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Respiratory psychophysiology and COVID-19: A research agenda

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A B S T R A C T

After multiple waves of the COVID-19 pandemic, it has become clear that the impact of SARS-CoV-2 will carry on for years to come. Acutely infected patients show a broad range of disease severity, depending on virus variant, vaccination status, age and the presence of underlying medical and physical conditions, including obesity. Additionally, a large number of patients who have been infected with the virus present with post-COVID syndrome. In September 2020, the International Society for the Advancement of Respiratory Psychophysiology organized a virtual interest meeting on 'Respiratory research in the age of COVID-19', which aimed to discuss how research in respiratory psychophysiology could contribute to a better understanding of psychophysiological interactions in COVID-19. In the resulting current paper, we propose an interdisciplinary research agenda discussing selected research questions on acute and long-term neurobiological, physiological and psychological outcomes and mechanisms related to respiration and the airways in COVID-19, as well as research questions on comorbidity and potential treatment options, such as physical rehabilitation.

1. Case report

"Ten days ago, Catharina, a 64-year old retired teacher, had a positive coronavirus test. She suffered from fatigue, diffuse muscle pain, intermittent fever and loss of taste. In addition to Acetaminophen, she took her daily dose of antihypertensive medication and stayed indoors for a week. However, dyspnea[1] became gradually worse, which made her consult the emergency physician at the local hospital. On admission, she had a peripheral oxygen saturation of 85% while breathing ambient air, a fever of 39.1 degrees Celsius and a respiration rate of 17 breaths/min. After initiating supplemental oxygen therapy (5 L/min), arterial blood gas levels showed a PO_2 of 64 mmHg with normal pH and lactate levels. A chest X-Ray showed bilateral lung infiltrates and confirmed the diagnosis of COVID-19 pneumonia with potential bacterial superinfection. Catharina was transferred to the COVID-19 ward where systemic corticosteroids (Dexamethasone 1 ×6 mg/d PO) and prophylactic antibiotics

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[1] Dyspnea is defined as "a subjective experience of breathing discomfort that consists of qualitatively distinct sensations that vary in intensity" (Parshall et al., 2012, p.436).

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(Augmentin 4 ×1 g/d IV) were started. An anticoagulant medication (Fraxiparine 1 ×0.6 ml SC daily) was added to prevent thrombo-embolic complications. On Day 3 after admission, her condition worsened with increasing dyspnea. Catharina was transferred to the intensive care facility for high flow oxygen therapy and invasive monitoring. Because of COVID-19 associated isolation measures, she barely saw her three children and husband during the illness. Hospital policy did not allow visitors on COVID-19 wards. She had an intense fear of dying alone without seeing her family again. Hospital staff, faced with a new disease was not able to provide information on the prognosis with confidence. Catharina recovered, and while her peripheral oxygen saturation returned to normal, her symptoms of dyspnea and fatigue persisted, and she developed post-COVID syndrome, including cognitive disturbances and anxiety. She currently participates in a rehabilitation program hoping to relieve remaining symptoms."

This clinical vignette of a COVID-19 patient outlines a representative symptom profile and treatment decisions consistent with a very severe, acute case of COVID-19, followed by the development of post-COVID syndrome. This case demonstrates how the COVID-19 pandemic has provided both opportunities and challenges for medicine and science. The key responsibilities and perspectives of respiratory psychoneurobiological research in the light of the COVID-19 pandemic were discussed at the 2020 virtual meeting of the International Society for the Advancement of Respiratory Psychophysiology (ISARP). During this meeting, an ad-hoc panel of experts in the domains of psychoneurobiology of breathing and behavioral medicine of respiratory diseases was formed to discuss topics and priorities for future research. Following this meeting, panel members integrated the various perspectives and ideas that had arisen from this exchange and invited additional experts in the domain of respiratory research to enrich the discussions. Based on the contributions of this expanded interdisciplinary panel of experts in respiratory and cardiovascular physiology, psychoneuroimmunology, psychology and rehabilitation science, an interdisciplinary research agenda on key respiratory psychoneurobiological topics in COVID-19 emerged.

The overall aim of this research agenda is to inspire researchers in the field of respiratory psychoneurobiology by formulating research questions of interest pertaining to COVID-19. The current research agenda focuses particularly on specific interactions between psychological and neurobiological aspects of breathing related to COVID-19, challenging and encouraging researchers to initiate or continue interdisciplinary research aligning with and extending beyond their specialization. To visualize these psychoneurobiological interactions, we integrated the selected topics of discussion in the current research agenda in a summary figure (Fig. 1). By means of this summary figure, we aim to (1) represent the core psychoneurobiological interactions discussed in this paper in an ad-hoc model of respiratory research on COVID-19, and (2) evoke many more research questions based on the readers' background and expertise.

In line with the model in Fig. 1, we will present a selected research agenda on respiratory psychophysiology related to COVID-19 pertaining to the following topics. First, we will introduce the clinical and physiological basis of COVID-19. Next, we propose research questions pertaining to the neurobiological and psychological characteristics of COVID-19, and interactions between both, as they are relevant to the study of respiratory psychophysiology. In addition, we will discuss important research avenues related to comorbidity with respiratory diseases, such as asthma and chronic obstructive pulmonary disease (COPD), and anxiety disorders. Finally, we outline research directions on potential treatment options, such as physical rehabilitation. Given the specific aim of this research agenda, we do not attempt to provide an in-depth state of the art of psychoneurobiological research related to COVID-19. Rather, we aim to highlight the breadth of challenges and opportunities COVID-19 has created for the discipline of respiratory psychophysiology.

Post-COVID syndrome, also referred to as Post-Acute Sequelae of SARS-CoV-2 (PASC) or long COVID, is the persistence of symptoms, typically including respiratory symptoms and fatigue, three months post COVID that cannot be explained by an alternative diagnosis, for a duration of at least two months (World Health Organization, 2021). Estimations of such long-term consequences of COVID-19 infection ranged between 25 % and 50 % of survivors of all severity grades, which could present a massive present and future challenge for health research and care worldwide (Groff et al., 2021). Taking into account the level of pre-COVID symptoms and comparing with a matched non-COVID sample, a more recent study found elevated symptoms at 3–5 months due to the COVID infection in 12.7 % of the cases (Ballering et al., 2022). This appears markedly lower, but still translates into 12 million cases in the USA alone (based on close to 96 million total cases in the US - as of September 23, 2022, according to the Center for Disease Control [CDC] Data Tracker, https://covid.cdc.gov/covid-data-tracker/#datatracker-home). Although mechanisms of post-COVID syndrome are still widely investigated (Castanares-Zapatero et al., 2022), our research agenda will also address emerging trends in the study of this condition.

1.1. The cardiorespiratory physiology of COVID-19

The primary clinical manifestation of COVID-19 viral infections that require hospitalization is acute hypoxic failure of the respiratory system. This is the result of the action of the virus on the pulmonary vasculature and diffusion exchange area (Radovanovic et al., 2020). The viral infection elicits a severe hypercoagulation affecting the perfusion of the pulmonary vessels (Cleveland Manchanda et al., 2019; Nopp et al., 2020; Ranucci et al., 2020; Spiezia et al., 2020). The coagulation pattern is widespread pulmonary microthrombosis that leads to ventilation-perfusion inequalities. The obstruction of perfusion to regions of alveoli results in an increase in physiological dead space, ventilated but underperfused alveoli. Since the entire right ventricular cardiac output passes through the pulmonary circulation, blockage of any pulmonary vessel results in redistribution of increased blood flow through patent vessels. This results in an increased blood flow velocity and a decreased capillary transit time, reducing the time available for oxygen equilibration between alveoli and pulmonary capillary. The areas of increased pulmonary blood flow will also have an increased capillary filtration pressure increasing fluid flow out of the capillary producing expansion of the pulmonary interstitial space resulting in pulmonary edema. The pulmonary edema causes the diffusing capacity of the lung for carbon monoxide (DLCO[2]) to decrease. The increase in physiological dead space and the decreases in DLCO result in acute hypoxemia with either normal or low levels of carbon dioxide (Mo et al., 2020). In hospitalized COVID-19 patients, lung compliance and airway resistance remain within normal values (Ziehr et al., 2020). However, there is some evidence of reduced total lung capacity (TLC) due to a decreased residual volume (RV). Thus, the initial effects of the SARS-CoV-2 infection are on the pulmonary vasculature with smaller effects on lung mechanics. Long-term effects are more likely of a restrictive than obstructive nature (Smet et al., 2021; Stockley et al., 2021).

1.2. A research agenda

Below, we outline research areas relevant to the study of respiratory psychophysiology and emerging research questions and challenges pertaining to the neurobiology and psychology of COVID-19 infection and post-COVID syndrome.

[2] DLCO is a standard test to assess the transfer capacity of oxygen from inspired air to red blood cells by means of inhaled carbon monoxide as a surrogate for oxygen.

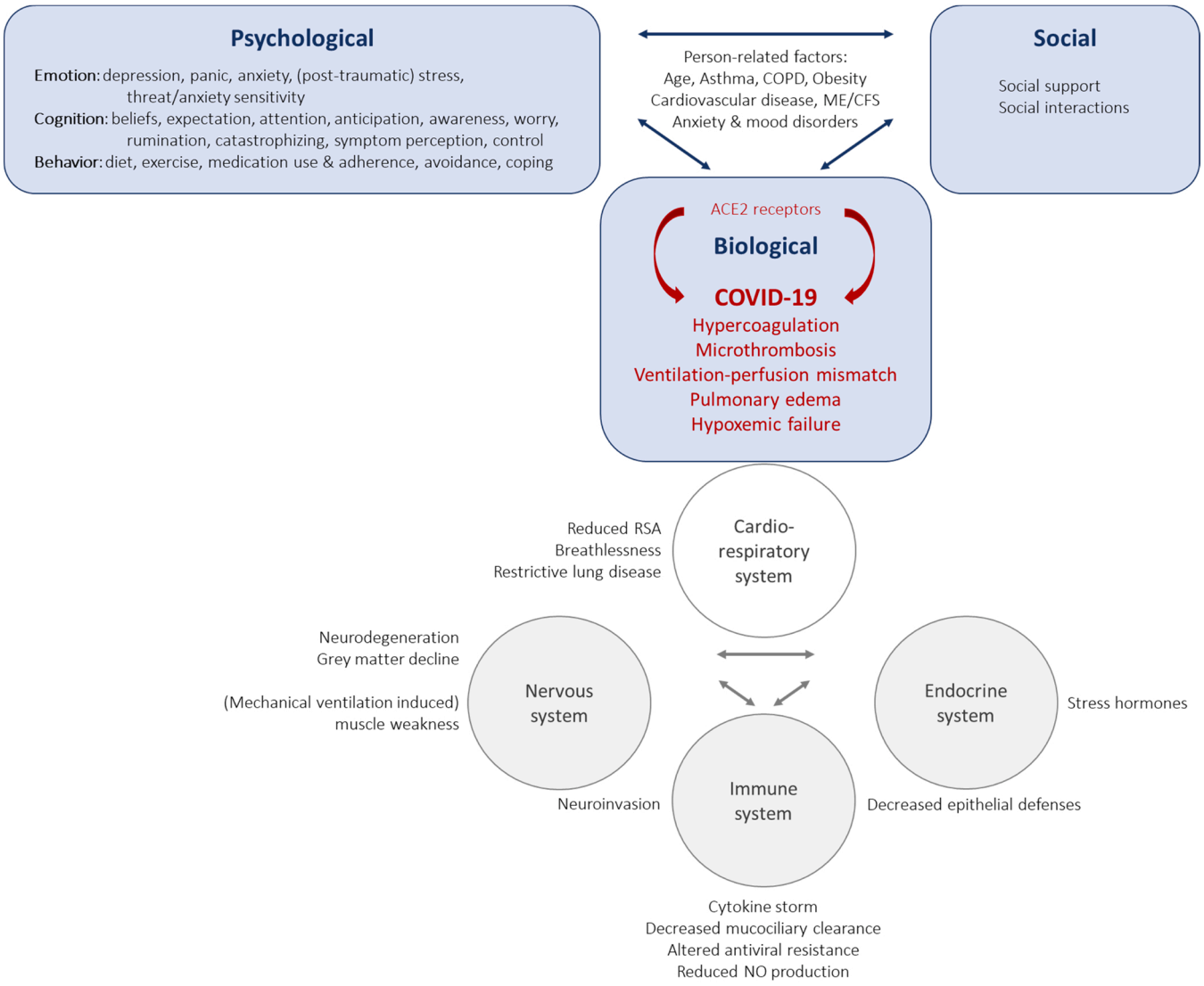

Fig. 1. A psychoneurobiological model of respiratory research on COVID-19.

2. Psychoneuroimmunology and psychoendocrinology of COVID-19

2.1. Cytokine imbalance in the central nervous system (CNS)

As patients experience respiratory symptoms, the first thought is that these symptoms are explained by the infected lung. However, this is only a partial explanation, since inflammatory processes within the lung lead rapidly to changes in the CNS, in particular within the neuronal networks in the brainstem that control breathing and cardiorespiratory coupling (Boldrini et al., 2021; Sarubbo et al., 2022). A cytokine storm within these central networks would have dramatic consequences on breathing and cardiorespiratory coupling, while at the same time affecting psychological well-being. The peripheral inflammatory response to infection has been shown to trigger sickness behavior characterized by dysphoria, fatigue, and fever, due to proinflammatory cytokine activity that acts centrally on microglia, either directly by crossing the blood-brain barrier, or indirectly through vagal afferents (Dantzer et al., 2008; Lasselin et al., 2020). Even greater sequelae can be expected through massive mobilization of cytokines in SARS-CoV-2 infection (Debnath et al., 2020). However, animal research suggests that effects on respiration in the context of hypoxia may differ between types of proinflammatory cytokines, whereby IL-1β and TNF-1α levels appear to blunt compensatory ventilation increases, while IL-6 accentuates it and also inhibits post-hypoxic breathing restoration (Donina et al., 2021).

Concrete studies to characterize the cytokine storm within the CNS and its effects on respiration and psychological wellbeing could include:

- assessing inflammatory markers in identified brainstem regions known to be critical for the control of breathing and cardiorespiratory coupling,
- characterizing the inflammatory response complemented by a characterization of oxidative and hypoxic stress as well as microglial activation,
- examining differential cytokine effects on CNS control of breathing, cardiorespiratory integration, and ventilation,
- assessing specific psychological symptom profiles of excessive cytokine activity,
- exploring effects on respiration secondary to the psychological symptomatology of excessive cytokine activity,
- exploring how psychological stress (e.g. associated with post-COVID syndrome) can moderate effects of excessive cytokine activity.

Moreover, as the virus enters cells by binding to the angiotensin-converting enzyme (ACE) 2 receptors, it is conceivable that neurons

and glia within the CNS that contain these receptors are directly affected. To better assess the consequences of ACE2 binding on cardio-respiratory coupling and breathing, it will be critical to:

- characterize the distribution of ACE2 receptors in critical brainstem regions. For this it is important to conduct such a study in human brain tissue, since the distribution and characteristics of ACE2 receptors is known to differ in animal models,
- compare ACE2 receptor distribution in younger and older patients to address the question whether changes in ACE2 receptors could explain the increased risk for sudden death in older patients,
- compare ACE2 receptor distribution in patients with comorbidities known to increase the risk to succumb to COVID-19,
- study the expression of ACE2 receptors under conditions of chronic psychological stress (e.g. typically associated with post-COVID syndrome).

2.2. Neurodegeneration and neuroplasticity

Several studies have demonstrated that COVID-19 can be associated with damage of brain tissue including both macro- and micro-hypoxic or ischemic injuries and infarcts (Bhola et al., 2022; Boldrini et al., 2021; Manca et al., 2021). The exact underlying mechanisms are yet to be elucidated, but likely include peripheral inflammatory signaling to the CNS via immune-to-brain signaling pathways and/or neuroinvasion (a direct SARS-CoV-2 infection of neurons in the CNS) (Sarubbo et al., 2022). Such disease-related processes in the CNS may also impact the structure and function of higher brain areas (above the brainstem respiratory centers) related to respiration and the perception of respiratory symptoms, such as breathlessness and cough (Davenport & Vovk, 2009; Evans, 2010; Marlow et al., 2019). Breathlessness, or dyspnea, is a common symptom in COVID-19 patients, in particular those with longer lasting symptomatology (Lopez-Leon et al., 2021; Nasserie et al., 2021). COVID-19 survivors show signs of gray matter decline or tissue damage in frontal, olfactory cortex, and limbic regions as well as greater reduction in global brain size (Douaud et al., 2022). Moreover, COVID-19 effects on the brain may also impact the known interactions of these symptoms with cognitive, emotional and social factors (von Leupoldt & Denutte, 2020), and relate to the frequently reported cognitive-emotional symptoms such as depression, anxiety and cognitive impairments (Bhola et al., 2022; Nalbandian et al., 2021; Taquet et al., 2021). For a better understanding of these interactions, various techniques ranging from functional/structural brain imaging (e.g., Kandemirli et al., 2020) and electrophysiological/-magnetic measures in humans to cellular, synaptic and molecular read outs in animal models (e.g., Frank et al., 2022) might be used. Important studies for improving our current knowledge could include:

- extensive testing of COVID-19 related brain injuries and potential neurodegeneration including underlying pathways,
- systematic examination of COVID-19 related short-term and long-term neural plasticity,
- studying acute and chronic functional brain responses to inflammatory processes and respiratory sensations in COVID-19 patients,
- testing the potential role of respiratory neural gating[3] with regards to increased burden of breathlessness in COVID-19 patients (Herzog et al., 2018),
- examining the potential role of (para-)limbic and pre-frontal cortex structure and function for respiratory and cognitive-emotional symptoms in COVID-19 patients,
- studying potential benefits of brain stimulation on respiratory and cognitive-emotional symptoms in COVID-19 patients,
- testing the role of functional and structural neural changes in response to treatments, as well as for post-COVID syndrome trajectories, in particular for persistent cognitive-emotional symptoms.

2.3. Airway immune defense

Psychological stress is known to elevate the risk for common cold and other viral respiratory infections (Falagas et al., 2010; Pedersen et al., 2010). Evidence for this comes from both observational and experimental respiratory infection studies (Cobb & Steptoe, 1998; Cohen et al., 1991). On the other hand, greater social support is protective against the development of respiratory infection symptoms (Cohen et al., 1997). The high psychological stress levels and weakened social support during the global COVID-19 pandemic has created an immune environment that facilitates the viral infection. Further, the psychophysiological and clinical dysfunction associated with post-COVID syndrome fosters increased and persistent anxiety, depression and heightened stress perception (Lamontagne et al., 2021).

The immune system commands over a number of defense mechanisms against pathogens. The airways, forming a first line of defense, use a range of mechanisms to protect against viral assault, such as epithelial barrier function, mucociliary clearance, and secretion of immune active peptides and other molecules. Psychosocial stress has been shown to negatively affect these functions in various ways (Peters et al., 2021; Trueba & Ritz, 2013). Mucociliary clearance, which helps eliminating pathogens from the nasal mucosa, was weakened in chronically stressed guinea pigs (Almeida-Reis et al., 2010) and greater social support in human experimental rhinovirus infection was related to better clearance (Cohen et al., 1997). Mucosal protection in early phases of SARS-CoV-2 infection of the upper airways is also provided by secretory immunoglobulin A, which protects epithelia by blocking attachment of viruses to epithelia, neutralizing them, and facilitating their removal by mucus (Russell et al., 2020). As with other immune functions (Dhabhar, 2009), acute stress often serves to strengthen epithelial defenses, whereas chronic stress has weakening effects, due to stress hormones or neurotransmitter systems, which can be expected to be activated in pandemic stress. For example, glucocorticoids, mobilized in longer lasting, chronic states of stress and depression (Agorastos & Chrousos, 2022; Dhabhar, 2009; McEwen, 1998), can weaken tight junctions between epithelial cells and increase permeability of the skin and intestines for pathogens (Choe et al., 2018; Peters et al., 2021). Among many other immunosuppressant effects, stress-induced glucocorticoids also compromise interferon-gamma production (Marshall et al., 1998), which is critical in antiviral defense. All barrier forming cells, including the airway epithelium, express ACE2 receptors, which are the main entry point for the SARS-CoV-2 virus (Hanchard et al., 2020). Infected epithelial goblet cells lead to inflammation and impaired mucociliary clearance. Inflammatory processes could also be enhanced by glucocorticoid receptor sensitivity, as a consequence of chronically elevated glucocorticoid levels (Cohen et al., 2012). Experiences of traumatic stress related to pandemic events or chronic fatigue may also reduce cortisol levels and thus favor an inflammatory state (Fries et al., 2005).

Based on this evidence, more research is recommended in the following areas:

- elucidating whether stressors and emotional states of (post-traumatic) anxiety, depression and fatigue, acutely and post COVID during the COVID-19 pandemic increase vulnerability to SARS-CoV-2 infection through compromise of epithelial protective pathways,
- studying the effect of pandemic-related stressors and emotional states on stress hormone levels and hormonal receptor sensitivity as mediators of altered airway inflammation and susceptibility to infection,
- exploring the potential synergistic role of psychosocial stress and SARS-CoV-2 infection on mucosal immunity and its effect on severity and treatment outcome for COVID-19,

[3] Respiratory neural gating refers to the neural filter mechanism that allows normal breathing and breathing sensations to occur outside awareness.

- examining potentially diverging effects of acute and chronic stress on epithelial function and differential vulnerability to SARS-CoV-2 infection,
- studying the role of stressors and emotional states of (post-traumatic) anxiety, depression and fatigue, acutely and post COVID in inducing variability in COVID-19 vaccination response and thus elevated upper and lower airway infection susceptibility.

Nitric oxide (NO) secreted by epithelial cells constitutes a major innate defense mechanism of the airways against respiratory viruses. In respiratory infections, NO in exhaled air is markedly elevated (Proud, 2005), and higher levels of airway NO (either endogenous or induced by a dietary NO donor) reduce the susceptibility to respiratory infections in periods of stress (Ritz et al., 2018; Ritz et al., 2019). Longer lasting stress or depression are associated with reduced NO levels (Cepeda et al., 2016; Kullowatz et al., 2008; Ritz et al., 2015; Trueba et al., 2013), and conversely, social support has been associated with higher exhaled NO levels (Trueba et al., 2014). Defects in NO production of the nasal epithelia compromise mucociliary clearance. The mechanisms behind stress-induced NO deficits are not yet fully understood, but may be related to oxidative stress and other competitors that reduce bioavailability of NO precursors or converting enzyme levels (van den Berg et al., 2018).

NO levels are also affected by SARS-CoV-2 infection, which incapacitates ACE2 receptors that are critical for the pathway generating endothelial NO, accounting for at least some of the cardiovascular dysregulation seen in COVID-19. Inhaled NO has been in use for treating severely infected coronavirus patients, with both vasodilatory and anti-viral effects as the rationale (Ignarro, 2020). Thus, boosting airway NO in the context of the COVID-19 pandemic, which is also accompanied by significant long-term distress and depletion of social support, could be assumed to be protective (Ritz et al., 2021).

Our current understanding of epithelial defenses and stress in the context of COVID-19 would profit from the following lines of research:

- examining the potential of NO donors (dietary, pharmacological, inhaled etc.) for prevention and treatment of COVID-19 in patients with varying acute and chronic background stress levels,
- exploring whether patients with existing respiratory disease, and varying phenotypes of it, are more vulnerable to weakening of epithelial defenses through stress and COVID-19,
- exploring whether production of NO by various cells is differentially affected by psychosocial stress and differentially protective against infections (e.g. high levels of NO through other immune cells like macrophages or eosinophils),
- exploring how gene polymorphisms related to production of interferon gamma, NO synthases, or antioxidants moderate the effects of stress on NO and protective effects of NO, and NO donors, against SARS-CoV-2 infection.

For further general considerations regarding the psychoneuroimmunology of COVID-19 beyond respiration, the reader is referred to relevant publications (e.g., Debnath et al., 2020; Peters et al., 2021; Raony et al., 2020; Troyer et al., 2020).

3. Breathing regulation and cardiovascular interactions

3.1. Breathing patterns

To keep blood gas levels and lung function within normal boundaries, breathing is flexibly regulated to respond to a constantly varying internal state and its environment (Bruce & Daubenspeck, 1995; Hess et al., 2013; Jaworski & Bates, 2019). As a result, breathing is highly variable, with variations in respiratory time and volume, sighs, gasps and yawns, respiratory pauses and apneas, thoracic and abdominal contributions and synchrony between both (Ramirez & Baertsch, 2018, 2019; Vlemincx et al., 2013). These breathing patterns are essentially adaptive, but physiological and behavioral factors may cause specific breathing patterns (e.g. sighs, gasps, yawns, apneas) to occur too few or too frequent, rendering them maladaptive or dysfunctional (Boulding et al., 2016; Vlemincx et al., 2013). Effective regulation of breathing elicits complex breathing patterns, but also conversely, complex breathing patterns guarantee effective breathing regulation (Bruce & Daubenspeck, 1995; Hess et al., 2013; Jaworski & Bates, 2019). Similarly, breathing patterns are also bi-directionally related to stress and emotions (Boiten et al., 1994; Vlemincx et al., 2013).

Since COVID-19 disrupts the vascular endothelium and normal vasoregulation and causes a ventilation-perfusion mismatch together with hypoxemia and sympathetic over-activity, the ventilatory pattern changes to a rapid shallow breathing and upper chest breathing. This is associated with suboptimal alveolar recruitment, elevated dead space ventilation and (a tendency to) hypocapnia. Eventually, a persistent unpleasant sensation of breathing discomfort may ensue that increases with exertion. Overall, it is likely that COVID-19 patients will show altered breathing patterns, which may be or become maladaptive by compromising efficient breathing regulation and exacerbating symptoms. In this respect it is interesting that, while most cardiorespiratory dysfunctions after COVID-19 return to normal within the first six months, persistent symptoms may remain that are not associated with parameters of cardiopulmonary health (Cassar et al., 2021). These symptoms may be due to hyperventilation and dysfunctional breathing patterns during rest and exercise, as was observed in post COVID patients (Mancini et al., 2021; Motiejunaite et al., 2021; Stockley et al., 2021; Taverne et al., 2021; von Gruenewaldt et al., 2022).

Research clarifying the role of breathing patterns in COVID-19 could include:

- assessing breathing patterns and their typology (e.g., breathing irregularity, excessive sigh frequency, thoracic dominance), in COVID-19 patients, during rehabilitation and long-term follow up, both during rest and exercise conditions, and during emotional or cognitive challenges (e.g. stress, depression and/or anxiety inductions),
- investigating which COVID-19 related respiratory dysfunctions (e.g. ventilation-perfusion mismatch, hypoxemia, hypocapnia, respiratory muscle weakness and cardiovascular problems) contribute to chronic maladaptive breathing patterns, and how these effects are moderated by psychological factors (e.g. chronic stress, anxiety, depression),
- investigating whether COVID-19 induced emotional states of (post-traumatic) anxiety, depression and fatigue, acutely and post COVID, contribute to maladaptive breathing patterns,
- investigating the mutual relationships between maladaptive breathing patterns and respiratory symptoms of shortness of breath elicited by COVID-19, and in post-COVID syndrome,
- examining to what extent and which breathing patterns contribute to hyperventilation during rest, exercise, emotional and cognitive challenges, post COVID,
- studying the added value of breathing exercises targeting breathing patterns for improvement of breathing regulation, and reductions in shortness of breath, anxiety and fatigue in post-COVID syndrome and post-COVID rehabilitation.

3.2. Feedforward breathing regulation

Breathing regulation is importantly driven by anticipation or feedforward regulation, suggesting that COVID-19 patients may not just react to actual disruptive factors, but may also develop more permanent breathing regulation problems. The important role of predictive regulation has been extensively demonstrated for blood glucose levels, and -more broadly- for food intake and digestion, for the development of tolerance and addiction to drugs and for blood pressure regulation. However, the breathing system has been less targeted using this

perspective, despite good arguments to do so: (1) both animal and human studies suggest the role of learning in CO_2-regulation (Gallego et al., 2001; Zaman et al., 2014), (2) clinical phenomena such as exercise hyperpnea and hyperventilation can be considered examples of predictive regulation, (3) the breathing system, being tied into both the autonomic (involuntary) and somatic (voluntary) nervous system, is open to behavioral influences, such as emotions and cognitive load that are highly sensitive to anticipatory processes (Vlemincx et al., 2013), (4) dyspnea is a powerful stimulus for fear conditioning (Pappens et al., 2012), after which a milder respiratory sensation can be sufficient to evoke anticipatory fear responses, subsequent breathing dysregulation (e.g. hyperventilation) and dyspnea (Alius et al., 2013; Van den Bergh et al., 1997).

Feedforward regulation has adaptive benefits: strong perturbations are avoided resulting in more steady, yet highly flexible physiological systems (Dworkin, 1993; Ramsay & Woods, 2014, 2016). However, a downside may emerge when cues launch predictive regulation in response to an expected perturbation that is actually not occurring. Anticipation of breathlessness and sensations of breathing distress of COVID-19 may therefore contribute to more permanent breathing dysregulation, creating vicious circles.

Respiratory psychophysiology can address many research questions from this perspective in the context of COVID-19, such as:

- How does anticipation of breathlessness impact O_2 and CO_2 regulation in COVID-19 patients? Does anticipation impact each regulatory subsystem (e.g. mechano-, stretch- and chemoreceptors)? How flexible and variable are individual set points for these parameters?
- What are the psychological conditions for and consequences of behavioral factors overruling breathing in accordance of metabolic needs? How is this corrected?
- Can vicious circles emerge if anticipated breathlessness triggers breathing that further induces breathlessness?
- Given that hyperventilation has been observed post COVID in patients (Motiejunaite et al., 2021; Taverne et al., 2021), to what extent does it contribute to the so-called post-COVID syndrome? How can this be remedied?
- What is the role of predictive breathing regulation in the bidirectional relationship between respiratory diseases and psychological disorders such as anxiety, panic and depression (von Leupoldt et al., 2013)?

3.3. Cardiorespiratory interactions

One of the most visible indicators of cardiorespiratory interaction is respiratory sinus arrhythmia (RSA), the heart rate variability located in the typical range of respiration rate. It has been extensively used as an indicator of cardiac vagal activity and related to a host of psychological and health variables (Grossman & Taylor, 2007). It is thought to result from respiratory gating of outflow from medullary vagal motor nuclei to the heart (Eckberg, 2003). A number of studies have shown reductions in RSA indices during the course of COVID-19 infections (Hasty et al., 2021; Hirten et al., 2021; Natarajan et al., 2020; Pan et al., 2021), although increases in RSA metrics have also been reported (Kaliyaperumal et al., 2021; Stute et al., 2021), possibly related to variations in measurement relative to infectious stages. It remains unclear to which extent this is due to alterations in respiratory gating or vagal motor outflow. Patients exhibit higher respiration rates in the infectious state, and respiration rate in conjunction with heart rate have been used successfully as predictors of infection (Natarajan et al., 2020). However, lower RSA prior to the pandemic has also been linked to suboptimal adjustment to the pandemic, predicting elevated systemic inflammation in COVID-19 infected patients (Hasty et al., 2021), internalizing symptoms (Szenczy & Nelson, 2021), coping expectancies (I. Gordon et al., 2021), or aspects of worrying (Wekenborg et al., 2022).

Neuroinvasion of the vagal nerve at the level of the medulla (Vitale-Cross et al., 2022) and in cell cultures from medullary respiratory and cardiovascular control centers by the virus through ACE2 receptors has been demonstrated post-mortem (Meinhardt et al., 2021). This raises the possibility that cardiorespiratory integration is compromised from central top-down pathways. Infection of motor and sensory neurons has also been shown in ex vivo studies of hamster brainstem cell cultures (Ferren et al., 2021). However, changes in RSA do not lend themselves easily to inferences on underlying damage through COVID-19. Deficits in vagal motor outflow are possible, but damage to respiratory control centers could also interfere with respiratory gating of normal vagal outflow. Empirically, observed increases in respiration rate in COVID-19 could produce lower RSA as an epiphenomenon, given the substantial dependence of RSA on rate and amplitude of breathing, independent from vagal activity (Eckberg, 2003; Grossman & Taylor, 2007; Hirsch & Bishop, 1981; Ritz & Dahme, 2006). Additionally, RSA could also be reduced through psychological stress resulting from the infectious state and patients' concerns over its short- and long-term consequences. Beyond that, using basal RSA levels as predictors of pandemic health requires consideration of a range of confounding variables beyond respiration. The modest relation between RSA and basal cardiac vagal output has also been pointed out (Farmer et al., 2016; Grossman & Kollai, 1993).

Research questions to be addressed are, for example:

- What are the central and peripheral neural underpinnings of respiration rate increases and RSA decreases in COVID-19 patients?
- What are the temporal trajectories of these measures across infectious and pre- and post-infectious periods?
- What is the contribution of psychological stress to alterations in respiration rate and RSA observed across infectious periods?

4. Symptom perception

4.1. Breathlessness

The experienced symptoms associated with acute COVID-19 are primarily fever, cough, shortness of breath (SOB), fatigue, muscle ache and loss of smell (CDC, 2022; Chen et al., 2020). The cough and SOB appear to be related to the effect of COVID-19 on ventilation-perfusion mismatch. Also, pulmonary embolism and pulmonary hypertension can elicit SOB (Bulajic et al., 2019; Cleveland Manchanda et al., 2019). However, the lack of a change in lung compliance and airway resistance suggests effort dependent dyspnea is not a critical element in the initial development of COVID-19 SOB.

While hypoxemia probably results from ventilation-perfusion mismatch with hypocapnia due to increased alveolar ventilation elicited by the hypoxemia, hypoxemia does not elicit a sensation of SOB. In fact, silent hypoxemia has been reported in about 5–30 % of COVID-19 patients, either presenting at the emergency department, or admitted to the hospital (Alhusain et al., 2021; Brouqui et al., 2021; Busana et al., 2021; García-Grimshaw et al., 2021; Okuhama et al., 2021). These individuals have a significantly reduced PaO_2 with hypocapnia (Ottestad & Søvik, 2020). While COVID-19 patients may present at first with silent hypoxemia, dyspnea may persist when silent hypoxia has resolved.

Overall, breathlessness or SOB is a complex and difficult symptom to assign a specific origin and psychological factors such as affective states and traits contribute significantly to its experience (Parshall et al., 2012; von Leupoldt & Denutte, 2020). There is a wide range of physiological possibilities to probe, including cardiovascular, respiratory, and neuromuscular systems, and lastly, behavioral mechanisms. Regarding assessment of the respiratory system, breathlessness could be due to changes in the mechanical properties of the lung, gas exchange efficiency, neuro-control centers affecting the awareness of breathing, and/or affective feelings induced from respiratory feedback. All of these may be influenced by a COVID-19 infection, which may have effects that linger on and interact with other mechanisms. As an example, patients

with obesity often complain of dyspnea on exertion. Future research investigating dyspnea (in response to exertion) in obesity may need separate experimental groups defined by the history of a COVID-19 infection (i.e., obesity, non-obese, and obese post COVID-19 infection groups). The same may be said of heart failure patients with preserved ejection fraction who already display symptoms of breathlessness on exertion. Athletes may also be a special population for study as even the smallest change in cardiopulmonary function could affect high levels of performance (Gluckman et al., 2022). In fact, all physiological investigations of breathlessness may need to include an assessment of pulmonary function at a minimum. This would comprise basic spirometry with and without bronchodilator, lung volumes, diffusion capacity, and potentially a cardiopulmonary exercise test to assess ventilatory and gas exchange response to exercise, and breathlessness ratings. Preliminary investigations could start by testing controls without COVID-19 vs. controls post COVID-19 with different disease severity (e.g., mild symptoms, hospitalization, intensive care unit), or different virus variants. However, pre-existing conditions could alter the effects of COVID-19, and obesity may be one of the most important populations to begin testing.

Due to the complexity of breathlessness and the extensive range of physiological causes (Davenport & Vovk, 2009), the assessment of breathlessness should include more than asking the patient if they are breathless (i.e., more than a global statement of breathlessness). Qualifying and quantifying breathlessness could include ratings of both the sensory (intensity) and affective (unpleasantness) dimensions of breathlessness. Patient descriptions and ratings of what they are feeling (i.e., effort, work, breathing heavy, etc.) and any negative emotions provoked by the breathlessness could be very useful in a better assessment of effects of COVID-19 on breathlessness and the potential source or origin of the breathlessness.

Lastly, deconditioning could also be a source of respiratory symptoms. It only takes a few days-weeks of bedrest to induce significant deconditioning (Babb et al., 2012). In the absence of baseline changes in heart or lung function, and no significant abnormal physiological responses to exercise, deconditioning could play a role (Mancini et al., 2021; Raman et al., 2022; Writing Committee et al., 2022). Deconditioning is usually suggested as a diagnosis of exclusion but it could be a very real finding in adults of all ages.

Research clarifying the role of COVID-19 in breathlessness could include:

- investigating cardiorespiratory responses to exercise and measurements of exercise tolerance in post COVID-19 patients with and without symptoms,
- assessing pulmonary function and respiratory mechanics at rest and during exercise in post COVID-19 patients with and without symptoms,
- studying the intensity of breathlessness and feelings of unpleasantness at rest and during exercise in post COVID-19 patients with and without symptoms,
- examining effects of COVID-19 on pulmonary function, respiratory mechanics, gas exchange, cardiac function, cardiorespiratory responses to exercise, exercise tolerance and breathlessness in special populations such as patients with asthma, COPD, obesity, and heart failure (e.g., heart failure with preserved ejection), and older adults,
- investigating the moderating role of psychological trait variables in these effects,
- testing which treatment strategies are effective in alleviating breathlessness in patients that suffer from COVID-19 or post COVID-19 conditions,
- exploring contributions of deconditioning to respiratory COVID-19 symptoms,
- examining sensory and affective dimensions of breathlessness in COVID-19.

4.2. Body-symptom correspondence

Like many other somatic symptoms, respiratory symptoms are not a direct expression of underlying pathophysiological mechanisms, but also depend on characteristics of the environment, the person and their interaction (Van den Bergh, Witthöft et al., 2017). This implies that the relationship between the experience of physical symptoms and indicators of physiological dysfunction is highly variable and often weak or absent, resulting in “medically unexplained” or functional somatic symptoms. For example, persons characterized by threat sensitivity tend to weigh the affective component (unpleasantness) more heavily, resulting in an elevated breathlessness rating for the same physical stimulus (von Leupoldt et al., 2011). Also, repeated and/or chronic breathlessness can turn contextual cues into triggers for the experience of breathlessness that is dissociated from its original physiological cause (nocebo effect, Van den Bergh, Brown et al., 2017; Van den Bergh et al., 1997; Vlemincx et al., 2021). In general, a symptom will be closely related to the pathophysiology in acute and intense phases (when somatic input is highly reliable), but when the physical condition improves, more room is left for contextual and personal characteristics to moderate the symptom experience. Also, social interactions can acutely impact breathlessness perception (Herzog et al., 2019), while memory processes can modify retrospectively how breathlessness was experienced (Van den Bergh & Walentynowicz, 2016).

This suggests that COVID-19 patients may develop symptoms that eventually are unrelated to physiological dysfunction. Substantial evidence is accumulating that a significant proportion of the COVID-19 patients is developing post-COVID syndrome, referring to persistent somatic symptoms that may linger on for months (Cirulli et al., 2020; Sudre et al., 2021). Interestingly, the likelihood of developing persistent physical symptoms does not seem to be associated with severity of the acute phase. Also, post-COVID patients with initially mild symptoms who were participating in a rehabilitation program after COVID-19 had better lung function parameters, but reported stronger dyspnea than patients with severe disease courses that required hospitalization (Hayden et al., 2021). Furthermore, findings of a large population-based French cohort study suggest that persistent physical symptoms after COVID-19 are associated more with the belief in having been infected with SARS-CoV-2 than with having laboratory-confirmed COVID-19 infection (Matta et al., 2022).

Symptoms of post-COVID syndrome include chest pain, difficulties with breathing, loss of taste or smell, painful muscles, tingling extremities, lump in throat, feeling hot and cold alternately, heavy arms or legs, and general tiredness. However, the most prevalent symptoms after COVID-19 were not the most distinctive ones. Particularly, loss of taste or smell (19 times more prevalent after COVID-19), painful muscles and general tiredness were most distinctive (Ballering et al., 2022). The symptom profile is in part also determined by gender. Elevated symptoms (e.g. feeling hot and cold alternately, lump in throat, and general tiredness) persisted longer in women than in men after COVID-19 (Ballering et al., 2022). The general symptom profile suggests the possibility of hyperventilation being involved, to explain at least part of the symptom profile (Ballering et al., 2022). Since hyperventilation has been shown to act as a learning base for developing symptoms unrelated to bodily dysfunction (Bresseleers et al., 2010; Van Diest et al., 2006), these mechanisms should be investigated in post-COVID syndrome. Mental health problems following COVID-19, such as post-traumatic stress disorder, anxiety, and depression (Mazza et al., 2020; Taquet et al., 2021), are also associated with elevated reports of bodily symptoms. All this suggests that psycho(patho)logical and pathophysiological processes become deeply intertwined to complicate symptom reporting, disability, and recovery from this disease.

Disentangling these mechanisms constitutes a major research challenge for respiratory psychophysiology. For example:

- To what extent are threat sensitivity and related characteristics (e.g. perseverative negative thinking, such as worry, catastrophizing, etc.) moderating breathlessness (and other COVID-19) symptoms?
- Under which conditions is breathlessness closely related to pathophysiological mechanisms and when is breathlessness more influenced by expectancy and attentional processes?
- To what extent are symptoms from post-COVID syndrome related to hyperventilation and resulting learning processes that may produce symptoms unrelated to physiological processes?
- To what extent is there a bi-directional influence between anxiety, depression and panic on the one hand, and breathing difficulty, symptoms and disability on the other hand (von Leupoldt & Denutte, 2020)?
- To what extent are psychological treatments contributing to recovery and reintegration of post- COVID syndrome patients?

5. Comorbidity

5.1. Comorbidity with respiratory disease

Asthma is an inflammatory airway disease that can be exacerbated by several well-known factors such as allergen exposure in susceptible individuals and viral infections that can further enhance the inflammatory milieu, both systemically and in the airways (Robinson et al., 2017). The nature of the altered immune response in asthma is fundamentally a dysregulation which changes the natural immune balance that protects against foreign pathogens while remaining controlled so as not to induce intrinsic tissue damage. Psychological distress has a well-defined adverse effect on asthma. Mechanisms include both decreasing the normal immunoregulatory pathways and creating a pro-inflammatory imbalance in the local immune milieu (Marshall & Tull, 2018). Asthma was originally considered to be a risk factor for increased morbidity and mortality from COVID-19 (Jin et al., 2020). Fortunately, in patients who are well controlled, asthma does not appear to increase severe morbidity or mortality risk (Liu et al., 2020). However, asthma patients have a compromised disease control under high levels of perceived stress, anxiety and depression. This could be due to physiological effects of stress, as well as poorer therapeutic adherence related to anxiety and depression. Accordingly, infection with SARS-CoV-2 in patients with high stress levels can result in increased morbidity and mortality (Lacwik et al., 2021). Thus, a therapeutic plan for asthma patients that includes recognition of various stress, depression and anxiety components (such as associated with the pandemic), and developing a specific plan to address it to improve outcomes is both appropriate and desirable (Marshall, 2019; Pope et al., 2014).

Future research areas include:

- an assessment of immune and clinical impacts of COVID-associated stress, anxiety and depression on course of asthma in COVID-19 patients with varying clinical severities,
- studying the risk for SARS-CoV-2 infection in asthma patients in high stress environments,
- examining CoV-2 vaccine responsiveness in asthma patients who are well vs. not well controlled associated with measured psychological stress areas,
- testing the impact of an integrative approach to asthma management that distinctly includes stress, anxiety and depression mitigation components on the risk for infection and severity of COVID-19,
- examining the impact of chronic stress, anxiety and/or depression on the risk for developing post-COVID syndrome in asthma patients.

COVID-19 is a novel respiratory disease but, as in many respiratory disorders, there may be non-respiratory consequences related to mental health. Learning from patients with asthma, research has demonstrated that depression and anxiety can adversely affect an individual's perception of their asthma symptoms. The latter can often have more significant clinical effects than measures of pulmonary function in predicting individuals' self-management and health care use (Feldman et al., 2013, 2021). It has also been reported that individual patients' symptom perception is often diminished (Feldman et al., 2012). Recent research has shown that anxiety elicited within the context of an asthma exacerbation may be adaptive and lead to improved pulmonary function and asthma control and decreased acute healthcare utilization (Feldman et al., 2019). However, additional research is needed to fully understand the behavioral pathways of depression, general anxiety, and adaptive anxiety on symptom perception, medication use (controller and quick relief), and asthma outcomes. The COVID-19 pandemic has introduced another layer of complexity in optimal asthma/COPD management regarding symptom perception, individuals' anxiety and depression, perceived vulnerability to illness, pulmonary function (short- and long-term) and self-management behaviors. This is particularly germane since persistent fatigue, cognitive dysfunction and worsening dyspnea have all been associated with inadequate or poor asthma control.

The following research topics are important for studies to clarify the role of COVID-19 in respiratory symptom perception:

- identifying symptoms of COVID-19 vs. asthma/COPD to inform optimal self-management of multiple conditions,
- differentiating between adaptive illness-related vigilance vs. excessive anxiety/over-perception vs. under-perception in recognizing respiratory symptoms of COVID-19,
- examining long-term changes to pulmonary function following COVID-19 and its impact on perception of airflow obstruction,
- studying the effects of depression and anxiety on COVID-19 respiratory symptom perception
- studying whether respiratory symptom perception improves or declines during peaks of COVID-19 in geographic areas,
- investigating whether depression and/or anxiety during COVID-19 surges correspond to changes in respiratory symptom perception in COVID-19 patients,
- assessing acute and chronic effects of COVID-19 on perceived vulnerability to disease exacerbations in asthma/COPD,
- investigating illness representations and asthma/COPD self-management behaviors (e.g., controller medication adherence, symptom perception, trigger avoidance) in acute COVID-19 patients,
- distinguishing between affective and sensory components of dyspnea in acute COVID-19 patients,
- testing health psychology models (e.g., Common Sense Model) in COVID-19 patients to identify predictors of self-management behaviors and respiratory symptom perception.

5.2. Comorbidity with anxiety and panic

Respiration is known to be significantly affected by emotions and stress (Boiten et al., 1994). Maladaptive breathing, in particular hyperventilation, has also been at the core of biological theories of panic disorder (for reviews, see Meuret & Ritz, 2010; Roth et al., 2005). In that, it has either been interpreted as a consequence of a hyperactive suffocation alarm system that responds to rising CO_2 levels (Klein, 1993),[4] or as a primary generator of feared symptoms (Ley, 1985).[5] In general, hyperventilation arises as a result of failed active coping attempts, associated with feeling overwhelmed and loss of control (Boiten et al., 1994). It can be elicited in vulnerable individuals by situations that involve suffocation (Van Diest et al., 2005). Patients with respiratory disease have an elevated risk of developing panic disorder (Hasler

[4] Klein's suffocation alarm theory assumes that panic patients have developed low CO_2 detection thresholds, resulting in increased CO_2 sensitivity, leading to sensations of dyspnea, which may cause panic symptoms.

[5] Ley's hyperventilation theory assumes that acute hypocapnic hyperventilation, often outside the patient's awareness, causes panic attacks.

et al., 2005; Nardi et al., 2009; Smoller et al., 1996) and higher comorbidity of respiratory disease with anxiety disorders is well-documented (Livermore et al., 2010). A host of studies has documented elevated anxiety disorders and major depression across populations worldwide as a consequence of the COVID-19 pandemic (Nochaiwong et al., 2021; Santomauro et al., 2021). Fear of COVID-19 has specifically been associated with a tendency to panic (Hasratian et al., 2021). Given the key role of respiratory system pathology and resulting symptoms of dyspnea in COVID-19, it can be expected that vulnerable individuals (such as those with higher levels of anxiety sensitivity) or individuals suffering from anxiety disorders are particularly affected by the disease.

Emerging research questions include:

- How does SARS-CoV-2 infection affect onset, consolidation, and/or progression of anxiety disorders, in particular respiration-related panic disorder?
- Are severe episodes of infection that require emergency treatment or ventilatory support associated with subsequent onset of panic disorder?
- How does mask wearing affect PCO_2 levels of individuals with anxiety disorders; does it reduce the risk of panic attacks (in the sense of Ley's symptom generator idea) or increase it (in the sense of Klein's false suffocation alarm idea)?
- Does preexisting anxiety and panic elevate the risk for SARS-CoV-2 infection?
- Does acute and chronic hypocapnia influence different stages of the SARS-CoV-2 infection?
- Can the treatment of anxiety and panic reduce the symptom burden of a SARS-CoV-2 infection, including post-COVID syndrome trajectories?

6. Physical rehabilitation

Patients that recover from COVID-19 often report dyspnea with exercise (Raman et al., 2021). In these patients, gas exchange abnormalities persist even months after the index infection (Aparisi et al., 2021). Mechanical ventilation can lead to decreased inspiratory muscle strength. Thus, muscle weakness and mechanical ventilation may be factors in SOB reported post COVID-19, but the extent to which these symptoms find ground in continued physiological abnormalities (muscle weakness, cardiovascular abnormality, remaining pulmonary problems) is not yet fully explored. In addition, it is becoming increasingly clear that symptoms may persist even when exercise performance is improved (Cassar et al., 2021). At hospital discharge, skeletal muscle weakness and functional impairment has been demonstrated (Paneroni et al., 2021). Three months after hospital discharge, dyspnea, fatigue and myalgia remain important symptoms (Arnold et al., 2021) and there is an increasing amount of data that functional impairment and abnormal exercise responses remain, months after the index infection (Huang et al., 2021). Overall, there is consensus on the need for rehabilitation in patients that suffered from severe COVID-19, with or without mechanical ventilation. In these patients, there is clear evidence of a profound physiological impact with skeletal muscle weakness, reduced exercise tolerance and persistent symptoms of breathlessness and/or fatigue much similar to the symptoms seen in survivors of critical illness (Paneroni et al., 2021; Van Aerde et al., 2020).

Pulmonary rehabilitation is an individualized and multidisciplinary set of interventions tailored to the physiological and psychosocial needs of a patient with an underlying respiratory condition (Spruit et al., 2013). Such pulmonary rehabilitation programs can be organized in many settings and are well equipped to tackle the problems of patients suffering from sequelae of COVID-19 (Spruit et al., 2020). Rehabilitation programs are unanimously supported for these patients if problems persist six to eight weeks after discharge, at which point patients should be screened for rehabilitation (Singh et al., 2020; Spruit et al., 2020). In these patients there is accumulating evidence of the benefits of pulmonary rehabilitation (Daynes et al., 2021; Li et al., 2021). Although there are reports of persistent symptoms in patients that suffered from mild COVID-19, the actual prevalence of the need for rehabilitation in this population and the possible effects of rehabilitation are less clear. Particularly in patients that suffer from post viral encephalomyelitis/-chronic fatigue syndrome (ME/CFS), it is likely that high intensity exercise training should be part of the treatment plan. Low intensity (graded) exercise may be a more appropriate approach (Larun et al., 2019) and needs to be combined with other aspects of multidisciplinary rehabilitation (e.g. cognitive behavioral therapy). Positive effects of pulmonary rehabilitation on anxiety and depression have been shown for other chronic respiratory illnesses such as COPD (C. S. Gordon et al., 2019) and asthma (Zampogna et al., 2020). Primary care clinicians should be aware that some patients may still experience symptoms long after a SARS-CoV-2 infection. Such patients can be referred for physiological and psychological screening and rehabilitation programs may be started. The effectiveness of such programs, however, is yet unclear.

Taken together, potential gaps in clinical practice and/or research related to post COVID-19 rehabilitation, which require future efforts, include:

- increasing efforts to assess rehabilitation needs in patients 6–8 weeks after being discharged from the hospital with moderate to severe COVID-19,
- increasing awareness in primary health care providers that there may be persistent symptoms that can be tackled with physical therapy, exercise prescriptions or more comprehensive rehabilitation,
- further investigation on the exact exercise prescription or rehabilitation content as well as its effectiveness, which needs to address the physiological and psychological problems in patients suffering from post-COVID syndrome,
- further characterization of patients with post-COVID syndrome suffering from persistent symptoms and the mechanisms thereof,
- investigation of rehabilitation techniques (including graded exercise) to improve symptoms as well as physical activity and exercise tolerance in patients with post-COVID syndrome,
- examine how pulmonary rehabilitation benefits psychopathology in COVID-19 patients, and the extent to which improvements in pulmonary function mediate such improvements.

7. Conclusion

While our consideration of future challenges for COVID-19 research is limited to specific questions in respiratory psychophysiology, an elaborate list of potentially interesting research topics is emerging. However, consistent with the continuously evolving nature of the COVID-19 phenomenon, this research agenda is fluid. In that, we hope that it will stimulate additional hypotheses and study protocols linked to research programs of individual experts in relevant fields. Moreover, while these research questions are easily formulated, setting up the real research and interpreting respective research findings can become challenging, given the lag in knowledge as the virus transforms, the variety of neurobiological manifestations and symptom profiles in various patient populations of COVID-19 infection and its variants, and hereto unknown interactions with other physical and mental health conditions. This applies importantly to research on the long-term consequences of COVID-19 infection, and post-COVID syndrome. Any COVID-19 research agenda will be complicated by the further development and distribution of vaccines and antiviral medications. Different types of vaccines and alternative design of vaccine delivery (e.g., by nasal route) will additionally modulate the risk of infection, its natural course and eventual outcomes. Adoption of such measures will also vary along economic, cultural, and ideological lines, and substantial disparities in the availability of such preventative and treatment measures exist. These factors give rise to a host of moderator and mediator

variables that will have to be considered in future psychophysiological research. The complexity of the issues introduced by the unfolding epidemic may also serve as a warning for the field to not return to business as usual, given the uncertainty about the natural course of the current pandemic and possible future ones. Despite these challenges, we hope that this proposed research agenda can stimulate the advancement and innovation of respiratory psychophysiology research that addresses COVID-19 and viral pandemics beyond it.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

No data was used for the research described in the article.

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