Neuropathology and Neurological Manifestations in ME/CFS and Long COVID with focus on Post-Exertional Symptom Exacerbation: a Literature Review

Abstract

A significant proportion of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infected people develop long-lasting complaints and are diagnosed with Long COVID. Common symptoms reported by Long COVID patients include fatigue, post-exertional symptom exacerbation (PESE) and cognitive dysfunction. Research shows that COVID-19 patients with an acute infection demonstrate abnormalities in the central nervous system (CNS), which could potentially lead to chronic neurological deficits and Long COVID symptoms. However, underlying neuropathology remains unclear. A large subgroup of Long COVID patients resembles patients with myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) in terms of symptoms and, in many cases, the infectious trigger. A core symptom of ME/CFS is PESE, which is uncommon in other fatiguing illnesses, but frequently observed in Long COVID patients. Due to the significant symptom overlap and lack of research on PESE, neuropathology associated with Long COVID and ME/CFS in general as well as after physical exertion was investigated. Findings indicate that ME/CFS seems to be associated with various CNS abnormalities which are also proposed for Long COVID. These include neuroinflammation, reduced brain volume, cerebral hypoperfusion and cerebral spinal fluid abnormalities. Furthermore, exercise seems to result in exacerbation of neuropathology and symptoms in ME/CFS, in turn resulting in an increase in neuronal activity required to complete a task. This is demonstrated by increased brain activity throughout various brain regions following exercise. Importantly, Long COVID seems to consist of different subgroups of which a large part fulfills the diagnostic criteria for ME/CFS. Therefore, evidence-based management principles of ME/CFS patients may be transferable to this subgroup of Long COVID patients. This requires further research, which should take subgroups of Long COVID into consideration.

Layman summary

Many of the people that get infected with the Coronavirus develop long-lasting complaints and are diagnosed with Long COVID after the acute infection is gone. These complains can last several months or years and include fatigue, cognitive impairment, sleeping problems and post-exertional symptom exacerbation (PESE). Research shows that COVID-19 patients with an acute infection have abnormalities in their brain, which could potentially lead to long-lasting neurological problems and symptoms. However, although many researchers are trying to uncover the underlying mechanisms, Long COVID is still very new. The underlying mechanisms causing and maintaining the disease are therefore unclear. A large group of Long COVID patients resembles patients with myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) in terms of symptoms and, in many cases, the viral trigger of the disease. A core symptom of ME/CFS is PESE, which is uncommon in other fatiguing illnesses, but frequently seen in Long COVID patients. PESE involves an abnormal worsening of symptoms and cognitive and physical functions after any type of normal activity. Because of the large symptom overlap and lack of knowledge regarding PESE, underlying brain-mechanisms associated with Long COVID and ME/CFS in general as well as after physical exertion were investigated. The findings of this review indicate that ME/CFS is associated with several abnormalities in the brain which are also proposed to be present in Long COVID patients. Such abnormalities include inflammation of the brain, shrinkage of the brain and less blood flow to the brain. After physical exertion, these abnormalities might be exacerbated in ME/CFS patients. This results in a brain that needs to work harder than the healthy brain to complete a task. It is demonstrated by increased brain activity in several brain regions after physical exertion and general symptom exacerbation. Since the two diseases seem to have a large overlap in symptoms and underlying brain-mechanisms, this finding might apply to patients with long COVID as well. Importantly, Long COVID seems to consist of different subgroups of which a large part fulfills the criteria for ME/CFS. Treatment and therapy for ME/CFS patients is therefore likely transferable to this subgroup of Long COVID patients, with explicit attention towards the PESE phenomenon. More research is needed to uncover the underlying mechanisms as well as correct treatment approach of these diseases. Future research should take subgroups of Long COVID into account.

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1. Introduction

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is a virus which causes the coronavirus disease 19 (COVID-19) infecting primarily the lungs, yet other organs are also affected (Lou et al., 2021). Long COVID, or post-acute COVID-19 syndrome (PACS), is a condition resulting from an infection with SARS-CoV-2. It is typically diagnosed when symptoms persist or develop for at least three months after onset of the SARS-CoV-2 infection, which is the case in 10%-30% of SARS-CoV-2 infected people (Shah et al., 2021). Besides the large burden this disease puts on patients, it has a substantial societal and economic impact (Rajan et al., 2021), all of which makes it crucial to disentangle its underlying mechanisms. Symptoms may occur during or following the acute infection and tend to be unrelated to the initial disease severity (Davis et al., 2021; Townsend et al., 2020). Common symptoms reported after six months include fatigue, post exertional malaise (PEM)/post-exertional symptom exacerbation (PESE), cognitive dysfunction, dyspnea, and non-refreshing sleep (Davis et al., 2021; Michelen et al., 2021; Shah et al., 2021) (Table 1). Research shows that COVID-19 patients with an acute infection demonstrate abnormalities of the central nervous system (CNS) such as changes in brain volume and neuroinflammation (Douaud et al., 2022; Lee et al., 2022; Matschke et al., 2020; Schurink et al., 2020b), potentially causing long-term neurological deficits contributing to Long COVID symptoms. Despite the rapid development of Long COVID research, underlying mechanisms remain unsolved and there is, to date, no effective treatment.

Although consensus is still lacking, different subgroups of Long COVID have been proposed based on current literature (Munblit et al., 2022; Reese et al., 2022; Yong & Liu, 2022). A large subgroup of Long COVID patients experience reduced physical activity and exercise capacity as well as PESE (Durstenfeld et al., 2022; Tabacof et al., 2022; Twomey et al., 2021). This, in addition to the common symptoms mentioned above has large overlap with myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) (Jason et al., 2021; Jason & Dorri, 2022; Sukocheva et al., 2022; Wong & Weitzer, 2021), which is a chronic, multi-systemic disease characterized by disabling fatigue that is not improved by rest and accompanied by symptoms associated with immune, autonomic and cognitive dysfunction (Institute of Medicine, 2015) (Table 1). ME/CFS is a complex disease, often triggered by an infection such as herpesviruses (e.g., Epstein-Barr virus or human herpesviruses 6A and 6B (HHV-6)) or SARS-CoV-1 and is classified as a neurological disorder by World Health Organization (WHO) (Institute of Medicine, 2015; Komaroff & Lipkin, 2021; World Health Organization, 2022). PESE is a core symptom of the ME/CFS and is synonymous with PEM, but arguably a better description of this symptom. PESE is uncommon in other fatiguing illnesses, it is not a result of deconditioning, and it involves an abnormal worsening of symptoms and deterioration of both cognitive and physical functions (Chu et al., 2018). It is triggered by ordinary mental or physical activity or sensory stimuli, often a delayed, disproportionate response to the exertion and can last days, weeks or even months. As in ME/CFS, there is currently no consensus on underlying pathology of this phenomenon in Long COVID patients, although various biomedical- and provocation studies have identified an abnormal response to exertion in ME/CFS patients (Davenport et al., 2019). PESE has serious consequences for daily activity and treatment approach and is often describe it as the most debilitating aspect of the disease (Brown & Jason, 2020). In Long COVID research, this phenomenon is often overlooked, which may have adverse consequences for the validity and applicability of results across different Long COVID subgroups. Another frequently observed phenomenon in ME/CFS is an increase in symptoms while maintaining an upright position and a relief of symptoms when lying down. This phenomenon is called orthostatic

intolerance and has also been described in people with Long COVID (Amekran et al., 2022; Davis et al., 2021; Franco et al., 2022; van Campen & Visser, 2022). Although unraveling the underlying neurobiology of these core symptoms may be crucial to disentangle disease mechanisms, knowledge remains scarce.

Table 1: *Summary of the main physical and neurological symptoms in ME/CFS and Long COVID.*

Domain	ME/CFS	Long COVID
Physical symptoms		
PESE	✓	✓
Disabling fatigue	✓	✓
Muscle pain	✓	✓
Joint pain	✓	✓
Gastrointestinal symptoms	✓	?
Shortness of breath		✓
Flu-like symptoms	✓	✓
Neurological/neurocognitive symptoms		
Cognitive impairment/brain fog	✓	✓
- Memory impairment	✓	✓
- Concentration difficulties	✓	✓
- Attention problems	✓	✓
- Information processing difficulties	✓	✓
Sleeping disturbances	✓	✓
Anosmia		✓
Dysgeusia		✓
Orthostatic intolerance	✓	✓

The significant symptom-overlap and, in many cases, similar trigger of the two diseases provides ground for further investigation of potentially common underlying mechanisms. As Long COVID research is growing rapidly and previous findings in ME/CFS might be unknown to Long COVID researchers, it is beneficial to investigate potential similarities. This could lead to knowledge transfer, beneficial for research as well as treatment in ME/CFS and Long COVID. Possible mechanisms causing many of the mentioned symptoms, particularly PESE, orthostatic intolerance and cognitive impairments, might be explained by neuropathology demonstrated in both ME/CFS and Long COVID patients. For this reason, the aim of this review is to provide an overview of neuropathology associated with ME/CFS and Long COVID in general as well as after physical exertion. In addition, it will be explored whether the knowledge and treatment approach of the PESE phenomenon and observations of neuropathology following physical exertion in ME/CFS are transferable to Long COVID.

2. ME/CFS and Long COVID triggers and neuropathology

Although ME/CFS has been observed for many decades, its underlying biology remains unsolved and not well understood. A biomarker for the disease is still missing, however, numerous abnormalities have been identified, including central nervous system pathology (Maksoud et al., 2020). In Long COVID patients, similar findings as well as diagnostic challenges are present (Komaroff & Lipkin, 2021).

2.1 Triggers

ME/CFS can be triggered by physiological stressors such as injury, exposure to toxins, surgery, or the cause is unknown (Institute of Medicine, 2015). Moreover, patients often report that their symptoms were initiated by a viral infection, including herpes viruses (e.g., Epstein-Barr and HHV-6), SARS-CoV-1, Ebola virus, influenza and dengue (Jason et al., 2022; Komaroff & Lipkin, 2021). Such a strong association between a variety of viruses and ME/CFS implicates an impaired host response that might lead to disease. It seems plausible that Long COVID is caused by similar mechanisms resulting from the SARS-CoV-2 virus (Komaroff & Lipkin, 2021). Following such a viral infection or stress response, immune cells such as monocytes and leukocytes are activated peripherally in the blood and centrally in the organs and CNS. Normally, after a viral infection or other stressor, the peripheral inflammatory response subsides and causes no long-term harm. If the inflammatory response persists it may cause damage to the CNS blood-brain barrier (BBB), usually protecting the brain from peripheral immune responses. In turn, leukocytes and inflammatory mediators (e.g., cytokines and chemokines) cross blood vessels entering the CNS. Here they locally induce an immune response and glial cell activation which increases the release of cytokines and neurotoxic factors (Morris & Maes, 2013b; Renz-Polster et al., 2022). When this response becomes chronic, as is proposed for ME/CFS and Long COVID, abnormal signaling to the CNS triggers chronic activation of microglia and astrocytes, mediating the production of proinflammatory cytokines and an inflammatory response. In turn, this may result in chronic neuroinflammation, which can cause glial cell dysregulation and neuronal damage. Consequently, this can lead to neural circuit dysfunction and neurological manifestations (Mackay, 2021; Mackay & Tate, 2018; Monje & Iwasaki, 2022; Tate et al., 2022).

2.2 Neuroinflammation

2.2.1 ME/CFS

In the past years, the investigation of CNS inflammation in ME/CFS has increased. Methods used to study neuroinflammation include positron emission tomography (PET) commonly using translocator protein 18kDa (TSPO) binding ligands (e.g. [^{11}C]-(R)-PK11195) (Nakatomi et al., 2014) and magnetic resonance spectroscopy (MRS) (VanElzakker et al., 2019). Such imaging studies have identified neuroinflammation in several brain regions of patients with ME/CFS, including the cingulate region, thalamus, hippocampus, amygdala, midbrain and pons. This is evidenced by increased TSPO signalling, which is expressed by activated microglia and astrocytes and in turn indicates presence of neuroinflammation (Nakatomi et al., 2014). In addition, the increased TSPO PET signal in the thalamus and cingulate region correlated with neurocognitive symptoms such as pain, fatigue and cognitive impairment. Furthermore, in a whole-brain MRS study in ME/CFS patients, abnormalities in brain metabolites, including an increase in choline, were found in large parts of the brain, but especially in the anterior cingulate cortex. Due to choline's important

role in membrane health, it is an indicator of BBB permeability and is closely related to glial activation. Therefore, it is considered a marker for neuroinflammation (Mueller et al., 2020; VanElzakker et al., 2019). Similar results (i.e., increased choline) have previously been found in the occipital cortex (Puri et al., 2002) and frontal white matter (Tomoda et al., 2000).

Another brain region possibly affected in ME/CFS patients is the hypothalamic paraventricular nucleus (PVN). Triggers of ME/CFS, such as a viral infection or other physiological stressors might target the PVN, which is a group of neurons within the hypothalamus that have a key regulatory function of the hypothalamic pituitary adrenal (HPA) axis and autonomic nervous system (ANS) (Mackay & Tate, 2018). The hypothalamic PVN receives stress signals and activates the HPA axis once these incoming signals are integrated and processed, therefore regulating whole body homeostasis (Ferguson et al., 2008). In ME/CFS, disturbances of the HPA axis and PVN have consistently been reported (Mackay & Tate, 2018; Tomas et al., 2013) and may explain patients' low tolerance to any kind of stressor and thus causing PESE. When a certain "stress-threshold" is exceeded due to an ME/CFS trigger or other external stimuli, the hypothalamic PVN might facilitate a microglial-mediated neuroinflammatory response (see "2.1 Triggers"), impacting the hypothalamus and the limbic-system (Mackay, 2021), leading to a dysfunctional HPA axis. A dysfunctional hypothalamic PVN and HPA axis is proposed to be a key mechanism maintaining the disease (Mackay & Tate, 2018; Tate et al., 2022).

Cerebrospinal fluid (CSF) seems to have a distinct profile in ME/CFS, consistent with CNS immune activation. This is indicated by decreased levels of interleukin (IL) 10, which might be a consequence of dysfunctional microglia, which produce IL-10. Moreover, IL-10 seems to have a substantial anti-inflammatory role in the CNS (Peterson et al., 2015). Hornig et al., (2016) found an increase in plasma levels of CCL11 using a magnetic bead-based 51-plex immunoassay. In addition, elevated protein levels, white blood cell counts, IL-10 and IL-8 levels have been detected in CSF, though not in the entire patient sample. The latter was mainly seen in ME/CFS triggered by a viral infection. Such abnormalities are in line with the reported underlying neuropathology of ME/CFS (Natelson et al., 2005).

2.2.2 Long COVID

Like in ME/CFS, neuroinflammation has recently been identified in Long COVID patients (Petersen et al., 2022; Visser et al., 2022). Using PET, Visser et al., (2022) observed increased TSPO ligand [^{18}F]DPA-714 binding throughout the brain of two Long COVID patients, indicating widespread neuroinflammation. However, the small sample size makes it impossible to draw conclusions and these findings need to be replicated in larger samples. Another study done by Petersen et al., (2022) detected an increase in average extracellular free water and mean diffusivity in the white matter of individuals recovering from mild to moderate COVID-19 (i.e., 9.7 months post infection) compared to healthy controls. This imaging characteristic might be an indirect marker of a sustained neuroinflammatory response (Monje & Iwasaki, 2022; Petersen et al., 2022). Importantly, this sample did not report any neuropsychological complaints, raising questions regarding the clinical relevance of these findings.

Elevated levels of cytokines and chemokines in the CSF of Long COVID patients have been identified. In addition, CCL11 was elevated in the plasma of Long COVID patients, like in ME/CFS. These levels positively correlate with impaired cognition and neurogenesis (Fernández-Castañeda et al., 2022). Interestingly, the levels of CSF 14-3-3 and CSF NfL of acute COVID-19 patients seemed to correlate with

long-term neurological complaints (Guasp et al., 2022). Clearly, Long COVID is a new phenomenon, and more research is needed to reproduce findings and draw firm conclusions regarding structural and functional abnormalities in the brain.

Notably, several postmortem studies have identified neuroinflammation in patients with acute COVID-19, characterized by an increase in activated microglia and astrocytes, in addition to infiltration of cytotoxic T lymphocytes (Lou et al., 2021; Matschke et al., 2020; Schurink et al., 2020). This was present in various brain areas, but most prominent in the medulla oblongata, olfactory bulb, brainstem and cerebellum. These findings might be related to persisting symptoms such as anosmia and deterioration of the respiratory system in COVID-19 and Long COVID patients (Matschke et al., 2020; Schurink et al., 2020b). Furthermore, the stress responses resulting from a SARS-CoV-2 infection and its host receptor (i.e., angiotensin-converting enzyme 2 (ACE2)) might activate the HPA axis. Chronic activation of the HPA axis may lead to a dysfunctional feedback loop, potentially impairing the ability to adapt and respond to stressors (Steenblock et al., 2020). These findings resemble those made in ME/CFS patients and are proposed to play a role in Long COVID as well (Mackay, 2021), as described above for ME/CFS.

2.3 Neurodegeneration

As a consequence of increased glial activation, pro-inflammatory cytokines and thus neuroinflammation, neurodegeneration may develop. Neurodegeneration involves progressive loss of neuronal structure and function in the CNS, resulting in chronic impairments (Chen et al., 2016). This phenomenon is commonly observed in diseases such as Alzheimer disease (AD), multiple sclerosis (MS), Parkinson's disease (PD) and amyotrophic lateral sclerosis (ALS), all classified as neurodegenerative diseases.

2.3.1 ME/CFS

The increase in cytokines and general inflammatory states observed in ME/CFS patients indicate a risk of neurodegeneration. Neurodegeneration may lead to reduced grey and white matter as well as symptoms such as cognitive dysfunction, which have all been identified in ME/CFS patients (Glassford, 2017; Puri et al., 2012). Yet, there is currently no evidence that ME/CFS is a neurodegenerative disease. Interestingly, the disease has many features in common with MS, all of which are in line with typical neurological impairments (Morris & Maes, 2013a). Like in MS, ME/CFS patients seem to have increased oxidative and nitrosative stress (O+NS), inducible nitric oxide synthase (iNOS), cycly-oxygenase 2 (COX2) and nuclear factor kappa-light-chain-enhancer (NF-κB) of activated B cells (Maes et al., 2007, 2011; Morris & Maes, 2013a). Such increases may be accompanied by neuronal damage and death (Carlson et al., 2010; Morris & Maes, 2013a). In addition, while NF-κB can have a protective function of neurons, its activation in microglia during neuroinflammation seems to stimulate neurodegeneration (Bonetti et al., 1999). Importantly, this was identified in MS patients. In sum, it is unclear whether neurodegeneration plays a role in ME/CFS and more research is needed to draw conclusions.

2.3.2 Long COVID

The neurotrophic and neuroinvasive etiology of SARS-CoV-2 (Moriguchi et al., 2020) leads to an increase in proinflammatory cytokines and thus higher levels of oxidative stress (Hascup & Hascup, 2020). The increase in oxidative stress causes damage to cell membranes and downregulates expression of excitatory

amino acid transporters, preventing the uptake of glutamate. The accumulation of glutamate leads to an excitotoxic environment which stimulates neuronal damage and death (Hascup & Hascup, 2020; Malik & Willnow, 2019). In a recent autopsy study, neurodegeneration was observed in the brainstem and its neural connections in six (i.e., the entire study population) COVID-19 victims (von Weyhern et al., 2020). It is unknown if this persists once the acute infection is over. This underlying etiology provides solid ground for further investigation of this phenomenon in Long COVID patients.

2.4 Other changes in brain structure and functioning

2.4.1 ME/CFS

Other neurological manifestations in ME/CFS include reduced cerebral blood flow. Using computed tomography (CT), Yoshiuchi et al., (2006) found that ME/CFS patients had reduced blood flow in bilateral cerebral arteries. Several other studies have identified this phenomenon using Doppler or other imaging techniques, by measuring flow velocity and vessel diameter of cerebral arteries (Bou-Holaigah et al., 1995; Razumovsky et al., 2003; Shan et al., 2020; van Campen et al., 2021). Van Campen et al.,(2020a; 2020b) found that cerebral blood flow was reduced in many patients after both tilt testing and sitting. This explains the orthostatic intolerance experienced by many ME/CFS patients, including symptoms like dizziness and lightheadedness (van Campen et al., 2021).

Several neuroanatomical changes have been reported in ME/CFS patients. De Lange et al., (2005) reported smaller bilateral prefrontal cortex (PFC) volume, while Puri et al., (2012) identified smaller grey and white matter volumes. This was especially observed in the occipital lobes, while reduced grey matter was also observed in the right angular gyrus and parahippocampal gyrus. These are highly relevant findings as they might help explain symptoms such as memory impairment and other functional deficits (Puri et al., 2012; Rosenthal et al., 2009). Importantly, some studies fail to find such differences between ME/CFS and healthy controls (Perrin et al., 2010), while others find contradicting results. For example, Finkelmeyer et al., (2018) demonstrated an increase in grey matter volume of the insula and amygdala, while white matter volume was decreased in the midbrain, pons and right temporal lobe. White matter reduction is consistent with symptoms of cognitive dysfunction, as white matter facilitates information processing and other cognitive operations (Filley & Fields, 2016).

Functional magnetic resonance imaging (fMRI) studies have frequently reported decreased functional connectivity (FC) or dysfunctional connectivity across various brain regions and neural networks (Gay et al., 2016; Kim et al., 2015; Shan et al., 2020; Wortinger et al., 2017). This includes FC between the posterior and anterior cingulate cortices (PCC and ACC) in the default mode network (DMN) (Boissoneault et al., 2016; Kim et al., 2015). Such disturbances influence many aspects of cognition including fatigue processing and concentration abilities (Filley & Fields, 2016). Importantly, there is a lack of consistency in FC findings across studies as some do not find dysfunctional connectivity in these areas (Gay et al., 2016; Shan et al., 2020). Another recent finding is intracranial hypertension (IH) in brains of patients with severe ME/CFS. This was established by neuroradiological parameters in an MRI study in which it was found that 83% had signs of IH, which is significantly more than in a healthy adult population. This was reported by Bragée et al., (2020), who suggest that this may contribute to several ME/CFS symptoms, such as cognitive complaints, headache, dizziness and fatigue. Similarly, Higgins et al., (2017) previously suggested an association between ME/CFS-related symptoms and IH.

2.4.2 Long COVID

Like in ME/CFS, orthostatic intolerance and reduced cerebral blood flow have been reported in Long COVID patients (van Campen & Visser, 2022). This was found using extracranial Doppler during a tilt table test, where the decrease in cerebral blood flow was similar in Long COVID and ME/CFS patients. Other neurological abnormalities reported in Long COVID patients include a general, small decrease in brain volume, changes in olfactory-related areas, limbic system, cerebellum and white matter tracts. Such changes include atrophy and increased diffusion measures, indicating tissue damage (Douaud et al., 2022; Monje & Iwasaki, 2022; Paolini et al., 2023). In a recent imaging study, altered resting-state functional connectivity patterns were observed in the right frontal pole and middle temporal gyrus of Long COVID patients with cognitive complaints, compared to patients without such complaints (Paolini et al., 2023). This was studied through multivariate pattern connectivity analysis. It is noteworthy that all participants had been hospitalized during the acute SARS-CoV-2 infection.

See Table 2 for an overview of neuropathology and onset triggers of ME/CFS and Long COVID.

Table 2: Overview of neuropathology and onset triggers in ME/CFS and Long COVID.

Domain	References	ME/CFS	Long COVID
Triggers			
Viral infection	Michelen et al., 2021 Institute of Medicine, 2015	✓	✓
Physiological stressor	Institute of Medicine, 2015	✓	
- Infection		✓	
- Surgery		✓	
- Autoimmune disorders		✓	
Unknown	Institute of Medicine, 2015	✓	
Neuropathology			
Neuroinflammation - Microglia & astrocyte activation - Increased production of proinflammatory cytokines	Cook et al., 2017; Nakatomi et al., 2014; Petersen et al., 2022; Visser et al., 2022	✓	✓
CSF abnormalities - Increase in pro-inflammatory cytokines	Fernández-Castañeda et al., 2022; Hornig et al., 2016; Natelson et al., 2005; Peterson et al., 2015	✓	✓
Reduced cerebral blood flow	Biswal et al., 2011; van Campen & Visser, 2022	✓	✓
Structural abnormalities	Douaud et al., 2022		
- In the limbic system	Cook et al., 2017	✓	✓
- Cerebellum	Mueller et al., 2020		✓
- Decreased brain volume	De Lange et al., 2005	✓	✓
- Changes throughout the olfactory system	Douaud et al., 2022	✓	✓
- Changes in grey and white matter volume	Paolini et al., 2023; Shepherd, 2022; Puri et al., 2012		✓
Impaired HPA axis	Komaroff & Lipkin, 2021; Mackay & Tate, 2018; Mackay, 2021	✓	?
Altered brain connectivity	Douaud et al., 2022; Paolini et al., 2023; Gay et al., 2016; Kim et al., 2015	✓	✓

2.5 Impact of physical activity on brain functioning in patients with PESE

Physical activity and exercise are generally associated with a variety of both brain- and physical health benefits. In short, studies show that aerobic exercise increases hippocampal-, cortical- and white matter volume, promotes neurogenesis and improves sleep, chronic pain, and mood (Hillman et al., 2008; Reid et al., 2022), many of which are affected in Long COVID and ME/CFS. Furthermore, these exercise-induced benefits result in improved cognitive performance, prevention of various diseases and counteraction of brain aging (Stillman et al., 2020). Generally, prescribed physical activity or exercise therapy is therefore common and considered highly beneficial across various patient groups (Pedersen & Saltin, 2015; Reid et al., 2022). Like in the general population, some sub-groups of Long COVID patients likely also benefit from this approach, as demonstrated by various studies (Fernández-Lázaro et al., 2022). However, as different sub-groups of Long COVID have been described (Yong & Liu, 2022), it is likely that they respond differently to exercise depending on the nature of symptoms. In this review, there will be a distinction between Long COVID with and without PESE, with focus on the latter.

2.5.1 Physical activity in ME/CFS

Contrary to the general population and some sub-groups of Long COVID, it seems that exertion leads to an abnormal response in ME/CFS patients, including worsening of symptoms (Keech et al., 2015; Meeus et al., 2011; Nijs et al., 2008; White et al., 2010). In a study by Cook et al., (2017), functional brain imaging data was obtained one week prior to- and 24 hours following submaximal exercise in ME/CFS patients and healthy controls. It was found that the worsening of symptoms was associated with impaired cognitive performance and altered brain functioning. ME/CFS patients demonstrated significantly increased brain activity in the inferior frontal, parietal and cingulate cortices after exercise (Table 3), making their brain responses distinguishable from healthy controls. The increase in neuronal activity in these areas was positively correlated with symptoms of PESE (i.e., exacerbation of experienced symptoms and decrease in overall functioning). This is in line with the critical role of these areas in cognitive processing, pain, experience of fatigue, filtering of information and executive function. In other words, it is likely that PESE causes an increase in neuronal activity required to perform a certain task. Importantly, this distinction between patients and controls was only present after fatiguing tasks and exercises. Healthy controls demonstrated reduced brain responses in corresponding brain areas after exercise. This finding was associated with improved cognitive performance (i.e., less errors during a cognitive task), suggesting that less neural resources are required for both executive functioning and cognitive tasks in the healthy brain. These results demonstrate opposite responses to exercise in ME/CFS patients and healthy controls as the greater brain activity observed in ME/CFS patients is associated with reduced cognitive performance and an increase in symptoms. Similarly, increased blood oxygenation level dependent (BOLD) signals in the midbrain ascending arousal network nuclei have been reported after exercise, in contrast to healthy controls who showed no such change (Baraniuk, 2022; Baraniuk et al., 2022). In addition, Washington et al., (2020) reported increased activation of the dorsal midbrain and insula. Moreover, Rayhan & Baraniuk, (2021) reported increased activity in de medial prefrontal cortex (mPFC) of the anterior node of the DMN (aDMN) after submaximal exercise. As demonstrated by Cook et al., (2017), controls showed an opposite response (i.e., reduced activity in this region). The DMN is a group of brain regions that activate “by default” during rest and deactivate when executing a task and is involved in processes such as mind-

wandering and memory retrieval (Spreng & Grady, 2010). Rayhan & Baraniuk, (2021) suggest that the exercise-induced activation of the mPFC in ME/CFS patients might represent impaired regulatory input and decoupling from posterior nodes of the DMN, which may be caused by glial dysfunction (Renz-Polster et al., 2022). This may be a pathological consequence and biomarker of PESE. Finally, White et al., (2010) reported an increase in cytokines IL-6, IL-8, IL-10, IL-12, IL-13 and IL-1β in the serum of ME/CFS patients after exercise, positively correlating with symptom exacerbation. In sum, these results provide objective findings for the subjective symptoms experienced by ME/CFS patients. In addition, it seems that PESE has a substantial negative impact on the brain.

2.5.2 Physical activity in Long COVID patients with PESE

A large proportion of Long COVID patients report PESE as one of their symptoms. In line with this, 75% of participants in a cross-sectional study about the relationship between physical activity and Long COVID symptoms reported worsening of symptoms after physical activity (Wright et al., 2022). Furthermore, less than 1% reported improvement of symptoms (Wright et al., 2022). In a study by Davis et al., (2021), 71% of the participants reported worsening of symptoms after physical activity. These findings indicate that PESE indeed plays a role in this subgroup of Long COVID patients.

Although the neurological effects of exercise in Long COVID patients with PESE have not received much attention yet, there are indicators of abnormal CNS responses. Besides the abnormal response in terms of symptoms exacerbation after physical activity, van Campen & Visser, (2022) identified similar responses of Long COVID and ME/CFS patients during tilt testing, indicating orthostatic intolerance and thus reduced cerebral blood flow in in both diseases. In sum, more research is needed to draw conclusions regarding the effects of exercise in Long COVID patients and whether these might differ across different subgroups.

Table 3: *Overview of neuropathology post exertion in ME/CFS and Long COVID*

Domain	References	ME/CFS	Long COVID
Neuropathology Post Exertion			
Increased levels of 6 different cytokines	White et al., 2010	✓	?
Increased brain activity/BOLD signal	Cook et al., 2017		
- Parietal cortex		✓	?
- Cingulate cortices		✓	
- mPFC – aDMN	Rayhan & Baranuik, 2021	✓	
- Dorsal midbrain and insula	Washington et al., 2020	✓	
- Midbrain ascending arousal network nuclei	Baranuik, 2022; Baranuik et al., 2022	✓	

3. Discussion

A large overlap of neurological symptoms has been observed in ME/CFS and Long COVID, including the specific shared phenomenon of symptom-exacerbation following exertion (i.e., PESE) (Jason et al., 2021; Twomey et al., 2022; Wong & Weitzer, 2021). Many of these symptoms, both in rest and following exertion, may be a consequence of CNS pathology. Although post-viral diseases are not a new phenomenon, the COVID-19 pandemic uncovered a large knowledge gap about the sequalae of post-acute viral diseases (Choutka et al., 2022). This review therefore aimed to provide an overview of CNS pathology in ME/CFS and Long COVID patients. In addition, it was explored how physical exertion affected CNS pathology in these patients. The large number of resources and attention that is being devoted to Long COVID research bring promise to the highly needed progression in this field, which might benefit several other patient groups experiencing similar post-acute chronic disabilities, such as ME/CFS patients. Due to the seemingly large overlap between ME/CFS and Long COVID, another objective of this review was to assess possible knowledge transfer between the two diseases.

3.1 Overlap in neuropathological findings and consequential symptoms

In line with previous findings, the two diseases indeed seem to have substantial overlap. Not only regarding symptom profile, but also in terms of CNS pathology such as the inflammatory response and structural changes. These pathological findings may explain several symptoms of both diseases, such as cognitive dysfunction, commonly labelled “brain fog” which might appear as result of cytokine production. An increase in pro-inflammatory cytokines has been observed in both ME/CFS and Long COVID (Fernández-Castañeda et al., 2022; Nakatomi et al., 2014; Petersen et al., 2022; White et al., 2010) and is known to have a profound effect on cognition (Felger, 2018). In one study, the increase in TSPO binding in several brain areas, indicative of neuroinflammation in these regions, correlated with cognitive symptom severity of ME/CFS patients (Nakatomi et al., 2014). Moreover, neuroinflammation might result in neural circuit dysfunction and thus cognitive impairment, all of which are proposed or identified in Long COVID and established in ME/CFS (Gay et al., 2016; Monje & Iwasaki, 2022; Nakatomi et al., 2014; Wortinger et al., 2017). Additionally, a dysfunctional hypothalamus and HPA axis have, although less clear in Long COVID, been reported in both diseases (Mackay, 2021; Mackay & Tate, 2018; Steenblock et al., 2020; Tomas et al., 2013). This may contribute to the low tolerance of stressors and thus PESE, which is a core symptom of ME/CFS and experienced by many Long COVID patients (Twomey et al., 2021; Wright et al., 2022). It could also explain several ME/CFS- and Long COVID-like symptoms such as cognitive dysfunction, hypersensitivity to light and sound, partially also the lack of refreshing sleep, orthostatic intolerance and fatigue (Friedberg et al., 2014; Mackay & Tate, 2018) Furthermore, decreased brain volume, reduced white and grey matter and other structural changes have been identified in both diseases (de Lange et al., 2005; Douaud et al., 2022; Monje & Iwasaki, 2022; Puri et al., 2012). Such abnormalities influence many aspects of cognition including memory, attention and concentration abilities (Filley & Fields, 2016).

Van Campen & Visser, (2022) identified cerebral hypoperfusion and similar physiological responses to tilt testing in both diseases. This explains the orthostatic intolerance experienced by many patients, including symptoms like dizziness and lightheadedness. Comparison of the two groups in terms of self-reported symptoms, severity of symptoms, orthostatic intolerance complaints in daily life and objective

abnormalities regarding orthostatic intolerance demonstrated highly similar findings as well (van Campen et al., 2021; Davis et al., 2021; van Campen & Visser, 2022). It was therefore proposed that SARS-CoV-2 infection is the cause of ME/CFS development in these Long COVID patients. In addition, they ruled out that the orthostatic intolerance was related to deconditioning.

However, some findings were exclusively present in one of the two diseases. Intracranial hypertension is not discovered in Long COVID patients. This may, however, be due to a lack of research rather than the absence of this feature in Long COVID. Furthermore, disturbances of the HPA axis and PVN have not been established nor studied well in Long COVID. Notably, Long COVID seems to be a much more heterogenous disease than ME/CFS and therefore demonstrates a larger variety of symptoms. Consequently, findings such as respiratory problems, changes in the olfactory system and thus anosmia and dysgeusia are specific to Long COVID.

3.2 Post-exertional symptom exacerbation

Symptom exacerbation following exertion is a hallmark symptom in ME/CFS according to current accepted diagnostic criteria for ME/CFS (Nacul et al., 2021; NICE, 2021). A large proportion of Long COVID patients also report worsening of symptoms after exertion (i.e., PESE) (Davis et al., 2021; Wright et al., 2022). However, it is not entirely clear how PESE affects the brain and if findings of CNS pathology in ME/CFS patients also apply to Long COVID. In ME/CFS patients, findings imply that PESE might reflect exacerbation of neuropathology such as neuroinflammation or neuroglial dysfunction, which is induced by exertion (Renz-Polster et al., 2022). In turn, PESE negatively affects the brain and requires increased neural resources and thus activation of brain areas such as the inferior frontal, parietal and cingulate cortices to execute tasks and actions. In healthy controls, brain responses after exercise are associated with improved cognitive performance and reduced brain activation in corresponding areas (i.e., opposite of ME/CFS) (Baraniuk et al., 2022; Cook et al., 2017; Washington et al., 2020). Rayhan et al., (2021) proposed that exercise-induced activation of the anterior node of the DMN is a consequence of PESE, although Renz-Polster et al., (2022) suggests that it indicates neuroglial dysfunction which in turn may cause PESE. In sum, it seems likely that the described neuropathology can induce a vicious circle-like mechanism in which neuropathology might cause exertion intolerance and subsequently exertion causes increased neuropathology and -symptoms.

Although PESE is a common symptom in Long COVID, little research has been done on its effect on the brain of patients with Long COVID. However, the findings of this review, in line with several other studies, suggest that the two diseases affect the CNS in similar ways (Komaroff & Bateman, 2021; Mackay, 2021; Tate et al., 2022). This might imply that findings of PESE in ME/CFS patients are likely transferable to Long COVID patients who experience PESE. If this notion is true, Long COVID patients with PESE should receive similar treatment as ME/CFS patients (Jason & Dorri, 2022; Shepherd, 2022; Twomey et al., 2021; van Campen & Visser, 2022). Moreover, future research should explore the described potential biomarkers of PESE in Long COVID patients who experience this symptom and thus belong to a specific subgroup of Long COVID.

3.3 Diagnostic specificity

Due to the heterogenous Long COVID patient population, diagnostic specificity and sub-grouping is a determining factor in studies investigating underlying pathology as well as the effect of exercise and treatment in patients with Long COVID. Diagnostic specificity has also shown to be crucial for research and treatment approach of ME/CFS patients. Previously accepted and commonly used criteria were less specific and did not require PESE as a symptom, leading to inclusion of a much more heterogenous group who might suffer from other chronic and fatiguing illnesses than ME/CFS (Lim & Son, 2020). As a result of using such heterogenous diagnostic criteria, research might lead to contradicting or irrelevant results, as is often seen in neurological research in this field. As different subgroups of Long COVID have been proposed, it is crucial to take these into consideration when conducting research. Therefore, the proposition that Long COVID and ME/CFS are highly similar diseases might not apply to all subgroups of Long COVID. Typically, studies report that 13%-58% of Long COVID patients fulfill the ME/CFS criteria after six months (Davis et al., 2021; González-Hermosillo et al., 2021; Jason & Dorri, 2022; Kedor et al., 2021; Yong & Liu, 2022). Clearly, this proportion varies substantially, which is likely due to the differences in applied diagnostic criteria (i.e., more specific criteria vs. less specific criteria). Moreover, it seems that Long COVID patients will be a growing subgroup of ME/CFS. Currently, the complexity of these diseases, small sample sizes and no controlling for heterogeneity may explain inconsistencies in the literature and lack of biomarkers. Reaching consensus on case definitions of different Long COVID subtypes should therefore be a high priority. Furthermore, future diagnostic and therapeutic research should take subtypes as well as disease severity into account.

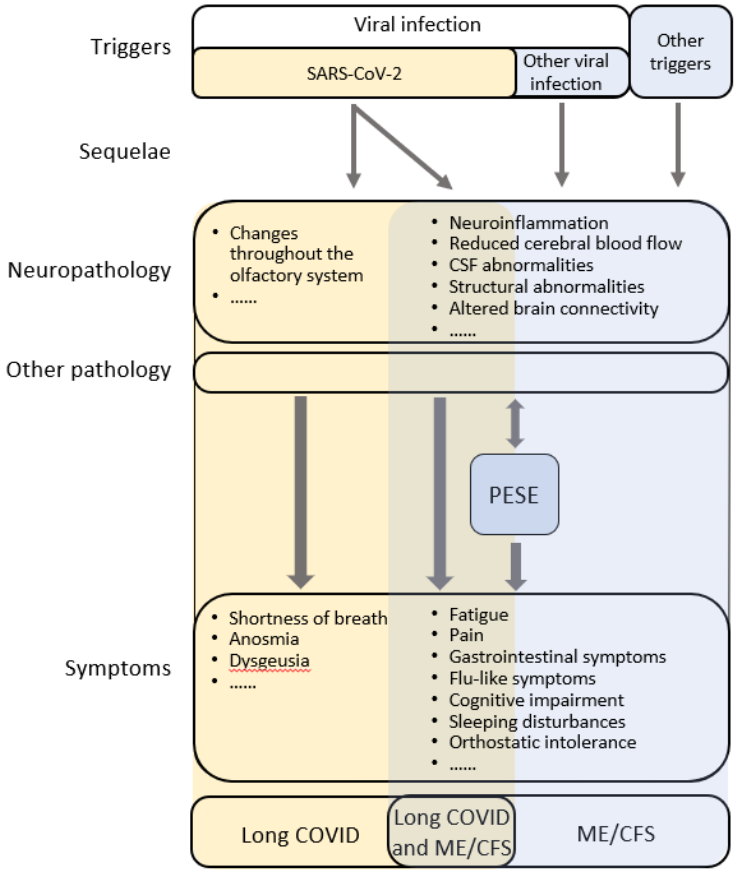

***Figure 1**. Simplified model and hypothesis of Long COVID and ME/CFS overlap and differences: Following an initial trigger, (neuro)pathological responses are activated, resulting in a wide range of symptoms. In ME/CFS and a subgroup of Long COVID patients, (neuro)pathology leads to specific symptoms, including PESE. PESE may in turn lead to exacerbation of (neuro)pathology and symptoms, precipitating chronic disease and relapses. A large subgroup of Long COVID patients ("Long COVID" in blue) fulfil the diagnostic criteria for ME/CFS.*

3.4 Treatment approach of ME/CFS and Long COVID

To this date, there is no effective treatment for ME/CFS or Long COVID. However, the growing body of evidence pointing towards neuroinflammation has led to trials of drugs with anti-inflammatory properties (Mackay, 2021), including fractalkine, low-dose naltrexone (LDN) and aripiprazole. LDN and aripiprazole have already shown promising results in ME/CFS patients by reducing symptoms to varying degrees (i.e., "reduction of some symptoms only" to "life changing reduction") (Bolton et al., 2020; Crosby et al., 2021).

Furthermore, evaluation of treatment methods such as graded exercise therapy has previously demonstrated some effect for patients with ME/CFS but has generally been of low research quality (NICE, 2021). When only considering the patient group diagnosed with specific criteria with PESE as a core symptom, exercise therapies did not seem to lead to any clinical improvement or increased work participation, rather the opposite (NICE, 2021). Preventing PESE seems crucial. It has been shown that regardless of the type of treatment, the significant factor for improvement in fatigue and function over time is whether the ME/CFS patient has learned pacing strategies for energy saving, that is, to maintain appropriate energy consumption in relation to available energy reserves (Jason 2013). Non-pharmacological treatment should therefore be carefully adapted to each person individually, with a main focus on symptom management and functional improvement in the long-term. For ME/CFS, pacing seems to be favored by patients and entails a self-management strategy that facilitates activity with minimal symptom exacerbation (Centers for Disease Control and Prevention, 2021). This may be beneficial for all patients experiencing PESE (Twomey et al., 2021); this has been emphasized in the current management recommendations of WHO for long COVID patients (Health Organization, 2023). Importantly, all Long COVID patients will not benefit from the same treatments. For example, Long COVID patients who suffered from acute respiratory distress syndrome or multi-organ failure require a different treatment approach than Long COVID patients fitting the ME/CFS-subgroup. In fact, exercise might be crucial in the treatment approach of other Long COVID subgroups, in line with many other chronic and fatiguing illnesses (Reid et al., 2022).

3.5 Limitations

In this review, several studies with small sample sizes were discussed. As mentioned, many did not take heterogeneity or phenotypes into account, potentially resulting in invalid conclusions. Inconsistencies in results may be due to the application of unspecific, older case criteria and diverse subgroups. A limitation of this review is therefore that this was not explicitly taken into consideration in the presentation of results. Furthermore, as publication bias occurs with negative findings it is not always clear whether the absence of pathological findings are in fact not present or not reported. Since ME/CFS is a heavily understudied and misinterpreted illness and Long COVID is still a very new condition, this may be very relevant in this field. This review exclusively discussed neurological research, which provides a limited overview as other biomedical research is highly relevant to disentangle the pathophysiology of ME/CFS and Long COVID (Davis et al., 2023). Finally, PESE is generally an unknown and unrecognized phenomenon. Research in Long COVID is therefore often unspecific regarding the presence of PESE. Presented findings may consequently be rather unspecific towards subgroups and prevalence of pathological findings may be inaccurate.

4. Conclusion

Long COVID and ME/CFS have many commonalities, both regarding symptoms and underlying neuropathology. Neuroinflammation, reduced brain volume and cerebral hypoperfusion are among the characteristics that have been reported in both diseases, typically resulting in symptoms such as cognitive impairment, PESE, fatigue and non-refreshing sleep. In ME/CFS patients, exercise seems to cause an increase in neural resources required to execute tasks or functions. This may be a consequence of neuropathology causing exertion intolerance and subsequently exertion causing increased neuropathology and -symptoms. Similar underlying neuropathology and symptoms implies that these findings might also apply to Long COVID patients with PESE. However, more research is needed to draw firm conclusion regarding underlying neuropathology and treatment approach of both diseases. As indicated by the different subgroups proposed for Long COVID, patients suffer from various complaints and therefore require different treatment approaches. This should be implicated and taken into consideration in future research and clinical approach.

References

Amekran, Y., Damoun, N., & Hangouche, A. J. el. (2022). Postural orthostatic tachycardia syndrome and post-acute COVID-19. In *Global Cardiology Science and Practice* (Vol. 2022, Issues 1–2). HBKU Press. https://doi.org/10.21542/gcsp.2022.13

Baraniuk, J. N. (2022). Review of the Midbrain Ascending Arousal Network Nuclei and Implications for Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS), Gulf War Illness (GWI) and Postexertional Malaise (PEM). In *Brain Sciences* (Vol. 12, Issue 2). MDPI. https://doi.org/10.3390/brainsci12020132

Baraniuk, J. N., Amar, A., Pepermitwala, H., & Washington, S. D. (2022). Differential Effects of Exercise on fMRI of the Midbrain Ascending Arousal Network Nuclei in Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS) and Gulf War Illness (GWI) in a Model of Postexertional Malaise (PEM). *Brain Sciences*, *12*(1), 78. https://doi.org/10.3390/brainsci12010078

Biswal, B., Kunwar, P., & Natelson, B. H. (2011). Cerebral blood flow is reduced in chronic fatigue syndrome as assessed by arterial spin labeling. *Journal of the Neurological Sciences*, *301*(1–2), 9–11. https://doi.org/10.1016/j.jns.2010.11.018

Boissoneault, J., Letzen, J., Lai, S., O'Shea, A., Craggs, J., Robinson, M. E., & Staud, R. (2016). Abnormal resting state functional connectivity in patients with chronic fatigue syndrome: An arterial spin-labeling fMRI study. *Magnetic Resonance Imaging*, *34*(4), 603–608. https://doi.org/10.1016/j.mri.2015.12.008

Bolton, M. J., Chapman, B. P., & van Marwijk, H. (2020). Low-dose naltrexone as a treatment for chronic fatigue syndrome. *BMJ Case Reports*, *13*(1), e232502. https://doi.org/10.1136/bcr-2019-232502

Bonetti, B., Stegagno, C., Cannella, B., Rizzuto, N., Moretto, G., & Raine, C. S. (1999). Activation of NF-κB and c-jun Transcription Factors in Multiple Sclerosis Lesions. *The American Journal of Pathology*, *155*(5), 1433–1438. https://doi.org/10.1016/S0002-9440(10)65456-9

Bou-Holaigah, I., Rowe, P. C., Kan, J., & Calkins, H. (1995). The relationship between neurally mediated hypotension and the chronic fatigue syndrome. *JAMA*, *274*(12), 961–967.

Bragée, B., Michos, A., Drum, B., Fahlgren, M., Szulkin, R., & Bertilson, B. C. (2020). Signs of Intracranial Hypertension, Hypermobility, and Craniocervical Obstructions in Patients With Myalgic Encephalomyelitis/Chronic Fatigue Syndrome. *Frontiers in Neurology*, *11*. https://doi.org/10.3389/fneur.2020.00828

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

Carlson, N. G., Rojas, M. A., Redd, J. W., Tang, P., Wood, B., Hill, K. E., & Rose, J. W. (2010). Cyclooxygenase-2 expression in oligodendrocytes increases sensitivity to excitotoxic death. *Journal of Neuroinflammation*, *7*(1), 25. https://doi.org/10.1186/1742-2094-7-25

Centers for Disease Control and Prevention. (2021). *Treatment of ME/CFS*.

Chen, W. W., Zhang, X., & Huang, W. J. (2016). Role of neuroinflammation in neurodegenerative diseases (Review). *Molecular Medicine Reports*, *13*(4), 3391–3396. https://doi.org/10.3892/mmr.2016.4948

Choutka, J., Jansari, V., Hornig, M., & Iwasaki, A. (2022). Unexplained post-acute infection syndromes. *Nature Medicine*, *28*(5), 911–923. https://doi.org/10.1038/s41591-022-01810-6

Chu, L., Valencia, I. J., Garvert, D. W., & Montoya, J. G. (2018). Deconstructing post-exertional malaise in myalgic encephalomyelitis/ chronic fatigue syndrome: A patient-centered, cross-sectional survey. In *PLoS ONE* (Vol. 13, Issue 6, p. e0197811). Public Library of Science. https://doi.org/10.1371/journal.pone.0197811

Cook, D. B., Light, A. R., Light, K. C., Broderick, G., Shields, M. R., Dougherty, R. J., Meyer, J. D., VanRiper, S., Stegner, A. J., Ellingson, L. D., & Vernon, S. D. (2017). Neural consequences of post-exertion malaise in Myalgic Encephalomyelitis/Chronic Fatigue Syndrome. *Brain, Behavior, and Immunity*, *62*, 87–99. https://doi.org/10.1016/j.bbi.2017.02.009

Crosby, L. D., Kalanidhi, S., Bonilla, A., Subramanian, A., Ballon, J. S., & Bonilla, H. (2021). Off label use of Aripiprazole shows promise as a treatment for Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS): a retrospective study of 101 patients treated with a low dose of Aripiprazole. *Journal of Translational Medicine*, *19*(1), 50. https://doi.org/10.1186/s12967-021-02721-9

Davenport, T. E., Lehnen, M., Stevens, S. R., VanNess, J. M., Stevens, J., & Snell, C. R. (2019). Chronotropic Intolerance: An Overlooked Determinant of Symptoms and Activity Limitation in Myalgic Encephalomyelitis/Chronic Fatigue Syndrome? *Frontiers in Pediatrics*, *7*. https://doi.org/10.3389/fped.2019.00082

Davis, H. E., Assaf, G. S., McCorkell, L., Wei, H., Low, R. J., Re'em, Y., Redfield, S., Austin, J. P., & Akrami, A. (2021). Characterizing long COVID in an international cohort: 7 months of symptoms and their impact. *EClinicalMedicine*, *38*, 101019. https://doi.org/10.1016/j.eclinm.2021.101019

Davis, H. E., McCorkell, L., Vogel, J. M., & Topol, E. J. (2023). Long COVID: major findings, mechanisms and recommendations. *Nature Reviews Microbiology*. https://doi.org/10.1038/s41579-022-00846-2

de Lange, F. P., Kalkman, J. S., Bleijenberg, G., Hagoort, P., van der Meer, J. W. M., & Toni, I. (2005). Gray matter volume reduction in the chronic fatigue syndrome. *NeuroImage*, *26*(3), 777–781. https://doi.org/10.1016/j.neuroimage.2005.02.037

Douaud, G., Lee, S., Alfaro-Almagro, F., Arthofer, C., Wang, C., McCarthy, P., Lange, F., Andersson, J. L. R., Griffanti, L., Duff, E., Jbabdi, S., Taschler, B., Keating, P., Winkler, A. M., Collins, R., Matthews, P. M., Allen, N., Miller, K. L., Nichols, T. E., & Smith, S. M. (2022). SARS-CoV-2 is associated with changes in brain structure in UK Biobank. *Nature*, *604*(7907), 697–707. https://doi.org/10.1038/s41586-022-04569-5

Durstenfeld, M. S., Sun, K., Tahir, P., Peluso, M. J., Deeks, S. G., Aras, M. A., Grandis, D. J., Long, C. S., Beatty, A., & Hsue, P. Y. (2022). Use of Cardiopulmonary Exercise Testing to Evaluate Long COVID-19 Symptoms in Adults. *JAMA Network Open*, *5*(10), e2236057. https://doi.org/10.1001/jamanetworkopen.2022.36057

Ferguson, A. v, Latchford, K. J., & Samson, W. K. (2008). The paraventricular nucleus of the hypothalamus – a potential target for integrative treatment of autonomic dysfunction. *Expert Opinion on Therapeutic Targets*, *12*(6), 717–727. https://doi.org/10.1517/14728222.12.6.717

Fernández-Castañeda, A., Lu, P., Geraghty, A. C., Song, E., Lee, M.-H., Wood, J., O'Dea, M. R., Dutton, S., Shamardani, K., Nwangwu, K., Mancusi, R., Yalçın, B., Taylor, K. R., Acosta-Alvarez, L., Malacon, K., Keough, M. B., Ni, L., Woo, P. J., Contreras-Esquivel, D., … Monje, M. (2022). Mild respiratory COVID can cause multi-lineage neural cell and myelin dysregulation. *Cell*, *185*(14), 2452-2468.e16. https://doi.org/10.1016/j.cell.2022.06.008

Fernández-Lázaro, D., Santamaría, G., Sánchez-Serrano, N., Lantarón Caeiro, E., & Seco-Calvo, J. (2022). Efficacy of Therapeutic Exercise in Reversing Decreased Strength, Impaired Respiratory Function, Decreased Physical Fitness, and Decreased Quality of Life Caused by the Post-COVID-19 Syndrome. *Viruses*, *14*(12), 2797. https://doi.org/10.3390/v14122797

Filley, C. M., & Fields, R. D. (2016). White matter and cognition: making the connection. *Journal of Neurophysiology*, *116*(5), 2093–2104. https://doi.org/10.1152/jn.00221.2016

Finkelmeyer, A., He, J., Maclachlan, L., Watson, S., Gallagher, P., Newton, J. L., & Blamire, A. M. (2018). Grey and white matter differences in Chronic Fatigue Syndrome – A voxel-based morphometry study. *NeuroImage: Clinical*, *17*, 24–30. https://doi.org/10.1016/j.nicl.2017.09.024

Franco, J. V. A., Garegnani, L. I., Oltra, G. V., Metzendorf, M.-I., Trivisonno, L. F., Sgarbossa, N., Ducks, D., Heldt, K., Mumm, R., Barnes, B., & Scheidt-Nave, C. (2022). Long-Term Health Symptoms and Sequelae Following SARS-CoV-2 Infection: An Evidence Map. *International Journal of Environmental Research and Public Health*, *19*(16), 9915. https://doi.org/10.3390/ijerph19169915

Friedberg, F., Bateman, L., Bested, A. C., Haematological Pathologist Toronto, F., Todd Davenport, C., Friedman, K. J., Gurwitt, A., Jason, L. A., Lapp, C. W., & Stevens, S. R. (2012). *ME/CFS: A Primer for Clinical Practitioners Members of the IACFS/ME Primer Writing Committee*. www.iacfsme.org

Gay, C. W., Robinson, M. E., Lai, S., O'Shea, A., Craggs, J. G., Price, D. D., & Staud, R. (2016). Abnormal Resting-State Functional Connectivity in Patients with Chronic Fatigue Syndrome: Results of Seed and Data-Driven Analyses. *Brain Connectivity*, *6*(1), 48–56. https://doi.org/10.1089/brain.2015.0366

Glassford, J. A. G. (2017). The neuroinflammatory etiopathology of myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS). *Frontiers in Physiology*, *8*(FEB). https://doi.org/10.3389/fphys.2017.00088

González-Hermosillo, J. A., Martínez-López, J. P., Carrillo-Lampón, S. A., Ruiz-Ojeda, D., Herrera-Ramírez, S., Amezcua-Guerra, L. M., & Martínez-Alvarado, M. del R. (2021). Post-Acute COVID-19 Symptoms, a Potential Link with Myalgic Encephalomyelitis/Chronic Fatigue Syndrome: A 6-Month Survey in a Mexican Cohort. *Brain Sciences*, *11*(6), 760. https://doi.org/10.3390/brainsci11060760

Guasp, M., Muñoz-Sánchez, G., Martínez-Hernández, E., Santana, D., Carbayo, Á., Naranjo, L., Bolós, U., Framil, M., Saiz, A., Balasa, M., Ruiz-García, R., & Sánchez-Valle, R. (2022). CSF Biomarkers in COVID-19 Associated Encephalopathy and Encephalitis Predict Long-Term Outcome. *Frontiers in Immunology*, *13*. https://doi.org/10.3389/fimmu.2022.866153

Hascup, E. R., & Hascup, K. N. (2020). Does SARS-CoV-2 infection cause chronic neurological complications? *GeroScience*, *42*(4), 1083–1087. https://doi.org/10.1007/s11357-020-00207-y

Health Organization, W. (2023). *Guideline Clinical management of COVID-19: living guideline*. http://apps.who.int/bookorders.

Higgins, J. N. P., Pickard, J. D., & Lever, A. M. L. (2017). Chronic fatigue syndrome and idiopathic intracranial hypertension: Different manifestations of the same disorder of intracranial pressure? *Medical Hypotheses*, *105*, 6–9. https://doi.org/10.1016/j.mehy.2017.06.014

Hillman, C. H., Erickson, K. I., & Kramer, A. F. (2008). Be smart, exercise your heart: exercise effects on brain and cognition. *Nature Reviews Neuroscience*, *9*(1), 58–65. https://doi.org/10.1038/nrn2298

Hornig, M., Gottschalk, G., Peterson, D. L., Knox, K. K., Schultz, A. F., Eddy, M. L., Che, X., & Lipkin, W. I. (2016). Cytokine network analysis of cerebrospinal fluid in myalgic encephalomyelitis/chronic fatigue syndrome. *Molecular Psychiatry*, *21*(2), 261–269. https://doi.org/10.1038/mp.2015.29

Institute of Medicine (IOM). Committee on the Diagnostic Criteria for Myalgic Encephalomyelitis/Chronic Fatigue Syndrome; Board on the Health of Select Populations (2015). *Beyond Myalgic Encephalomyelitis/Chronic Fatigue Syndrome*. National Academies Press. https://doi.org/10.17226/19012

Jason, L. A., & Dorri, J. A. (2022). ME/CFS and Post-Exertional Malaise among Patients with Long COVID. *Neurology International*, *15*(1), 1–11. https://doi.org/10.3390/neurolint15010001

Jason, L. A., Islam, M. F., Conroy, K., Cotler, J., Torres, C., Johnson, M., & Mabie, B. (2021). COVID-19 symptoms over time: comparing long-haulers to ME/CFS. *Fatigue: Biomedicine, Health & Behavior*, *9*(2), 59–68. https://doi.org/10.1080/21641846.2021.1922140

Jason, L. A., Yoo, S., & Bhatia, S. (2022). Patient perceptions of infectious illnesses preceding Myalgic Encephalomyelitis/Chronic Fatigue Syndrome. *Chronic Illness*, *18*(4), 901–910. https://doi.org/10.1177/17423953211043106

Kedor C, Meyer-Arndt L, Wittke K, Rudolf G, Hd, V., Paul F, & Bellmann-Strobl, J. (2021). *Chronic COVID-19 Syndrome and Chronic Fatigue Syndrome (ME/CFS) following the first pandemic wave in Germany – a first analysis of a prospective observational study*. https://doi.org/10.1101/2021.02.06.21249256

Keech, A., Sandler, C. X., Vollmer-Conna, U., Cvejic, E., Lloyd, A. R., & Barry, B. K. (2015). Capturing the post-exertional exacerbation of fatigue following physical and cognitive challenge in patients with chronic fatigue syndrome. *Journal of Psychosomatic Research*, *79*(6), 537–549. https://doi.org/10.1016/j.jpsychores.2015.08.008

Kim, B. H., Namkoong, K., Kim, J. J., Lee, S., Yoon, K. J., Choi, M., & Jung, Y. C. (2015). Altered resting-state functional connectivity in women with chronic fatigue syndrome. *Psychiatry Research - Neuroimaging*, *234*(3), 292–297. https://doi.org/10.1016/j.pscychresns.2015.10.014

Komaroff, A. L., & Bateman, L. (2021). Will COVID-19 Lead to Myalgic Encephalomyelitis/Chronic Fatigue Syndrome? *Frontiers in Medicine*, *7*. https://doi.org/10.3389/fmed.2020.606824

Komaroff, A. L., & Lipkin, W. I. (2021). Insights from myalgic encephalomyelitis/chronic fatigue syndrome may help unravel the pathogenesis of postacute COVID-19 syndrome. In *Trends in Molecular Medicine* (Vol. 27, Issue 9, pp. 895–906). Elsevier Ltd. https://doi.org/10.1016/j.molmed.2021.06.002

Lee, M. H., Perl, D. P., Steiner, J., Pasternack, N., Li, W., Maric, D., Safavi, F., Horkayne-Szakaly, I., Jones, R., Stram, M. N., Moncur, J. T., Hefti, M., Folkerth, R. D., & Nath, A. (2022). Neurovascular injury with complement activation and inflammation in COVID-19. *Brain*, *145*(7), 2555–2568. https://doi.org/10.1093/brain/awac151

Lim, E.-J., & Son, C.-G. (2020). Review of case definitions for myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS). *Journal of Translational Medicine*, *18*(1), 289. https://doi.org/10.1186/s12967-020-02455-0

Lou, J. J., Movassaghi, M., Gordy, D., Olson, M. G., Zhang, T., Khurana, M. S., Chen, Z., Perez-Rosendahl, M., Thammachantha, S., Singer, E. J., Magaki, S. D., Vinters, H. v., & Yong, W. H. (2021). Neuropathology of COVID-19 (neuro-COVID): clinicopathological update. In *Free Neuropathology* (Vol. 2). University of Muenster. https://doi.org/10.17879/freeneuropathology-2021-2993

Mackay, A. (2021). A Paradigm for Post-Covid-19 Fatigue Syndrome Analogous to ME/CFS. *Frontiers in Neurology*, *12*. https://doi.org/10.3389/fneur.2021.701419

Mackay, A., & Tate, W. P. (2018). A compromised paraventricular nucleus within a dysfunctional hypothalamus: A novel neuroinflammatory paradigm for ME/CFS. *International Journal of Immunopathology and Pharmacology*, *32*, 205873841881234. https://doi.org/10.1177/2058738418812342

Maes, M., Kubera, M., Uytterhoeven, M., Vrydags, N., & Bosmans, E. (2011). Increased plasma peroxides as a marker of oxidative stress in myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS). *Medical Science Monitor*, *17*(4), SC11–SC15. https://doi.org/10.12659/MSM.881699

Maes, M., Mihaylova, I., Kubera, M., & Bosmans, E. (2007). Not in the mind but in the cell: increased production of cyclo-oxygenase-2 and inducible NO synthase in chronic fatigue syndrome. *Neuro Endocrinology Letters*, *28*(4), 463–469.

Maksoud, R., du Preez, S., Eaton-Fitch, N., Thapaliya, K., Barnden, L., Cabanas, H., Staines, D., & Marshall-Gradisnik, S. (2020). A systematic review of neurological impairments in myalgic encephalomyelitis/chronic fatigue syndrome using neuroimaging techniques. *PLOS ONE*, *15*(4), e0232475. https://doi.org/10.1371/journal.pone.0232475

Malik, & Willnow. (2019). Excitatory Amino Acid Transporters in Physiology and Disorders of the Central Nervous System. *International Journal of Molecular Sciences*, *20*(22), 5671. https://doi.org/10.3390/ijms20225671

Matschke, J., Lütgehetmann, M., Hagel, C., Sperhake, J. P., Schröder, A. S., Edler, C., Mushumba, H., Fitzek, A., Allweiss, L., Dandri, M., Dottermusch, M., Heinemann, A., Pfefferle, S., Schwabenland, M., Sumner Magruder, D., Bonn, S., Prinz, M., Gerloff, C., Püschel, K., … Glatzel, M. (2020). Neuropathology of patients with COVID-19 in Germany: a post-mortem case series. *The Lancet Neurology*, *19*(11), 919–929. https://doi.org/10.1016/S1474-4422(20)30308-2

Meeus, M., van Eupen, I., van Baarle, E., de Boeck, V., Luyckx, A., Kos, D., & Nijs, J. (2011). Symptom fluctuations and daily physical activity in patients with chronic fatigue syndrome: A case-control study. *Archives of Physical Medicine and Rehabilitation*, *92*(11), 1820–1826. https://doi.org/10.1016/j.apmr.2011.06.023

Michelen, M., Manoharan, L., Elkheir, N., Cheng, V., Dagens, A., Hastie, C., O'Hara, M., Suett, J., Dahmash, D., Bugaeva, P., Rigby, I., Munblit, D., Harriss, E., Burls, A., Foote, C., Scott, J., Carson, G., Olliaro, P., Sigfrid, L., & Stavropoulou, C. (2021). Characterising long COVID: A living systematic review. In *BMJ Global Health* (Vol. 6, Issue 9). BMJ Publishing Group. https://doi.org/10.1136/bmjgh-2021-005427

Monje, M., & Iwasaki, A. (2022). The neurobiology of long COVID. In *Neuron*. Cell Press. https://doi.org/10.1016/j.neuron.2022.10.006

Moriguchi, T., Harii, N., Goto, J., Harada, D., Sugawara, H., Takamino, J., Ueno, M., Sakata, H., Kondo, K., Myose, N., Nakao, A., Takeda, M., Haro, H., Inoue, O., Suzuki-Inoue, K., Kubokawa, K., Ogihara, S., Sasaki, T., Kinouchi, H., … Shimada, S. (2020). A first case of meningitis/encephalitis associated with SARS-Coronavirus-2. *International Journal of Infectious Diseases*, *94*, 55–58. https://doi.org/10.1016/j.ijid.2020.03.062

Morris, G., & Maes, M. (2013a). Myalgic encephalomyelitis/chronic fatigue syndrome and encephalomyelitis disseminata/multiple sclerosis show remarkable levels of similarity in phenomenology and neuroimmune characteristics. *BMC Medicine*, *11*(1), 205. https://doi.org/10.1186/1741-7015-11-205

Morris, G., & Maes, M. (2013b). A neuro-immune model of Myalgic Encephalomyelitis/Chronic fatigue syndrome. *Metabolic Brain Disease*, *28*(4), 523–540. https://doi.org/10.1007/s11011-012-9324-8

Mueller, C., Lin, J. C., Sheriff, S., Maudsley, A. A., & Younger, J. W. (2020). *Evidence of widespread metabolite abnormalities in Myalgic Encephalomyelitis/Chronic Fatigue Syndrome: Assessment with whole-brain Magnetic Resonance Spectroscopy*.

Munblit, D., O'Hara, M. E., Akrami, A., Perego, E., Olliaro, P., & Needham, D. M. (2022). Long COVID: aiming for a consensus. In *The Lancet Respiratory Medicine* (Vol. 10, Issue 7, pp. 632–634). Elsevier Ltd. https://doi.org/10.1016/S2213-2600(22)00135-7

Nacul, L., Authier, F. J., Scheibenbogen, C., Lorusso, L., Helland, I. B., Martin, J. A., Sirbu, C. A., Mengshoel, A. M., Polo, O., Behrends, U., Nielsen, H., Grabowski, P., Sekulic, S., Sepulveda, N., Estévez-López, F., Zalewski, P., Pheby, D. F. H., Castro-Marrero, J., Sakkas, G. K., … Lacerda, E. M. (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. *Medicina*, *57*(5), 510. https://doi.org/10.3390/medicina57050510

Nakatomi, Y., Mizuno, K., Ishii, A., Wada, Y., Tanaka, M., Tazawa, S., Onoe, K., Fukuda, S., Kawabe, J., Takahashi, K., Kataoka, Y., Shiomi, S., Yamaguti, K., Inaba, M., Kuratsune, H., & Watanabe, Y. (2014). Neuroinflammation in patients with chronic fatigue syndrome/myalgic encephalomyelitis: An11C-

(R)-PK11195 PET study. *Journal of Nuclear Medicine*, *55*(6), 945–950. https://doi.org/10.2967/jnumed.113.131045

Natelson, B. H., Weaver, S. A., Tseng, C.-L., & Ottenweller, J. E. (2005). Spinal Fluid Abnormalities in Patients with Chronic Fatigue Syndrome. *Clinical and Vaccine Immunology*, *12*(1), 52–55. https://doi.org/10.1128/CDLI.12.1.52-55.2005

NICE. (2021). *NICE guideline [NG206]. Myalgic encephalomyelitis (or encephalopathy)/chronic fatigue syndrome: diagnosis and management.*

Nijs, J., Paul, L., & Wallman, K. (2008). *CHRONIC FATIGUE SYNDROME: AN APPROACH COMBINING SELF-MANAGEMENT WITH GRADED EXERCISE TO AVOID EXACERBATIONS**.

Paolini, M., Palladini, M., Mazza, M. G., Colombo, F., Vai, B., Rovere-Querini, P., Falini, A., Poletti, S., & Benedetti, F. (2023). Brain correlates of subjective cognitive complaints in COVID-19 survivors: A multimodal magnetic resonance imaging study. *European Neuropsychopharmacology*, *68*, 1–10. https://doi.org/10.1016/j.euroneuro.2022.12.002

Pedersen, B. K., & Saltin, B. (2015). Exercise as medicine - evidence for prescribing exercise as therapy in 26 different chronic diseases. *Scandinavian Journal of Medicine & Science in Sports*, *25*, 1–72. https://doi.org/10.1111/sms.12581

Perrin, R., Embleton, K., Pentreath, V. W., & Jackson, A. (2010). Longitudinal MRI shows no cerebral abnormality in chronic fatigue syndrome. *The British Journal of Radiology*, *83*(989), 419–423. https://doi.org/10.1259/bjr/85621779

Petersen, M., Felix, † ;, Nägele, L., Mayer, C., Schell, M., Petersen, E., Kühn, S., Gallinat, J., Fiehler, J., Pasternak, O., Matschke, J., Glatzel, M., Twerenbold, R., Gerloff, C., Thomalla, G., & Cheng, B. (2022). *Brain imaging and neuropsychological assessment of individuals recovered from a mild to moderate SARS-CoV-2 infection*. https://doi.org/10.1101/2022.07.08.22277420

Peterson, D., Brenu, E. W., Gottschalk, G., Ramos, S., Nguyen, T., Staines, D., & Marshall-Gradisnik, S. (2015). Cytokines in the Cerebrospinal Fluids of Patients with Chronic Fatigue Syndrome/Myalgic Encephalomyelitis. *Mediators of Inflammation*, *2015*, 1–4. https://doi.org/10.1155/2015/929720

Puri, B. K., Counsell, S. J., Zaman, R., Main, J., Collins, A. G., Hajnal, J. v., & Davey, N. J. (2002). Relative increase in choline in the occipital cortex in chronic fatigue syndrome. *Acta Psychiatrica Scandinavica*, *106*(3), 224–226. https://doi.org/10.1034/j.1600-0447.2002.01300.x

Puri, B. K., Jakeman, P. M., Agour, M., Gunatilake, K. D. R., Fernando, K. A. C., Gurusinghe, A. I., Treasaden, I. H., Waldman, A. D., & Gishen, P. (2012). Regional grey and white matter volumetric changes in myalgic encephalomyelitis (chronic fatigue syndrome): a voxel-based morphometry 3 T MRI study. *The British Journal of Radiology*, *85*(1015), e270–e273. https://doi.org/10.1259/bjr/93889091

Rajan, S., Khunti, K., Alwan, N., Steves, C., MacDermott, N., Morsella, A., Angulo, E., Winkelmann, J., Bryndová, L., Fronteira, I., & ... (2021). *In the wake of the pandemic: Preparing for Long COVID. European Observatory on Health Systems and Policies.*

Rayhan, R. U., & Baraniuk, J. N. (2021). Submaximal Exercise Provokes Increased Activation of the Anterior Default Mode Network During the Resting State as a Biomarker of Postexertional Malaise in Myalgic Encephalomyelitis/Chronic Fatigue Syndrome. *Frontiers in Neuroscience*, *15*. https://doi.org/10.3389/fnins.2021.748426

Razumovsky, A. Y., DeBusk, K., Calkins, H., Snader, S., Lucas, K. E., Vyas, P., Hanley, D. F., & Rowe, P. C. (2003). Cerebral and systemic hemodynamics changes during upright tilt in chronic fatigue syndrome. *Journal of Neuroimaging : Official Journal of the American Society of Neuroimaging*, *13*(1), 57–67.

Reese, J. T., Blau, H., Bergquist, T., Loomba, J. J., Callahan, T., Laraway, B., Antonescu, C., Casiraghi, E., Coleman, B., Gargano, M., Wilkins, K. J., Cappelletti, L., Fontana, T., Ammar, N., Antony, B., Murali, T. M., Karlebach, G., McMurry, J. A., Williams, A., … RECOVER Consortium. (2022). Generalizable Long COVID Subtypes: Findings from the NIH N3C and RECOVER Programs. *MedRxiv : The Preprint Server for Health Sciences*. https://doi.org/10.1101/2022.05.24.22275398

Reid, H., Ridout, A. J., Tomaz, S. A., Kelly, P., & Jones, N. (2022). Benefits outweigh the risks: a consensus statement on the risks of physical activity for people living with long-term conditions. *British Journal of Sports Medicine*, *56*(8), 427–438. https://doi.org/10.1136/bjsports-2021-104281

Renz-Polster, H., Tremblay, M. E., Bienzle, D., & Fischer, J. E. (2022). The Pathobiology of Myalgic Encephalomyelitis/Chronic Fatigue Syndrome: The Case for Neuroglial Failure. *Frontiers in Cellular Neuroscience*, *16*. https://doi.org/10.3389/fncel.2022.888232

Rosenthal, C. R., Roche-Kelly, E. E., Husain, M., & Kennard, C. (2009). Response-Dependent Contributions of Human Primary Motor Cortex and Angular Gyrus to Manual and Perceptual Sequence Learning. *Journal of Neuroscience*, *29*(48), 15115–15125. https://doi.org/10.1523/JNEUROSCI.2603-09.2009

Schurink, B., Roos, E., Radonic, T., Barbe, E., Bouman, C. S. C., de Boer, H. H., de Bree, G. J., Bulle, E. B., Aronica, E. M., Florquin, S., Fronczek, J., Heunks, L. M. A., de Jong, M. D., Guo, L., du Long, R., Lutter, R., Molenaar, P. C. G., Neefjes-Borst, E. A., Niessen, H. W. M., … Bugiani, M. (2020a). Viral presence and immunopathology in patients with lethal COVID-19: a prospective autopsy cohort study. *The Lancet Microbe*, *1*(7), e290–e299. https://doi.org/10.1016/S2666-5247(20)30144-0

Schurink, B., Roos, E., Radonic, T., Barbe, E., Bouman, C. S. C., de Boer, H. H., de Bree, G. J., Bulle, E. B., Aronica, E. M., Florquin, S., Fronczek, J., Heunks, L. M. A., de Jong, M. D., Guo, L., du Long, R., Lutter, R., Molenaar, P. C. G., Neefjes-Borst, E. A., Niessen, H. W. M., … Bugiani, M. (2020b). Viral presence and immunopathology in patients with lethal COVID-19: a prospective autopsy cohort study. *The Lancet Microbe*, *1*(7), e290–e299. https://doi.org/10.1016/S2666-5247(20)30144-0

Shah, W., Hillman, T., Playford, E. D., & Hishmeh, L. (2021). Managing the long term effects of covid-19: summary of NICE, SIGN, and RCGP rapid guideline. *BMJ*, n136. https://doi.org/10.1136/bmj.n136

Shan, Z. Y., Barnden, L. R., Kwiatek, R. A., Bhuta, S., Hermens, D. F., & Lagopoulos, J. (2020). Neuroimaging characteristics of myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS): a systematic review. *Journal of Translational Medicine*, *18*(1), 335. https://doi.org/10.1186/s12967-020-02506-6

Shepherd. (2022). *LONG COVID AND ME/CFS ARE THEY THE SAME?*

Spreng, R. N., & Grady, C. L. (2010). Patterns of Brain Activity Supporting Autobiographical Memory, Prospection, and Theory of Mind, and Their Relationship to the Default Mode Network. *Journal of Cognitive Neuroscience*, *22*(6), 1112–1123. https://doi.org/10.1162/jocn.2009.21282

Steenblock, C., Todorov, V., Kanczkowski, W., Eisenhofer, G., Schedl, A., Wong, M.-L., Licinio, J., Bauer, M., Young, A. H., Gainetdinov, R. R., & Bornstein, S. R. (2020). Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and the neuroendocrine stress axis. *Molecular Psychiatry*, *25*(8), 1611–1617. https://doi.org/10.1038/s41380-020-0758-9

Stillman, C. M., Esteban-Cornejo, I., Brown, B., Bender, C. M., & Erickson, K. I. (2020). Effects of Exercise on Brain and Cognition Across Age Groups and Health States. *Trends in Neurosciences*, *43*(7), 533–543. https://doi.org/10.1016/j.tins.2020.04.010

Sukocheva, O. A., Maksoud, R., Beeraka, N. M., Madhunapantula, S. v., Sinelnikov, M., Nikolenko, V. N., Neganova, M. E., Klochkov, S. G., Amjad Kamal, M., Staines, D. R., & Marshall-Gradisnik, S. (2022). Analysis of post COVID-19 condition and its overlap with myalgic encephalomyelitis/chronic fatigue syndrome. *Journal of Advanced Research*, *40*, 179–196. https://doi.org/10.1016/j.jare.2021.11.013

Tabacof, L., Tosto-Mancuso, J., Wood, J., Cortes, M., Kontorovich, A., McCarthy, D., Rizk, D., Rozanski, G., Breyman, E., Nasr, L., Kellner, C., Herrera, J. E., & Putrino, D. (2022). Post-acute COVID-19 Syndrome Negatively Impacts Physical Function, Cognitive Function, Health-Related Quality of Life, and Participation. *American Journal of Physical Medicine & Rehabilitation*, *101*(1), 48–52. https://doi.org/10.1097/PHM.0000000000001910

Tate, W., Walker, M., Sweetman, E., Helliwell, A., Peppercorn, K., Edgar, C., Blair, A., & Chatterjee, A. (2022). Molecular Mechanisms of Neuroinflammation in ME/CFS and Long COVID to Sustain Disease and Promote Relapses. *Frontiers in Neurology*, *13*. https://doi.org/10.3389/fneur.2022.877772

Tomas, C., Newton, J., & Watson, S. (2013). A Review of Hypothalamic-Pituitary-Adrenal Axis Function in Chronic Fatigue Syndrome. *ISRN Neuroscience*, *2013*, 1–8. https://doi.org/10.1155/2013/784520

Tomoda, A., Miike, T., Yamada, E., Honda, H., Moroi, T., Ogawa, M., Ohtani, Y., & Morishita, S. (2000). Chronic fatigue syndrome in childhood. *Brain and Development*, *22*(1), 60–64. https://doi.org/10.1016/S0387-7604(99)00111-4

Townsend, L., Dyer, A. H., Jones, K., Dunne, J., Mooney, A., Gaffney, F., O'Connor, L., Leavy, D., O'Brien, K., Dowds, J., Sugrue, J. A., Hopkins, D., Martin-Loeches, I., Ni Cheallaigh, C., Nadarajan, P., McLaughlin, A. M., Bourke, N. M., Bergin, C., O'Farrelly, C., … Conlon, N. (2020). Persistent fatigue following SARS-CoV-2 infection is common and independent of severity of initial infection. *PLOS ONE*, *15*(11), e0240784. https://doi.org/10.1371/journal.pone.0240784

Twomey, R., Demars, J., Franklin, K., Culos-Reed, S. N., Weatherald, J., & Wrightson, J. G. (2021). *Chronic fatigue and post-exertional malaise in people living with long COVID*. https://doi.org/10.1101/2021.06.11.21258564

van Campen, C. (Linda) M. C., Rowe, P. C., & Visser, F. C. (2021). Cerebral blood flow remains reduced after tilt testing in myalgic encephalomyelitis/chronic fatigue syndrome patients. *Clinical Neurophysiology Practice*, *6*, 245–255. https://doi.org/10.1016/j.cnp.2021.09.001

van Campen, C. (Linda) M. C., Verheugt, F. W. A., Rowe, P. C., & 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. *Clinical Neurophysiology Practice*, *5*, 50–58. https://doi.org/10.1016/j.cnp.2020.01.003

van Campen, C. (Linda) M. C., & Visser, F. C. (2022). Orthostatic Intolerance in Long-Haul COVID after SARS-CoV-2: A Case-Control Comparison with Post-EBV and Insidious-Onset Myalgic Encephalomyelitis/Chronic Fatigue Syndrome Patients. *Healthcare (Switzerland)*, *10*(10). https://doi.org/10.3390/healthcare10102058

van Campen, C. (Linda) M. C. van, Rowe, P. C., & Visser, F. C. (2021). Orthostatic Symptoms and Reductions in Cerebral Blood Flow in Long-Haul COVID-19 Patients: Similarities with Myalgic Encephalomyelitis/Chronic Fatigue Syndrome. *Medicina*, *58*(1), 28. https://doi.org/10.3390/medicina58010028

van Campen, C. (Linda) M. van, Rowe, P. C., & Visser, F. C. (2020). Reductions in Cerebral Blood Flow Can Be Provoked by Sitting in Severe Myalgic Encephalomyelitis/Chronic Fatigue Syndrome Patients. *Healthcare*, *8*(4), 394. https://doi.org/10.3390/healthcare8040394

VanElzakker, M. B., Brumfield, S. A., & Lara Mejia, P. S. (2019). Neuroinflammation and Cytokines in Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS): A Critical Review of Research Methods. *Frontiers in Neurology*, *9*. https://doi.org/10.3389/fneur.2018.01033

Visser, D., Golla, S. S. v, Verfaillie, S. C. J., Coomans, E. M., Rikken, R. M., van de Giessen, E. M., den Hollander, M. E., Verveen, A., Yaqub, M., Barkhof, F., Horn, J., Koopman, B., Schober, P., Koch, D. W., Schuit, R. C., Windhorst, A. D., Kassiou, M., Boellaard, R., van Vugt, M., … van Berckel, B. N. M.

(2022). *Long COVID is associated with extensive in-vivo neuroinflammation on [18 F]DPA-714 PET*. https://doi.org/10.1101/2022.06.02.22275916

von Weyhern, C. H., Kaufmann, I., Neff, F., & Kremer, M. (2020). Early evidence of pronounced brain involvement in fatal COVID-19 outcomes. *The Lancet*, *395*(10241), e109. https://doi.org/10.1016/S0140-6736(20)31282-4

Washington, S. D., Rayhan, R. U., Garner, R., Provenzano, D., Zajur, K., Addiego, F. M., VanMeter, J. W., & Baraniuk, J. N. (2020). Exercise alters brain activation in Gulf War Illness and Myalgic Encephalomyelitis/Chronic Fatigue Syndrome. *Brain Communications*, *2*(2). https://doi.org/10.1093/braincomms/fcaa070

White, A. T., Light, A. R., Hughen, R. W., Bateman, L., Martins, T. B., Hill, H. R., & Light, K. C. (2010). Severity of symptom flare after moderate exercise is linked to cytokine activity in chronic fatigue syndrome. *Psychophysiology*, *47*(4), 615–624. https://doi.org/10.1111/j.1469-8986.2010.00978.x

Wong, T. L., & Weitzer, D. J. (2021a). Long COVID and myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS)-A systemic review and comparison of clinical presentation and symptomatology. *Medicina (Lithuania)*, *57*(5). https://doi.org/10.3390/medicina57050418

World Health Organization. (2022, January 1). *International Statistical Classification of Diseases and Related Health Problems (ICD)*. Https://Www.Who.Int/Standards/Classifications/Classification-of-Diseases.

Wortinger, L. A., Glenne Øie, M., Endestad, T., & Bruun Wyller, V. (2017). Altered right anterior insular connectivity and loss of associated functions in adolescent chronic fatigue syndrome. *PLOS ONE*, *12*(9), e0184325. https://doi.org/10.1371/journal.pone.0184325

Wright, J., Astill, S. L., & Sivan, M. (2022). The Relationship between Physical Activity and Long COVID: A Cross-Sectional Study. *International Journal of Environmental Research and Public Health*, *19*(9). https://doi.org/10.3390/ijerph19095093

Yong, S. J., & Liu, S. (2022). Proposed subtypes of post-COVID-19 syndrome (or long-COVID) and their respective potential therapies. In *Reviews in Medical Virology* (Vol. 32, Issue 4). John Wiley and Sons Ltd. https://doi.org/10.1002/rmv.2315

Yoshiuchi, K., Farkas, J., & Natelson, B. H. (2006). Patients with chronic fatigue syndrome have reduced absolute cortical blood flow. *Clinical Physiology and Functional Imaging*, *26*(2), 83–86. https://doi.org/10.1111/j.1475-097X.2006.00649.x