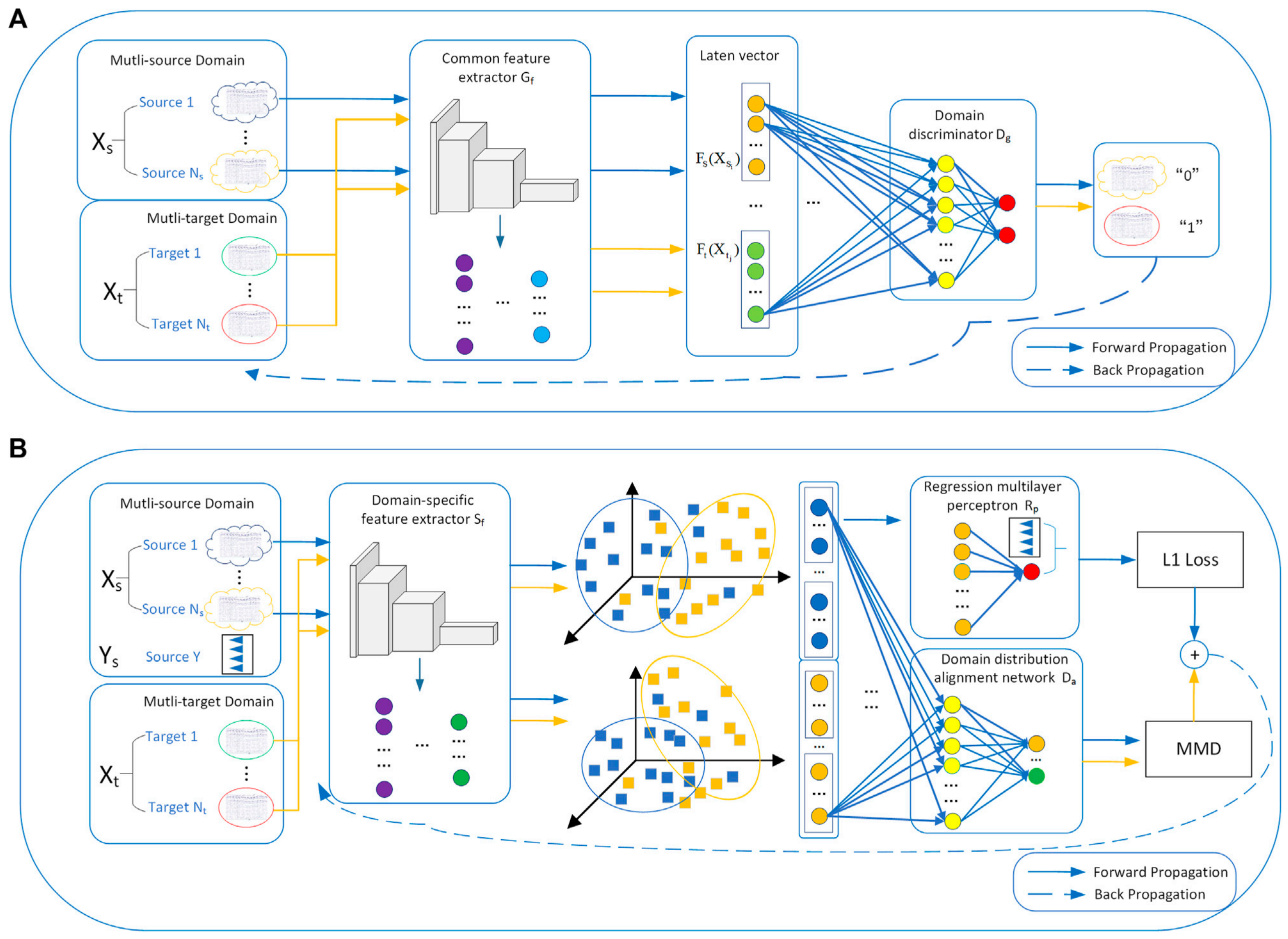


FIGURE 5
Regression method for EEG-based cross-dataset fatigue detection: **(A)** pre-training and **(B)** domain-specific adaptive step. In the pre-training step, the multi-source domain and multi-target domain data are input into G_f and then fed into D_g. In the domain-specific adaptive step, the specific features of the two domains are extracted by S_f. Then, the distance MMD between the specific features is calculated by D_a, and the fatigue index of the source domain is fitted by R_p.

position of the simulated vehicle. This study compares the channels of the SEED dataset with those of the multi-channel dataset and selects the channels according to the one-to-one correspondence principle, as shown in Figure 3. In particular, if there are more datasets, channel selection should be based on the dataset with the lowest number of channels.

2.2.4 EEG segmentation division

In our previous work, we found that the random sampling method can reduce overfitting. It is shown in Figure 4. The specific process is as follows. Assuming that the EEG sequence length is N and the sample length of the EEG segment is T, the EEG sequence of length N contains a number of EEG sub-sequence $[N_i, N_{i+1}]$, and each has its own index. For example, the EEG sub-sequence $[N_0, N_1]$ corresponds to $index_{N_1}$ and the EEG sub-sequence $[N_1, N_2]$ corresponds to $index_{N_2}$, and so on. A random offset of $[0, T-1]$ will be set for the EEG sequence and EEG segments in each training iteration, which means that different EEG segments will be used in each iteration. The relationship between the EEG segment $[iT, (i+1)T]$ and the corresponding index $index_{[iT,(i+1)T]}$ is shown in Equation 2.

$$index_{[iT,(i+1)T]} = \begin{cases} index_{N_1}, & if \quad 0 < iT < N_1, \\ \dfrac{\int_{iT}^{N_1} index_{N_1} d_t + \int_{N_1}^{(i+1)T} index_{N_2} d_t}{T}, & if \ N_1 < iT < N_2, \\ \dfrac{\int_{iT}^{N_1} index_{N_1} d_t + \int_{N_1}^{N_2} index_{N_2} d_t + \int_{N_2}^{(i+1)T} index_{N_3} d_t}{T}, & if \ N_2 < iT < N_3. \\ \ldots, \ldots & \end{cases} \tag{2}$$

In this study, the EEG data on the SEED dataset were used as the independent variable and the PERCLOS was used as the dependent variable. In addition, the PERCLOS values provided in the SEED database were calculated every 8 s, so the PERCLOS values between two 8 s EEG segments were obtained by the aforementioned interpolation method. In the multi-channel dataset, EEG data were used as the independent variable and the DI as the dependent variable, and the DI values were obtained by the aforementioned interpolation method.

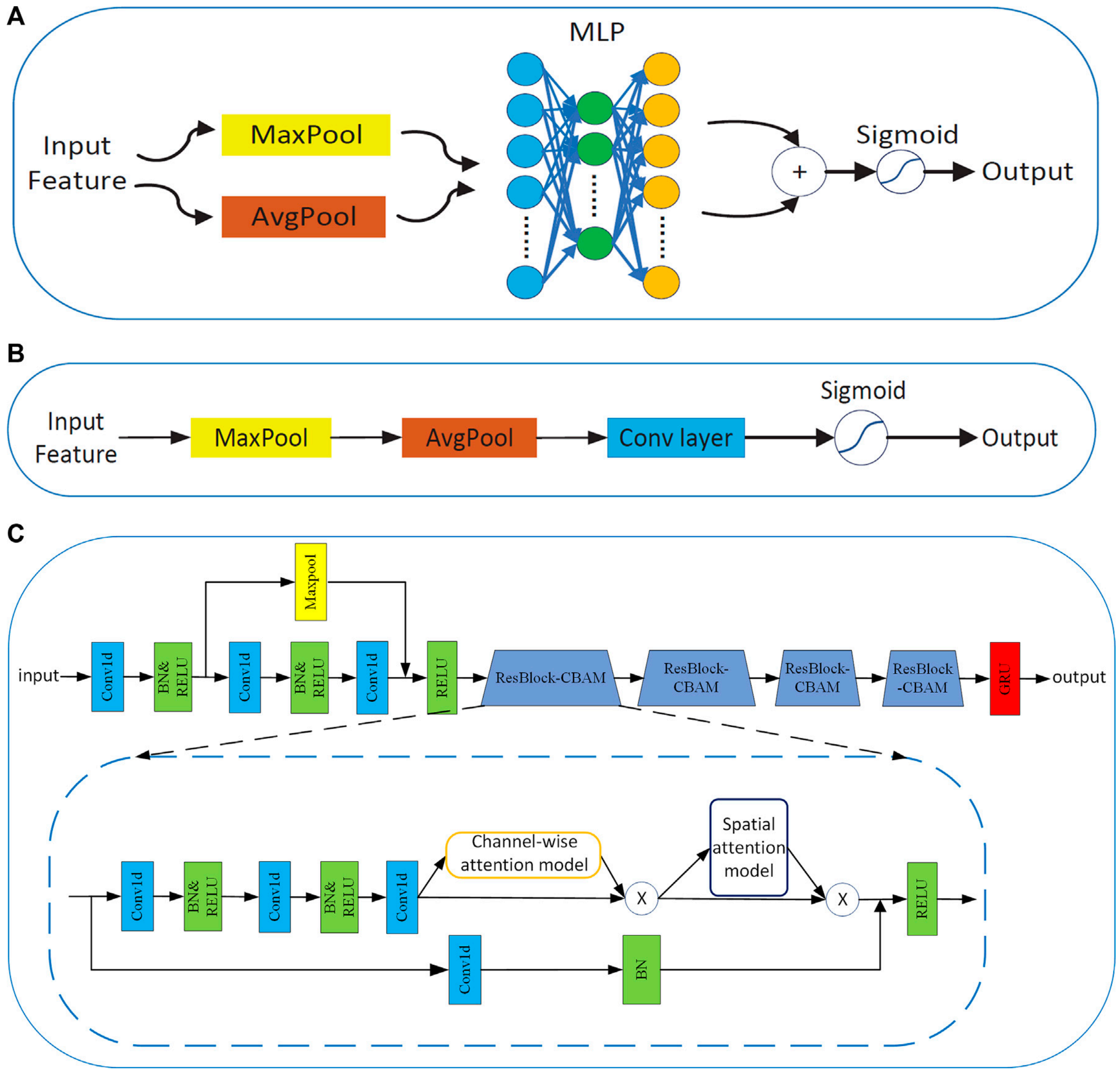


FIGURE 6
(A) Channel-wise attention model. **(B)** Spatial attention model. **(C)** Network structure of the common feature extractor.

2.3 Proposed method

In order to get a fatigue detection model that can adapt to different tasks, this study proposes a regression method for EEG-based cross-dataset fatigue detection, as shown in Figure 5. In the pre-training step (Figure 5A), X_s and X_t are input into the common feature extractor G_f to extract specific features ($F_s(X_{s_i})$ and $F_t(X_{t_j})$) for different tasks. Then, the domain discriminator D_g is used to determine whether these specific features come from X_s ("0") or X_t ("1"). The cross-entropy loss is calculated and backpropagated to optimize the network. In this way, the specific features of different fatigue-induced tasks can be obtained.

In the domain-specific adaptive step (Figure 5B), this study proposes an EEG-based domain-adaptive fatigue detection network. In addition, it includes a domain-specific feature extractor S_f, domain distribution alignment network D_a, and regression multilayer perceptron R_p. First, the specific features of X_s and X_t are extracted by S_f. Then, the distance MMD (Chen et al., 2021) between the specific features is calculated by D_a, and the fatigue index of the source domain is fitted by R_p to calculate the mean squared error (MSE). Finally, the MMD and MSE were backpropagated to constantly update the network parameters and narrow the differences between features. The method can make the distribution domains of D_s and D_t more uniform, that is, $\lim_{t \to s} [P_s(X_s) = P_t(X_t)]$ and $\lim_{t \to s} [P_s(Y_s|X_s) = P_t(Y_t|X_t)]$. Its aim is to extract the invariant features among domains and reveal the relationships between instances of the different datasets (Ye et al., 2022).

In terms of the design of a network structure, this study introduces the attention mechanism to extract the discriminative spatial representations and introduces the GRU to capture the relationship of EEG samples and the long-range information about EEG slices. The implementation processes of the proposed method are described in detail in Section 2.3.1 and Section 2.3.2.

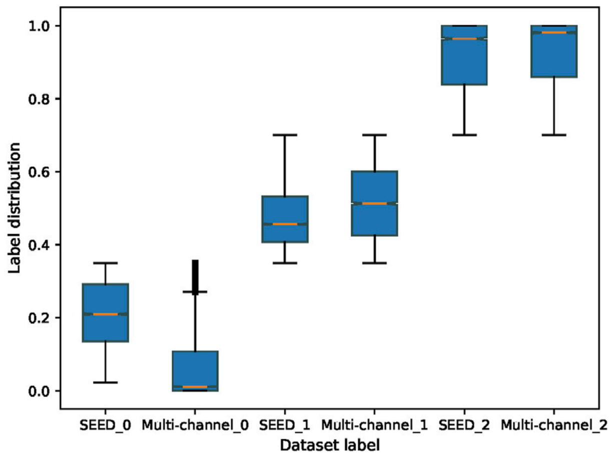


FIGURE 7
Fatigue index distribution of the SEED and multi-channel datasets. SEED_0, SEED_1, and SEED_2 indicate awake, fatigue, and drowsy states of the SEED dataset, respectively. Multi-channel_0, multi-channel_1, and multi-channel_2 indicate awake, fatigue, and drowsy states of the multi-channel dataset, respectively.

2.3.1 Design of a common feature extractor

In prior work, this study observed that the performance of shallower models more quickly saturated to lower performance levels, as compared to the deeper networks. If the shallow network depth is increased only, it is easy to cause overfitting and deteriorate the network performance. The residual network (ResNet) solves the problems of traditional convolutional neural network (CNN) degradation and gradient disappearance/explosion by adding jump connections.

Apart from these factors, this study investigates a different aspect of architectural design: attention. The significance of attention has been studied extensively in the literature (Mnih et al., 2014; Gregor et al., 2015). In addition, it plays an important role in deciding ‘where’ to focus, as shown in Chen et al. (2017). Woo et al. (2018) exploited CBAM, which is both channel-wise and spatial attention-based on efficient architecture. They integrated CBAM into ResNet and applied it to computer vision, and this method showed very good performance. Thus, the attention mechanism is very good at capturing spatial representations. However, there are few applications for fatigue detection (Wang H. et al., 2021).

In this study, ResNet50 was selected as the CNN to extract spatial local features of one-dimensional EEG samples. In addition, the CBAM network is integrated into ResNet50 by referring to the experiment of Woo et al. (2018). The channel-wise attention and spatial attention models are shown in Figures 6A, B. The method can adaptively estimate the importance of EEG channels without any prior information and effectively learn the discriminative spatial representations in EEG slices. In addition, several pioneering works mainly focus on the relationship of EEG samples or the connection between different channels, whereas few studies considered capturing the information about EEG slices. The GRU is added to capture the latent long-range temporal information on EEG signals. The network structure design of the common feature extractor G_f is shown in Figure 6C.

2.3.2 Domain-specific adaptive step

In the domain-specific adaptive step, this study builds the domain-specific feature extractor S_f. The domain-specific feature extractor S_f extracts multi-representations of X_s and X_t, that is, $\left\{R_{X_{s_i}}\right\}_i^{N_s}$ *and* $\left\{R_{X_{t_j}}\right\}_j^{N_t}$. S_f maps them to a common subspace ∅ and preserves the key features of each domain and S_f by using a G_f-based shared feature extractor, i.e., $S_f = G_f$, which is unlike the totally unshared architectures that require an extra network and increase the complexity of the model. Therefore, most domain-adaptive algorithms adopted this shared design (Eldele et al., 2022; He et al., 2022). To make these high-level features with different representations closer, this study employed MMD to estimate the distance between the domains in the latent space (Chen et al., 2021; Tao and Dan, 2021; Cao et al., 2022). In addition, it is calculated by

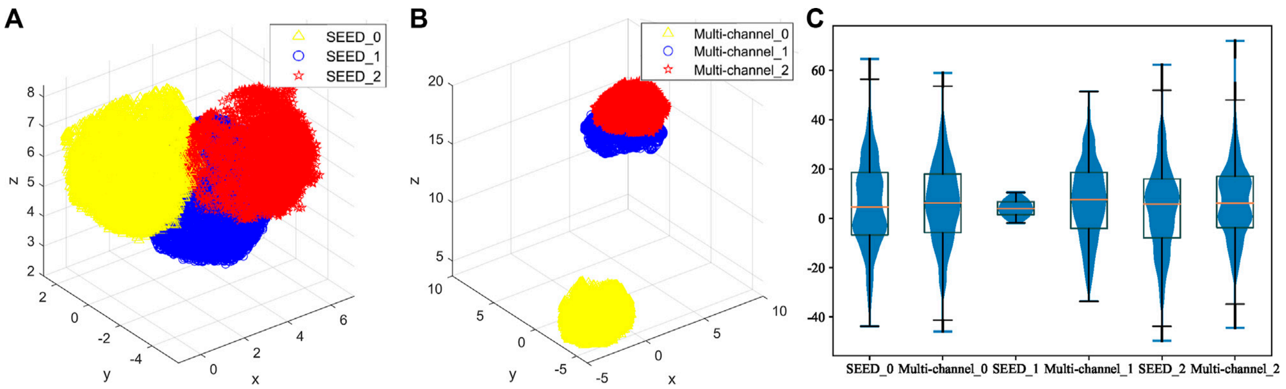


FIGURE 8
Distributions of the three states of the two datasets. **(A)** 3-D scatter plot of EEG samples of the SEED dataset. **(B)** 3-D scatter plot of EEG samples of the multi-channel dataset. Yellow color indicates the awake state of the two datasets, blue indicates the fatigue state, and red indicates the drowsy state in **(A)** and **(B)**. **(C)** Boxplot and violin plot of EEG samples of the two datasets. SEED_0, SEED_1, and SEED_2 indicate awake, fatigue, and drowsy states of the SEED dataset, respectively. Multi-channel_0, multi-channel_1, and multi-channel_2 indicate awake, fatigue, and drowsy states of the multi-channel dataset, respectively.

the domain distribution alignment network D_a. The final MMD is the sum of the MMD of each source domain expression and the corresponding target domain expression, as shown in Equation 3.

$$MMD\left(\left\{R_{X_{s_i}}\right\}_i^{N_s}, \left\{R_{X_{t_j}}\right\}_j^{N_t}\right) = \left\| \frac{1}{N_s}\sum\nolimits_{i=1}^{N_s}\varnothing\left(\left\{R_{X_{s_i}}\right\}_i\right) - \frac{1}{N_t}\sum\nolimits_{j=1}^{N_t}\varnothing\left(\left\{R_{X_{t_j}}\right\}_j\right)\right\|^2. \tag{3}$$

Finally, the multi-representation vector $\left\{R_{X_{s_i}}\right\}_i^{N_s}$ is connected to a new vector and fed into the regression multilayer perceptron R_p to predict the fatigue index. We use the MSE to calculate loss, as shown in Equation 4. The total loss function can be expressed as Equation 5.

$$MSE\left(\hat{Y}, Y\right) = \frac{1}{N_s}\sum_{i=1}^{N_s}\left(\hat{y}_i - y_i\right)^2, \tag{4}$$

$$L_{loss} = MSE\left(\hat{Y}, Y\right) + \alpha \times MMD\left(\left\{R_{X_{s_i}}\right\}_i^{N_s}, \left\{R_{X_{t_j}}\right\}_j^{N_t}\right), \tag{5}$$

where α is the proportionality coefficient.

The training is based on Equation 5. Minimizing this formula is to minimize the MMD and MSE so that the distance between the source domain and the target domain can be as small as possible in different potential spaces, and the index prediction is as close as possible to the actual index.

In summary, the method proposed in this study follows the algorithm, as shown in Algorithm 1.

```
    Input: The EEG data on the source domain and target domain, $X_s$ and $X_t$.
    The labels of source domain $Y_s$, epoch N and batch size B, learning rate lr, parameters $\alpha$;
    Output: prediction of target domain data, $\{\hat{Y}\}$.
Step 1:
    Pre-training
    Initialize the parameters of the model
        for (epoch ← 1; epoch ≤ N; epoch ← epoch + 1) do
        repeat
        Sample source examples $\{x_{s_i}\}_{i=1}^{N_s}$ from $\{X_s\}$;
        Sample target examples $\{x_{t_j}\}_{j=1}^{N_t}$ from $\{X_t\}$;
        Sample labels "0" (source domain) and "1" (target domain);
        Use $G_f$ to extract $F_s(X_{s_i})$ and $F_t(X_{t_j})$;
        $F_s(X_{s_i})$ and $F_t(X_{t_j})$ are input into the $D_g$ to compute the cross-entropy loss;
        Update the model by minimizing the cross-entropy loss;
        end for
Step 2: Domain-specific adaptive
    Initialize domain-specific feature extractor $S_f$
        for (epoch ← 1; epoch ≤ N; epoch ← epoch + 1) do
        repeat
        Sample source examples $\{(x_{s_i}, y_{s_i})\}_{i=1}^{N_s}$ from $\{X_s, Y_s\}$;
        Sample target examples $\{x_{t_j}\}_{j=1}^{N_t}$ from $\{X_t\}$;
        Use $S_f$ to extract $\{R_{X_{s_i}}\}_i^{N_s}$ and $\{R_{X_{t_j}}\}_j^{N_t}$;
        $\{R_{X_{s_i}}\}_i^{N_s}$ and $\{R_{X_{t_j}}\}_j^{N_t}$ are input into $D_a$ to compute $MMD(\{R_{X_{s_i}}\}_i^{N_s}, \{R_{X_{t_j}}\}_j^{N_t})$ (3);
        Concat $\{R_{X_{s_i}}\}_i^{N_s}$ to regression multilayer perceptron $R_p$ to calculate the $MSE(\hat{Y}, Y)$ (4);
        The total loss is $L_{loss}$ (5);
        Update the model by minimizing the total loss;
        end for
        Input $\{X_t\}$ into the updated model to predict;
        return prediction of target domain data, $\{\hat{Y}\}$.
```

Algorithm 1: A regression method for EEG-based cross-dataset fatigue detection.

3 Results

3.1 Dataset evaluation

In order to develop a model that can adapt to different fatigue tasks, we need to select a dataset with large information as the source domain and another as the target domain. Therefore, we need to reasonably judge the richness of each dataset and the information it contains.

First, this study evaluates the distributions of two datasets. The SEED dataset and multi-channel dataset have different experimental tasks, so they may present different features. Therefore, the amount of information contained in each dataset should be evaluated comprehensively in order to select the appropriate source and target domains. Figure 7 shows the boxplot of the fatigue index distribution of the SEED and multi-channel datasets. Meanwhile, in order to see the distributions of the three states of the two datasets more directly, this study randomly picked out almost 256 EEG samples from the two datasets (each dataset has 128 samples) to visualize them with Uniform Manifold Approximation and Projection (UMAP) (Banville et al., 2021) *via* a 3-D scatter plot, as shown in Figures 8A, B. In addition, their boxplot and violin plot are displayed in Figure 8C.

It can be seen from Figure 7 that the fatigue index of the SEED dataset has a more centralized distribution with no outliers, while that of the multi-channel dataset has more outliers on "multi-channel_0." Also, the multi-channel dataset is wider than the SEED dataset. It means that the changes of the multi-channel dataset are greater and scattered. In addition, it can be seen from Figure 8A that the SEED dataset has more transition features from awake to fatigue and from fatigue to drowsy states. However, the multi-channel dataset has less crossover (Figure 8B), which is not conducive to extract the transition features. We can observe from Figures 8A, C that the SEED dataset had a more concentrated EEG distribution and fewer outliers. Therefore, the SEED dataset is more suitable as the source domain. It is noteworthy that for different data, the range of the data after dimensionality reduction is different (Li et al., 2022). This study only shows the visualization effect of the proposed method here.

3.2 Experiment details

It should be noted although all the samples in the SEED and multi-channel datasets are labeled, the labels of the multi-channel dataset are used only for assessment but not for training. In the experiment, one sample size was 17*1024. In addition, the size of the GRU hidden layer is 64, and the number of hidden layers is 1. The

TABLE 1 Recall, precision, F1 score, accuracy, and RMSE performances.

Method	SEED → multi-channel					Multi-channel → SEED				
	Recall (%)	Precision (%)	F1 score (%)	Accuracy (%)	RMSE	Recall (%)	Precision (%)	F1 score (%)	Accuracy (%)	RMSE
Proposed method	**44.81**	**47.83**	**46.27**	**59.10**	**0.27**	**39.89**	39.26	**49.57**	**45.21**	**0.29**
TCA	34.26	36.52	35.35	42.38	0.34	33.56	34.21	33.88	34.61	0.31
MIDA	35.12	45.98	39.82	48.38	0.31	34.89	36.87	35.85	36.97	0.31
InstanceEasyTL	42.87	37.68	40.11	53.21	0.28	38.92	**41.79**	40.30	42.59	0.30
DDA	38.34	46.58	42.06	45.16	0.28	37.85	39.73	38.77	41.26	0.30
ADAST	40.21	39.64	39.92	50.36	0.27	39.46	38.45	38.95	38.95	0.30

The values in bold represent better results.

optimizer uses a combination of the stochastic gradient descent and cosine gradually warm-up learning rate. In the cosine learning rate, every 100 epochs are half of the period of the cosine function, and the learning rate is 0.05 at most and 0.001 at least. In the gradually warm-up learning rate, the learning rate in the first 10 epochs is very small, and the learning rate starts to follow the change of the cosine learning rate from the epoch 11. The momentum in the optimizer is 0.9, and the weight decay rate is 0.001. α is 0.3. To avoid overfitting the source domain, this study also adds a dropout with a rate of 0.25 to the model. At each epoch, every 32 samples as a batch are used to train the network. The study used a single-layer multilayer perceptron (MLP) with one node as the regression multilayer perceptron and MLP with a 64-node domain distribution alignment network. All experiments are conducted in PyTorch libraries with an NVIDIA GeForce GTX 3060 GPU. All codes generated in this study are available at GitHub: https://github.com/yangyangyang-github/RMCDFD.

3.3 Performance evaluation

Different performance measurements, such as precision, recall, F1 score, accuracy, and root mean square error (RMSE), have been used to confirm the performance of the proposed method.

$$Precision = \frac{TP}{TP + FP}, \tag{6}$$

$$Recall = \frac{TP}{TP + FN}, \tag{7}$$

$$F1score = \frac{2{*}Precision{*}Recall}{Precision + Recall}, \tag{8}$$

$$Accuracy = \frac{TP + TN}{TP + TN + FN + FP}, \tag{9}$$

$$RMSE\left(Y, \hat{Y}\right) = \sqrt{\frac{1}{N}\sum_{i=1}^{N}\left(y_i - \hat{y}_i\right)^2}, \tag{10}$$

where TP, TN, FP, and FN represent the number of true positive, true negative, false positive, and false negative values. $Y = (y_1, y_2, \ldots, y_N)^T$ is the true value, and $\hat{Y} = (\hat{y}_1, \hat{y}_2, \ldots, \hat{y}_N)^T$ is the prediction.

3.4 Result

To validate the proposed method, this study compares the proposed method with the random value (33.33%). Likewise, we also compare the performance with that of other state-of-the-art domain adaptation methods, including transfer component analysis (TCA) (Pan et al., 2011), MIDA (Liu et al., 2020), InstanceEasyTL (Zeng et al., 2020), dynamic domain adaptation (DDA) (Li et al., 2022), and ADAST (Eldele et al., 2022). Meanwhile, in order to verify the effectiveness of source domain and target domain selection, this study compares the performance of all methods under two scenarios: 1) SEED → multi-channel and 2) multi-channel → SEED. These baselines are summarized as follows, and Table 1 shows the main results of five-fold cross-validation, which is averaged after 10 runs.

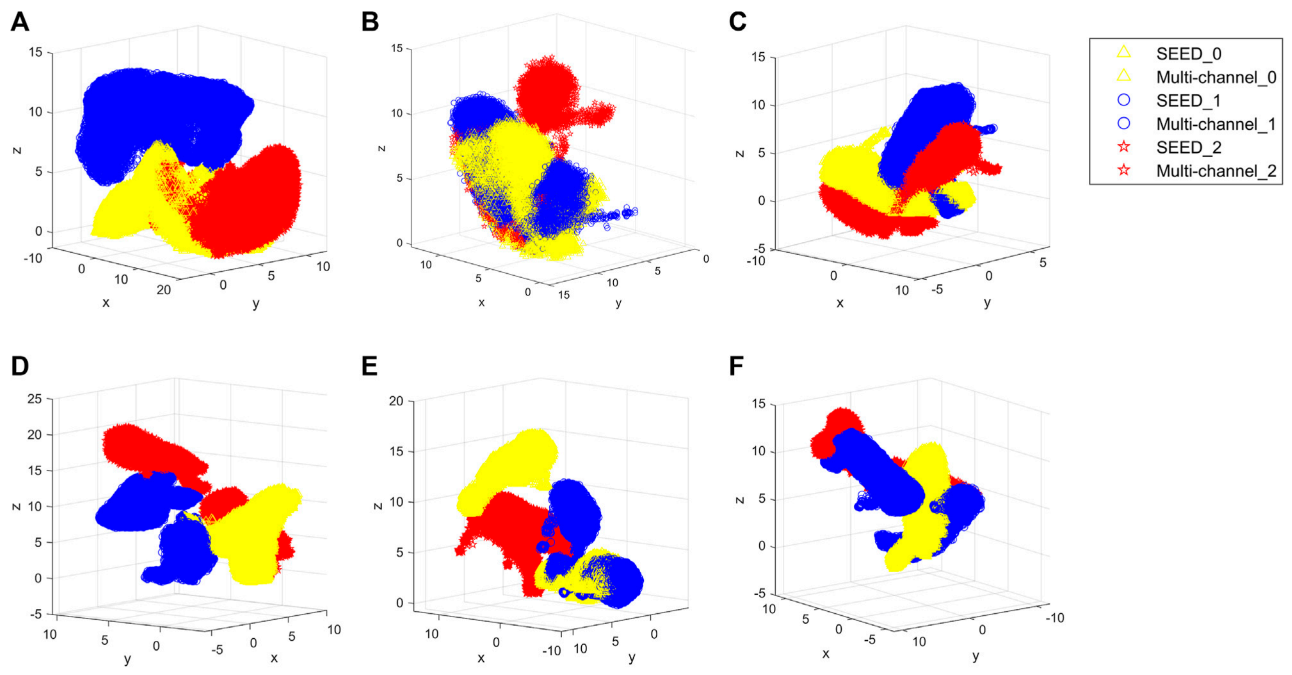


FIGURE 9
Visualized results of all methods. **(A)** Proposed method. **(B)** TCA. **(C)** MIDA. **(D)** InstanceEasyTL. **(E)** DDA. **(F)** ADAST. Yellow color indicates the awake state of the dataset, blue indicates the fatigue state, and red indicates the drowsy state. SEED_0, SEED_1, and SEED_2 indicate awake, fatigue, and drowsy states of the SEED dataset, respectively. Multi-channel_0, multi-channel_1, and multi-channel_2 indicate the awake, fatigue, and drowsy states of the multi-channel dataset, respectively.

TCA: It seeks a projection to a latent subspace, where the projected source data and target data achieve a reduced MMD in a reproducing kernel Hilbert space, which measures the distance between the empirical means of two distributions.

MIDA: It uses the Hilbert–Schmidt independence criterion to evaluate the independence of potential subspaces and hopes that the maximum independence of subspaces can be achieved.

InstanceEasyTL: In order to match the different distribution of EEG signals from different subjects, it adopts a strategy of alignment with certain weights to align EEG samples collected from both source and target domains.

DDA: It introduces a dynamic training strategy where the model focuses on optimizing the global domain discrepancy in the early training steps and then gradually switches to the local subdomain discrepancy.

ADAST: It develops a mechanism to preserve the domain-specific features in both domains. In addition, it designs an iterative self-training strategy to improve the classification performance on the target domain *via* target domain pseudo labels.

Table 1 reports the recall, precision, F1 score, accuracy, and RMSE metrics of the proposed methods in two-domain transfer scenarios. It can be seen from Table 1 that the proposed method achieves a better result in the two-domain transfer scenarios. In the first scenario, the recall, precision, F1 score, and accuracy metrics achieved by the proposed method are 44.81%, 47.83%, 46.27%, and 59.10%, which significantly outperforms TCA by 10.55%, 11.31%, 10.92%, and 16.72%, respectively. In the second scenario also, the proposed method performs better than the others. In addition, the recall, precision, and F1 score metrics of the first scenario are about 5% higher than those of the second scenario, and the accuracy metric is 13.89% higher than that in the second scenario. Meanwhile, the RMSE in the first scenario was 0.02 higher than in the second scenario. Therefore, the comparison of the two scenarios in Table 1 verifies the effectiveness of the selection of the source and target domains. In the following experimental verification, the first scenario is taken as an example.

In Table 1, the results illustrate the advantages of the proposed method over other methods. To make the comparison more intuitive, this study visualizes the results of all methods using UMAP (Banville et al., 2021), and they are shown in Figure 9.

3.5 Ablation experiment

In order to deeply understand the effect of attention, GRU, and pre-training, this study also compares the performance of the proposed method without attention (no attention), without GRU (no GRU), and without pre-training (no pre-training). It is also shown in Table 2.

As can be observed from Table 2, the proposed method's accuracy is about 10% more than those of other methods. Specifically, the precision of the proposed method in the drowsy state is 40% higher than that of no pre-training, the recall is more than 20%, and the F1 score is more than 30%. It can also be seen from Table 2 that no pre-training method shows poor recognition performance in the drowsy state. The other three methods all have a pre-training part, and all of them perform better than the no pre-training model in terms of indicators of the drowsy state. Moreover,

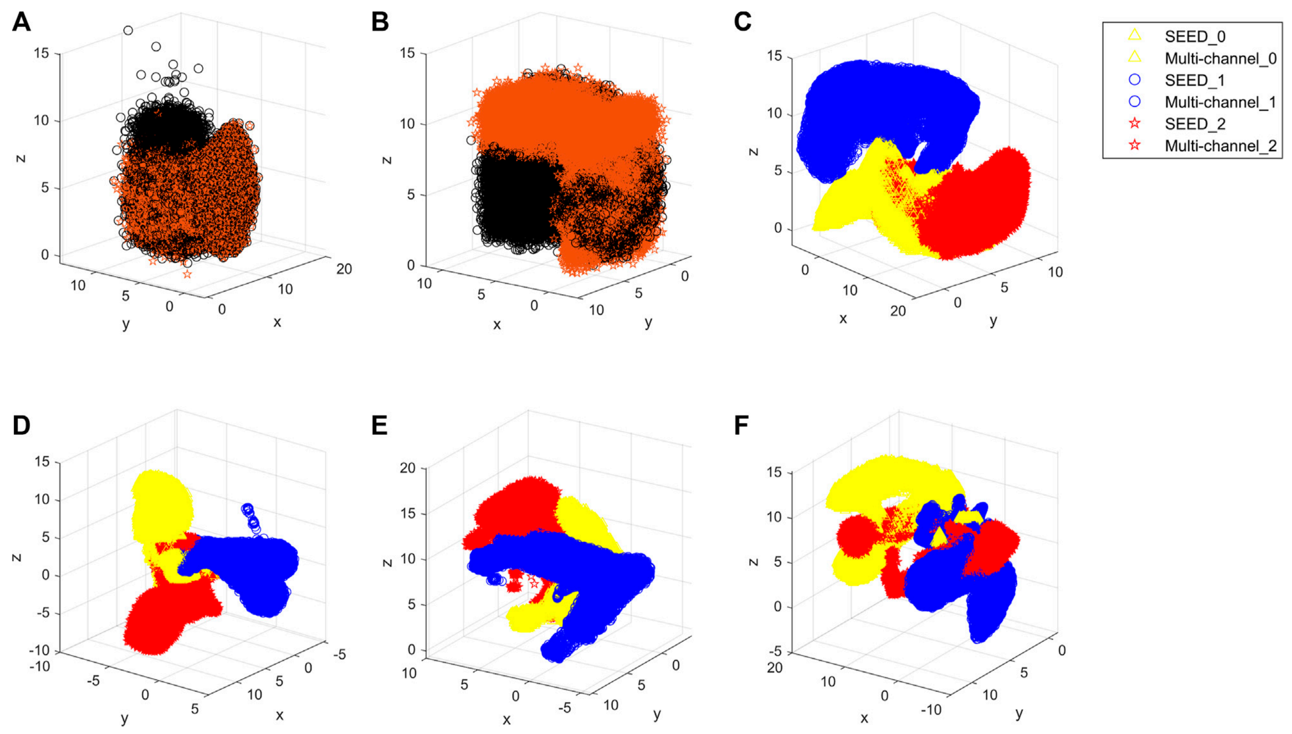


FIGURE 10
Outputs of the different stages. **(A)** Original EEG sample distribution of the two datasets. **(B)** Distribution after pre-training. Specifically, black indicates the SEED dataset, and red indicates the multi-channel dataset of **(A)** and **(B)**. **(C)** Distribution after the domain-specific adaptive step. **(D)** Distribution of no attention. **(E)** Distribution of no GRU. **(F)** Distribution of no pre-training. In **(C)**, **(D)**, **(E)**, and **(F)**, yellow indicates the awake state of the dataset, blue indicates the fatigue state, and red indicates the drowsy state. SEED_0, SEED_1, and SEED_2 indicate awake, fatigue, and drowsy states of the SEED dataset, respectively. Multi-channel_0, multi-channel_1, and multi-channel_2 indicate the awake, fatigue, and drowsy states of the multi-channel dataset, respectively.

TABLE 2 Cross-dataset fatigue detection results.

		Proposed method	No attention	No GRU	No pre-training
Accuracy (%)		59.10	49.56	44.45	46.74
Precision (%)	Awake	77.25	92.50	81.07	47.13
	Fatigue	17.46	20.30	17.81	46.67
	Drowsy	48.79	9.32	20.45	0
Recall (%)	Awake	73.71	57.76	52.44	23.57
	Fatigue	35.72	90.53	76.55	87.29
	Drowsy	25.00	0.24	1.13	0
F1 score	Awake	75.44	71.11	63.68	31.42
	Fatigue	23.45	33.17	28.89	60.82
	Drowsy	33.06	0.46	2.14	0
RMSE		0.27	0.27	0.35	0.27

it is of note that although a certain module is removed, the proposed method is still better than the random value.

In order to intuitively show how the proposed method reduces the distribution discrepancies between the domains, this study exhibits the outputs of the different stages *via* UMAP. Figures 10A–C show the distributions of original EEG samples, distributions after pre-training, and distributions after domain-specific adaptation, respectively. The distributions of the no attention, no GRU, and no pre-training are shown in Figures 10D–F, respectively. As can be seen from Figure 10B, the raw

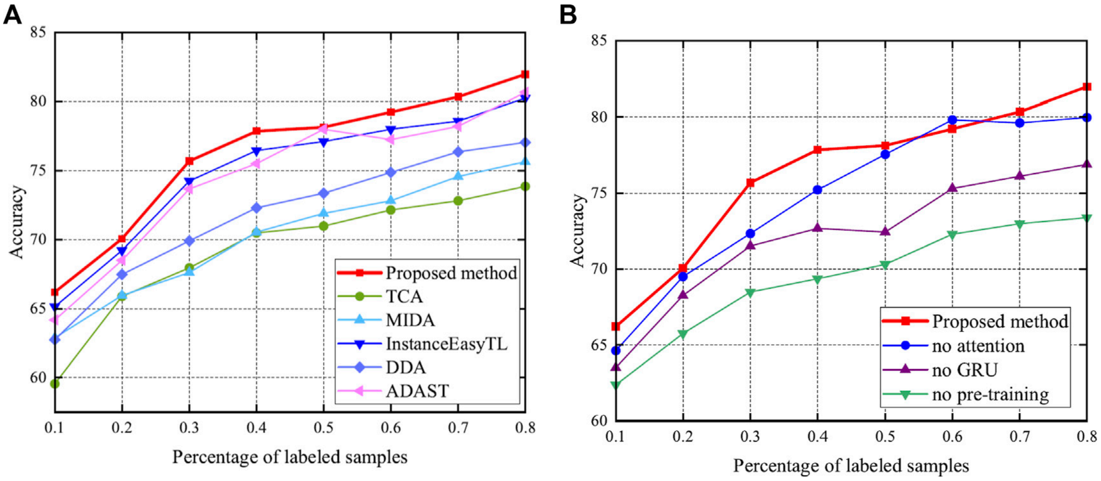


FIGURE 11
Accuracy after adding labels. Specifically, bold red indicates the accuracy of the proposed method. **(A)** Results compared with methods of Section 3.4. **(B)** Results compared with methods of Section 3.5.

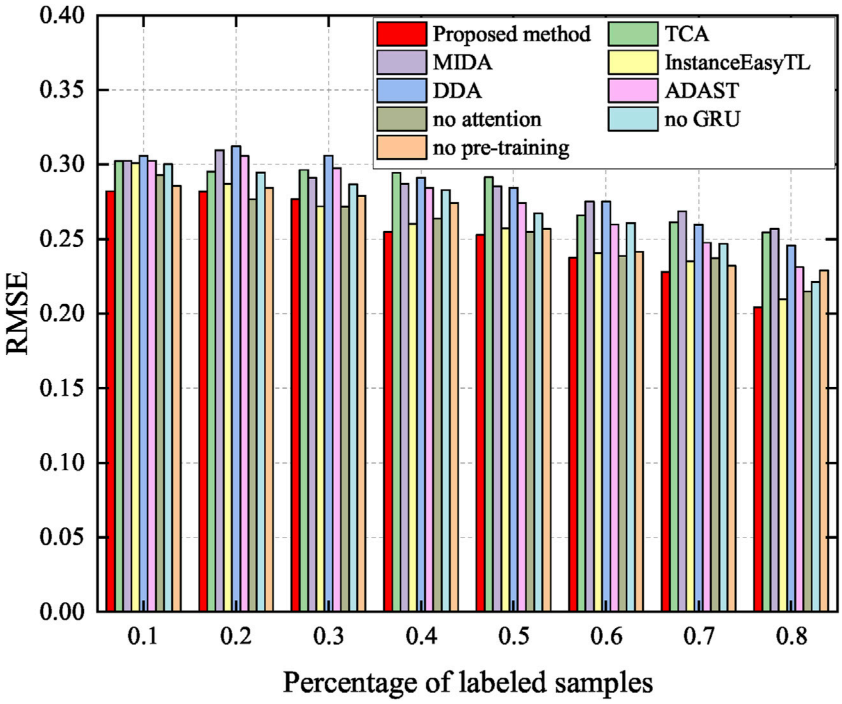


FIGURE 12
RMSE after adding labels. Specifically, red indicates the accuracy of the proposed method, which achieves better performance.

EEG data from the source and target domains are gathered into two groups by pre-training, which demonstrates the data distribution discrepancy between the source and target domains. Figure 10C proves that the proposed method reduces the difference at the domain level. It is obvious from Figures 10D–F that the three methods all have scattered data points that have not been aggregated, and the classification boundary is not obvious.

3.6 Effects of labeled data

Utilization of a small amount of target labels can effectively improve accuracy (Li et al., 2022). Thus, this study deliberately investigates the relationship between the amount of target labels and the method performance. Here, 0.1, 0.2, 0.3, 0.4, 0.5, 0.6, 0.7, and 0.8 of the number of target labels are added to fine-tune the model. The performance of the proposed method is compared to the methods presented in Section 3.4 and Section 3.5. The accuracy and RMSE are shown in Figures 11, 12, respectively.

As shown in Figure 11, once the labeled data are added, the performance of the method significantly improves, as expected (Li et al., 2022). This emphasizes the importance of the labeled data. In particular, the proposed method shows excellent performance in a small number of labeled samples. Meanwhile, it can be seen from Figure 12 that the RMSE of the proposed method is kept at a low level, and with the increase of labeled samples, the RMSE of all methods decreases.

4 Discussion

In terms of fatigue detection methods, fatigue is mainly judged from facial expressions, physiological signals, and questionnaire surveys. The existing fatigue detection methods are almost within-subject and cross-subject fatigue detection. However, they need a large amount of EEG data for training, which is resource-consuming and impractical when faced with a new dataset. It is a worth exploring question to develop a model that can adapt to a variety of datasets.

Therefore, this study proposes a regression method for EEG-based cross-dataset fatigue detection. To validate the performance, this study compares the proposed method with that of other state-of-the-art domain adaptation methods. It can be seen from Table 1 that the proposed method outperforms all other methods, which does not need any labeled target data. Meanwhile, the comparison of the two scenarios in Table 1 verifies the validity of the selection of source and target domains, which means that the dataset with rich information is more suitable for the source domain. In addition, as can be seen from Figure 9A, the proposed method better aggregates each state, while other methods (Figures 9B–F) do not overlap the center of the same state.

For the proposed method, in the pre-training step, different domains should be mapped into the same space to distinguish samples of different datasets to extract specific features for different tasks. As can be seen from Table 2, the model without pre-training performs worse in the drowsy state than the model with pre-training. As can be seen from Figure 10F, the distribution of the model without pre-training is not concentrated in the drowsy state. Pre-trained models have a more aggregated distribution with fewer scattered data points. These validate the results of Table 2 and suggest that pre-training contributes to cross-dataset fatigue detection.

Then, the domain-specific adaptive step makes the multi-source domain and the multi-target domain closer, and the sample is highly aggregated. We can notice that this step can reduce the domain discrepancy at the domain level in the comparison between Figures 10B, C. It shows that it is effective to perform adaption alignment on top of specific features, which can avoid the occurrence of misalignment and learn fatigue-aware fine-grained transfer features (Li et al., 2022).

Since fatigue is a continuously changing sequence rather than several discrete states, the accuracies of no attention and no GRU are lower. We can see from Figures 10D, E that the conditional distribution of source and target domains using no attention and no GRU model matched, and aligned distributions are not well aggregated. As shown in the fatigue state in Figure 10D, there are still scattered points that have not been aggregated. In addition, fatigue and drowsy states are not concentrated in one area, so is the drowsy state in Figure 10E. This may be due to a lack of temporal and spatial information related to fatigue.

In addition, this study studies the effect of labeled samples on the results. We can observe from Figure 11 that the more labeled the data, the better the classification. This further validates the idea of supervised learning. However, considering a weak correlation between the target and source domains, blindly increasing the amount of source data does not improve the accuracy and causes computational burden (Wang Y. et al., 2021). It can also be seen from the results of Figure 11 that with the increase in the number of labeled samples, the performance does not increase monotonously. There is no denying that with the increase in the samples, the performance of the proposed method is clearly improved. At the same time, this also shows that if there are labeled samples in the actual target, then these samples should be used. We choose the unsupervised domain adaptation approach only when the target is completely unmarked.

Although this study proposes a regression method for EEG-based cross-dataset fatigue detection, there are still some limitations. Although the specific experimental design of the two datasets is different, they are all fatigue caused by driving tasks. The model may not perform well in the face of more fatigue datasets, such as those caused by sleep deprivation. Therefore, we will further study how to minimize the differences in fatigue caused by different tasks. In addition, the accuracy of the proposed method is only 59.10%. It is a little low, and part of the reason may be that the fatigue evaluation indexes are not necessarily 100% correct. The use of the behavioral index (RT in this study) to evaluate fatigue needs further development.

5 Conclusion

Since the cross-dataset fatigue detection model can extract general features of fatigue, it does not need to be retrained when facing new datasets. However, no one has studied this problem previously. Therefore, the study proposes a regression method for EEG-based cross-dataset fatigue detection, which mainly includes two steps: pre-training and the domain-specific adaptive step. In the pre-training step, this study designs a pretext task to distinguish data from the source or target domain. In this way, the specific features of different fatigue-induced tasks can be obtained. In the domain-specific adaptive step, this study proposes an EEG-based domain-adaptive fatigue detection network, including a domain-specific feature extractor, domain distribution alignment network, and regression multilayer perceptron. This step focuses on minimizing the data distribution difference between the source and target domains by using MMD. The accuracy and RMSE achieved by the proposed method are 59.10% and 0.27, respectively, which significantly outperforms state-of-the-art domain adaptation methods. In addition, this study also discusses the effect of labeled samples. When the number of labeled samples is 10% of the total number, the accuracy of the proposed model can reach 66.21%. The proposed method can be used for reference in the field of cross-dataset fatigue detection. In the future, we will investigate the EEG-based cross-dataset fatigue detection method due to different fatigue-induced tasks.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary Material; further inquiries can be directed to the corresponding authors.

Author contributions

DY, JY, CL, and PZ conceived and designed the study. DY, CL, and JY organized the database. DY, JY, and PZ drafted the manuscript. DY, PZ, YJ, and XX revised the manuscript. All authors contributed to the article and approved the submitted version.

Funding

This work was sponsored by the Science and Technology Commission of Shanghai Municipality (No. 22xtcx00300) and the Development Fund for Shanghai Talents (No. 2020010).

Acknowledgments

The authors would like to thank PZ and CL for their help with designing this study.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

References

Banville, H., Chehab, O., Hyvärinen, A., Engemann, D.-A., and Gramfort, A. (2021). Uncovering the structure of clinical EEG signals with self-supervised learning. *J. Neural Eng.* 18, 046020. doi:10.1088/1741-2552/abca18

Bulling, A., Ward, J. A., Gellersen, H., and Tröster, G. (2011). Eye movement analysis for activity recognition using electrooculography. *IEEE Trans. Pattern Anal. Mach. Intell.* 33, 741–753. doi:10.1109/TPAMI.2010.86

Cao, J., He, X., Yang, C., Chen, S., Li, Z., and Wang, Z. (2022). Multi-source and multi-representation adaptation for cross-domain electroencephalography emotion recognition. *Front. Psychol.* 12, 809459. doi:10.3389/fpsyg.2021.809459

Cao, Z., Chuang, C.-H., King, J.-K., and Lin, C.-T. (2019). Multi-channel EEG recordings during a sustained-attention driving task. *Sci. Data* 6, 19. doi:10.1038/s41597-019-0027-4

Chen, H., Jin, M., Li, Z., Fan, C., Li, J., and He, H. (2021). MS-MDA: Multisource marginal distribution adaptation for cross-subject and cross-session EEG emotion recognition. *Front. Neurosci.* 15, 778488. doi:10.3389/fnins.2021.778488

Chen, L., Zhang, H., Xiao, J., Nie, L., Shao, J., Liu, W., et al. (2017). "SCA-CNN: Spatial and Channel-wise attention in convolutional networks for image captioning," in IEEE Conference on Computer Vision and Pattern Recognition (CVPR), Honolulu, HI, USA, 21-26 July 2017.

Ding, K. M., Kimura, T., Fukui, K. i., and Numao, M. (2021). "EEG emotion enhancement using task-specific domain adversarial neural network," in International Joint Conference on Neural Networks (IJCNN), Shenzhen, China, 18-22 July 2021.

Du, G., Long, S., Li, C., Wang, Z., and Liu, P. X. (2022). A product fuzzy convolutional network for detecting driving fatigue. *IEEE Trans. Cybern.* 1-14, 1–14. doi:10.1109/tcyb.2021.3123842

Eldele, E., Ragab, M., Chen, Z., Wu, M., Kwoh, C. K., Li, X., et al. (2022). Adast: Attentive cross-domain EEG-based sleep staging framework with iterative self-training. *IEEE Trans. Emerg. Top. Comput. Intell.* 7. 210–221. doi:10.1109/TETCI.2022.3189695

Foong, R., Ang, K. K., Zhang, Z., and Quek, C. (2019). An iterative cross-subject negative-unlabeled learning algorithm for quantifying passive fatigue. *J. Neural Eng.* 16, 056013. doi:10.1088/1741-2552/ab255d

Gao, Z., Li, S., Cai, Q., Dang, W., Yang, Y., Mu, C., et al. (2019). Relative wavelet entropy complex network for improving EEG-based fatigue driving classification. *IEEE Trans. Instrum. Meas.* 68, 2491–2497. doi:10.1109/tim.2018.2865842

Gregor, K., Danihelka, I., Graves, A., Rezende, D. J., and Wierstra, D. (2015). Draw: A recurrent neural network for image generation. *Int. Conf. Mach. Learn.* 37, 1462–1471.

He, H., and Wu, D. (2020). Different set domain adaptation for brain-computer interfaces: A label alignment approach. *IEEE Trans. Neural Sys. Rehabilitation Eng.* 28, 1091–1108. doi:10.1109/TNSRE.2020.2980299

He, Z., Zhong, Y., and Pan, J. (2022). An adversarial discriminative temporal convolutional network for EEG-based cross-domain emotion recognition. *Comput.Bio. Med.* 141, 105048. doi:10.1016/j.compbiomed.2021.105048

Hu, S., and Zheng, G. (2009). Driver drowsiness detection with eyelid related parameters by Support Vector Machine. *Expert Syst. Appl.* 36, 7651–7658. doi:10.1016/j.eswa.2008.09.030

Huang, K. C., Huang, T. Y., Chuang, C. H., King, J. T., Wang, Y. K., Lin, C. T., et al. (2016). An EEG-based fatigue detection and mitigation system. *Int. J. neural Syst.* 26, 1650018. doi:10.1142/S0129065716500180

Iyer, A., Das, S. S., Teotia, R., Maheshwari, S., and Sharma, R. R. (2023). CNN and LSTM based ensemble learning for human emotion recognition using EEG recordings. *Multimed. Tools Appl.* 82, 4883–4896. doi:10.1007/s11042-022-12310-7

Kong, W., Jiang, B., Fan, Q., Zhu, L., and Wei, X. (2018). Personal identification based on brain networks of EEG signals. *J. Appl. Math. Comput. Sci.* 28, 745–757. doi:10.2478/amcs-2018-0057

Kostas, D., Aroca-Ouellette, S., and Rudzicz, F. (2021). Bendr: Using transformers and a contrastive self-supervised learning task to learn from massive amounts of EEG data. *Front. Hum. Neurosci.* 15, 653659. doi:10.3389/fnhum.2021.653659

Krigolson, O. E., Hammerstrom, M. R., Abimbola, W., Trska, R., Wright, B. W., Hecker, K. G., et al. (2021). Using muse: Rapid mobile assessment of brain performance. *Front. Neurosci.* 15, 634147. doi:10.3389/fnins.2021.634147

Li, Z., Zhu, E., Jin, M., Fan, C., He, H., Cai, T., et al. (2022). Dynamic domain adaptation for class-aware cross-subject and cross-session EEG emotion recognition. *IEEE J. Biomed. Health Inf.* 26, 5964–5973. doi:10.1109/JBHI.2022.3210158

Liqiang, Y., Li, R., Cui, J., and Mohammed, S. Y. (2022). Entropy-guided robust feature domain adaptation for eeg-based cross-dataset drowsiness recognition. [Preprint]. Available at SSRN: https://ssrn.com/abstract=4274381.

Liu, W., Qian, J., Yao, Z., Jiao, X., and Pan, J. (2019a). Convolutional two-stream network using multi-facial feature fusion for driver fatigue detection. *Future Internet* 11, 115. doi:10.3390/fi11050115

Liu, Y., Lan, Z., Cui, J., Sourina, O., and Müller-Wittig, W. (2019b). "EEG-based cross-subject mental fatigue recognition," in International Conference on Cyberworlds (CW), Kyoto, Japan, 02-04 October 2019.

Liu, Y., Lan, Z., Cui, J., Sourina, O., and Müller-Wittig, W. (2020). Inter-subject transfer learning for EEG-based mental fatigue recognition. *Adv. Eng. Inf.* 46, 101157. doi:10.1016/j.aei.2020.101157

Mnih, V., Heess, N., Graves, A., and Kavukcuoglu, K. (2014). Recurrent Models of Visual Attention advances in neural information processing systems. *Neural Inf. Process. Syst. (NIPS)* 27.

Murugan, S., Selvaraj, J., and Sahayadhas, A. (2020). Detection and analysis: Driver state with electrocardiogram (ECG). *Phy. Eng. Sci. Med.* 43, 525–537. doi:10.1007/s13246-020-00853-8

Ni, T., Ni, Y., Xue, J., and Wang, S. (2021). A domain adaptation sparse representation classifier for cross-domain electroencephalogram-based emotion classification. *Front. Psychol.* 12, 721266. doi:10.3389/fpsyg.2021.721266

Pan, S. J., Tsang, I. W., Kwok, J. T., and Yang, Q. (2011). Domain adaptation via transfer component analysis. *IEEE Trans. Neural Netw.* 22, 199–210. doi:10.1109/TNN.2010.2091281

Peng, Y., Wong, C. M., Wang, Z., Rosa, A. C., Wang, H. T., and Wan, F. (2021). Fatigue detection in SSVEP-BCIs based on wavelet entropy of EEG. *IEEE Access* 9, 114905–114913. doi:10.1109/access.2021.3100478

Qi, M. S., Yang, W. J., Xie, P., Liu, Z. J., Zhang, Y. Y., and Cheng, S. C. (2018). *Chinese automation congress (CAC).* Piscataway: IEEE.

Qin, X., Yang, P., Shen, Y., Li, M., Hu, J., and Yun, J. (2020). International symposium on computer. Consumer and control (IS3C).

Sharma, R., Sahu, S. S., Upadhyay, A., Sharma, R. R., and Sahoo, A. K. (2021). "Sleep stages classification using DWT and dispersion entropy applied on EEG signals," in *Analysis of medical modalities for improved diagnosis in modern healthcare* (Boca Raton: CRC Press), 344.

Smith, M. R., Coutts, A. J., Merlini, M., Deprez, D., Lenoir, M., and Marcora, S. M. (2016). Mental fatigue impairs soccer-specific physical and technical performance. *Med. Sci. Sports Exerc.* 48, 267–276. doi:10.1249/MSS.0000000000000762

Tao, J., and Dan, Y. (2021). Multi-source Co-adaptation for EEG-based emotion recognition by mining correlation information. *Front. Neurosci.* 15, 677106. doi:10.3389/fnins.2021.677106

Wang, H., Xu, L., Bezerianos, A., Chen, C., and Zhang, Z. (2021a). Linking attention-based multiscale CNN with dynamical GCN for driving fatigue detection. *IEEE Trans. Instrum. Meas.* 70, 1–11. doi:10.1109/tim.2020.3047502

Wang, Y., Liu, J., Ruan, Q., Wang, S., and Wang, C. (2021b). Cross-subject EEG emotion classification based on few-label adversarial domain adaption. *Expert sys. app.* 185, 115581. doi:10.1016/j.eswa.2021.115581

Wei, C. S., Lin, Y. P., Wang, Y. T., Lin, C. T., and Jung, T. P. (2018). A subject-transfer framework for obviating inter- and intra-subject variability in EEG-based drowsiness detection. *NeuroImage* 174, 407–419. doi:10.1016/j.neuroimage.2018.03.032

Woo, S., Park, J., Lee, J.-Y., and Kweon, I. S. (2018). "Cbam: Convolutional block attention module," in Computer Vision – ECCV, Munich, Germany, September 8-14, 2018.

Yang, Y., Gao, Z., Li, Y., Cai, Q., Marwan, N., and Kurths, J. (2021b). A complex network-based broad learning system for detecting driver fatigue from EEG signals. *IEEE Trans. Sys., Man. Cyb. Sys.* 51, 5800–5808. doi:10.1109/tsmc.2019.2956022

Yang, Y., Gao, Z., Li, Y., and Wang, H. (2021a). A CNN identified by reinforcement learning-based optimization framework for EEG-based state evaluation. *J. Neural Eng.* 18, 046059. doi:10.1088/1741-2552/abfa71

Ye, J., Xiao, Q., Wang, J., Zhang, H., Deng, J., and Lin, Y. (2022). CoSleep: A multi-view representation learning framework for self-supervised learning of sleep stage classification. *IEEE Sig. Pro. Lett.* 29, 189–193. doi:10.1109/lsp.2021.3130826

Zeng, H., Li, X., Borghini, G., Zhao, Y., Aricò, P., Di Flumeri, G., et al. (2021). An EEG-based transfer learning method for cross-subject fatigue mental state prediction. *Sensors* 21, 2369. doi:10.3390/s21072369

Zeng, H., Zhang, J., Zakaria, W., Babiloni, F., Gianluca, B., Li, X., et al. (2020). InstanceEasyTL: An improved transfer-learning method for EEG-based cross-subject fatigue detection. *Sensors* 20, 7251. doi:10.3390/s20247251

Zheng, W.-L., and Lu, B.-L. (2017). A multimodal approach to estimating vigilance using EEG and forehead EOG. *J. Neural Eng.* 14, 026017. doi:10.1088/1741-2552/aa5a98

frontiers | Frontiers in Neuroscience

TYPE Original Research
PUBLISHED 26 June 2023
DOI 10.3389/fnins.2023.1203514

OPEN ACCESS

EDITED BY
Sławomir Kujawski,
Ludwik Rydygier Collegium Medicum in Bydgoszcz Nicolaus Copernicus University in Toruń, Poland

REVIEWED BY
Francisco Westermeier,
FH Joanneum, Austria
Diogo Carneiro,
University of Coimbra, Portugal

*CORRESPONDENCE
Suzanne D. Vernon
✉ sdvernon@batemanhornecenter.org

RECEIVED 10 April 2023
ACCEPTED 19 May 2023
PUBLISHED 26 June 2023

CITATION
Day H, Yellman B, Hammer S, Rond C, Bell J, Abbaszadeh S, Stoddard G, Unutmaz D, Bateman L and Vernon SD (2023) Cognitive impairment in post-acute sequelae of COVID-19 and short duration myalgic encephalomyelitis patients is mediated by orthostatic hemodynamic changes. *Front. Neurosci.* 17:1203514. doi: 10.3389/fnins.2023.1203514

Cognitive impairment in post-acute sequelae of COVID-19 and short duration myalgic encephalomyelitis patients is mediated by orthostatic hemodynamic changes

Heather Day[1], Brayden Yellman[2], Sarah Hammer[2], Candace Rond[2], Jennifer Bell[2], Saeed Abbaszadeh[2], Greg Stoddard[1], Derya Unutmaz[3], Lucinda Bateman[2] and Suzanne D. Vernon[2]*

[1]School of Medicine, The University of Utah, Salt Lake City, UT, United States, [2]Bateman Horne Center, Salt Lake City, UT, United States, [3]Jackson Laboratory for Genomic Medicine, School of Medicine, University of Connecticut, Farmington, CT, United States

Introduction: Cognitive impairment is experienced by people with myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) and post-acute sequelae of COVID-19 (PASC). Patients report difficulty remembering, concentrating, and making decisions. Our objective was to determine whether orthostatic hemodynamic changes were causally linked to cognitive impairment in these diseases.

Methods: This prospective, observational cohort study enrolled PASC, ME/CFS, and healthy controls. All participants underwent clinical evaluation and assessment that included brief cognitive testing before and after an orthostatic challenge. Cognitive testing measured cognitive efficiency which is defined as the speed and accuracy of subject's total correct responses per minute. General linear mixed models were used to analyze hemodynamics and cognitive efficiency during the orthostatic challenge. Additionally, mediation analysis was used to determine if hemodynamic instability induced during the orthostatic challenge mediated the relationship between disease status and cognitive impairment.

Results: Of the 276 participants enrolled, 256 were included in this study (34 PASC, 71 <4 year duration ME/CFS, 69 >10 year ME/CFS duration, and 82 healthy controls). Compared to healthy controls, the disease cohorts had significantly lower cognitive efficiency scores immediately following the orthostatic challenge. Cognitive efficiency remained low for the >10 year ME/CFS 2 and 7 days after orthostatic challenge. Narrow pulse pressure less than 25% of systolic pressure occurred at 4 and 5min into the orthostatic challenge for the PASC and ME/CFS cohorts, respectively. Abnormally narrow pulse pressure was associated with slowed information processing in PASC patients compared to healthy controls (−1.5, $p = 0.04$). Furthermore, increased heart rate during the orthostatic challenge was associated with a decreased procedural reaction time in PASC and <4 year ME/CFS patients who were 40 to 65 years of age.

Discussion: For PASC patients, both their disease state and hemodynamic changes during orthostatic challenge were associated with slower reaction time and decreased response accuracy during cognitive testing. Reduced cognitive efficiency in <4 year ME/CFS patients was associated with higher heart rate in response to orthostatic stress. Hemodynamic changes did not correlate with cognitive impairment for >10 year ME/CFS patients, but cognitive impairment remained. These findings underscore the need for early diagnosis to mitigate direct hemodynamic and other physiological effects on symptoms of cognitive impairment.

KEYWORDS

post-acute sequelae of SARS-CoV-2 (PASC), long COVID, ME/CFS, myalgic encephalomyelitis, cognitive impairment, orthostatic hemodynamic changes

Introduction

Evidence that myalgic encephalomyelitis (ME/CFS) is a prototypical post-infectious disease dates to an epidemic in Iceland in 1949 that simulated poliomyelitis and many had still not recovered 6 years later (Sigurdsson et al., 1950; Sigurdsson, 1956). There is a recognition of the chronic consequences of acute infection, such as chronic arthritis from acute infection with chikungunya virus or long-term, neurological changes from West Nile virus (Baldwin et al., 2016; Pathak et al., 2019; Clé et al., 2020). Now with more than 750 million confirmed cases of COVID-19 worldwide [WHO Coronavirus (COVID-19) dashboard][1] research on post-acute sequelae of COVID-19 (PASC) has intensified. It is estimated at least 10% of people that had COVID-19 will continue to experience symptoms for more than 3 months (Centers for Disease Control and Prevention)[2]. Although there are unique signs and symptoms in response to any acute infection, there is also a common, stereotyped post-infectious syndrome characterized by fatigue that impairs physical function, post-exertional malaise, unrefreshing sleep, orthostatic intolerance, and cognitive impairment (Hickie et al., 2006). ME/CFS and many with PASC share these stereotyped post-infectious symptoms.

Dysautonomia occurs when the nerves that regulate nonvoluntary functions, such as heart rate and blood pressure, malfunction (Karemaker, 2017). Orthostatic intolerance (OI) describes the signs and symptoms that occur in upright posture and improve when supine and may include an inability to stay upright due to dizziness and fainting, fast or slow heartbeat, inappropriate drop or rise of blood pressure, and cognitive problems, to name a few (Rowe, 2002). OI is included in the diagnostic criteria for ME/CFS (Institute of Medicine, 2015) and is now widely recognized as one of the primary clinical manifestations of PASC (Jammoul et al., 2023). Cognitive impairment that results in difficulty remembering, concentrating, and making decisions is prevalent in both ME/CFS and PASC (Komaroff and Bateman, 2021; Komaroff and Lipkin, 2021). Recently, we demonstrated that when ME/CFS and PASC patients underwent an orthostatic challenge, cognitive reaction time significantly worsened in both ME/CFS and PASC patients (Vernon et al., 2022).

This led us to hypothesize that orthostatic intolerance and the hemodynamic changes that occur during orthostatic challenge may be causing or contributing to cognitive impairment in both ME/CFS and PASC. To test this, a brief cognitive assessment was done before and immediately after a passive stand test and then 2 and 7 days later. Mediation analysis was used to identify and attempt to explain the extent to which disease status and hemodynamic instability explain impaired cognition.

Materials and methods

PASC cohort

Between April and September 2021, we enrolled PASC patients who were 18 to 65 years old with symptoms of fatigue, exercise intolerance or other unwellness that persisted for at least 3 months and that the participant, or their doctor thought were related to COVID-19. Other inclusion criteria were good general health prior to sickness with COVID-19 and evidence of SARS-CoV-2 by PCR or antigen (provided by the subject or their provider) or presence of IgG antibodies to SARS-CoV-2 prior to receiving COVID-19 vaccination. Exclusion criteria included, (1) hospitalized for >72 h for COVID-19, (2) documented organ damage as a result of COVID-19 infection, (3) other active and untreated disease processes that explain the major symptoms of fatigue, sleep disturbance, pain, and cognitive dysfunction, (4) untreated primary sleep disorders, (5) rheumatological disorders, (6) immune disorders, (7) neurological disorders, (8) other infectious disease, (9) psychiatric disorders that alter perception of reality or ability to communicate clearly or impair physical health and function, and (10) laboratory testing or imaging are available that support an alternate exclusionary diagnosis.

ME/CFS cohorts

Beginning in January 2018, we enrolled ME/CFS patients who had been sick for <4 years or sick for >10 years. No ME/CFS patients with duration ≥4 years and ≤ 10 years were enrolled in order to have clear distinctions between short and long duration of illness with ME/CFS. All participants were 18 to 65 years old at the time of enrollment. ME/CFS diagnosis according to the Institute of Medicine clinical diagnostic criteria and disease duration of <4 years were confirmed during clinical differential diagnosis and thorough medical work up (Institute of Medicine, 2015). Additional inclusion criteria required, (1) a substantial reduction or impairment in the ability to engage in

---

[1] https://covid19.who.int/

[2] https://www.cdc.gov/nchs/pressroom/nchs_press_releases/2022/20220622.htm

pre-illness levels of occupational, educational, social, or personal activities that persists for more than 6 months and less than 4 years and is accompanied by fatigue, which is often profound, is of new or definite onset (not lifelong), is not the result of ongoing excessive exertion, and is not substantially alleviated by rest, and (2) post-exertional malaise. Exclusionary criteria for the <4 year ME/CFS cohort were, (1) morbid obesity BMI > 40, (2) other active and untreated disease processes that explain most of the major symptoms of fatigue, sleep disturbance, pain, and cognitive dysfunction, (3) untreated primary sleep disorders, (4) rheumatological disorders, (5) immune disorders, (6) neurological disorders, (7) infectious diseases, (8) psychiatric disorders that alter perception of reality or ability to communicate clearly or impair physical health and function, (9) laboratory testing or imaging are available that support an alternate exclusionary diagnosis, and (10) treatment with short-term (less than 2 weeks) antiviral or antibiotic medication within the past 30 days.

For the >10 year ME/CFS cohort, disease duration of >10 year and clinical criteria was confirmed to meet the Institute of Medicine criteria for ME/CFS during clinical evaluation and medical history review (Institute of Medicine, 2015). Other than disease duration, inclusion and exclusion criteria were the same as for <4 year ME/CFS cohort.

Healthy control cohort

Healthy control participants were also between 18 to 65 years of age and in general good health. Enrollment began in 2018 and subjects were selected to match the <4 year ME/CFS cohort by age (within 5 years), race, and sex (~2:1 female to male ratio). Exclusion criteria for healthy controls included, (1) a diagnosis or history of ME/CFS, (2) morbid obesity BMI > 40, (3) treatment with short-term (less than 2 weeks) antiviral or antibiotic medication within the past 30 days or (4) treatment long-term (longer than 2 weeks) antiviral medication or immunomodulatory medications within the past 6 months.

Approval was received before enrolling any subjects in the study (The Jackson Laboratory Institutional Review Board, 17-JGM-13). All participants were educated about the study prior to enrollment and signed all appropriate informed consent documents. Research staff followed Good Clinical Practices (GCP) guidelines to ensure subject safety and privacy.

Cognitive testing

Upon arrival at the Bateman Horne Center, participants downloaded the Defense Automated Neurobehavioral Assessment (DANA) Brain Vital app to their smartphones (Lathan et al., 2013). DANA Brain Vital is a test that includes three reaction time and information processing measurements: simple reaction time (SRT), procedural reaction time (PRT), and sustained attention or Go-No-Go (GNG) (Resnick and Lathan, 2016). The test results are reported as cognitive efficiency calculated accuracy x speed x 60,000. SRT is a simple reaction time task in which the user taps an orange target symbol as soon as it appears on the screen. PRT incorporates choice by having the user differentiate between two sets of characters: a 2, 3, 4, or 5 appears on the screen and the user taps one of two buttons [2 or 3] or [4 or 5]. GNG is a forced choice measure of reaction time where either a gray foe or green friend appears on the screen. The user is instructed to tap the screen only when the gray foe appears. Participants completed DANA Brain Vital just before then immediately after the orthostatic challenge and again at home 2 and 7 days after the orthostatic challenge.

Orthostatic challenge

The 10-min NASA Lean Test (NLT) is a standardized passive stand test and was used as the orthostatic challenge in this study (Lee et al., 2020). Briefly, participants rested supine on an exam table for 10 min. Baseline blood pressure (BP) and heart rate (HR) were measured twice during the last 2 min of the supine rest. Participants then stood with only their shoulder blades touching the wall. Their heels were positioned 6–8 inches from the wall. Systolic BP (SBP), diastolic BP (DBP), and HR were recorded every minute during the 10-min NLT. Pulse pressure (PP) was calculated according to the consensus equation: PP = SBP − DBP. Peripheral perfusion was roughly estimated using PP/SBP, defined as abnormal PP/SBP less than 25% (Homan et al., 2022).

Data analysis

To estimate the effect between disease status and cognition after the NLT, we ran three different general linear models comparing baseline measurements to the three time points (immediately post-NLT, 2 and 7 days post NLT). A general linear mixed model with time, group, and time x group interaction as fixed effects and subject ID as the random effect, was used to compare the post-fit marginal estimates of the average effect (5.5 min) and final effect (10 min) the NLT had on hemodynamic variables for the four cohorts. Both a random intercept and random slope across time was specified for each participant. In this model, time (minutes) was a continuous variable and analysis of covariance (ANCOVA) was used to control for any differences between the baseline hemodynamic measurements among the four cohorts. The above models were controlled for age, sex, ethnicity, race, and BMI.

Mediation analysis

The change in hemodynamic variables after completing the NLT were tested as potential mediators in the relationship between disease state and reduction in cognitive efficiency scores. Specifically, we used the change in PP and HR as the mediators and only looked at the immediate post-NLT change in cognitive efficiency scores. Our mediation models were examples of partial mediation. In our mediation analysis, we first considered the total effect between disease status and cognitive performance through simple linear regression. Second, again using simple linear regression, we evaluated the effect between disease status and orthostatic variables (HR and PP), which showed a significant effect. Third, we tested the effect of the orthostatic variables on cognitive performance. This was done using a regression model with both disease status and the change in HR/PP with the change in cognitive performance after the orthostatic challenge as our dependent variable. Lastly, we estimated causal mediation through bootstrapping (a nonparametric resampling method that allows for non-normal sampling distribution) using the mediation package in

TABLE 1 Cohort characteristics.

	PASC	ME/CFS		Healthy	*p* value
		<4 years	>10 years		
	N =34	*N* =71	*N* =69	*N* =82	
Age, years (±SD)	43 (±10.1)	39 (±13.2)	46 (±12.4)	40.0 (±13.3)	0.009
Sex					0.115
Female	29 (85%)	52 (73%)	50 (72%)	52 (63%)	
Male	5 (15%)	19 (27%)	19 (28%)	30 (37%)	
BMI	27.8 (±5.7)	25 (±5.4)	27.4 (±5.4)	26.3 (±5.3)	0.04
Ethnicity					0.1092
Hispanic	2 (6%)	4 (6%)	0 (0%)	1 (1%)	
Non-Hispanic	32 (94%)	65 (92%)	64 (93%)	78 (95%)	
Unknown	0 (0%)	1 (1%)	0 (0%)	0 (0%)	
Not reported	0 (0%)	1 (1%)	5 (7%)	3 (4%)	
Race					0.339
White	33 (97%)	69 (97%)	66 (96%)	77 (94%)	
Other	1 (3%)	0 (0%)	3 (4%)	2 (2%)	
Not reported	0 (0%)	2 (3%)	0 (0%)	3 (4%)	
Disease duration					
<1 year	28 (82%)	8 (11%)	0 (0%)	–	
<2 years	6 (18%)	21 (30%)	0 (0%)	–	
2–3 years	0 (0%)	25 (35%)	0 (0%)	–	
3–4 years	0 (0%)	17 (24%)	0 (0%)	–	
>10 years	0 (0%)	0 (0%)	69 (100%)	–	

RStudio to compare the direct and indirect effects. The mediation models were adjusted or stratified for age, sex, time since diagnosis, and BMI due to their impact on the hemodynamic variables and cognition. We specifically considered 2 different models: (1) The mediating effect of change in HR and PP on the relationship between disease state and change in cognitive scores, when controlling for age, sex, and BMI and, (2) The mediating effect of change in HR and PP on the relationship between disease state and change in cognitive scores, when controlling for sex, BMI, and time since diagnosis, while additionally stratifying by age (<40 and ≥ 40). Less than 40 and ≥ 40 years was chosen because of similar distributions in each cohort (<40 group included 45 HCs, 15 PASC, 39 < 4 year ME/CFS and 23 > 10 year ME/CFS and the ≥40 group included 37 HCs, 19 PASC, 32 < 4 year ME/CFS and 42 > 10 year ME/CFS). All analyses were performed using RStudio (RStudio Team, 2020) with a significance level of $p < 0.05$.

Missing and outlier data

Participants that were unable to finish the 10-min NLT or unable to complete cognitive testing after the NLT because of severe symptoms (e.g., fainting) were categorized as missing not at random. To account for missing hemodynamic data, we imputed the missing values by carrying forward the last recorded measurement. This method assumes their hemodynamic variables would not have changed if they had remained in the NLT and as a result, estimations are likely a lower bound on their individual treatment effect. To address the missing post-NLT cognitive measurements, we replaced the missing cognitive scores with the mean cognitive scores of those in the same cohort that had similar HR (+/− 5 bpm) at the time they stopped the NLT. Cognitive scores missing at baseline, 2 days and 7 days following the orthostatic challenge were assumed to be missing completely at random and were dropped from the analyses. Additionally, missing BMI, age, and sex measurements were assumed to be missing completely at random amongst the subjects and were also excluded from our final analyses. Outliers for cognitive scores were defined as being outside 4 standard deviations (SD) from the mean scores. There were 4 subjects with cognitive scores outside the −/+ 4 SD outlier thresholds. These outlier cognitive scores were replaced with cognitive scores minimum or maximum value at the +/− 4 SD threshold.

Results

A total of 276 subjects were enrolled in the study (35 PASC, 75 < 4 year ME/CFS, 72 > 10 year ME/CFS, and 94 healthy controls). Twenty participants were excluded because they were missing their baseline DANA Brain Vital results or BMI measurements, resulting in 256 participants (34 PASC, 71 < 4 year ME/CFS, 69 > 10 year ME/CFS, and 82 healthy controls). Table 1 shows the demographics and clinical characteristics of the 256 participants included in the analyses.

Twenty-six (10.2%) participants were unable to finish the NLT and 11 (4.3%) participants were unable to take the DANA Brain Vital

TABLE 2 Number of participants that dropped out at a specific time during the NLT.

Minute of NLT	Number of participants that dropped out				Reason for dropping out
	PASC	<4 ME/ CFS	>10 ME/ CFS	HC	
1 min	0	0	0	0	
2 min	0	1	0	0	Fainted
3 min	0	0	0	3	Light headache, lightheaded, fainted
4 min	0	0	0	0	
5 min	0	0	0	2	Dizziness, fainted
6 min	0	0	0	2	Dizziness, fainted
7 min	2	2	0	0	Dizziness, fainted
8 min	1	2	4	0	Nausea, lightheaded, feeling faint
9 min	0	1	3	0	Fainted
10 min	0	1	2	0	Feeling shaky, lightheaded
Total	3	7	9	7	

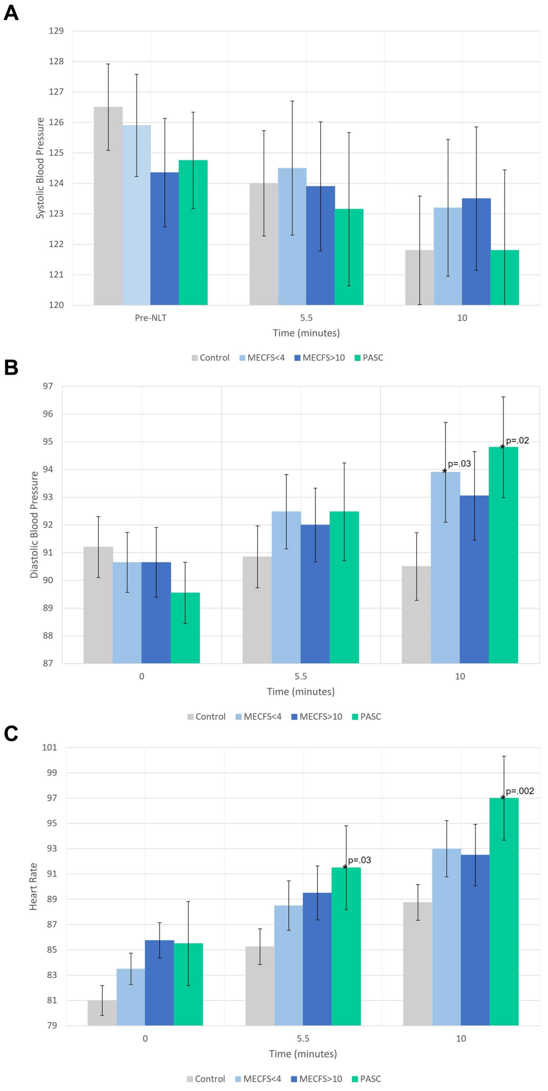


FIGURE 1
A comparison of the average effect at 5.5min and the final effect at 10min during the NLT on blood pressure and heart rate. In **(A)** SBP is within normal range for all cohorts. **(B)** Shows DBP increasing during the NLT for PASC, <4 year and >10 year ME/CFS cohorts and decreasing during the NLT for the healthy control cohort. **(C)** Shows a significant HR increase for the PASC cohort while the ME/CFS cohorts increased but not significantly more than healthy controls.

immediately after the NLT due to severe symptoms (e.g., fainting). Participants dropped out of the NLT throughout the 10-min testing period (Table 2) and dropout rates were similar among the 4 cohorts (3 PASC (8.8%), 7 <4 year ME/CFS (9.9%), 9 >10 year ME/CFS (13.0%), and 7 healthy controls (8.5%)).

The average effect at 5.5 min and the final effect at 10 min on hemodynamics during the NLT was examined first. There were no significant changes from baseline to 5.5 or 10 min for SBP for any of the disease cohorts compared to the healthy controls (Figure 1A). For both the <4 year ME/CFS and PASC cohorts, DBP was significantly higher than healthy controls at the end of the NLT (Figure 1B). The PASC cohort had significantly higher HR compared to healthy controls at both 5.5 min and at the end of the NLT (Figure 1C).

When pulse pressure is less than 25% of SBP, PP is abnormally low or narrowed (Homan et al., 2022). Figure 2 shows the mean PP per minute of the NLT for each cohort. By 4 min into the NLT, the PP for the PASC and < 4 year ME/CFS cohorts narrowed to 23 and 24%, respectively. The PP continued to narrow with the PP dropping for the PASC cohort to 20 mmHg by the end of the NLT. The PP for the >10 year ME/CFS and healthy control cohorts were similar throughout the NLT and did not drop below 25% of SBP.

The cognitive efficiency scores before and after the NLT are shown in Figure 3. Notably, the disease cohorts had lower cognitive efficiency at baseline. The orthostatic challenge caused significant worsening of cognitive efficiency in all cognitive tests for the three disease cohorts compared to the healthy controls (Figures 3A–C). PASC and < 4 year ME/CFS participants returned to baseline cognitive efficiency levels by Day 2. On Day 7, GNG cognitive efficiency was significantly lower for PASC and > 10 year ME/CFS compared to <4 year ME/CFS and healthy controls (Figure 3C). Yet, the >10 year ME/CFS cohort had significantly lower cognitive efficiency scores compared to healthy controls at all time points for all three reaction time measures of the DANA Brain Vital battery (Figures 3A–C).

Mediation analysis was used to determine if the hemodynamic perturbations that occurred during the NLT were contributing to the decrease in cognitive efficiency (Figure 4A). In our first mediation model, when controlling for age, sex, and BMI, the change in PP in the PASC cohort during the NLT mediated slowed information processing assessed by GNG testing (−1.5, non-parametric bootstrap 95% CI: (−3.7, −0.04), $p = 0.04$) (Figure 4B). With change in PP as a mediator, there was a significant direct effect between the PASC vs. healthy control cohorts and change in cognitive performance (−9.0, non-parametric bootstrap 95% CI: (−15.8, −2.5), $p = 0.01$). (Figure 4B). Elevated HR that occurred during the NLT was not a significant mediator of slowed cognitive efficiency for any of the disease cohorts (data not shown).

The second mediation model stratified the cohorts into two age groups, <40 years and ≥ 40 years. This model found that a change in HR during the NLT was associated with slowed PRT in both the

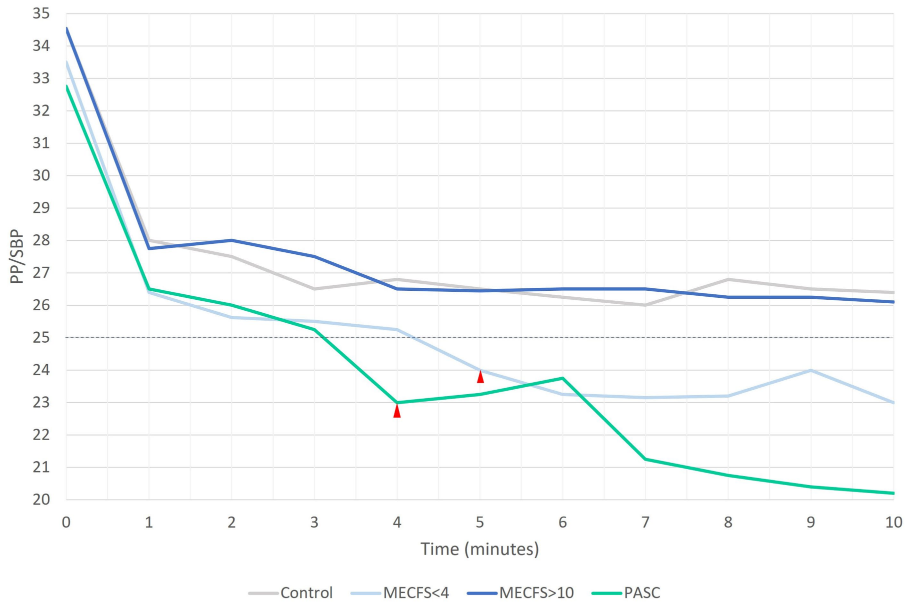


FIGURE 2
A PP that is less than 25% of SBP is inappropriately narrow. Both PASC and <4 year ME/CFS cohorts have narrow PP by 4 and 5min into the NLT, respectively.

PASC (Figure 4C) and < 4 years ME/CFS cohorts (Figure 4D) in the ≥40 years group (PASC: −1.7, non-parametric bootstrap 95% CI: (−4.0.4, −0.04), $p = 0.04$ and ME/CFS <4 years: −2.4, non-parametric bootstrap 95% CI: (−6.2, −0.1), $p = 0.03$). There was a significant direct effect of PASC disease on slowed PRT (Figure 4C) (−10.4, non-parametric bootstrap 95% CI: (−18.0, −2.3), $p = 0.01$). The direct effect of <4 year ME/CFS disease on PRT did not reach significance (Figure 4D) (−14.6, non-parametric bootstrap 95% CI: (−27.5, 1.8), $p = 0.08$). Change in PP was not a significant mediator for disease state and cognitive efficiency for both age groups (data not shown).

Discussion

There is significant clinical overlap of PASC with ME/CFS and because of this, research into the mechanisms of PASC may elucidate mechanisms of ME/CFS (Komaroff and Bateman, 2021; Komaroff and Lipkin, 2021; Choutka et al., 2022; Sukocheva et al., 2022). Recognizing these commonalities, several studies have documented dysautonomia and cognitive impairment in ME/CFS and PASC (Cook et al., 2017; Lee et al., 2020; Davis et al., 2021; Goodman et al., 2021; Wirth et al., 2021; Carmona-Torre et al., 2022; Gaglio et al., 2022; Natelson et al., 2022; Vernon et al., 2022; Walitt and Johnson, 2022; Jammoul et al., 2023). There is a consistent finding of a link between orthostatic intolerance and cerebral hypoperfusion causing corresponding cognitive deficits. This study is one of the first large scale, clinical research, time series analyses to compare short illness duration ME/CFS patients with PASC patients. Since OI is one of the common symptoms experienced by post-infection ME/CFS and PASC patients, we hypothesize that cerebral hypoperfusion that occurs from orthostatic challenge causes decreased cognitive efficiency and slower reaction times.

Orthostatic challenge is a test of venous return, atrial pre-load and ventricular filling. When a person moves from a lying to a standing position, blood pools in the lower extremities causing a drop in blood pressure that rapidly stabilizes in healthy people. PP is normal at 30–40 mmHg and is inappropriately narrow when it is 25% or less of systolic pressure. All cohorts showed an initial drop in PP when moving from lying to standing. Blood pressures stabilized for the remainder of the NLT showing no abnormal narrowing of pulse pressure for either healthy control or the >10 year ME/CFS cohorts. In contrast, PP progressively narrowed for both the PASC and < 4 year ME/CFS cohorts and by 4 and 5 min, PP was less than 25% of SBP. Abnormally narrowed pulse pressures occur in several diseases including heart failure (decreased pump effectiveness), blood loss, (decreased blood volume), aortic stenosis (reduced stroke volume), and cardiac tamponade (decreased filling time) and are due to decreases in systolic pressures while diastolic pressures remain stable (Homan et al., 2022). In contrast, we found that the narrow PP in PASC and < 4 year ME/CFS cohorts was due to a rise in DBP with relatively stable SBP. The mechanistic basis for the elevated DBP and narrowing pulse pressure during the orthostatic challenge is not clear for PASC but we hypothesize it may be a physiologically adaptive mechanism designed to mitigate the physiological stress of hemodynamic challenge. Research on ME/CFS patients indicates hemodynamic changes during orthostatic or exercise challenge results in reduced ventricular filling caused by the peripheral circulatory changes rather than primary cardiopulmonary perturbation (Lee et al., 2020; Singh et al., 2022).

There have been two reports of abnormally narrowed PP due to increased DBP in PASC and ME/CFS patients (van Campen and Visser, 2022; Vernon et al., 2022) but this is the first time narrow PP similar to PASC has been detected in short duration

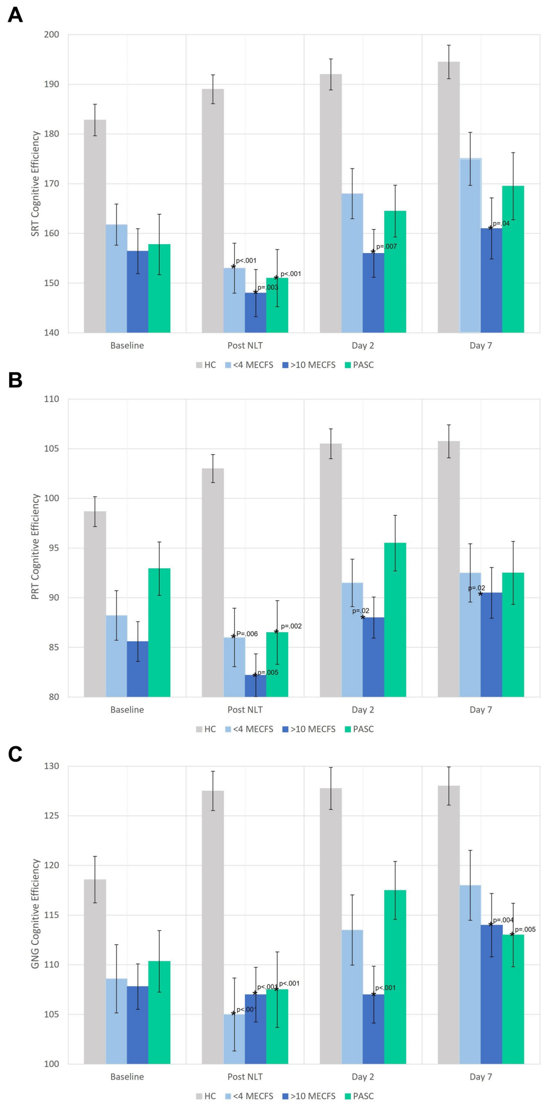


FIGURE 3
(A–C) DANA Brain Vital cognitive efficiency scores before and after the NLT. The disease cohorts had lower baseline cognitive efficiency scores on all three cognitive tests that significantly worsened immediately after the NLT. The >10 year ME/CFS cognitive efficiency scores remained significantly below healthy control cohort scores on days 2 and 7. The healthy control cohort had normal or improved cognitive efficiency scores after the NLT.

of illness ME/CFS patients. This points to the importance of illness duration studying ME/CFS and PASC. Forty one percent (29/71) of the <4 year ME/CFS cohort were sick for <2 years which makes these patients more comparable from a duration of illness perspective to the patients in the PASC cohort. The hemodynamic and cognitive similarities between the <4 year ME/CFS and PASC cohorts supports the post-viral commonalities and overlap between ME/CFS and PASC. The >10 year cohort experienced no significant hemodynamic changes during the NLT. We suspect that it is because these ME/CFS patients have been sick for a long time and experienced compensatory changes in heart rate in blood pressure response to chronic orthostatic stress even though cerebral perfusion remains abnormal (Shan et al., 2020). Nacul et al. proposed a framework for understanding the natural history of ME/CFS and made a strong case that the longer the disease duration, system abnormalities and cell dysfunction become more pronounced (Nacul et al., 2020).

All disease cohorts started with lower baseline cognitive efficiency prior to orthostatic stressor than the healthy controls and experienced further decrements in cognitive efficiency immediately after the NLT. DANA Brain Vital was designed to detect changes in cognitive function in response to trauma, illness, or exposure to environmental stressors (Lathan et al., 2013) and was effective in detecting the change in cognitive efficiency in response to the orthostatic challenge in this study as well. Slowed reaction time is one of the most sensitive measures of impaired cognitive functioning and is one of the cognitive domains with consistent evidence to be impaired in ME/CFS (Institute of Medicine, 2015; Coffman et al., 2018). Reduced cerebral blood flow due to hemodynamic decompensation during orthostatic challenge may explain why cognitive efficiency worsened immediately after the NLT (van Campen et al., 2020; Vernon et al., 2022). Both PASC and < 4 year ME/CFS cohorts returned to their baseline cognitive efficiency levels which were still below that of healthy controls.

The >10 year ME/CFS cohort had the lowest cognitive efficiency scores even though their hemodynamic response was similar to that of healthy controls. Cerebral perfusion is reduced in the ME/CFS patients and is not explained by a drop in blood pressure (van Campen et al., 2020). Chronic cerebral hypoperfusion is associated with neurocognitive disorders and cognitive impairment (Ciacciarelli et al., 2020) and it is possible that just being in an upright posture contributes to intermittent brain hypoperfusion and cognitive impairment. This could explain why the three disease cohorts all had low baseline cognitive efficiency scores; even coming to the clinic to participate in the study was an orthostatic stress. It is possible that the day 2 and 7 cognitive efficiency scores returned to baseline levels because testing was done at home.

Mediation analysis was used to determine the direct and indirect effects of disease state and orthostatic hemodynamic changes on cognitive impairment in PASC and ME/CFS. There was a significant direct effect of PASC on PRT and GNG cognitive efficiency. Neurological sequelae including cognitive impairment are known to occur following a variety of different viral infections (Clé et al., 2020). There was also a significant indirect effect of PP on GNG cognitive efficiency, implicating reduced cerebral blood flow on executive function. The GNG test targets executive functioning, recording speed and accuracy of targets, and omissions and commissions (Resnick and Lathan, 2016). Furthermore, increased HR in the PASC cohort had a significant indirect effect on PRT cognitive efficiency. The PRT test also targets executive functioning along with decision-making capabilities. Executive function includes processes such as working memory, attention, problem solving, and flexible thinking to successfully execute daily activities and goals. There is substantial evidence of neurologic involvement in acute COVID-19 and PASC (Hingorani et al., 2022) but this is one of the first studies to demonstrate the impact of orthostatic hemodynamic change on cognition in PASC.

Interestingly, there was a significant indirect effect of increased HR on lower PRT cognitive efficiency in the <4 year ME/CFS cohort. The direct effect of ME/CFS disease was not significant and notably, there were no significant effects in the mediation models for the

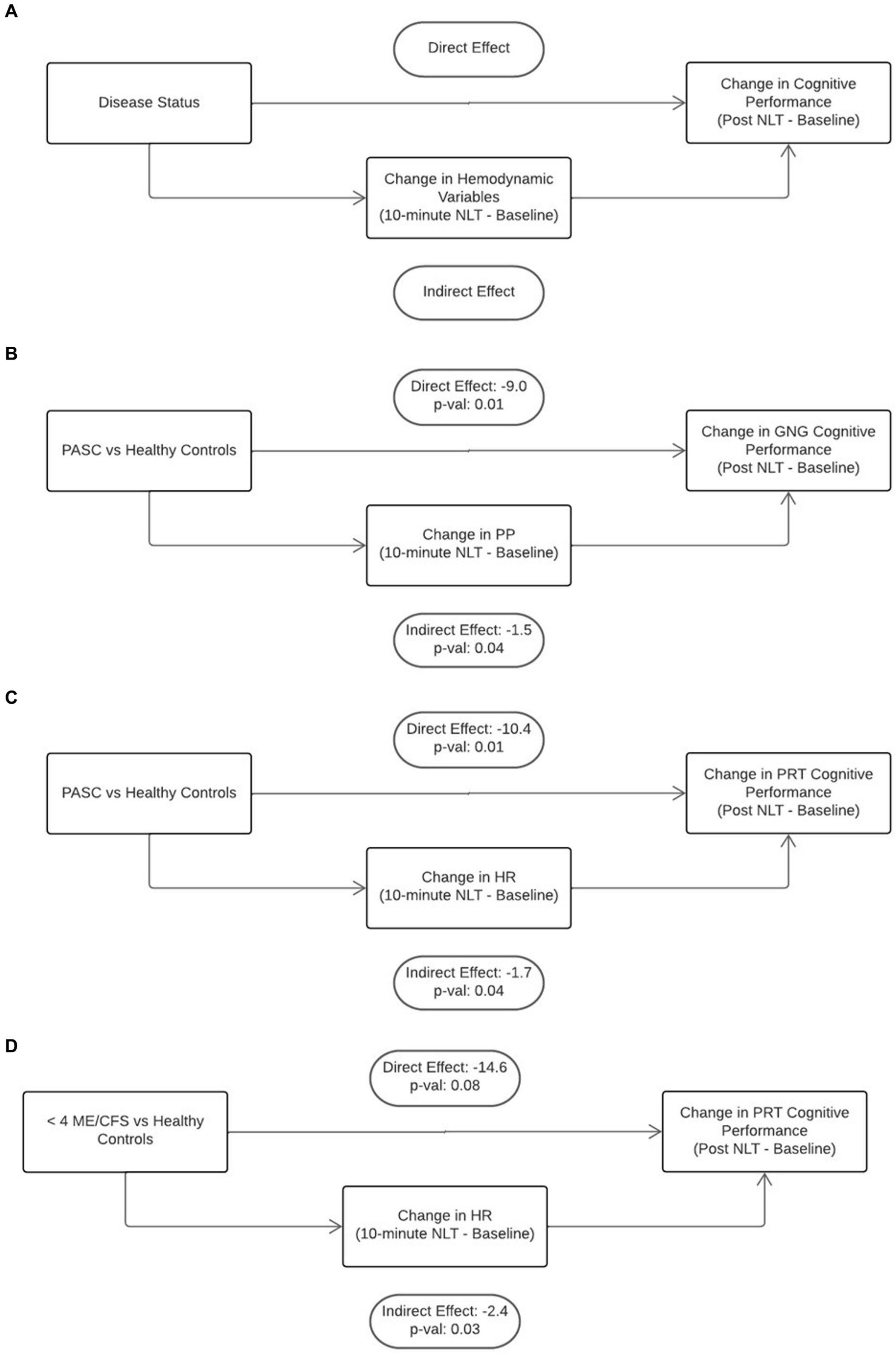


FIGURE 4
Mediation analysis was used to gain insight into the direct effect of disease on cognition and the indirect or mediating effect of orthostatic challenge on cognition **(A)**. There was a significant direct effect of PASC disease state as well as a significant indirect effect of decreased PP and increased HR on poorer cognitive efficiency **(B,C)**. The was a significant indirect effect of increased HR on worsened cognitive efficiency in the <4 year ME/CFS cohort **(D)**.

>10 year ME/CFS cohort. This type of cognitive impairment is not explained by anoxic injury to the brain since the markers of tissue damage seen in other diseases characterized by chronic hypoperfusion have not been detected in ME/CFS (Singhal et al., 2002). It is possible that a cognitive impairment could be explained by oxidative stress from repeated ischemia–reperfusion injury that accompanies orthostatic intolerance and occurs from daily living with ME/CFS (Kell and Pretorius, 2022). This underscores the need for early diagnosis of PASC and ME/CFS to mitigate cognitive impairment and improve quality of life.

The predominant white female study population limits generalizing the results of this study to other nonwhite and other gender populations. The significant differences in age and BMI could affect the results of this study. However, that is not likely as the models controlled for sex, BMI, and time since diagnosis, while additionally stratifying by age (<40 and ≥ 40). The NLT is a point-of-care assessment that uses readily available equipment to monitor blood pressure and pulse oximetry that is easily implemented and analyzed in the clinic. However, the use of these methods is prone to user error and can give inaccurate readings as opposed to accurate and objective invasive blood pressure and heart rate monitoring. Since we used last observation carried forward to account for missing hemodynamic data for the most extreme cases, our estimates are likely an underestimate of the actual hemodynamic effects. The lack of deep hemodynamic data limits our ability to extrapolate these findings to specific pathways and pathophysiology.

In conclusion, being sick with PASC together with the accompanying orthostatic intolerance explained decreased cognitive efficiency that affected executive functioning. Poorer cognitive efficiency in ME/CFS patients sick for <4 years was partially associated with the likely adaptive response of elevated heart rate. It appears that the longer the duration of illness with ME/CFS, the more likely cognition is impaired in response to physiological stressors. Whether the cognitive deficits in executive function are stable, waxing-and-waning, or progressive is not known. Regardless, cognitive impairment affects daily life causing problems in remembering, concentrating and decision making. These findings underscore the need for early diagnosis and treatment of ME/CFS and PASC to improve daily cognitive functioning.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving human participants were reviewed and approved by The Jackson Laboratory Institutional Review Board (protocol 17-JGM-13). The patients/participants provided their written informed consent to participate in this study.

Author contributions

SV, LB, and DU conceptualized the study design, supervised study implementation and assessments, and supervised the data collection. HD and GS were responsible for statistical analysis. SH, CR, BY, JB, and SA were responsible for patient recruitment and clinical assessment. SV and HD wrote the manuscript. SH, BY, CR, JB, SA, GS, DU, and LB reviewed and approved the manuscript. All authors contributed to the article and approved the submitted version.

Funding

The study was funded by a grant to Derya Unutmaz from the National Institutes of Health (1U54NS105539).

Acknowledgments

The authors are grateful to all the patient partners and participants that made this study possible.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher’s note

References

Baldwin, N. L., Murray, K. O., Garcia, M. N., and Bateman, L. (2016). Treatment of postural orthostatic tachycardia syndrome and management of myalgic encephalomyelitis/chronic fatigue syndrome following suspected West Nile virus infection. *Fatigue* 4, 226–236. doi: 10.1080/21641846.2016.1247971

Carmona-Torre, F., Mínguez-Olaondo, A., López-Bravo, A., Tijero, B., Grozeva, V., Walcker, M., et al. (2022). Dysautonomia in COVID-19 patients: a narrative review on clinical course, diagnostic and therapeutic strategies. *Front. Neurol.* 13:886609. doi: 10.3389/fneur.2022.886609

Choutka, J., Jansari, V., Hornig, M., and Iwasaki, A. (2022). Unexplained post-acute infection syndromes. *Nat. Med.* 28, 911–923. doi: 10.1038/s41591-022-01810-6

Ciacciarelli, A., Sette, G., Giubilei, F., and Orzi, F. (2020). Chronic cerebral hypoperfusion: an undefined, relevant entity. *J. Clin. Neurosci.* 73, 8–12. doi: 10.1016/j.jocn.2020.01.026

Clé, M., Eldin, P., Briant, L., Lannuzel, A., Simonin, Y., Van de Perre, P., et al. (2020). Neurocognitive impacts of arbovirus infections. *J. Neuroinflammation* 17:233. doi: 10.1186/s12974-020-01904-3

Coffman, I., Resnick, H. E., Drane, J., and Lathan, C. E. (2018). Computerized cognitive testing norms in active-duty military personnel: potential for contamination by psychologically unhealthy individuals. *Appl. Neuropsychol. Adult* 25, 497–503. doi: 10.1080/23279095.2017.1330749

Cook, D. B., Light, A. R., Light, K. C., Broderick, G., Shields, M. R., Dougherty, R. J., et al. (2017). Neural consequences of post-exertion malaise in Myalgic encephalomyelitis/chronic fatigue syndrome. *Brain Behav. Immun.* 62, 87–99. doi: 10.1016/j.bbi.2017.02.009

Davis, H. E., Assaf, G. S., McCorkell, L., Wei, H., Low, R. J., Re'em, Y., et al. (2021). Characterizing long COVID in an international cohort: 7 months of symptoms and their impact. *EclinicalMedicine* 38:101019. doi: 10.1016/j.eclinm.2021.101019

Gaglio, C. L., Islam, M. F., Cotler, J., and Jason, L. A. (2022). Orthostatic intolerance and neurocognitive impairment in Myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS). *Epidemiol. Methods* 11:20210033. doi: 10.1515/em-2021-0033

Goodman, B. P., Khoury, J. A., Blair, J. E., and Grill, M. F. (2021). COVID-19 Dysautonomia. *Front. Neurol.* 12:624968. doi: 10.3389/fneur.2021.624968

Hickie, I., Davenport, T., Wakefield, D., Vollmer-Conna, U., Cameron, B., Vernon, S. D., et al. (2006). Post-infective and chronic fatigue syndromes precipitated by viral and non-viral pathogens: prospective cohort study. *BMJ* 333:575. doi: 10.1136/bmj.38933.585764.AE

Hingorani, K. S., Bhadola, S., and Cervantes-Arslanian, A. M. (2022). COVID-19 and the brain. *Trends Cardiovasc. Med.* 32, 323–330. doi: 10.1016/j.tcm.2022.04.004

Homan, TD, Bordes, SJ, and Cichowski, E. *Physiology, pulse pressure*. Treasure Island, FL: StatPearls Publishing; (2022).

Institute of Medicine. *Beyond myalgic encephalomyelitis/chronic fatigue syndrome: redefining an illness*. Washington, DC: The National Academies; (2015).

Jammoul, M., Naddour, J., Madi, A., Reslan, M. A., Hatoum, F., Zeineddine, J., et al. (2023). Investigating the possible mechanisms of autonomic dysfunction post-COVID-19. *Auton. Neurosci.* 245:103071. doi: 10.1016/j.autneu.2022.103071

Karemaker, J. M. (2017). An introduction into autonomic nervous function. *Physiol. Meas.* 38, R89–R118. doi: 10.1088/1361-6579/aa6782

Kell, D. B., and Pretorius, E. (2022). The potential role of ischaemia–reperfusion injury in chronic, relapsing diseases such as rheumatoid arthritis, long COVID, and ME/CFS: evidence, mechanisms, and therapeutic implications. *Biochem. J.* 479, 1653–1708. doi: 10.1042/BCJ20220154

Komaroff, A. L., and Bateman, L. (2021). Will COVID-19 Lead to Myalgic encephalomyelitis/chronic fatigue syndrome? *Front. Med.* 7:606824. doi: 10.3389/fmed.2020.606824

Komaroff, A. L., and Lipkin, W. I. (2021). Insights from myalgic encephalomyelitis/chronic fatigue syndrome may help unravel the pathogenesis of postacute COVID-19 syndrome. *Trends Mol. Med.* 27, 895–906. doi: 10.1016/j.molmed.2021.06.002

Lathan, C., Spira, J. L., Bleiberg, J., Vice, J., and Tsao, J. W. (2013). Defense automated neurobehavioral assessment (DANA)—psychometric properties of a new field-deployable neurocognitive assessment tool. *Mil. Med.* 178, 365–371. doi: 10.7205/MILMED-D-12-00438

Lee, J., Vernon, S. D., Jeys, P., Ali, W., Campos, A., Unutmaz, D., et al. (2020). Hemodynamics during the 10-minute NASA lean test: evidence of circulatory decompensation in a subset of ME/CFS patients. *J. Transl. Med.* 18:314. doi: 10.1186/s12967-020-02481-y

Nacul, L., O'Boyle, S., Palla, L., Nacul, F. E., Mudie, K., Kingdon, C. C., et al. (2020). How Myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) progresses: the natural history of ME/CFS. *Front. Neurol.* 11:826. doi: 10.3389/fneur.2020.00826

Natelson, B. H., Lin, J. M. S., Blate, M., Khan, S., Chen, Y., and Unger, E. R. (2022). Physiological assessment of orthostatic intolerance in chronic fatigue syndrome. *J. Transl. Med.* 20:95. doi: 10.1186/s12967-022-03289-8

Pathak, H., Mohan, M. C., and Ravindran, V. (2019). Chikungunya arthritis. *Clin. Med.* 19, 381–385. doi: 10.7861/clinmed.2019-0035

Resnick, H. E., and Lathan, C. E. (2016). From battlefield to home: a mobile platform for assessing brain health. *Mhealth.* 2:30. doi: 10.21037/mhealth.2016.07.02

Rowe, P. C. (2002). Orthostatic intolerance and chronic fatigue syndrome: new light on an old problem. *J. Pediatr.* 140, 387–389. doi: 10.1067/mpd.2002.124318

RStudio Team *RStudio: integrated development for R*. Boston, MA: R. RStudio, PBC, (2020). Available at: http://www.rstudio.com/

Shan, Z. Y., Barnden, L. R., Kwiatek, R. A., Bhuta, S., Hermens, D. F., and Lagopoulos, J. (2020). Neuroimaging characteristics of myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS): a systematic review. *J. Transl. Med.* 18:335. doi: 10.1186/s12967-020-02506-6

Sigurdsson, B. (1956). Clinical findings six years after outbreak of Akureyri disease. *Lancet* 267, 766–767. doi: 10.1016/S0140-6736(56)91236-3

Sigurdsson, B., Sigurjónsson, J., Sigurdsson, J. H., Thorkelsson, J., and Gudmundsson, K. R. (1950). A disease epidemic in Iceland simulating poliomyelitis. *Am. J. Epidemiol.* 52, 222–238. doi: 10.1093/oxfordjournals.aje.a119421

Singh, I., Joseph, P., Heerdt, P. M., Cullinan, M., Lutchmansingh, D. D., Gulati, M., et al. (2022). Persistent Exertional intolerance after COVID-19: insights from invasive cardiopulmonary exercise testing. *Chest* 161, 54–63. doi: 10.1016/j.chest.2021.08.010

Singhal, A. B., Topcuoglu, M. A., and Koroshetz, W. J. (2002). Diffusion MRI in three types of anoxic encephalopathy. *J. Neurol. Sci.* 196, 37–40. doi: 10.1016/S0022-510X(02)00019-9

Sukocheva, O. A., Maksoud, R., Beeraka, N. M., Madhunapantula, S. V., Sinelnikov, M., Nikolenko, V. N., et al. (2022). Analysis of post COVID-19 condition and its overlap with myalgic encephalomyelitis/chronic fatigue syndrome. *J. Adv. Res.* 40, 179–196. doi: 10.1016/j.jare.2021.11.013

van Campen, C., Verheugt, F. W. A., Rowe, P. C., and Visser, F. C. (2020). Cerebral blood flow is reduced in ME/CFS during head-up tilt testing even in the absence of hypotension or tachycardia: a quantitative, controlled study using Doppler echography. *Clin. Neurophysiol. Pract.* 5, 50–58. doi: 10.1016/j.cnp.2020.01.003

van Campen, C., and Visser, F. C. (2022). Psychogenic Pseudosyncope: real or imaginary? Results from a case-control study in Myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) patients. *Medicina* 58:98. doi: 10.3390/medicina58010098

Vernon, S. D., Funk, S., Bateman, L., Stoddard, G. J., Hammer, S., Sullivan, K., et al. (2022). Orthostatic challenge causes distinctive symptomatic, hemodynamic and cognitive responses in long COVID and Myalgic encephalomyelitis/chronic fatigue syndrome. *Front. Med.* 9:917019. doi: 10.3389/fmed.2022.917019

Walitt, B., and Johnson, T. P. (2022). The pathogenesis of neurologic symptoms of the postacute sequelae of severe acute respiratory syndrome coronavirus 2 infection. *Curr. Opin. Neurol.* 35, 384–391. doi: 10.1097/WCO.0000000000001051

Wirth, K. J., Scheibenbogen, C., and Paul, F. (2021). An attempt to explain the neurological symptoms of Myalgic encephalomyelitis/chronic fatigue syndrome. *J. Transl. Med.* 19:471. doi: 10.1186/s12967-021-03143-3

frontiers | Frontiers in Physiology

TYPE Methods
PUBLISHED 29 June 2023
DOI 10.3389/fphys.2023.1220464

OPEN ACCESS

EDITED BY
Sławomir Kujawski,
Ludwik Rydygier Collegium Medicum in Bydgoszcz Nicolaus Copernicus University in Toruń, Poland

REVIEWED BY
Ardalan Shariat,
Tehran University of Medical Sciences, Iran
Marcelo Navega,
São Paulo State University, Brazil

*CORRESPONDENCE
Banafsheh Amiri,
✉ amiri11@uniba.sk

RECEIVED 10 May 2023
ACCEPTED 19 June 2023
PUBLISHED 29 June 2023

CITATION
Amiri B and Zemková E (2023), Diaphragmatic breathing exercises in recovery from fatigue-induced changes in spinal mobility and postural stability: a study protocol.
Front. Physiol. 14:1220464.
doi: 10.3389/fphys.2023.1220464

Diaphragmatic breathing exercises in recovery from fatigue-induced changes in spinal mobility and postural stability: a study protocol

Banafsheh Amiri* and Erika Zemková

Department of Biological and Medical Sciences, Faculty of Physical Education and Sport, Comenius University in Bratislava, Bratislava, Slovakia

Prolonged periods of sitting at work can increase trunk muscle fatigue from the continuous contraction of deep trunk muscles. Insufficient activity of these muscles can decrease muscular support to the spine and increases stress on its passive structures. This can lead to reduced spinal mobility and impaired postural stability. It may also stimulate nociceptor activity leading to pain. However, frequently used recovery modalities such as muscle strengthening and stretching exercises, can be time-consuming, impractical, and difficult to implement in the workplace. Diaphragmatic breathing exercises, which increase the activity of the deep trunk muscles by raising intra-abdominal pressure, seem to be a suitable alternative. However, little is known as to what extent diaphragmatic breathing exercises contribute to the reduction of fatigue induced by prolonged sitting. This paper presents a study protocol that aims to investigate the acute effect of diaphragmatic breathing exercises on recovery of fatigue-induced changes in spinal mobility and postural stability in sedentary middle-aged adults at risk of developing non-specific low back pain. Twenty sedentary adults aged between 25 and 44 years will perform Abt's fatigue protocol, followed by 1) active recovery using diaphragmatic breathing exercises and 2) passive recovery in the form of lying on the bed, respectively. There will be 1 week of rest in-between. Pre-fatigue, post-fatigue, and after the active and passive recovery, spinal mobility and postural stability will be evaluated using the spinal mouse device and a posturography system, respectively. The electromyography will be used to determine the muscle-fatigue conditions. We hypothesize that active recovery in a form of diaphragmatic breathing exercises would be more effective in restoring spinal mobility and postural stability followed by the fatigue of back and hamstring muscles compared to passive recovery in sedentary adults. Increasing core and respiratory muscle strength via these exercises could be beneficial for overall mobility and stability of the spine. Reducing compressive stress on the passive structures of the spine may be also beneficial for lowering low back pain. Therefore, we believe that diaphragmatic breathing exercises have the possibility to be incorporated into the workplace and contribute to better back health in sedentary middle-aged adults.

Clinical Trial Registration: [https://www.irct.ir/trial/67015], identifier [IRCT20221126056606N1].

KEYWORDS

electromyography, fatigue, low back pain, sedentary adults, trunk and hamstring muscles

1 Introduction

Modern life have resulted in sedentary behaviors among human societies (Egger et al., 2001; Jans et al., 2007). These behaviors are characterized by low levels of physical activity and an energy expenditure of at least 1.5 metabolic equivalents (Freire et al., 2022). The daily job is a major factor in adults' sedentary behavior (Kett and Sichting, 2020). Office workers sit for 6.6–10.0 h per day on average (Kett and Sichting, 2020). Continuous contraction of the trunk muscles during prolonged sitting can lead to deep trunk muscle fatigue (Saiklang et al., 2022). Fatigability depends on both the contractile capability of the muscles involved in the task as well as the capacity of the nervous system to provide adequate activation signals to accomplish it (Zemková et al., 2021a). The decreased muscle contractile efficiency and limited capacity of the nervous system can increase articular structural stiffness, and delay muscle response time (Hamaoui et al., 2004). Thus, spinal loading decreases which plays an important role in the mobility of the spine (Yang et al., 2005).

Spinal mobility depends on two anatomical and physiological factors (Hamaoui et al., 2004). The anatomical factor corresponds to articular structural stiffness and determines the range of motion capacity (Hamaoui et al., 2004; Hamaoui et al., 2007). The physiological factor corresponds to muscular excitation (by delayed muscle response time) and determines dynamic mobility capacity (Hamaoui et al., 2004; Hamaoui et al., 2007). These features of the spine may be influenced by prolonged sitting (Hamaoui et al., 2004). While the first one is related to a decrease in the spine's range of motion, the second one is related to a decrease in spine velocity (Hamaoui et al., 2004). Assessment using the spinal mouse suggests that spinal mobility may be impaired as a result of fatigue induced by prolonged sitting (Lenková and Vasilišinová, 2019). Decreased spinal mobility leads to abnormal lumbar vertebrae movement as a compensatory mechanism (Sung et al., 2014). This exacerbates facet joint instability and increases the risk of experiencing lower back pain (Sung et al., 2014).

Additionally, the combination of decreased muscle contractile efficiency (Tajali et al., 2022), and decreased capacity of the nervous system including insufficient integration of sensory information, and impaired neuromuscular functions under fatigue can alter feedforward and feedback control of postural sway (Akulwar and Mulgaonkar, 2017; Zemková et al., 2021a). For example, fatigued healthy subjects exposed to external perturbations have shown longer activation latencies, an increase in electromyographic amplitude, reduced muscle activity, and increased co-contraction (Zemková et al., 2021a; Zemková et al., 2021b). Also postural control strategies can be altered by acute back muscle fatigue (Johanson et al., 2011). These strategies are similar in healthy individuals when postural demands increased to those used by people with recurrent low back pain. The Zemkova (2021) study discovered that lumbar muscle fatigue can cause alterations in the lumbar spinal curvature, which may play a functional role in explaining the reduced ability to maintain balance when subjected to external perturbations. To measure spinal mobility, the study employed the spinal mouse, while the balance was evaluated using the posturography system (Zemková et al., 2021a). Such an altered postural stability can cause predisposing agents for musculoskeletal disorders, especially low back pain (Hanna et al., 2019; Zhang et al., 2020; Suresh et al., 2021). Due to the fact that low back pain strongly correlates with trunk muscle corset condition (Jabłońska et al., 2021), there is a need to control and recover trunk muscle fatigue.

The muscle fatigue recovery process refers to a return of the functional capacity of body tissues after the onset of fatigue (Yi et al., 2022). Physical exercises play a pivotal role in early intervention and are usually recommended at workplace (Kaeding et al., 2017). Two frequently employed recovery modality types are compensatory exercises and relaxation exercises, both of which can be beneficial for releasing tension and reducing fatigue in the musculoskeletal system (Soares et al., 2019). Compensatory exercises are referred to as short active breaks, involving the discontinuation of job tasks for exercising, and typically include muscle strengthening, flexibility, stretching, and breathing exercises (Soares et al., 2019). Conversely, relaxation exercises are typically performed at the end of the working day and include flexibility, stretching, breathing, and self-massage exercises (Soares et al., 2019). It might also be combined to complementary therapies representing mind-body interventions, such as acupuncture, yoga, Pilates, progressive muscle relaxation and meditation (Soares et al., 2019). Complementary therapies modality seeks to rehabilitate employees with work-related musculoskeletal disorders according to their individual complaints (Soares et al., 2019). Therefore, these exercises do not serve as a primary preventive measure (Soares et al., 2019). Furthermore, it is important to note that the success of a movement-related intervention is reliant on the motivation and adherence of participants (Kaeding et al., 2017). Therefore, short and sharp interventions are recommended as they have been found to achieve high levels of adherence, with an expected compliance rate of approximately 76% (Bell and Burnett, 2009). However, muscle strengthening, stretching, and flexibility exercises can be time-consuming, impractical, and difficult to implement in the workplace. Employers must provide appropriate locations for exercise at adequate intervals to address these issues. To avoid these shortcomings, one can use diaphragmatic breathing exercises during prolonged sitting periods at the workplace. Diaphragmatic breathing involves the contraction of the diaphragm muscle located between the chest and abdomen, which can improve breathing efficiency and oxygen delivery (Dhalla, 2022). Normal respiration, also known as tidal breathing, is driven by a group of muscles known as the "respiratory pump," with the diaphragm being the major respiratory muscle (Russo et al., 2017). When the diaphragm contracts during normal inspiration, it pushes on the abdomen and causes the lower ribs to expand outwards, generating a trans-diaphragmatic pressure that allows for ventilation of the lungs and gas exchange (Russo et al., 2017). Expiration is generally passive, but the expiratory muscles become active during increased breathing effort. Studies Vostatek et al. (2013); Russo et al. (2017) have shown that optimal respiration requires active control of the diaphragm, with the lower ribs staying low and only expanding laterally during inspiration, while the abdomen expands instead of the chest. Diaphragmatic breathing has been found to facilitate slow respiration, with trained individuals achieving slower respiratory rates and greater diaphragm excursion during slow breathing (Russo et al., 2017). Correct and balanced diaphragm performance has been shown to help maintain abdominal pressure and smooth respiration

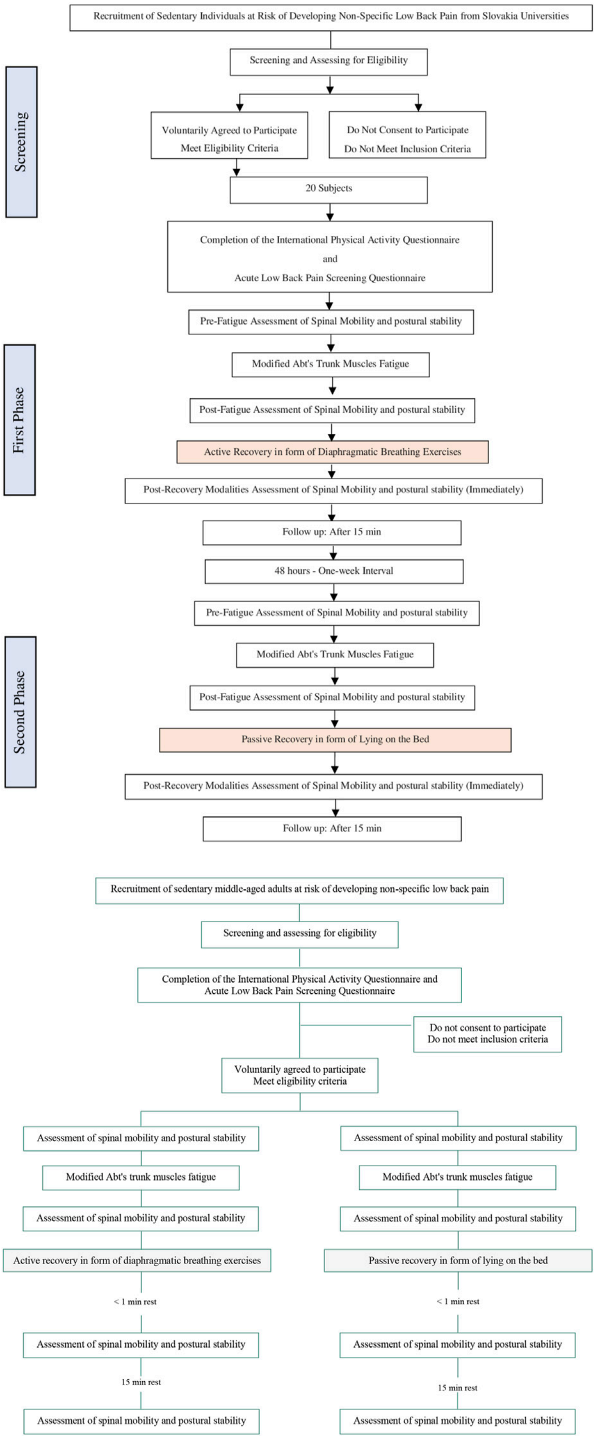


FIGURE 1
Flow-diagram of the study protocol.

(Russo et al., 2017; Hamasaki, 2020). Increasing intra-abdominal pressure in turn causes activation of the abdominal wall and pelvic floor muscles (Rasheed et al., 2021). This muscle activation provide posterior and anterolateral and inferior stability, thus increasing overall spinal stability (Rasheed et al., 2021). Kang et al. (2016) reported that intra-abdominal pressure that is produced by the connection of trunk stabilization and respiratory muscles affects waist stability and protects the trunk. Training of respiratory muscles increases muscle firing, proprioception of the diaphragm, low back musculature, deep core musculature, and respiratory muscle strength (Stephens et al., 2017). This can have a positive effect on spinal mobility and postural stability. For example, physiotherapeutic breathing exercises, like yoga and Pilates, have been found equally effective in improving spinal mobility in healthy young women (Csepregi et al., 2022). In addition, Stephens et al. (Stephens et al., 2017) demonstrated improvement of postural stability after 8-week diaphragmatic breathing exercises in healthy persons. The improvement of static and dynamic balance have been also reported in athletes with chronic low back pain (Otadi et al., 2021).

Breathing exercises are also effective in the treatment of musculoskeletal complaints, such as low back pain (Kang et al., 2016; Ahmadnezhad et al., 2020; Otadi et al., 2021). For instance, the activation patterns of trunk muscles change immediately during the lifting task after performing an abdominal drawing-in exercise in subjects with recurrent low back pain (Suehiro et al., 2021). A session of respiratory muscle training can also reduce the activity of some ankle joint muscles while performing overhead squats in athletes with chronic low back pain (Borujeni and Yalfani, 2020).

Although the effect of diaphragmatic, exhalation, and inspiratory breathing exercises on spinal mobility (Kang et al., 2018; Lenková and Vasilišinová, 2019) and postural stability (Tajali et al., 2022; Stephens et al., 2017; Armstrong et al., 2018; D'souza et al., 2021; Farzami and Anbarian, 2020; Roth et al., 2021; Ferraro et al., 2020) has been investigated, there are no studies dealing with their recovery following by prolonged sitting at the workplace. People exposed to repetitive, prolonged sitting at their work are prone of back problems, especially in late middle-age. There is also growing concern over the effects of sedentary lifestyles on the young people's health. However, prevention programs for them are rare. This paper presents a study protocol that aims to investigate the acute effect of diaphragmatic breathing exercises on recovery of fatigue-induced changes in spinal mobility and postural stability in sedentary middle-aged adults at risk of developing non-specific low back pain.

2 Materials and methods

2.1 Study design

This experimental pre-post study is designed to investigate the acute effect of diaphragmatic breathing exercises on recovery of fatigue-induced changes in spinal mobility and postural stability in sedentary middle-aged adults at risk of developing non-specific low back pain. This is a study protocol that will be carried out and reported in accordance with the Standard Protocol Items: Recommendations for Interventional Trials statement (SPIRIT). Figure 1 illustrates the study design. The study has been approved by the ethics committee of the Faculty of Physical Education and Sport, Comenius University in Bratislava (No. 5/2022) and the Ethics Committee of Kerman University of Medical Sciences (IR.KMU.REC.1401.386). It also has been approved by

Iranian Registry of Clinical Trials (registration reference: IRCT20221126056606N1).

2.2 Participants and setting

This study will be performed on 20 sedentary individuals aged 25–44 years old, at risk of developing non-specific low back pain, who will mainly be employees of university. This effect size is sufficient to determine the significant effects of diaphragmatic breathing exercises on the recovery of spinal mobility and postural stability due to trunk muscles fatigue.

The present study will be performed at the Faculty of Physical Education and Sport, Comenius University in Bratislava, Slovakia.

2.2.1 Inclusion and exclusion criteria

Inclusion criteria for the participants were established as follows: The sedentary middle-aged adults (aged 25–44 years old) at a risk of developing non-specific low back pain, and self-reporting of sitting for at least 2 hours on any working day (Saiklang et al., 2022). Potential participants will be screened for the study using the international physical activity questionnaire (IPAQ) to recognize those who are sedentary and using the Acute LBP Screening Questionnaire (ALBPSQ) to identify those who are at risk of developing non-specific low back pain. The volunteers will be excluded if they meet any of the following criteria: pregnancy (Abboud et al., 2014); history of spinal, femoral, or intra-abdominal surgery in the previous 12 months (Sitthipornvorakul et al., 2015); have been diagnosed with a congenital anomaly of the spine, arthritis, rheumatoid, infection of the spine and discs, spondylolisthesis, ankylosing spondylitis, spondylosis, tumor, systemic lupus erythematosus, or osteoporosis (Sitthipornvorakul et al., 2015); receiving physiotherapy services 1 month before the beginning of the study (Fortun-Rabadan et al., 2021); having suffered any kind of mental health disorder, including anxiety and depression, during the past 3 years (Fortun-Rabadan et al., 2021).

2.2.2 Sample size estimation and sampling method

A prior sample size estimation was done using the G*Power software package (version 3.1.9.7) based on the study by Fonta et al. (2021). The input parameters were as follows: statistical test = repeated measures, within - between interaction; effect size F = 0.25; α err prob = 0.05; and power $(1 - \beta$ err prob$) = 0.80$. As a result, the total sample size was calculated to be 11 subjects. In consideration of the possibility of dropouts, a slightly larger number of subjects will be recruited to participate in this study. The total sample size would be approximately 20 subjects.

A purposeful sampling strategy will be used and participants based on their age, sedentary behavior, and other relevant factors that are related to the study's focus and have been explained in inclusion and exclusion criteria section will be selected.

2.3 Procedures

Each participant will take part in two phases of the experiment including familiarization and data collection.

2.3.1 Familiarization

In the first phase, all subjects will undergo a familiarization session, about 1–2 h before data collection. The study objectives and procedures will be explained to participants and informed consent will be taken from each participant before the study. In the second phase, participants will complete a questionnaire that includes personal and baseline characteristics. Body mass will be measured using a calibrated digital scale, and height will be measured using a single stadiometer. The weight plates used in the trunk muscles fatigue protocol for each participant will be chosen during the familiarization phase. The heaviest weight that participants can perform each exercise 20 times in 40 s in the correct form will be used (Askari and Esmaeili, 2021). During this phase, subjects will be asked to eat their normal meal while avoiding strenuous exercise and performance-enhancing energy drinks for the 48 h prior to data collection sessions (Armstrong et al., 2018).

2.3.1.1 Health and safety considerations

Participants will complete a "health and medical questionnaire" before the study and will be closely monitored by professionals to minimize injury risk. Participants will stop exercises if experience pain or discomfort. Adverse events will be documented and addressed, with modifications to the protocol if necessary.

2.3.2 Data collection

Data from all participants will be collected under three conditions:

1. Pre-fatigue assessment (at baseline),
2. Post-fatigue assessment (immediately after fatigue protocol),
3. Post-recovery modalities assessment (immediately, and 15-min after cessation of active and passive modality, respectively).

Assessing the effects of the intervention at the 15-min follow-up can provide insight into the potential duration of these effects.

All participants will be tested at the same time of day by the same examiners.

The study will involve gathering individual demographic information and outcome data. The study team will enter the questionnaire data into a database and verify its accuracy before using it. All information and outcome data will be kept on password-protected computers that only the authorized members of the study team will be able to access. Data management will outline the procedures for gathering, recording, storing, and archiving data.

2.3.2.1 Primary outcomes for screening

2.3.2.1.1 International physical activity questionnaire. Potential participants will be screened for the study using the International Physical Activity Questionnaire [IPAQ] to recognize those who are sedentary. The IPAQ is a formal self-report tool used to measure physical activity in one's normal daily routine (Mehta et al., 2018). This questionnaire is available in two versions, long and short (Demircioğlu et al., 2021). The IPAQ short form (IPAQ-SF) is used to screen physical activity levels in the population at large, while the IPAQ long form (IPAQ-LF) is used in research studies or clinical settings to assess physical activity levels (Mehta et al., 2018). In both versions of the questionnaire, the common objective is to assess the amount and intensity of physical activity an individual participates in per week (Mehta et al., 2018). Each version considers four domains: leisure-time physical activity work-related activities, domestic and gardening activities, and transport-related activities. The long interview administered version of the IPAQ, which contains 27 items in the four domains, will be used in the present study (Mehta et al., 2018). Using the long form, it will be possible to calculate domain-specific scores, activity-specific scores, and continuous scores. The continuous scores, expressed in metabolic equivalent minutes (MET), will be a measure of physical activity. According to these scores subjects will be categorized as engaging in low-, moderate-, or high-level physical activity (Mehta et al., 2018).

2.3.2.1.2 Acute low back pain screening questionnaire.

The Acute Low Back Pain Screening Questionnaire (ALBPSQ) identifies those who are at risk of developing non-specific low back pain. The questionnaire has been endorsed by guidelines from the New Zealand work health authority (Hanna et al., 2019). The level of back pain will be calculated based on the duration and intensity of the pain. A Likert rating scale from 0 (no pain) to 5 (pain as bad as it can get) will be used to assess perceived beliefs about the psychological impact of pain on the participant. Ratings on the scored items will be subsequently summed to determine a total score and domain sum score. A higher rating indicates a higher level of risk.

2.3.2.2 Secondary outcomes for intervention evaluation

2.3.2.2.1 Assessment of the trunk muscle fatigue.

The Delsys Trigno™ wireless EMG system, will be used to record electromyography signals from the trunk and hamstring muscles. These muscles will be the lumbar multifidus at the L5 level, and erector spinae muscles at the L1 level and hamstring muscles. Prior to electrode placement, the skin will be prepared by abrasion and cleaning with alcohol.

For the Multifidus Muscles

- Electrode placement: on the line connecting the caudal tip of the posterior superior iliac spine (SIPS) to the space between L1 and L2, at the level of the spinous process of L5, 2–3 cm from the medial line,
- Inter-electrode distance: 25 mm,
- Clinical test: maximum isometric strength of the back extensor muscles.

For the Longissimus Muscles: erector spinae

- Electrode placement: two fingers apart in a lateral direction from the spinous process L1,
- Inter-electrode distance: 25 mm,
- Clinical test: maximum isometric strength of the back extensor muscles.

For the Hamstring Muscles: medial hamstring

- Electrode placement: The medial hamstring on both lower extremities: the electrode for the medial hamstring will be placed midway between the ischial tuberosity and the medial epicondyle of the tibia,
- Clinical test: maximum isometric strength of the hamstring muscles.

The raw sEMG signals will be recorded at a sampling frequency of 2,000 Hz. Butterworth band-pass filters with a passband of 20 Hz and a stopband of 450 Hz will be applied to remove signals that will not be due to muscle activity. The features of muscle fatigue by EMG are amplitude increase and transformation from a high-frequency spectrum to a low-frequency spectrum. It is assumed that fatigue and recovery are mutually exclusive. Therefore, decrease amplitude and transformation from a low-frequency spectrum to a high-frequency spectrum are features of muscle recovery by EMG. In the present study, the mean amplitude (root mean square, RMS) and the frequency features (mean power frequency, MPF, and median frequency MDF) of the sEMG signals will be used to evaluate muscle fatigue and recovery. To accomplish this, the raw EMG signal will be processed with a fast Fourier transformation to determine the mentioned variables. The fast Fourier transform is a mathematical technique used to transform a time-domain signal into its frequency-domain representation (Mateo and Talavera, 2018).

2.3.2.2.2 Assessment of the spinal mobility.

Intersegmental mobility, overall and regional spinal range of motion will be measured in the sagittal plane in the standing position using a Spinal Mouse device (Csuhai et al., 2020). It is a wireless electronic, and non-invasive skin-surface tool for computer-assisted imaging and radiation-free examination (Post and Leferink, 2004). The Spinal Mouse's reliability and validity have been established in populations that were healthy and symptomatic, including back pain (Topalidou et al., 2014). Before starting the examination, every subject will be registered in Spinal Mouse software with gender, age and randomly allocated study codes. Subjects will be asked to take three different standing positions: relaxed but erect (not corrected), maximal flexion and maximal extension of the spine. After undressing the upper body, spinous processes will be palpated, and C7 and S3 will be marked with a body-marker. Spinal Mouse will run paravertebrally along the spinous processes of marked segments. It makes the system capable of recording the contour of skin above the vertebral bodies in the sagittal plane. Positions include:

1. Neutral in standing: Subject will be asked to maintain a relaxed position with the feet shoulder width apart, with straight knees and arms by the side, looking and facing straight horizontally towards the wall.
2. Maximal flexion in standing: Subject will be asked to flex the trunk with straight knees as far as possible with slow motion from segment to segment, aiming to touch the ground with fingertips.
3. Maximal extension in standing: Subject will be asked to cross arms in front of the chest and extend the trunk as far as possible, keeping the knees straight, without extension of the cervical spine.

No warm-up will be performed before the examination and each test will be done once (Post and Leferink, 2004). The mobility values of the segments, including range of flexion from upright (U-F), range of extension from upright (U-E) and total range from extension to flexion (E-F), will be measured (Csuhai et al., 2020).

2.3.3.2.3 Assessment of the postural stability.

Participants will be asked to stand barefoot on a force plate with their arms relaxed comfortably at their sides. They will be instructed to stand in an upright position with their feet abducted at 10° and their heels separated mediolaterally by a distance of 6 cm. A series of trials will be conducted in a randomized order under varied conditions: tandem stance on a force plate with eyes open, tandem stance on a force plate with eyes closed, tandem stance on a foam mat (Airex Balance Pad) placed on the force plate with eyes open, tandem stance on a foam mat (Airex Balance Pad) placed on the force plate with eyes closed (Zemková et al., 2016). Subjects will perform one set of 30s under each condition. Short rest periods break will be allowed after every two trials (Zemková et al., 2021c).

Postural stability will be assessed using a FiTRO Sway Check (FiTRONiC, Bratislava, Slovakia). The system measures the actual force in the corners of the force plate and calculates an instant position of the CoP (sampling rate: 100Hz, 12-bit AD signal conversion, resolution of the CoP position: less than 0.1mm, measuring range: 0–1,000/s, non-linearity: ±0.02%FS, combined error: 0.03%, sensitivity: 2 mV/V ± 0.25%, overload capacity: 150%/sensor). FiTRO Sway Check has been shown to have good to excellent reliability of CoP variables, according to a recent study by Zemkova et al. (2021) (Zemková et al., 2021c). The Romberg quotient (eyes closed/eyes open (EC/EO) sway ratio) will also be calculated. Under unstable conditions, variables of postural stability will be registered by using the FiTRO Sway Check (FiTRONiC, Bratislava, Slovakia). The device consists of a square platform supported by four springs with an elasticity coefficient of 40N/mm. Shifting the CoP in the horizontal plane leads to changes of body weight distribution to the four corners of the platform. Force acting in each corner is calculated as a product of the coefficient of elasticity of the spring used and vertical distance measured by means of a fine sensor. The analogue signals are AD-converted and sampled by computer at the rate of 100Hz. Calculations of instant CoP position is based on force distribution to the four corners of the platform. Basic parameters of postural stability (i.e., mean CoP velocity and mean CoP displacements in medio-lateral and anterior-posterior directions) will be analyzed (Zemková et al., 2021c).

2.3.3 Fatigue protocol

The modified Abt protocol will be used in order to induce fatigue of trunk muscles (Abt et al., 2007). The protocol lasts 32 min and consists of four consecutive cycles of eight exercises. Each set consists of exercises in the following order:1) trunk rotation with a medicine ball in a sitting position, 2) prone static torso extension with a medicine ball, 3) lower torso rotation with a medicine ball in a supine position, 4) sit-ups on the incline bench with a weight plate, 5) lateral side binding with a weight plate, 6) lumbar extension rotation with weighted plate, 7) trunk rotation with weighted pulley resistance in standing position, and 8) supine isometric bridge hold. The selection of weight plates for each subject will be performed on a separate day before testing. The heaviest weight with which subjects can perform each exercise 20 times in 40 s in the correct form will be used. Prior to trunk muscle fatigue protocol, a 10- minutes warm-up will be performed including 5 min of *insitu* warming, and 5 min of aerobic stretching, with an emphasis on the hamstring and trunk muscles. Then fatigue protocol will be started. Subjects will perform 20 repetitions of each exercise in 40 s (each repetition in 2 seconds). A pause of 20 s will be between each exercise. The fatigue protocol will be terminated in two ways: 1) when subjects will be no longer able to continue the fourth set of exercises (the last set) with the correct form, and 2) when the subjects will be unable to perform each repetition in 2 seconds in the last set exercises. To ensure occurrence of fatigue, subjects will be rated on their perceived exertion at the end of each phase of the protocol using the 15-point Borg scale (rank 6–20) (Borg, 1970). The point of six represents the absence of fatigue and point of 17–20 indicates failure to perform exercises. If the subjects in the end of fourth round report number 17 or higher, it means the end of the fatigue protocol. If they will report fewer points, they should perform another round until they report the point 17 (Askari and Esmaeili, 2021).

2.3.4 Recovery modalities

2.3.4.1 Diaphragmatic breathing exercises

Subjects will be in crook lying position. They will be advised to deeply inhale through the nose so that they could see their abdomen expanding. They should hold this position for 5 s and then exhale through mouth. To ensure that the subjects are performing the exercise correctly, they will be instructed to place one hand on their chest and the other on their abdomen. They will be advised to breathe in so deeply that they should feel only the movement of the hand on their abdomen and not that of the hand on their chest. Each subject will perform the assigned exercise 10 times per session. They will take 1-min rest between each session (Rasheed et al., 2021).

2.3.4.2 Passive recovery

The subjects will be asked to lie on a bed in a darkened room and do nothing for 24 min after Abt's trunk muscle fatigue protocol (Seidi et al., 2019).

2.4 Statistical analysis

Statistical analyses will be carried out using SPSS Statistics (SPSS Statistics Version 24; IBM Corporation©, United States). Prior to statistical comparisons, a Shapiro-Wilk test of normality will be performed for all variables. Not normally distributed data will be analyzed using nonparametric tests. Friedman's test followed by Dunn's *post hoc* test will be used for the comparison of the spinal mobility, postural stability and EMG variables at different assessment times (at baseline, immediately after Abt's fatigue protocol, immediately after recovery modalities, 15-min after recovery modalities, 30-min after recovery modalities). The Kruskal–Walli's test will be used for the inter-group comparisons (experimental group A vs. experimental group B) at each assessment. For the normally distributed data, a repeated measures Analysis of Variance (ANOVA) will be performed. Repeated measures ANOVA will be used to confirm if there are differences in each group (within-group comparisons), considering each group in isolation, between the five assessments in each of the spinal mobility variables (at baseline, immediately after Abt's fatigue protocol, immediately after recovery modalities, 15-min after recovery modalities, 30-min after recovery modalities). To calculate between-group differences from baseline assessment to final follow up, a five-way repeated-measures ANOVA will be performed. With the spinal mobility and/or postural stability and/or EMG variables outcome as dependent factor, with five levels corresponding to every time of assessment (t1, t2, t3, t4, and t5), and the two groups (experimental group A vs. experimental group B) as independent factors. The Bonferroni correction will be applied to control for the increased probability of significant findings due to multiple testing. Between- and within-group effect sizes for all quantitative variables will be measured with the Cohen d coefficient: small effect (less than $d = 0.2$ and $\eta p2 = 0.01$); moderate effect (approximately $d = 0.5$ and $\eta p2 = 0.06$); and large effect (greater than $d = 0.8$ and $\eta p2 = 0.14$) (Cohen, 2013). The α-level will be set to 0.05 for all statistical tests.

3 Discussion

The present study will address the modeling of trunk muscle fatigue and recovery-related changes in spinal mobility and postural stability in sedentary middle-aged adults at risk of developing non-specific low back pain. People who spend most of their working hours seated, due to their work nature, are more susceptible to developing musculoskeletal disorders (Hanna et al., 2019). Low back pain is the most prevalent occupational musculoskeletal disorder (Csuhai et al., 2020; Zemková et al., 2021c). During prolonged sitting, the static loading of the lumbar spine can cause deep trunk muscles fatigue that may arise from continuous contraction of the muscles (Areeudomwong et al., 2012). Consequently, the neural control subsystem attempts to maintain spinal stability by increasing superficial trunk muscles activation in order to compensate for deep trunk muscles dysfunction (Saiklang et al., 2022). Under fatigue, there is an increased activity of superficial trunk muscles which can reduce the muscular support to the spine and increase stress on ligaments and intervertebral discs. Consequently, it reduces intervertebral disc height, leading to impaired spinal mobility. The reduction of disc height increases the amount of compression on sensitive spinal structures. This may stimulate nociceptor activity, which could be one of the reason for developing pain (Saiklang et al., 2022).

In addition to decrease trunk muscle activity under fatigue, proprioceptive sensitivity also decreases by muscle fatigue (Tajali et al., 2022). The combination of these two factors, can lead to impairment of postural stability (Larson and Brown, 2018). Adverse effect of trunk muscle fatigue on ability of maintain balance can be explained by alternation of neurophysiological mechanisms. Repeated muscular contractions caused by mechanical constraints reduce the activity of muscle spindles (Macefield et al., 1991). Motoneurons activation also reduces under fatigue, which results in decreasing of the discharge frequency of sensorial fibers in muscle spindles (Madigan et al., 2006). Thus, the integration of sensory inputs and the firing patterns of motoneurons are influenced, which leads to fewer motor units being recruited to control postural sway (Gribble and Hertel, 2004). Additionally, the central nervous system does not get accurate information about body location in space at any moment due to variations in proprioceptive input brought on by weariness (Martin et al., 2006). Under fatigue, inputs from group III and IV muscle afferents from antagonist or homonymous muscles decrease extensor motor neurons, whilst flexor motor neurons innervations are facilitated (Martin et al., 2006). Especially the fatigue of lumbar extensor muscles decreases the joint movement sense (Taimela et al., 1999), which initially increases larger lumbar motions and subsequently also postural sways (Pline et al., 2005).

The break is recommended to be applied during prolonged sitting at workplace (Waongenngarm et al., 2018). In particular, active breaks in the form of exercise have a positive effect on the recovery of musculoskeletal discomforts (Maciel et al., 2018), mainly low back pain symptoms in employees (Gobbo et al., 2019). The most frequently used are muscle strengthening and stretching exercises (Shariat et al., 2018; del Pozo-Cruz et al., 2013; Macedo et al., 2011; Sufreshtri and Puspitasari, 2020). However, there are some disadvantages when these exercises are performed at workplace. This includes insufficient time to exercise, financial situation and costs, difficult access to on-site gyms and/or exercise classes, fear of being injured, individualization of exercises, and boredom (Mayer et al., 2013; Skrebutėnaitė and Karanauskienė, 2019). Diaphragmatic breathing exercises seem to be a suitable alternative because they are feasible, effective, safe, affordable, and easy to implement. Due to their simplicity and attractivity, people are more motivated and interested to participate in the exercise program.

Breathing exercises are also beneficial for back health. These exercises have been shown to decrease spinal loading by raising intra-abdominal pressure (Shah et al., 2020). Increased intra-abdominal pressure reduces spine compression force (Kwon et al., 2021). This could play an important role in spinal mobility (Yang et al., 2005). Raising intra-abdominal pressure can also activate the pelvic floor and abdominal wall muscles that improve inferior stability and posterior and anterolateral stability (Rasheed et al., 2021). It helps to stabilize the lumbar spine during static (e.g., standing on tiptoes) and dynamic (e.g., walking with head turns) movements that challenge balance (Ferraro et al., 2020). Moreover, the breathing exercises may increase the strength of the diaphragm and deep core musculature. Muscle firing, and proprioception increase through the diaphragm breathing exercise (Stephens et al., 2017). Both an increase core muscle strength and an improvement in proprioceptive function may contribute to better postural stability. An improvement in diaphragmatic breathing pattern may also be considered as another factor associated with improved balance (Stephens et al., 2017). Despite of the fact that postural stability and spinal mobility are related to low back pain (Mellin, 1987; Mellin, 1990; Karimi and Saeidi, 2013; Thakkar and Kumar, 2015), there are no controlled studies that investigated the acute effect of breathing exercises on these abilities in sedentary middle-aged adults at risk of low back pain.

The management of musculoskeletal problems requires a multidisciplinary approach (Sabo et al., 2016). Starting at the earliest moment possible can increase its effectiveness. Prevention is the first step in the management of low back pain, and physical exercise has a primary effect on it (Schaafsma et al., 2015). However, despite all the efforts in studying the effectiveness of exercise based-break at the workplace on the prevention of musculoskeletal disorders, the focus on people at risk of low back pain is limited. In practice, most people who participate in exercise programs already suffer from some kind of back problem (Džubera et al., 2016). Therefore, focusing on prevention programs can avoid serious chronic musculoskeletal disorders in the future. In addition, more active employees are more productive, require less sick leave, and have overall lower healthcare costs (Taulaniemi et al., 2019). For example, Del Pozo-Cruz et al. (del Pozo-Cruz et al., 2012) found that a web-based exercise program could reduce the social cost of low back pain by €500.00 per episode.

Based on the narrative review by Hamasaki (2020), diaphragmatic breathing can potentially improve respiratory function, reduce stress, anxiety, and depression, and enhance cognitive performance (Hamasaki, 2020). It seems that if diaphragmatic breathing exercises are implemented as an active recovery in the workplace, they could ultimately lead to improved productivity and employee wellbeing. However, performing these exercises as a prevention program for low back pain in employees is rare. The results of our ongoing study will contribute to an understanding of the effects of this technique and its potential application in the prevention of low back pain in employees at the workplace.

We believe that the addition of a diaphragmatic breathing exercises as an active recovery can be successfully implemented in workplace conditions. The evidence allows us to propose that these exercises can help to restore postural stability and spinal mobility in sedentary adults following fatigue of the core muscles induced by prolonged sitting. Proposed recovery modalities could contribute to the improvement of back health by reducing trunk muscles fatigue. Due to the fact that these exercises require very few supplies and can be done almost anywhere, we believe that a large portion of the population could benefit from them.

Data availability statement

The original contributions presented in the study are included in the article/supplementary materials, further inquiries can be directed to the corresponding author.

Ethics statement

The studies involving human participants were reviewed and approved by the ethics committee of the Faculty of Physical Education and Sport, Comenius University in Bratislava (No. 5/2022) and the Ethics Committee of Kerman University of Medical Sciences (IR.KMU.REC.1401.386). It also has been approved by the Iranian Registry of Clinical Trials (registration reference: IRCT20221126056606N1). All methods will be carried out in accordance with relevant guidelines and regulations or the Declaration of Helsinki. Written consent will be obtained from all the study participants and/or their legal guardian(s) for the study.

Author contributions

BA Writing-Original draft preparation, and Editing. EZ Supervision, Reviewing, and Editing. All authors contributed to the article and approved the submitted version.

Funding

This work was supported by the Scientific Grant Agency of the Ministry of Education, Science, Research and Sport of the Slovak Republic and the Slovak Academy of Sciences (No. 1/0725/23).

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

References

Abboud, J., Nougarou, F., Pagé, I., Cantin, V., Massicotte, D., and Descarreaux, M. (2014). Trunk motor variability in patients with non-specific chronic low back pain. *Eur. J. Appl. physiology* 114 (12), 2645–2654. doi:10.1007/s00421-014-2985-8

Abt, J. P., Smoliga, J. M., Brick, M. J., Jolly, J. T., Lephart, S. M., and Fu, F. H. (2007). Relationship between cycling mechanics and core stability. *J. Strength & Cond. Res.* 21 (4), 1300–1304. doi:10.1519/R-21846.1

Ahmadnezhad, L., Yalfani, A., and Borujeni, B. G. (2020). Inspiratory muscle training in rehabilitation of low back pain: A randomized controlled trial. *J. sport rehabilitation* 29 (8), 1151–1158. doi:10.1123/jsr.2019-0231

Akulwar, I., and Mulgaonkar, S. (2017). Effect of trunk extensor muscle fatigue on postural stability in healthy young adults. *Physiother. Rehabil.* 2 (144), 2573–0312. doi:10.4172/2573-0312.1000144

Areeudomwong, P., Puntumetakul, R., Kaber, D. B., Wanpen, S., Leelayuwat, N., and Chatchawan, U. (2012). Effects of handicraft sitting postures on lower trunk muscle fatigue. *Ergonomics* 55 (6), 693–703. doi:10.1080/00140139.2012.658086

Armstrong, R., Brogden, C. M., Milner, D., Norris, D., and Greig, M. (2018). The influence of fatigue on star excursion balance test performance in dancers. *J. Dance Med. Sci.* 22 (3), 142–147. doi:10.12678/1089-313X.22.3.142

Askari, Z., and Esmaeili, H. (2021). Effect of trunk muscles fatigue on plantar pressure distribution in novice runners. *J. Biomechanics* 122, 110487. doi:10.1016/j.jbiomech.2021.110487

Bell, J. A., and Burnett, A. (2009). Exercise for the primary, secondary and tertiary prevention of low back pain in the workplace: a systematic review. *J. Occup. Rehabil.* 19, 8–24.

Borg, G. (1970). Perceived exertion as an indicator of somatic stress. *Scand. J. rehabilitation Med.* 2, 92–98. doi:10.2340/1650197719702239298

Borujeni, B. G., and Yalfani, A. (2020). Effect of respiratory muscle training session on ankle muscle activity in athletes with chronic low back pain performing overhead squats: A randomized controlled trial. *JBI Evid. Implement.* 18 (2), 256–264. doi:10.1097/XEB.0000000000000204

Cohen, J. (2013). *Statistical power analysis for the behavioral sciences*. New York: Routledge.

Csepregi, É., Gyurcsik, Z., Veres-Balajti, I., Nagy, A. C., Szekanecz, Z., and Szántó, S. (2022). Effects of classical breathing exercises on posture, spinal and chest mobility among female university students compared to currently popular training programs. *Int. J. Environ. Res. Public Health* 19 (6), 3728. doi:10.3390/ijerph19063728

Csuhai, É. A., Nagy, A. C., Váradi, Z., and Veres-Balajti, I. (2020). Functional analysis of the spine with the Idiag SpinalMouse System among sedentary workers affected by non-specific low back pain. *Int. J. Environ. Res. Public Health* 17 (24), 9259. doi:10.3390/ijerph17249259

D'souza, C. J., Santhakumar, H., Bhandary, B., and Rokaya, A. (2021). Immediate effect of stabilization exercises versus conventional exercises of the trunk on dynamic balance among trained soccer players. *Hong Kong Physiother. J.* 42, 23–30. doi:10.1142/s1013702522500032

del Pozo-Cruz, B., Adsuar, J. C., Parraca, J., del Pozo-Cruz, J., Moreno, A., and Gusi, N. (2012). A web-based intervention to improve and prevent low back pain among office workers: A randomized controlled trial. *J. Orthop. sports Phys. Ther.* 42 (10), 831–841. doi:10.2519/jospt.2012.3980

del Pozo-Cruz, B., Gusi, N., del Pozo-Cruz, J., Adsuar, J. C., Hernandez-Mocholí, M., and Parraca, J. A. (2013). Clinical effects of a nine-month web-based intervention in subacute non-specific low back pain patients: A randomized controlled trial. *Clin. Rehabil.* 27 (1), 28–39. doi:10.1177/0269215512444632

Demircioğlu, A., Osman, D., and Özkal, Ö. (2021). Yeni Fiziksel Aktivite Anketi'nin Türkçe versiyonunun geçerlik ve güvenirliği. *Cukurova Med. J.* 46 (2), 742–755. doi:10.17826/cumj.870655

Dhalla, Z. (2022). Student sleep patterns when exposed to mindfulness reminders.

Džubera, A., Sabo, V., Chochol, J., and Illeš, R. (2016). Neck spine spondylosis – do we operate a patient or an image? *Rehabil* 53, 209–216.

Egger, G. J., Vogels, N., and Westerterp, K. R. (2001). Estimating historical changes in physical activity levels. *Med. J. Aust.* 175 (11-12), 635–636. doi:10.5694/j.1326-5377.2001.tb143758.x

Farzami, A., and Anbarian, M. (2020). The effects of fatigue on plantar pressure and balance in adolescent volleyball players with and without history of unilateral ankle injury. *Sci. Sports* 35 (1), 29–36. doi:10.1016/j.scispo.2019.03.011

Ferraro, F. V., Gavin, J. P., Wainwright, T. W., and McConnell, A. K. (2020). Comparison of balance changes after inspiratory muscle or Otago exercise training. *PloS one* 15 (1), e0227379. doi:10.1371/journal.pone.0227379

Fonta, M., Tsepis, E., Fousekis, K., and Mandalidis, D. (2021). Acute effects of static self-stretching exercises and foam roller self-massaging on the trunk range of motions and strength of the trunk extensors. *Sports* 9, 159. s Note: MDPI stays neutral with regard to jurisdictional claims in published 2021. doi:10.3390/sports9120159

Fortun-Rabadan, R., Jiménez-Sánchez, C., Flores-Yaben, O., and Bellosta-López, P. (2021). Workplace physiotherapy for musculoskeletal pain-relief in office workers: A pilot study. *J. Educ. Health Promot.* 10, 75. doi:10.4103/jehp.jehp_888_20

Freire, A. P. C. F., de Oliveira, C. B. S., Christofaro, D. G. D., Shumate, S., Marques, L. B. F., and Pinto, R. Z. (2022). Isotemporal substitution of sedentary behavior by different physical activity intensities on pain and disability of patients with chronic low back pain: A cross-sectional study. *Archives Phys. Med. Rehabilitation* 103, 1944–1950. doi:10.1016/j.apmr.2022.03.017

Gobbo, S., Bullo, V., Bergamo, M., Duregon, F., Vendramin, B., Battista, F., et al. (2019). Physical exercise is confirmed to reduce low back pain symptoms in office workers: A systematic review of the evidence to improve best practices in the workplace. *J. Funct. Morphol. Kinesiol.* 4 (3), 43. doi:10.3390/jfmk4030043

Gribble, P. A., and Hertel, J. (2004). Effect of hip and ankle muscle fatigue on unipedal postural control. *J. Electromyogr. Kinesiol.* 14 (6), 641–646. doi:10.1016/j.jelekin.2004.05.001

Hamaoui, A., Do, M-C., and Bouisset, S. (2004). Postural sway increase in low back pain subjects is not related to reduced spine range of motion. *Neurosci. Lett.* 357 (2), 135–138. doi:10.1016/j.neulet.2003.12.047

Hamaoui, A., Le Bozec, S., Poupard, L., and Bouisset, S. (2007). Does postural chain muscular stiffness reduce postural steadiness in a sitting posture? *Gait posture* 25 (2), 199–204. doi:10.1016/j.gaitpost.2006.03.012

Hamasaki, H. (2020). Effects of diaphragmatic breathing on health: A narrative review. *Medicines* 7 (10), 65. doi:10.3390/medicines7100065

Hanna, F., Daas, R. N., El-Shareif, T. J., Al-Marridi, H. H., Al-Rojoub, Z. M., and Adegboye, O. A. (2019). The relationship between sedentary behavior, back pain, and psychosocial correlates among University employees. *Front. public health* 7, 80. doi:10.3389/fpubh.2019.00080

Jabłońska, M., Mączyński, J., Fryzowicz, A., and Ogurkowska, M. B. (2021). Electromyographic assessment of muscle fatigue after the Biering-Sorensen test in subjects with low back pain who underwent the McKenzie treatment. *Acta Bioeng. Biomechanics* 23 (3). doi:10.37190/abb-01823-2021-03

Jans, M. P., Proper, K. I., and Hildebrandt, V. H. (2007). Sedentary behavior in Dutch workers: Differences between occupations and business sectors. *Am. J. Prev. Med.* 33 (6), 450–454. doi:10.1016/j.amepre.2007.07.033

Johanson, E., Brumagne, S., Janssens, L., Pijnenburg, M., Claeys, K., and Pääsuke, M. (2011). The effect of acute back muscle fatigue on postural control strategy in people with and without recurrent low back pain. *Eur. Spine J.* 20 (12), 2152–2159. doi:10.1007/s00586-011-1825-3

Kaeding, T., Karch, A., Schwarz, R., Flor, T., Wittke, T. C., Kück, M., et al. (2017). Whole-body vibration training as a workplace-based sports activity for employees with chronic low-back pain. *Scand. J. Med. Sci. sports* 27 (12), 2027–2039. doi:10.1111/sms.12852

Kang, J-I., Jeong, D-K., and Choi, H. (2016). Effect of exhalation exercise on trunk muscle activity and oswestry disability index of patients with chronic low back pain. *J. Phys. Ther. Sci.* 28 (6), 1738–1742. doi:10.1589/jpts.28.1738

Kang, J-Y., Seo, D-K., Cho, J-C., and Lee, B-K. (2018). Effectiveness of breathing exercises on spinal posture, mobility and stabilization in patients with lumbar instability. *J. Korean Soc. Phys. Med.* 13 (3), 81–89. doi:10.13066/kspm.2018.13.3.81

Karimi, A., and Saeidi, M. (2013). Review of relationship between fear avoidance beliefs and postural stability in non specific chronic low back pain. *J. Spine* 2 (4), 100. doi:10.4172/2165-7939.1000139

Kett, A. R., and Sichting, F. (2020). Sedentary behaviour at work increases muscle stiffness of the back: Why roller massage has potential as an active break intervention. *Appl. Ergon.* 82, 102947. doi:10.1016/j.apergo.2019.102947

Kwon, J. W., Park, S. Y., Baek, K. H., Youk, K., and Oh, S. (2021). Breathing exercise called the maximal abdominal contraction maneuver. *Medicina* 57 (2), 129. doi:10.3390/medicina57020129

Larson, D. J., and Brown, S. H. (2018). The effects of trunk extensor and abdominal muscle fatigue on postural control and trunk proprioception in young, healthy individuals. *Hum. Mov. Sci.* 57, 13–20. doi:10.1016/j.humov.2017.10.019

Lenková, R., and Vasilišinová, V. (2019). Spinal mobility in women with sedentary job. *Acta Fac. Educ. Phys. Univ. Comen.* 59 (2), 138–147. doi:10.2478/afepuc-2019-0012

Macedo, A. C., Trindade, C. S., Brito, A. P., and Socorro Dantas, M. (2011). On the effects of a workplace fitness program upon pain perception: A case study encompassing office workers in a Portuguese context. *J. Occup. rehabilitation* 21 (2), 228–233. doi:10.1007/s10926-010-9264-2

Macefield, G., Hagbarth, K-E., Gorman, R., Gandevia, S., and Burke, D. (1991). Decline in spindle support to alpha-motoneurones during sustained voluntary contractions. *J. physiology* 440 (1), 497–512. doi:10.1113/jphysiol.1991.sp018721

Maciel, R. R. B. T., Dos Santos, N. C., Portella, D. D. A., Alves, P. G. J. M., and Martinez, B. P. (2018). Effects of physical exercise at the workplace for treatment of low back pain: A systematic review with meta-analysis. *Rev. Bras. Med. do Trab.* 16 (2), 225–235. doi:10.5327/Z1679443520180133

Madigan, M. L., Davidson, B. S., and Nussbaum, M. A. (2006). Postural sway and joint kinematics during quiet standing are affected by lumbar extensor fatigue. *Hum. Mov. Sci.* 25 (6), 788–799. doi:10.1016/j.humov.2006.04.004

Martin, P. G., Smith, J. L., Butler, J. E., Gandevia, S. C., and Taylor, J. L. (2006). Fatigue-sensitive afferents inhibit extensor but not flexor motoneurons in humans. *J. Neurosci.* 26 (18), 4796–4802. doi:10.1523/JNEUROSCI.5487-05.2006

Mateo, C., and Talavera, J. A. (2018). Short-time Fourier transform with the window size fixed in the frequency domain. *Digit. Signal Process.* 77, 13–21. doi:10.1016/j.dsp.2017.11.003

Mayer, J. M., Nuzzo, J. L., and Dagenais, S. (2013). Use of participant focus groups to identify barriers and facilitators to worksite exercise therapy adherence in randomized controlled trials involving firefighters. *Patient Prefer. adherence* 7, 207–215. doi:10.2147/PPA.S42507

Mehta, S. P., Jarvis, A., Standifer, D., and Warnimont, C. (2018). International physical activity questionnaire. *Crit. Reviews™ Phys. Rehabilitation Med.* 30 (2), 125–127. doi:10.1615/critrevphysrehabilmed.2018026180

Mellin, G. (1987). Correlations of spinal mobility with degree of chronic low back pain after correction for age and anthropometric factors. *Spine* 12 (5), 464–468. doi:10.1097/00007632-198706000-00008

Mellin, G. (1990). Decreased joint and spinal mobility associated with low back pain in young adults. *Clin. Spine Surg.* 3 (3), 238–243. doi:10.1097/00002517-199009000-00007

Otadi, K., Nakhostin Ansari, N., Sharify, S., Fakhari, Z., Sarafraz, H., Aria, A., et al. (2021). Effects of combining diaphragm training with electrical stimulation on pain, function, and balance in athletes with chronic low back pain: A randomized clinical trial. *BMC Sports Sci. Med. Rehabilitation* 13 (1), 20–10. doi:10.1186/s13102-021-00250-y

Pline, K. M., Madigan, M. L., Nussbaum, M. A., and Grange, R. W. (2005). Lumbar extensor fatigue and circumferential ankle pressure impair ankle joint motion sense. *Neurosci. Lett.* 390 (1), 9–14. doi:10.1016/j.neulet.2005.07.047

Post, R., and Leferink, V. (2004). Spinal mobility: Sagittal range of motion measured with the SpinalMouse, a new non-invasive device. *Archives Orthop. Trauma Surg.* 124 (3), 187–192. doi:10.1007/s00402-004-0641-1

Rasheed, H., Ahmad, I., Javed, M. A., Rashid, J., and Javeed, R. S. (2021). Effects of diaphragmatic breathing maneuver and abdominal drawing-in maneuver on trunk stability in stroke patients. *Phys. Occup. Ther. Geriatrics* 39 (1), 1–10. doi:10.1080/02703181.2020.1770395

Roth, R., Donath, L., Zahner, L., and Faude, O. (2021). Acute leg and trunk muscle fatigue differentially affect strength, sprint, agility, and balance in young adults. *J. Strength & Cond. Res.* 35 (8), 2158–2164. doi:10.1519/JSC.0000000000003112

Russo, M. A., Santarelli, D. M., and O'Rourke, D. (2017). The physiological effects of slow breathing in the healthy human. *Breathe* 13 (4), 298–309. doi:10.1183/20734735.009817

Sabo, V., Džubera, A., Gábor, M., and Sabo, J. (2016). When is FBSS really FBSS? *Rehabil* 53, 233–238.

Saiklang, P., Puntumetakul, R., and Chatprem, T. (2022). The effect of core stabilization exercise with the abdominal drawing-in maneuver technique on stature change during prolonged sitting in sedentary workers with chronic low back pain. *Int. J. Environ. Res. Public Health* 19 (3), 1904. doi:10.3390/ijerph19031904

Schaafsma, F. G., Anema, J. R., and van der Beek, A. J. (2015). Back pain: Prevention and management in the workplace. *Best Pract. Res. Clin. Rheumatology* 29 (3), 483–494. doi:10.1016/j.berh.2015.04.028

Seidi, F., Hamedani, P. D., Rajabi, R., Sheikhhoseini, R., and Khoshroo, F. (2019). A new fatigue protocol to assess postural sway in collegiate female athletes. *Fatigue Biomed. Health & Behav.* 7 (4), 218–228. doi:10.1080/21641846.2019.1699640

Shah, S., Shirodkar, S., and Deo, M. (2020). Effectiveness of core stability and diaphragmatic breathing vs. core stability alone on pain and function in mechanical non-specific low back pain patients: A randomised control trial. *Int. J. Health Sci. Res.* 10 (2), 232–241.

Shariat, A., Cleland, J. A., Danaee, M., Kargarfard, M., Sangelaji, B., and Tamrin, S. B. M. (2018). Effects of stretching exercise training and ergonomic modifications on musculoskeletal discomforts of office workers: A randomized controlled trial. *Braz. J. Phys. Ther.* 22 (2), 144–153. doi:10.1016/j.bjpt.2017.09.003

Sitthipornvorakul, E., Janwantanakul, P., and Lohsoonthorn, V. (2015). The effect of daily walking steps on preventing neck and low back pain in sedentary workers: A 1-year prospective cohort study. *Eur. spine J.* 24 (3), 417–424. doi:10.1007/s00586-014-3577-3

Skrebutėnaitė, I. E., and Karanauskienė, D. (2019). Perceived physical activity benefits and barriers in sedentary adults. *Baltic J. sport health Sci.* 2 (113). doi:10.33607/bjshs.v2i113.788

Soares, C. O., Pereira, B. F., Gomes, M. V. P., Marcondes, L. P., de Campos Gomes, F., and de Melo-Neto, J. S. (2019). Preventive factors against work-related musculoskeletal disorders: Narrative review. *Rev. Bras. Med. do Trab.* 17 (3), 415–430. doi:10.5327/Z1679443520190360

Stephens, R. J., Haas, M., Moore, W. L., III, Emmil, J. R., Sipress, J. A., and Williams, A. (2017). Effects of diaphragmatic breathing patterns on balance: A preliminary clinical trial. *J. Manip. physiological Ther.* 40 (3), 169–175. doi:10.1016/j.jmpt.2017.01.005

Suehiro, T., Ishida, H., Kobara, K., Osaka, H., Kurozumi, C., and Watanabe, S. (2021). Immediate changes in trunk muscle activation patterns during a lifting task following an abdominal drawing-in exercise in subjects with recurrent low back pain. *J. Back Musculoskelet. Rehabilitation* 34 (1), 77–85. doi:10.3233/BMR-191549

Sufreshtri, H., and Puspitasari, N. (2020). Pengaruh workplace stretching active dynamic back exercise terhadap peningkatan aktivitas fungsional low back pain myogenic pada penjahit. *Visikes J. Kesehat. Masy.* 19 (01). doi:10.33633/visikes.v19i01.3779

Sung, Y-B., Lee, J-H., and Park, Y-H. (2014). Effects of thoracic mobilization and manipulation on function and mental state in chronic lower back pain. *J. Phys. Ther. Sci.* 26 (11), 1711–1714. doi:10.1589/jpts.26.1711

Suresh, A. K. D., Behera, T. P., Wilson, E., and Kumar, R. D. (2021). Comparison of isometric endurance of abdominal and back extensor muscles in manual and sedentary males in the age group of 20-40 years. *J. Aging Sci.* 9 (254), 1–7. doi:10.35248/2329-8847.21.9.254

Taimela, S., Kankaanpää, M., and Luoto, S. (1999). The effect of lumbar fatigue on the ability to sense a change in lumbar position: A controlled study. *Spine* 24 (13), 1322–1327. doi:10.1097/00007632-199907010-00009

Tajali, S., Roozbehfar, N., Mehravar, M., Goharpey, S., and Gayem, K. (2022). Effects of back extensor and hip abductor fatigue on dynamic postural stability in patients with nonspecific chronic low back pain: A case-control study. *Physiother. Theory Pract.* 38 (12), 1987–1995. doi:10.1080/09593985.2021.1913775

Taulaniemi, A., Kankaanpää, M., Tokola, K., Parkkari, J., and Suni, J. H. (2019). Neuromuscular exercise reduces low back pain intensity and improves physical functioning in nursing duties among female healthcare workers; secondary analysis of a randomised controlled trial. *BMC Musculoskelet. Disord.* 20 (1), 1–15. doi:10.1186/s12891-019-2678-x

Thakkar, H. H., and Kumar, S. (2015). Static and dynamic postural stability in subjects with and without chronic low back pain. *Int. J. Res. Med. Sci.* 3 (9), 2405–2409. doi:10.18203/2320-6012.ijrms20150639

Topalidou, A., Tzagarakis, G., Souvatzis, X., Kontakis, G., and Katonis, P. (2014). Evaluation of the reliability of a new non-invasive method for assessing the functionality and mobility of the spine. *Acta Bioeng. biomechanics* 16 (1), 117–124. doi:10.5277/abb140114

Vostatek, P., Novák, D., Rychnovský, T., and Wild, J. (2013). Diaphragm postural function analysis using magnetic resonance imaging. *PloS one* 8 (3), e56724. doi:10.1371/journal.pone.0056724

Waongenngarm, P., Areerak, K., and Janwantanakul, P. (2018). The effects of breaks on low back pain, discomfort, and work productivity in office workers: A systematic review of randomized and non-randomized controlled trials. *Appl. Ergon.* 68, 230–239. doi:10.1016/j.apergo.2017.12.003

G. Yang, R. Splittstoesser, G. Knapik, D. Trippany, S. V. Korkmaz, J. Hoyle, et al. (2005). "Comparison of spinal loads in kneeling and standing postures during manual materials handling," *Proceedings of the human factors and ergonomics society annual meeting* (Los Angeles, CA: SAGE Publications Sage CA).

Yi, C., Tang, F., Li, K-W., Hu, H., Zuo, H., and Zhao, C. (2022). Modeling and validation of fatigue and recovery of muscles for manual demolition tasks. *Int. J. Environ. Res. Public Health* 19 (2), 930. doi:10.3390/ijerph19020930

Zemková, E., Štefániková, G., and Muyor, J. (2016). Load release balance test under unstable conditions effectively discriminates between physically active and sedentary young adults. *Hum. Mov. Sci.* 48, 142–152. doi:10.1016/j.humov.2016.05.002

Zemková, E., Cepková, A., and Muyor, J. M. (2021a). The association of reactive balance control and spinal curvature under lumbar muscle fatigue. *PeerJ* 9, e11969. doi:10.7717/peerj.11969

Zemková, E., Ďurinová, E., Džubera, A., Horníková, H., Chochol, J., Koišová, J., et al. (2021b). The relationship between reactive balance control and back and hamstring strength in physiotherapists with non-specific back pain: Protocol for a cross-sectional study. *Int. J. Environ. Res. Public Health* 18 (11), 5578. doi:10.3390/ijerph18115578

Zemková, E., Ďurinová, E., Džubera, A., Chochol, J., Koišová, J., Šimonová, M., et al. (2021c). Simultaneous measurement of centre of pressure and centre of mass in assessing postural sway in healthcare workers with non-specific back pain: Protocol for a cross-sectional study. *BMJ open* 11 (8), e050014. doi:10.1136/bmjopen-2021-050014

Zhang, C., Zhang, Z., Li, Y., Feng, C., Meng, H., Gao, Y., et al. (2020). Pain catastrophizing is related to static postural control impairment in patients with nonspecific chronic low back pain: A cross-sectional study. *Pain Res. Manag.* 2020, 9629526. doi:10.1155/2020/9629526

frontiers | Frontiers in Neuroscience

TYPE Perspective
PUBLISHED 21 July 2023
DOI 10.3389/fnins.2023.1202930

OPEN ACCESS

EDITED BY
Pawel Zalewski,
Nicolaus Copernicus University in Toruń,
Poland

REVIEWED BY
Tymoteusz Zera,
Medical University of Warsaw, Poland

*CORRESPONDENCE
Diana Araja
✉ Diana.Araja@rsu.lv

RECEIVED 09 April 2023
ACCEPTED 30 June 2023
PUBLISHED 21 July 2023

CITATION
Araja D, Kruminaer M, Nora-Krukle Z, Schneider ME, Berkis U and Murovska M (2023) Coaching to strengthen critical success factors in integrative care for chronic fatigue patients: the Patient Needs-Resources model. *Front. Neurosci.* 17:1202930. doi: 10.3389/fnins.2023.1202930

Coaching to strengthen critical success factors in integrative care for chronic fatigue patients: the Patient Needs-Resources Model

Diana Araja[1]*, Angelika Krumina[2], Zaiga Nora-Krukle[1], Marion E. Schneider[3], Uldis Berkis[4] and Modra Murovska[1]

[1]Institute of Microbiology and Virology, Riga Stradins University, Riga, Latvia, [2]Department of Infectology, Riga Stradins University, Riga, Latvia, [3]Department of Experimental Anesthesiology, University of Ulm, Ulm, Germany, [4]Development and Project Department, Riga Stradins University, Riga, Latvia

Theoretical and empirical studies discover that an integrative approach is particularly important in chronic disorders and multiple long-term conditions, such as chronic fatigue. Chronic fatigue syndrome (CFS) is a classic example of a potentially severe, multisystemic illness with a wide diversity of symptoms and the corresponding diagnostic complexity. The prevalence of CFS-like syndromes expanded in the context of the COVID-19 pandemic, increasing the disorder and treatment burden. Thus, this article aimed to draw attention to the possibilities to strengthen the integrative approach to diagnosing and treating chronic disorders and multiple long-term conditions. The main critical success factors identified for integrative approaches were: a holistic approach, that provides a more comprehensive diagnostic and personalized treatment strategy, a multidisciplinary team, and patient engagement. The strengths and weaknesses of these factors were explored and coaching was identified as a potential unifying and reinforcing element. Coaching has a wide spectrum of manifestations clearly representing a holistic approach, that has been successfully used in multidisciplinary team building. Moreover, coaching exposes support addressing the patient engagement issues identified by the Patient Needs-Resources Model (PN-R Model) such as low levels of self-efficacy, optimism, and subjective well-being. Coaching may assist patients to identify and prioritize their goals, becoming aware of their personal resources, developing strategies for managing symptoms, and building skills to increase their self-efficacy and active engagement in the treatment process. Therefore, the authors emphasize coaching as a perspective element of optimization of patient care, that requires additional theoretical and long-term empirical research.

KEYWORDS

myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS), holistic approach, multidisciplinary team, patient engagement, health-related quality of life (HRQoL)

Introduction

Chronic fatigue is manifested in different perspectives – as a complex disorder such as chronic fatigue syndrome (CFS) or myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS), or chronic fatigue as a medical condition accompanying other disorders. CFS is a heterogenous disorder of multiple disabling symptoms with complex manifestations in which patients experience a wide range of symptoms that are broadly categorized as neurological, immunological, autonomic and endocrinological (Kujawski et al., 2021). Principal component analyses, utilized to identify symptom subgroups and the relationships with functioning and quality of life, suggested four statistically distinct and clinically meaningful subgroups of symptoms: inflammatory, pain, neurocognitive, and autonomic; all symptom subgroups correlated significantly with measures of fatigue, mood, functioning and quality of life (Jonsjö et al., 2017).

CFS is also characterized by neuro-psychiatric (e.g., depression, irritability, sleep disorders, autonomic symptoms and neurocognitive defects) and physio-somatic (fatigue, a flu-like malaise, hyperalgesia, irritable bowel, muscle pain and tension) symptoms (Maes, 2015). According to a review of case definitions, at least 25 case definitions/diagnostic criteria based on three conceptual factors (aetiology, pathophysiology, and exclusionary disorders) were developed between 1986 and 2020 (Lim and Son, 2020).

Regarding prevalence, ME/CFS affects 0.4% of the population, 25% of which experience the severe and very severe categories; these are defined as being wheelchair-, house-, and bed-bound (Strassheim et al., 2021). CFS spectrum is expanded as a result of the disease caused by the SARS-CoV-2 virus (COVID-19) pandemic and as a concomitant element of long-COVID (Araja et al., 2021; Davis et al., 2021; Friedman et al., 2021; Gaber, 2021; Graham et al., 2021; Jason et al., 2021; Komaroff and Bateman, 2021; Komaroff and Lipkin, 2021; Paul et al., 2021; Poenaru et al., 2021; Simani et al., 2021; Townsend et al., 2021; Wong and Weitzer, 2021; Araja et al., 2022). At the same time, the financial burden increases accordingly. Prior to the COVID-19 pandemic, researchers estimated a United States (U.S.) ME/CFS prevalence of 1.5 million and an annual economic impact of $36–51 billion (Mirin et al., 2022). In 2022, due to the COVID-19 pandemic and its resulting post-acute sequalae, it was estimated that total ME/CFS prevalence could rise to between five and nine million. This would incur an annual U.S. economic impact of $149 to $362 billion in medical expenses and lost income, exclusive of other costs, such as disability benefits, social services, and lost wages of caretakers (Mirin et al., 2022).

Due to difficulties in diagnosing and treating CFS (or ME/CFS), its different manifestations, and its severity, patients are exposed to a significant burden of the disorder. At the same time, the humanistic or patient-centric view argues strongly that populations with physical, developmental or cognitive disabilities – often with related chronic conditions or complex illnesses – endow the concept of healthcare integration with a unique logic and meaning (Kodner and Spreeuwenberg, 2002). Vulnerable individuals, such as the diverse group described above, have complicated and ongoing needs (which frequently are part-medical, part-physical, part-psychological, and part-social), experience difficulties in everyday living, require a mix of services delivered sequentially or simultaneously by multiple providers and receive both cure and care in the home, community and institutional settings (Kodner and Spreeuwenberg, 2002).

Therefore, the authors considered that CFS is a classic example of a disorder in which integrative care should play a key role in the choice and implementation of diagnostic, treatment and care pathways. However, given the slow uptake of this approach in practice, the authors posed a research question within this perspective: what are the critical success factors of an integrative approach in chronic disorders and multiple long-term conditions and how can these be strengthened? Accordingly, this article aimed to explore the possibilities to strengthen the integrative care approach.

After reviewing the theoretical background and practical considerations, the authors came to the intermediate conclusion that a holistic approach, a multidisciplinary team, and patient engagement are the critical success factors for an integrative approach. In order to identify phenomena that could strengthen this triad, the traits of their development were assessed and a potentially strengthening element was identified – coaching, which is characterized by the holistic approach, is applicable for promoting team cohesion and strengthening patients' personal resources. Coaching, which includes working with a trained professional to set goals, develop strategies, and build skills, has the potential to encourage a holistic approach and improve multidisciplinary team building and patient engagement in the management of chronic disorders such as CFS.

Integrative care for patients with chronic disorders: critical success factors

A contemporary multidisciplinary stakeholder-informed definition of integrative healthcare is generated by Leach et al. (2018), based on a thematic analysis of data drawn from healthcare consumers/providers, integrative healthcare organization webpages, and eligible articles. The consensus is reached on a single definition of integrative healthcare: "Integrative healthcare is a collaborative, coordinated, transdisciplinary, person-centered model of care informed by a holistic model of health and the best available evidence; care is facilitated by an interdependent, multi-disciplinary team of like-minded, biomedical, allied and complementary health professionals that work together in a collegial, non-hierarchical, communicative and respectful environment in order to prevent illness and optimize health, healing, and wellness in individual clients" (Leach et al., 2018).

This definition includes a number of conceptual notions, and each of them is worth exploring in more depth, including the client-centered approach which is not a new concept – it dates back to the 1940s when Rogers described non-directive client-centered therapy (Rogers, 1946). Unlike other therapies in which the skills of the therapist are to be exercised upon the client, in this approach the skills of the therapist are focused on creating a psychological atmosphere in which the client can work with his/her own residing constructive forces whose strength and uniformity have been either entirely unrecognized or grossly underestimated (Rogers, 1946).

Later, in the 1950–1960s, Balint reinforced this approach and introduced the term "patient-centered medicine" which called for examining patients' psychological needs in addition to their biological symptoms and for a view of the patient as a unique human being, in contrast to "illness-oriented medicine" (Balint, 1955; Balint, 1969). The illness-oriented biomedical model represents the application to the medicine of the classical factor-analytic approach, focuses on the disease, and does not consider patients' experience of their illness or how their social environment and circumstances affect how they view their illness (Engel, 1980).

In the 1970–1980s, Engel introduced the biopsychosocial model as a scientific model constructed to take into account the missing dimensions of the biomedical model and to promote the holistic health view (Engel, 1980). Since patient-centered approach's inception, many models and definitions have been proposed in the literature (Gerteis et al., 1993; Mead and Bower, 2000; Stewart et al., 2000; Davis et al., 2005; Epstein et al., 2005; Clayton et al., 2011; Barry and Edgman-Levitan, 2012; Fredericks et al., 2012; Van Berckelaer et al., 2012; Kitson et al., 2013; Stewart et al., 2013; Moreau et al., 2020), although their practical implementation is lagging behind the theory, as this approach requires significant core changes in the norms and expectations for most healthcare systems.

The results of examining the evolution of healthcare integration (Evans et al., 2013) through a review and synthesis of over 25 years of international academic research and literature, demonstrated six major, inter-related shifts in integration strategies: (a) from a focus on horizontal integration to an emphasis on vertical integration; (b) from acute care and institution-centered models of integration to a broader focus on community-based health and social services; (c) from economic arguments for integration to an emphasis on improving quality of care and creating value; (d) from evaluations of integration using an organizational perspective to an emerging interest in patient-centered measures; (e) from a focus on modifying organizational and environmental structures to an emphasis on changing ways of working and influencing underlying cultural attitudes and norms; and (f) from integration for all patients within defined regions to a strategic focus on integrating care for specific populations (Evans et al., 2013). Additionally, it was noted that many of these shifts are a growing recognition of the value of understanding healthcare integration as processes situated in Complex-Adaptive Systems (CAS; Evans et al., 2013). Assuming the healthcare system as a CAS provides additional opportunities for understanding a healthcare system's functioning, governance, and decision-making (Araja, 2022).

Integrative care is represented mostly in the context of integrated care, which also has many definitions and interpretations that complicate its perception and implementation. There are multiple levels of integrated care, and four levels of health services delivery are investigated more often: the personal, the professional, the management, and the system level (Valentijn et al., 2013; Zonneveld et al., 2020) In addition to the different levels, researchers present two crucial dimensions of integration: systemic integration, which includes the coherence of rules and policies in the healthcare system, and normative integration, which comprises the role of shared values in coordination and collaboration (Valentijn et al., 2013; Valentijn, 2016; Zonneveld et al., 2020).

The integrative approach is most closely linked to the two levels of the integrated healthcare system: the personal (the interaction between patient and care provider) and the professional (the interaction between care providers). The research and thematic analysis performed by Leach et al. (2018) identified seven distinct themes on integrative healthcare, which could be refined into three interrelated and interdependent constructs, as the triad (critical success factors) of integrative healthcare – the client, the team, and the approach to care.

The authors formulated this triad in the framework of the current study as a holistic approach, multidisciplinary team, and patient engagement.

Holistic approach, multidisciplinary team, and patient engagement models

The theoretical framework of the holistic approach is mainly based on Smuts' concepts defined in the book "Holism and Evolution" (1926), among other insights declared, that "Personality as a whole, as a form, is indeed the highest form of Holism" (Smuts, 1926). Accordingly, holistic medicine concepts have evolved over time, but there remain contradictions with the dominant biomedical paradigm. Value-based healthcare implies that healthcare issues are addressed most effectively with the "physicians in the lead" strategy. However, according to diverse stakeholders, (Malik et al., 2018) "physicians in the lead" strategy does not support a holistic healthcare delivery approach, primarily because of the strong biomedical focus of the physicians. Although physicians can be educated to place more emphasis on holistic outcomes, holistic care delivery requires greater integration and teamwork in the care chain. As different healthcare professions are complementary to each other, a new strategy of a "team in the lead" was suggested to meet the holistic healthcare demands (Malik et al., 2018).

There are positive examples in the literature of multidisciplinary assessment of chronic fatigue, following a holistic approach that is based on the biopsychosocial model (Mariman et al., 2013), but a multidisciplinary team is more often seen in the diagnosis setting than in the treatment process. Also, some findings (Kvarnström, 2008) show difficulties related to the team dynamic that arose when team members acted toward one another as representatives of their professions, difficulties that occurred when the members' various knowledge contributions interacted in the team, and difficulties related to the influence of the surrounding organization. The perceived consequences of the difficulties, beyond individual consequences, were restrictions on the use of collaborative resources to arrive at a holistic view of the patient's problem, and barriers to providing patient care and service in the desired manner (Kvarnström, 2008).

Therefore, the authors propose to recognize multidisciplinary team building as a deliberately managed process in the context of human resources (HR) management and co-creation. HR co-creation is a continuous process in which HR and stakeholders optimize value through collaborative efforts to innovate in the design and use of HR practices to better satisfy multiple stakeholders' needs (Hewett and Shantz, 2021). In the framework of interaction with stakeholders, it is useful to use already established models, such as the Harvard model, (Bondarouk and Brewster, 2016) that detail interactions with different stakeholders, which in the case of chronic diseases will include patients, families, care providers, patient organizations, local authorities, public institutions, scientific representatives and other stakeholders.

At the same time, the authors assume that the patient's personal resources are the crucial aspect in the co-creation of disease management and recovery. Personal resources mainly include self-efficacy, optimism, and subjective well-being. According to Bandura, the self-efficacy portion of Social Cognitive Theory addresses the origin of self-efficacy beliefs, their structure and functional properties, their diverse effects, the processes through which they work, and how to develop and enlist such beliefs for personal and social change (Bandura, 1997). Optimism refers to the expectancy of a positive outcome that encourages persistence in the face of obstacles, and subjective well-being, in turn, refers to a psychological asset that helps individuals to carry out their objectives in the best psychological conditions (Neveu et al., 2023). The Conservation of Resources theory predicts that resource loss is the principal ingredient in the stress process (Hobfoll, 2001).

Therefore, the common trait of integrative approaches is that they require both a multidisciplinary team and the active engagement of patients in the treatment process. A concept analysis performed by Higgins et al. (2017) revealed four defining attributes of patient engagement: personalization, access, commitment, and therapeutic alliance. Patient engagement is defined as the desire and capability to actively choose to participate in care in a way uniquely appropriate to the individual, in cooperation with a healthcare provider or institution, for the purposes of maximizing outcomes or improving experiences of care (Higgins et al., 2017).

Researchers had proposed different models for patient engagement, one of the most well-known being the Patient Health Engagement Model (PHE Model), developed by Graffigna and colleagues (Graffigna et al., 2014). According to this model, the disease onset has a great influence on the patient's psychological functioning, and a better balance is expected to be produced among the three experiential dimensions implied in the health management process: think (cognitive level), feel (emotional level), and act (behavioral level) (Graffigna et al., 2014). Other models such as the Patient-derived Model of Patient Engagement *via* Patient and Family Advisory Councils (PFACs; Dukhanin et al., 2020), the "Ottawa Model" for patient engagement in research (Vanderhout et al., 2022), and Pre-screening Models for Patient Engagement: the MOPEAD project (Boada et al., 2020) are also used. However, it should be noted that, despite the methodological basis, the practical patient engagement process is slowed.

Discussion

The authors assume that current models do not adequately address the crucial aspect – the patient's personal resources. It is therefore worth paying attention to HR models, such as the Job Demands-Resources (JD-R) model (Demerouti and Bakker, 2011). The JD-R model is a theoretical framework that tries to integrate two fairly independent research traditions: the stress research tradition and the motivation research tradition. According to the JD-R model, job demands are initiators of a health impairment process and job resources (social support, performance feedback, autonomy) are initiators of a motivational process (Demerouti and Bakker, 2011). However, the focus of this model is mostly on the relationship between job demand and job resources, not on personal resources.

Based on the theories observed, the authors propose an option of the Patient Needs-Resources Model (PN-R Model), the conceptual framework of which is shown in Figure 1.

The PN-R Model (Figure 1) suggests that Health-related quality of life (HRQoL) is the dependent variable; Healthcare resources and Personal resources are the independent variables. Accordingly, Patient engagement is a mediator, and Unmet needs – are a moderator. The impact of specific diseases on HRQoL might be taken into account, as for example, ME/CFS can reduce the score of HRQoL by an average of 40 points out of 100, measured by the Visual Analogue Scale (Brenna et al., 2021). Healthcare resources can be defined in the context of the World Health Organization's healthcare system building blocks: service delivery, health workforce, information, medical technologies, financing, leadership and governance, which are used also in the evaluation of healthcare resilience (Fridell et al., 2020). Unmet medical needs may be related to the availability, accessibility, affordability, and acceptability of healthcare, assessed by Multi-criteria Decision Analysis, and specific needs related to a particular diagnosis or medical condition (Araja, 2018).

The PN-R Model might operate in such a way that, by using healthcare resources and personal resources and being aware of unmet needs, the patient actively engages in a treatment process that improves their HRQoL, which returns as enhanced personal resources. However, in real life, personal resources, which include self-efficacy, optimism, and subjective well-being, are the weakest point in ensuring patient engagement. It should be noted that a person needs energy, strength, and a clear mind to demonstrate self-efficacy, optimism, and subjective well-being, which most often patients do not have, especially chronic fatigue patients.

In this context, and in light of the authors' performed recent research on the advantages of an integrative approach in the primary healthcare of post-COVID-19 and ME/CFS patients (Araja et al., 2023), the authors suggest that coaching is important in working with chronic fatigue patients. A case study analysis demonstrates significant improvements in the health status of ME/CFS and post-COVID-19 patients assessed by the EuroQol-5D-5L tool (Araja et al., 2023). Current evidence, produced by a systematic review and meta-analysis of randomized controlled trials, suggests also that health coaching could reduce blood pressure, improve dietary behaviors, and increase self-efficacy and awareness among patients in the example of hypertension (Meng et al., 2023) and type-2 diabetes mellitus (Verma et al., 2022). Meta-analyses provide evidence that health coaching reduces both disability and pain in people with chronic low back pain and reduces disability in people with knee osteoarthritis (Prior et al., 2023).

Health coaching is a client-centered approach to engaging users in setting personal goals to achieve positive health behavior changes that lead to improvements in self-care (Clason et al., 2023). Coaching is consistent with Rogers's non-directive therapy theory assumed that "the capacity of the individual to reorganize his attitudes and behavior in ways not determined by external factors

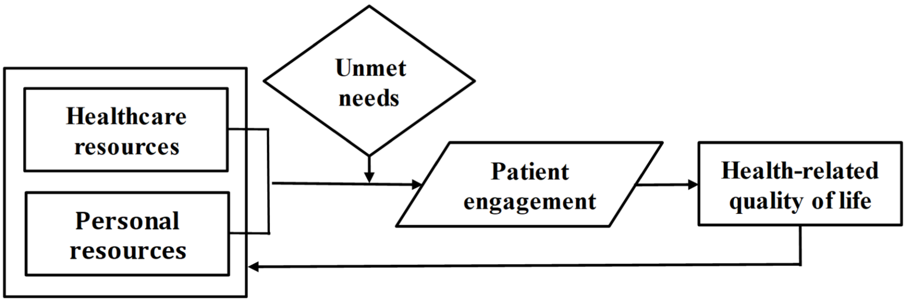


FIGURE 1
Conceptual framework of the proposed Patient Needs-Resources Model (PN-R Model).

nor by previous elements in his own experience, but determined by his own insight into those factors, is an impressive capacity" (Rogers, 1946). These are realized by the holistic competencies of health coaching: the spirit of health coaching relationship and 50/50 patient/provider partnership in health; patient/client engagement through motivational interviewing and empathy; guiding the agenda and goal setting; communication style; cultural competence; active listening, mindfulness; facilitating behavior change; evidence-based practice interventions for wellness, prevention, and chronic health conditions (Huffman, 2016).

Coaching has the potential to reduce the treatment burden for people with chronic disorders and multiple long-term conditions (Matthews et al., 2023), including chronic fatigue, and facilitate the patient-centered care pathway (Gartner et al., 2022). In light of the strengthening of multidisciplinary team building, the coach acts as a complementary agent of the integrative approach, an implementer of team coaching, and a professional supporter of care providers (Körner et al., 2017, 2018; Rosen et al., 2022; Stephany et al., 2023).

In this article, the authors focused on the problems in patients with chronic diseases and multiple long-term conditions, with the example of chronic fatigue (CFS and ME/CFS), which often has a long time to diagnose, while post-diagnostic treatment is usually symptomatic and generalized. In these circumstances, an integrative approach from the diagnostic stage can both speed up the setting of diagnosis and improve the outcomes of treatment. The scientific literature points to the potential of coaching to strengthen the success factors of integrative care: a holistic approach, multidisciplinary team, and patient engagement. The authors underline the importance of further research on the perspective of coaching in integrated care.

Data availability statement

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author.

Author contributions

DA, MS, AK, ZN-K, UB, and MM: conceptualization and writing – review and editing. DA and MS: methodology. MS, AK, ZN-K, UB, and MM: validation. DA: formal analysis, investigation, writing – original draft preparation, and visualization. MM: supervision. All authors contributed to the article and approved the submitted version.

Funding

The research was supported by the Horizon 2020 Project/Agreement No. 952376 "Reducing networking gaps between Riga Stradins University (RSU) and internationally leading counterparts in viral infection-induced autoimmunity research (VirA)" and Latvian Council of Science FARP Grant Number: LZP-2019/1-0380, "Selection of biomarkers in ME/CFS for patient stratification and treatment surveillance/optimization."

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

References

Araja, D. (2018). Multi-criteria decision analysis as a tool for evaluation of unmet needs in health care. *SHS Web Conf.* 51:51.02001. doi: 10.1051/shsconf/20185102001

Araja, D. (2022). Resilience and complex adaptive systems: a perspective on healthcare. *J. Bus. Manag.* 20:23. doi: 10.32025/JBM22006

Araja, D., Berkis, U., Lunga, A., and Murovska, M. (2021). Shadow burden of undiagnosed myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) on society: retrospective and prospective – in light of COVID-19. *J. Clin. Med.* 10:3017. doi: 10.3390/jcm1014301

Araja, D., Berkis, U., and Murovska, M. (2022). COVID-19 pandemic-revealed consistencies and inconsistencies in healthcare: a medical and organizational view. *Health* 10:1018. doi: 10.3390/healthcare10061018

Araja, D., Krumina, A., Berkis, U., Nora-Krukle, Z., and Murovska, M. (2023). "The advantages of an integrative approach in the primary healthcare of Post-COVID-19 and ME/CFS patients," in *COVID-19 pandemic, mental health and neuroscience – New scenarios for understanding and treatment*. eds. S. Palermo and B. Olivier (London: Intech Open).

Balint, M. (1955). The doctor, his patient, and the illness. *Lancet* 265, 683–688. doi: 10.1016/s0140-6736(55)91061-8

Balint, E. (1969). The possibilities of patient-centered medicine. *J. R. Coll. Gen. Pract.* 17, 269–276.

Bandura, A. *Self-efficacy: the exercise of control*. New York: W H Freeman/Times Books/Henry Holt & Co (1997)

Barry, M. J., and Edgman-Levitan, S. (2012). Shared decision making-pinnacle of patient-centered care. *N. Engl. J. Med.* 366, 780–781. doi: 10.1056/NEJMp1109283

Boada, M., Winblad, B., Jessen, F., Visser, P. J., Kramberger, M. G., Rodrigo, A., et al. (2020). Pre-screening models for patient engagement: the MOPEAD project. *Alzheimers Dement.* 16:e044796. doi: 10.1002/alz.044796

Bondarouk, T., and Brewster, C. (2016). Conceptualising the future of HRM and technology research. *Int. J. Hum. Resour. Manage* 27, 2652–2671. doi: 10.1080/09585192.2016.1232296

Brenna, E., Araja, D., and Pheby, D. F. H. (2021). Comparative survey of people with ME/CFS in Italy, Latvia, and the UK: a report on behalf of the Socioeconomics Working Group of the European ME/CFS Research Network (EUROMENE). *Medicina* 57:300. doi: 10.3390/medicina57030300

Clason, C., Sterner-Stein, K., Hirschman, K. B., Barg, F. K., and Riegel, B. (2023). Developing effective health coaches: experience gained in a clinical trial of a health coach intervention. *Patient Educ. Couns.* 108:107592. doi: 10.1016/j.pec.2022.107592

Clayton, M. F., Latimer, S., Dunn, T. W., and Haas, L. (2011). Assessing patient-centered communication in a family practice setting: how do we measure it, and whose opinion matters? *Patient Educ. Couns.* 84, 294–302. doi: 10.1016/j.pec.2011.05.027

Davis, H. E., Assaf, G. S., McCorkell, L., Wei, H., Low, R. J., Re'em, Y., et al. (2021). Characterizing long COVID in an international cohort: 7 months of symptoms and their impact. *Lancet* 38:101019. doi: 10.1016/j.eclinm.2021.101019

Davis, K., Schoenbaum, S. C., and Audet, A.-M. (2005). A 2020 vision of patient-centered primary care. *J. Gen. Intern. Med.* 20, 953–957. doi: 10.1111/j.1525-1497.2005.0178.x

Demerouti, E., and Bakker, A. B. (2011). The job demands-resources model: challenges for future research. *SA J. Industr. Psychol.* 37:974. doi: 10.4102/sajip.v37i2.974

Dukhanin, V., Feeser, S., Berkowitz, S. A., and DeCamp, M. (2020). Who represents me? A patient-derived model of patient engagement via patient and family advisory councils (PFACs). *Health Expect.* 23, 148–158. doi: 10.1111/hex.12983

Engel, G. L. (1980). The clinical application of the biopsychosocial model. *Am. J. Psychiatry* 137, 535–544. doi: 10.1176/ajp.137.5.535

Epstein, R. M., Franks, P., Fiscella, K., Shields, C. G., Meldrum, S. C., Kravitz, R. L., et al. (2005). Measuring patient-centered communication in patient-physician consultations: theoretical and practical issues. *Soc. Sci. Med.* 61, 1516–1528. doi: 10.1016/j.socscimed.2005.02.001

Evans, J. M., Baker, G. R., Berta, W., and Barnsley, J. (2013). The evolution of integrated health care strategies. *Adv. Health Care Manag.* 15:125. doi: 10.1108/s1474-8231(2013)0000015011

Fredericks, S., Lapum, J., Schwind, J., Beanlands, H., Romaniuk, D., and McCay, E. (2012). Discussion of patient-centered care in health care organizations. *Qual. Manag. Health Care* 21, 127–134. doi: 10.1097/QMH.0b013e31825e870d

Fridell, M., Edwin, S., von Schreeb, J., and Saulnier, D. D. (2020). Health system resilience: what are we talking about? A scoping review mapping characteristics and keywords. *Int. J. Health Policy Manag.* 9, 6–16. doi: 10.15171/ijhpm.2019.71

Friedman, K. J., Murovska, M., Pheby, D. F. H., and Zalewski, P. (2021). Our evolving understanding of ME/CFS. *Medicina* 57:200. doi: 10.3390/medicina57030200

Gaber, T. (2021). Assessment and management of post-COVID fatigue. *Prog. Neurol. Psychiatry* 25, 36–39. doi: 10.1002/pnp.698

Gartner, J. B., Abasse, K. S., Bergeron, F., Landa, P., Lemaire, C., and Côté, A. (2022). Definition and conceptualization of the patient-centered care pathway, a proposed integrative framework for consensus: a concept analysis and systematic review. *BMC Health Serv. Res.* 22:558. doi: 10.1186/s12913-022-07960-0

Gerteis, M., Edgman-Levitan, S., Daley, J., and Delbanco, T. L. (1993). "Introduction" in *Through the patient's eyes: understanding and promoting patient-centered care* (San Francisco, CA: Jossey-Bass)

Graffigna, G., Barello, S., Riva, G., and Bosio, A. C. (2014). Patient engagement: the key to redesign the exchange between the demand and supply for healthcare in the era of active ageing. *Stud. Health Technol. Inform.* 203, 85–95. doi: 10.3233/978-1-61499-425-1-85

Graham, E. L., Clark, J. R., Orban, Z. S., Lim, P. H., Szymanski, A. L., Taylor, C., et al. (2021). Persistent neurologic symptoms and cognitive dysfunction in non-hospitalized Covid-19 'long haulers'. *Ann. Clin. Transl. Neurol.* 8, 1073–1085. doi: 10.1002/acn3.51350

Hewett, R., and Shantz, A. (2021). A theory of HR co-creation. *Hum. Resour. Manage Rev.* 31:100823. doi: 10.1016/j.hrmr.2021.100823

Higgins, T., Larson, E., and Schnall, R. (2017). Unraveling the meaning of patient engagement: a concept analysis. *Patient Educ. Couns.* 100, 30–36. doi: 10.1016/j.pec.2016.09.002

Hobfoll, S. E. (2001). The influence of culture, community, and the nested-self in the stress process: advancing conservation of resources theory. *Appl. Psychol.* 50:337. doi: 10.1111/1464-0597.00062

Huffman, M. H. (2016). Advancing the practice of health coaching: differentiation from wellness coaching. *Workplace Health Saf* 64, 400–403. doi: 10.1177/2165079916645351

Jason, L. A., Islam, M. F., Conroy, K., Cotler, J., Torres, C., Johnson, M., et al. (2021). COVID-19 symptoms over time: comparing long-haulers to ME/CFS. *Fatigue* 9, 59–68. doi: 10.1080/21641846.2021.19221409

Jonsjö, M. A., Wicksel, R. K., Holmström, L., Andreasson, A., and Bileviciute-Ljungar Olsson, G. L. (2017). Identifying symptom subgroups in patients with ME/CFS – relationships to functioning and quality of life. *Fatigue* 5, 33–42. doi: 10.1080/21641846.2017.1287546

Kitson, A., Marshall, A., Bassett, K., and Zeitz, K. (2013). What are the core elements of patient-centred care? A narrative review and synthesis of the literature from health policy, medicine and nursing. *J. Adv. Nurs.* 69, 4–15. doi: 10.1111/j.1365-2648.2012.06064.x

Kodner, D. L., and Spreeuwenberg, C. (2002). Integrated care: meaning, logic, applications, and implications – a discussion paper. *Int. J. Integr. Care* 2:e12. doi: 10.5334/ijic.67

Komaroff, A. L., and Bateman, L. (2021). Will COVID-19 lead to myalgic encephalomyelitis/chronic fatigue syndrome? *Front. Med.* 7:606824. doi: 10.3389/fmed.2020.606824

Komaroff, A. L., and Lipkin, W. I. (2021). Review insights from myalgic encephalomyelitis/chronic fatigue syndrome may help unravel the pathogenesis of postacute COVID-19 syndrome. *Trends Mol. Med.* 27, 895–906. doi: 10.1016/j.molmed.2021.06.00289

Körner, M., Becker, S., Dinius, J., Müller, C., Zimmermann, L., and Rundel, M. (2018). A patient-centred team-coaching concept for medical rehabilitation. *J. Interprof. Care* 32, 123–126. doi: 10.1080/13561820.2017.1357542

Körner, M., Luzay, L., Plewnia, A., Becker, S., Rundel, M., Zimmermann, L., et al. (2017). A cluster-randomized controlled study to evaluate a team coaching concept for improving teamwork and patient-centeredness in rehabilitation teams. *PLoS One* 13.12(7):e0180171. doi: 10.1371/journal.pone.018011

Kujawski, S., Słomko, J., Newton, J. L., Eaton-Fitch, N., Staines, D. R., Marshall-Gradisnik, S., et al. (2021). Network analysis of symptoms co-occurrence in chronic fatigue syndrome. *Int. J. Environ. Res. Public Health* 18:10736. doi: 10.3390/ijerph182010736

Kvarnström, S. (2008). Difficulties in collaboration: a critical incident study of interprofessional healthcare teamwork. *J. Interprof. Care* 22, 191–203. doi: 10.1080/13561820701760600

Leach, M. J., Wiese, M., Thakkar, M., and Agnew, T. (2018). Integrative health care – toward a common understanding: a mixed method study. *Complement. Ther. Clin. Pract.* 30, 50–57. doi: 10.1016/j.ctcp.2017.12.007

Lim, E. J., and Son, C. G. (2020). Review of case definitions for myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS). *J. Transl. Med.* 18:289. doi: 10.1186/s12967-020-02455-0

Maes, M. (2015). A new case definition of neuro-inflammatory and oxidative fatigue (NIOF), a neuroprogressive disorder, formerly known as chronic fatigue syndrome or myalgic encephalomyelitis: results of multivariate pattern recognition methods and external validation by neuro-immune biomarkers. *Neuroendocrinol. Lett.* 36, 320–329.

Malik, R. F., Hilders, C. G. J. M., and Scheele, F. (2018). Do 'physicians in the lead' support a holistic healthcare delivery approach? A qualitative analysis of stakeholders' perspectives. *BMJ Open* 8:e020739. doi: 10.1136/bmjopen-2017-020739

Mariman, A., Delesie, L., Tobback, E., Hanoulle, I., Sermijn, E., Vermeir, P., et al. (2013). Undiagnosed and comorbid disorders in patients with presumed chronic fatigue syndrome. *J. Psychosom. Res.* 75, 491–496. doi: 10.1016/j.jpsychores.2013.07.010

Matthews, K. S. H., Rennoldson, S. C., and Fraser, S. D. S. (2023). Influence of health-system change on treatment burden: a systematic review. *Br. J. Gen. Pract.* 73, e59–e66. doi: 10.3399/BJGP.2022.0066

Mead, N., and Bower, P. (2000). Patient-centredness: a conceptual framework and review of the empirical literature. *Soc. Sci. Med.* 51, 1087–1110. doi: 10.1016/S0277-9536(00)00098-8

Meng, F., Jiang, Y., Yu, P., Song, Y., Zhou, L., Xu, Y., et al. (2023). Effect of health coaching on blood pressure control and behavioral modification among patients with hypertension: a systematic review and meta-analysis of randomized controlled trials. *Int. J. Nurs. Stud.* 138:104406. doi: 10.1016/j.ijnurstu.2022.104406

Mirin, A. A., Dimmock, M. E., and Jason, L. A. (2022). Updated ME/CFS prevalence estimates reflecting post-COVID increases and associated economic costs and funding implications. *Fatigue* 10, 83–93. doi: 10.1080/21641846.2022.2062169

Moreau, J. L., Hamilton, A. B., Yano, E. M., Rubenstein, L. V., and Stockdale, S. E. (2020). The impact of job role on health-care workers' definitions of patient-centered care. *Patient Exp.* 7, 1634–1641. doi: 10.1177/2374373520910335

Neveu, J.-P., Khan, R., and Murtaza, G. (2023). Investing in resources: an interaction model of personal resources, commitment, and work achievement. *J. Pers.*:1-17. doi: 10.1111/jopy.12826

Paul, B. D., Lemle, M. D., Komaroff, A. L., and Snyder, S. H. (2021). Redox imbalance links COVID-19 and myalgic encephalomyelitis/chronic fatigue syndrome. *Proc. Natl. Acad. Sci. U. S. A.* 118:e2024358118. doi: 10.1073/pnas.2024358118

Poenaru, S., Abdallah, S. J., and Corrales-Medina, V. (2021). COVID-19 and post-infectious myalgic encephalomyelitis/chronic fatigue syndrome: a narrative review. *Ther Adv Infect Dis* 8, 1–16. doi: 10.1177/20499361211009385

Prior, J. L., Vesentini, G., Michell De Gregorio, J. A., Ferreira, P. H., Hunter, D. J., and Ferreira, M. L. (2023). Health coaching for low back pain and hip and knee osteoarthritis: a systematic review with meta-analysis. *Pain Med.* 24, 32–51. doi: 10.1093/pm/pnac099

Rogers, C. R. (1946). Significant aspects of client-centered therapy. *Am. Psychol.* 1, 415–422. doi: 10.1037/h0060866

Rosen, B., Preisman, M., Read, H., Chaukos, D., Greenberg, R. A., Jeffs, L., et al. (2022). Providers' perspectives on implementing resilience coaching for healthcare workers during the COVID-19 pandemic. *BMC Health Serv. Res.* 22:780. doi: 10.1186/s12913-022-08131-x

Simani, L., Ramezani, M., Darazam, I. A., Sagharichi, M., Aalipour, M. A., Ghorbani, F., et al. (2021). Prevalence and correlates of chronic fatigue syndrome and post-traumatic stress disorder after the outbreak of the COVID-19. *J. Neuro Virol.* 27, 154–159. doi: 10.1007/s13365-021-00949-1

Smuts, J. C. (1926). *Holism and evolution*, New York: Kessinger Publisher, MT.

Stephany, A. M., Archuleta, P., Sharma, A., and Hull, S. K. (2023). Professional Coaching in Medicine and Health Care. *Clinics in Sports Medicine* 42, 195–208. doi: 10.1016/j.csm.2022.11.001

Stewart, M., Brown, J. B., Donner, A., McWhinney, I. R., Oates, J., Weston, W. W., et al. (2000). The impact of patient-centered care on outcomes. *J. Fam. Pract.* 49, 796–804.

Stewart, M, Brown, JB, Weston, W, McWhinney, IR, McWilliam, CL, and Freeman, T. (2013). *Patient-centered medicine: transforming the clinical method* (*3rd*). Boca Raton CRC Press

Strassheim, V., Newton, J. L., and Collins, T. (2021). Experiences of living with severe chronic fatigue syndrome/myalgic encephalomyelitis. *Healthcare* 9:2.168. doi: 10.3390/healthcare9020168

Townsend, L., Moloney, D., Finucane, C., McCarthy, K., Bergin, C., Bannan, C., et al. (2021). Fatigue following COVID-19 infection is not associated with autonomic dysfunction. *PLoS One* 16:e0247280. doi: 10.1371/journal.pone.0247280

Valentijn, P. P. (2016). Rainbow of Chaos: a study into the theory and practice of integrated primary care. *Int. J. Integr. Care* 16:3. doi: 10.5334/ijic.2465

Valentijn, P. P., Schepman, S. M., Opheij, W., and Bruijnzeels, M. A. (2013). Understanding integrated care: a comprehensive conceptual framework based on the integrative functions of primary care. *Int. J. Integr. Care* 13:e010. doi: 10.5334/ijic.886

Van Berckelaer, A., DiRocco, D., Ferguson, M., Gray, P., Marcus, N., and Day, S. (2012). Building a patient-centered medical home: obtaining the patient's voice. *J. Am. Board Fam. Med.* 25, 192–198. doi: 10.3122/jabfm.2012.02.100235

Vanderhout, S., Nicholls, S., Monfaredi, Z., Hampel, C., Ashdown, L., Bilodeau, M., et al. (2022). Facilitating and supporting the engagement of patients, families and caregivers in research: the “Ottawa model” for patient engagement in research. *Res. Involv. Engagem.* 8:25. doi: 10.1186/s40900-022-00350-0

Verma, I., Gopaldasani, V., Jain, V., Chauhan, S., Chawla, R., Verma, P. K., et al. (2022). The impact of peer coach-led type 2 diabetes mellitus interventions on glycaemic control and self-management outcomes: a systematic review and meta-analysis. *Prim. Care Diabetes* 16, 719–735. doi: 10.1016/j.pcd.2022.10.007

Wong, T. L., and Weitzer, D. J. (2021). Long COVID and Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS) – a systemic review and comparison of clinical presentation and symptomatology. *Medicina* 57:418. doi: 10.3390/medicina57050418

Zonneveld, N., Raab, J., and Minkman, M. M. N. (2020). Towards a values framework for integrated health services: an international Delphi study. *BMC Health Serv. Res.* 20:224. doi: 10.1186/s12913-020-5008-y

frontiers | Frontiers in Public Health

TYPE Systematic Review
PUBLISHED 28 July 2023
DOI 10.3389/fpubh.2023.1192121

OPEN ACCESS

EDITED BY
Sławomir Kujawski,
Ludwik Rydygier Collegium Medicum in Bydgoszcz Nicolaus Copernicus University in Toruń, Poland

REVIEWED BY
Mirko Manchia,
University of Cagliari, Italy
Grażyna Bączyk,
Poznan University of Medical Sciences, Poland

*CORRESPONDENCE
Chang-Gue Son
✉ ckson@dju.ac.kr

†These authors have contributed equally to this work

RECEIVED 24 March 2023
ACCEPTED 13 July 2023
PUBLISHED 28 July 2023

CITATION
Yoon J-H, Park N-H, Kang Y-E, Ahn Y-C, Lee E-J and Son C-G (2023) The demographic features of fatigue in the general population worldwide: a systematic review and meta-analysis. *Front. Public Health* 11:1192121. doi: 10.3389/fpubh.2023.1192121

The demographic features of fatigue in the general population worldwide: a systematic review and meta-analysis

Ji-Hae Yoon[1†], Na-Hyun Park[1†], Ye-Eun Kang[1†], Yo-Chan Ahn[2], Eun-Jung Lee[3] and Chang-Gue Son[1,4*]

[1]Research Center for CFS/ME, Daejeon Oriental Hospital of Daejeon University, Daejeon, Republic of Korea, [2]Department of Health Service Management, Daejeon University, Daejeon, Republic of Korea, [3]Department of Korean Rehabilitation Medicine, College of Korean Medicine, Daejeon University, Daejeon, Republic of Korea, [4]Institute of Bioscience and Integrative Medicine, Daejeon University, Daejeon, Republic of Korea

Background: Fatigue is one of the most common subjective symptoms that impairs daily life and predict health-related events. This study aimed to estimate the prevalence of fatigue in the global population.

Methods: PubMed and the Cochrane Library were used to search for relevant articles from inception to December 31, 2021. Studies with prevalence data of fatigue in the general population were selected and reviewed by three authors independently and cross-checked. Regarding subgroups, adults (≥18 years), minors (<18 years), and specific occupation population (participants in each study being limited to a specific occupational group), and fatigue types and severity, meta-analysis was conducted to produce point estimates and 95% confidence intervals (95% CI).

Results: From the initial 3,432 studies, 91 studies accounting for 115 prevalence data points (623,624 participants) were finally selected. The prevalence of general fatigue (fatigue lasting <6 months, or fatigue of unspecified duration) was 20.4% (95% CI, 16.7–25.0) in adults, 11.7% (95% CI, 5.2–26.6) in minors, and 42.3% (95% CI, 33.0–54.2) in specific occupations. Chronic fatigue (fatigue lasting more than 6 months) affected 10.1% (95% CI, 8.2–12.5) of adults, 1.5% (95% CI, 0.5–4.7) of minors, and 5.5% (95% CI, 1.4–21.6) of subjects in specific occupations. There was an overall female-predominant prevalence for all subgroup analyses, with a total odds ratio of 1.4 (95% CI, 1.3–1.6). Regarding the severity and presence of medical causes, the total prevalence of moderate fatigue [14.6% (95% CI, 9.8–21.8)] was 2.4-fold that of severe fatigue [6.1% (95% CI, 3.4–11.0)], while unexplained fatigue (fatigue experienced by individuals without any underlying medical condition that can explain the fatigue) was ∼2.7-fold that of explained fatigue (fatigue experienced by individuals with a medical condition that can explain the fatigue); as proportion of 40.0% of physical, 8.6% of mental, and 28.4% of mixed cause.

Conclusions: This study has produced the first comprehensive picture of global fatigue prevalence in the general population, which will provide vital reference data contributing to fatigue-related research, including the prevention of diseases.

Systematic review registration: Identifier: CRD42021270498.

KEYWORDS

fatigue, chronic fatigue, prevalence, general population, global population, systematic review, meta-analysis

Background

Fatigue refers to subjective symptoms including tiredness, weakness, lack of energy, and/or inability to concentrate (1). Fatigue can be a physiological response to stressful conditions that disappears after resting (2). However, uncontrolled fatigue (fatigue not relieved with rest), especially chronic fatigue, is a medical issue that impairs health-related quality of life (3) and productivity (4). Fatigue has been demonstrated to have significant economic implications for society (5), with an estimated cost of £1906 per chronic fatigue and chronic for fatigue syndrome (CFS) patient (mean cost for 3 months) in the United Kingdom (6). CFS represents the most severe manifestation within the spectrum of chronic fatigue-related disorders, which is characterized by core symptoms including unrefreshing sleep, post-exertional malaise (PEM), and cognitive dysfunction persisting for a duration of over six months. The economic impact of CFS on patients in the United States has reached a staggering $11,780 per year per patient (7).

In practice, fatigue is one of the top five most frequently presented health complaints in primary care (8) and can be classified by a sustained period or the presence of medical causes (9). Although fatigue is one of the most prevalent complaints in subjects suffering certain diseases, likely prevalence rate 49% in cancer patients (including both undergoing and after treatment) (10), it is also common among people without specific diagnosis (11). Furthermore, fatigue itself may indicate the development of diseases, including cancers (12). A prospective observational cohort study found that 46.9% of adults with a new episode of fatigue were diagnosed with one or more disorders in a year (13). Fatigue in the general population is also related to an increased risk of mortality (odd ratio = 2.14) (14).

Therefore, early assessment of fatigue and proper care can reduce health-related risks and economic costs. To implement proper clinical management for subjects with fatigue, determining epidemiological features, particularly prevalence, is necessary. To date, many studies showed great differences of fatigue prevalence from 4.9% (15) to 67.9% (16) among the general populations. In general, fatigue prevalence can be affected by sex, age, economic status, cultural differences and ethnicity (17–20). Thus far, most systematic reviews of fatigue prevalence have mainly focused on patients with certain diseases (21–23) or CFS (24–26), but to our knowledge, no study has been conducted in the general population.

This study aimed to create a comprehensive overview of the global prevalence and clinical features related to severity and cause of fatigue in general population.

Methods

Study design

To study the epidemiological features of fatigue in the general population worldwide, we systematically reviewed and analyzed fatigue-related data using public databases. This study was conducted according to the International Prospective Register of Systematic Reviews (PROSPERO) after registration (Registration # CRD42021270498).

Data sources and keywords

This study included a search of two databases, PubMed and the Cochrane Library from inception through December 31, 2021. The search keywords were "fatigue" and "prevalence" [MeSH term]. The search terms were "(fatigue[Title]) AND ((Prevalence[Title/Abstract]) OR (Frequency[Title/Abstract]))" in PubMed, while "fatigue[Record Title] AND prevalence[Title Abstract Keyword]" and "fatigue[Record Title] AND frequency[Title Abstract Keyword]" in the Cochrane Library. All languages were included.

Eligibility criteria

Studies were screened using the following inclusion criteria: (1) studies investigating prevalence of fatigue and (2) subjects from the general population or healthy control groups that did not have specific diseases. The exclusion criteria were as follows: (1) lifetime prevalence of fatigue, (2) fatigue measured after any interventions, (3) studies on only emotional or compassion fatigue, (4) a small number of participants (having fewer than 300 adults and minors, and <100 for specific occupations), and (5) review studies.

Review process and data extraction

First, three authors performed a search and screened all titles and abstracts retrieved. Based on the inclusion criteria, the full texts of the eligible studies were independently reviewed by three authors. All data were cross-checked, and further discussion was conducted with the corresponding author (Son CG) in cases of disagreement to decide. Author contact was attempted to obtain missing data. To assess the quality of the included studies, we employed the Newcastle-Ottawa Scale (NOS), which is commonly utilized in observational studies. We considered studies with a score of 7 or higher to be of high quality (27, 28). The data extracted from each study were as follows: characteristics of participants (total number, age and sex), description and number of fatigue cases, severity or medical cause information for fatigue, study design (cross-sectional/longitudinal), data collection method, fatigue assessment tool and cutoff score used, study period, publication year, and country where study was conducted. The types of fatigue were classified as general or chronic, and each prevalence was recorded. This process was determined by the consensus of researchers through discussion. The definition of fatigue subtypes (encompassing both moderate/severe fatigue and explained/unexplained fatigue) followed the different criteria as chosen by the respective authors or researchers in their original articles.

Abbreviations: CI, confidence intervals; OR, odds ratio; CFS, chronic fatigue syndrome; CFQ, Chalder Fatigue Questionnaire; CIS(a), Checklist Individual Strength; FSS, Fatigue Severity Scale; CIS(b), Clinical Interview Schedule.

Data coding and synthesis

The data from each study were subgrouped as follows: characteristics of participants (adults, ≥18 years; minors, <18 years population; specific occupation), fatigue types (general, chronic), severity of fatigue (moderate, severe), medical cause of fatigue (physical, mental, mixed, drug-induced), data collection method (questionnaire, interview, telephone survey, physician reports), fatigue assessment tool (Chalder Fatigue Questionnaire, Checklist Individual Strength, Clinical Interview Schedule, Fatigue Severity Scale, Self-designed tool, Others), study year (before 2000, 2001–2010, 2011–2020), and continent where study was conducted (Europe, America, Asia, Others).

We categorized fatigue into two primary types: general fatigue, encompassing fatigue lasting <6 months or fatigue of unspecified duration, and chronic fatigue, which denotes fatigue persisting for more than 6 months. To produce an overall characteristics fatigue prevalence, we employed a hierarchical approach. Therefore, concerning the prevalence of chronic fatigue syndrome (CFS) or CFS-like conditions, we specifically considered studies that provided simultaneous reports on the prevalence of CFS or CFS-like conditions, alongside chronic fatigue. However, we excluded prevalence data that solely focused on CFS or CFS-like illnesses.

Total fatigue includes general and chronic fatigue, while CFS-prevalence were included in that of chronic fatigue. Moreover, if articles contained data for severity-related prevalence, we further conducted binary classification (moderate or severe). We ignored the data for "mild or no" in cases of three stages (mild or no/moderate/severe fatigue).

To avoid duplicate or missing data, if fatigue prevalence was measured over multiple follow-up periods for the same participants, only the first one was included in the data. When several prevalence rates were presented with overlapping participants according to the different definitions of fatigue within a study, the prevalence defined in the broadest sense was used. Otherwise, when a study contained several prevalence rates that did not overlap, the prevalence was calculated by adding the number of participants for each definition. Regarding the analysis of the study year, the midpoint between the start and the end of the study period was used, and in case of no description, 1 year before the publication year was used.

Statistical analysis and meta-analysis

We performed a meta-analysis using a random-effects model to produce point estimates and 95% confidence intervals (95% CI) of fatigue prevalence with subgroup analysis. The reported prevalence from each study underwent a log transformation to improve statistical properties, and pooled estimates were then back-transformed into the original prevalence scale. To account for the potentially high interstudy heterogeneity, the pooled outcome measures and their corresponding 95% CI were calculated using a random-effects model fitted with the restricted maximum likelihood estimator. The I^2 statistic was used to evaluate the degree of heterogeneity between studies. All analyses were conducted using the "meta" package (by Guido Schwarzer) in R version 4.2.1. Statistical significance was determined by a hypothesis test for the analysis of differences between groups. In all analyses, $p < 0.05$ indicated statistical significance.

Results

Characteristics of the included studies

Of the initial 554 studies relevant to our study question, 91 studies (86 cross-sectional; 5 longitudinal) finally met the inclusion criteria and contained a total of 115 prevalence data points (76 general fatigue; 39 chronic fatigue; Figure 1, Supplementary Table 4). According to the results of the quality assessment, 54% (49 studies) were categorized as high quality, while 46% (42 studies) were classified as medium quality. These studies were conducted in 32 different countries beginning with a report from Finland in 1989 (29). The total number of participants was 623,624 (mean ± SD, 5,423 ± 10,992; 547,057 adults, 58,019 minors, and 18,548 specific occupation population, which included 16 occupations). Within the 115 data points, 51 data points had sex information (males 157,220; females 157,971). Thirteen data points had information on fatigue severity (moderate/severe), while 13 data points had information on the medical cause of fatigue (Table 1).

Most of the studies (85 data points) collected data by questionnaire, and the remaining studies (39 data points) used interviews, telephone surveys, or physician reports. Thirty-six fatigue-assessment tools (including researcher-directed designed tools for 26 data points) were used, including the Chalder Fatigue Questionnaire (CFQ; 34 data points), Checklist Individual Strength [CIS(a); 10 data points], Fatigue Severity Scale (FSS; 6 data points), and Clinical Interview Schedule [CIS(b); 5 data points; Table 1].

Total prevalence rate of fatigue

The meta-analyses showed prevalence rates of 16.4% (95% CI, 13.6–19.9) for total fatigue (115 data points), 24.2% (95% CI, 19.9–29.5) for general fatigue (76 data points), and 7.7% (95% CI, 5.7–10.3) for chronic fatigue (39 data points; Table 2). Adults showed higher fatigue prevalence rates (20.4 and 10.1% for general and chronic fatigue, respectively) than minors (11.7 and 1.5%, respectively). The specific occupation population showed prevalence rates of 42.3% (95% CI, 33.0–54.2) for general fatigue and 5.5% (95% CI, 1.4–21.6) for chronic fatigue. The differences between groups in both types of fatigue were statistically significant ($p < 0.05$; Figure 2).

Regarding sex-related fatigue prevalence (51 data points), total fatigue prevalence was 14.6% in males vs. 18.3% in females which showed female predominant ($p = 0.23$) with an odds ratio (OR) of 1.4. Prevalence rates for subgroups were 22.0% (male) vs. 27.1% (female) for general fatigue ($p = 0.25$); 6.6% (male) vs. 8.6% (female) for chronic fatigue ($p = 0.35$; Figure 3A).

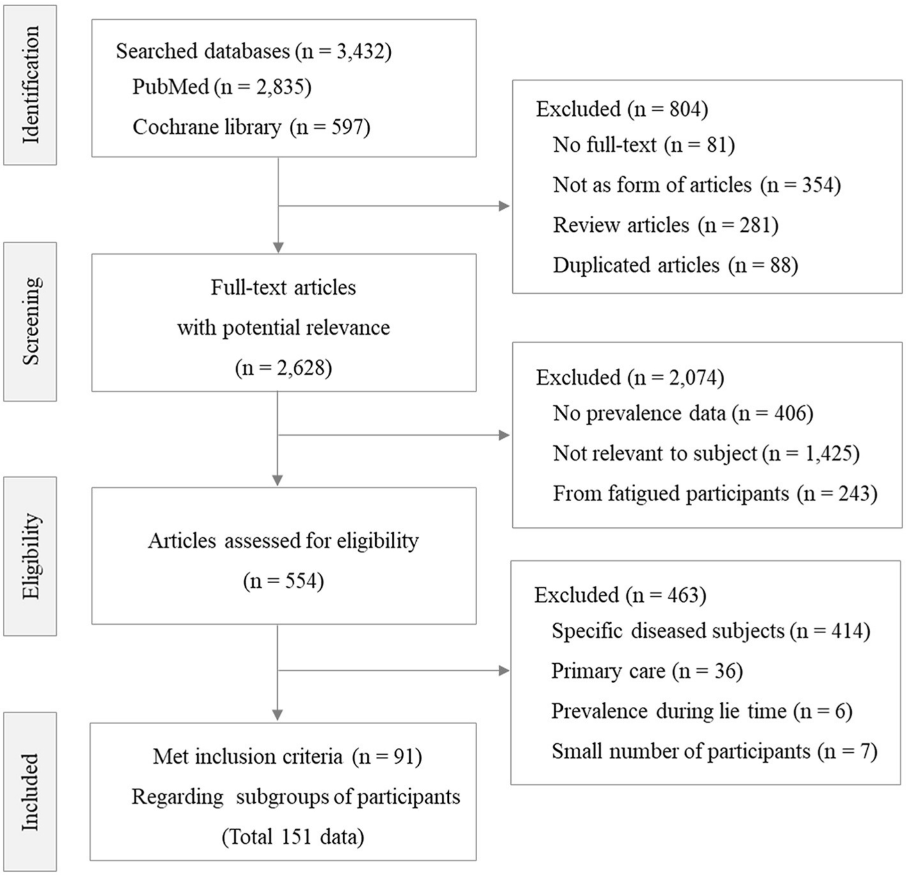


FIGURE 1
Flow diagram.

Prevalence rate by fatigue severity

Thirteen data points reported the prevalence by severity (moderate/severe). The total prevalence of moderate fatigue [14.6% (95% CI, 9.8–21.8)] was $\sim$2.4-fold that of severe fatigue [6.1% (95% CI, 3.4–11.0); $p < 0.05$]. The ratio (moderate to severe) was $\sim$3.6-fold in adults [12.5% (95% CI, 8.3–18.9) vs. 3.5% (95% CI, 1.8–6.9); 8 data points] and 2.2-fold in the specific occupations [34.2% (95% CI, 19.2–60.7) vs. 15.8% (95% CI, 6.3–39.9); 3 data points], while the reverse pattern (0.6-fold) was shown for minors [7.6% (95% CI, 3.1–18.8) vs. 12.9% (95% CI, 5.1–32.5); 2 data points; Figure 3B].

Proportion of medically explained vs. unexplained fatigue

From 13 data points that reported the medical causes explaining the fatigue, the total prevalence of unexplained fatigue [4.1% (95% CI, 2.0–8.5)] was $\sim$2.7-fold that of explained fatigue [1.5% (95% CI, 0.5–4.6); $p = 0.13$]. In adults (nine data points), the prevalence of unexplained fatigue [7.6% (95% CI, 4.2–13.7)] was 3.3-fold that of explained fatigue [2.3% (95% CI, 0.6–8.6); $p = 0.11$], while it was 5.0-fold in minors [0.5% (95% CI, 0.4–0.7) vs. 0.1% (95% CI, 0.0–0.9); 2 data points; $p = 0.13$]. In the specific occupations (2 data points), no notable difference was observed [2.0% (95% CI, 0.3–13.4) vs. 2.4% (95% CI, 0.2–31.4); $p = 0.91$; Table 2].

Regarding causes of fatigue, 40.0% were attributed to physical causes (three data points), 8.6% to mental causes (one data point), 28.4% to mixed causes (four data points), and 1.0% to drug-induced causes (one data point) in adults, while minor-derived data showed only 16.3% to mixed causes (two data points). In the specific occupations, 46.2% were attributed to physical causes (one data point) and 62.9% to mixed causes (one data point) (Table 2).

Prevalence rate by data collection method and fatigue assessment tool

Fatigue prevalence rates were significantly different among the four data collection methods ($p < 0.05$). Questionnaire showed the highest prevalence [19.1% (95% CI, 15.7–23.3); 85 data points] followed by interviews [13.0% (95% CI, 8.1–20.7); 25 data points]. In adults, the prevalence rates were similar; interviews [15.8% (95% CI, 10.4–23.9); 19 data points] vs. questionnaires [15.0% (95% CI, 12.3–18.3); 49 data points], followed by telephone surveys [10.9% (95% CI, 6.8–17.5); 9 data points] and physician reports [8.6% (95% CI, 4.8–15.3); 2 data points; Supplementary Table 2].

TABLE 1 Characteristics of the included studies.

Group		Adults (≥18 years)	Minors (<18 years)	Specific occupation	Total
Total *n*. of included studies		55	8	28	91
Cross-sectional/longitudinal		52/3	6/2	28/0	86/5
Total *n*. of prevalence data		71	15	29	115
Total *n*. of participants		547,057	58,019	18,548	623,624
Mean *n*. of participants ± SD		(7,705 ± 13,379)	(3,868± 3,405)	(640 ± 631)	(5,423 ± 10,992)
Data with gender information		34	6	11	51
Participants *n* (M:F ratio)		288,842 (50:50)	21,696 (49:51)	4,653 (48:52)	315,191 (50:50)
N. of prevalence data by subgroup (*N*. of participants)					
Type[a]	General fatigue	40 (409,251)	10 (36,525)	26 (15,460)	76 (461,236)
	Chronic fatigue	31 (137,806)	5 (21,494)	3 (3,088)	39 (162,388)
	CFS/CFS-like[b]	9 (84,530)	2 (9,428)	2 (2,445)	13 (96,403)
Severity[c]	Present	8 (51,555)	2 (1,306)	3 (1,063)	13 (53,924)
	Absent	63 (495,502)	13 (56,713)	26 (17,485)	102 (569,700)
Medical cause	Described	9 (180,938)	2 (17,172)	2 (2,445)	13 (200,555)
	Undescribed	62 (366,119)	13 (40,847)	27 (16,103)	102 (423,069)
Data collection	Questionnaire	49 (187,164)	10 (29,040)	26 (17,223)	85 (233,427)
	Interview	19 (155,996)	3 (11,807)	3 (1,325)	25 (169,128)
	Telephone survey	9 (218,277)	2 (17,172)	N/A	11 (235,449)
	Physician reports	2 (2,108)	N/A	1 (194)	3 (2,302)
Assessment tool[d]	CFQ	28 (83,496)	2 (10,603)	4 (4,284)	34 (98,383)
	CIS(a)	6 (36,567)	3 (4,773)	1 (647)	10 (41,987)
	FSS	2 (5,341)	N/A	4 (1,679)	6 (7,020)
	CIS(b)	5 (25,723)	N/A	N/A	5 (25,723)
	Self-designed tool	14 (264,219)	8 (36,592)	4 (3,239)	26 (304,050)
	Others	25 (219,198)	3 (11,807)	16 (8,699)	44 (239,704)
Continent[e]	Europe	37 (185,597)	12 (30,724)	5 (4,208)	54 (220,529)
	America	15 (262,732)	3 (27,295)	10 (5,492)	28 (295,519)
	Asia	13 (27,331)	N/A	13 (8,713)	26 (36,044)
	Others	6 (71,397)	N/A	1 (135)	7 (71,532)
Study year	Before 2000	24 (161,972)	4 (12,161)	2 (1,860)	30 (175,993)
	2001–2010	32 (259,458)	9 (34,544)	12 (5,791)	53 (299,793)
	2011–2020	15 (125,627)	2 (11,314)	15 (10,897)	32 (147,838)

[a] General fatigue represents fatigue lasting less than 6 months or fatigue of unspecified duration.

[b] Including chronic fatigue syndrome (CFS) or CFS-like data that were presented simultaneously with chronic fatigue.

[c] Studies that measured the severity of fatigue as moderate and severe were included.

[d] CFQ, Chalder Fatigue Questionnaire; CIS(a), Checklist Individual Strength; FSS, Fatigue Severity Scale; CIS(b), Clinical Interview Schedule; Self-designed tool, tools created by researchers; Others: Brief Fatigue Inventory, CDC 1988 criteria, CDC 1994 criteria, Center for Epidemiologic Studies-Depression scale, CFS Screening Questionnaire, CFS Symptom Severity Questionnaire, Chronic Fatigue Scale, Composite International Diagnostic Interview, version 3.0 (CIDI), Development and Well-being Assessment, Diagnostic Interview Schedule, Emotional State Questionnaire, Epworth Sleepiness Scores, Fatigue Assessment Scale, Fatigue Questionnaire by Japan Association of Industrial Health, Fatigue Questionnaire (30), Fatigue Scale-14, General Health Questionnaire-12, ICD-10 criteria, InterRAI-HC assessment, Iowa Fatigue Scale, Maslach Burnout Inventory, Multidimensional Assessment of Fatigue, Pediatric Screening Questionnaire, Piper Fatigue Scale, Fatigue Pictogram, Schedule of Fatigue and Anergia, Short Form Health Survey, Shortened Fatigue Questionnaire, Standard Shiftwork Index, Structured Clinical Interview for DSM-IV, Visual Analog Scale.

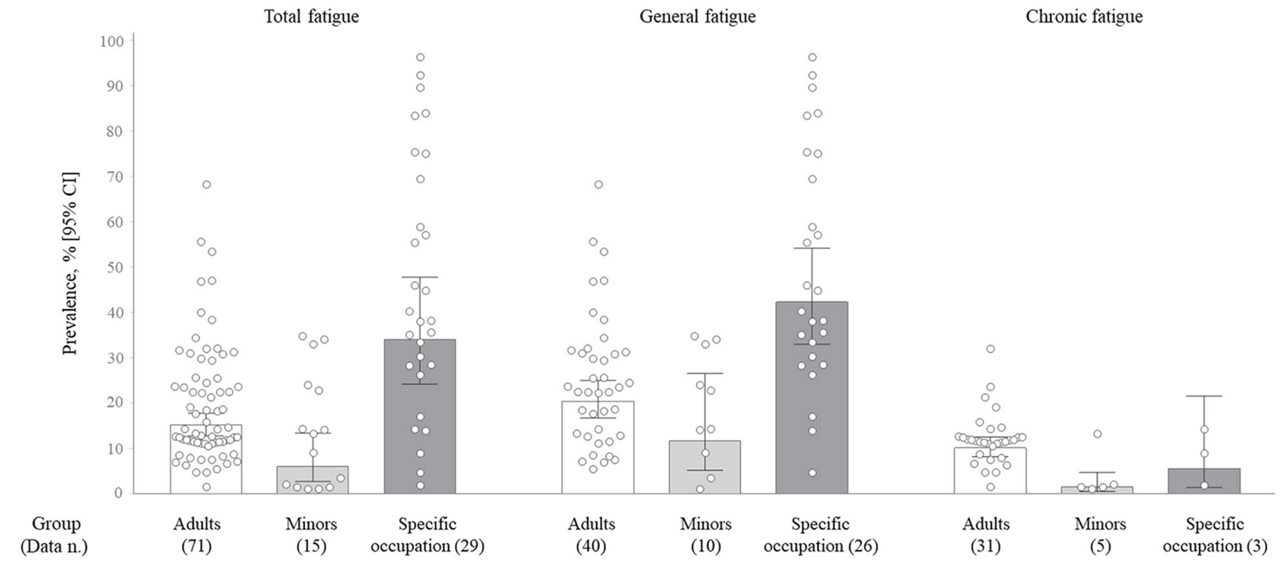
[e] Others: Oceania, Africa and Mixed.

Among the top four most frequently used fatigue assessment tools, the FSS showed the highest prevalence for total, followed by the CIS (a), CIS (b) and CFQ. The difference between groups was statistically significant ($p < 0.05$; Supplementary Table 2).

TABLE 2 Fatigue prevalence by type and medical cause.

Group	General	Chronic	CFS/CFS-like	Total
Participants *n*. (data *n*.)	461,236 (76)	162,388 (39)	96,403 (13)	623,624 (115)
(mean ± SD)	6,069 ± 12,802	4,162 ± 6,045	7,416 ± 9,244	5,423 ± 10,992
Prevalence % [95% CI]	24.2 [19.9–29.5]	7.7 [5.7–10.3]	1.2 [0.6–2.5]	16.4 [13.6–19.9]
Group	**Adults (≥18 years)**	**Minors (<18 years)**	**Specific Occupation**	**Total**
Participants *n*. (data *n*.)	180,938 (9)	17,172 (2)	2,445 (2)	200,555 (13)
(mean ± SD)	20,104 ± 22,592	8,586 ± 0	1,223 ± 356	15,427 ± 19,953
Unexplained fatigue	7.6 [4.2–13.7]	0.5 [0.4–0.7]	2.0 [0.3–13.4]	4.1 [2.0–8.5]
Explained fatigue[a]	2.3 [0.6–8.6]	0.1 [0.0–0.9]	2.4 [0.2–31.4]	1.5 [0.5–4.6]
Physical cause[b]	40.0 [28.6–56.0] (3)	N/A	46.2 [20.7–100.0] (1)	40.6 [30.2–54.5] (4)
Mental cause	8.6 [6.7–11.1] (1)	N/A	N/A	8.6 [6.7–11.1] (1)
Mixed cause	28.4 [11.0–73.5] (4)	16.3 [3.4–78.3] (2)	62.9 [52.8–74.8] (1)	28.1 [14.3–55.3] (7)
Drug-induced	1.0 [0.5–2.1] (1)	N/A	N/A	1.0 [0.5–2.1] (1)

[a] Prevalence data from studies with information on the presence or absence of medical causes for reported fatigue were included, analyzed and divided into explained and unexplained fatigue.
[b] Proportion (%) of participants reporting causes of fatigue compared to total fatigue was estimated from independent data. Mixed cause included data having no description for physical and/or mental causes separately. The (number) indicates the number of data for each results.



Group (Data n.)	Adults (71)	Minors (15)	Specific occupation (29)	Adults (40)	Minors (10)	Specific occupation (26)	Adults (31)	Minors (5)	Specific occupation (3)
Participants n.	547,057	58,019	18,548	40,925	36,525	15,460	137,806	21,494	3,088
Prevalence, % [95% CI]	15.1 [12.8-17.8]	6.0 [2.7-13.4]	34.0 [24.2-47.8]	20.4 [16.7-25.0]	11.7 [5.2-26.6]	42.3 [33.0-54.2]	10.1 [8.2-12.5]	1.5 [0.5-4.7]	5.5 [1.4-21.6]

FIGURE 2
Fatigue prevalence rate by fatigue type. The bar graph shows the pooled prevalence (%), and the error bar shows the corresponding 95% confidence intervals (95% CI) by the random-effects meta-analysis model. Each dot represents the value of each study included in this analysis.

Prevalence rate by continent and study year

Fatigue prevalence rates were significantly different among the continents studied ($p < 0.05$). For adults, the prevalence rate was highest in Asia [23.5% (95% CI, 13.1–42.2); 13 data points], followed by America [13.3% (95% CI, 9.5–18.7); 15 data points], and Europe [12.7% (95% CI, 10.9–14.8); 37 data points]. For the minors, the prevalence rate was highest in Europe [9.2% (95% CI, 4.1–20.9); 12 data points] and America [1.1% (95% CI, 0.4–3.0); 3 data points; Supplementary Table 3, Supplementary Figure 1].

When we compared fatigue prevalence rates by study year, there was also a significant difference between groups ($p < 0.05$). For adults, the years 2011–2020 showed the highest prevalence rates [19.8% (95% CI, 14.7–26.6); 15 data points], followed by before 2000 [15.6% (95% CI, 11.7–20.8); 24 data points]

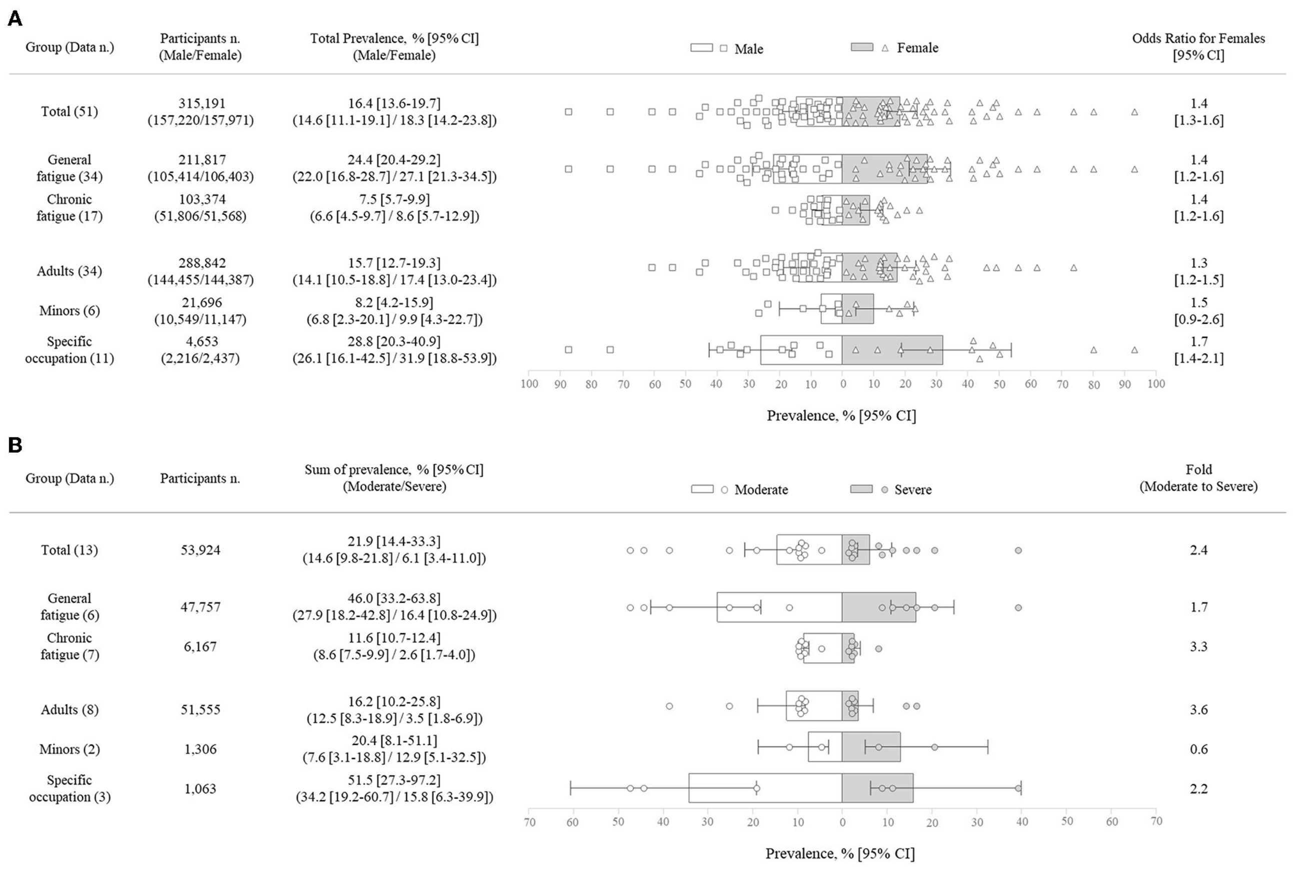


FIGURE 3
Fatigue prevalence rate by sex **(A)** and severity. **(B)** White (or gray) bar graph indicates the pooled prevalence (%) of moderate fatigue (or severe fatigue), and the error bar shows their corresponding 95% confidence intervals (95% CI) by a random-effects meta-analysis model. Each white (or gray) dot represents the value of each study included in this analysis.

and 2001–2010 [12.9% (95% CI, 10.0–16.7); 32 data points; Supplementary Table 3].

Discussion

Fatigue is an evolved sense in human beings to protect the body from deleterious conditions, which could occur in healthy populations (31, 32). Fatigue is frequently neglected by individuals, family members and even medical practitioners (33). However, there are reports that approximately half of the people who complain of fatigue receive one or more diagnoses within a year, including infections, anemia, thyroid dysfunction, diabetes mellitus and cancer (13). Clinically, fatigue is classified by duration, severity, or the existence of underlying disease (2, 34, 35). Commonly, chronic fatigue (≥ 6 months) presents as severe fatigue, leading to notable impairments in daily life, including poor mental health (36, 37). In the present systematic review, the average prevalence of chronic fatigue in whole data was 7.7% (95% CI, 5.7–10.3), while general fatigue (i.e., fatigue lasting <6 months or with unspecified duration) had an average prevalence of 24.2% (95% CI, 19.9–29.5; Table 2). From the analysis for separately adults and minor population, we found that approximately a quarter and one of ten adults complain general fatigue [20.4%, (95% CI 16.7–25.0)] and chronic fatigue [11.7%, (95% CI 5.2–26.6)]. Meanwhile, one of ten or 50 adolescents presented general fatigue [10.1%, (95% 8.2–12.5)] or chronic fatigue [1.5%, (95% 0.5–4.7); Figure 2].

Fatigue appears in patients with various physical and mental diseases and is frequently not disease-specific but transdiagnostic or generic (38). Therefore, differentiating primary vs. secondary and comorbid fatigue is often a challenge (39). Nine data points indicated the predominant pattern of unexplained fatigue among adults as 3.3-fold that of explained fatigue (7.6 vs. 2.3%). Regarding the proportion of explained fatigue by medical cause, the proportion was high in the order of physical causes, mixed causes, mental causes, and drug-induced causes in total (Table 2). In general, patients with unexplained fatigue are difficult to manage in clinical care and have been reported to have a lower quality of life than those with explained fatigue (33). However, the interpretation of these results is limited because the proportion of each cause was obtained not simultaneously but individually in separate studies.

On the other hand, CFS is the most serious form of unexplained fatigue, as 52%−94% of patients are reported to work only part-time or not at all and are at greater risk of suicide (standardized mortality ratio of 6.85, compared to healthy subjects) (40, 41). No therapeutics or objective diagnostic method exists due to the unexplored etiology and pathophysiology (42). Our previous meta-analysis reported the global prevalence of CFS as 0.89% (95% CI, 0.60–1.33; 34 data points) according to CDC-1994 criteria (43). The present study calculated the proportion of CFS among subjects with chronic fatigue. From 13 data points simultaneously presenting the prevalence of both chronic fatigue and CFS (or CFS-like), 16% of chronic fatigue cases were classified as CFS(-like), which indicated a CFS(-like) prevalence of 1.2% (95% CI, 0.6–2.5) in the general population (Table 1, Supplementary Table 1). The higher prevalence of CFS in the present study than in our previous study (1.2 vs. 0.9%) might result from the inclusion of CFS-like cases in the present study. These data would be practically helpful to clinicians because unexplained chronic fatigue could be a precursor to the development of CFS (44).

Fatigue is usually recognized as a symptom cluster that accompanies other symptoms, such as pain or depression. One study reported that six out of 10 members of the general population with fatigue had pain or depression at the same time (45). These comorbid symptoms are linked to the severity of fatigue, so the guidelines for the management of fatigue recommend assessing the severity of fatigue, not just the presence of fatigue (46). In the present study, we found that moderate fatigue [14.6% (95% CI, 9.8–21.8)] accounts for 2.4-fold the prevalence of severe fatigue [6.1% (95% CI, 3.4–11.0)], similar to the pattern in most of our subgroup data, except for the minor group (1.7-fold more severe than moderate fatigue prevalence; Figure 3B). A longitudinal study showed the medical impact of severe fatigue in adolescents; 42.1% of them were diagnosed with chronic fatigue at follow-up, and they had an increased risk for the development of depression, anxiety, and CFS-related symptoms (47). The reason that the minors has more severe fatigue than moderate fatigue in present study is unclear due to the inadequate number of related studies; accordingly, our findings require caution in interpretation.

It is known that female sex and specific occupations contribute to fatigue prevalence (48, 49). Our results showed the predominance of females over males in fatigue prevalence as a 1.4 OR (95% CI, 1.3–1.6) in total and as very similar in all subgroups (Figure 3A). One proposed reason for female-predominant fatigue is an inflammatory model, rendering females more vulnerable to the detrimental effects of immune-driven behavioral changes (including fatigue, worsened mood and pain sensitivity) (50). In addition, psychosocial factors indicative of poor mental health and gender inequality can make such a difference (18, 51). As we expect, subjects working in 16 different occupations (e.g., nurses, pilots, medical workers, etc.) showed a 2.3-fold higher prevalence of total fatigue than the adult group (Figure 2). Job-related factors, including long shift hours or psychosocial work characteristics, are associated with greater fatigue (52, 53). Based on the independent risk factors for being injured in an occupational accident, fatigue in a specific occupation should be further stressed (54). Alongside gender and environmental vulnerabilities, genetic background also contributes to fatigue prevalence (55). When we analyzed data from three continents, the prevalence of fatigue in the Asian population was noticeably high, nearly twice that of the European and American populations (Supplementary Table 3, Supplementary Figure 1). Such differences across continents could be explained not only by ethnicity (56) but also by various sociodemographic features (20).

Researchers conducted many systematic reviews on fatigue prevalence, then they mainly targeted disease populations so far. This study has several limitations that need to be acknowledged. Firstly, the research was conducted using only two databases. Additionally, due to the significant heterogeneity in the fatigue measurement tools employed across studies, standardization was not feasible. Furthermore, the amount of available data for analyzing the severity and causality of fatigue was insufficient, which could impact the comprehensiveness of our conclusions. Nevertheless, to the best of our knowledge, this is the first systematic review and meta-analysis to explore the epidemiologic features of the fatigue prevalence rate in the general population worldwide.

Conclusions

Based on the increasing health-related impact of fatigue and chronic fatigue, these results provide a valuable reference for numerous medical fields and for the prevention of diseases. The global population of 15.1% (adults) and 6.0% (minors) complain fatigue, while 10.1% of adults and 1.5% of minors are suffering from chronic fatigue, respectively. Along with 1.4-fold female-predominant prevalence, the prevalence of medically unexplained fatigue is 2.7-fold higher than explained fatigue.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary material, further inquiries can be directed to the corresponding author.

Author contributions

J-HY, N-HP, and Y-EK had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Y-CA conducted statistical analysis. J-HY and C-GS designed the study and drafted the manuscript. C-GS obtained the funding and supervised the whole process of this study. All authors have read and approved the final manuscript.

Funding

This research was supported by the National Research Foundation of Korea (NRF) funded by the Ministry of Science, ICT & Future Planning (NRF-2018R1A6A1A03025221).

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpubh.2023.1192121/full#supplementary-material

References

1. Landmark-Høyvik H, Reinertsen KV, Loge JH, Kristensen VN, Dumeaux V, Fosså SD, et al. The genetics and epigenetics of fatigue. *PM&R.* (2010) 2:456–65. doi: 10.1016/j.pmrj.2010.04.003

2. Rosenthal TC, Majeroni BA, Pretorious R, Malik K. Fatigue: an overview. *Am Fam Physician.* (2008) 78:1173–9.

3. Jelsness-Jørgensen LP, Bernklev T, Henriksen M, Torp R, Moum B. Chronic fatigue is associated with impaired health-related quality of life in inflammatory bowel disease. *Aliment Pharmacol Ther.* (2011) 33:106–14. doi: 10.1111/j.1365-2036.2010.04498.x

4. Reynolds KJ, Vernon SD, Bouchery E, Reeves WC. The economic impact of chronic fatigue syndrome. *Cost Eff Resour Alloc.* (2004) 2:1–9. doi: 10.1186/1478-7547-2-4

5. Brenna E, Gitto L. The economic burden of chronic fatigue syndrome/myalgic encephalomyelitis (CFS/ME): an initial summary of the existing evidence and recommendations for further research. *Eur J Pers Cent Healthc.* (2017) 5:413–20. doi: 10.5750/ejpch.v5i3.1379

6. Lin J-MS, Resch SC, Brimmer DJ, Johnson A, Kennedy S, Burstein N, et al. The economic impact of chronic fatigue syndrome in Georgia: direct and indirect costs. *Cost Eff Resour Alloc.* (2011) 9:1–12. doi: 10.1186/1478-7547-9-1

7. McCrone P, Darbishire L, Ridsdale L, Seed P. The economic cost of chronic fatigue and chronic fatigue syndrome in UK primary care. *Psychol Med.* (2003) 33:253–61. doi: 10.1017/S0033291702006980

8. Nicholson K, Stewart M, Thind A. Examining the symptom of fatigue in primary care: a comparative study using electronic medical records. *BMJ Health Care Inform.* (2015) 22:235–43. doi: 10.14236/jhi.v22i1.91

9. Dittner AJ, Wessely SC, Brown RG. The assessment of fatigue: a practical guide for clinicians and researchers. *J Psychosom Res.* (2004) 56:157–70. doi: 10.1016/S0022-3999(03)00371-4

10. Al Maqbali M, Al Sinani M, Al Naamani Z, Al Badi K. Prevalence of fatigue in patients with cancer: a systematic review and meta-analysis. *J Pain Symptom Manage.* (2021) 61:167–89.e14. doi: 10.1016/j.jpainsymman.2020.07.037

11. Koch H, van Bokhoven MA, Riet Gt, van der Weijden T, Dinant GJ, Bindels PJ. Demographic characteristics and quality of life of patients with unexplained complaints: a descriptive study in general practice. *Qual Life Res.* (2007) 16:1483–9. doi: 10.1007/s11136-007-9252-y

12. Ingebrigtsen SG, Scheel BI, Hart B, Thorsen T, Holtedahl K. Frequency of 'warning signs of cancer' in norwegian general practice, with prospective recording of subsequent cancer. *Fam Pract.* (2013) 30:153–60. doi: 10.1093/fampra/cms065

13. Nijrolder I, Van der Windt D, De Vries H, Van der Horst H. Diagnoses during follow-up of patients presenting with fatigue in primary care. *CMAJ.* (2009) 181:683–7. doi: 10.1503/cmaj.090647

14. Knoop V, Cloots B, Costenoble A, Debain A, Azzopardi RV, Vermeiren S, et al. Fatigue and the prediction of negative health outcomes: a systematic review with meta-analysis. *Ageing Res Rev.* (2021) 67:101261. doi: 10.1016/j.arr.2021.101261

15. van't Leven M, Zielhuis GA, van der Meer JW, Verbeek AL, Bleijenberg G. Fatigue and chronic fatigue syndrome-like complaints in the general population. *Eur J Public Health.* (2010) 20:251–7. doi: 10.1093/eurpub/ckp113

16. Moreh E, Jacobs JM, Stessman J. Fatigue, function, and mortality in older adults. *J Gerontol A Biomed Sci Med Sci.* (2010) 65:887–95. doi: 10.1093/gerona/glq064

17. Galland-Decker C, Marques-Vidal P, Vollenweider P. Prevalence and factors associated with fatigue in the lausanne middle-aged population: a population-based, cross-sectional survey. *BMJ Open.* (2019) 9:e027070. doi: 10.1136/bmjopen-2018-027070

18. Engberg I, Segerstedt J, Waller G, Wennberg P, Eliasson M. Fatigue in the general population-associations to age, sex, socioeconomic status, physical activity, sitting time and self-rated health: the Northern Sweden Monica Study 2014. *BMC Public Health.* (2017) 17:1–9. doi: 10.1186/s12889-017-4623-y

19. Skapinakis P, Lewis G, Mavreas V. Cross-cultural differences in the epidemiology of unexplained fatigue syndromes in primary care. *Br J Psychiatry.* (2003) 182:205–9. doi: 10.1192/bjp.182.3.205

20. Dinos S, Khoshaba B, Ashby D, White PD, Nazroo J, Wessely S, et al. A systematic review of chronic fatigue, its syndromes and ethnicity: prevalence, severity, co-morbidity and coping. *Int J Epidemiol.* (2009) 38:1554–70. doi: 10.1093/ije/dyp147

21. Stocchi F, Abbruzzese G, Ceravolo R, Cortelli P, D'Amelio M, De Pandis MF, et al. Prevalence of fatigue in Parkinson disease and its clinical correlates. *Neurology.* (2014) 83:215–20. doi: 10.1212/WNL.0000000000000587

22. Nagaraj K, Taly AB, Gupta A, Prasad C, Christopher R. Prevalence of fatigue in patients with multiple sclerosis and its effect on the quality of life. *J Neurosci Rural Pract.* (2013) 4:278–82. doi: 10.4103/0976-3147.118774

23. Singer S, Kuhnt S, Zwerenz R, Eckert K, Hofmeister D, Dietz A, et al. Age- and sex-standardised prevalence rates of fatigue in a large hospital-based sample of cancer patients. *Br J Cancer.* (2011) 105:445–51. doi: 10.1038/bjc.2011.251

24. Rusu C, Gee ME, Lagace C, Parlor M. Chronic fatigue syndrome and fibromyalgia in canada: prevalence and associations with six health status indicators. *Health Promot Chronic Dis Prev Can.* (2015) 35:3–11. doi: 10.24095/hpcdp.35.1.02

25. Bhui KS, Dinos S, Ashby D, Nazroo J, Wessely S, White PD. Chronic fatigue syndrome in an ethnically diverse population: the influence of psychosocial adversity and physical inactivity. *BMC Med.* (2011) 9:26. doi: 10.1186/1741-7015-9-26

26. Hamaguchi M, Kawahito Y, Takeda N, Kato T, Kojima T. Characteristics of chronic fatigue syndrome in a japanese community population: chronic fatigue syndrome in Japan. *Clin Rheumatol.* (2011) 30:895–906. doi: 10.1007/s10067-011-1702-9

27. Wells GA, Shea B, O'Connell D, Peterson J, Welch V, Losos M, et al. *The Newcastle-Ottawa Scale (NOS) for Assessing the Quality of Nonrandomised Studies in Meta-Analyses.* Oxford (2000).

28. Herzog R, Álvarez-Pasquin M, Díaz C, Del Barrio JL, Estrada JM, Gil Á. Are healthcare workers' intentions to vaccinate related to their knowledge, beliefs and attitudes? A systematic review. *BMC Public Health.* (2013) 13:1–17. doi: 10.1186/1471-2458-13-154

29. Luntamo T, Sourander A, Santalahti P, Aromaa M, Helenius H. Prevalence changes of pain, sleep problems and fatigue among 8-year-old children: years 1989, 1999, and 2005. *J Pediatr Psychol.* (2012) 37:307–18. doi: 10.1093/jpepsy/jsr091

30. David A, Pelosi A, McDonald E, Stephens D, Ledger D, Rathbone R, et al. Tired, weak, or in need of rest: fatigue among general practice attenders. *BMJ.* (1990) 301:1199–202. doi: 10.1136/bmj.301.6762.1199

31. Ament W, Verkerke GJ. Exercise and fatigue. *Sports Med.* (2009) 39:389–422. doi: 10.2165/00007256-200939050-00005

32. Boullosa DA, Nakamura FY. *The Evolutionary Significance of Fatigue*. Lausanne: Frontiers Media SA (2013), p. 309. doi: 10.3389/fphys.2013.00309

33. Yoo EH, Choi ES, Cho SH, Do JH, Lee SJ, Kim J-H. Comparison of fatigue severity and quality of life between unexplained fatigue patients and explained fatigue patients. *Korean J Fam Med.* (2018) 39:180. doi: 10.4082/kjfm.2018.39.3.180

34. Jason LA, Jordan KM, Richman JA, Rademaker AW, Huang C-F, Mccready W, et al. A community-based study of prolonged fatigue and chronic fatigue. *J Health Psychol.* (1999) 4:9–26. doi: 10.1177/135910539900400103

35. Wang XS, Zhao F, Fisch MJ, O'Mara AM, Cella D, Mendoza TR, et al. Prevalence and characteristics of moderate to severe fatigue: a multicenter study in cancer patients and survivors. *Cancer.* (2014) 120:425–32. doi: 10.1002/cncr.28434

36. Efficace F, Baccarani M, Breccia M, Cottone F, Alimena G, Deliliers G, et al. Chronic fatigue is the most important factor limiting health-related quality of life of chronic myeloid leukemia patients treated with imatinib. *Leukemia.* (2013) 27:1511–9. doi: 10.1038/leu.2013.51

37. Chou K-L. Chronic fatigue and affective disorders in older adults: evidence from the 2007 British National Psychiatric Morbidity Survey. *J Affect Disord.* (2013) 145:331–5. doi: 10.1016/j.jad.2012.08.012

38. Goërtz YM, Braamse AM, Spruit MA, Janssen DJ, Ebadi Z, Van Herck M, et al. Fatigue in patients with chronic disease: results from the population-based lifelines cohort study. *Sci Rep.* (2021) 11:1–12. doi: 10.1038/s41598-021-00337-z

39. Penner I-K, Paul F. Fatigue as a symptom or comorbidity of neurological diseases. *Nat Rev Neurol.* (2017) 13:662–75. doi: 10.1038/nrneurol.2017.117

40. Pendergrast T, Brown A, Sunnquist M, Jantke R, Newton JL, Strand EB, et al. Housebound versus nonhousebound patients with myalgic encephalomyelitis and chronic fatigue syndrome. *Chronic Illn.* (2016) 12:292–307. doi: 10.1177/1742395316644770

41. Roberts E, Wessely S, Chalder T, Chang C-K, Hotopf M. Mortality of people with chronic fatigue syndrome: a retrospective cohort study in england and wales from the South London and Maudsley NHS Foundation Trust Biomedical Research Centre (SLAM BRC) Clinical Record Interactive Search (CRIS) Register. *Lancet.* (2016) 387:1638–43. doi: 10.1016/S0140-6736(15)01223-4

42. Jason LA, Sunnquist M, Brown A, Evans M, Vernon SD, Furst JD, et al. Examining case definition criteria for chronic fatigue syndrome and myalgic encephalomyelitis. *Fatigue.* (2014) 2:40–56. doi: 10.1080/21641846.2013.862993

43. Lim E-J, Ahn Y-C, Jang E-S, Lee S-W, Lee S-H, Son C-G. Systematic review and meta-analysis of the prevalence of chronic fatigue syndrome/myalgic encephalomyelitis (CFS/ME). *J Transl Med.* (2020) 18:1–15. doi: 10.1186/s12967-020-02269-0

44. Huibers MJ, Kant IJ, Knottnerus JA, Bleijenberg G, Swaen GM, Kasl SV. Development of the chronic fatigue syndrome in severely fatigued employees: predictors of outcome in the maastricht cohort study. *J Epidemiol Community Health.* (2004) 58:877–82. doi: 10.1136/jech.2003.017939

45. Reyes-Gibby CC, Aday LA, Anderson KO, Mendoza TR, Cleeland CS. Pain, depression, and fatigue in community-dwelling adults with and without a history of cancer. *J Pain Symptom Manage.* (2006) 32:118–28. doi: 10.1016/j.jpainsymman.2006.01.008

46. Manning K, Kauffman BY, Rogers AH, Garey L, Zvolensky MJ. Fatigue severity and fatigue sensitivity: relations to anxiety, depression, pain catastrophizing, and pain severity among adults with severe fatigue and chronic low back pain. *Behav Med.* (2022) 48:181–9. doi: 10.1080/08964289.2020.1796572

47. ter Wolbeek M, van Doornen LJ, Kavelaars A, Heijnen CJ. Predictors of persistent and new-onset fatigue in adolescent girls. *Pediatrics.* (2008) 121:e449–57. doi: 10.1542/peds.2007-1093

48. Schwarz R, Krauss O, Hinz A. Fatigue in the general population. *Oncol Res Treat.* (2003) 26:140–4. doi: 10.1159/000069834

49. Tang F-C, Li R-H, Huang S-L. The Association between job-related psychosocial factors and prolonged fatigue among industrial employees in Taiwan. *PLoS ONE.* (2016) 11:e0150429. doi: 10.1371/journal.pone.0150429

50. Lasselin J, Lekander M, Axelsson J, Karshikoff B. Sex Differences in how inflammation affects behavior: what we can learn from experimental inflammatory models in humans. *Front Neuroendocrinol.* (2018) 50:91–106. doi: 10.1016/j.yfrne.2018.06.005

51. Patel V, Kirkwood BR, Weiss H, Pednekar S, Fernandes J, Pereira B, et al. Chronic fatigue in developing countries: population based survey of women in India. *BMJ.* (2005) 330:1190. doi: 10.1136/bmj.38442.636181.E0

52. Smith-Miller CA, Shaw-Kokot J, Curro B, Jones CB. An integrative review. *J Nurs Adm.* (2014) 44:487–94. doi: 10.1097/NNA.0000000000000104

53. Bültmann U, Kant IJ, Van Den Brandt PA, Kasl SV. Psychosocial work characteristics as risk factors for the onset of fatigue and psychological distress: prospective results from the maastricht cohort study. *Psychol Med.* (2002) 32:333–45. doi: 10.1017/S0033291701005098

54. Swaen G, Van Amelsvoort L, Bültmann U, Kant I. Fatigue as a risk factor for being injured in an occupational accident: results from the maastricht cohort study. *Occup Environ Med.* (2003) 60:i88–92. doi: 10.1136/oem.60.suppl_1.i88

55. Ball HA, Siribaddana SH, Sumathipala A, Kovas Y, Glozier N, Rijsdijk F, et al. Genetic and environmental contributions to the overlap between psychological, fatigue and somatic symptoms: a twin study in Sri Lanka. *Twin Res Hum Genet.* (2011) 14:53–63. doi: 10.1375/twin.14.1.53

56. Andrea H, Kant I, Beurskens A, Metsemakers J, Van Schayck C. Associations between fatigue attributions and fatigue, health, and psychosocial work characteristics: a study among employees visiting a physician with fatigue. *Occup Environ Med.* (2003) 60:i99–104. doi: 10.1136/oem.60.suppl_1.i99

frontiers | Frontiers in Psychology

TYPE Original Research
PUBLISHED 11 August 2023
DOI 10.3389/fpsyg.2023.1213721

EDITED BY
Sławomir Kujawski,
Ludwik Rydygier Collegium Medicum in Bydgoszcz Nicolaus Copernicus University in Toruń, Poland

REVIEWED BY
Annapoorna Kuppuswamy,
University College London, United Kingdom
Rongguo Zhao,
Xiangtan University, China
Rebeca Robles,
National Institute of Psychiatry Ramon de la Fuente Muñiz (INPRFM), Mexico

*CORRESPONDENCE
Olaf von dem Knesebeck
✉ o.knesebeck@uke.de

RECEIVED 28 April 2023
ACCEPTED 31 July 2023
PUBLISHED 11 August 2023

CITATION
von dem Knesebeck O and Barbek R (2023) Public stigma toward fatigue—do social characteristics of affected persons matter? Results from the SOMA.SOC study.
Front. Psychol. 14:1213721.
doi: 10.3389/fpsyg.2023.1213721

Public stigma toward fatigue—do social characteristics of affected persons matter? Results from the SOMA.SOC study

Olaf von dem Knesebeck* and Rieke Barbek

Institute of Medical Sociology, University Medical Center Hamburg-Eppendorf, Hamburg, Germany

Objectives: Although public stigma imposes a great burden on those affected with manifold negative consequence there is not much known about public stigma related to fatigue. Therefore, this study addresses the following research questions: (1) What is the magnitude of public stigma toward individuals with fatigue? (2) Are there differences in public stigma depending on the social characteristics of the affected person (sex, occupation, and migration)?

Methods: Analyses are based on a national telephone survey in Germany ($N = 1{,}209$). A vignette describing a person with symptoms of fatigue was presented to the respondents. Vignettes were varied according to sex, occupational status, and migration status. Stigma toward the person presented in the vignette was measured by stereotypes and negative emotional reactions (anger).

Results: Of the stereotypes under study, "hypersensitive" was most frequently endorsed by the respondents (35.7%), followed by "weak will" (27.2%). About 15–20% of the respondents agreed that they react with anger, annoyance or incomprehension. There were considerable differences in fatigue stigma according to the social characteristics of the affected person. In two social groups public stigma was particularly pronounced: (1) male persons with a low occupational status and a migration background; (2) female persons with a high occupational status and without a migration status. In contrast, women with a low occupational status and a migration background were less stigmatized.

Conclusion: Individuals suffering from fatigue symptoms are confronted with stereotypes and negative emotional reactions by the public. Magnitude of public stigma considerably varies according to social characteristics of the afflicted person. Future studies should consider applying an intersectional approach to identify groups that are at risk of multiple stigma.

KEYWORDS

fatigue, public stigma, stereotypes, anger, intersectionality, social inequalities, SOMA.SOC

Introduction

According to Link and Phelan (2001), stigma is defined as a process in which labeling, stereotyping, status loss and discrimination co-occur in a situation where power is exercised. Public stigma is usually assessed by different beliefs endorsed by the general population, such as the ascription of attributes (stereotypes), emotional response upon meeting an afflicted person (e.g., anger or fear) or the desire to socially distance oneself (Knesebeck et al., 2015). Public stigma imposes a great burden on those affected with negative consequences for their health (Alvarez-Galvez and Salvador-Carulla, 2013; Schomerus et al., 2015) and help-seeking behavior (Griffiths et al., 2011; Clement et al., 2015). Moreover, stigma can be a barrier that impedes diagnosis of somatoform and related disorders (Murray et al., 2016).

Many somatic symptoms cannot exclusively ascribed to somatic diseases (e.g., vascular or inflammatory disease) or mental disorders (e.g., depressive or anxiety disorders) (Löwe et al., 2022). In this regard, a dualistic view classifying symptoms as either somatic or psychological is often inappropriate. With reference to the description of bodily distress disorder in the International Classification of Diseases, 11th edition (World Health Organization, 2023), persistent somatic symptoms are defined as being present on most days for at least several months. Fatigue is a persistent somatic symptom with an estimated prevalence of about 30% among adults in Germany (Kocalevent et al., 2011). It can be expected that this prevalence has increased in the last years as fatigue is a frequent symptom of long COVID (Global Burden of Disease Long COVID Collaborators, 2022). It has been reported that persons afflicted by fatigue symptoms may carry a burden of stigma because their symptoms are poorly understood and often unrecognized or unacknowledged by health professionals and the public (Green et al., 1999; Jason et al., 2004). Most empirical studies examining stigma related to fatigue primarily focus on perceived or anticipated stigma, and not on public stigma. In these studies, patients are asked whether they experienced or anticipate to be stigmatized because of their symptoms (e.g., Grover et al., 2021; Froehlich et al., 2022). In this regard, a recent review (Ko et al., 2022) explored the differences between patients with a chronic fatigue syndrome (CFS) and patients with comparable explained conditions concerning perceived and experienced stigma. Results based on the two studies (Looper and Kirmayer, 2004; Baken et al., 2018) included in the review showed that patients with CFS experienced higher levels of stigma. One study on public stigma toward people affected by somatic symptom disorder (SSD, Knesebeck et al., 2018) used vignettes that differed regarding main type of symptom (pain vs. fatigue) and existence of an earlier disease (yes vs. no). Results indicated public stigma (stereotypes, negative emotional reactions, and desire for social distance) toward people affected by SSD in Germany. Magnitude of SSD stigma was similar, irrespective of main type of symptom and existence of an earlier disease. Altogether, there is a lack of research on public stigmatizing beliefs toward individuals affected by fatigue.

Many studies look at health-related stigma without considering other (social) conditions that also may be associated with stigmatization (e.g., poverty, low socio-economic status, ethnic minority). The circumstance that individuals potentially belong to more than one stigmatized group is conceptualized as "layered stigma" (Henkel et al., 2008), "multiple stigma" (Makowski et al., 2019), or "intersectional stigma" (Turan et al., 2019). These concepts suggest that a convergence of multiple stigmatized identities within a person or group will result in joint or cumulative effects. Empirical studies examining this hypothesis yielded mixed findings (Grollman, 2015; Knesebeck et al., 2017; Makowski et al., 2019; Turan et al., 2019). Women, ethnic minorities and people with a low socio-economic status (SES) are often mentioned groups potentially affected by layered stigma (Gary, 2005; Henkel et al., 2008; Pecosolido and Martin, 2015; Turan et al., 2019). However, to our knowledge there is no study that empirically analyses whether individuals belonging to these groups and afflicted by fatigue are confronted with multiple stigma. Therefore, we address the following research questions: (1) What is the magnitude of public stigma in terms of stereotypes and anger toward individuals with fatigue? (2) Are there differences in public stigma depending on the social characteristics of the affected person (sex, occupation, and migration)?

Materials and methods

Study design and sample

Analyses are based on cross-sectional data collected between March and May 2022 via a telephone survey (computer assisted telephone interview) of the adult population (age $\geq$ 18 years) living in Germany. About 70% of the sample was drawn from all registered private telephone numbers at random, additional computer-generated numbers allowed for inclusion of ex-directory households (landline numbers). The other 30% of the sample consisted of randomly generated mobile phone numbers (Random Digit Dialling). For a random selection of participants in the households, the Kish-Selection Grid was applied (Kish, 1949). Oral informed consent was given in the beginning of the interview. In total, $N = 2,413$ individuals participated in the survey, reflecting a response rate of 45%. To gain a representative sample of the adult population living in Germany, the data set was weighted. Comparison of sociodemographic characteristics of the sample with official statistics indicates that distribution of age, gender, and education is similar to the general adult population in Germany.

The survey is part of a project on social inequalities in aggravating factors of persistent somatic symptoms (SOMA.SOC, Knesebeck et al., 2023) which is embedded in the Research Unit 5211 "Persistent SOMAtic Symptoms ACROSS Diseases: From Risk Factors to Modification (SOMACROSS)" (Löwe et al., 2022). The study design was approved by the Ethics Commission of the Hamburg Medical Chamber (No. 2020-10194-BO-ff).

Vignettes

At the beginning of the interviews, a vignette describing a person with symptoms of fatigue or irritable bowel syndrome (IBS) was presented to the respondents in the survey. We chose these two specific conditions as they appear relatively frequently in the German population and other projects of the research unit also focussed on fatigue and IBS. Vignettes were developed with the input of clinicians (colleagues of the SOMACROSS research unit, i.e., specialists from psychosomatic, general and internal medicine) considering typical symptoms described in the International Classification of Diseases (DIMDI, 2019). One of the two vignettes (fatigue or IBS) was randomly assigned to half of the sample, respectively. As the following analyses will focus on fatigue, half of the total sample ($n = 1,209$) will be used. In terms of the fatigue vignette, different symptoms like exhaustion, weakness, and cognitive limitations were described (DIMDI, 2019; AWMF, 2022, please see Appendix). To examine differences in public stigma, vignettes were varied according to sex (male/female), occupational status (high/low), and migration status (yes/no). Thus, eight different fatigue vignettes were used (please see

TABLE 1 Eight variations of the fatigue vignette presented in the survey.

	Combination of social factors
1	Male, migration history, lawyer
2	Male, no migration history, lawyer
3	Male, migration history, cleaner
4	Male, no migration history, cleaner
5	Female, migration history, lawyer
6	Female, no migration history, lawyer
7	Female, migration history, cleaner
8	Female, no migration history, cleaner

TABLE 2 Sample description.

	n	%
Gender		
Female	634	52.7
Male	570	47.3
Age groups (in years)		
18–24	114	9.4
25–39	272	22.5
40–59	379	31.3
60–64	118	9.7
≥65	326	27.0
Education (in years)		
≤9	351	30.8
10	374	32.8
≥12	415	36.4
Household income (per month, net, in euro)		
<1,500	243	24.9
1,500 – <2,500	289	29.7
2,500 – <3,500	170	17.5
≥3,500	271	27.9
Migration status		
Non-migrant	945	78.4
Migrant foreign born	127	10.5
Migrant born in Germany	134	11.1

Table 1) that each were randomly assigned to about 150 respondents (i.e., about 12.5% of the analysed sample). A sample size of $n = 150$ per vignette allowed for the detection of small to medium differences (statistical power 80%, Type-I error = 0.05). In terms of migration status, the person in the vignette had a Turkish name and it is said that the person came from Turkey to Germany 10 years ago. Turkey was chosen as country of origin because about 2.9 million inhabitants in Germany with a Turkish background are forming the largest migrant group (Schürer, 2018). In the high occupational status vignette, it is said that the respective person is a lawyer and in the low status vignette the person is a cleaner. The vignettes were audio-recorded with a trained speaker with a clear voice. In order to increase reliability and to neutralize possible interviewer-associated effects, this file was presented to the respondents directly from the computer via telephone line. We used unlabelled vignettes, i.e., the respondents were not informed that the person in the vignette had fatigue.

Indicators

To assess stigma toward the person presented in the vignette, two components of the stigma process [1] were considered: stereotypes and negative emotional reactions (anger). In terms of stereotypes, respondents were asked to indicate to what extent they agree or disagree with the following statements (McLoed et al., 2007; Angermeyer et al., 2013; Knesebeck et al., 2018) on a four-point Likert scale: (1) "People with symptoms like Mrs./Mr. E. are hypersensitive." (2) "Mrs./Mr. E. does not have a real disease." (3) "A possible cause for the symptoms of Mrs./Mr. E. is a weak will." Based on a study of Angermeyer and Matschinger (2003), three items ("I react angrily.," "I feel annoyed by this person.," and "I react with incomprehension.") were used to assess anger reactions. Again, responses were given on a four-point Likert scale ranging from "completely agree" to "completely disagree." As in previous studies (Angermeyer and Matschinger, 2003; Knesebeck et al., 2018), the items were summed up to build an anger scale (range 0–9; Cronbach's Alpha 0.71).

Analyses

Pearson's chi-square test (items) and analyses of variance (scale) were applied to test differences in stigma toward male vs. female, migrant vs. non-migrant, and high vs. low occupational status persons with fatigue. For the chi-square tests, the items were dichotomized to compare agreement (yes/no) between the subgroups. In terms of the scale (anger), the corresponding items were summed up. Percentages (items), means as well as standard errors (scale) and significances (*p*-values) are reported. Statistical procedures were performed with the statistical program package SPSS 27.

Results

A description of the socio-demographic characteristics of the used sample is shown in Table 2. About 27% of the respondents completely or rather agreed that a possible cause for the symptoms of the person depicted in the vignette is a weak will (Figure 1). About 14% agreed that the person in the vignette does not have a real disease, and more than 1/3 indicated that the person is hypersensitive. In terms of emotional reactions, about 15–20% of the respondents agreed that they react with anger, annoyance or incomprehension in case of a person showing symptoms of fatigue.

Table 3 shows that, in case of a male vignette, significantly more respondents agreed that the person is hypersensitive. Also, more respondents reacted with incomprehension in case of the male vignette. However, when the person in the vignette was female, significantly more respondents felt annoyed. In terms of migration background, there were two significant differences in public stigma: Attribution to a weak will and anger reactions were less pronounced when the person with fatigue symptoms was a migrant. With regard to occupational status, significantly more respondents agreed that the

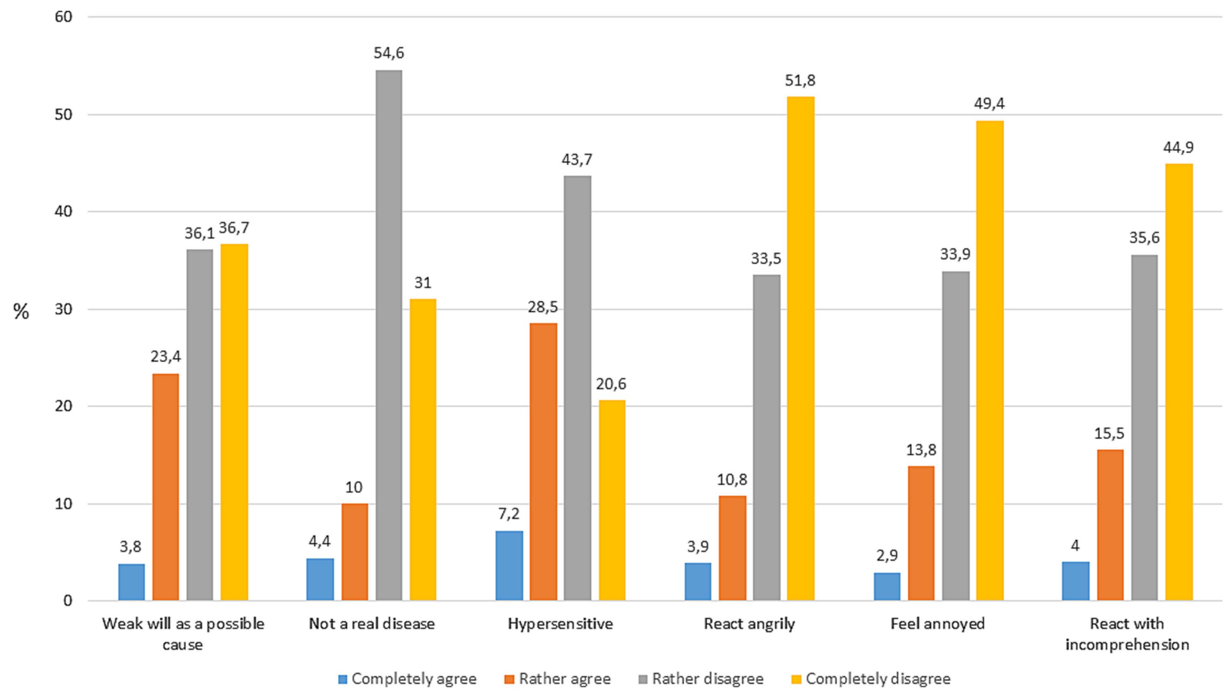


FIGURE 1
Distribution of the public stigma indicators (*n* = 1,209).

TABLE 3 Stigma toward an individual with fatigue depending on social characteristics of the afflicted person in the vignette (sex, migration, occupation).

Stereotypes	Female (*n* = 609)	Male (*n* = 600)	*p*[b]	Migrant (*n* = 597)	Non-migrant (*n* = 612)	*p*[b]	Cleaner (*n* = 591)	Lawyer (*n* = 618)	*p*[b]
Weak will[a]	25.6	28.9	0.214	**23.2**	**31.0**	**0.003**	28.9	25.5	0.201
Not a real disease[a]	15.1	13.6	0.448	15.8	13.2	0.204	13.4	15.3	0.361
Hypersensitive[a]	**31.9**	**39.6**	**0.006**	35.4	35.9	0.865	**32.8**	**38.6**	**0.040**
Emotional reactions									
Angrily[a]	15.4	13.9	0.461	13.4	15.9	0.224	**17.6**	**11.8**	**0.004**
Annoyed[a]	**20.9**	**12.2**	**<0.001**	15.9	17.4	0.461	16.5	16.7	0.916
Incomprehension[a]	**16.2**	**22.9**	**0.004**	19.7	19.4	0.878	17.5	21.5	0.083
Anger scale (0–9), mean (standard deviation)	2.16 (2.01)	2.14 (1.92)	0.922	**2.02 (2.04)**	**2.28 (1.89)**	**0.027**	2.14 (2.02)	2.16 (1.91)	0.841

[a] % of agreement.
[b] Significance of Chi^2 tests/analyses of variance (anger scale).
Significant differences ($p < 0.05$) are bold.

person is hypersensitive in case of a lawyer, while more respondents reacted angrily when the depicted person was a cleaner.

Differences between the eight combinations of the social characteristics depicted in the fatigue vignettes are shown in Table 4. These differences are significant for all indicators of stigma under study ($p < 0.05$). In terms of weak will, agreement varies between 14.3% (female cleaner with migrant background) and 35.1% (male cleaner with migrant background). 6.3% of the respondents agreed that the person in the vignette does not have a real disease in case of a female cleaner with migrant background, 25.6% agreed for the male counterpart. Variance of agreement was 25.5 to 43.2% for the stereotype 'hypersensitive'. When the person in the vignette was a male migrant lawyer, 8% reacted angrily, 13.5% less than for the non-migrant counterpart. Variance of those who felt annoyed was from 7.2% (male, non-migrant, lawyer) to 29.6% (female, non-migrant, lawyer). In terms of incomprehension, agreement varied from 10.6 to 27.6% and for the anger sum scale, mean was lowest in case of a male lawyer with a migrant background and highest in case of a female, non-migrant lawyer.

Discussion

In this study, the magnitude of public stigma in terms of stereotypes and anger toward individuals with fatigue was explored by using a vignette based population survey conducted in Germany. Of

TABLE 4 Stigma toward an individual with fatigue depending on the combination of the social characteristics in the eight vignettes.

Stereotypes	Female, migrant, cleaner (*n* = 146)	Female, migrant, lawyer (*n* = 156)	Female, non-migrant, cleaner (*n* = 151)	Female, non-migrant, lawyer (*n* = 156)	Male, migrant, cleaner (*n* = 142)	Male, migrant, lawyer (*n* = 154)	Male, non-migrant, cleaner (*n* = 152)	Male, non-migrant, lawyer (*n* = 153)	p^b
Weak will[a]	14.3	20.8	32.6	33.8	35.1	23.2	34.0	23.8	<0.001
Not a real disease[a]	6.3	20.7	16.8	17.1	25.0	12.0	7.4	11.9	<0.001
Hypersensitive[a]	25.5	31.3	28.9	41.2	42.0	43.2	35.8	37.7	0.007
Emotional reactions									
Angrily[a]	19.9	12.3	14.7	15.5	14.3	8.0	21.5	11.9	0.028
Annoyed[a]	14.5	20.9	17.9	29.6	18.6	9.2	15.0	7.2	<0.001
Incomprehension[a]	15.9	13.8	10.6	24.5	27.6	22.2	16.6	25.8	<0.001
Anger scale (0–9), mean (standard deviation)	1.92 (2.07)	2.06 (2.12)	2.04 (1.86)	2.61 (1.93)	2.22 (2.11)	1.90 (1.84)	2.38 (2.05)	2.09 (1.66)	0.030

[a] % of agreement.

[b] Significance of Chi² tests/analyses of variance (anger scale).

the stereotypes under study, "hypersensitive" was most frequently endorsed by the respondents (35.7% completely or rather agreed), followed by "weak will" (27.2% agreement). About 15–20% of the respondents agreed that they react with anger, annoyance or incomprehension in case of a person showing symptoms of fatigue. We additionally analysed differences in stigma depending on the social characteristics of the affected person (sex, occupation, and migration). Accordingly, autochthonous individuals with fatigue were more often stigmatized than those with a Turkish migrant background, while differences according to sex and occupational status (low: cleaner vs. high: lawyer) were inconsistent. A more detailed analysis regarding the combinations of the social characteristics revealed considerable differences between the eight subgroups. In fact, there were differences of about 20% in the endorsement of stereotypes according to the combined social characteristics although the fatigue symptoms described in the vignette were the same. In two social groups public stigma was particularly pronounced: (1) male persons with a low occupational status and a migration background; (2) female persons with a high occupational status and without a migration status. In contrast, women with a low occupational status and a migration background were less stigmatized.

This is one of the first studies analysing public stigma toward people affected by fatigue. There was one previous study with a similar design on public stigma related to SSD (Knesebeck et al., 2018, 2020). Levels of anger reactions as well as endorsement of a weak will were similar to those found in the present study. Our findings can also be compared with previous studies on public stigma toward people with (mental) disorders. In this regard, occurrence of anger reactions was similar in a study on public depression stigma (Knesebeck et al., 2017), while there were lower levels of anger in cases of bulimia nervosa and anorexia nervosa (Makowski et al., 2015). Attribution to a weak will, however, was more pronounced among persons with these eating disorders than in the present study on fatigue. In part, these differences between the results can be explained by varying sample characteristics of the studies. On the other hand, it is known that the magnitude of public stigma varies for different conditions (Pecosolido and Martin, 2015; Knesebeck et al., 2018).

In recent years, it has been claimed that stigma research should pay more attention to multiple social identities and their interaction to influence health-related stigma (Turan et al., 2019). Accordingly, individuals can belong to more than one stigmatized group (e.g., someone who suffers from fatigue and has a deprived social status) and, thus, can be exposed to intersectional or multiple stigma. In this regard, differences according to sex and occupational status in our analyses were inconsistent, while stigmatizing beliefs were less pronounced when the person with fatigue symptoms was a migrant. These findings do not support the hypothesis of multiple stigma which is in line with a previous study focussing on depression stigma (Knesebeck et al., 2017). However, other studies found evidence for multiple stigma. For example, in a study by Makowski et al. (2019), public obesity stigma was more pronounced when the afflicted person has a low socio-economic status. Studies exploring whether respondents showed lower levels of stigma when confronted with a vignette depicting an afflicted person with similar social characteristics like themselves revealed inconsistent results (Makowski et al., 2015; Makowski and Knesebeck, 2017). The role of responders' social background for stigmatizing attitudes toward affected persons with varying social characteristics should be considered in future studies.

To meet the complex nature of intersectional stigma, we additionally applied an intercategorical approach (Turan et al., 2019) by analysing combinations of the three social characteristics. In doing so, large stigma differences between the eight subgroups were found. In terms of the hypothesis of multiple stigma, inconsistent findings emerged. On the one hand, women with a low occupational status and a migration background were less stigmatized, which contradicts the hypothesis. On the other hand, among male persons with a low occupational status and a migration background, fatigue stigma was particularly pronounced, supporting the hypothesis, at least with regard to migration and socio-economic status. One possible explanation of these inconsistent findings might be that we combined social characteristics (sex, occupation, and migration) representing different horizontal and vertical dimensions of social inequalities. These dimensions can be associated with different forms of discrimination and thus, may be differently connected with disease related stigma. Our results overall indicate that the magnitude of intersectional stigma appears dependent on the combination of the potentially stigmatized social characteristics.

Several limitations should be considered when interpreting present results. In terms of sample quality, 55% of the selected eligible persons refused to participate or were not available and, thus, selection bias cannot be ruled out. On the other hand, comparison of sociodemographic characteristics in the sample with official statistics did not indicate that distribution of age, gender, and education is different from the general adult population in Germany. Although analyses were based on instruments measuring public stigma that were used in previous studies (McLoed et al., 2007; Alvarez-Galvez and Salvador-Carulla, 2013; Angermeyer et al., 2013; Knesebeck et al., 2018), the number and range of indicators of stereotypes and emotional reactions were limited. While the use of vignettes as a standardizing stimulus can be considered established in stigma research, they have to be short to be included into surveys. This affected the presentation of the fatigue symptoms and of the varied social characteristics. The fatigue vignette was developed with the input of clinicians but had to be limited to the major symptoms. Moreover, description of duration of symptoms in the vignette was not substantiated by giving an exact time period. We used unlabelled vignettes, i.e., the respondents were not informed that the person in the vignette had fatigue. Thus, their answers referred only to the described symptoms in the vignette. To distinguish the social groups according to migration and occupational status, only the first sentence in the vignette was varied. Furthermore, only two groups for each of the social characteristics were compared (lawyer vs. cleaner and Turkish migrant background yes vs. no). This must be considered a simplified way to represent aspects of social inequalities. Moreover, other social characteristics of the affected person (e.g., education, religion) that may be relevant for public fatigue stigma, were not considered in the present study. Finally, we cannot exclude that social desirability may have influenced responses regarding stigmatizing attitudes.

It is known that public stigma imposes a great burden on those affected with manifold negative consequences. Results presented here indicate that individuals suffering from fatigue symptoms are confronted with stereotypes and negative emotional reactions by the public. Magnitude of public stigma varies according to social characteristics of the afflicted person. Men with fatigue symptoms, a low occupational status and a migration background seem to be affected by multiple stigma. Future studies analysing public fatigue stigma should consider applying an intersectional approach to identify groups that are at special risk of being stigmatized. In terms of practical implications, three strategies to reduce stigma have been suggested (Corrigan and Penn, 1999): protest or social activism, education of the public, and contact to those affected. A meta-analysis of studies on effects of these anti-stigma approaches came to the result that depending on the target group, education and contact had positive effects on reducing stigma (Corrigan et al., 2012). Our results suggest to consider social characteristics of the affected persons in respective interventions.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The study design was approved by the Ethics Commission of the Hamburg Medical Chamber (No. 2020-10194-BO-ff). The studies were conducted in accordance with the local legislation and institutional requirements. Written informed consent for participation was not required from the participants or the participants' legal guardians/next of kin because Oral informed consent was given in the beginning of the telephone interview.

Author contributions

OK designed the study, interpreted the data, and drafted the manuscript. RB conducted the analyses, critically revised the manuscript, and approved the final version. All authors contributed to the article and approved the submitted version.

Funding

This work was carried out within the framework of Research Unit 5211 (FOR 5211) “Persistent SOMAtic Symptoms ACROSS Diseases: From Risk Factors to Modification (SOMACROSS),” funded by the German Research Foundation (Deutsche Forschungsgemeinschaft, DFG). The DFG grant number for this project (P 06) “Social Inequalities in Aggravating Factors of Somatic Symptom Persistence (SOM.SOC)” is 445297796.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher’s note

References

Alvarez-Galvez, J., and Salvador-Carulla, L. (2013). Perceived discrimination and self-rated health in Europe: evidence from the European social survey (2010). *PLoS One* 8:e74252. doi: 10.1371/journal.pone.0074252

Angermeyer, M. C., and Matschinger, H. (2003). The stigma of mental illness: effects of labelling on public attitudes towards people with mental disorder. *Acta Psychiatr. Scand.* 108, 304–309. doi: 10.1034/j.1600-0447.2003.00150.x

Angermeyer, M. C., Mnich, E., Daubmann, A., Herich, L., Wegscheider, K., Kofahl, C., et al. (2013). Biogenetic explanations and public acceptance of people with eating disorders. *Soc. Psychiatry Psychiatr. Epidemiol.* 48, 1667–1673. doi: 10.1007/s00127-012-0648-9

AWMF. (2022). [Fatigue] [S3-Guideline]. Available at: https://register.awmf.org/de/leitlinien/detail/053-002 (Accessed March 27, 2023).

Baken, D. M., Harvey, S. T., Bimler, D. L., and Ross, K. J. (2018). Stigma in myalgic encephalomyelitis and its association with functioning. *Fatigue Biomed. Health Behav.* 6, 30–40. doi: 10.1080/21641846.2018.1419553

Clement, S., Schauman, O., Graham, T., Maggioni, F., Evans-Lacko, S., Bezborodovs, N., et al. (2015). What is the impact of mental health-related stigma on help-seeking? A systematic review of quantitative and qualitative studies. *Psychol. Med.* 45, 11–27. doi: 10.1017/S0033291714000129

Corrigan, P. W., Morris, S. B., Michaels, P. J., Rafacz, J. D., and Rüsch, N. (2012). Challenging the public stigma of mental illness: a meta-analysis of outcome studies. *Psychiatr. Serv.* 63, 963–973. doi: 10.1176/appi.ps.201100529

Corrigan, P. W., and Penn, D. L. (1999). Lessons from social psychology on discrediting psychiatric stigma. *Am. Psychol.* 54, 765–776. doi: 10.1037/0003-066X.54.9.765

DIMDI. (2019). ICD-10-WHO version 2019. Available at: https://www.dimdi.de/static/de/klassifikationen/icd/icd-10-who/kode-suche/htmlamtl2019/ (Accessed March 27, 2023).

Froehlich, L., Hattesohl, D. B. R., Cotler, J., Jason, L. A., Scheibenbogen, C., and Behrends, U. (2022). Causal attributions and perceived stigma for myalgic encephalomyelitis/chronic fatigue syndrome. *J. Health Psychol.* 27, 2291–2304. doi: 10.1177/13591053211027631

Gary, F. A. (2005). Stigma: barrier to mental health care among ethnic minorities. *Issues Ment. Health Nurs.* 26, 979–999. doi: 10.1080/01612840500280638

Global Burden of Disease Long COVID Collaborators (2022). Estimated global proportions of individuals with persistent fatigue, cognitive, and respiratory symptom clusters following symptomatic COVID-19 in 2020 and 2021. *JAMA* 328, 1604–1615. doi: 10.1001/jama.2022.18931

Green, J., Romei, J., and Natelson, B. H. (1999). Stigma and chronic fatigue syndrome. *J. Chronic Fatigue Syndr.* 5, 63–75. doi: 10.1300/J092v05n02_04

Griffiths, K. M., Crisp, D. A., Jorm, A. F., and Christensen, H. (2011). Does stigma predict a belief in dealing with depression alone? *J. Affect. Disord.* 132, 413–417. doi: 10.1016/j.jad.2011.03.012

Grollman, E. A. (2015). Multiple disadvantaged statuses and health: the role of multiple forms of discrimination. *J. Health Soc. Behav.* 55, 3–19. doi: 10.1177/0022146514521215

Grover, S., Sahoo, S., Mishra, E., Singh Gill, A., Mehra, A., Nehra, R., et al. (2021). Fatigue, perceived stigma, self-reported cognitive deficits and psychological morbidity in patients recovered from COVID-19 infection. *Asian J. Psychiatr.* 64:102815. doi: 10.1016/j.ajp.2021.102815

Henkel, K. E., Brown, K., and Kalichman, S. C. (2008). AIDS-related stigma in individuals with other stigmatized identities in the USA: a review of layered stigmas. *Soc. Personal. Psychol. Compass* 2, 1586–1599. doi: 10.1111/j.1751-9004.2008.00116.x

Jason, L. A., Holbert, C., and Torres-Harding, S. (2004). Stigma and the term chronic fatigue syndrome. *J. Disabil. Policy Stud.* 14, 222–228. doi: 10.1177/10442073040140040401

Kish, L. (1949). A procedure for objective respondent selection within the household. *J. Am. Stat. Assoc.* 44, 380–387. doi: 10.1080/01621459.1949.10483314

Knesebeck, O. V. D., Barbek, R., and Makowski, A. (2023). Social inequalities in aggravating factors of somatic symptom persistence (SOMA.SOC): study protocol of a mixed method observational study focussing on irritable bowel syndrome and fatigue. *BMJ Open* 13:e070635. doi: 10.1136/bmjopen-2022-070635

Knesebeck, O. V. D., Kofahl, C., and Makowski, A. (2017). Differences in depression stigma towards ethnic and socio-economic groups in Germany – exploring the hypothesis of double stigma. *J. Affect. Disord.* 208, 82–86. doi: 10.1016/j.jad.2016.08.071

Knesebeck, O. V. D., Lehmann, M., Löwe, B., and Lüdecke, D. (2020). Causal attributions for somatic symptom disorders – results of a German population survey. *J. Psychosom. Res.* 129:109910. doi: 10.1016/j.jpsychores.2019.109910

Knesebeck, O. V. D., Lehmann, M., Löwe, B., and Makowski, A. (2018). Public stigma towards individuals with somatic symptom disorders – survey results from Germany. *J. Psychosom. Res.* 115, 71–75. doi: 10.1016/j.jpsychores.2018.10.014

Knesebeck, O. V. D., Mnich, E., Angermeyer, M. C., Kofahl, C., and Makowski, A. (2015). Changes in depression stigma after the Germanwings crash - findings from German population surveys. *J. Affect. Disord.* 186, 261–265. doi: 10.1016/j.jad.2015.07.029

Ko, C., Lucassen, P., van der Linden, B., Ballering, A., and Hartmann, T. O. (2022). Stigma perceived by patients with functional somatic syndromes and its effect on health outcomes – a systematic review. *J. Psychosom. Res.* 154:110715. doi: 10.1016/j.jpsychores.2021.110715

Kocalevent, R. D., Hinz, A., Brähler, E., and Klapp, B. F. (2011). Determinants of fatigue and stress. *BMC. Res. Notes* 4:238. doi: 10.1186/1756-0500-4-238

Link, B. G., and Phelan, J. C. (2001). Conceptualizing stigma. *Annu. Rev. Sociol.* 27, 363–385. doi: 10.1146/annurev.soc.27.1.363

Looper, K. J., and Kirmayer, L. J. (2004). Perceived stigma in functional somatic syndromes and comparable medical conditions. *J. Psychosom. Res.* 57, 373–378. doi: 10.1016/j.jpsychores.2004.03.005

Löwe, B., Andresen, V., van den Bergh, O., Huber, T., Knesebeck, O. V. D., Lohse, A., et al. (2022). Persistent SOMAtic symptoms ACROSS diseases - from risk factors to modification: scientific framework and overarching protocol of the interdisciplinary SOMACROSS research unit (RU 5211). *BMJ Open* 12:e057596. doi: 10.1136/bmjopen-2021-057596

Makowski, A. C., Kim, T. J., Luck-Sikorski, C., and Knesebeck, O. V. D. (2019). Social deprivation, gender, and obesity: multiple stigma? Results of a population survey from Germany. *BMJ Open* 9:e023389. doi: 10.1136/bmjopen-2018-023389

Makowski, A. C., and Knesebeck, O. V. D. (2017). Depression stigma and migration – results of a survey from Germany. *BMC Psychiatry* 17:381. doi: 10.1186/s12888-017-1549-y

Makowski, A. C., Mnich, E., Angermeyer, M. C., Löwe, B., and Knesebeck, O. V. D. (2015). Sex differences in attitudes towards females with eating disorders. *Eat. Behav.* 16, 78–83. doi: 10.1016/j.eatbeh.2014.10.017

McLoed, J. D., Fettes, D. L., Jensen, P. S., Pescosolido, B. A., and Martin, J. K. (2007). Public knowledge, beliefs, and treatment preferences concerning attention-deficit hyperactivity disorder. *Psychiatr. Serv.* 58, 626–631. doi: 10.1176/ps.2007.58.5.626

Murray, A. M., Toussaint, A., Althaus, A., and Löwe, B. (2016). The challenge of diagnosing non-specific, functional, and somatoform disorders: a systematic review of barriers to diagnosis in primary care. *J. Psychosom. Res.* 80, 1–10. doi: 10.1016/j.jpsychores.2015.11.002

Pecosolido, B. A., and Martin, J. K. (2015). The stigma complex. *Annu. Rev. Sociol.* 41, 87–116. doi: 10.1146/annurev-soc-071312-145702

Schomerus, G., Evans-Lacko, S., Rüsch, N., Mojtabai, R., Angermeyer, M. C., and Thornicroft, G. (2015). Collective levels of stigma and national suicide rates in 25 European countries. *Epidemiol. Psychiatr. Sci.* 24, 166–171. doi: 10.1017/S2045796014000109

Schürer, S. (2018). *[people from Turkey in Germany]. BAMF working paper 81*. Available from: [https://www.bamf.de/SharedDocs/Anlagen/EN/Forschung/WorkingPapers/wp81-tuerkeistaemmige-in-deutschland.html?nn=403984]

Turan, J. M., Elafros, M. A., Logie, C. H., Banik, S., Turan, B., Crockett, K. B., et al. (2019). Challenges and opportunities in examining and addressing intersectional stigma and health. *BMC Med.* 17:7. doi: 10.1186/s12916-018-1246-9

World Health Organization (2023). *International classification of disease, ICD-11*. Available from: (https://icd.who.int/browse11/l-m/en)

Appendix

Vignettes (two examples).

Ten years ago, 37-year-old Gülsen E. came to Germany from Turkey and she works as a cleaner. [1]She has been suffering from total exhaustion for some time now. She feels constantly tired, weak and lacking concentration despite an increased number of breaks. The troubles restrict Ms. E. very much in her everyday life and sometimes she cannot go to work. A few months ago, she had a virus infection. Current examinations have not provided any indication of a threatening illness.

37-year-old Martin E. works as a lawyer (see footnote 1). He has been suffering from total exhaustion for some time now. He feels constantly tired, weak and lacking concentration despite an increased number of breaks. The troubles restrict Mr. E. very much in his everyday life and sometimes he cannot go to work. A few months ago, he had a virus infection. Current examinations have not provided any indication of a threatening illness.

---

[1] Migration history (yes/no), sex (male/female), and occupational status (lawyer/cleaner) were systematically varied, resulting in eight different vignettes (please see also Table 1).

frontiers | Frontiers in Neuroscience

TYPE Review
PUBLISHED 05 October 2023
DOI 10.3389/fnins.2023.1231321

OPEN ACCESS

EDITED BY
Sławomir Kujawski,
Nicolaus Copernicus University in Toruń, Poland

REVIEWED BY
Franca Tecchio,
National Research Council (CNR), Italy
Alexandre Brandão,
Brazilian Institute of Neuroscience and Neurotechnology (BRAINN), Brazil

*CORRESPONDENCE
Tjalf Ziemssen
✉ tjalf.ziemssen@uniklinikum-dresden.de

RECEIVED 30 May 2023
ACCEPTED 18 September 2023
PUBLISHED 05 October 2023

CITATION
Pinarello C, Elmers J, Inojosa H, Beste C and Ziemssen T (2023) Management of multiple sclerosis fatigue in the digital age: from assessment to treatment.
Front. Neurosci. 17:1231321.
doi: 10.3389/fnins.2023.1231321

Management of multiple sclerosis fatigue in the digital age: from assessment to treatment

Chiara Pinarello[1], Julia Elmers[1,2], Hernán Inojosa[1], Christian Beste[2] and Tjalf Ziemssen[1]*

[1]Center of Clinical Neuroscience, Department of Neurology, University Hospital Carl Gustav Carus, Technical University of Dresden, Dresden, Germany, [2]Cognitive Neurophysiology, Department of Child and Adolescent Psychiatry, Faculty of Medicine, Technical University of Dresden, Dresden, Germany

Fatigue is one of the most disabling symptoms of Multiple Sclerosis (MS), affecting more than 80% of patients over the disease course. Nevertheless, it has a multi-faceted and complex nature, making its diagnosis, evaluation, and treatment extremely challenging in clinical practice. In the last years, digital supporting tools have emerged to support the care of people with MS. These include not only smartphone or table-based apps, but also wearable devices or novel techniques such as virtual reality. Furthermore, an additional effective and cost-efficient tool for the therapeutic management of people with fatigue is becoming increasingly available. Virtual reality and e-Health are viable and modern tools to both assess and treat fatigue, with a variety of applications and adaptability to patient needs and disability levels. Most importantly, they can be employed in the patient's home setting and can not only bridge clinic visits but also be complementary to the monitoring and treatment means for those MS patients who live far away from healthcare structures. In this narrative review, we discuss the current knowledge and future perspectives in the digital management of fatigue in MS. These may also serve as sources for research of novel digital biomarkers in the identification of disease activity and progression.

KEYWORDS

multiple sclerosis, fatigue, digital health, virtual reality, digital biomarkers, wearable devices, disease management, apps

1. Introduction

Multiple Sclerosis (MS) is a chronic inflammatory autoimmune disease of the central nervous system (CNS). The multifactorial pathophysiology of MS leads to demyelination of axons in the CNS affecting every neurological functional system (National Multiple Sclerosis Society, 1991). Consequently, the clinical presentation is extremely heterogeneous including, among several other symptoms, fatigue. Fatigue is one of the most disabling complaints of MS patients, affecting up to 80% over the disease course (Chalah et al., 2015; Rooney et al., 2019; Palotai and Guttmann, 2020; Oliva Ramirez et al., 2021). Patients across every disease phenotype may be affected already in the early stages of the disease, with high interpersonal variability in the quality, frequency, and severity of fatigue (Filippi and Rocca, 2020).

However, management of this symptom is often limited in clinical and scientific practice, even considering its relevance for the care of patients. Therapy success is directly related to a correct assessment and monitoring of fatigue. Objective measures for assessing fatigue beyond the anamnesis have been, nonetheless lacking until the most recent years, as novel outcome measures and tools have emerged (Voigt et al., 2021; Ziemssen and Haase, 2021). These include patient-reported outcome measures as well as several digital tools for the assessment of the disease at several levels. Similarly, effective symptomatic treatment is currently relatively limited as few evidence-based options are available. As pharmacotherapy in the treatment of fatigue is not established, cognitive training and neuro-rehabilitation seem to play a key role in disease management (Sailer et al., 2023).

In this review, we discuss a clinical and digital perspective regarding assessing and managing fatigue. Moreover, we explore the state of the art in the technological field of treating this fundamental symptom from current definitions to diagnosis and discuss procedures used in daily practice (clinical evaluation, EDSS, cognitive and neuropsychological tests). We focused on the critical points and limitations of current procedures and potential improvements through digital tools. In this context, we highlight current and future uses of newer resources such as apps and wearable devices for patient awareness and active management of the disease. The use of digital applications may additionally offer a resource beyond assessment but also for the treatment of patients with fatigue.

2. Current state-of-the-art in fatigue in MS

2.1. Definition and diagnosis

A clear and strict definition of fatigue is fundamental for proper assessment and treatment taking advantage of digital tools. This is, in contrast to several other MS-related symptoms, frequently not clear or standard in clinical practice as a broad spectrum of complaints or features is reported (Mills and Young, 2008). Additionally, several classifications and considerations may apply in the assessment of this symptom.

Mills and Young (2008) defined fatigue in an MS population as a "reversible, motor and cognitive impairment with reduced motivation and desire to rest".

A broad spectrum of features is described by patients with fatigue, including motor or cognitive dysfunction, lack of motivation, and rest complaints or behavioral responses (e.g., daytime resting, activity avoidance) (Mills and Young, 2008).

When discussing fatigue, a distinction between perceived fatigue and performance fatigability, the two facets contributing to its definition, is of capital importance (Enoka and Duchateau, 2016). In the framework of a neurologic disease such as MS, perceived fatigue represents an individual's perception of tiredness and thus disparity between the energy exerted in an activity and the actual outcome of it. In other words, the energy exerted in overcoming a task is greater than the one the task normally requires (Kluger et al., 2013; Enoka and Duchateau, 2016). Performance fatigability is the actual and measurable physical and cognitive drop in performance due to this state of exhaustion. Consequently, it is important to distinguish between the perception of the patient (perceived fatigue) and the tangible and measurable decrease in performance (performance fatigability). In MS, perceived fatigue can be reported by the patient through a self-assessment-designed questionnaire either at resting state or when carrying out an activity, whereas performance fatigability is preferably estimated during motor effort (e.g., walking long distances). Additionally, the latter can be measured in terms of change in task achievement over some time (Kluger et al., 2013; Enoka and Duchateau, 2016; Linnhoff and Heinze, 2019; Enoka et al., 2021). Additionally, cognitive fatigability (which is documented to decrease attention, processing speed, and memory) has to be differentiated from motor fatigability (which affects the ability to carry out physical tasks) (Enoka and Duchateau, 2016; Harrison et al., 2017).

Some authors also divide fatigue into state and trait fatigue, which is a further definition based on time and change: the former refers to a more acute situation, whereas trait fatigue belongs to a more chronic manifestation of fatigue (Kluger et al., 2013; Linnhoff and Heinze, 2019).

Although fatigue and fatigability essentially result from a central phenomenon (since MS is a disease of the central nervous system), there are some central al peripheral factors to take into consideration when exploring the phenomenology of fatigue. On the one end, central factors related to the pathophysiology of MS include damage to the cortical and subcortical areas, which then show further functional instability as the connectivity and therefore the performance is impaired.

The damage caused in the brain by MS is macro-structural (i.e., brain atrophy and volume loss) and microstructural (e.g., disrupted white matter integrity), involving precise areas of the nervous system (Jameen et al., 2019). In a vicious cycle, the interruption of the white matter (WM) tracts between the brain stem and the brain itself promotes the "neuro-immune reaction", that is to say, the imbalance between the production of inflammatory cytokines and the inhibition of anti-inflammatory ones (Carandini et al., 2021).

As far as the specific pathophysiological mechanism of MS fatigue, the damage in the cortico-striato-thalamo-cortical loop (CSTCL, represented in Figure 1) seems to play a role in its onset at a central level. This loop conveys high cognitive functions like planning, problem-solving, and goal-setting. The demyelination of such fibers produces a slower transmission rate and a consequent difficulty in carrying on cognitively intense tasks (Jameen et al., 2019; Capone et al., 2020). Monoamines such as dopamine, serotonin, and noradrenaline are other keystones of CNS functional integrity, representing a bridge between the immune and the nervous system. In addition, the meso-cortico-limbic circuit is responsible for carrying dopamine from the ventral tegmental area to the nucleus accumbens, amygdala, hippocampus, and prefrontal cortex. This is also called "the reward pathway" for its importance in motivation and arousal, which lack in fatigued MS patients (Carandini et al., 2021).

On the other hand, peripheral factors involve local muscle activation (Kluger et al., 2013). Nevertheless, this distinction must not be taken as a standard definition, as the perception of fatigue

---

Abbreviations: ADL, activities of daily living; CNS, Central Nervous System; CSF, Cerebro-spinal fluid; CSTCL, Cortico-Striato-Thalamo-Cortical Loop; DLPFC, Dorsolateral Prefrontal Cortex; EDSS, Expanded Disability Status Scale; HCP, Healthcare Professional; MFIS, Modified Fatigue Impact Scale; MRI, Magnetic Resonance Imaging; MS, Multiple Sclerosis; MSQOL-54, Multiple Sclerosis Quality of Life; NfL, Neurofilament Light Chain; NIBS, Non-Invasive Brain Stimulation; PROs, Patient-Reported Outcomes; QoL, Quality of Life; RRMS, Relapsing-Remitting Multiple Sclerosis; SDMT, Symbol Digit Modality Test; tDCS, transcranial Direct Current Stimulation; VR, Virtual Reality; WM, White Matter.

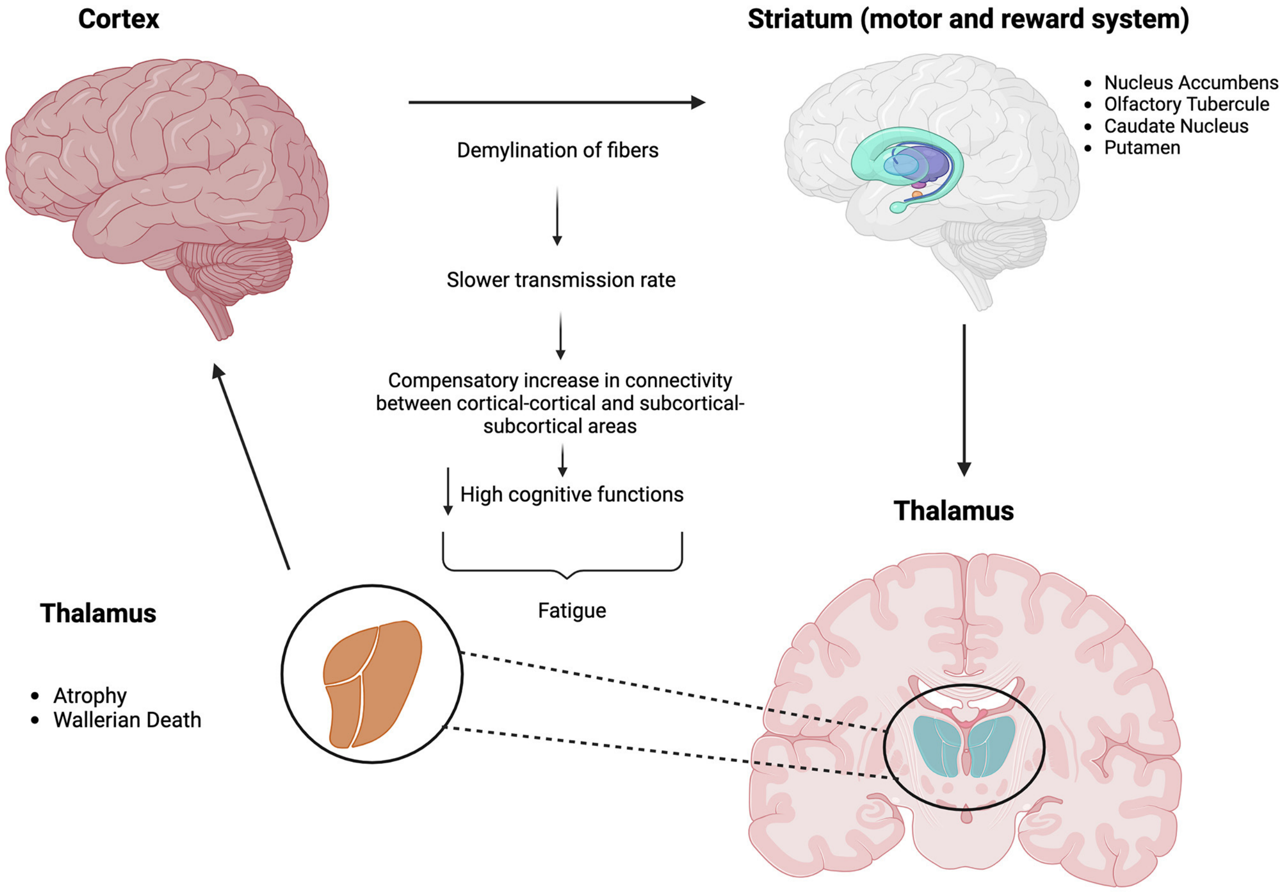


FIGURE 1
The cortico-striato-thalamo-cortical loop (CSTCL). This circuit involves the cortex, the basal ganglia (striatum, in turn consisting of nucleus accumbens, olfactory tubercule, caudate nucleus, and putamen), and the thalamus and ends up in the cortex. The fibers present in this circuit convey dopamine and glutamine among others. They control cognition and more especially decision-making, problem-solving, and planning. Created with BioRender.com.

and performance fatigability are intertwined and the physiological processes contributing to these conditions are complex (Enoka and Duchateau, 2016).

At later stages, a smoldering neurodegenerative process, partially driven by early inflammation, results in additional motor and cognitive deterioration (Giovannoni et al., 2022). Local neuro-axonal loss, Wallerian death, demyelination, and autoimmune reaction only partly account for the clinical and functional decline. Chronic inflammatory activity is decisive in determining disease progression and the pathophysiological base of fatigue (Giovannoni et al., 2022).

Finally, some factors responsible for secondary fatigue are depression, sleep deprivation, infections, pain, and adverse reactions to medications (Kluger et al., 2013; Khan et al., 2014; Adibi et al., 2022). Identifying and ruling out these concurring conditions is necessary for the differential diagnosis of primary MS and secondary fatigue (Kluger et al., 2013).

2.2. Impact of fatigue on quality of life

Fatigue is not only present in people with progressive MS but also in the early stages of the disease (Jameen et al., 2019; Rooney et al., 2019; Chang et al., 2023). Young patients with MS, at the peak of their productivity, may complain of this symptom, as up to 40–60% consider fatigue the most disabling MS symptom (Bakshi, 2003; Shah, 2015). Similarly to the MS epidemiology, a higher prevalence of fatigue is observed in women and patients with a higher disability or more active disease (Broch et al., 2021). The poignancy of fatigue as a pivotal symptom of MS is shown in recent literature as the patients regard it as a fundamental element when it comes to the therapy of choice. Tervonen et al. observed how they are more willing to endure an increased rate of relapses and accelerated progression in exchange for alleviating cognitive and physical fatigue. This was especially true when considering the ones who had received their diagnosis more than a decade before (Tervonen et al., 2023).

Fatigue may result in a significant economic burden related to high absence rates at work, unemployment, and the need for disability pensions (Oliva Ramirez et al., 2021). Frequently, it leads to a reduction in working hours and productivity, unemployment, or even early retirement (Braley and Chervin, 2010; Schiavolin et al., 2013; Mäcken et al., 2021). Fatigue may cause working MS patients to quit their jobs around 3 years after the diagnosis (García-Domínguez et al., 2019). Nevertheless, while fatigue has traditionally been considered a prognostic factor for unemployment, recent scientific literature has introduced a counterargument. In particular, emerging evidence highlights cognitive performance fatigability, with a particular emphasis on alertness, as a more potent predictor, in contrast to the self-reported fatigue that individuals with multiple sclerosis might convey through surveys and questionnaires (García-Domínguez et al., 2019; Dettmers et al., 2021; Oliva Ramirez et al., 2021).

Another consequence of fatigue in MS patients is social isolation, as the motivation to have social encounters or even simple conversations may be impaired. Moreover, daily activities such as housekeeping or self-hygiene might represent tremendous efforts. Lack of energy and motivation affects not only motor capability but also cognitive functions, making patients less confident and more dependent on caregivers in general (Penner et al., 2020; Battaglia et al., 2022). Quality of Life (QoL), which can be evaluated through scales like the MSQOL-54 (Multiple Sclerosis Quality of Life) (Janardhan and Bakshi, 2002), is therefore significantly affected by fatigue in MS patients. It is a self-reported questionnaire encompassing their health status. It includes both MS-specific and non-specific items and is a valid instrument to assess the impact of MS on the patient's daily routine (Vickrey et al., 1995). Fatigue has a significant impact on QoL along with the level of disability, as observed by Janardhan and Bakshi (2002). A more recently developed scale is the PROMIS fatigue 8a, a shorter version of the PROMIS scale, retrospectively measuring the specific impact of MS fatigue in 7 days. It is quick to administer, precise, and sensitive to subtle changes in fatigue level, which makes it another useful assessment tool in clinical practice (Kamudoni et al., 2022).

2.3. Traditional assessment of MS fatigue

In clinical care, assessment of fatigue is frequently limited to the patient's clinical history and the classical clinical examination (Sander et al., 2017; Gumus, 2018). In the setting of clinical trials, examinations may be more extensive although still limited, as specific scales or questionnaires have been established to quantify MS symptoms. Following, we describe the most used tools for assessing fatigue. Some of these measures are already taking advantage of digitalization and research advances, as digital devices aid the collection of data.

The EDSS is the most used scale for evaluating disability in MS patients. Through the clinical examination of eight domains (visual, brainstem, pyramidal, cerebellar, sensory, bowel and bladder, cerebral, and ambulatory) the clinician and therefore the clinical researcher can rate the patients' disability on a 1–10 scale. In particular, the Cerebral Functions domain provides an estimation of depression, cognitive dysfunction, and fatigue (Kurtzke, 1983a,b). The evaluation of fatigue is here limited to a single subdomain and rated through an extremely simplified method. A known limitation is the lack of responsiveness and sensitivity of the EDSS to detect disability changes, especially in domains beyond motor dysfunction (Inojosa et al., 2020). Moreover, the focus of the Cerebral Functions domain in the EDSS does not include an extensive analysis of fatigue and its correlates in the patient's life and activities of daily living (Cadavid et al., 2017; Schmidt and Jöstingmeyer, 2019; Dillenseger et al., 2021; Giovannoni et al., 2022).

Patient-reported outcomes (PROs) are evaluations of health status performed by patients themselves (El Gaafary, 2016). Through PROs, they provide an insight into their perception of a symptom (e.g., fatigue) (Bharadia et al., 2022) and therefore assure high test-retest reliability (Inojosa et al., 2020). In the last decade, PRO measures emerged as a relatively effective, simple, and reliable method to assess disability in MS. In the specific evaluation of fatigue, fatigue diaries and numerous scales for the clinical and neuropsychological examination are summarized in Table 1.

The inclusion of extensive neuropsychological examinations is increasingly gaining importance in the quantification of fatigue and related cognitive manifestations, which are just partially rated in the EDSS (Strober et al., 2019). In the correct setting, neuropsychological tests include some of the most accurate predictors of outcomes related to occupation and the activities of daily living (ADL) in MS (Weber et al., 2019). One of the most established tests is the Symbol Digit Modalities Test (SDMT). The SDMT is a paper-based test in which patients have to pair numbers and symbols as fast as possible, referring to a legend present at the top of the sheet (Benedict et al., 2006). Although the SDMT is not specifically developed for the assessment of fatigue and it cannot replace an extensive neuropsychological assessment, data shows a tendency toward emerging fatigue during cognitively demanding and goal-oriented tasks (Sander et al., 2017; Sandry et al., 2021). Evaluations of fatigue and cognitive function are intrinsically related, and the neuropsychological examination seems to be a valuable resource to properly assess fatigue, cognitive impairment, and psychological-driven complaints. As previously mentioned, it is objective cognitive fatigability that is more predictive of lower employment outcomes in the future of the patients rather than the perception of fatigue. Cognitive fatigability is easily and quickly assessed through TAP (Test for Attention) alertness examinations. The goal of these is to test their sustained attention during tasks requiring processing visual stimuli as quickly as possible. This correlates accurately with fatigue levels and unemployment status after a 3-month rehabilitation (Zangemeister et al., 2020; Dettmers et al., 2021).

Overall, good management of fatigue in MS starts with accurate, continuous, and multimodal monitoring. This includes the PROs and objective data regarding acute symptoms, chronic impairments, and comorbidities (Voigt et al., 2023).

2.4. Traditional management

2.4.1. Pharmacological treatment

An extensive discussion of pharmacological and non-pharmacological treatment of fatigue is beyond the scope of this paper. It is however well-known that therapeutic management of fatigue is extremely limited in MS. No consensus is available regarding pharmacological measures as no specific, evidence-based options are available.

The use of DMTs may improve fatigue symptoms, among other neurological deficits, as observational studies including

TABLE 1 **Fatigue scales mostly in use.**

Name	Author	Date	Content	Scoring	References
Fatigue Severity Scale (FSS)	Krupp et al.	1983	9 items: motivation, exercise, physical functioning, difficulty in carrying out tasks, work and private life impairment	7-points likert scale 1 = strongly disagree 7 = strongly agree Range: 9–63	Krupp, 1983a,b; Krupp et al., 1988; Schwartz et al., 1993
Modified Fatigue Impact Scale (MFIS)*	Fisk et al.	1994	21 items: physical (0–36), cognitive (0–40), psychosocial (0–8) subscale	5-points likert scale 0 = never 4 = almost always Range: 0–84	Fisk et al., 1994a,b
Fatigue Scale For Motor and Cognitive Functions (FSMC)*	Penner et al.	2005	20 items: motor (0-50) and cognitive (0-50) subscale	5-points likert scale: 1 = does not apply 5 = applies completely Range: 20-100	Penner et al., 2005, 2009
Neurological Fatigue Index (NFI-MS)*	Mills et al.	2010	23 items: physical subscale (8 items), cognitive subscale (4 items), diurnal sleep subscale (6 items), abnormal nocturnal sleep subscale (5 items)	4-point likert scale: 0 = strongly disagree 3 = strongly agree Range: 0–69 Another 10 points can be given in the summary section (range: 0–30)	Mills et al., 2010
Fatigue Assessment Inventory (FAI)*	Schwartz et al.	1993	29 items: severity of fatigue, impact on physical activity and daily life, interaction with rest, mood	7-points likert scale: 1 = disagree 7 = agree Range: 29–203	Schwartz et al., 1993
Fatigue Descriptive Scale (FDS)*	Iriarte et al.	1999	5 items: initiative (patient explains perception of fatigue), modality of onset, gravity, frequency, Unthoff's phenomenon	3-point likert scale Range: 0–17	Iriarte et al., 1999
Rochester Fatigue Diary (RFD)*	Schwid et al.	2002	Visual scale, fatigue level	100 mm visual analog scale, patient should mark his/her fatigue level every hour for 1 day 0 = maximal fatigue 100 = no fatigue	Schwid et al., 1987, 1999, 2002
PROMIS-Fatigue (MS)*	Cook et al.	2012	8 items: capacity to think clearly, enjoy life, tiredness, interference with social activities	5-points likert scale 1 = never 5 = always Range: 8–40	Cook et al., 2012; UWCORR, 2020
Multidimensional Fatigue Inventory (MFI)*	Smets et al.	1995	20 items: general, physical, cognitive, reduced motivation, reduced activity subscales	5-points likert scale 1 = true 5 = not true Range: 20–100	Smets et al., 1995
Fatigue Assessment Scale (FAS)*	Michielsen et al.	2003	10 items: fatigue intensity, onset, limitations, concentration	5-points likert scale: 1 = never 5 = always Range: 10–50	Michielsen et al., 2003

*RF (Shahid et al., 2012; Gumus, 2018; Rietberg and van Wegen, 2019).

the use of glatiramer acetate, interferon or natalizumab suggest an improvement. However, high-quality evidence including blinded, randomized, controlled trials is lacking (Metz, 2004; Svenningsson et al., 2013; Neuhaus et al., 2021).

Evidence is dispersed, fragmented, and contradictory (Pucci et al., 2007; Jensen et al., 2014), partially due to the not fully understood pathogenesis of fatigue. Several medications have been originally developed for other diseases and tested in MS (e.g., sleep disorders, influenza, Parkinson's, ADHD, etc...) (Zielińska-Nowak et al., 2020; Moss-Morris et al., 2021; Tarasiuk et al., 2022). Amantadin, 4-aminopyridine, and modafinil are, to date, the most often prescribed drugs, although their range of reliability has been low. They comprehend all off-label preparations, being, respectively an antiviral, an anti-spastic, and an anti-narcolepsy drug, and bearing numerous contraindications and side effects (e.g., heart, liver, and kidney damage as well as a potential teratogenic effect for amantadine) (Jensen et al., 2014; Picariello et al., 2022; Deutsche Multiple Sklerose Gesellschaft B e. V., 2023). A few other preparations have been tested to treat fatigue and they are summarized in Table 2.

TABLE 2 **Most prescribed drugs against fatigue.**

Name	Mechanism	Effect	Dose*	Most common adverse reactions	References
4-Aminoipyridine (4-AP)	Voltage-gated potassion channel inhibitor	Improves neurochemical conduction of demyelinated axons, increases release of neurotransmitters (dopaminergic effect)	10–40 mg/day	Paresthesia, restlessness, balance disorders, UTI, insomnia, dizziness, headache, nausea	Jensen et al., 2014; Zielińska-Nowak et al., 2020; Dietrich et al., 2021
Amantadine	Antiviral, immune-mediated, amphetamine-like activity	Improves cholinergic and dopaminergic transmission, non-specific CNS stimulant (approved by the FDA for Influenza and Parkinson’s)	100–200 mg/day	Livido reticularis, insomnia, orthostatic hypotension, peripheral edema, headache, insomnia, dizziness	Krupp, 2003; Pucci et al., 2007; Braley and Chervin, 2010; Zielińska-Nowak et al., 2020; Cocco and Fadda, 2022; Tarasiuk et al., 2022
Modafinil	Non-amphetamine, CNS stimulant	Promotes wakefulness, probable sympathomimetic activity (used for narcolepsy or shift-work sleep disorders)	200–400 mg/day	Headache, anxiety, dizziness, nausea, hypertension, palpitations, insomnia	Braley and Chervin, 2010; Niepel et al., 2013; Zielińska-Nowak et al., 2020; Cocco and Fadda, 2022
Paroxetine and other anti-depressants	Inhibition of reuptake of serotonine/noradrenaline (SSRI/SNRI)	Antidepressants	Depending on drug in use	Typical side effects of anti-depressants	Krupp, 2003; Zielińska-Nowak et al., 2020; Stamoula et al., 2021
Methylphenidate	Enhancement of dopaminergic effects, CNS stimulants	Improves transmission of dopamine and inhibits its reuptake (typically prescribed for ADHD)	5–20 mg/day (TRIUMPHANT-MS)	Cardiac, psychiatric, gastrointestinal disorders	Nourbakhsh et al., 2018; Cercignani et al., 2021; Tarasiuk et al., 2022
Acetyl-L-Carnitine (ALCAR)	Mitochondrial functionality and ATP production improvement	Increases energy levels based on biochemical production of ATP	2 g/day	Nausea, agitation, insomnia, and increased appetite	Krupp, 2003; Pennisi et al., 2020; Cocco and Fadda, 2022
Pemoline	CNS stimulant	Increases attention and wakefulness (normally used in ADHD)	18.75 mg/day (some studies start from 37.5 mg and decrease to 18.75)	Irritability, restlessness, insomnia, liver function test changes	Krupp, 2003; Braley and Chervin, 2010; Khan et al., 2014; Cocco and Fadda, 2022

*Most commonly prescribed.

2.4.2. Non-pharmacological treatment

2.4.2.1. Supportive strategies

Supportive approaches such as physical rehabilitation, physiotherapy or aerobic exercises, and relaxing sessions (e.g., yoga) have been proven to relieve patients from MS fatigue (Jensen et al., 2014; Picariello et al., 2022; Deutsche Multiple Sklerose Gesellschaft B e. V., 2023). Occupational, cognitive-behavioral, or psychological therapy may be key in the management of fatigue as handling and anticipating triggers to prevent fatigue can be learned (Picariello et al., 2022) as a way to boost self-determination and confidence (Askari et al., 2022).

2.4.2.2. Transcranial stimulation

Among the more innovative treatment strategies, transcranial and non-invasive brain stimulation (NIBS) emerges as an alternative option. Its basic principle is targeting the somatosensory, post-central, and frontal areas with scalp-attached electrodes and low-current stimulation (Ayache and Chalah, 2018; Bertoli et al., 2023). Further, the immediate benefits observed in the QoL of the fatigued MS patients hint at anodal transcranial direct current stimulation (tDCS) as an innovative therapeutic method for fatigue (Ayache and Chalah, 2018; Linnhoff and Heinze, 2019; Bertoli and Tecchio, 2020; Mortezanejad et al., 2020; Zielińska-Nowak et al., 2020). By targeting the primary somatosensory area, Bertoli et al. also managed to lower fatigue levels thus explaining how the mechanism underlying fatigue is rather central than peripheral. Concluding, the main pathophysiological processes take place in neuronal connectivity rather than at a neuromuscular level (Bertoli et al., 2023).

3. The concept of digital assessment and management of multiple sclerosis fatigue

As mentioned above, several of the currently used measures for the assessment of fatigue are already profiting from digitalization in data collection, as PROs are easily available, or eHealth approaches make them broadly available. Digital tools are also emerging as diagnostic and therapeutic resources, partially self-supervised or with minimal support from caregivers. As MS patients are often diagnosed at the age of 20–40s, they could be the perfect candidates for the implementation of digital tools in the early phases of their disease. Current generations of newly diagnosed patients are already familiar with digital-based activities. Furthermore, they are highly motivated to find solutions to the limitations MS puts ahead of them (Haase et al., 2021; Scholz et al., 2021).

The use of modern digital solutions might represent an efficient way of sharing information between patients and clinicians, who could thereby build a trusted network with their patients and improve "doctor-patient"-relationships. As data may become easily available, quantifiable, and continuous remote monitoring of fatigue would be possible. These network communications might play an important role for patients who live in underserved areas, where the first healthcare structure is usually distant and difficult to reach. Those patients may especially benefit from long-distance medical care through eHealth (De Angelis et al., 2021; Haase et al., 2021; Ziemssen and Haase, 2021). This was evident during the COVID-19 pandemic as regular outpatient visits were frequently not performable due to the lockdown-related restrictions or their fear of being infected. Therefore, eHealth is proposed as an expedient to bridge the temporal and spatial gap between the visits in the clinics (Haase et al., 2021; Scholz et al., 2021; van der Walt et al., 2021; Voigt et al., 2023).

Voigt et al. have envisioned a way to digitally handle patients through artificial intelligence tools: the concept of the "digital twins" consists of collecting all the data regarding the patients in a digital cloud, which the clinician can easily consult. This enables to monitoring of the disease step-by-step and in an individualized manner so that no detail of acute relapse symptomatology or any kind of worsening condition goes lost or overlooked. At the same time, it is a means to include the patients in the clinical pathway, also as far as medications are concerned, intending to predict the future of this "thousand-faces disease" with a custom-made approach (Voigt et al., 2021, 2023). This all can be achieved thanks to a thorough planning of the resources and a following implementation of apps, wearable devices, machine-learning instruments, and data collection and analysis systems (Dillenseger et al., 2021).

However, patient safety and data protection is also an aspect for consideration in digital tools in MS. Digital applications may be regulated in several countries as they may be considered medical devices (van der Walt et al., 2021). Similar definitions are seen both in the United States, through the Food and Drugs Administration (FDA), and in the European Union, via the Medical Device Regulation (MDR). These are seen simplified as instruments, appliances, software, or other articles intended for medical purposes, including, among others, use in diagnosis, treatment, or prevention (Maaß et al., 2022).

3.1. Current implementations in digital fatigue assessment

3.1.1. Apps

Health and medical apps are becoming increasingly available in MS, especially considering, as mentioned above, the young age of MS populations at diagnosis (Zayas-Garcia and Cano-de-la-Cuerda, 2018; Howard et al., 2023). Health apps are "software programs on mobile devices that process health-related data on or for their user" (Maaß et al., 2022). These could be used by every individual, including patients, family, or caregivers. If these applications are used for medical purposes, such as early diagnosis, monitoring, or treatment, they could be considered medical apps and further, medical devices.

In Germany, as an example, medical apps are regulated through the Federal Institute of Drugs and Medical Devices with the definition of Digital Health Applications (DiGAs, in German *digital Gesundheitsanwendungen*). These are HCP-prescribed mobile applications fully financially covered by insurance companies. The German government is still performing thorough licensing processes and studies to regulate DiGAs proposed by different companies, with very restrictive and precise requirements to assure standardized and continuous care, but also personal data protection (Bundesinstitut für Arzneimittel und Medizinprodukte, 2023). This is also the case with several MS-related apps used for the management of fatigue and other clinical complaints. This regulation enables the app owner to feel safe and meanwhile learn content about symptoms and conditions, which are sometimes difficult to access or understand.

The interactive nature of medical apps makes patients feel accompanied in the management of their disease and gives them the advantage of getting notifications and reminders as regards taking medication, asking for prescriptions, and remembering appointments. Financial support from insurance companies makes them an accessible tool for patients, regardless of their financial status or geographical distance from the nearest point of care (Bundesinstitut für Arzneimittel und Medizinprodukte, 2023).

Additionally, clinical experience with these apps is fundamental in the research field, where medical apps can be thoroughly assessed in their advantages and disadvantages, providing collaboration between establishing companies and HCPs (Bundesinstitut für Arzneimittel und Medizinprodukte, 2023). The new era of fatigue treatment begins with its assessment through consistent, standardized, and easy-to-manage resources.

Previously, we discussed the difficulty of building a diagnostic path for fatigue and the utility of fatigue diaries to monitor symptoms, also from the patient's perspective. An automated assessment is in this way a compromise between a steady observation of fatigue and the need for the patient to develop a good insight of this feature of MS. In the following, we discuss apps that demonstrate exemplary practical distance- and home-based evaluation strategies that could also be advantageous for the patient's self-perception and autonomy. Several of these apps have a mixed function including patient education, communication, and administration of medical findings or even neuro-rehabilitation.

Currently, further medical apps are in the pipeline for the assessment of fatigue.

A good example of promoting self-tracking is represented by ELEVIDA, a German DiGA established by GAIA (ELEVIDA, 2002; Pöttgen et al., 2018; GAIA AG, 2022; Bundesinstitut für Arzneimittel und Medizinprodukte, 2023). ELEVIDA is specifically designed for MS patients with fatigue in need of special and continuous support. This app involves a digital neuro-rehabilitation (see Table 3) beyond an assessment of fatigue. They can download the app for a limited time based on prescriptions and find exercises, strategies, and virtual dialogues to self-assess and handle fatigue (ELEVIDA, 2002; Pöttgen et al., 2018). It promotes the patient's self-determination and raises awareness on the recognition of one's perception of fatigue, making the experience of e-Health flexible, tailored, and goal-oriented (ELEVIDA, 2002; Dillenseger et al., 2021; GAIA AG, 2022; Stern et al., 2022). The ELEVIDA study carried out by Pöttgen et al. confirmed the beneficial effect of this home-based tool on fatigue levels, with an additional increase in QoL, especially in the cognitive area. A follow-up was also performed, yielding positive results concerning both fatigue and everyday-living efficacy, which must be a primary endpoint in the field of a disabling disease like MS (Pöttgen et al., 2018).

The ElevateMS app is another tool used to continuously assess MS-related symptoms, including fatigue (Pratap et al., 2020). In its pilot study, 62% of patients reported fatigue, and interestingly, fatigue triggers such as high temperature, stress, and late bedtime could be properly documented. Patients were self-tested not only through questionnaires, but also with more clinical-based evaluations such as the finger-tapping, balance test, and a modified version of the SDMT to assess cognitive information processing speed (Pratap et al., 2020). Objective identification of symptoms and triggers beyond a limited subjective feeling could support the development of future therapeutic strategies. Digital health, however, is continuously changing to adapt to the patient's needs (Voigt et al., 2021). MS patients may have vision disturbances, motility disorders, or hearing problems. These limitations need special consideration in the development of apps or software specifically envisioned for them and therefore tailored to address all the different facets of MS. This is particularly considered in the BRISA app, where the patients can fill out brief questionnaires about the symptoms they can regularly report (i.e., bladder dysfunctions, concentration disorders, or fatigue). Even more interestingly, they can rate their disturbances on a scale from 0 to 4 based on a smiley-face scale (where the 0-smiley represents a poorer state and the 4-smiley a better condition). Apart from that, standardized medical questionnaires (like the Modified Fatigue Impact Scale) are required to be filled out every 2 weeks (Fisk et al., 1994a; BRISA, 2022; Mountford et al., 2023). Although the PROs are still the state-of-the-art method to collect data on the symptoms, this digital solution provides a more immediate and intuitive way to communicate one's symptoms, without having to spend long every day on a retrospective questionnaire. Digital health tools must encounter the patient's need for a quick and steady evaluation method, which leaves no room for interpretation or ambiguity (especially for people with cognitive, linguistic, or visual limitations). Mountford et al. (2023) were able to correlate the daily reported disturbances with the PROs and a rather satisfactory compliance rate, even in the elder patient group.

The Energize app has a more educational function. Through seven sections (i.e., MS, Behavior, Thoughts, Emotions, Body, Future, and World), users learn new concepts and engage in interactive activities (Babbage et al., 2019). The content is displayed through videos and animations (e.g., about fatigue, depression, and rest), whereas MS patients can then report pain, sleep disturbances, deconditioning, and other factors contributing to fatigue. Quizzes are also performed to test the knowledge after the learning phases (Babbage et al., 2019; van Kessel et al., 2021). Apps are also useful for documenting interactions and sharing medical information between HCPs and MS patients. For this purpose, apps such as icompanionMS and icobrainMS were developed (Icompanion, 2022; icometrix, 2023). IcompanionMS is a software in which patients report symptoms, learn strategies to manage fatigue, and share their progress with clinicians. HCPs can view MRIs uploaded by patients on the icobrainMS portal. An artificial intelligence system reads the scans and makes a correlation with functional deficits, such as fatigue, quickly available. The app enables long-distance monitoring and assessment of fatigue symptoms and cognitive disturbances through the Quality of Life in Neurological Disorders (Neuro-QoL), a PRO to assess various domains such as cognition, pain, and social performance in MS (Cella et al., 2012). Regular documentation of symptoms and MRIs, supports the observation of minimal changes in the disease course, although protecting data privacy and without requiring additional hardware. Surveyed patients and HCPs reported positive feedback after using this app as it aided in their therapeutic decision-making (Cella et al., 2012; Medina et al., 2019; Van Hecke et al., 2021; Icompanion, 2022; icometrix, 2023).

Digital monitoring and self-monitoring of MS are also the main focus of the Floodlight MS app (F. Hoffmann-La Roche Ltd., 2021). Floodlight MS focuses on cognition, upper extremity function, and mobility. These are measured through brief exercises (e.g., drawing a shape or matching symbols), balance tests, and walking (Mike Baker and van Band, 2023). In the study carried out by Montalban et al., the tests were successfully correlated with the paper-based examinations used in clinical practice, such as the 9-hole Peg Test, SDMT, and Timed 25-foot walk test (Kellor et al., 1971; Benedict et al., 2006; Motl et al., 2017; Montalban et al., 2022). More conclusive data are collected when other devices are connected to the smartphone containing the app (e.g., smartwatch; see wearables). In this sense, monitoring does not only rely on dedicated tests and questionnaires on smartphones but also on passive monitoring, as highlighted by Montalban et al. (2022).

3.1.2. Wearable devices

Not only apps measuring fatigue through questionnaires but also wearable devices have proved to be useful in the continuous monitoring of fatigued MS patients (Sparaco et al., 2018; Tong et al., 2019; Block et al., 2022). These "health technologies" usually have an internet or smartphone connection and therefore allow non-stop collection of data about physiological parameters (e.g., heart rate, sleep levels) and track any kind

TABLE 3 **Summary of the concepts regarding digitalizing MS fatigue assessment and therapy.**

Application	Developer	Year	Requirements	Contents	Goal	Evidence
Elevida (Gold et al., 2001; ELEVIDA, 2002; Pöttgen et al., 2018; GAIA AG, 2022)	GAIA AG	2018	Smartphone Internet connection	90-days prescription-based program Fatigue specific contents Exercises introduced by videos Interactive journaling	Assessment Management	Decreased fatigue levels as measured by the Chalder Fatigue Scale and FSMC, even after 12 and 24 weeks (follow-up); QoL increased in the fatigue section of the HAQUAMS (Hamburg Quality of Life Questionnaire in Multiple Sclerosis); good effect on ADLs
ElevateMS (Novartis SB, 2017; Pratap et al., 2020)	Novartis Sage Bionetworks	2017	Smartphone Internet connection	Questionnaires Symptom tracking Activity tracking Customizable reminders Clinical-based exercises (e.g., finger-tappingbalance tests, SDMT)	Assessment	High rate of reports on fatigue on the app; data refers to a population located across the US (far-reaching abilities of the app). Increased compliance in MS patients whose link with the clinic has been aided by their HCPs
BRISA App (Fisk et al., 1994a; BRISA, 2022; Mountford et al., 2023)	Temedica GmbH Roche	2022	Smartphone Internet connection	Smiley-based self-assessment and rating of MS symptoms Daily diary	Assessment	High correlation between smiley-based reported fatigue and completion of MFIS (Modified Fatigue Impact Scale) in MS patients, independently of age, sex or time since diagnose
Energize (Babbage et al., 2019; van Kessel et al., 2021)	Duncan Babbage Kirsten van Kessel Paula Kersten	2019	Smartphone (iOS) Internet connection	7-module based course (MS, Beaviour, Thoughts, Emotions, Body, Future and World) Explanatory videos Sleep diary Self-evaluation of fatigue Planning section Quizzes and tests	Assessment Social rehabilitation	Promising results as far as the acceptance by fatigued MS patients (self-management and learning content) although the cognitive effort to complete the units was sometimes high and itself fatiguing
icompanionMS (Van Hecke et al., 2021; Icompanion, 2022)	icometrix	2021	Smartphone Computer Internet connection	Self-tracking Appointment reminder Cognition tests MRI scans upload function HCP portal	Assessment Management	Feasible instrument to assess and monitor fatigue over time (clinically relevant changes as referred to the Neuro-QoL)
icobrainMS (Van Hecke et al., 2021; icometrix, 2023)	Icometrix	2021	Computer Internet connection	Ai software for magnetic resonance analysis	Assessment (not MS specific)	Feasibility of the AI-based MRI reading, high rate of lesion-detection and MS subtypes differentiation

(Continued)

TABLE 3 (Continued)

Application	Developer	Year	Requirements	Contents	Goal	Evidence
Floodlight (F. Hoffmann-La Roche Ltd., 2021; van der Walt et al., 2021; Roche Fachportal, 2023)	Roche	2021	Smartphone Internet and connection	Motor and cognition functions assessment Shape-drawing (SDMT) Pinching tomatoes (9 HPT) 2-min walk test (Timed-25-Foot Walk Test)	Assessment	Correlation between app-based and clinically administered tests
Samsung gear S2 (Krupp, 1983a, 2003; Abbadessa et al., 2021)	Samsung	2021	Smartphone Smartwatch Internet and Bluetooth connection	Passive and continuous data collection about walking endurance	Assessment	Strong influence of fatigue as measured through the FSS (Fatigue Severity Scale) and the maximum distance walked by MS patients
Fitbit Inspire (Fisk et al., 1994a; Chikersal et al., 2022)	Fitbit Inc.	2021	Smartphone Smartwatch Internet connection	Passive steps, heart rate, sleep tracking	Assessment	Digital phenotyping and passive data collecting to predict fatigue; link between fatigue (according to MFIS, Modified Fatigue Impact Scale) and depression and global MS burden during the COVID-19 pandemic
GENEactive accelerometer (Krupp, 1983a; Guo et al., 2021; Activinsights Ltd., 2023)	Activinsights	2021	Smartphone Smartwatch Internet connection	Passive data on ADLs	Assessment	Digital phenotyping to correlate the ADLs and MS symptoms i.e., fatigue (previously assessed with the FSS and monitored with a fatigue diary); positive correlation between fatigue and depression and poor sleep quality
More Stamina (Krupp, 1983a; Cella and Chalder, 2010; Giunti et al., 2018, 2020; Stamina, 2022)	University of Oulu	2018	Smartphone Internet connection	Self-reported energy estimation and management Gamified collection of points based on energy spent and allocated	Assessment Management	Feasibility, acceptability, and usability studies are ongoing. App-based completion of FSS and Chalder Fatigue Scale and gamification-aided fatigue self-management
Fimo app (Mäcken et al., 2021; Fimo Health GmbH, 2022)	Fimo Health	2021	Smartphone Internet connection	8-week program Learning contents Rehabilitation through yoga sessions, relaxation methods, games and tests for cognition Medication and appointments reminder Social rehabilitation	Management	Proof of feasibility still ongoing

(Continued)

TABLE 3 (Continued)

Application	Developer	Year	Requirements	Contents	Goal	Evidence
Transcranial direct current stimulation (tDCS) (Krupp, 1983a; Shahid et al., 2011; Charvet et al., 2018; UWCORR, 2020; Bertoli et al., 2023)			Transcranial stimulation kit	Specific targeting of somatosensory and motor cortex with low current stimulation alleviating fatigue levels	Therapy	Significant reduction of fatigue measured through FSS, VAS (Visual Analog Scale) and PROMIS of study (Patient-Reported Outcome Measures Information System) after tDCS (targeting dorsolateral prefrontal cortex); correlation between number of sessions and fatigue levels (most of all for severely fatigued MS patients)
Virtual Reality (VR) (Al-Sharman et al., 2019; Maggio et al., 2019a,b; Cuesta-Gómez et al., 2020; Manuli et al., 2020; Ozkul et al., 2020; Yazgan et al., 2020; Cortés-Pérez et al., 2021; Leonardi et al., 2021; Nascimento et al., 2021; Pagliari et al., 2021; Altunkaya et al., 2022; Casuso-Holgado et al., 2022; Hollywood et al., 2022; Kalron et al., 2022; Moeinzadeh et al., 2022; Dogan et al., 2023; Hsu et al., 2023)			Computer and mouse/controllers (non-immersive VR) Screens, controllers, sensors (semi-immersive VR) Headsets, controllers and/or sensors (immersive VR)	Neuro-rehabilitation through gamification (serious gaming or exergaming) Relaxation exercises Cognition training Motor and balance training Memory and motor memory rehabilitation	Neuro-rehabilitation	Higher reduction of fatigue levels as opposed to conventional therapy or physiotherapy alone, result even more significant when the two are combined. Physical excercise through VR might increase the patients' activity level and therefore lower fatigue ones. Additional increase in compliance through gamification and interaction. Link between improvements in balance and fatigue levels through lower energy outlay.

of physical activities through accelerometers and sensors (Sparaco et al., 2018).

When routinely worn, wearables can deliver useful information about motor activities, which are strongly influenced by fatigue (e.g., gait, balance, social contacts, sports, etc.). These are non-invasive instruments provided with sensors that can be worn daily. Additionally, the patients can retrieve constant feedback and be aware of performance changes (Alexander et al., 2021). These devices convey a measure of objective fatigue, also known as fatigability, which does not necessarily correlate with the retrospective reports represented by the questionnaires (Linnhoff and Heinze, 2019). Furthermore, objective measures give an insight into state fatigue, that is to say, they precisely quantify its severity in a precise instant (Block et al., 2019). Finding a homogenous system to deliver clinically relevant information about a subjective symptom such as fatigue is necessary. Similarly, an overview of the patient's daily limitations, which are not always possible to objectively observe during the visits, may be relevant in future practice (Block et al., 2022).

Currently, several monitoring systems using data collected through varied wearable devices are becoming available, varying from widely used motion-based models (e.g., acceleration, rate of rotation) to complex indirect reference measures (such as heart rate variability, or even electroencephalography, electromyography, or galvanic skin responses. Machine learning is emerging as a tool for understanding these complex data and its relationship with fatigue. A critical point in the implementation of wearables to detect fatigue is the difficulty of relating it to the triggering task when having the patient keep the wearable outside the hospital or laboratory. In other words, as fatigue is usually provoked by a motor or cognitive activity, not knowing the nature of this activity poses a gap in understanding how and when fatigue caves in. This is the reason why supervised monitoring in the laboratory is still more effective than the long-distance, long-term one. Furthermore, the use of physiological signs to gauge fatigue provides quite an objective mean for real-time monitoring at the individual level. However, individuals have a high variability of responding to stress and fatigue, which translates into a scarce homogeneity of retrieved data. Future works should focus on establishing data-collecting models to better phenotype fatigued MS patients (Adão Martins et al., 2021).

Finding a homogenous system to deliver clinically relevant information about a subjective symptom such as fatigue is necessary. Similarly, an overview of the patient's daily limitations, which are not always possible to objectively observe during the visits, may be relevant in future practice (Block et al., 2022).

The importance of passive data collecting, and wearable devices becomes even more evident when it comes to the correlation between fatigue and other factors influencing the QoL, like ADL, social functioning, but also other comorbidities like depression or sleep disorders. Thereby, sensors can, for example, document the amount and quality of sleep and therefore provide insight into a concomitant factor contributing to fatigue as a PRO cannot assess precisely the scope of this type of disturbances (Bradshaw et al., 2017). The helpfulness of wearables ranges from fall risk management to the gathering of biological digital biomarkers in an uninterrupted period of time, aside from the patient's direct involvement or realization (Vandyk et al., 2022). Another possible advantage is a potential reduction of healthcare costs, as continuous and automatic data generation may represent fewer appointments with the practitioners (Dillenseger et al., 2021).

In a recent study, Abbadessa et al. correlated fatigue PROs with fatigue, depression, and ADL with walking endurance in 25 MS patients. They consequently described the influence of fatigue on the maximum amount of steps per day and the correlation of this objective and passive evaluation with subjective and patient-dependent reports, namely personal evaluations of fatigue and related symptoms (Abbadessa et al., 2021).

In a different approach, Chikersal et al. conducted a study involving a smartphone app and sensor (Fitbit) to check the status of the patients during the COVID-19 lockdown, in which they were homebound and social contacts were reduced. Through comparison between digital biomarkers retrieved by these sensors and the MFIS (completed by the patients every 4 weeks), the burden of fatigue and its worsening through social isolation could be reported. Additionally, a significant overlap with depression was demonstrated (Chikersal et al., 2022).

A similar method involved a fatigue diary to fill every day while at the same time wearing a GENEactive smartwatch to passively record the patients' daily physical biomarkers. The approach established by Guo et al. linked data sampled by the sensors (GENEactive smartwatch) with clinical data from the PROs and daily completion of a fatigue diary. From this 1-week pilot study, a significant relationship between fatigue and depression and sleep quality was objectively assessed. This enabled the authors to build different behavioral phenotypes of MS patients, which present various combinations of different symptoms and therefore require different treatments. A step further has been made in the direction of patient-based care (Guo et al., 2021; Activinsights Ltd., 2023).

In conclusion, the relationship between the completion of the questionnaires and device-reported data specifically concerning fatigue revealed that not only the two kinds of measures can be linked but the technological and objective outcome measure is useful to predict the subjective perception of fatigue. This finding might be a sustainable solution to promote the patient's home-based self-assessment independently from the regular visits but also reinforce the clinician's ability to escort the patients into more conscious joint planning of the long-term disease management (Krupp, 1983a; EQ-5D EG, 2009; Tong et al., 2019; EuroQol Research Foundation, 2021).

3.2. Digital neuro-rehabilitation for MS fatigue

Although several studies have examined the use of digital tools for the assessment and treatment of fatigue, especially through mobile apps, clear evidence of digital implementations to target fatigue is relatively scarce. We summarize available evidence for recently developed apps and strategies with virtual reality (VR), as these have been proven to improve the deficits in MS patients. We believe further research may potentially provide insights regarding the use of other digital hardware, such as body scanners, smartwatches, sensors (e.g., gamifying), or wearables in neuro-rehabilitation.

3.2.1. Home-based tools

The crucial focus of developing fatigue-focused software and apps is to demonstrate and strengthen the patients' autonomy. Learning how to recognize the triggering factors and concomitant symptoms with the aid of technological resources is essential to successfully handle or avoid them.

The More Stamina app boosts the patient's self-determination by requiring them to distribute their own resources. MS patients are compelled to autonomously estimate energy levels and motivation to perform given and planned tasks. Based on the activity levels, points can be gathered and through an adaptive interface and game-like design, patients can benefit from positive reinforcement assuring good adherence and participation. They are thereby the active protagonists of their fatigue management through the development of effective energy-distribution strategies (Giunti et al., 2020).

In the Fimo app (Fimo Health GmbH, 2022), home-based digital health support is more steadily conceived: it is an 8-week self-care path, complementary to the one provided by the doctors. It begins with a learning phase about MS and its related fatigue syndrome and then the patients can actively accomplish strategies to overcome it through sports sessions, meditation, relaxation methods, or any kind of action. The cognitive tests provided by this app can be undertaken more often by the patients, who can also report both triggering factors for fatigue and even other kinds of symptoms possibly contributing to a state of discomfort. Besides, the app consists of different steps through which MS patients can finally reconnect to the outside world and have a more efficacious social and work life. As previously mentioned, fatigued MS patients tend to isolate and give up any kind of interaction, fearing the effects fatigue might have on them. An interesting aim of this app is to develop symptom-coping strategies and overcome daily limitations due to fatigue (Mäcken et al., 2021; Fimo Health GmbH, 2022).

Several apps that were primarily developed for the assessment of fatigue in MS patients are also being implemented for neuro-rehabilitation. As mentioned above, the ELEVIDA, Energize, or More Stamina apps could provide innovative management strategies not only for the assessment but also for a self-guided treatment of patients (see Table 3) (ELEVIDA, 2002; Giunti et al., 2018, 2020; Pöttgen et al., 2018; Babbage et al., 2019; van Kessel et al., 2021; Stamina, 2022).

Previously, we discussed the current use of tDCS in the clinical setting. Charvet et al. (2018) discussed in their work the possibility of having it as a home-based neuro-rehabilitation tool. After assessing the disability level through the EDSS and the cognitive functions with the SDMT, participants were treated with a 5-week-long, home-based, HCP-supervised tDCS at home. The target of this stimulation was the dorsolateral prefrontal cortex (DLPFC), a known pathologically relevant area for the onset of fatigue. The study shows how fatigue levels were improved over a short period of time, so it was quickly effective. On top of that, the results proved more significant after 20 sessions compared with the fatigue scores reported by MS patients who received 10 sessions. This lets us hypothesize that tDCS can be a cost-effective and practicable tele-rehabilitation method (Charvet et al., 2018).

Control gained by patients on their condition represents an important step to make them feel in charge of their own situation not only as chronic patients but also as individuals. HCPs are, nevertheless, available and can support them over this monitoring, adding to safety, collaboration, and involvement. The above-mentioned apps can detect daily fluctuations and improvements with the additional benefit of being cost-effective, intuitive in function, and easily updatable and adaptable to the patient's needs and desires (Mäcken et al., 2021).

3.2.2. Virtual reality

VR is a tool for assessing and treating various aspects of MS, including fatigue, as it allows to perform physical but also cognitive rehabilitation, restores neural plasticity, and therefore mends the patients' functional performance, which is severely affected by the pathophysiological damage underlying of fatigue (Leonardi et al., 2021).

On a technical level, non-immersive VR tools comprise task-oriented games without complete isolation, i.e., with computers and a mouse or controllers but no headsets or big screens (Kalron et al., 2022). Semi-immersive VR is achieved through the use of screens of larger dimensions, which usually enable interaction and might also integrate the tracking of movements (Webster et al., 2021; Kalron et al., 2022). Finally, immersive VR is typically delivered through headsets and controllers to perform activities in a fully isolated environment (Cortés-Pérez et al., 2021).

This immersion enhances the patients' involvement, amusement, and finally motivation. This is also valid for the visuo-auditory feedback offered by the system, which is described by Hollywood et al. (2022) as the response to a correctly achieved task by the system itself. Fatigue as a rehabilitation target can be achieved through VR even when the tasks involved include balance and motor performance. Through the head-mounted display, MS patients can only see the virtual surroundings and an avatar reproduction of their body. Without the distractions of the real world and through complete isolation, patients could manage to focus only on the task and restore their memory regarding a specific movement. Importantly, this kind of training must be performed safely in a controlled environment where the patient can be confident that they can move without fear of falling (Ozkul et al., 2020; Yazgan et al., 2020; Hollywood et al., 2022).

The mirror neuron system seems to play a role in this, as the self-representation achieved through VR triggers neuro-plastic connections in the sensory-motor cortical and subcortical areas (Maggio et al., 2019b; Manuli et al., 2020). This provides a prompt and reliable measure of the patient's performance, thus boosting self-awareness and promoting a re-establishment of motor memory. This multisensory experience drives the patient to train further and consequently to gain results from a constant and consistent training program (Maggio et al., 2019b).

Exergaming-based VR, where developing new skills is achieved through actual video games, might be a viable tool to reach the patients' compliance with fatigue-managing programs (Maggio et al., 2019b; Moeinzadeh et al., 2022). Nevertheless, games can also be designed from a rehabilitating perspective and disability-oriented (i.e., serious gaming) (Maggio et al., 2019b). Fatigue plays a role in motor performance and vice versa, in consequently treating or improving the latter aspect, we might retrieve positive results in the former one (Al-Sharman et al., 2019; Yazgan et al., 2020). As observed by Al-Sharman et al., fatigue is a decisive element when planning rehabilitation in the motor domain. By first assessing fatigue and cognition through paper-based tests and then training the motor functions, the impact of the non-motor disability on the physical one was confirmed (Al-Sharman et al., 2019). Ozkul et al. performed an immersive VR-based rehabilitation program targeting balance and mobility but also fatigue. In their study, they used a Microsoft Kinect to collect image analysis data on motion. This data was then handed to the physiotherapist, who adapted the exercise regimen to the patients' capabilities. Lastly, the VR headset presented the virtual environment to the patients, where they carried out the desired task (Ozkul et al., 2020). This example of task- and patient-oriented neuro-rehabilitation method demonstrates how VR can be tailored to the patients.

Pagliari et al. carried out a study involving a VR home-based tele-rehabilitation program accompanied by a clinician's feedback. They witnessed how fatigued MS patients can benefit from VR-based therapy as far as emotional drive is concerned, although they lack the energy to perform simple day-to-day activities. These patients might retrieve so much psychological and physical profit from the therapy that they might eventually go back to work and engage in the social or sports activities they had given up (Pagliari et al., 2021).

A recurring issue in treating MS fatigue is the uneven distribution of resources among the patients, even as far as healthcare structures are concerned. The fact that some of them are already available on the market pictures the future chance to carry out long-distance rehabilitation programs for both upper and lower limbs (Hollywood et al., 2022). An interesting point of view was offered by Manuli et al., who successfully merged digital neuro-rehabilitation through robotics and VR and the Hub-and-Spoke healthcare system, consisting of a central clinic aided by peripheral centers. As a matter of fact, MS patients often require comprehensive and ongoing care. However, when they reside at a significant distance from the clinics where their preferred HCP practice, the implementation of neuro-rehabilitation becomes a challenging endeavor. In this vision, being the peripheral neuro-rehabilitation team trained in the Hub center and always communicating with it, they can provide the patients with continuous care in a place that is closer to their homes (Manuli et al., 2020).

As a challenging aspect, we must address the dropout rates and compliance of MS patients in VR-based therapy. Some studies have hinted at the fact that a longer duration of the rehabilitation program could cause fatigued patients with MS to lose motivation and thus adherence. Consensus about the right duration of a VR therapy session is one more time difficult to find in the literature, but it is strategic to keep in mind the potential obstacles of VR, which can hinder efficacy and cost-effectiveness (Bevens et al., 2022; Casuso-Holgado et al., 2022). Manuli et al. viewed a possible solution to this gap by adding the patients' reported opinions and outcomes to the concept of feasibility. In their work based on conventional, robotic, and VR-based training, they involved the patients in the evaluation of the activities in terms of usability, perception of the obtained motor, and cognitive goals, and QoL. As these rehabilitation tools are and have to be designed on the patient's baseline disability, training performance, and achievements, this method is a fundamental milestone in the feasibility assessment of these technologies (Manuli et al., 2020). Table 3 summarizes the concepts regarding digitalizing MS fatigue assessment and management and Figure 2 depicts the clinical pathway for fatigued MS patients.

4. Discussion and conclusion

Although the anatomical correlates of fatigue in MS patients are not yet fully clear as its subtle nature makes it difficult to evaluate it objectively and to share a common strategy of encompassing it, both in the clinical and the research field. Nevertheless, updated, feasible, and digital are highly promising to make a difference in observing fatigue even at the beginning of its onset. Additionally, the management strategies offered by digital biomarkers, self-assessment instruments, and VR represent the most reliable complementary source of data and treatment outcomes complementary to the HCPs' observation.

As far as the therapeutic use of VR and apps is concerned, published literature is promising but more efforts are required. Nonetheless, in the smoldering frame of MS, where the underlying inflammation plays an equal role as the relapses, the digitalization of neuro-rehabilitation must be addressed as a fundamental element. MS is a complex and multi-faceted disease characterized by thousands of different limitations making the patients different from one another but also differently burdened. The concept of a homogeneous tracking method, as well as a scientific and clinical consensus regarding the healing process, brings us a step closer to changing the face of MS itself. The cost and time effectiveness of the above-discussed tools has been proved by various studies and they could even render a more objective and precise insight into the patient's clinical situation. To reach this goal, eHealth apps and wearable devices deliver a double advantage in assessment: the passive but constant data collection and a successful connection of clinic appointments with HCPs. Furthermore, autonomy could be enhanced as MS patients manage fatigue and learn how to observe and control the triggering factors.

Moreover, VR seems to represent a feasible ally in the field of neuro-rehabilitation. Many studies have highlighted its efficacy in restoring cognitive abilities, thanks to the simulation of motor tasks and simulations of ADLs. For example, Leonardi et al. offered both a neuropsychological evaluation and cognitive training before performing non-immersive VR training with patients. The experimental group improved not only in the motor and cognitive domains but also in the mood, which further demonstrates the effective role of VR in the psychological involvement of MS patients (Leonardi et al., 2021). Additionally, restoring motor memory is a crucial aspect. With standard feedback stimulation, as available through VR devices, this type of memory can be consolidated, along with the awareness of one's motor and cognitive abilities (Manuli et al., 2020). This is especially valid if VR—and gaming-based VR—is administered with conventional therapy. Along with the latter aspect, Leonardi et al., raised awareness of the importance of boosting the cognitive reserve of such patients, as they are very often diagnosed at a younger age. This, together with the increased flexibility and acceptance these younger patients may have toward VR, makes them a target group for a deeper exploration of VR exposure therapy (Leonardi et al., 2021). The concept of ADLs is thereby important: living with MS poses difficulties in day-to-day tasks, ultimately leading to social isolation and even unemployment. Fatigue is in this framework one of the most present symptoms and has therefore to be targeted. By boosting compliance through game-like activities, which request total presence and focus (e.g., immersive VR), we can obtain progress in the memory storing capabilities, motor functions, and QoL outcomes.

Restoring the individual's motor and cognitive functions is not only an integrative approach to be added to the disease-modifying therapies but it represents the therapy itself. As already commented, MS is currently widely considered a "smoldering" and underlying unremitting inflammatory process with superimposed relapses (Giovannoni et al., 2022). This concept paves the way to seeing neuro-rehabilitation as a way to address specific disabilities in order to enhance functional and social capabilities, an outcome which pharmacological therapy has been demonstrated to be lacking to achieve (Maggio et al., 2019b; Giovannoni et al., 2022).

The ultimate stage of this path might be changing the setting of therapy from a hospital- to a home-based one, where MS patients can feel safe and perform tasks with complete autonomy, although always with the support of their HCPs. The next step is to create a safe and secure data-collecting cloud and a trusted relationship between the patients and the new digital implementations, closely followed by a collaboration between patients and clinicians, with the common goal of finding a customized way of care.

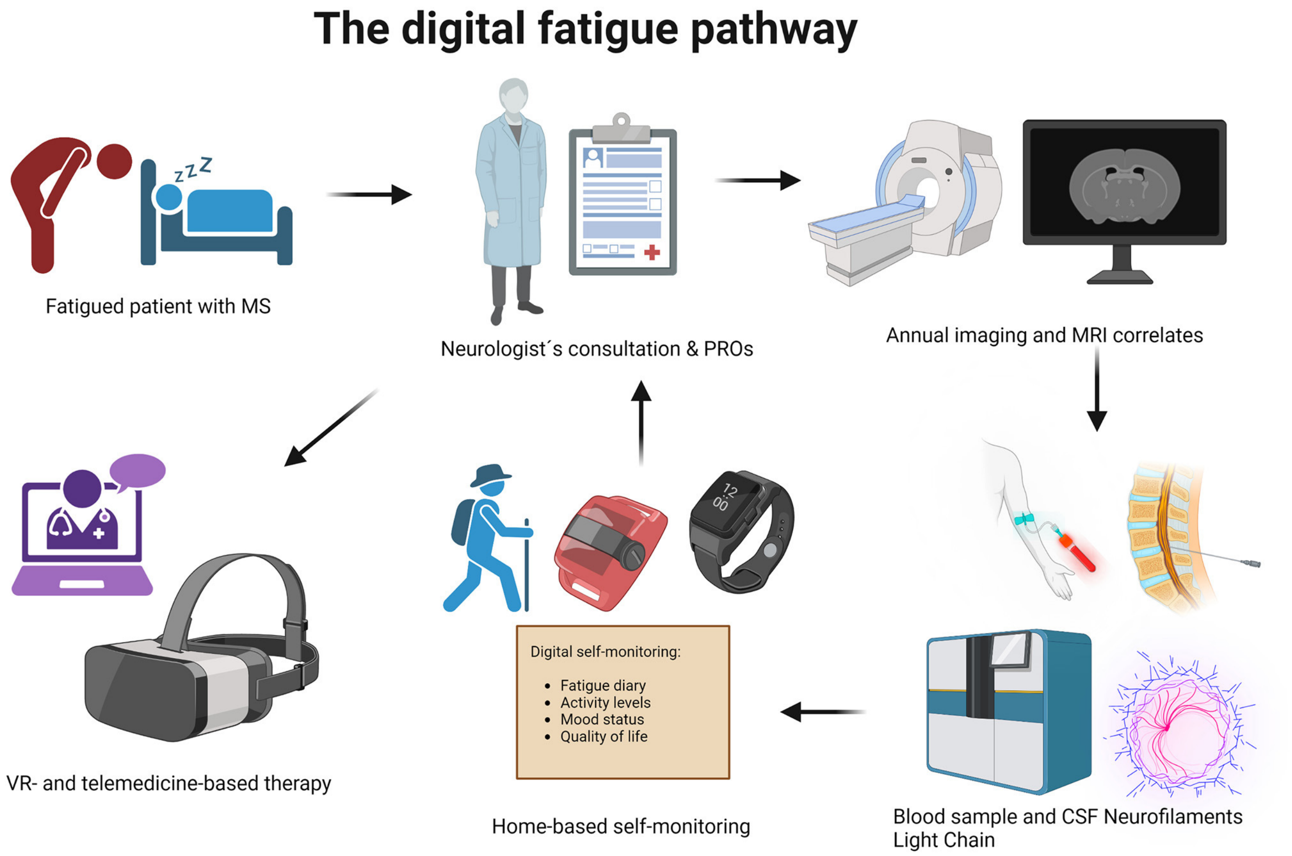


FIGURE 2
The fatigue path. The clinical pathway usually begins with the MS patient reporting fatigue and exhaustion, which leads them to a consultation with an HCP. In the MS clinical practice, an MRI is to be performed once a year to detect anatomical correlates regarding the clinical evolution of MS. NfL levels are also retrieved in blood and CSF as biomarkers of both physical and cognitive development of MS and fatigue. The observation of fatigue proceeds with the PROs, questionnaires, diaries, and scales. Up until now they have been the most reliable tool to assess fatigue in MS patients. Here, we propose a new way of assessing fatigue in MS patients. With the aid of apps and wearable devices, our clinical pathway model adds a feasible tool to the monitoring of MS fatigue, most of all between visits and at long distances. Finally, neuro-rehabilitation through hospital- and home-based tools and in-clinic virtual reality training can be implemented. Created with BioRender.com.

5. Unmet needs and future perspectives

A controversial topic in the field of digital health and telemedicine is the double requirement of having an individualized pathway to offer to the patients but at the same time providing them with a reliable and standardized assessment. Additionally, data security is an essential point that must not be discounted given that patients and users must have the chance to trust the digital system as they would trust their physician. To achieve this goal, firm protocolling must be made to rule a potential source of both clinical and research advantages but also economic and legislative dark sides e.g., data collection and protection (van der Walt et al., 2021). The collaboration between HCPs, researchers, and developers of digital solutions is crucial to adapt the assessment and the neuro-rehabilitation to MS patients. Similarly, as paper-based methods and symptomatic therapies, digital tools need to reach a high level of reliability to be referred to as “software as medical devices” (van der Walt et al., 2021). The matter of cost and benefits calculations must also be addressed, as it is always a key aspect in the introduction of every new procedure in the medical field. The cost-effectiveness must be advantageous for patients, who are already burdened by the disease and costs related to medical care, and the possible disadvantages of living in a developing country where the technological resources are extremely limited, as well as the digital literacy (De Angelis et al., 2021; Dillenseger et al., 2021). Furthermore, the costs of digital data collection should provide the clinician and the patient with the chance to choose app-based monitoring to aid therapeutic solutions. The same applies to the expenditures in the field of home-based and home-worn devices, which are surely appealing but in many cases also price-intensive (Dillenseger et al., 2021).

Detection of new symptoms must also be punctual and precise, to generate valid data for early identification of disease activity (Cloosterman et al., 2021). Furthermore, digital biomarkers retrieved through the mentioned innovative instruments must allow HCPs to clearly understand them as important parts of the patient’s disease history. They must be coded and stored in such a way that is easily accessed and routinely consulted (Voigt et al., 2023).

As far as gaps in the literature are concerned, most studies include almost exclusively female patients, whose EDSS ranges from 0 to 5 or 6, and with RRMS (Ozkul et al., 2020; Nascimento et al., 2021; Moeinzadeh et al., 2022). Unfortunately, most articles failed to describe test batteries or treatment efforts in very highly burdened patients, who might also suffer from fatigue along with all the physical limitations they might present. A future perspective might be a more extensive use of VR in patients with high-grade paralysis or fatigue levels, given the fact that a large amount of VR systems encompass an extreme variety of exercises and tasks (Ozkul et al., 2020).

Another important point in using VR as a therapy is the treatment intensity, duration, and type of tasks. As in every other therapy concept, a standardized length of session must be found for the patient to benefit from it. A final issue to overcome is the precise recruitment of MS patients to collaborate in research and therapeutic pathways, given that not every patient might benefit from these innovative systems, owing to their poor technological ability, older age, or willingness to learn new strategies from scratch (Dillenseger et al., 2021). At the same time, the caregiving and social environment should be considered and actively involved to complement the patient's difficulties in using a new device having disabilities (De Angelis et al., 2021).

All in all, the digital age of fatigue in the field of MS has begun, although with many challenges ahead. Linking standardized assessments and training to customized and goal-oriented individualized remains a central element in the research. Future studies should therefore concentrate their effort on reaching this milestone to routinely implement digital strategies for mitigating and eradicating fatigue in MS patients.

Author contributions

CP and TZ designed and conceptualized this paper. CP wrote the first draft and organized the methodology under the supervision and with the reviewing of TZ, JE, CB, and HI. All authors contributed to the article and agreed to the submitted version.

Funding

The Article Processing Charges (APC) were funded by the joint publication funds of the TU Dresden, including Carl Gustav Carus Faculty of Medicine, and the SLUB Dresden as well as the Open Access Publication Funding of the DFG.

Conflict of interest

HI received speaker honoraria from Roche and financial support for research activities from Biogen and Alexion. TZ reports scientific advisory board and/or consulting for Biogen, Roche, Novartis, Celgene, and Merck; compensation for serving on speakers bureaus for Roche, Novartis, Merck, Sanofi, Celgene, and Biogen; and research support from Biogen, Novartis, Merck, and Sanofi.

The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

References

Abbadessa, G., Lavorgna, L., Miele, G., Mignone, A., Signoriello, E., Lus, G., et al. (2021). Assessment of multiple sclerosis disability progression using a wearable biosensor: a pilot study. *J. Clin. Med.* 10, 1–7. doi: 10.3390/jcm10061160

Activinsights Ltd. (2023). *GENEActiv: Raw Data Accelerometry*. Available from: https://activinsights.com/technology/geneactiv/ (accessed September 10, 2023).

Adão Martins, N. R., Annaheim, S., Spengler, C. M., and Rossi, R. M. (2021). Fatigue monitoring through wearables: a state-of-the-art review. *Front. Physiol.* 12, 790292. doi: 10.3389/fphys.2021.790292

Adibi, I., Sanayei, M., Tabibian, F., Ramezani, N., Pourmohammadi, A., Azimzadeh, K., et al. (2022). Multiple sclerosis-related fatigue lacks a unified definition: a narrative review. *J. Res. Med. Sci.* 27, 1–9. doi: 10.4103/jrms.jrms_1401_20

Alexander, S., Peryer, G., Gray, E., Barkhof, F., and Chataway, J. (2021). Wearable technologies to measure clinical outcomes in multiple sclerosis: a scoping review. *Mult. Scler. J.* 27, 1643–1656. doi: 10.1177/1352458520946005

Al-Sharman, A., Khalil, H., El-Salem, K., Alghwiri, A. A., Khazaaleh, S., Khraim, M., et al. (2019). Motor performance improvement through virtual reality task is related to fatigue and cognition in people with multiple sclerosis. *Physiother. Res. Int.* 24, 1–7. doi: 10.1002/pri.1782

Altunkaya, J., Craven, M., Lambe, S., Beckley, A., Rosebrock, L., Dudley, R., et al. (2022). Estimating the economic value of automated virtual reality cognitive therapy for treating agoraphobic avoidance in patients with psychosis: findings from the gamechange randomized controlled clinical trial. *J. Med. Int. Res.* 24, e39248. doi: 10.2196/39248

Askari, S., Kessler, D., Smyth, P., and Finlayson, M. (2022). Evaluating occupational performance coaching to support fatigue management for people with multiple sclerosis: a feasibility study. *Clin. Rehabil.* 36, 1244–1256. doi: 10.1177/02692155221107074

Ayache, S. S., and Chalah, M. A. (2018). Transcranial direct current stimulation: a glimmer of hope for multiple sclerosis fatigue? *J. Clin. Neurosci.* 55, 1–3. doi: 10.1016/j.jocn.2018.06.002

Babbage, D. R., van Kessel, K., Drown, J., Thomas, S., Sezier, A., Thomas, P., et al. (2019). MS Energize: field trial of an app for self-management of fatigue for people with multiple sclerosis. *Int. Interv.* 18, 100291. doi: 10.1016/j.invent.2019.100291

Bakshi, R. (2003). Fatigue associated with multiple sclerosis: diagnosis, impact and management. *Mult. Scler. J.* 9, 219–227. doi: 10.1191/1352458503ms904oa

Battaglia, M. A., Bezzini, D., Cecchini, I., Cordioli, C., Fiorentino, F., Manacorda, T., et al. (2022). Patients with multiple sclerosis: a burden and cost of illness study. *J. Neurol.* 269, 5127–5135. doi: 10.1007/s00415-022-11169-w

Benedict, R. H. B., Cookfair, D., Gavett, R., Gunther, M., Munschauer, F., Garg, N., et al. (2006). Validity of the minimal assessment of cognitive function in multiple sclerosis (MACFIMS). *J. Int. Neuropsychol. Soc.* 12, 549–558. doi: 10.1017/S1355617706060723

Bertoli, M., Tataranni, A., Porziani, S., Pasqualetti, P., Gianni, E., Grifoni, J., et al. (2023). Effects on corticospinal tract homology of faremus personalized neuromodulation relieving fatigue in multiple sclerosis: a proof-of-concept study. *Brain Sci*. 13, 1–14. doi: 10.3390/brainsci13040574

Bertoli, M., and Tecchio, F. (2020). Fatigue in multiple sclerosis: does the functional or structural damage prevail? *Mult. Scler. J*. 26, 1809–1815. doi: 10.1177/1352458520912175

Bevens, W., Weiland, T., Gray, K., Jelinek, G., Neate, S., Simpson-Yap, S., et al. (2022). Attrition within digital health interventions for people with multiple sclerosis: systematic review and meta-analysis. *J. Med. Int. Res*. 24, 1–16. doi: 10.2196/27735

Bharadia, T., Vandercappellen, J., Chitnis, T., Eelen, P., Bauer, B., Brichetto, G., et al. (2022). Patient-reported outcome measures in MS: do development processes and patient involvement support valid quantification of clinically important variables? *Mult. Scler. J. Exp. Transl. Clin*. 8, 1–18. doi: 10.1177/20552173221105642

Block, V. J., Bove, R., and Nourbakhsh, B. (2022). The role of remote monitoring in evaluating fatigue in multiple sclerosis: a review. *Front. Neurol*. 13, 1–7. doi: 10.3389/fneur.2022.878313

Block, V. J., Bove, R., Zhao, C., Garcha, P., Graves, J., Romeo, A. R., et al. (2019). Association of continuous assessment of step count by remote monitoring with disability progression among adults with multiple sclerosis. *JAMA Netw. Open* 2, 1–15. doi: 10.1001/jamanetworkopen.2019.0570

Bradshaw, M. J., Farrow, S., Motl, R. W., and Chitnis, T. (2017). Wearable biosensors to monitor disability in multiple sclerosis. *Neurol. Clin. Pract*. 7, 354–362. doi: 10.1212/CPJ.0000000000000382

Braley, T. J., and Chervin, R. D. (2010). Fatigue in multiple sclerosis: mechanisms, evaluation, and treatment. *Sleep* 33, 1061–1067. doi: 10.1093/sleep/33.8.1061

BRISA (2022). *GmbH, Temedica, AG RP. Brisa App*. Available from: https://www.brisa-app.de/ (accessed September 10, 2023).

Broch, L., Simonsen, C. S., Flemmen, H. Ø., Berg-Hansen, P., Skardhamar, Å., Ormstad, H., et al. (2021). High prevalence of fatigue in contemporary patients with multiple sclerosis. *Mult. Scler. J. Exp. Transl. Clin*. 7, 1–10. doi: 10.1177/2055217321999826

Bundesinstitut für Arzneimittel und Medizinprodukte (2023). *DIGA - digitale Gesundheitsanwendungen*. Available from: https://www.bfarm.de/DE/Medizinprodukte/Aufgaben/DiGA-und-DiPA/DiGA/_node.html (accessed September 10, 2023).

Cadavid, D., Cohen, J. A., Freedman, M. S., Goldman, M. D., Hartung, H. P., Havrdova, E., et al. (2017). The EDSS-Plus, an improved endpoint for disability progression in secondary progressive multiple sclerosis. *Mult. Scler. J*. 23, 94–105. doi: 10.1177/1352458516638941

Capone, F., Collorone, S., Cortese, R., Di Lazzaro, V., and Moccia, M. (2020). Fatigue in multiple sclerosis: the role of thalamus. *Mult. Scler. J*. 26, 6–16. doi: 10.1177/1352458519851247

Carandini, T., Mancini, M., Bogdan, I., Rae, C. L., Barritt, A. W., Sethi, A., et al. (2021). Disruption of brainstem monoaminergic fibre tracts in multiple sclerosis as a putative mechanism for cognitive fatigue: a fixel-based analysis. *NeuroImage Clin*. 30, 102587. doi: 10.1016/j.nicl.2021.102587

Casuso-Holgado, M. J., García-Muñoz, C., Martín-Valero, R., Lucena-Anton, D., Moral-Munoz, J. A., Cortés-Vega, M., et al. (2022). Dropout rate in randomised controlled trials of balance and gait rehabilitation in multiple sclerosis: is it expected to be different for virtual reality-based interventions? A systematic review with meta-analysis and meta-regression. *Virtual Real*. 1–17. doi: 10.1007/s10055-022-00733-4

Cella, D., Lai, J. S., Nowinski, C. J., Victorson, D., Peterman, A., Miller, D., et al. (2012). Neuro-QOL: brief measures of health-related quality of life for clinical research in neurology. *Neurology* 78, 1860–1867. doi: 10.1212/WNL.0b013e318258f744

Cella, M., and Chalder, T. (2010). Chalder fatigue scale. *J. Psychosom*. 27, 6. doi: 10.1016/j.jpsychores.2009.10.007

Cercignani, M., Dipasquale, O., Bogdan, I., Carandini, T., Scott, J., Rashid, W., et al. (2021). Cognitive fatigue in multiple sclerosis is associated with alterations in the functional connectivity of monoamine circuits. *Brain Commun*. 3, 10. doi: 10.1093/braincomms/fcab023

Chalah, M. A., Riachi, N., Ahdab, R., Créange, A., Lefaucheur, J.-P., Ayache, S. S., et al. (2015). Fatigue in multiple sclerosis: neural correlates and the role of non-invasive brain stimulation. *Front. Cell. Neurosci*. 9, 1–15. doi: 10.3389/fncel.2015.00460

Chang, Y. T., Kearns, P. K., Carson, A., Gillespie, D. C., Meijboom, R., Kampaite, A., et al. (2023). Network analysis characterizes key associations between subjective fatigue and specific depressive symptoms in early relapsing-remitting multiple sclerosis. *Mult. Scler. Relat. Disord*. 69, 1–9. doi: 10.1016/j.msard.2022.104429

Charvet, L. E., Dobbs, B., Shaw, M. T., Bikson, M., Datta, A., Krupp, L. B., et al. (2018). Remotely supervised transcranial direct current stimulation for the treatment of fatigue in multiple sclerosis: results from a randomized, sham-controlled trial. *Mult. Scler. J*. 24, 1760–1769. doi: 10.1177/1352458517732842

Chikersal, P., Venkatesh, S., Masown, K., Walker, E., Quraishi, D., Dey, A., et al. (2022). Predicting multiple sclerosis outcomes during the COVID-19 stay-at-home period: observational study using passively sensed behaviors and digital phenotyping. *JMIR Ment. Heal*. 9, 1–13. doi: 10.2196/38495

Cloosterman, S., Wijnands, I., Huygens, S., Wester, V., Lam, K. H., Strijbis, E., et al. (2021). The potential impact of digital biomarkers in multiple sclerosis in the netherlands: an early health technology assessment of MS Sherpa. *Brain Sci*. 11, 1–13. doi: 10.3390/brainsci11101305

Cocco, E., and Fadda, P. (2022). Treatment of multiple sclerosis fatigue with the synthetic psychoactive drug modafinil. *Exp. Neurol*. 347, 113906. doi: 10.1016/j.expneurol.2021.113906

Cook, K. F., Bamer, A. M., Roddey, T. S., Kraft, G. H., Kim, J., Amtmann, D., et al. (2012). A PROMIS fatigue short form for use by individuals who have multiple sclerosis. *Qual. Life Res*. 21, 1021–1030. doi: 10.1007/s11136-011-0011-8

Cortés-Pérez, I., Sánchez-Alcalá, M., Nieto-Escámez, F. A., Castellote-Caballero, Y., Obrero-Gaitán, E., Osuna-Pérez, M. C., et al. (2021). Virtual reality-based therapy improves fatigue, impact, and quality of life in patients with multiple sclerosis. A systematic review with a meta-analysis. *Sensors* 21, 7389. doi: 10.3390/s21217389

Cuesta-Gómez, A., Sánchez-Herrera-Baeza, P., Oña-Simbaña, E. D., Martínez-Medina, A., Ortiz-Comino, C., Balaguer-Bernaldo-de-Quirós, C., et al. (2020). Effects of virtual reality associated with serious games for upper limb rehabilitation in patients with multiple sclerosis: randomized controlled trial. *J. Neuroeng. Rehabil*. 17, 1–10. doi: 10.1186/s12984-020-00718-x

De Angelis, M., Lavorgna, L., Carotenuto, A., Petruzzo, M., Lanzillo, R., Brescia Morra, V., et al. (2021). Digital technology in clinical trials for multiple sclerosis: systematic review. *J Clin Med*. 10, 1–14. doi: 10.3390/jcm10112328

Dettmers, C., Marchione, S., Weimer-Jaekel, A., Godde, B., and Joebges, M. (2021). Cognitive Fatigability, not Fatigue predicts employment status in patients with MS three months after rehabilitation. *Mult. Scler. Relat. Disord*. 56, 1–6. doi: 10.1016/j.msard.2021.103215

Deutsche Multiple Sklerose Gesellschaft B e. V. (2023). *Welche Ziele verfolgt die Symptomatische Therapie?* Available from: https://www.dmsg.de/multiple-sklerose/ms-behandeln/therapiesaeulen/symptomatische-therapie (accessed July 20, 2023).

Dietrich, M., Hartung, H. P., and Albrecht, P. (2021). Neuroprotective properties of 4-aminopyridine. *Neurol. Neuroimmunol. Neuroinflamm*. 8, 1–8. doi: 10.1212/NXI.0000000000000976

Dillenseger, A., Weidemann, M. L., Trentzsch, K., Inojosa, H., Haase, R., Schriefer, D., et al. (2021). Digital biomarkers in multiple sclerosis. *Brain Sci*. 11, 1–26. doi: 10.3390/brainsci11111519

Dogan, M., and Ayvat, E., Kilinç, M. (2023). Telerehabilitation versus virtual reality supported task-oriented circuit therapy on upper limbs and trunk functions in patients with multiple sclerosis: a randomized controlled study. *Mult. Scler. Relat. Disord*. 71, 104558. doi: 10.1016/j.msard.2023.104558

El Gaafary, M. A. (2016). "Guide to PROMs methodology and selection criteria," in *Patient Reported Outcome Measures in Rheumatic Diseases* (Cham: Springer International Publishing), 21–58. Available from: http://link.springer.com/10.1007/978-3-319-32851-5_2 (accessed July 20, 2023).

ELEVIDA (2002). *ELEVIDA*. Available from: https://elevida.de/ (accessed September 10, 2023).

Enoka, R. M., Almuklass, A. M., Alenazy, M., Alvarez, E., and Duchateau, J. (2021). Distinguishing between fatigue and fatigability in multiple sclerosis. *Neurorehabil. Neural Repair*. 35, 960–973. doi: 10.1177/15459683211046257

Enoka, R. M., and Duchateau, J. (2016). Translating fatigue to human performance. *Med. Sci. Sport Exerc*. 48, 2228–2238. doi: 10.1249/MSS.0000000000000929

EQ-5D EG (2009). *EuroQoL Questionnaire (EQ-5D-5L)*. Rotterdam: EuroQol Office, 1–2.

EuroQol Research Foundation (2021). *EQ-5D-5L User Guide,* 1–36. Available from: https://euroqol.org/publications/user-guides/ (accessed July 20, 2023).

F. Hoffmann-La Roche Ltd. (2021). *FloodlightMS*. Available from: https://www.floodlightms.de/?sem=sem-SI-20220501-none-OCR-go-10005861andgclid=Cj0KCQjwnMWkBhDLARIsAHBOftpjZBuVwmvdVFj-8EEzJ8OW-ZbaT5zoBE05ULpogUmjnO964Ycn14QaAv7_EALw_wcB (accessed September 10, 2023).

Filippi, M., and Rocca, M. A. (2020). "Multiple sclerosis," in *White Matter Diseases* (Cham: Springer International Publishing), 1–35. Available from: http://link.springer.com/10.1007/978-3-030-38621-4_1 (accessed July 20, 2023).

Fimo Health GmbH (2022). *Fimo Health*. Available from: https://en.fimohealth.com/ (accessed September 10, 2023).

Fisk, J. D., Ritvo, P. G., Ross, L., Haase, D. A., Marrie, T. J., and Schlech, W. F. (1994a). *Modified Fatigue Impact Scale (MFIS)*, 1–2. Available from: https://www.sralab.org/sites/default/files/2017-06/mfis.pdf (accessed July 20, 2023).

Fisk, J. D., Ritvo, P. G., Ross, L., Haase, D. A., Marrie, T. J., Schlech, W. F., et al. (1994b). Measuring the functional impact of fatigue: Initial validation of the fatigue impact scale (FIS-40). *Clin. Infect. Dis*. 18, S79–S83. doi: 10.1093/clinids/18.Supplement_1.S79

GAIA AG (2022). *GAIA*. Available from: https://gaia-group.com/en/ (accessed September 10, 2023).

García-Domínguez, J. M., Maurino, J., Martínez-Ginés, M. L., Carmona, O., Caminero, A. B., Medrano, N., et al. (2019). Economic burden of multiple sclerosis in a population with low physical disability. *BMC Public Health* 19, 609. doi: 10.1186/s12889-019-6907-x

Giovannoni, G., Popescu, V., Wuerfel, J., Hellwig, K., Iacobaeus, E., Jensen, M. B., et al. (2022). Smouldering multiple sclerosis: the 'real MS.' *Ther. Adv. Neurol. Disord.* 15, 175628642110667. doi: 10.1177/17562864211066751

Giunti, G., Mylonopoulou, V., and Rivera Romero, O. (2018). More Stamina, a Gamified mHealth solution for persons with multiple sclerosis: research through design. *JMIR mHealth uHealth* 6, 1–18. doi: 10.2196/mhealth.9437

Giunti, G., Rivera-Romero, O., Kool, J., Bansi, J., Sevillano, J. L., Granja-Dominguez, A., et al. (2020). Evaluation of more stamina, a mobile app for fatigue management in persons with multiple sclerosis: protocol for a feasibility, acceptability, and usability study. *JMIR Res. Protoc.* 9, 1–11. doi: 10.2196/18196

Gold, S. M., Heesen, C., Schulz, H., Guder, U., Mönch, A., Gbadamosi, J., et al. (2001). Disease specific quality of life instruments in multiple sclerosis: validation of the Hamburg Quality of Life Questionnaire in Multiple Sclerosis (HAQUAMS). *Mult. Scler. J.* 7, 119–130. doi: 10.1177/135245850100700208

Gumus, H. (2018). Fatigue can be objectively measured in multiple sclerosis. *Arch. Neuropsychiatry* 55, 76–79. doi: 10.29399/npa.23396

Guo, G., Zhang, H., Yao, L., Li, H., Xu, C., Li, Z., et al. (2021). MSLife: digital behavioral phenotyping of multiple sclerosis symptoms in the wild using wearables and graph-based statistical analysis. *Proc. ACM Interact. Mobile Wear. Ubiquit. Technol.* 5, 1–35. doi: 10.1145/3494970

Haase, R., Voigt, I., Scholz, M., Schlieter, H., Benedict, M., Susky, M., et al. (2021). Profiles of ehealth adoption in persons with multiple sclerosis and their caregivers. *Brain Sci.* 11, 2–12. doi: 10.3390/brainsci11081087

Harrison, A. M., das Nair, R., and Moss-Morris, R. (2017). Operationalising cognitive fatigability in multiple sclerosis: a Gordian knot that can be cut? *Mult. Scler. J.* 23, 1682–1696. doi: 10.1177/1352458516681862

Hollywood, R.-A., Poyade, M., Paul, L., and Webster, A. (2022). "Proof of concept for the use of immersive virtual reality in upper limb rehabilitation of multiple sclerosis patients," in *Advances in Experimental Medicine and Biology*, ed P. M. Rea (Cham: Springer), 73–93. Available from: https://link.springer.com/10.1007/978-3-030-87779-8_4 (accessed July 20, 2023).

Howard, Z., Win, K. T., and Guan, V. (2023). Mobile apps used for people living with multiple sclerosis: a scoping review. *Mult. Scler. Relat. Disord.* 73, 1–10. doi: 10.1016/j.msard.2023.104628

Hsu, W.-Y., Goverover, Y., and Bove, R. M. (2023). Capturing cognitive changes in multiple sclerosis by performance-based functional and virtual reality assessments. *Ann. Phys. Rehabil. Med.* 66, 1–9. doi: 10.1016/j.rehab.2022.101677

icometrix (2023). *iCobrain MS*. Available from: https://icometrix.com/services/icobrain-ms (accessed September 10, 2023).

Icompanion (2022). *iCompanion MS*. Available from: https://icompanion.ms/ (accessed September 10, 2023).

Inojosa, H., Schriefer, D., and Ziemssen, T. (2020). Clinical outcome measures in multiple sclerosis: a review. *Autoimmun. Rev.* 19, 31. doi: 10.1016/j.autrev.2020.102512

Iriarte, J., Katsamakis, G., and De Castro, P. (1999). fatigue descriptive scale (FDS): A useful tool to evaluate fatigue in multiple sclerosis. *Mult. Scler.* 5, 10–16. doi: 10.1177/135245859900500103

Jameen, A. R. M., Ribbons, J., Lechner-Scott, K., and Ramadan, J. (2019). Evaluation of MS related central fatigue using MR neuroimaging methods: scoping review. *J. Neurol. Sci.* 400, 52–71. doi: 10.1016/j.jns.2019.03.007

Janardhan, V., and Bakshi, R. (2002). Quality of life in patients with multiple sclerosis. *J. Neurol. Sci.* 205, 51–58. doi: 10.1016/S0022-510X(02)00312-X

Jensen, H. B., Ravnborg, M., Dalgas, U., and Stenager, E. (2014). 4-Aminopyridine for symptomatic treatment of multiple sclerosis: a systematic review. *Ther. Adv. Neurol. Disord.* 7, 97–113. doi: 10.1177/1756285613512712

Kalron, A., Frid, L., Fonkatz, I., Menascu, S., Dolev, M., Magalashvili, D., et al. (2022). The design, development, and testing of a virtual reality device for upper limb training in people with multiple sclerosis: single-center feasibility study. *JMIR Ser. Games* 10, 1–8. doi: 10.2196/36288

Kamudoni, P., Johns, J., Cook, K. F., Salem, R., Salek, S., Raab, J., et al. (2022). A comparison of the measurement properties of the PROMIS fatigue (MS) 8a against legacy fatigue questionnaires. *Mult. Scler. Relat. Disord.* 66, 1–8. doi: 10.1016/j.msard.2022.104048

Kellor, M., Frost, J., Silberberg, N., Iversen, I., and Cummings, R. (1971). Hand strength and dexterity. *Am. J. Occup. Ther.* 25, 77–83.

Khan, F., Amatya, B., and Galea, M. (2014). Management of fatigue in persons with multiple sclerosis. *Front. Neurol.* 5, 1–15. doi: 10.3389/fneur.2014.00177

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

Krupp, L. B. (1983a). *Fatigue Severity Scale (FSS)*. Chicago, IL: JAMA NEtwork.

Krupp, L. B. (1983b). The fatigue severity scale. *Arch. Neurol.* 46, 1121–1123. doi: 10.1001/archneur.1989.00520460115022

Krupp, L. B. (2003). Fatigue in multiple sclerosis. *CNS Drugs* 17, 225–234. doi: 10.2165/00023210-200317040-00002

Krupp, L. B., Alvarez, L. A., LaRocca, N. G., and Scheinberg, L. C. (1988). Fatigue in multiple sclerosis. *Arch. Neurol.* 45, 435–437. doi: 10.1001/archneur.1988.00520280085020

Kurtzke, J. F. (1983a). Rating neurologic impairment in multiple sclerosis: an expanded disability status scale (EDSS). *Neurology* 33, 1444–1452. doi: 10.1212/WNL.33.11.1444

Kurtzke, J. F. (1983b). *Definitions for a Standardised, Quantified Neurological Examination and Assessment of Kurtzke's Functional Systems and Expanded Disability Status Scale in Multiple Sclerosis (EDSS)*. Basel: University Hospital Basel.

Leonardi, S., Maggio, M. G., Russo, M., Bramanti, A., Arcadi, F. A., Naro, A., et al. (2021). Cognitive recovery in people with relapsing/remitting multiple sclerosis: a randomized clinical trial on virtual reality-based neurorehabilitation. *Clin. Neurol. Neurosurg.* 208, 1–6. doi: 10.1016/j.clineuro.2021.106828

Linnhoff, F., and Heinze, Z. (2019). Cognitive fatigue in multiple sclerosis: an objective approach to diagnosis and treatment by transcranial electrical stimulation. *Brain Sci.* 9, 100. doi: 10.3390/brainsci9050100

Maaß, L., Freye, M., Pan, C. C., Dassow, H. H., Niess, J., and Jahnel, T. (2022). The definitions of health apps and medical apps from the perspective of public health and law: qualitative analysis of an interdisciplinary literature overview. *JMIR mHealth uHealth* 10, 1–18. doi: 10.2196/37980

Mäcken, J., Wiegand, M., Müller, M., Krawinkel, A., and Linnebank, M. A. (2021). Mobile app for measuring real time fatigue in patients with multiple sclerosis: introducing the Fimo Health App. *Brain Sci.* 11, 1–10. doi: 10.3390/brainsci11091235

Maggio, M. G., Maresca, G., De Luca, R., Stagnitti, M. C., Porcari, B., Ferrera, N. C., et al. (2019a). The Growing Use of Virtual Reality in Cognitive Rehabilitation: Fact, Fake or Vision? *A Scoping Review. J Natl Med Assoc.* 111, 457–463. doi: 10.1016/j.jnma.2019.01.003

Maggio, M. G., Russo, M., Cuzzola, M. F., Destro, M., La Rosa, G., Molonia, F., et al. (2019b). Virtual reality in multiple sclerosis rehabilitation: a review on cognitive and motor outcomes. *J. Clin. Neurosci.* 65, 106–111. doi: 10.1016/j.jocn.2019.03.017

Manuli, A., Maggio, M. G., Tripoli, D., Gullì, M., Cannavò, A., La Rosa, G., et al. (2020). Patients' perspective and usability of innovation technology in a new rehabilitation pathway: an exploratory study in patients with multiple sclerosis. *Mult. Scler. Relat. Disord.* 44, 9. doi: 10.1016/j.msard.2020.102312

Medina, L. D., Torres, S., Alvarez, E., Valdez, B., and Nair, K. V. (2019). Patient-reported outcomes in multiple sclerosis: validation of the quality of life in neurological disorders (Neuro-QoL^{TM}) short forms. *Mult. Scler. J. Exp. Transl. Clin.* 5, 205521731988598. doi: 10.1177/2055217319885986

Metz, L. M. (2004). The effect of immunomodulatory treatment on multiple sclerosis fatigue. *J. Neurol. Neurosurg. Psychiatr.* 75, 1045–1047. doi: 10.1136/jnnp.2002.007724

Michielsen, H. J., De Vries, J., and Van Heck, G. L. (2003). Psychometric qualities of a brief self-rated fatigue measure. *J. Psychosom. Res.* 54, 345–352. doi: 10.1016/S0022-3999(02)00392-6

Mike Baker, J., and van Band, C. G. (2023). *Digital Health: Smartphone-Based Monitoring of Multiple Sclerosis Using Floodlight*. Available from: https://www.nature.com/articles/d42473-019-00412-0 (accessed September 10, 2023).

Mills, R. J., and Young, C. A. (2008). A medical definition of fatigue in multiple sclerosis. *QJM Ann. Int. J. Med.* 101, 49–60. doi: 10.1093/qjmed/hcm122

Mills, R. J., Young, C. A., Pallant, J. F., and Tennant, A. (2010). Development of a patient reported outcome scale for fatigue in multiple sclerosis: The Neurological Fatigue Index (NFI-MS). *Health Qual. Life Outcomes* 8, 1–10. doi: 10.1186/1477-7525-8-22

Moeinzadeh, A. M., Calder, A., Petersen, C., Hoermann, S., and Daneshfar, A. (2022). Comparing virtual reality exergaming with conventional exercise in rehabilitation of people with multiple sclerosis: a systematic review. *Neuropsychol. Rehabil.* 33, 1–26. doi: 10.1080/09602011.2022.2107021

Montalban, X., Graves, J., Midaglia, L., Mulero, P., Julian, L., Baker, M., et al. (2022). A smartphone sensor-based digital outcome assessment of multiple sclerosis. *Mult. Scler. J.* 28, 654–664. doi: 10.1177/13524585211028561

Mortezanejad, M., Ehsani, F., Masoudian, N., Zoghi, M., and Jaberzadeh, S. (2020). Comparing the effects of multi-session anodal trans-cranial direct current stimulation of primary motor and dorsolateral prefrontal cortices on fatigue and quality of life in patients with multiple sclerosis: a double-blind, randomized, sham-controlled tr. *Clin. Rehabil.* 34, 1103–1111. doi: 10.1177/0269215520921506

Moss-Morris, R., Harrison, A. M., Safari, R., Norton, S., van der Linden, M. L., Picariello, F., et al. (2021). Which behavioural and exercise interventions targeting fatigue show the most promise in multiple sclerosis? A systematic review with narrative synthesis and meta-analysis. *Behav. Res. Ther.* 137, 103464. doi: 10.1016/j.brat.2019.103464

Motl, R. W., Cohen, J. A., Benedict, R., Phillips, G., LaRocca, N., Hudson, L. D., et al. (2017). Validity of the timed 25-foot walk as an ambulatory performance outcome measure for multiple sclerosis. *Mult. Scler. J.* 23, 704–710. doi: 10.1177/1352458517690823

Mountford, S., Kahn, M., Balakrishnan, P., Jacyshyn-Owen, E., Eberl, M., Friedrich, B., et al. (2023). Correlation and differences of patient-reported outcomes vs. Likert-Rating of MS symptoms in a real-world cohort using a digital patient app. *Digit. Health* 9, 1–9. doi: 10.1177/20552076231173520

Nascimento, A. S., Fagundes, C. V., dos Mendes, S., and Leal, J. C. (2021). Effectiveness of virtual reality rehabilitation in persons with multiple sclerosis: a systematic review and meta-analysis of randomized controlled trials. *Mult. Scler. Relat. Disord.* 54, 9. doi: 10.1016/j.msard.2021.103128

National Multiple Sclerosis Society (1991). *Definition of MS : National Multiple Sclerosis Society*. National Multiple Sclerosis Society. Available from: https://www.nationalmssociety.org/What-is-MS/Definition-of-MS (accessed May 30, 2023).

Neuhaus, O., Köhler, W., Then Bergh, F., Kristoferitsch, W., Faiss, J., Rosenkranz, T., et al. (2021). Glatiramer acetate treatment in multiple sclerosis-associated fatigue—beneficial effects on self-assessment scales but not on molecular markers. *Biomolecules* 11, 1–10. doi: 10.3390/biom11030393

Niepel, G., Bibani, R. H., Vilisaar, J., Langley, R. W., Bradshaw, C. M., Szabadi, E., et al. (2013). Association of a deficit of arousal with fatigue in multiple sclerosis: effect of modafinil. *Neuropharmacology* 64, 380–388. doi: 10.1016/j.neuropharm.2012.06.036

Nourbakhsh, B., Revirajan, N., and Waubant, E. (2018). Treatment of fatigue with methylphenidate, modafinil and amantadine in multiple sclerosis (TRIUMPHANT-MS): study design for a pragmatic, randomized, double-blind, crossover clinical trial. *Contemp. Clin. Trials* 64, 67–76. doi: 10.1016/j.cct.2017.11.005

Novartis SB (2017). *ElevateMS*. Available from: http://www.elevatems.org/ (accessed September 10, 2023).

Oliva Ramirez, A., Keenan, A., Kalau, O., Worthington, E., Cohen, L., Singh, S., et al. (2021). Prevalence and burden of multiple sclerosis-related fatigue: a systematic literature review. *BMC Neurol.* 21, 468. doi: 10.1186/s12883-021-02396-1

Ozkul, C., Guclu-Gunduz, A., Yazici, G., Atalay Guzel, N., and Irkec, C. (2020). Effect of immersive virtual reality on balance, mobility, and fatigue in patients with multiple sclerosis: a single-blinded randomized controlled trial. *Eur. J. Integr. Med.* 35, 101092. doi: 10.1016/j.eujim.2020.101092

Pagliari, C., Di Tella, S., Jonsdottir, J., Mendozzi, L., Rovaris, M., De Icco, R., et al. (2021). Effects of home-based virtual reality telerehabilitation system in people with multiple sclerosis: a randomized controlled trial. *J. Telemed. Telecare* 1–12. doi: 10.1177/1357633X211054839

Palotai, M., and Guttmann, C. R. (2020). Brain anatomical correlates of fatigue in multiple sclerosis. *Mult. Scler. J.* 26, 751–764. doi: 10.1177/1352458519876032

Penner, I., Raselli, C., Stöcklin, M., Opwis, K., Kappos, L., Calabrese, P., et al. (2009). The Fatigue Scale for Motor and Cognitive Functions (FSMC): validation of a new instrument to assess multiple sclerosis-related fatigue. *Mult. Scler. J.* 15, 1509–1517. doi: 10.1177/1352458509348519

Penner, I. K., McDougall, F., Brown, T. M., Slota, C., Doward, L., Julian, L., et al. (2020). Exploring the impact of fatigue in progressive multiple sclerosis: a mixed-methods analysis. *Mult. Scler. Relat. Disord.* 43, 1–7. doi: 10.1016/j.msard.2020.102207

Penner, I. K., Raselli, C., Stöcklin, M., Opwis, K., Kappos, L., and Calabrese, P. (2005). *The Fatigue Scale for Motor And Cognitive Functions (FSMC)*, 1–2. Available from: https://neuroreg.se/media/prulg4lj/questionnaire_kappos_et_al-php1.pdf (accessed July 20, 2023).

Pennisi, M., Lanza, G., Cantone, M., D'Amico, E., Fisicaro, F., Puglisi, V., et al. (2020). Acetyl-L-carnitine in dementia and other cognitive disorders: a critical update. *Nutrients* 12, 1–23. doi: 10.3390/nu12051389

Picariello, F., Freeman, J., and Moss-Morris, R. (2022). Defining routine fatigue care in multiple sclerosis in the United Kingdom: what treatments are offered and who gets them? *Mult. Scler. J. Exp. Transl. Clin.* 8, 1–12. doi: 10.1177/20552173211072274

Pöttgen, J., Moss-Morris, R., Wendebourg, J. M., Feddersen, L., Lau, S., Köpke, S., et al. (2018). Randomised controlled trial of a self-guided online fatigue intervention in multiple sclerosis. *J. Neurol. Neurosurg. Psychiatr.* 89, 970–976. doi: 10.1136/jnnp-2017-317463

Pratap, A., Grant, D., Vegesna, A., Tummalacherla, M., Cohan, S., Deshpande, C., et al. (2020). Evaluating the utility of smartphone-based sensor assessments in persons with multiple sclerosis in the real-world using an app (elevateMS): observational, prospective pilot digital health study. *JMIR mHealth uHealth* 8, 1–19. doi: 10.2196/22108

Pucci, E., Brañas Tato, P., D'Amico, R., Giuliani, G., Solari, A., Taus, C., et al. (2007). Amantadine for fatigue in multiple sclerosis. *Cochr. Database Syst. Rev.* 1–20. doi: 10.1002/14651858.CD002818.pub2

Rietberg, M. B., and van Wegen, E. E. (2019). Clinimetrics: the neurological fatigue index for multiple sclerosis. *J. Physiotherapy* 65, 1–8. doi: 10.1016/j.jphys.2019.07.003

Roche Fachportal (2023). *Was ist Floodlight MS?*. Available from: https://www.portal.roche.de/products/neurologie/digitale-gesundheitsloesungen/floodlight-ms/uebersicht-floodlight-ms.html (accessed September 10, 2023).

Rooney, S., Wood, L., Moffat, F., and Paul, L. (2019). Prevalence of fatigue and its association with clinical features in progressive and non-progressive forms of multiple sclerosis. *Mult. Scler. Relat. Disord.* 28, 276–282. doi: 10.1016/j.msard.2019.01.011

Sailer, M., Sweeney-Reed, C. M., and Lamprecht, J. (2023). "Non-drug treatment approaches and neurorehabilitation," in *Fatigue in Multiple Sclerosis* (Cham: Springer International Publishing), 193–200. Available from: https://link.springer.com/10.1007/978-3-031-13498-2_16 (accessed July 20, 2023).

Sander, C., Voelter, H.-U., Schlake, H.-P., Eling, P., and Hildebrandt, H. (2017). Assessment of fatigue in multiple sclerosis. *Neurol. Int. Open* 1, 79–85. doi: 10.1055/s-0043-104752

Sandry, J., Simonet, D. V., Brandstadter, R., Krieger, S., Katz Sand, I., Graney, R. A., et al. (2021). The Symbol Digit Modalities Test (SDMT) is sensitive but non-specific in MS: lexical access speed, memory, and information processing speed independently contribute to SDMT performance. *Mult. Scler. Relat. Disord.* 51, 1–6. doi: 10.1016/j.msard.2021.102950

Schiavolin, S., Leonardi, M., Giovannetti, A. M., Antozzi, C., Brambilla, L., Confalonieri, P., et al. (2013). Factors related to difficulties with employment in patients with multiple sclerosis. *Int. J. Rehabil. Res.* 36, 105–111. doi: 10.1097/MRR.0b013e32835c79ea

Schmidt, S., and Jöstingmeyer, P. (2019). Depression, fatigue and disability are independently associated with quality of life in patients with multiple Sclerosis: results of a cross-sectional study. *Mult. Scler. Relat. Disord.* 35, 262–269. doi: 10.1016/j.msard.2019.07.029

Scholz, M., Haase, R., Schriefer, D., Voigt, I., and Ziemssen, T. (2021). Electronic health interventions in the case of multiple sclerosis: from theory to practice. *Brain Sci.* 11, 180. doi: 10.3390/brainsci11020180

Schwartz, J. E., Jandorf, L., and Krupp, L. B. (1993). The measurement of fatigue: a new instrument. *J. Psychosom. Res.* 37, 753–762. doi: 10.1016/0022-3999(93)90104-N

Schwid, S. R., Covington, M., Segal, B. M., and Goodman, A. D. (1987). The rochester fatigue diary. *J. Rehabil. Res. Dev.*

Schwid, S. R., Covington, M., Segal, B. M., and Goodman, A. D. (2002). Fatigue in multiple sclerosis: current understanding and future directions. *J. Rehabil. Res. Dev.* 39, 211–224.

Schwid, S. R., Thornton, C. A., Pandya, S., Manzur, K. L., Sanjak, M., Petrie, M. D., et al. (1999). Quantitative assessment of motor fatigue and strength in MS. *Neurology* 53, 743–743. doi: 10.1212/WNL.53.4.743

Shah, P. (2015). Symptomatic management in multiple sclerosis. *Ann. Indian Acad. Neurol.* 18, 35. doi: 10.4103/0972-2327.164827

Shahid, A., Wilkinson, K., Marcu, S., and Shapiro, C. M. (2011). *Visual Analogue Scale to Evaluate Fatigue Severity (VAS-F). STOP, THAT and One Hundred Other Sleep Scales*. New York, NY: Springer New York, 399–402. Available from: http://link.springer.com/10.1007/978-1-4419-9893-4_100 (accessed July 20, 2023).

Shahid, A., Wilkinson, K., Marcu, S., and Shapiro, C. M. (2012). *STOP THAT and one hundred other sleep scales. STOP, THAT One Hundred Other Sleep Scales,* 1–406. Available from: https://www.med.upenn.edu/cbti/assets/user-content/documents/FatigueAssessmentInventory(FAI).pdf (accessed July 20, 2023).

Smets, E. M. A., Garssen, B., Bonke, B., and De Haes, J. C. J. M. (1995). The multidimensional Fatigue Inventory (MFI) psychometric qualities of an instrument to assess fatigue. *J. Psychosom. Res.* 39, 315–325. doi: 10.1016/0022-3999(94)00125-O

Sparaco, M., Lavorgna, L., Conforti, R., Tedeschi, G., and Bonavita, S. (2018). The role of wearable devices in multiple sclerosis. *Mult. Scler. Int.* 2018, 1–7. doi: 10.1155/2018/7627643

Stamina (2022). *More Stamina*. Available from: https://www.morestaminaapp.com/about/ (accessed September 10, 2023).

Stamoula, E., Siafis, S., Dardalas, I., Ainatzoglou, A., Matsas, A., Athanasiadis, T., et al. (2021). Antidepressants on multiple sclerosis: a review of *in vitro* and *in vivo* models. *Front. Immunol.* 12, 1–20. doi: 10.3389/fimmu.2021.677879

Stern, A. D., Brönneke, J., Debatin, J. F., Hagen, J., Matthies, H., Patel, S., et al. (2022). Advancing digital health applications: priorities for innovation in real-world evidence generation. *Lancet Digit. Heal.* 4, 200–206. doi: 10.1016/S2589-7500(21)00292-2

Strober, L., DeLuca, J., Benedict, R. H., Jacobs, A., Cohen, J. A., Chiaravalloti, N., et al. (2019). Symbol digit modalities test: a valid clinical trial endpoint for measuring cognition in multiple sclerosis. *Mult. Scler. J.* 25, 1781–1790. doi: 10.1177/1352458518808204

Svenningsson, A., Falk, E., Celius, E. G., Fuchs, S., Schreiber, K., Berkö, S., et al. (2013). Natalizumab treatment reduces fatigue in multiple sclerosis. Results from the TYNERGY trial; a study in the real life setting. *PLoS ONE* 8, 1–7. doi: 10.1371/journal.pone.0058643

Tarasiuk, J., Kapica-Topczewska, K., Czarnowska, A., Chorazy, M., Kochanowicz, J., Kułakowska, A., et al. (2022). Co-occurrence of fatigue and depression in people with multiple sclerosis: a mini-review. *Front. Neurol.* 12, 1–8. doi: 10.3389/fneur.2021.817256

Tervonen, T., Fox, R. J., Brooks, A., Sidorenko, T., Boyanova, N., Levitan, B., et al. (2023). Treatment preferences in relation to fatigue of patients with relapsing multiple sclerosis: a discrete choice experiment. *Mult. Scler. J. Exp. Transl. Clin.* 9, 1–11. doi: 10.1177/20552173221150370

Tong, C., Craner, M., Vegreville, M., and Lane, N. D. (2019). Tracking fatigue and health state in multiple sclerosis patients using connnected wellness devices. *Proc. ACM Interact. Mobile Wear. Ubiquit. Technol.* 3, 1–19. doi: 10.1145/3351264

UWCORR (2020). *PROMIS Fatigue Short Form for Multiple Sclerosis (PROMIS-Fatigue MS)*. University of Washington Center on Outcomes Research in Rehabilitation. Available from: http://nihpromis.org (accessed July 20, 2023).

van der Walt, A., Butzkueven, H., Shin, R. K., Midaglia, L., Capezzuto, L., Lindemann, M., et al. (2021). Developing a digital solution for remote assessment in multiple sclerosis: from concept to software as a medical device. *Brain Sci.* 11, 1–13. doi: 10.3390/brainsci11091247

Van Hecke, W., Costers, L., Descamps, A., Ribbens, A., Nagels, G., Smeets, D., et al. (2021). A Novel digital care management platform to monitor clinical and subclinical disease activity in multiple sclerosis. *Brain Sci.* 11, 1–25. doi: 10.3390/brainsci11091171

van Kessel, K., Babbage, D. R., Kersten, P., Drown, J., Sezier, A., Thomas, P. W., et al. (2021). Design considerations for a multiple sclerosis fatigue mobile app MS Energize: A pragmatic iterative approach using usability testing and resonance checks. *Int. Interv.* 24, 1–14. doi: 10.1016/j.invent.2021.100371

Vandyk, T., Meyer, B., Member, S., Depetrillo, P., Donahue, N., Leary, A. O., et al. (2022). *Digital Phenotypes of Instability and Fatigue Derived from Daily Standing Transitions in Persons with Multiple Sclerosis Digital Phenotypes of Instability and Fatigue Derived from Daily Standing Transitions in Persons with Multiple Sclerosis.* Techrxiv. 1–9. Available from: https://www.techrxiv.org/articles/preprint/Digital_Phenotypes_of_Instability_and_Fatigue_Derived_from_Daily_Standing_Transitions_in_Persons_with_Multiple_Sclerosis/21558216 (accessed July 20, 2023).

Vickrey, B. G., Hays, R. D., Harooni, R., Myers, L. W., and Ellison, G. W. (1995). A health-related quality of life measure for multiple sclerosis. *Qual. Life Res.* 4, 187–206. doi: 10.1007/BF02260859

Voigt, I., Inojosa, H., Dillenseger, A., Haase, R., Akgün, K., Ziemssen, T., et al. (2021). Digital twins for multiple sclerosis. *Front. Immunol.* 12, 1–17. doi: 10.3389/fimmu.2021.669811

Voigt, I., Inojosa, H., Wenk, J., Akgün, K., and Ziemssen, T. (2023). Building a monitoring matrix for the management of multiple sclerosis. *Autoimmun. Rev.* 22, 1–10. doi: 10.1016/j.autrev.2023.103358

Weber, E., Goverover, Y., and DeLuca, J. (2019). Beyond cognitive dysfunction: relevance of ecological validity of neuropsychological tests in multiple sclerosis. *Mult. Scler. J.* 25, 1412–1419. doi: 10.1177/1352458519860318

Webster, A., Poyade, M., Rooney, S., and Paul, L. (2021). *Upper Limb Rehabilitation Interventions Using Virtual Reality for People With Multiple Sclerosis: A Systematic Review, Vol. 47, Multiple Sclerosis and Related Disorders.* Amsterdam: Elsevier B.V.

Yazgan, Y. Z., Tarakci, E., Tarakci, D., Ozdincler, A. R., and Kurtuncu, M. (2020). Comparison of the effects of two different exergaming systems on balance, functionality, fatigue, and quality of life in people with multiple sclerosis: a randomized controlled trial. *Mult. Scler. Relat. Disord.* 39, 1–21. doi: 10.1016/j.msard.2019.101902

Zangemeister, W. H., Heesen, C., Roehr, D., and Gold, S. (2020). Oculomotor fatigue and neuropsychological assessments mirror multiple sclerosis fatigue. *J. Eye Mov. Res.* 13, 1–19. doi: 10.16910/jemr.13.4.6

Zayas-Garcia, S., and Cano-de-la-Cuerda, R. (2018). Mobile applications related to multiple sclerosis: a systematic review. *Rev. Neurol.* 67, 473–483. doi: 10.33588/rn.6712.2018147

Zielińska-Nowak, E., Włodarczyk, L., Kostka, J., and Miller, E. (2020). New strategies for rehabilitation and pharmacological treatment of fatigue syndrome in multiple sclerosis. *J Clin Med.* 9, 1–18. doi: 10.3390/jcm9113592

Ziemssen, T., and Haase, R. (2021). Digital innovation in multiple sclerosis management. *Brain Sci.* 12, 40. doi: 10.3390/brainsci12010040

frontiers | Frontiers in Physiology

TYPE Perspective
PUBLISHED 04 December 2023
DOI 10.3389/fphys.2023.1257557

OPEN ACCESS

EDITED BY
Pawel Zalewski,
Nicolaus Copernicus University in Toruń,
Poland

REVIEWED BY
Kirsten Wittke,
Charité University Medicine Berlin,
Germany
Sławomir Kujawski,
Ludwik Rydygier Collegium Medicum in
Bydgoszcz Nicolaus Copernicus
University in Toruń, Poland

*CORRESPONDENCE
Nina K. Vøllestad,
✉ nina.vollestad@medisin.uio.no

RECEIVED 12 July 2023
ACCEPTED 22 November 2023
PUBLISHED 04 December 2023

CITATION
Vøllestad NK and Mengshoel AM (2023), Post-exertional malaise in daily life and experimental exercise models in patients with myalgic encephalomyelitis/chronic fatigue syndrome.
Front. Physiol. 14:1257557.
doi: 10.3389/fphys.2023.1257557

Post-exertional malaise in daily life and experimental exercise models in patients with myalgic encephalomyelitis/chronic fatigue syndrome

Nina K. Vøllestad* and Anne Marit Mengshoel

Department of Interdisciplinary Health Science, Institute of Health and Society, University of Oslo, Oslo, Norway

Post-exertional malaise (PEM) is commonly recognized as a hallmark of myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) and is often used as one of several criteria for diagnosing ME/CFS. In this perspective paper we want to reflect on how PEM is understood, assessed, and evaluated in scientific literature, and to identify topics to be addressed in future research. Studies show that patients use a wide variety of words and concepts to label their experience of PEM in everyday life, and they report physical or mental exertions as triggers of PEM. They also report that PEM may have an immediate or delayed onset and may last from a few days to several months. When standardized exercise tests are used to trigger PEM experimentally, the exacerbation of symptoms has a more immediate onset but still shows a wide variability in duration. There are indications of altered muscular metabolism and autonomic nervous responses if exercise is repeated on successive days in patients with ME/CFS. The decreased muscular capacity appears to be maintained over several days following such controlled exercise bouts. These responses may correspond to patients' experiences of increased exertion. Based on this background we argue that there is a need to look more closely into the processes occurring in the restitution period following exercise, as PEM reaches the peak in this phase.

KEYWORDS

post-exertional malaise (PEM), myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS), exercise, cardiopulmonary exercise test (CPET), neuroendocrinological system, muscle weakness, adrenaline, noradrenaline

Introduction

Myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) is a symptom-based diagnosis characterized by patient-reported inexplicable, incapacitating, persistent or relapsing fatigue, unrefreshing sleep, cognitive dysfunctions, and musculoskeletal pain that heavily impact patients' lives (Nacul et al., 2021). Over the years several sets of diagnostic criteria have been developed to classify ME/CFS. Examples are the Oxford Criteria (Sharpe et al., 1991), the Fukuda Criteria (Fuku et al., 1994), and the International Consensus Criteria, ICC (Carruthers et al., 2011). Post-exertional malaise (PEM) was included in the CFS case definition by Fukuda and co-workers (Fuku et al., 1994) in 1994, although PEM was not explained nor further defined by these authors. In their criteria, PEM was one of nine symptoms to be considered for the diagnosis although PEM did not

TABLE 1 Self-reported post-exertional (PEM) symptom in patients with myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS).

Authors	Purpose of the study	Case definition	Study design	Patients	PEM descriptions	PEM triggers	PEM onset and duration
Country							
Qualitative interviews							
Krabbe et al. (2022)	What do young women who are in recovery from ME/CFS tell about their experience of falling severely ill during childhood and adolescence?	Self-reported diagnosis set by a physician	Narrative qualitative interviews with overarching open-ended questions	13 women with ME/CFS during childhood or adolescence now in recovery or recovered	Gradually developing unhomeliness and feeling pushed toward the edge; and left abandoned on the sidelines		
Norway				Age range at time of interviews 16–30 years			
Parslow et al. (2018)	Describe adolescents with ME/CFS' experiences of fatigue, symptom fluctuation	Diagnosis set in clinics by an experienced pediatrist	Qualitative semi-structured interviews	21 adolescents with ME/CFS and their parents	Fluctuations in fatigue and other symptoms create good and bad days. Worsening could appear for no reason and as a payback after activity; worded as "wiped out," "absolute crash," 'knocked out,", "zonked out," and "out cold"		
UK				Age range 12–17 years			
Olson et al. (2015)	Explore the meaning of fatigue	Fukuda criteria	Ethnoscience interviews with overarching open-ended questions	13 women and 1 man	Tiredness expresses prior to illness, in remission, or "good days". Fatigue describes ME/CFS on daily basis. Exhaustion expresses overexertion		
Canada				Age range 37–68			
Stussman et al. (2020)	Expand the understanding of PEM, its manner of onset, timeframes for onset, peak, duration	Diagnosed by physicians and referred to a cardio-pulmonary exercise test	Focus group interviews	43 subjects	PEM was described as "Flu-like" exhaustion, Cognitive problems of thinking clearly, finding words, and complete fog	Three broad categories of activity: physical activity, cognitive effort, and emotional moments. The threshold for activity depends on their baseline	After daily activities: onset after 12–48 h, peak 48 h, duration 2–7 days
USA			Had undergone cardio-pulmonary exercise test	21% men	Neuromuscular complaints as pain/aches and weakness		After exercise test: immediate onset, peak 24 h, duration 72 h
				Age range 30–69 years			
Structured questions with open ended responses							
Hartle et al. (2021)	Examine patients' responses on PEM triggers, experiences, recovery, and prevention	Fulfilling at least one of diagnostic criteria: Fukuda, International Consensus Criteria, Canadian Consensus Clinical Criteria	Online survey of PEM questionnaire designed for the study with 4 items with open-ended responses and 2 with predefined alternatives	75 subjects sick ≥4 years and 76 sick ≥10 years	Fatigue 21% of the symptoms (e.g., weakness, heavy limbs, flu-like symptoms, feeling ill), pain/musculoskeletal symptoms 18%, orthostatic intolerance 14%	Most common exertion induced by medium levels of physical (71%) and cognitive activities, at any levels these two factors accounted for 89%	Onset: Within minutes 35%
US				Age range 18–65 years	Rest used as strategies for recovering, and pacing for prevention	Stress by those <4 years sick (19%)	Within hours 40%

(Continued on following page)

TABLE 1 (*Continued*) Self-reported post-exertional (PEM) symptom in patients with myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS).

Authors Country	Purpose of the study	Case definition	Study design	Patients	PEM descriptions	PEM triggers	PEM onset and duration
				26% men			Within ≥ 1 day 25%
							Duration: At least 1 day 31%
							Several days 48%
							At least 1 week 13%

need to be present. In the International Consensus Criteria, however, PEM is considered a hallmark used to differentiate ME/CFS patients from patients with other chronic illnesses and persistent fatigue (Carruthers et al., 2011). These authors describe PEM as a perceived exacerbation of some, or all symptoms of ME/CFS after physical or cognitive exertion. Further, PEM is described as a disproportional worsening of symptoms due to physical or cognitive efforts that previously was well tolerated, typically with a delayed onset and lasting for variable and often extended periods of time (Nacul et al., 2021). In the later years, PEM has been investigated by qualitative interviews of patients, assessed by standardized self-reports alone or in combination with experimental triggering actions such as exercise tests or mental challenges (Nacul et al., 2021). However, to our knowledge the relationship between PEM as experienced in every-day life and experimentally induced PEM is scarcely examined.

On this background, the purpose of this perspective paper is to examine if there is coherence between PEM as described by patients with their own words, PEM assessed by standardized questionnaires, as well as exercise-induced PEM by experimental models. In addition, we will discuss how the exercise tests can be further developed to capture relevant aspects of PEM and the possible underlying biological mechanisms.

PEM as experienced in everyday life

PEM is narrated by patients as well as assessed by structured self-reports. Moreover, PEM has been examined in terms of exacerbation of ME/CFS symptoms, what triggers the exacerbations in daily life, as well as the time of onset and duration of symptoms before recovery. The literature used is summarized in Table 1. PEM is found to relate to exacerbations of fatigue, cognitive difficulties (cannot think clearly, memory problems), sleep problems, neuromuscular complaints (pain/aches and weakness), bodily heaviness, flulike symptoms and impacts on daily functioning (Baraniuk et al., 2013; Chu et al., 2018; Jason et al., 2018; Davenport et al., 2023a). These findings were also supported by a focus group interview with patients (Stussman et al., 2020). It is noteworthy that high PEM also seems to associate with more symptoms, psychological distress, and social burden (May et al., 2020).

The US Committee on the Diagnostic Criteria for ME/CFS reports that patients typically call PEM a "crash," "flare-up," "collapse," "debility" or "set-back" (Locher and IOM, 2015). In a similar vein, two qualitative studies showed that patients express their experience in terms of "wiped out", "absolute crash," "knocked out," "zonked out" (Parslow et al., 2018), or a "bodily lock down" (Krabbe et al., 2022). A survey of international respondents showed that the most preferred wordings for PEM were "crash" and "exhaustion" (Jason et al., 2018). Interestingly, a Canadian study showed that patients themselves discriminate fluctuations in ME/CFS by using the words of tiredness, fatigue, and exhaustion (Olson et al., 2015). Tiredness was used to describe experiences prior to the diagnosis or on good days (i.e., what they find normal and healthy), whereas fatigue referred to how it was like on daily basis with ME/CFS. In contrast, exhaustion described the experiences after overexertion, i.e. related to PEM.

A frequently applied questionnaire for assessing symptoms among patients with ME/CFS is the DePaul Symptom Questionnaire (DSQ) (Jason and Sunnquist, 2018). Based on the five PEM items from DSQ and five additional questions, Cotler and coworkers developed a scale to identify the presence of PEM (Cotler et al., 2018). Respondents are asked to rate how bothersome and frequent the following symptoms are: "Dead, heavy feeling after starting to exercise," "Next day soreness or fatigue after non-strenuous, everyday activities," "Mentally tired after the slightest effort," "Minimum exercise makes you physically tired," "Physically drained or sick after mild activity" (Cotler et al., 2018). Thus, there is a discrepancy between wordings used by patients to describe PEM and those used in items of the standardized questionnaire. "Dead, heavy feeling" may better be captured by "flu-like" or "crash" experience used by patients. Moreover, "tiredness" and "fatigue" in the questionnaire differ from the term "exhaustion" used by patients to describe PEM. Furthermore, non-strenuous everyday activities and minimum exercise are rather unspecific terms. Neither of the terms necessarily discriminate between daily activities and an extraordinary triggering event. Although, the DSQ is found to have a good internal consistency (Brown and Jason, 2014; Jason et al., 2015a), one may question the items' face validity since there are deviations between the expressions used by patients in qualitative studies and in questionnaires.

Focus group interviews have outlined that a broad set of non-strenuous daily activities may trigger PEM, such as household chores, social activities, physical exercise, cognitive activities, and emotional moments (Stussman et al., 2020). Another qualitative study also underscores that all kinds of activities can lead to a "payback time" the following days, and these authors identified also a symptom fluctuation unrelated to triggers, portrayed as a state where ME/CFS operates "on its own" (Parslow et al., 2018). A quantitative study categorized the triggers as emotional stress, activities in daily life, positional changes, noise, and other sensory overloads (Holtzman et al., 2019). Engagement in high-strenuous activities can also be accompanied by discomfort in terms of fatigue and muscle soreness among healthy people. However, for patients with ME/CFS, this seems to occur even after low-strenuous physical and cognitive activities (Holtzman et al., 2019; Hartle et al., 2021; Davenport et al., 2023a). Moreover, patients also describe a symptom fluctuation over time displayed as "booms and busts" (Strassheim et al., 2021) or as a gradual down-spiraling deterioration process accompanied by an increasing intolerance of triggers (Krabbe et al., 2022). It thus seems to be good coherence between freely voiced triggering experiences and assessments of triggers.

A study of 704 respondents examined whether PEM was a unified entity or composed of different constructs (McManimen et al., 2019). A factor analysis of a large set of symptoms combined with triggers demonstrated that PEM is composed of two different constructs: generalized fatigue and muscle-specific fatigue. The first comprised symptoms of more generalized feeling of physical and mental fatigue, whereas the muscular construct included symptoms that referred to pain, weakness or fatigue in muscles following exertion. This finding may have important implications, particularly considering the various types of triggers reported. An interesting question is whether the two components of PEM are connected to specific and different triggers.

It is also a question whether there is a typical timeline for when PEM begins, reaches a peak and subsides. The US Committee on the Diagnostic Criteria for ME/CFS describes PEM as having an immediate onset or occurring within 30 h, but it is outlined that PEM may also develop hours or days after the trigger has ceased (Locher and IOM, 2015). Moreover, the committee describes an unpredictable duration of PEM as it may last for hours, days, weeks, and even months. In accord, a survey demonstrated a large variability in reported onset and duration of PEM, and most of the respondents reported that they sometimes experienced an immediate onset and sometimes a delayed onset (Holtzman et al., 2019). The delay ranged from 1 h to a week, and the duration could last from 1 day to several months. Similar results have been reported by others (Chu et al., 2018; Stussman et al., 2020). Thus, the onset and duration of PEM have no definite pattern and seem to vary both within and between patients.

PEM in relation to experimental exercise tests

Due to the lack of objective signs or a clear and uniform picture of how the patients present PEM and in what triggers PEM, standardized tests have been employed and recommended for diagnostic purpose (Nacul et al., 2021). These tests may be important tools not only in the diagnostic process, but also in generating scientific knowledge that may lead to a shift from symptom-based to biology-based diagnosis. Applying exercise protocols for research purposes may help us to understand biological underlying mechanisms for PEM. This approach may be valuable for diagnostic and research purposes, although for instance the NICE guidelines recommend caution in applying exercise as part of management (NICE, 2021). The controlled conditions of the experimental tests with a follow-up over time, is in keeping with diagnostic recommendations (Nacul et al., 2021).

The exercise tests have several important qualities, including standardization of workload and the possibility of matching patients and healthy controls with regard to differences in for instance gender, age, and physical fitness. Furthermore, the exercise tests can require a workload beyond the physical demand of daily activities. The symptoms induced by exercise will thus reflect a response to an extraordinary and a well-defined physical exertion. We will below present and discuss exercise-induced symptoms when exercise is used as a trigger and compare the responses during and after exercise seen in persons with ME/CFS with healthy controls. Three relatively recent systematic reviews and meta-analyses will be used (summarized in Table 2) together with additional studies published more recently.

The most frequently self-reported responses to exercise in ME/CFS patients, are perceived exertion, fatigue and pain (Table 2). Ratings of perceived exertion (RPE) reflects the person's evaluation of effort during exercise, whereas fatigue will here be understood as the subjective experience in the period following exercise. In a review and meta-analysis of 15 studies, Barhorst and co-workers showed that patients with ME/CFS perceived exercise as more effortful than healthy controls based on the ratings of perceived exertion (RPE) during exercise (Barhorst et al., 2020). This difference remained when controlling for confounding and moderating factors. It is important, however, that only one of the included studies had physical fitness as one of the matching criteria (Oosterwijck et al., 2017). More recently, a higher RPE reported by patients was also observed after matching patients and controls for fitness to achieve comparison at similar relative workload (Cook et al., 2022). Hence, the literature is quite consistent in reporting that patients with ME/CFS report higher exertion of effort during exercise than healthy controls, even when they do not differ in physical fitness.

Another systematic review and meta-analysis by Loy and co-workers examined the changes in fatigue after exercise (Loy et al., 2016). Even though the number of studies and participants was relatively low, they found that exercise triggered a larger increase in fatigue after exercise among patients with ME/CFS compared with controls. The group differences were most pronounced when fatigue was measured 4 h or later after end of exercise. Furthermore, enhanced fatigue was observed following different types of exercise (e.g., intermittent bouts or continuous) and workload (submaximal and maximal) (Sandler et al., 2016). A recent study examined the temporal pattern following two exercise bouts separated by 24 h (Moore et al., 2023). Patients with ME/CFS reported increased fatigue reaching a peak approximately 2 days after the last exercise bout. In contrast, fatigue remained low without any exacerbation among the healthy controls in the post-exercise period. In another recent study Davenport and co-workers found a prevalence of increased fatigue in approximately 60%–65% of the patients with ME/CFS 1 week after exercise (Davenport et al., 2023b). There appears to be a consistent finding that patients

TABLE 2 Responses to exercise in persons with ME/CFS or long Covid compared with controls. Summary of systematic reviews and meta-analyses.

Authors Country	Main purpose and methodology	No included studies and no of participants included in meta-analysis	Types of exercise included	Main results
Barhorst et al. (2020)	Quantify the perceived exertion (RPE) response to acute aerobic exercise involving people with ME/CFS compared with healthy controls	37 studies	Cycle ergometer—continuous increasing (CPET)- from low to high intensity	Elevated RPE in people with ME/CFS during exercise
	Systematic review and meta-analysis	1,086 patients with ME/CFS	Treadmill—continuous increasing- from low to high intensity	
		686 healthy controls	Combined arm-leg ergometer—continuous steady—moderate intensity	
			Cycle ergometer—continuous steady—moderate intensity	
Loy et al. (2016)	Estimate the effect of completing a single bout of exercise on fatigue states in people with ME/CFS compared with health controls	7 studies	Cycle ergometer—continuous increasing (CPET)- from low to high intensity	During exercise fatigue increases more in people with ME/CFS than in healthy controls
	Systematic review and meta-analysis	159 patients with ME/CFS	Treadmill—continuous increasing- from low to high intensity	The effects were heterogeneous between studies
		Number of healthy controls not provided	Arm-leg ergometer—continuous steady—moderate intensity	The largest difference was seen 4 h or later after exercise
			Combined arm-leg ergometer—continuous steady—moderate intensity	
			Treadmill—continuous steady—moderate intensity	
			Handgrip—repeated—moderate	
Barhorst et al. (2022)	Quantify the effect of a single aerobic exercise bout on pain symptom severity in people with ME/CFS and FM	15 studies	Cycle ergometer—continuous increasing (CPET)- from low to high intensity	People with ME/CFS and FM experience small to moderate increases in pain symptom severity after exercise
	Systematic review and meta-analysis	306 patients with ME/CFS	Combined arm-leg ergometer—continuous steady—moderate intensity	
		292 healthy controls	Cycle ergometer—continuous steady—moderate intensity	
			Treadmill—continuous steady—moderate intensity	
			Arm ergometer—continuous—high intensity	
Nelson et al. (2019)	To determine whether there were differences in heart rate parameters between patients with ME/CFS and healthy controls	24 studies[a]	Cycle ergometer—continuous increasing (CPET)- from low to high intensity	Heart rate parameters during exercise differed between people with ME/CFS and healthy controls, indicating reduced vagal and increased sympathetic modulation of heart rate
	Systematic review and meta-analysis	1,129 patients with ME/CFS[a]	Treadmill—continuous increasing- from low to high intensity	
		626 healthy controls[a]	Cycle ergometer—continuous steady—moderate intensity	
			Treadmill—continuous increasing- from low to moderate intensity	

(Continued on following page)

TABLE 2 (*Continued*) **Responses to exercise in persons with ME/CFS or long Covid compared with controls. Summary of systematic reviews and meta-analyses.**

Authors Country	Main purpose and methodology	No included studies and no of participants included in meta-analysis	Types of exercise included	Main results
Durstenfeld et al. (2022)	To estimate the difference in exercise capacity between individuals with and without long COVID symptoms and to elucidate possible mechanisms	3 studies	Cycle ergometer (upright or supine)– continuous increasing (CPET)- from low to high intensity	Aerobic capacity was lower in individuals with long COVID symptoms
	Systematic review and meta-analysis	1,228 individuals with long COVID 932 individuals without long COVID symptoms	Treadmill—continuous increasing- from low to high intensity	Several factors may contribute to decreased aerobic capacity, including deconditioning

[a]Only studies and participants studied with exercise models.
ME/CFS, Myalgic encephalomyelitis/chronic fatigue syndrome.
FM, fibromyalgia.
CPET, cardiopulmonary exercise test.

with ME/CFS differ from healthy controls in developing a long-lasting fatigue following exercise, and that patients need many days to recover to pre-exercise fatigue.

In addition to fatigue and perceived exertion, exercise may induce a substantial increase in pain intensity. A systematic review and meta-analysis from 2022 by Barhorst and co-workers reported that exercise triggered higher pain intensity in patients with either fibromyalgia or ME/CFS compared with healthy controls (Barhorst et al., 2022). Five of the studies only included patients with fibromyalgia. Both patient groups showed a significantly higher pain response compared with the control groups. The largest differences in pain intensity were seen 1–3 days after exercise. Together with the recent finding of increased prevalence of pain in ME/CFS patients in the restitution phase following exercise (Davenport et al., 2023b), the review clearly indicates that exercise triggers an aggravated pain response in ME/CFS patients compared with healthy controls, and similar to that seen in patients with fibromyalgia.

Exercise may also trigger other symptoms, for instance discomfort, sleep disturbances, headache, and neurological symptoms (Sandler et al., 2016; Stussman et al., 2020; Davenport et al., 2023b). Some studies have also used more composite scales for assessment of multiple symptoms, or simply asked for the number of days to recover (Baraniuk et al., 2013; Strand et al., 2019; Hodges et al., 2020; Moore et al., 2023). The results of these studies further support that ME/CFS patients report a higher level of various symptoms post-exercise compared with healthy controls. Two studies examined the patients' own assessment of recovery after the second day with exercise and reported a time for recovery varying from 6 to 12 days (Hodges et al., 2020; Moore et al., 2023). Also, the duration of aggravated symptoms varied from a few days and up to weeks. The variability in symptom duration may partly be due to different exercise models employed, but there seems to be an additional heterogeneity that has other causes.

Biological responses to experimental exercise tests

The experience of PEM reported by patients with ME/CFS after exertion has led to a series of studies to examine possible underlying biological mechanisms and to identify leads for diagnostic criteria. Factors related to responses in the neuroendocrine and cardiovascular systems, as well as metabolism and muscular weakness have been main targets of research. The exercise models are of particular interest to use as triggers of potential biological mediators of the aggravated fatigability and slow restitution. One line of research has been to investigate deviations in the autonomic function, for instance as reflected in neuroendocrine responses. Another has been to examine metabolism and energy consumption (Lim et al., 2020). During exercise the pulmonary and cardiovascular systems need to adjust to match the energy demand of the workload. Hence, the biological responses can be studied in a controlled way and thereby allow comparisons between patients and healthy controls.

A commonly used standardized exercise test is the cardiopulmonary exercise test (CPET) which provides a measure of functional capacity and indicators of how the body adjust and adapt to the increased metabolic demand. The test is typically performed on a cycle ergometer with stepwise increment in workload. Assessments include oxygen uptake, ventilation variables, heart rate, gas exchange, blood lactate and indicators autonomic responses (Lim et al., 2020). Oxygen uptake will increase as workload increases, until the cardiopulmonary system no longer can match the energy demand of the working muscles. With the use of cycle ergometers, the energy requirements will be determined by the chosen workload of the bike, and thus the same for all since the individual technique play a negligible role for this kind of exercise (Åstrand et al., 2003). Hence, at submaximal workload, when the cardiopulmonary system is able to provide sufficient amount of oxygen to the muscles, two persons exercising at the same absolute workload will have almost equal oxygen uptake. Other parameters may vary, such as frequency of ventilation and heart rate. At higher workloads, less fit individuals may approach or exceed their cardiopulmonary capacity to provide oxygen to the muscles and oxygen uptake will no longer be sufficient. Anaerobic energy sources will gradually be used, resulting in a steeper rise for instance in blood concentrations of lactate and CO_2. These physiological responses form the basis for using CPETs to investigate deviations in the cardiopulmonary system or muscular metabolism (Adachi, 2017).

Although two persons have the same energy requirement and oxygen uptake at a given submaximal workload, a less fit individual with lower maximal aerobic capacity, will exercise at a higher relative intensity compared with his maximal capacity. Thus, exercise intensity is often expressed as the percentage of their maximal oxygen uptake. A higher relative workload is typically accompanied by for instance a higher ventilation rate, higher heart rate and higher lactate concentration in blood (Åstrand et al., 2003). Comparisons of various physiological responses to exercise must therefore be done at similar relative workload, or ensure a careful matching of cases and control, including physical fitness.

Unfortunately, differences in physical fitness often insufficiently taken into consideration in studies comparing responses to exercise in ME/CFS patients and healthy controls. Some studies include exercise frequency (e.g., less than twice a week (Lien et al., 2019) or less than 30 min per week (Davenport et al., 2023b) to reduce the potential effect of different fitness. However, as shown in the two reviews in 2020 and 2022 by Barhorst and coworkers, almost no studies matched the participants on physical fitness (Barhorst et al., 2020; Barhorst et al., 2022). Hence, the results are difficult to interpret, as inactivity can lead to considerable decline in physical fitness and altered responses during exercise (Saltin et al., 1968).

In 2022 Cook and co-workers published a paper which examined exercise responses in fitness-matched patients with ME/CFS and healthy controls (Cook et al., 2022). In this well-controlled study, they found that most differences between healthy and controls disappeared after matching for physical fitness. Of particular interest is the lack of differences in cardiometabolic responses. However, the patients reported a higher RPE and had a lower respiration frequency and higher tidal volume. These observations indicate that several of the differences previously reported during exercise, can be explained by lower aerobic fitness among patients with ME/CFS compared with controls.

Over the last decade, a particular interest has been given to an exercise model involving two CPETs repeated within 1–3 days. By introducing a second exercise bout in the recovery period from exercise at Day 1, the idea is that deviations in fatigability or underlying biological responses might be more prominent and thus detectable. One advantage is that in this model the responses to exercise on the second day are compared with each individual's responses the first test day. To some extent, this reduces the problems with difficulty in matching on fitness level. Lim and co-workers reviewed the studies exploring CPET on repeated days in ME/CFS patients and controls (Lim et al., 2020). Although only five studies with 98 patients and 51 healthy controls were included, their meta-analysis showed that there were some important group differences in the changes from Day 1 to Day 2. Despite similar reduction in workload as controls on Day 2, the patients displayed a larger decline in oxygen consumption the second day compared with their measures on Day 1. They also found that the patients had a clearly reduced workload at the point when hyperventilation starts compared with controls. This suggests an earlier onset of anaerobic metabolism among the patients on Day 2, which is consistent with the finding of reduced workload for the onset of blood lactate on Day 2 (Lien et al., 2019). These observations can hardly be used for diagnostic purposes but suggest that the first day of exercise induces an altered metabolism in patients the following days. To what extent the altered responses are generalized or restricted to the exercising muscles, is unknown. However, these observations suggest that the CPET exercise model may be valuable in further investigations of metabolism in ME/CFS.

Muscular metabolism during exercise depends heavily on cardiovascular responses. Nelson and co-workers made a review and meta-analysis of heart rate parameters in relation to exercise and other triggers (Nelson et al., 2019). They found that patients with ME/CFS had deviations in numerous heart rate parameters, suggesting reduced vagal and increased sympathetic modulation of heart rate. A recent study of heart rate parameters measured before, during and after exercise indicate diminished cardiac parasympathetic and sympathetic activation during supine rest and exercise in patients with ME/CFS (Van Oosterwijck et al., 2021). Furthermore, they observed a reduced parasympathetic reactivation after exercise among patients compared with controls. In blood samples obtained before, during and after exercise, Strahler and coworkers found decreased level of adrenaline during exercise in patients (Strahler et al., 2013). In samples taken before or 30 min after exercise, the levels were not different from healthy controls.

Taken together, the studies of repeated CPETs indicate that the muscular metabolism and autonomic response are altered in patients with ME/CFS. Furthermore, exercise appears to induce a prolonged decrease in muscular force or maximal workload. These responses may correspond to patients' experiences of increased exertion.

Discussion

It is widely accepted that PEM is a hallmark of ME/CFS and that a broad range of events or activities can trigger PEM. The patients describe PEM with a wide variety of words and report that it lasts long, even up to months. This variation leads to challenges when comparing and synthesizing patients' experiences and expressions of PEM across patients and studies. As pointed out by Jason and co-workers slight differences in wording may have an impact on the results and conclusions (Jason et al., 2015b). Furthermore, differentiating between tiredness, fatigue and exhaustion may be of importance. This is of relevance for the qualitative as well as the questionnaire-based studies. Furthermore, the studies rarely define what they mean by PEM. It seems that the respondents are expected to have *a priori* understanding of the phenomenon. One way to go might be to distinguish more clearly between triggers that patients have in terms of load from their daily activities and extraordinary exertions such as intense bouts of exercise. Another approach might be to emphasize and discriminate between the two domains of PEM (generalized and muscular fatigue) or the three levels used by patients (tiredness, fatigue, and exhaustion) in future studies.

So far, research has not led to identification of underlying mechanisms of PEM. Interestingly, PEM is not unique and specific for ME/CFS but is quite frequent also in other chronic diseases (Nacul et al., 2021). Studies show relatively high prevalence of PEM-like symptoms in for instance persons with multiple sclerosis or long COVID (Morris and Maes, 2013; Learmonth et al., 2014; Hodges et al., 2018; Jason and Dorri, 2022). The descriptors used by other patient groups than ME/CFS are also similar, but the concept of PEM is not coined to the disease and not part of the diagnostic criteria for the other diseases. The rapidly emerging knowledge about individuals with long COVID symptoms may be of particular interest. These patients report similar perceptions of fatigue as patients with ME/CFS as well as some of the same indications of altered exercise responses (Wong and Weitzer, 2021; Joseph et al., 2023). It has been argued that the altered exercise responses may be caused by deconditioning (Rinaldo et al., 2021) and a recent brief report indicates that the altered responses may be normalized within 2 years (Rinaldo et al., 2023). Hence, also for individuals with long COVID symptoms, it is still uncertain whether the reported deviations in exercise responses is connected to the clinical condition and the symptoms, or if they can be simply explained by deconditioning (Durstenfeld et al., 2022).

It is also intriguing that symptoms very similar to PEM are typical for overtraining syndrome of athletes (Meeusen et al., 2013). Similarly, to patients with ME/CFS, they report elevated perceived exertion and fatigue during exercise. However, the magnitude of the responses is somewhat lower, and PEM attenuates faster. The causes of these differences are unknown, but a possible explanation may be related to the degree of severity of fatigue or disease. Overtrained athletes also show attenuated responses in adrenaline and noradrenaline and thus indicate altered neuroendocrinological responses (Armstrong et al., 2021). The similarities across various groups and conditions may be useful in further examination and research of underlying nature of PEM as distinct from everyday responses to activities.

The finding that PEM may be composed of two different constructs, generalized fatigue and muscle fatigue (McManimen et al., 2019), could be an important clue to enhance our understanding of PEM. An obvious hypothesis is that the self-reported muscle fatigue of PEM is closely related to a decrease in the muscular strength, which might be measured as maximal force. It is well known that the ability to generate force declines during an exercise session (Vøllestad, 1997). This response may be due to changes in the muscles capacity to generate force (muscular mechanisms), or it may be due to a decreased ability to drive the muscle to its full capacity (motor control mechanisms). It seems important that these different responses are studied also in ME/CFS following exercise, to help in understanding the mechanisms involved in at least the muscular component of PEM. It would also be of interest to compare the responses of not only ME/CFS and healthy controls but include other chronic diseases and overtraining syndrome of athletes. Furthermore, to our knowledge, no one has examined if for instance the presence or level of the two PEM constructs (muscle-specific fatigue and generalized fatigue) are closely linked. Or could it be that the construct of muscle-specific fatigue is particularly triggered by physical exertion, with less impact on generalized fatigue?

There are two striking post-exercise differences between patients with ME/CFS and healthy controls: The patients have a higher prevalence of symptoms and higher intensity of symptoms in the days following exercise. It is interesting, and somewhat surprising, that we have limited data on biological factors and processes in the restitution phase. The repeated CPETs performed on successive days show some deviations (e.g., in workload and lactate accumulation) in the exercise responses on Day 2 (Lien et al., 2019; Hodges et al., 2020). Thus, there is a need to conduct more comprehensive studies to examine for instance post-exercise changes in autonomic responses and in the ability of muscles to generate force. Apart from the studies employing repeated CPETs, the exercise models have predominantly focused on self-reported symptoms in the post-exercise period. Based on the patients' descriptions of days and weeks to recover from exercise, research of physiological responses should probably be extended to capture the restitution phase. The focus could then shift from what triggers PEM to why does PEM triggered by exercise show a slower restitution in ME/CFS patients than in healthy controls.

As shown above the symptoms described by patients with ME/CFS may take different forms and be expressed in different ways. From the words used by the patients, it seems that the word "tired" or "tiredness" could be used to describe a normal response to an exertion, experienced by healthy persons. In a situation when ME/CFS has been established, "fatigue" seems to be a common term to denote the every-day experience without prior triggers (Olson et al., 2015). When these persons exercise, they experience a combination of fatigue and tiredness, while PEM is the prolonged exacerbation seen in the post-exercise period. Such distinctions between the terms for fatigue, may create a better framework for research and clinical communication.

The forms and descriptions of triggers of PEM vary as well. Since patients with ME/CFS typically reduce their physical activity level, their reference frame will often be daily life and triggers include for instance household chores and social activities (Stussman et al., 2020). Yet, the research searching for biological causes of PEM, uses intense exercise such as CPET as triggers. This may restrict our knowledge generation to the responses of extraordinary exertions, with uncertain relevance for understanding PEM induced by daily activities. It is also important to emphasize that studies including exercise models, and in particular CPET, require eligible participants that are able to complete the expected work. Hence, these models will probably include a selected group of patients, either with a lighter disease burden or patients in a recovery phase. Furthermore, the kind of symptoms studied in the post exertional period to assess PEM, are rather narrow compared with the wide spectrum expressed by the patients in interviews. We believe these aspects and possible limitations of experimental exercise tests need attention in future research.

In summary, there are some indications that exercise induces symptoms and metabolic or neuroendocrine responses in patients with ME/CFS that differ from what is seen in healthy individuals. However, similar deviations are also reported for other patient groups and overtrained athletes. The relevance of these deviations for case definition and diagnostic purposes thus needs further investigation. To enhance our understanding of underlying mechanisms of PEM or ME/CFS as a disease, we believe it is particularly important to look more closely into the processes occurring in the restitution period following exercise tests, as PEM reaches the peak in this phase.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary Material, further inquiries can be directed to the corresponding author.

Author contributions

NV: Conceptualization, Writing–original draft, Writing–review and editing. AM: Conceptualization, Writing–original draft, Writing–review and editing.

Funding

The author(s) declare that no financial support was received for the research, authorship, and/or publication of this article.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

References

Adachi, H. (2017). Cardiopulmonary exercise test. *Int. Heart J.* 58 (5), 654–665. doi:10.1536/ihj.17-264

Armstrong, L. E., Bergeron, M. F., Lee, E. C., Mershon, J. E., and Armstrong, E. M. (2021). Overtraining syndrome as a complex systems phenomenon. *Front. Netw. Physiol.* 1, 794392. doi:10.3389/fnetp.2021.794392

Åstrand, P. O., Rodahl, K., Dahl, H. A., and Strømme, S. B. (2003). *Textbook of work Physiology. Physiological bases of exercise*. 4th ed. Champaign, Ill: Human Kinetics.

Baraniuk, J. N., Adewuyi, O., Merck, S. J., Ali, M., Ravindran, M. K., Timbol, C. R., et al. (2013). A Chronic Fatigue Syndrome (CFS) severity score based on case designation criteria. *Am. J. Transl. Res.* 5 (1), 53–68.

Barhorst, E. E., Andrae, W. E., Rayne, T. J., Falvo, M. J., Cook, D. B., and Lindheimer, J. B. (2020). Elevated perceived exertion in people with myalgic encephalomyelitis/chronic fatigue syndrome and fibromyalgia: a meta-analysis. *Med. Sci. Sports Exerc* 52 (12), 2615–2627. doi:10.1249/mss.0000000000002421

Barhorst, E. E., Boruch, A. E., Cook, D. B., and Lindheimer, J. B. (2022). Pain-related post-exertional malaise in myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) and fibromyalgia: a systematic review and three-level meta-analysis. *Pain Med.* 23 (6), 1144–1157. doi:10.1093/pm/pnab308

Brown, A. A., and Jason, L. A. (2014). Validating a measure of myalgic encephalomyelitis/chronic fatigue syndrome symptomatology. *Fatigue Biomed. Health & Behav.* 2 (3), 132–152. doi:10.1080/21641846.2014.928014

Carruthers, B. M., van de Sande, M. I., De Meirleir, K. L., Klimas, N. G., Broderick, G., Mitchell, T., et al. (2011). Myalgic encephalomyelitis: international consensus criteria. *J. Intern Med.* 270 (4), 327–338. doi:10.1111/j.1365-2796.2011.02428.x

Chu, L., Valencia, I. J., Garvert, D. W., and Montoya, J. G. (2018). Deconstructing post-exertional malaise in myalgic encephalomyelitis/chronic fatigue syndrome: a patient-centered, cross-sectional survey. *Plos One* 13 (6), e0197811. doi:10.1371/journal.pone.0197811

Cook, D. B., VanRiper, S., Dougherty, R. J., Lindheimer, J. B., Falvo, M. J., Chen, Y., et al. (2022). Cardiopulmonary, metabolic, and perceptual responses during exercise in myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS): a multi-site clinical assessment of ME/CFS (mcam) sub-study. *PLoS One* 17 (3), e0265315. doi:10.1371/journal.pone.0265315

Cotler, J., Holtzman, C., Dudun, C., and Jason, L. A. (2018). A brief questionnaire to assess post-exertional malaise. *Diagn. (Basel)* 8 (3), 66. doi:10.3390/diagnostics8030066

Davenport, T. E., Chu, L., Stevens, S. R., Stevens, J., Snell, C. R., and Van Ness, J. M. (2023b). Two symptoms can accurately identify post-exertional malaise in myalgic encephalomyelitis/chronic fatigue syndrome. *Work* 74 (4), 1199–1213. doi:10.3233/wor-220554

Davenport, T. E., Stevens, S. R., Stevens, J., Snell, C. R., and Van Ness, J. M. (2023a). Development and measurement properties of the PEM/PESE activity questionnaire (PAQ). *Work* 74 (4), 1187–1197. doi:10.3233/WOR-220553

Durstenfeld, M. S., Sun, K., Tahir, P., Peluso, M. J., Deeks, S. G., Aras, M. A., et al. (2022). Use of cardiopulmonary exercise testing to evaluate long COVID-19 symptoms in adults: a systematic review and meta-analysis. *JAMA Netw. Open* 5 (10), e2236057. doi:10.1001/jamanetworkopen.2022.36057

Fukuda, K., Straus, S. E., Hickie, I., Sharpe, M. C., Dobbins, J. G., and Komaroff, A. (1994). The chronic fatigue syndrome: a comprehensive approach to its definition and study. International Chronic Fatigue Syndrome Study Group. *Ann. Intern Med.* 121 (12), 953–959. doi:10.7326/0003-4819-121-12-199412150-00009

Hartle, M., Bateman, L., and Vernon, S. D. (2021). Dissecting the nature of post-exertional malaise. *Fatigue (Abingdon, Eng.* 9 (1), 33–44. doi:10.1080/21641846.2021.1905415

Hodges, L., Nielsen, T., Cochrane, D., and Baken, D. (2020). The physiological time line of post-exertional malaise in Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS). *Transl. Sports Med.* 3 (3), 243–249. doi:10.1002/tsm2.133

Hodges, L. D., Nielsen, T., and Baken, D. (2018). Physiological measures in participants with chronic fatigue syndrome, multiple sclerosis and healthy controls following repeated exercise: a pilot study. *Clin. Physiol. Funct. Imaging* 38 (4), 639–644. doi:10.1111/cpf.12460

Holtzman, C. S., Bhatia, S., Cotler, J., and Jason, L. A. (2019). Assessment of post-exertional malaise (PEM) in patients with myalgic encephalomyelitis (ME) and chronic fatigue syndrome (CFS): a patient-driven survey. *Diagn. (Basel)* 9 (1), 26. doi:10.3390/diagnostics9010026

Jason, L. A., and Dorri, J. A. (2022). ME/CFS and post-exertional malaise among patients with long COVID. *Neurol. Int.* 15 (1), 1–11. doi:10.3390/neurolint15010001

Jason, L. A., Evans, M., So, S., Scott, J., and Brown, A. (2015b). Problems in defining post-exertional malaise. *J. Prev. Interv. Community* 43 (1), 20–31. doi:10.1080/10852352.2014.973239

Jason, L. A., McManimen, S. L., Sunnquist, M., and Holtzman, C. S. (2018). Patient perceptions of post exertional malaise. *Fatigue Biomed. Health & Behav.* 6 (2), 92–105. doi:10.1080/21641846.2018.1453265

Jason, L. A., and Sunnquist, M. (2018). The development of the DePaul symptom questionnaire: original, expanded, brief, and pediatric versions. *Front. Pediatr.* 6, 330. doi:10.3389/fped.2018.00330

Jason, L. A., Sunnquist, M., Brown, A., Furst, J., Cid, M., Farietta, J., et al. (2015a). Factor analysis of the DePaul symptom questionnaire: identifying core domains. *J. Neurol. Neurobiol.* 1 (4). doi:10.16966/2379-7150.114

Joseph, P., Singh, I., Oliveira, R., Capone, C. A., Mullen, M. P., Cook, D. B., et al. (2023). Exercise pathophysiology in myalgic encephalomyelitis/chronic fatigue syndrome and postacute sequelae of SARS-CoV-2: more in common than not? *Chest* 164 (3), 717–726. doi:10.1016/j.chest.2023.03.049

Krabbe, S. H., Mengshoel, A. M., Schroder Bjorbaekmo, W., Sveen, U., and Groven, K. S. (2022). Bodies in lockdown: young women's narratives of falling severely ill with ME/CFS during childhood and adolescence. *Health Care Women Int.* 2022, 1–23. doi:10.1080/07399332.2022.2043862

Learmonth, Y. C., Paul, L., McFadyen, A. K., Marshall-McKenna, R., Mattison, P., Miller, L., et al. (2014). Short-term effect of aerobic exercise on symptoms in multiple sclerosis and chronic fatigue syndrome: a pilot study. *Int. J. MS Care* 16 (2), 76–82. doi:10.7224/1537-2073.2013-005

Lien, K., Johansen, B., Veierød, M. B., Haslestad, A. S., Bøhn, S. K., Melsom, M. N., et al. (2019). Abnormal blood lactate accumulation during repeated exercise testing in myalgic encephalomyelitis/chronic fatigue syndrome. *Physiol. Rep.* 7 (11), e14138. doi:10.14814/phy2.14138

Lim, E. J., Kang, E. B., Jang, E. S., and Son, C. G. (2020). The prospects of the two-day cardiopulmonary exercise test (CPET) in ME/CFS patients: a meta-analysis. *J. Clin. Med.* 9 (12), 4040. doi:10.3390/jcm9124040

Locher, L., and IOM (2015). *Beyond myalgic encephalomyelitis/chronic fatigue syndrome: redefining an illness*. Washington, District of Columbia: The National Academies Press.

Loy, B. D., O'Connor, P. J., and Dishman, R. K. (2016). Effect of acute exercise on fatigue in people with ME/CFS/SEID: a meta-analysis. *Med. Sci. Sports Exerc* 48 (10), 2003–2012. doi:10.1249/MSS.0000000000000990

May, M., Milrad, S. F., Perdomo, D. M., Czaja, S. J., Fletcher, M. A., Jutagir, D. R., et al. (2020). Post-exertional malaise is associated with greater symptom burden and psychological distress in patients diagnosed with Chronic Fatigue Syndrome. *J. Psychosom. Res.* 129, 109893. doi:10.1016/j.jpsychores.2019.109893

McManimen, S. L., Sunnquist, M. L., and Jason, L. A. (2019). Deconstructing post-exertional malaise: an exploratory factor analysis. *J. Health Psychol.* 24 (2), 188–198. doi:10.1177/1359105316664139

Meeusen, R., Duclos, M., Foster, C., Fry, A., Gleeson, M., Nieman, D., et al. (2013). Prevention, diagnosis, and treatment of the overtraining syndrome: joint consensus statement of the European College of Sport Science and the American College of Sports Medicine. *Med. Sci. Sports Exerc* 45 (1), 186–205. doi:10.1249/MSS.0b013e318279a10a

Moore, G. E., Keller, B. A., Stevens, J., Mao, X., Stevens, S. R., Chia, J. K., et al. (2023). Recovery from exercise in persons with myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS). *Med. Kaunas.* 59 (3), 571. doi:10.3390/medicina59030571

Morris, G., and Maes, M. (2013). Myalgic encephalomyelitis/chronic fatigue syndrome and encephalomyelitis disseminata/multiple sclerosis show remarkable levels of similarity in phenomenology and neuroimmune characteristics. *BMC Med.* 11, 205. doi:10.1186/1741-7015-11-205

Nacul, L., Authier, F. J., Scheibenbogen, C., Lorusso, L., Helland, I. B., Martin, J. A., et al. (2021). European network on myalgic encephalomyelitis/chronic fatigue syndrome (EUROMENE): expert consensus on the diagnosis, service provision, and care of people with ME/CFS in europe. *Med. Kaunas.* 57 (5), 510. doi:10.3390/medicina57050510

Nelson, M. J., Bahl, J. S., Buckley, J. D., Thomson, R. L., and Davison, K. (2019). Evidence of altered cardiac autonomic regulation in myalgic encephalomyelitis/chronic fatigue syndrome: a systematic review and meta-analysis. *Med. Baltim.* 98 (43), e17600. doi:10.1097/md.0000000000017600

NICE (2021). *Myalgic encephalomyelitis (or encephalopathy)/chronic fatigue syndrome: diagnosis and management*. NICE guideline [NG206]. Available at: www.https://www.nice.org.uk/guidance/ng206/resources (Accessed October 29, 2021)

Olson, K., Zimka, O., and Stein, E. (2015). The nature of fatigue in chronic fatigue syndrome. *Qual. Health Res.* 25 (10), 1410–1422. doi:10.1177/1049732315573954

Oosterwijck, J. V., Marusic, U., De Wandele, I., Paul, L., Meeus, M., Moorkens, G., et al. (2017). The role of autonomic function in exercise-induced endogenous analgesia: a case-control study in myalgic encephalomyelitis/chronic fatigue syndrome and healthy people. *Pain Physician* 20 (3), E389–E399.

Parslow, R. M., Anderson, N., Byrne, D., Shaw, A., Haywood, K. L., and Crawley, E. (2018). Adolescent's descriptions of fatigue, fluctuation and payback in chronic fatigue syndrome/myalgic encephalopathy (CFS/ME): interviews with adolescents and parents. *BMJ Paediatr. Open* 2 (1), e000281. doi:10.1136/bmjpo-2018-000281

Rinaldo, R. F., Mondoni, M., Baccelli, A., Marchetti, F., Re, B., Degrassi, M., et al. (2023). SARS-CoV-2 infection sequelae on exercise response: persistent or reversible? A 2-year perspective. *ERJ Open Res.* 9 (4), 00234-2023. doi:10.1183/23120541.00234-2023

Rinaldo, R. F., Mondoni, M., Parazzini, E. M., Pitari, F., Brambilla, E., Luraschi, S., et al. (2021). Deconditioning as main mechanism of impaired exercise response in COVID-19 survivors. *Eur. Respir. J.* 58 (2), 2100870. doi:10.1183/13993003.00870-2021

Saltin, B., Blomqvist, G., Mitchell, J. H., Johnson, R. L., Jr., Wildenthal, K., Chapman, C. B., et al. (1968). A longitudinal study of adaptive changes in oxygen transport and body composition. *Circulation* 38 (5), Vii1–78. doi:10.1161/01.cir.38.5s7.vii-1

Sandler, C. X., Lloyd, A. R., and Barry, B. K. (2016). Fatigue exacerbation by interval or continuous exercise in chronic fatigue syndrome. *Med. Sci. Sports Exerc* 48 (10), 1875–1885. doi:10.1249/mss.0000000000000983

Sharpe, M. C., Archard, L. C., Banatvala, J. E., Borysiewicz, L. K., Clare, A. W., David, A., et al. (1991). A report--chronic fatigue syndrome: guidelines for research. *J. R. Soc. Med.* 84 (2), 118–121. doi:10.1177/014107689108400224

Strahler, J., Fischer, S., Nater, U. M., Ehlert, U., and Gaab, J. (2013). Norepinephrine and epinephrine responses to physiological and pharmacological stimulation in chronic fatigue syndrome. *Biol. Psychol.* 94 (1), 160–166. doi:10.1016/j.biopsycho.2013.06.002

Strand, E. B., Mengshoel, A. M., Sandvik, L., Helland, I. B., Abraham, S., and Nes, L. S. (2019). Pain is associated with reduced quality of life and functional status in patients with Myalgic Encephalomyelitis/Chronic Fatigue Syndrome. *Scand. J. Pain* 19 (1), 61–72. doi:10.1515/sjpain-2018-0095

Strassheim, V., Newton, J. L., and Collins, T. (2021). Experiences of living with severe chronic fatigue syndrome/myalgic encephalomyelitis. *Healthc. (Basel).* 9 (2), 168. doi:10.3390/healthcare9020168

Stussman, B., Williams, A., Snow, J., Gavin, A., Scott, R., Nath, A., et al. (2020). Characterization of post-exertional malaise in patients with myalgic encephalomyelitis/chronic fatigue syndrome. *Front. Neurol.* 11, 1025. doi:10.3389/fneur.2020.01025

Van Oosterwijck, J., Marusic, U., De Wandele, I., Meeus, M., Paul, L., Lambrecht, L., et al. (2021). Reduced parasympathetic reactivation during recovery from exercise in myalgic encephalomyelitis/chronic fatigue syndrome. *J. Clin. Med.* 10 (19), 4527. doi:10.3390/jcm10194527

Vøllestad, N. K. (1997). Measurement of human muscle fatigue. *J. Neurosci. Methods* 74 (2), 219–227. doi:10.1016/s0165-0270(97)02251-6

Wong, T. L., and Weitzer, D. J. (2021). Long COVID and myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS)-A systemic review and comparison of clinical presentation and symptomatology. *Med. Kaunas.* 57 (5), 418. doi:10.3390/medicina57050418

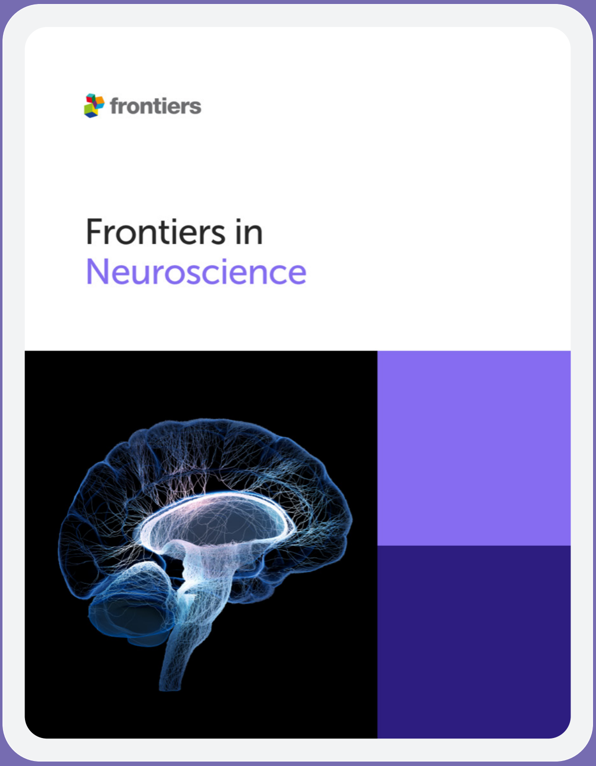
Frontiers in
Neuroscience

Provides a holistic understanding of brain function from genes to behavior

Part of the most cited neuroscience journal series which explores the brain - from the new eras of causation and anatomical neurosciences to neuroeconomics and neuroenergetics.

Discover the latest Research Topics

See more →



frontiers

Frontiers in
Neuroscience

Frontiers

Avenue du Tribunal-Fédéral 34
1005 Lausanne, Switzerland
frontiersin.org

Contact us

+41 (0)21 510 17 00
frontiersin.org/about/contact