Towards a mechanistic understanding of sensorimotor control and symptom perception in persistent physical symptoms

A Bayesian brain perspective

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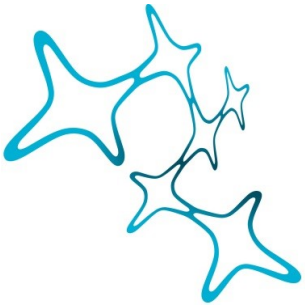

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Contents

Abstract

Distressing physical symptoms that persist for months are frequent, occur across all areas of medicine and strongly impact quality of life. The association with measurable and reproducible pathophysiological processes is often loose or even absent and for most persistent physical symptoms (PPS), positive diagnostic markers are lacking, which challenges diagnosis and treatment. This thesis aims to contribute towards a better mechanistic understanding of PPS that can inform treatment and diagnosis by investigating symptom perception and sensorimotor processing in two examples of PPS, i.e., functional dizziness and post COVID-19 condition.

We adopt a Bayesian brain perspective that proposes that the brain infers the most likely causes of sensory inputs by inverting an internal model that constitutes a probabilistic mapping between different states and sensory input as well as prior knowledge about these states. Recent theories have proposed that erroneous internal models can lead to the emergence of symptoms and dysfunctional motor processing, also in the absence of pathophysiological processes. Here, we provide further evidence in support of this hypothesis for functional dizziness and post COVID-19 condition. Using two different experimental paradigms, we were able to show that sensorimotor deficits (in functional dizziness) and increased breathlessness perception (in post COVID-19 condition) do not reflect altered and potentially pathological body states but rather are due to involvement of incorrect internal models. We highlight that different mechanisms could underlie these results and discuss the role of incorrect but highly precise priors in functional dizziness and maladaptive cost-functions in patients with post COVID-19 condition. In addition, we bridge the gap between experimental data and theories by developing a mathematical model that proposes a potential mechanism of how processing of respiratory data can lead to the emergence of breathlessness perception.

In summary, this thesis provides an explanatory framework, a measurable marker of incorrect internal model use and an improved mechanistic understanding for functional dizziness and post COVID-19 condition. These findings can contribute towards development and refinement of existing treatments and reduce stigmatization of PPS.

Chapter 1

Theoretical background

1.1 Persistent physical symptoms (PPS)

Experiencing fatigue, headache, abdominal pain or any other physical symptom is not uncommon. Around 80 % of the general population experience at least one physical symptom within the period of one month (Hinz et al., 2017; Green et al., 2001). While most of the time symptoms resolve on their own, for some individuals, they persist for months and are highly distressing and hence fall under the category of persistent physical symptoms.

1.1.1 Definition

Persistent physical symptoms (PPS) is "an umbrella term to describe subjectively distressing somatic[1] complaints, irrespective of their aetiology, that are present on most days for at least several months" (Löwe et al., 2022). Even though clusters of symptoms based on their inter-relation have been proposed, such as neurological, gastrointestinal, urogenital, cardiovascular, and musculoskeletal symptoms (Senger et al., 2022), the definition of PPS is not specific to a particular cluster, but refers to any persistent symptom that an individual experiences as distressing. Often patients experience several different symptoms and PPS are highly prevalent in diseases across all areas of medicine (Löwe et al., 2022; Löwe et al., 2024). For example, persistent fatigue is reported across a wide range of different chronic diseases (Goërtz et al., 2021) and constitutes a core symptom, that is often described as the most debilitating one, in multiple sclerosis (Barak and Achiron, 2006; Oliva Ramirez et al., 2021; Fisk et al., 1994) and cancer patients (Lawrence, 2004; Whitehead et al., 2016). PPS are also central to the diagnosis of functional disorders, where symptoms cannot be associated with a measurable and reproducible pathophysiological mechanism (Smith, 2023; Barsky and Borus, 1999; Rosmalen et al., 2021). Examples include bowel complaints such as constipation and diarrhea in irritable bowel syndrome (Ford et al., 2020), loss of balance due to functional dizziness (Popkirov et al., 2018), musculoskeletal

[1] As in this thesis, the terms "somatic" and "physical" symptoms are usually used interchangeably in the literature.

pain in fibromyalgia (Jahan et al., 2012), and tremor and paralysis in functional neurological disorders (Stone et al., 2020). In addition, PPS are often associated with mental diseases. Headaches (Muneer et al., 2018) and pain (Vaccarino et al., 2009), for example, are prominent symptoms in people with major depressive disorder. While the categorization into chronic biomedical, functional or mental disorders serves to illustrate that PPS can be found across all areas of medicine, it must be highlighted that these categories are artificial and not mutually exclusive. For example, patients with epilepsy can also experience functional seizures not caused by electrophysiological brain activity, but whose experience and clinical presentation is similar to epileptic seizures (Kutlubaev et al., 2018).

The definition of PPS does not presuppose a specific association (or strength thereof) with an underlying biomedical condition but rather focuses on the patient's subjective experience, independent of the underlying cause. It thereby acknowledges that finding a biomedical cause is in many cases challenging and unreliable: Almost half of all patients presenting in primary care report physical symptoms that cannot be attributed to a known organic disease (Haller et al., 2015) and the number of symptoms a patient presents with is inversely proportional to the frequency of identification of a biomedical origin thereof (Nimnuan et al., 2001). Even if a biomedical cause for a symptom is identified, symptoms and causes often only correlate poorly. For example, experienced breathlessness is in many cases independent of actual lung function, even in patients with severe lung diseases such as chronic obstructive pulmonary disease and asthma (Wolkove et al., 1989; Herigstad et al., 2017). Improvements in breathlessness after treatment or over the course of pulmonary rehabilitation can occur despite the absence of improvement in lung function or exercise capacity (Wadell et al., 2013; Teeter and Bleecker, 1998; Lacasse et al., 1996). Conversely, breathlessness can persist, for example in patients with post-COVID-19 condition, despite measurable improvements in lung function (Shah et al., 2021). Importantly, patients' impairment and suffering is independent of whether a biomedical cause can be identified (Joustra et al., 2015; Klaus et al., 2013). The definition of PPS thus values the patient's subjective experience, which ultimately determines suffering and impairment.

The burden of PPS is immense due to detrimental effects on quality of life and work participation which lead to a considerable increase in health care utilization (Joustra et al., 2015; Carson et al., 2011). Patients often report unpredictable variability in symptom onset and intensity, leading to a feeling of loss of control over their own body and making it hard to plan life and take part in social activities (Whitehead et al., 2016). It is thus paramount that patients receive a timely diagnosis that allows to establish an adequate treatment plan to alleviate suffering.

However, diagnosis of PPS is often challenging due to the loose association between symptoms and biomedical causes and for many PPS no clear positive diagnostic biomarkers exist. As a consequence, patients often have to endure numerous health care visits including invasive and stressful diagnostic procedures. In a considerable number of cases, even after years of diagnostic procedure, a biomedical cause cannot be identified (Stone et al., 2009). This is especially true for functional disorders. In current clinical practice, the diagnosis of a functional disorder is mostly still a diagnosis of exclusion, i.e., is only given once no biomedical cause of the symptoms can be revealed. This is based on diagnostic classification

schemes, such as the 10th revision of the International Classification of Diseases (ICD-10; WHO, 2004), where the absence of a biomedical cause is a diagnostic criterion. Since the same symptom can often be associated with a wealth of different underlying diseases, ruling out potential candidates can take an enormous amount of time, and on average, patients with functional disorders have to wait several years until they receive a diagnosis (Butler et al., 2021; Tinazzi et al., 2021). Even in the case of an actual diagnosis, patients hardly ever receive an adequate explanation thereof, leaving behind frustration and doubt about the validity of the diagnosis (Burton et al., 2015). What is more, in the absence of biomarkers, the cause of patients suffering often becomes 'invisible' to others. Unlike a broken arm, symptoms like fatigue, pain or dizziness cannot be 'seen' from the outside. Furthermore, symptoms such as chronic fatigue are often described by patients dissimilar to any previously experienced type of fatigue (Whitehead et al., 2016). Caretakers and physicians who have never suffered from chronic fatigue might falsely assume that the patient's fatigue is similar to the type of fatigue that they know and have experienced, for example after an exhausting day of work. Together with the lack of positive diagnostic markers, this can lead to stigmatization and misunderstandings with family, caretakers and physicians (Ballering et al., 2021; Treufeldt and Burton, 2024).

Nowadays, there is a paradigm shift in clinical medicine that aims to identify positive, diagnostic markers of PPS. Clear positive markers would considerably speed up diagnosis, which is fundamental to determine adequate treatment. For some functional disorders positive diagnostic markers exist. Among these positive signs for clinical examination is Hoover's sign or entrainment of tremor, which can be used to distinguish between neurostructural and functional impairments (for an overview of different positive signs for functional neurological disorders, see Stone et al., 2020; Espay et al., 2018). However, for most PPS positive and objectively measurable diagnostic markers are still missing.

Despite increasing attention and research focus on PPS in recent years, the exact causes and mechanisms underlying PPS are still largely unclear. While PPS can develop after an acute disease with a clear biomedical cause, the association with symptoms often becomes loose or even absent when symptoms persist over prolonged periods of time. Similarly, PPS can occur 'de-novo', i.e., without a known previous disease. The transition from short-term to persistent symptoms is complex and involves biomedical, psychosocial and sociodemographic factors, all of which can be present in one patient (Löwe et al., 2024). This calls for a systematic framework aimed at capturing the various factors underlying the transition from short-term to persistent symptoms and characterising their interactions. Such a framework enables improved understanding of the diverse set of backgrounds that may cause a particular patient's symptoms and thus provides additional value in the diagnostic process by painting a more comprehensive picture of the patient's (disease) history.

The biopsychosocial vulnerability stress-model by Henningsen et al. (2018b) and Löwe et al. (2022) incorporates predisposing, triggering, maintaining and aggravating factors. Predisposing factors include female sex and gender (Ballering et al., 2020), lower socioeconomic status (Kitselaar et al., 2023), early adverse life experiences, interpersonal stress, sleep problems, depression, anxiety, previous physical symptoms, elevated body mass index and some genetic profiles (Herzog and Schmahl, 2018; Kitselaar et al., 2023). Factors

that could trigger physical symptoms, especially in people with the aforementioned predisposing factors, include acute infections and injuries, medical procedures and surgery and stressful life events (Kitselaar et al., 2023; Löwe et al., 2024). Symptoms might persist and aggravate due to sustained immune activation (Bjurstrom et al., 2016), altered microbiome (Minerbi et al., 2019), affective conditions such as illness-related anxiety (Boersma and Linton, 2005), and alexithymia (Schnabel et al., 2022; De Gucht and Heiser, 2003), i.e., a deficit in recognising, experiencing and expressing emotions. By taking into account present and past psycho-social and biomedical experiences, this multifaceted framework highlights the interdisciplinary approach needed in diagnosis and management of PPS. This interdisciplinary perspective might also prove beneficial in better understanding the recent phenomenon of PPS after COVID-19.

1.1.2 PPS after COVID-19

Persistent symptoms after infectious diseases are a common clinical phenomenon. Many viruses, among them Epstein Barr virus, Ebola and Dengue infections, are known to cause post-infectious fatigue (Choutka et al., 2022). In 2020, patients first drew attention to prolonged and complex symptoms after a SARS-CoV-2 infection, mainly using social media channels. Soon, patient-led surveys (Assaf et al., 2020) followed that informed about the range and extent of symptoms after COVID-19. Such initiatives gained more and more attention and were later continued by peer-reviewed studies.[2] Patients often called themselves 'long-haulers' and used the hashtag #longCOVID on social media.

Today, both terms 'long-COVID' and 'post COVID-19 condition' (or short post-COVID) are mostly used interchangeably, with post COVID-19 condition often used in peer-reviewed studies and also by the World Health Organization (WHO), which published a clinical case definition in 2021: "Post COVID-19 condition occurs in individuals with a history of probable or confirmed SARS-CoV-2 infection, usually 3 months from the onset of COVID-19 with symptoms that last for at least 2 months and cannot be explained by an alternative diagnosis. Common symptoms include fatigue, shortness of breath, cognitive dysfunction but also others [...] which generally have an impact on everyday functioning. Symptoms may be new onset, following initial recovery from an acute COVID19 episode, or persist from the initial illness. Symptoms may also fluctuate or relapse over time. A separate definition may be applicable for children" (Soriano et al., 2022).

It is estimated that 45% of people surviving a SARS-CoV-2 infection still experience unresolved symptoms at a follow up time of around 4 months (O'Mahoney et al., 2023). Although a higher risk of developing post-COVID condition seems to be associated with severe COVID-19 disease courses requiring hospitalization (Ceban et al., 2022; Schou et al., 2021; Tsampasian et al., 2023), a considerable number of patients with initially mild COVID-19 is affected. One third of non-hospitalised patients still experience symptoms at an average follow-up time of 4 months (O'Mahoney et al., 2023) though prevalence rates

[2]For an overview of the development of patient-driven long-COVID research, see Callard and Perego, 2021.

differ considerably between studies and depend on sample size and characteristics as well as time of follow up. Symptom reports range over many different organ systems with some of the most commonly reported ones being fatigue, exercise intolerance, headache and breathlessness (Lopez-Leon et al., 2021; O'Mahoney et al., 2023; Tenforde et al., 2020). In many patients, the symptom profile largely overlaps with those known from chronic fatigue syndrome and fibromyalgia and some patients might qualify for several of these diagnoses (Haider et al., 2022).

Several pathophysiological changes have been observed in patients that provide first insights into possible disease mechanisms. Common hypotheses (for a review, see Davis et al., 2023; Nalbandian et al., 2021) include persistent SARS-CoV-2 reservoirs (Machkovech et al., 2024; Swank et al., 2023), dysregulated and sustained immune responses (Glynne et al., 2021; Phetsouphanh et al., 2022), virus reactivation (Chen et al., 2023), altered gut microbiota (Liu et al., 2022), endothelial dysfunction (Haffke et al., 2022) and blood brain barrier disruption leading to inflammatory processes and brain damage altering signalling in brain circuits (Boldrini et al., 2021; Sarubbo et al., 2022; Vlemincx et al., 2022). However, in many patients, symptoms cannot be explained by such pathophysiological processes or measurable organ deficits (El-Medany et al., 2024; Kaye et al., 2022; Lam et al., 2021; Shah et al., 2021; Sneller et al., 2022). In addition, it has repeatedly been shown that psychological and social factors play an important role in the emergence of post COVID-19 condition, such as psychological stress experienced pre-infection, loneliness, disease related anxiety and mental health disorders (Wang et al., 2022; Lemogne et al., 2023).

In summary, the disease picture of post-COVID condition is highly heterogeneous, with numerous persistent physical symptoms after SARS-CoV-2 infection bearing resemblance to those observed in other diseases with PPS, especially chronic fatigue syndrome and fibromyalgia (Haider et al., 2022).

1.1.3 Summary

PPS are frequent, highly disabling and can be found across all areas of medicine (Löwe et al., 2024). The loose association between symptoms and reproducible and measurable pathophysiological processes has challenged researchers and clinicians to explain symptoms, often leading to stigmatizing terms such as 'medically unexplained symptoms'. However, the understanding of PPS has markedly evolved and nowadays explanatory frameworks that allow the integration of biopsychosocial factors are available.

Mechanistic explanations see PPS as arising from maladaptive processing and integration of sensory signals arriving in the brain. Before explaining how dysfunctions in this processing can lead to PPS, the next sections will first introduce the general framework of Bayesian brain theories, which describe how the brain can optimally interpret sensory signals in the presence of noise and time delay.

1.2 The Bayesian brain theory

Neuroscientific accounts are based on the central idea that human behaviour and perception are a result of neural activity in the brain. Some of this activity is caused by afferent sensory signals sent by receptors within the body. These sensory receptors can detect (a limited range of) the properties of our environment. For example, photoreceptors in the retina of the eye detect photons and transmit information about the brightness of a light source. Some photoreceptors (cones) are sensitive only to certain wavelengths emitted from the light source which allows the brain to construct a perception of colour (Molday and Moritz, 2015). Sensory receptors do not only convey information about stimuli in the environment (external states) but also about processes and states within the body (internal states). For example, chemoreceptors detect the concentration of carbon dioxide in the blood and thereby inform about the current gas exchange in the lung (Guyenet et al., 2010). Together, these afferent signals allow the brain to form a representation (or internal model) of the bodily and external environment needed to regulate body states and interact with the environment.

A simplistic view is that conscious perception, and thus symptoms, are a direct representation of bodily dysfunction or tissue damage signalled via afferent sensory input. Therefore, the more severe the dysfunction, the stronger the symptom. This would mean that the brain is merely detecting and collecting information via sensors within the body, which is the only source of information used to initiate actions and form perception. However, already in the 19th century von Helmholtz (1867) proposed that perception is a construct of sensory signals and predictions. Today, this view is at the core of Bayesian theories of brain function.

The first part of this section covers Bayesian inference, which describes how the brain can optimally infer the cause of noisy and time-delayed sensory signals. In the second part, Bayesian decision theory is introduced. It describes the optimal decision process of how to plan actions based on inferred states by considering context-specific objectives. In the following part, one possible algorithmic scheme of how Bayesian inference could be implemented is described. Following, forward models are introduced that allow to predict how states will evolve over time. The section closes with a discussion of how dysfunctions in any of the aforementioned processes could lead to the emergence of PPS.

1.2.1 Bayesian inference

Since the brain has no direct access to states of the body and environment, it relies on afferent sensory signals transmitting the relevant information. These signals are noisy and inherently delayed with respect to the event that caused them. They can thus often be interpreted in multiple ambiguous ways and if the brain merely reacted to them, it could only intervene once body states have already deviated from the narrow range that is crucial for survival. The brain thus faces the challenge of an inversion problem, where based on noisy and delayed sensory signals, it needs to infer the states that caused the received signals.

The main idea of Bayesian theories of brain function is that perception is a probabilistic inference process aimed at inferring the most probable state of the world (external state) or own body (internal state), based on sensory input and prior knowledge (Ma et al., 2023). In order to do so, the brain needs to maintain a generative model (Knill and Richards, 1996; Barlow, 1961; Rao and Ballard, 1999). This kind of internal model describes how states *generate* observed sensory data (measurement distribution) and also includes all knowledge about statistical regularities of world states (stimulus distribution). Whereas the stimulus distribution describes the probability of occurrence of different (internal or external) states, the measurement distribution reflects the probability of different measurements (sensory inputs) if the same stimulus or state was encountered again. The width of this distribution is often called the measurement noise or sensory noise. The wider the distribution (i.e., higher variance or lower precision), the noisier the sensory measurements. Measurement and stimulus distribution fully describe the internal, generative model that maps from real world states to sensory data. However, the brain does not have access to the true world states, but needs to infer them based on sensory measurements. This corresponds to inverting the generative model. Based on the measurement distribution, the brain can compute a likelihood function. The likelihood function assigns probabilities to the different world states that could have caused the observed sensory input. It can intuitively be understood as the brain's belief of a state, only given the sensory data, i.e., without taking prior knowledge into account. In many cases, sensory input is ambiguous and different world states are equally likely to have caused the same sensory input. Here, it would be beneficial to additionally include prior knowledge about the probability of encountering a specific internal or external state. The brain can compute such a prior belief of how likely a state is based on the stimulus distribution of the generative model. The prior then represents the belief of a particular state even before sensory data have been received (Ma et al., 2023).
Bayes' theorem is a rule from statistics that describes how to optimally combine two different noisy signals, in this case prior knowledge and sensory input, to infer the common cause of both signals. According to this law, the posterior *p(x/y)*, i.e., the inferred world state x based on sensory measurement y is proportional to prior *p(x)* and likelihood *p(x/y)*:

$$p(x|y) \propto p(y|x)p(x) \tag{1.1}$$

$$posterior \propto likelihood * prior. \tag{1.2}$$

In the Bayesian sense, the probability distribution over different states is often termed *belief*. However, it is important to mention that this makes no implications of whether these beliefs can be consciously accessed or not. If a belief is held with high precision, the probability distribution will be concentrated over the most likely value, which, in a Gaussian setting, will be the mean or expectation. The posterior mean is a weighted combination of prior and likelihood. Depending on the respective precision, either prior or likelihood receive more weight, and thus influence the resulting inference more strongly. In other words, if sensory input is noisy and ambiguous (low precision), more weight is put on prior knowledge to infer the underlying state. In contrary, if no or imprecise prior knowledge

is available, more weight is put on the actual incoming sensory data. Bayesian inference can thus be seen as a framework that describes how the brain can update prior beliefs with sensory data, to obtain a posterior belief about states in the body or environment (Adams et al., 2013). Bayesian concepts are capable of describing a wide range of human behaviour and perception, such as decision making (Beck et al., 2008), motor control (Körding and Wolpert, 2004; Körding and Wolpert, 2006) and magnitude estimation (Petzschner and Glasauer, 2011).

In summary, the brain solves the inversion problem of inferring the causes of sensory inputs, by inverting its internal generative model. This is achieved by applying Bayes' rule which effectively amounts to the computation of posterior probability of hidden causes of the obtained sensory input. Depending on the associated certainty, either likelihood or prior influence the posterior belief more strongly. In the next section, Bayesian decision theory is introduced which describes how the brain should select one specific value of this distribution that represents the final estimate.

1.2.2 Bayesian decision theory: from inference to action

While Bayesian inference offers a way to compute a posterior distribution over hidden states, it does not define how the brain should decide on one particular action based on the inferred hidden state. Here, Bayesian decision theory comes into play by describing how the brain should combine posterior beliefs about different states with cost functions to decide on a final action. These actions can be of behavioural, physiological or perceptual nature. For example, actions can take on the form of a specific arm movement in a reaching task. Similarly, actions can constitute hormone release and thus a physiological reaction. Actions can also involve reporting perceptual estimates, such as a location of a hidden sound source. In these perceptual tasks, the estimate is sometimes interpreted to represent the content of perception itself (Ma, 2019).

Independent of its nature, each action a that the brain initiates will be associated with some costs. In Bayesian decision theory, the overall costs associated with a particular action are quantified by a cost function *C(x,a)*. It depends on the world state x and the action a. The expected cost of an action with respect to the posterior distribution is:

$$\mathbb{E}(C(a)) = \int p(x|y) * C(x,a)dx. \tag{1.3}$$

An optimal action is then defined as the one that minimizes the expected costs (or maximizes reward in the case of a utility instead of cost function). If the task is to optimally estimate a continuous state x (e.g., the location of a sound source), the cost-function can be defined as the squared error between the decided estimate a and the actual world state x. Minimizing this cost function will then yield the mean of the posterior distribution (Ma, 2019).

In most situations, actions are much more complex than the perceptual task to report the estimate of a world state (e.g., the location of a sound source). For example, a physician might have to decide whether to perform an expensive and burdensome diagnostic test to

rule-out an unlikely but serious diagnosis. Here, the cost function in Equation 1.3 can be adapted to incorporate more complex associations between actions and costs. Possible actions might also be decoupled from the world state inference. For example, one might infer the width of a river and then decide whether to jump across it or not. In this case, the cost function for the perceptual estimate (river width) might co-exist alongside a cost-function used for deciding on the appropriate action (Ma et al., 2023).

In summary, Bayesian decision theory describes how based on the posterior *distribution*, the brain should decide on one particular *estimate* (single value). These decisions can lead to actions that are of behavioural, physiological or perceptual nature.

1.2.3 Bayesian forward modeling

So far, the concepts in the last sections only took one particular point in time into account, such as inferring the current position of a ball in a tennis match. However, Bayesian computations also allow to predict future states, e.g., the trajectory of a flying ball, by applying an iterative algorithm, also known as Bayesian filtering. This is achieved via internal forward models $p_{fw}(x_{t+1}|x_t)$ that can predict the future state of the ball based on the posterior in the last time step that included sensory input $y_{1:t}$ until time point t:

$$p(x_{t+1}|y_{1:t}) = \int p_{fw}(x_{t+1}|x_t)p(x_t|y_{1:t})dx. \tag{1.4}$$

This internal forward model includes all information relevant for the dynamics, such as air resistance and gravity, in the example of a flying ball. It can additionally consider a motor control signal u, resulting in $p_{fw}(x_{t+1}|x_t, u_t)$. In the example of the tennis match, the forward model might then predict future states of the ball based on the current state as well as the motor command for moving the racquet when returning the ball back to the opponent. The likelihood function of new sensory information y_{t+1} can then be combined with the predictive distribution above to compute a new posterior:

$$p(x_{t+1}|y_{1:t+1}) \propto p(y_{t+1}|x_{t+1})p(x_{t+1}|y_{1:t}). \tag{1.5}$$

The ability to perform such predictive calculations has advantages that range over different time scales. For example, it enables to track the ball's trajectory with pursuit eye movements. In addition, it allows to position oneself in an optimal way to reach the ball and return it to the opponent (McNamee and Wolpert, 2019). Furthermore, Bayesian integration of the predicted sensory input from the forward model with actual sensory input, can reduce the noise in the final estimate (Wolpert et al., 1995). Forward models also enable a differentiation whether sensory input is due to own actions or changes in the environment. Only based on sensory input, the brain could not distinguish whether,e.g., optical flow during an eye movement is due to movement in the external environment or self-movement. The activation of retinal ganglion cells in the eye would be the same in both cases. It is assumed that copies of (planned) motor commands, so-called efference copies (von Holst and Mittelstaedt, 1950), are sent to a forward model that can predict

the sensory consequences of these motor commands. If this predicted sensory signal deviates from the actual sensory input, it can be inferred that the discrepancy between the two signals must have arisen due to sources other than the motor commands themselves (McNamee and Wolpert, 2019).

1.2.4 Bayesian predictive coding: an algorithmic framework

Considering Marr's levels of analysis (Marr, 1982), Bayesian inference serves to achieve the computational goal of the brain. In other words, it describes how the brain should optimally combine sensory input and prior expectations to infer hidden states and make sense of its environment. However, multiple different ways exist for the implementation of Bayesian inference on an algorithmic level (for an overview, see Aitchison and Lengyel, 2017). One possible implementation is predictive coding (Rao and Ballard, 1999). It proposes three computational quantities needed to implement Bayesian inference algorithmically: predictions, prediction errors and their relative precision. Prediction errors represent the difference between a predicted sensory signal and the actual sensory signal. Each level in the hierarchy receives the predicted sensory signal from hierarchically higher levels in the brain and sends prediction errors back to this higher level where they can serve to update the initial predictions. In that way, only the prediction error and not the signal itself needs to be processed, serving as a sparse way of representing information. Predictive coding thus assumes a hierarchy of different processing steps where predictions are sent down and prediction errors up the hierarchy.

The hierarchical structure of predictive coding proposes that the internal model maintained by the brain and resulting predictions are not localized in one specific area or processing step but rather distributed over many different processing hierarchies. At lower levels the predictions are about the direct sensory input. A classical example from neurobiology are receptive fields of retinal ganglion cells. These specific receptive fields allow to predict the light intensity in the center of the field by taking the surrounding activation into account. This reflects that visual scenes usually show some spatial coherence and regularity and intensities are not randomly occurring in the environment. Retinal ganglion cells then only send the prediction error between the actual light intensity and the predicted one to the brain (Srinivasan et al., 1982). Going up the hierarchy, receptive fields get increasingly complex and predictions are about more abstract features of the sensory input, such as direction and orientation of a visual stimulus in visual area 1 (Hubel and Wiesel, 1962).

A discrepancy between the predictions derived from the internal model and the actual sensory data gives rise to prediction errors. In theory, this discrepancy should result in an update of the internal model, which can be conceptualised as a form of learning. That way the brain can incorporate new experiences into the internal model and adapt to a changing environment. However, since sensory data is noisy, not all prediction errors represent meaningful deviations from predicted states. Therefore, the extent to which predictions are updated depends on the assumed precision of the prediction error relative to the prediction itself. Next to updating the internal model to better match future sensory input, predic-

tion errors can also be minimized by active inference (Friston, 2010). Action selection in active inference involves an alternative mechanistic proposal to Bayesian decision theory (subsection 1.2.2). Instead of explicit cost-functions, the information about costs is integrated into priors about future states and the action that minimizes surprise (free energy) is selected (Friston et al., 2012). Actions are initiated that are aimed at bringing future sensory input more closely to the predicted one. These actions can take on different forms such as volitional movements (e.g., putting on a jacket when core temperature decreases) or physiological processes (e.g., cutaneous vasoconstriction).

In summary, Bayesian predictive coding describes a possible algorithmic implementation of Bayesian inference. While Bayesian inference describes how the brain could compute the expected sensory input, it does not offer any suggestions on how this is implemented on an algorithmic level. Here, predictive coding comes into play by describing how efficient message passing could be implemented by only transmitting prediction errors instead of the signal itself. Thus, while Bayesian inference can be seen as describing the computation itself, predictive coding is an algorithmic scheme that next to Bayesian inference can also serve other computational goals (Aitchison and Lengyel, 2017).

The different computational quantities derived from Bayesian theories of brain function offer a way to investigate processing of bodily signals in the brain and alterations in these processes have been suggested to play a role in the emergence of PPS, discussed in the next section.

1.2.5 A Bayesian brain perspective on PPS

The Bayesian brain theory proposes that perception is not a direct representation of the actual real world processes but always a combination of model-based predictions (prior) and sensory input (likelihood). Optical illusions, such as Adelson's Checkerboard illusion (see Figure 1.1), are an impressive example in the exteroceptive [3] domain, where prior knowledge strongly biases perception away from actual sensory input.
Here, square A is perceived darker than square B, even though both squares are identical copies of each other, i.e., lead to the same sensory input. Prior knowledge of how a checkerboard is arranged and how shadows change the intensities of colors, leads to the construction of a perception that aligns with this model of the world. Thus, people usually perceive both squares as being different. Even if this illusion is explained and the actual physical reality is known, i.e., both squares are identical copies of each other, the illusion remains the perceived reality.

There is no reason to believe that such extremes do not occur for interoception, resulting in symptom perception even though sensory input does not signal any pathophysiological processes. This perspective has several important implications. First, symptoms are perceived in the same way, independently of whether they arise due to sensory input signalling pathophysiological processes or due to incorrect models about real world processes, man-

[3] Exteroception refers to inference processes of external states in the environment, while interoception refers to inference of body states (Craig, 2002).

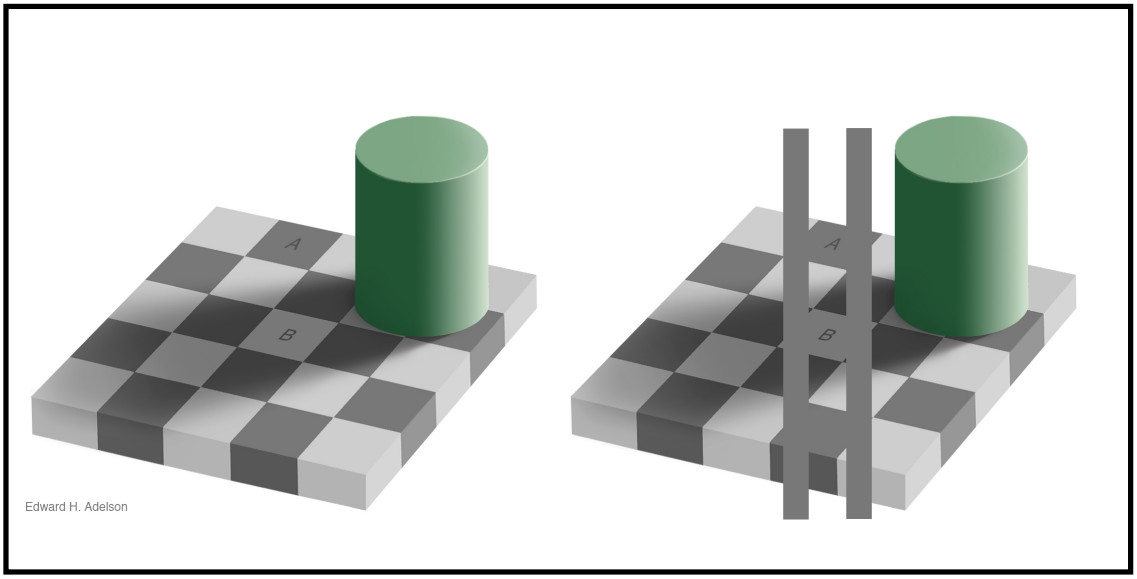

Figure 1.1: Adelson's Checkerboard illusion (Adelson, 1995). Square A is perceived as darker than square B by most people. However, square A is an identical copy of square B, which is illustrated with the bars on the right. Even when this knowledge about real world states is available, square A and B are still perceived differently when looking at the left side.

ifesting as aberrant expectations or prior beliefs in the brain. Second, the example of the optical illusion demonstrates that explicit knowledge about the actual real world states ('Both squares A and B are identical copies of each other') does not alter perception, highlighting that priors are mostly outside volitional control.

According to Bayesian inference and decision theory, the brain can optimally infer and regulate bodily states if prior and likelihood are based on an internal model that adequately describes relevant real world processes and if the inferred state is integrated with a function representing context-specific costs. This would require that the brain maintains a correct generative model, which it fully uses in the inference process. However, the brain might not have been able to learn the correct generative model. Recent theories have cast PPS in a Bayesian framework and have suggested that symptoms can arise due to incorrect internal models that lead to failures in inference and/or control of bodily states.

A common explanatory approach is that aberrant prior beliefs with excessively high precision can bias symptom perception away from actual sensory input. This can lead to symptoms in the absence of any pathophysiological process or organo-structural damage (Henningsen et al., 2018a; Petzschner et al., 2017; Pezzulo et al., 2019; Van Den Bergh et al., 2017). Such priors might arise, for example, due to associative learning. If a contextual cue (e.g., walking up a flight of stairs) is frequently paired with a specific symptom (e.g., an asthma attack), a strong association is formed between both. The more often this combination is experienced, the stronger the assumed association. This can lead to a highly precise prior of experiencing a bodily symptom when this cue is present. If this

association and thus the assumed precision of the prior becomes excessively high, the prior might be sufficient to trigger symptoms, even when no sensory input is supporting this (Van Den Bergh et al., 2017). Studies on pain placebo and nocebo (Jensen et al., 2015) support the notion that such learnt associations and formation of a prior can occur outside of conscious perception.

While most explanatory accounts for PPS focus on aberrant priors, an incorrect mapping between states and sensory input (likelihood function) could also lead to the emergence of symptoms. For example, an overly strong precision weighting of sensory input has been hypothesized to explain atypical features of perception in people with autism (Brock, 2012). A highly precise likelihood function would decrease the effect of prior knowledge which impedes generalization and interpretation of sensory input.

Similarly, maladaptive cost functions could assign disproportionately high or low costs to specific actions. The decision to exert an effort to perform a physical or cognitive task depends on the expected costs. For example, perceived fatigue has been theorised to increase these costs, which favors a strategy to reduce physical and cognitive effort (Matthews et al., 2023; Massar et al., 2018; Richter et al., 2016). While these studies have investigated volitional behaviours, such shifts in cost functions might also affect actions outside volitional control and could explain, for example, increased physiological stress responses.

In summary, failures in correctly maintaining and updating internal models and cost functions will affect inference and control of body states and can lead to symptom perception and maladapted behaviour in the absence of any sensory input signalling pathology.

1.3 Methodology

One way to gain insights into the nature of internal models is to experimentally perturb a bodily state and measure the neural (e.g., brain imaging), behavioural (e.g., motor behaviour) and/or perceptual (e.g., symptom reports) response to this perturbation. In the next sections, two experimental paradigms are introduced that measure the behavioural (eye-head paradigm and rebreathing paradigm) and perceptual (rebreathing paradigm) response to perturbation of body states. By doing so, they enable to investigate whether internal models capture relevant real-world processes and thus allow to correctly adapt symptom perception and behaviour.

1.3.1 The eye-head paradigm

The eye-head paradigm (Lehnen et al., 2003) allows to investigate eye-head motor control and the involvement of internal models. During the experiment, participants perform large gaze shifts, involving eye and head movement, to flashing light targets in a dark room. During a gaze shift, eye and head first move together. Once gaze has reached the target, the head usually continues to move and slightly overshoots and then oscillates around the target. By counteracting the head movement with eye movements into the

opposite direction, gaze is kept stable. During the experiment, participants' eye as well as head position and velocity are recorded. In addition, a helmet with attached weights, that participants have previously never seen or worn, can be introduced that artificially alters the head moment of inertia and thus perturbs the estimate of head characteristics and movement. This leads to incorrect movement planning since the internal model does not correctly capture these altered head characteristics and manifests as increased head oscillations at the end of gaze shifts, also in healthy participants. Patients with organo-structural vestibular deficits, i.e., bilateral vestibular loss and cerebellar ataxia, show increased head oscillations already during natural conditions, which are further exacerbated when head inertia is increased. While healthy participants and patients with cerebellar ataxia were able to reduce head oscillations under increased head inertia over time, patients with bilateral vestibular loss failed to do so (Sağlam and Lehnen, 2014; Sağlam et al., 2014; Lehnen et al., 2019). This highlights that cerebellar as well as vestibular inputs are necessary for head stabilization during gaze shifts and that vestibular input is needed to adapt to changing contexts. However, even though vestibular input in patients with functional dizziness is intact, their head oscillations are increased (Regnath et al., 2024), similarly to patients with organo-structural impairments (Lehnen et al., 2019). The potential transdiagnostic role of head oscillations as a marker of incorrect sensorimotor processing has been established by showing increased head oscillations also in patients with functional movement disorders (Regnath et al., 2024) and irritable bowel (Schröder et al., 2022), however, not pain (Regnath et al., 2023). These results point towards a general sensorimotor processing dysfunction in patients with functional disorders, but do not allow to specify the exact mechanism underlying the observed head oscillations, i.e., whether they arise due to incorrect internal models or sensory processing.

In chapter 2 we addressed this question by investigating gaze stabilization in patients with functional dizziness. Several kinds of sensory feedback, namely visual, vestibular and proprioceptive feedback, play a role in gaze stabilization. In particular, the vestibulo-ocular reflex (VOR) enables direct counteracting of passive head movements with the appropriate eye movement. In addition, feedforward models allow to plan eye-movements that counteract planned head movements (King and Shanidze, 2011; Straka and Chagnaud, 2017). Large gaze shifts involving eye and head movement include two different phases (Sağlam and Lehnen, 2014). During the so-called 'counter-rotation' (CR) phase, model-based motor planning initiates eye movements that actively counteract the expected head overshoot when reaching the gaze target, in addition to the VOR. During the subsequent 'oscillation phase' (OSC), small, unwanted head oscillations around the gaze target are mainly counterbalanced by feedback signals driving the VOR. Sağlam and Lehnen (2014) have validated the different nature of these gaze stabilization phases and provided further evidence for the involvement of model-based feedforward mechanisms contributing to gaze stabilization against planned head movements in the CR phase. They demonstrated that healthy participants can stabilize gaze similarly well in the CR and OSC phase. In contrast, patients with chronic bilateral vestibular loss, i.e., without vestibular input, performed worse in the OSC than in the CR phase. Due to the missing vestibular input, they were not able to counteract unexpected head movements, while they were still able to stabilize

gaze by using internal feedforward models.

Since patients with functional dizziness exhibit a normal VOR, we hypothesized that they can stabilize gaze in the oscillation phase, but show deficits in the internal model-based counter-rotation phase.

1.3.2 The rebreathing paradigm

A well-validated experimental paradigm to study symptom perception and breathing behaviour in response to manipulations of the respiratory body state is Read's rebreathing paradigm (Read, 1967).

During the experiment, participants either breathe normal room air or rebreathe from a bag filled with 5% CO_2 and 95% O_2. Participants are blinded in respect to the actual source of breathed air. During rebreathing, inhaled CO_2 concentration and thus blood pH gradually increase. This is detected by chemosensors and leads to an increase in breathing rate and depth to get rid of excess CO_2, which is usually accompanied by breathlessness.

The experiment has previously been used to study symptom perception in high symptom reporters in the general population (Bogaerts et al., 2005), in patients with functional breathlessness (Bogaerts et al., 2010), chronic fatigue and fibromyalgia (Van Den Houte et al., 2018), as well as in patients with mental health disorders including anxiety, depression and eating disorders (Lapidus et al., 2020). All studies showed an increased symptom response that exceeds the physiological and behavioural response, highlighting the potential of this paradigm to uncover transdiagnostic and disease-independent mechanisms of PPS that are specifically related to the symptom generating processes.

1.4 Aim of this Thesis

To date, a mechanistic understanding of PPS that can inform treatment and contribute to the development of positive diagnostic markers is still lacking. This especially concerns PPS that are currently not explained by a reproducible pathophysiological process. This thesis aims to contribute towards such a mechanistic understanding of PPS by investigating two different examples of PPS, functional dizziness and post COVID-19 condition. In particular, it investigates whether these diseases can be explained in a Bayesian framework that assumes dysfunctions in correctly maintaining and adapting internal models and cost functions.

In our first study (chapter 2), we asked whether gaze instability occurs due to dysfunctional internal models or whether these deficits are due to sensory, reflex-driven mechanisms. In the second study (chapter 3), we investigated whether patients with post-COVID fatigue show deficits in adapting breathing behaviour and/or symptom perception when the respiratory body state is perturbed. We further asked whether such potential dysfunctions are similar to the ones previously observed in different functional disorders, thereby investigating a possible transdiagnostic feature. In chapter 4, a theoretical model of breathless-

ness perception is introduced that allows to test specific theories of how breathing-related sensory signals could lead to the emergence of breathlessness perception using a Bayesian framework.

In summary, this dissertation project aimed to answer the following questions:

1. Can functional dizziness and post COVID-19 condition be cast in an explanatory framework of the Bayesian brain?
2. Is gaze instability in functional dizziness due to erroneous internal models?
3. How can processing of respiratory signals lead to breathlessness perception in the absence of lung impairment?
4. Do patients with post COVID-19 condition show deficits in breathing control and/or symptom perception? How could these be explained in a Bayesian framework?
5. Is there a transdiagnostic mechanism underlying post COVID-19 condition and functional disorders?

Chapter 2

Functional dizziness: Can dysfunctional internal models explain gaze instability?

The current chapter encloses the research article entitled "Unstable Gaze in Functional Dizziness: A Contribution to Understanding the Pathophysiology of Functional Disorders". The article is published in *Frontiers in Neuroscience*.

2.1 Summary

Patients with functional dizziness are able to stabilize gaze during sensory feedback driven phases, but show marked deficits in stabilizing gaze when active, model-based planning of coordinated eye and head movement is required. This finding makes two major contributions: a) it shows that sensory processing of vestibular input is intact, but dysfunctions in gaze stabilization result from model-based motor planning which b) holds potential for an easy to measure, non-invasive and objective marker of dizziness in the absence of underlying organ pathology.

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ORIGINAL RESEARCH
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Unstable Gaze in Functional Dizziness: A Contribution to Understanding the Pathophysiology of Functional Disorders

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Objective: We are still lacking a pathophysiological mechanism for functional disorders explaining the emergence and manifestation of characteristic, severely impairing bodily symptoms like chest pain or dizziness. A recent hypothesis based on the predictive coding theory of brain function suggests that in functional disorders, internal expectations do not match the actual sensory body states, leading to perceptual dysregulation and symptom perception. To test this hypothesis, we investigated the account of internal expectations and sensory input on gaze stabilization, a physiologically relevant parameter of gaze shifts, in functional dizziness.

Methods: We assessed gaze stabilization in eight functional dizziness patients and 11 healthy controls during two distinct epochs of large gaze shifts: during a counter-rotation epoch (CR epoch), where the brain can use internal models, motor planning, and resulting internal expectations to achieve internally driven gaze stabilization; and during an oscillation epoch (OSC epoch), where, due to terminated motor planning, no movement expectations are present, and gaze is stabilized by sensory input alone.

Results: Gaze stabilization differed between functional patients and healthy controls only when internal movement expectations were involved [$F(1,17) = 14.63$, $p = 0.001$, and partial $\eta^2 = 0.463$]: functional dizziness patients showed reduced gaze stabilization during the CR ($p = 0.036$) but not OSC epoch ($p = 0.26$).

Conclusion: While sensory-driven gaze stabilization is intact, there are marked, well-measurable deficits in internally-driven gaze stabilization in functional dizziness pointing at internal expectations that do not match actual body states. This experimental evidence supports the perceptual dysregulation hypothesis of functional disorders and is an important step toward understanding the underlying pathophysiology.

Keywords: functional dizziness, pathophysiology, predictive coding, internal models, somatic symptom disorder, bodily distress disorder

INTRODUCTION

A hallmark of functional disorders is the major discrepancy between patients' very real suffering from bodily symptoms, like fatigue, bowel irritation, chest pain, or dizziness, and an unimpressive exam and clinical workup, which does not account for the symptoms. There is no clear pathophysiological correlate (Baizabal-Carvallo et al., 2019; Drane et al., 2020; Martin and Van Den Bergh, 2020) matching patients' disability, distress, and lowered quality of life, which is often even more impaired than in patients with corresponding organic disorders (Carson et al., 2011; Vroegop et al., 2013). Diagnosis and, consequently, adequate treatment are typically delayed by many years. Such symptoms are common: dizziness, for example, has a lifetime prevalence of 30% (Neuhauser, 2009), and in 20–50% of the affected patients, symptoms are of functional nature (Staab and Ruckenstein, 2007; Stone et al., 2010). This comes with high psychiatric comorbidity (Eckhardt-Henn et al., 2003; Wiltink et al., 2009; Lahmann et al., 2015) and increased healthcare utilization (Wiltink et al., 2009). Traditionally, the absence of an explanatory organic impairment is part of the diagnostic criteria of functional disorders (e.g., in the current European diagnostic system ICD-10, World Health Organization, 2004). Today, we experience a major paradigm shift in clinical medicine, with positive signs becoming more and more important in the diagnosis of functional disorders (American Psychological Association, 2013; Stone, 2016; Stone et al., 2020). Within this paradigm shift, identifying a—potentially unifying—pathophysiological mechanism is of high clinical relevance, as it would help to improve the positive definition, swift diagnosis, and treatment of functional disorders.

A recent hypothesis reflecting this paradigm shift suggests that functional disorders emerge and manifest as a consequence of "perceptual dysregulation" in the central nervous system (CNS; Edwards et al., 2012; Van den Bergh et al., 2017; Henningsen et al., 2018; Pezzulo et al., 2019). Within the framework of predictive coding, central processing of incoming sensory information is biased by a mismatch resulting from incorrect internal expectations leading to symptom perception (**Figure 1**). Providing empirical validation of this hypothesis has been a current effort: several studies report "symptom-like" somatic illusions that could be evoked in healthy participants by experimentally altering internal expectations (e.g., Iodice et al., 2019; Bräscher et al., 2020; Wolters et al., 2020). Moreover, experimentally induced symptoms are more persistent in patients with functional disorders, uncoupled from corresponding sensory input (Bogaerts et al., 2010; Van Den Houte et al., 2018). The first evidence for altered sensorimotor processing is provided by our prior study investigating head control in patients with functional dizziness (Lehnen et al., 2019). When using combined eye–head movements to shift gaze to a new visual target, functional dizziness patients showed more pronounced head oscillations, a marker for the incongruency between sensory input and expectations in sensorimotor planning. This is a measurable marker clearly distinguishing functional patients from healthy controls. However, it does not identify the erroneous site within sensorimotor processing, which could be either faulty internal models or sensory input.

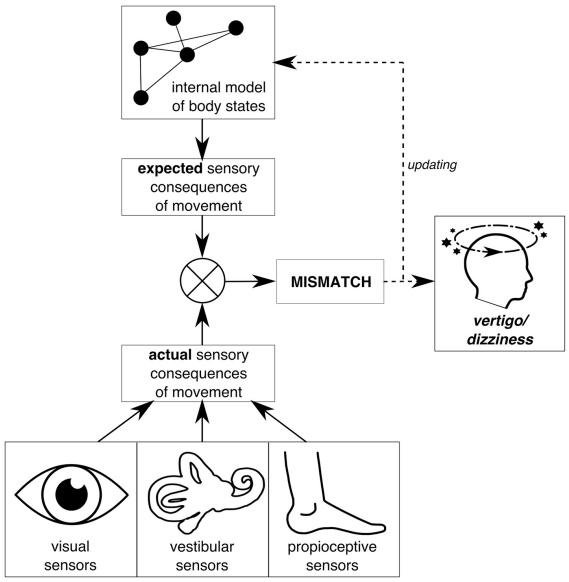

FIGURE 1 | Schematic illustration of symptom emergence in the predictive coding framework on the example of vertigo/dizziness. Predictive coding understands perception as a constant interplay between incoming sensory information and internal expectations about such sensory input. In balance perception, for example, the actual sensory consequences of movement are processed by the visual, vestibular, and proprioceptive systems. Expectations about sensory consequences of movement are derived from internal models about the world and the body that constitute central nervous system (CNS)-internal representations of previously learned or experienced causal relations within the body, the environment, and their interaction. Ideally, such internal models match reality; i.e., they are a valid and reliable representation of the true causal relations. If this is not the case, resulting expectations about sensory input do not match the actual sensory activation. This mismatch, if not used as error signal to update internal models, can lead to persistent symptom experience, i.e., vertigo/dizziness.

In the current paper, we assess a physiologically relevant parameter (gaze stability) in functional dizziness patients that helps to uncover this site. In our assessment, we make use of the fact that gaze stability in the context of an eye–head gaze shift to a new visual target is achieved in two epochs (**Figure 2**): first, a counter-rotation (CR) epoch, which is part of the planned movement toward the target, which means that efference copies and internal models can help to stabilize gaze (e.g., Roy and Cullen, 2004; Shanidze et al., 2010; King and Shanidze, 2011); second, an oscillation (OSC) epoch, where no self-initiated movements are expected, and stabilization thus depends on sensory feedback alone, i.e., mainly the vestibulo-ocular reflex.

Internal model and sensory input contribution to these two gaze stabilization epochs have been validated in a previous study

Abbreviations: CNS, central nervous system; CR, counter-rotation; HITD-FT, head impulse testing device—functional test; ICD-10, International Statistical Classification of Diseases and Health Related Problems 10; LED, light-emitting diode; MRI, magnetic resonance imaging; OSC, oscillation; rmANOVA, repeated-measures analysis of variance; SEM, standard error of the mean; vHIT, video head impulse Test; VOR, vestibulo-ocular reflex.

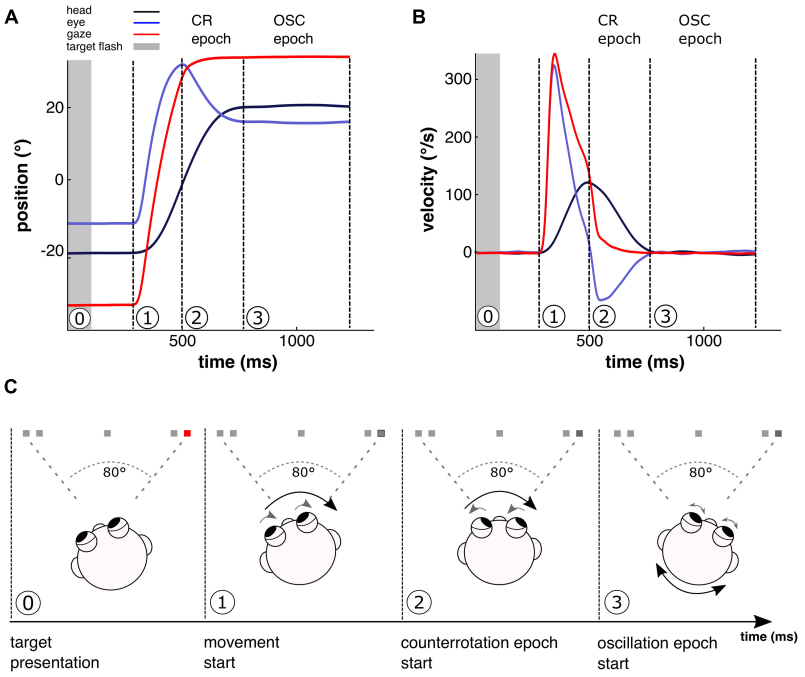

FIGURE 2 | Movement sequence over the course of a single 80° gaze shift. Shown are position **(A)** and velocity traces **(B)** of experimentally recorded eye and head movements during one exemplary 80° gaze shift as well as computed gaze movement. Gaze, i.e., the position of the eyes in space, is composed of eye position (recorded in relation to the head) and head position (recorded in relation to space). An 80° gaze shift requires combined eye–head movements and follows a typical sequence **(C)**, including two distinct gaze stabilization epochs. Beginning from the target position of the previous trial, quickly after the flashed target light (**0**, gray bar in **A**,**B**, and red spot in **C**) is extinguished, eyes and head begin to move jointly toward the remembered target position (dark spot in **C**) in a coordinated and voluntarily planned way, representing the start of the gaze shift movement (**1**). Due to the active nature of head motion here, the vestibulo-ocular reflex (VOR) is suppressed (e.g., Angelaki and Cullen, 2008). When the gaze movement toward the target is finished, i.e., the eyes have reached maximum amplitude, but the head continues to move toward the target, the eyes counteract the continuing head movement by a counter-rotation (CR) in order to achieve stable gaze in this first stabilization epoch. Like the joint eye and head movement in epoch 1, the coordinated eye–head movements in this CR epoch are part of the active gaze shift, where movements are voluntarily planned, initiated, and executed to shift gaze toward the target position. Therefore, for gaze stabilization, motor planning is used to expect the sensory consequences of the head movement (e.g., Shanidze et al., 2010; King and Shanidze, 2011). The contribution of motor planning information on gaze stabilization in the CR epoch of this experimental paradigm has been demonstrated previously in bilateral vestibular loss patients (Sağlam and Lehnen, 2014). Due to ongoing active head motion here, VOR is still suppressed in the CR epoch, although suppression is likely to be attenuated toward the end of the active movement (e.g., Lefèvre et al., 1992). When the head has finished its motion toward the target position, the active movement is completed (**3**). Now, the second stabilization epoch begins, where the eyes counteract small, unexpected passive head oscillations, further provoked by experimentally increased head inertia, which do not emerge as a consequence of motor planning of the active gaze shift. In this oscillation (OSC) epoch, in contrast to the CR epoch, no head movements are expected. Compensatory eye movements are driven by sensory feedback loops, mainly the VOR that is not suppressed anymore.

using the same experimental design (Sağlam and Lehnen, 2014): patients with complete bilateral vestibular loss show better gaze stabilization in the CR epoch than the OSC epoch, confirming the contribution of internal model and efference copy use in this stabilization epoch. Based on the "perceptual dysregulation" theory (Edwards et al., 2012; Van den Bergh et al., 2017; Henningsen et al., 2018; Pezzulo et al., 2019), during large eye–head gaze shifts, we expect functional dizziness patients to rely on incorrect internal models of their head, thus showing unstable gaze during the CR, but not the OSC epoch.

MATERIALS AND METHODS

This study investigates a dataset from patients with functional dizziness that has also been used in a prior publication (Lehnen et al., 2019). In this former publication, only head movement characteristics were analyzed. Now, we analyze further parameters from this dataset, as described in the following.

Subjects

Eight patients with functional dizziness (aged 35 ± 13 years, mean ± SD, five females) that corresponded to the criteria for persistent postural-perceptual dizziness of the Bárány Society (Staab et al., 2017) and 11 age- and gender-matched healthy subjects (aged 32 ± 6 years, mean ± SD, six females) were included. Functional dizziness patients were recruited from the German Center for Vertigo and Balance Disorders, a tertiary vertigo/dizziness center of the University Hospital of Munich where they presented with permanent dizziness symptoms (>3 months). Only patients without any known prior or current structural peripheral or central vestibular dysfunction were included. History and an extensive clinical workup including neurological exams, neuro-ophthalmological

and neuro-otological exams, caloric irrigation, subjective visual vertical, laser ophthalmoscopy, posturography, video head impulse test (vHIT), head impulse testing device—functional test (HITD-FT; after Ramaioli et al., 2014), and cranial magnetic resonance imaging (MRI) did not show any organ pathology. Healthy subjects, employees of the University Hospital of Munich who voluntarily participated in the study, reported no history of balance disorders and had a normal neurological exam. To ensure a structurally intact vestibular system on the day of examination, a vHIT was conducted prior to study conduction according to the EyeSeeCam vHIT manual (EyeSeeTec GmbH, Munich, Germany), revealing no deficits in functional dizziness patients [VOR gain at 0.06 s: left side: 1.02 ± 0.03, right side: 0.96 ± 0.04, mean, and standard error of the mean (SEM)] as well as healthy controls (VOR gain at 0.06 s: left side: 1.02 ± 0.02, right side: 0.98 ± 0.01).

All subjects gave their written consent prior to the study's data collection. The study protocol was approved by the Ethics Committee of the University of Munich, the study design is in line with the Declaration of Helsinki.

Experimental Procedure

Participants performed large horizontal (combined eye–head) gaze shifts toward visual targets, which were flashed in complete darkness (analogously to Lehnen, 2006). Subjects were seated in front of a desk at 1-m distance, with five light-emitting diodes (LEDs) placed at eye level in a line on the desk (one central and four peripheral LEDs, in 0.7- and 0.83-m distance left and right to the central LED), so that target eccentricity amounted to 0°, 35°, and 40° to the left and right with respect to participant's middle head position. One experimental round consisted of 52 gaze shifts, with the target lights flashing consecutively in randomized order (amounting to gaze shifts of 35°, 40°, 70°, 75°, and 80° magnitude) and with randomized time interval between flashing lights (1.2–1.8 s) in order to prevent anticipation. Each target light was flashed for less than 0.1 s to avoid visual feedback. Subjects were instructed to direct their gaze toward the flashing LEDs naturally, by engaging eye and head movements, and to keep final gaze position until the next target flash occurred. Every subject performed two rounds of the experiment: one in the natural condition (*unweighted*) and one with experimentally altered head characteristics (*weighted*). For the latter condition, a helmet with eccentrically placed masses on both sides was firmly attached to the subjects' heads, increasing the head moment of inertia 3.3-fold. All participants were unexperienced with respect to the experimental design and had never worn the helmet before. Eye and head movements were recorded with the EyeSeeCam measuring system (EyeSeeTec GmbH, Munich, Germany), by tracking movements of the left eye with video-oculography and head movements with 3D inertial sensors (resting state noise 0°–0.3°/s, SD 0.07°/s), placed in the middle of the forehead, both with a sampling rate of 220 Hz.

Data Analysis

Data were analyzed offline using MATLAB (MathWorks, Natick, MA, United States). Head velocity in the horizontal plane was directly derived from the horizontal inertial sensor of the EyeSeeCam measuring system. Head position was computed as the integral of head velocity over time for each time point, normalized by initial head position, where participants were asked to fixate the central LED for 10 s. Eye position was calculated from pupil rotation vectors, also normalized by initial eye position. Eye velocity was computed as the derivative of eye position at each time point. Both eye and head position and velocity were filtered with a low-pass Gaussian filter (cutoff frequency 20 Hz). Gaze position and velocity were then computed by adding up eye and head position and velocity, respectively, so that gaze (eye in space) corresponded to the sum of eye (eye in head) and head (head in space). Continuous data streams were cut into single trials, beginning with the LED onset and ending 0.1 s after the next LED onset, so that each trial represented one gaze shift. Only gaze shifts in response to 75° and 80° jumps (43 target trials) and fulfilling the requirement of a large gaze shift (i.e., measured amplitude of >40° amplitude) were considered for the analysis. To remove saccades during CR and OSC epochs, saccades were detected automatically with a gaze peak velocity criterion of 30°/s and with saccade start and end being defined as the last minimum before and the next minimum after gaze velocity peaks, respectively. Saccade detection was then inspected visually and corrected manually, by adding undetected saccades (<1% for all subjects) as well as correcting the detected minima (<1% for all subjects). Eye and head velocities during a saccade window were removed from the analysis.

Gaze gains were defined as the amount of compensatory eye movement in respect to head movement and were calculated as the slope of the linear regression between eye and head velocity profiles using the MATLAB built-in function *robustfit* (analogously to Sağlam and Lehnen, 2014). Gaze gains were computed for two gaze stabilization epochs: the internally-driven CR epoch as part of the planned gaze shift, using internal expectations and sensory information for stabilization, and the sensory-driven OSC epoch for sensory-dependent gaze stabilization after gaze shift end. CR epoch begins when the eye has reached maximum amplitude, but the head continues to move toward the target (**Figure 2**, picture 2). This was implemented by using the time window between the eye maximum eccentricity point and the point where head velocity reached 0°/s. OSC epoch begins when the active head movement has been terminated but the head continues to move passively, i.e., due to unexpected OSCs induced by increased head inertia (**Figure 2**, picture 3). We defined this epoch as the time window from the first zero crossing of head velocity until 0.1 s after the next LED flash. This was done to make sure that we harvest the data as long as possible. For both epochs, the resulting gain displays the amount of compensatory eye movement in relation to the head movement, with zero reflecting no compensatory eye movement at all and one reflecting perfect compensation. Only gaze shifts where the point of eye maximum eccentricity as well as the first head zero crossing could be detected were considered for the analysis. Of 43 gaze shifts in total, 34 ± 2 (mean ± SEM) and 33 ± 2 trials were taken into the analysis of mean CR and OSC gains, respectively, with no significant group differences [Wilks' lambda (1,17) = 0.79, $p = 0.15$].

Statistical Analysis

The Shapiro–Wilk test was used for normality assessment in all factor groups. Differences in gaze gains for CR epoch and OSC epoch (within-factor *epoch*), unweighted and weighted condition (within-factor *weight*), and gaze shifts to the left and right side (within-factor *side*) were analyzed with a $2 \times 2 \times 2$ repeated-measures ANOVA (rmANOVA). Group differences were analyzed by adding a between-subject factor (*group*: healthy subjects and patients with functional dizziness) to the rmANOVA. After a significant effect, for *post hoc* testing, Bonferroni-corrected comparisons were computed for the respective conditions. Significance levels were the same for each statistical test ($p = 0.05$).

Note that there are differences in gaze gains from the left and right side [main effect *side*: $F(1,17) = 43.4$, $p < 0.001$, and partial $\eta^2 = 0.72$], which are known from vHIT testing (Park et al., 2019) and attributed to the asymmetric camera position in the EyeSeeCam system. Although there was a significant interaction of gaze shift side with group in the rmANOVA [*side* * *group* interaction: $F(1,17) = 9.96$, $p = 0.006$, and partial $\eta^2 = 0.37$], in *post hoc* testing, those group differences did not reach statistical significance for neither the left ($p = 0.055$) nor the right side ($p = 0.44$). We therefore consider gaze gain alterations to the left and right side as similar for all conditions, so that factor and group comparisons should not be affected. For better readability, gaze gains in the written text are reported for gaze shifts to the left side only.

RESULTS

To investigate gaze stabilization during combined eye–head gaze shifts, we computed the amount of compensatory eye movements for gaze stabilization during two distinct epochs that either involve motor planning and internal expectations (internally-driven CR epoch) or not (sensory-driven OSC epoch). **Figure 3** shows representative eye and head movements during such gaze shifts for one healthy participant (upper panels) and one functional dizziness patient (lower panels) in the natural condition (left) and with increased head inertia (right). In the natural, unweighted condition, the healthy participant performed compensatory eye movements in the CR epoch that counteract head movements and stabilize gaze. Increasing the head inertia led to a decrease of compensatory eye movements in the healthy subject. In the functional dizziness patient, compensatory eye movements in the CR epoch were already smaller in the natural, unweighted condition and further decreased with increased head inertia. In the OSC epoch, compensatory eye movements did not differ between the healthy subject and the functional dizziness patient.

These characteristics were found for all subjects (**Figure 4**). During CR epoch, healthy subjects showed a gain of 0.97 ± 0.03 (mean $\pm$ SEM) in the unweighted condition and 0.87 ± 0.04 in the weighted condition, and functional dizziness patients displayed a gain of 0.83 ± 0.04 in the unweighted and 0.75 ± 0.03 in the weighted condition. In contrast, during OSC epoch, gaze gains of healthy controls were 0.96 ± 0.02 in the unweighted and 0.97 ± 0.03 in the weighted condition and 0.95 ± 0.03 and 0.98 ± 0.04 in the unweighted and weighted condition of functional patients, respectively. RmANOVA confirmed different gaze gains for the CR and OSC epoch [main effect *epoch*: $F(1,17) = 67.67$, $p < 0.001$, and partial $\eta^2 = 0.80$] influenced by group [*epoch* * *group* interaction: $F(1,17) = 14.63$, $p = 0.001$, and partial $\eta^2 = 0.463$]. *Post hoc* testing revealed that functional dizziness patients displayed significantly lower gaze stabilization than healthy subjects in the CR epoch ($p = 0.036$) but not the OSC epoch ($p = 0.26$). Increasing the head inertia influenced gaze stabilization in dependence of the epoch [*weight* * *epoch* interaction: $F(1,17) = 20.24$, $p < 0.001$; and partial $\eta^2 = 0.54$]. *Post hoc* tests showed reduced gaze stabilization with increased head inertia in the CR epoch ($p < 0.001$), but not in the OSC epoch ($p = 0.11$).

DISCUSSION

This study reveals marked deficits in gaze stabilization in functional dizziness patients. The deficits are only present during the internally-driven CR epoch of gaze shifts, where, based on motor planning and internal models, CNS expectations about the sensory outcome of the movement are used additionally to sensory input to stabilize gaze. During sensory-driven OSC epoch, when stabilization is only based on sensory input, gaze is stable.

As far as we know, this is the first study demonstrating a direct physiologically relevant pathology of functional dizziness. Importantly, this deficit is demonstrated in patients with a structurally fully intact peripheral and central vestibular system, as assessed by neurological, neuro-otological, and neuro-ophthalmological exams and an extensive workup, including subjective visual vertical, laser ophthalmoscopy, posturography, caloric irrigation, vHIT, HITD-FT, and cranial MRI. In analogy to the intact stabilization during the OSC epoch, vHIT, i.e., vestibular-driven ocular stabilization response to passive high-frequency head movements, was intact in these patients, also on the day of study.

Remarkably, however, during the CR epoch, where functional dizziness patients can use expectations together with sensory feedback for gaze stabilization, their deficits become visible and measurable: the eyes do not sufficiently counter-rotate to compensate for the head movement. As a consequence, gaze is not stable, but drifting. This effect—already present in the natural, unweighted condition—becomes even more pronounced when the head inertia is increased. In this weighted condition, when alterations in head characteristics are not yet reflected in CNS-internal representations, expectations are derived from the unweighted head internal model. Thus, wrong information is used to drive compensatory eye movements, leading to reduced gaze stabilization.

These findings demonstrate the significant role of both intact processing of vestibular feedback and expectation formation based on correct internal models, during eye–head gaze shifts. Their contribution over the course of the gaze shifts has been previously demonstrated within the same experimental paradigm, where patients with complete bilateral vestibular loss show gaze stabilization in the CR epoch despite missing sensory

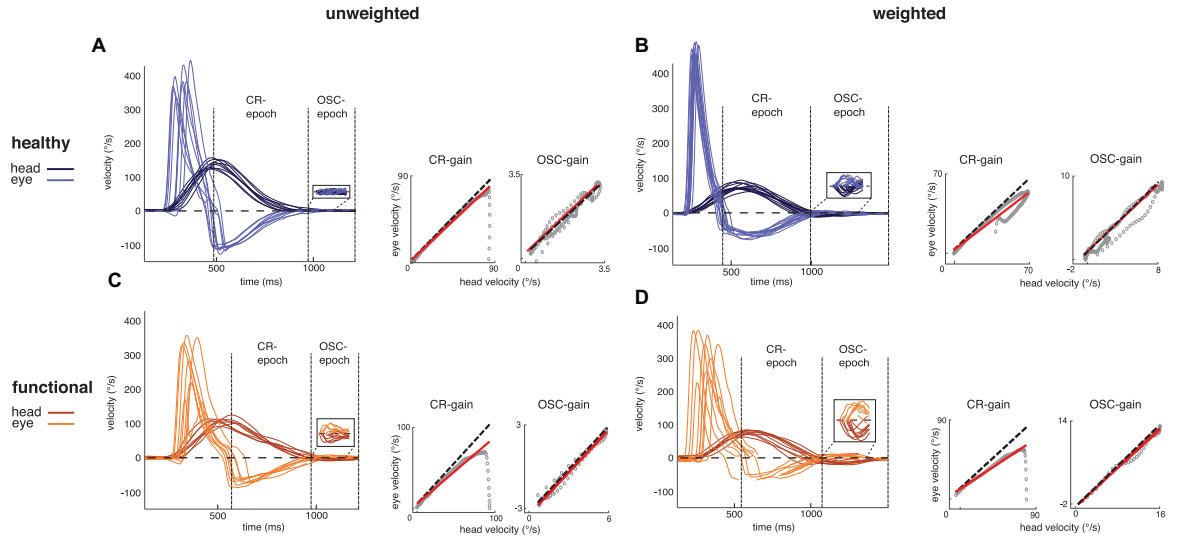

FIGURE 3 | Filtered raw data of experimental movement recordings with illustrated gain computation. **(A–D** left) Shown are representative eye (light) and head (dark) velocity traces of one typical healthy subject **(A,B)** and one typical functional patient **(C,D)** for the unweighted (natural, **A,C**) and weighted condition (increased head inertia, **B,D**). The dashed horizontal lines display the zero line. Head oscillations—and counteracting eye movements—are illustrated in the window with increased y-axis scale (note that the functional dizziness patient display more pronounced head oscillations than the healthy participant, even in the natural condition. Group analysis confirming these differences have been published in Lehnen et al., 2019). **(A–D** right) Shown is eye velocity plotted against head velocity (gray circles) for counter-rotation (CR) and oscillation (OSC) gain computation for one representative gaze shift. Gaze gains are displayed as the slope of the solid lines, which represent the linear regression of eye velocity in head depending on head velocity in space. Perfect gaze stabilization, i.e., a gaze gain of 1, is indicated by the dashed line. The healthy subject shows intact CR-gaze stabilization in the unweighted condition, which is reduced by increasing the head inertia in the weighted condition. The functional patient displays reduced CR-gaze stabilization in the unweighted condition, which is further reduced in the weighted condition. During OSC epoch, both the healthy subject and the functional patient show intact gaze stabilization.

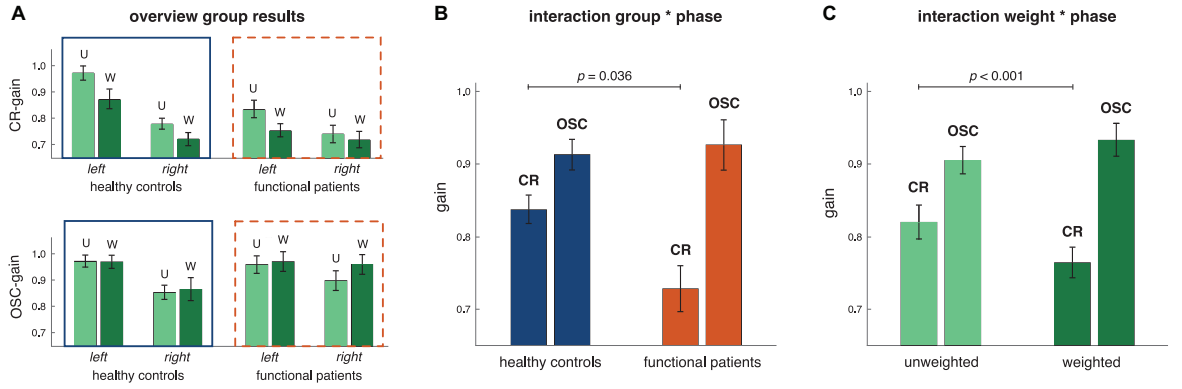

FIGURE 4 | Results of group analysis (controls n = 11, patients n = 8). **(A)** Shown are gaze gains (mean and SEM) for all factor steps of the rmANOVA, i.e., gains to the left vs. right side (within-factor *side*, left group vs. right group of bars), unweighted (U) vs. weighted (W, within-factor *weight*, left vs. right bar within each bar group), in the CR vs. OSC epoch (within-factor *epoch*, upper vs. lower bar plot) for the healthy controls as well as the functional patients (between-factor *group*, all bars within solid vs. dashed squares). **(B)** Shown are gaze gains (mean and SEM) for the *group * epoch* interaction. Gaze gains differed between healthy controls and functional patients [$F(1,17) = 14.63$, $p = 0.001$, and partial $\eta^2 = 0.463$]: functional patients displayed smaller gaze gains in the CR ($p = 0.036$) but not the OSC epoch ($p = 0.26$). **(C)** Shown are gaze gains (mean and SEM) for the *weight * epoch* interaction. Gaze gains differed between the unweighted and weighted conditions [$F(1,17) = 20.24$, $p < 0.001$; and partial $\eta^2 = 0.54$], being reduced with weight in the CR ($p < 0.001$) but not the OSC epoch ($p = 0.11$).

input (Sağlam and Lehnen, 2014). Together with the present results, by using the example of functional dizziness patients, we are one step closer in locating an erroneous site of perceptual dysregulation in functional disorders (Edwards et al., 2012; Van den Bergh et al., 2017; Henningsen et al., 2018; Pezzulo et al., 2019). While we could provide evidence for a general central sensorimotor deficit in functional dizziness in a previous paper (Lehnen et al., 2019), we can now demonstrate first experimental evidence for an incorrect internal model use that has the potential to explain symptom experience in functional dizziness patients.

The idea of the role of mismatching information in symptom experience is central to the explanation of physiological and

clinical vestibular vertigo. Vertigo is, by definition, a feeling of unsteadiness or movement, which occurs as a consequence of conflicting information in the CNS (Dieterich, 2004). Typically, by using expectations that rely on internal models about the body and the environment, the CNS establishes congruence between the different sensory or sensorimotor input sources, enabling stable positioning in and orientation within the environment. If the CNS fails to do so, e.g., in motion sickness (Money, 1970; Reason, 1978; Oman, 1982; Yardley, 1991; Oman and Cullen, 2014), the mismatch between expected and actual sensory input can elicit typical vertigo/dizziness feelings and nausea (**Figure 1**). Here, not only previous sensory experiences influence the expected sensory input but also higher-order cognitive motion beliefs, which are linked to certain contexts (Nooij et al., 2021). From this perspective, functional dizziness displays as a further dizziness/vertigo appearance, providing legitimation for the "realness" of symptom experience in patients with functional dizziness.

Studies investigating the direct pathophysiological mechanisms of functional dizziness are sparse. However, looking at imaging studies, several investigations report structural and functional brain alterations that can be related to our understanding of the underlying pathological mechanisms in functional dizziness patients. Structural gray matter decline (Wurthmann et al., 2017) as well as reduced functional resting state activity (Li et al., 2020) in functional dizziness patients were reported for brain areas that are important for spatial orientation and multisensory vestibular integration. Connectivity studies also demonstrated reduced resting-state functional connectivity between visual, vestibular, and spatial cognition areas (Lee et al., 2018; Li et al., 2020). Importantly, a special role of the cerebellum is highlighted (Lee et al., 2018; Huber et al., 2020): during a visual motion task, for example, cerebellar network activity of functional dizziness patients was reduced, whereas during static visual scenes, it was increased (Huber et al., 2020).

In our experiment, we were able to evoke unstable gaze in healthy controls, too: when head inertia was experimentally increased, our control subjects showed reduced compensatory eye movements in internally driven CR epoch and drifting gaze. The fact that creating a mismatch between expectations and actual sensory input by altering head mechanics is sufficient to reduce gaze stabilization provides further validation of our experimental paradigm as well as the supposed pathophysiological mechanism that underlies functional disorders. However, how this pathophysiological mechanism leads to symptom perception, remains to be seen. It is important to note that, while these findings have the potential to improve our understanding of "how" functional dizziness symptoms emerge and manifest, we cannot answer the "why" question of etiology. Furthermore, the interpretation of our study results presents only one possible explanation within a rather cognitive framework of symptom emergence and manifestation in patients with functional dizziness and does not exclude alternative interpretations. We understand this piece of evidence as a first experimental cornerstone that might guide future research toward transdiagnostic mechanisms for a positive definition of functional disorders. Further studies with functional dizziness patients as well as other patient groups are necessary to demonstrate the general validity of the perceptual dysregulation theory in functional disorders.

Nevertheless, we feel that an improved understanding of the pathophysiology of functional dizziness could constitute a great relief for both patients as well as caretakers. A measurable symptom correlate would most likely reduce stigma in this highly stigmatized patient group (Freidl et al., 2007; Rommelfanger et al., 2017; Eger Aydogmus, 2020). Also, providing measurable alterations has the potential of improving positive diagnosis of functional dizziness. In the long run, insights like these could further improve therapeutic strategies, e.g., in psychoeducation or sensorimotor adaptation training like it is already successfully done in unilateral and bilateral peripheral vestibular disorders (McDonnell and Hillier, 2007; Lehnen et al., 2018).

In summary, this study demonstrates unstable gaze in functional dizziness. During large eye-head gaze shifts toward visual targets gaze is unstable in the internally-driven CR epoch, i.e., when internal expectations are used to drive gaze stabilization, additionally to sensory input. In contrast, gaze is stable in the purely sensory-driven OSC epoch. Thereby, our findings provide further evidence for the predictive coding account of functional disorders, identifying—for the first time within the affected body system—internal expectations as the site where "perceptual dysregulation" arises (Edwards et al., 2012; Van den Bergh et al., 2017; Henningsen et al., 2018; Pezzulo et al., 2019). Together, these results have the potential to improve diagnosis and treatment in functional patients.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are publicly available. This data can be found here: https://doi.org/10.12751/g-node.sc1a64.

ETHICS STATEMENT

This study involving human participants were reviewed and approved by Ethics Committee of the University of Munich. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

NL designed the study. CR collected the data. LS, DW, TW, SG, and NL analyzed the data. LS and DW created the figures. LS and NL wrote the initial manuscript. All authors reviewed and edited the manuscript.

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Conflict of Interest: NL and SG are shareholders of EyeSeeTec GmbH, manufacturers of the measurement system used. NL was a paid consultant and CR was a paid employee of EyeSeeTec GmbH.

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

Chapter 3

Post-COVID fatigue: Can patients adapt breathing behaviour and symptom perception in a rebreathing experiment?

The current chapter contains the manuscript for a research article with the title "Increased breathlessness in post-COVID syndrome despite normal breathing patterns in a rebreathing challenge - A Bayesian Brain perspective". The article is published as a preprint (`https://osf.io/preprints/osf/nqb3h_v1`) and is accepted for peer review in *Nature Scientific Reports*.

3.1 Summary

Patients with post-COVID fatigue experience significantly higher breathlessness in a rebreathing paradigm, even though breathing patterns and physiological measures are not different to healthy control participants. The correct adaptation of breathing behaviour to the rebreathing challenge indicates correct inference of the body state for motor planning. Nevertheless, breathlessness was significantly increased in patients, suggesting dysfunctions specific to symptom perception.

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Increased breathlessness in post-COVID syndrome despite normal breathing patterns in a rebreathing challenge
- A Bayesian Brain perspective

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Abstract

Severe symptoms in the absence of measurable body pathology are a frequent hallmark of post-Covid syndrome. From a Bayesian Brain perspective, such symptoms can be explained by the use of incorrect internal models that the brain uses to interpret sensory signals. In this pre-registered study, we investigate whether induced breathlessness perception during a controlled rebreathing challenge is reflected by altered respiratory measures (physiology and breathing patterns), and propose different computational mechanisms that could explain our findings in a Bayesian Brain framework.
We analysed data from 40 patients with post-COVID syndrome and 40 healthy participants matched for age, sex and BMI. Results from lung function, neurological and neurocognitive examination of all participants were within normal limits on the day of the experiment.

Using a Bayesian repeated-measures ANOVA, we found that patients' breathlessness was strongly increased ($BF_{10,baseline}$=8.029, $BF_{10,rebreathing}$=11636, $BF_{10,recovery}$=43662) compared to controls. When excluding patients who hyperventilated (N=8, 20%) during the experiment from the analysis, differences in breathlessness remained ($BF_{10,baseline}$=1.283, $BF_{10,rebreathing}$=126.812, $BF_{10,recovery}$=751.282). For physiology and breathing patterns, all evidence pointed towards no difference between the two groups ($0.307>BF_{10}<0.704$).
In summary, we found intact breathing patterns and physiology but increased symptom perception in patients with post-COVID syndrome.

Introduction

The post-COVID syndrome encompasses a wide range of debilitating symptoms that considerably impair quality of life for many patients. Symptoms can affect different organ systems with some of the most prevalent symptoms being fatigue, exercise intolerance, several types of pain and breathlessness (Lopez-Leon et al., 2021; O'Mahoney et al., 2023; Tenforde et al., 2020). Biomedical findings have provided insights into potentially underlying pathophysiological changes of the disease. However, these findings typically only emerge at the group level. In individual patients, the association between symptoms and measurable pathophysiological findings can vary considerably, and, in some cases, symptoms cannot be explained by standard clinical diagnostic findings (El-Medany et al., 2024; Kaye et al., 2022; Lam et al., 2021; Shah et al., 2021; Sneller et al., 2022). This suggests that pathophysiological changes contribute to the manifestation of post-COVID syndrome, but are not always sufficient to explain symptoms.
The Bayesian brain theory offers a new explanatory perspective on how a divergence between symptoms and physiological body states could arise. The body and its environment are constantly changing. To keep the body in homeostasis, the brain must adapt behaviour and bodily processes (Ramsay and Woods, 2014). For this, it needs to translate information provided by sensors about the current state of body and environment into adequate actions. These actions will change the body state and elicit new sensory input that is again detected by sensors and sent to the brain. Since the brain does not have direct access to body states, it needs to infer them based on the sensory data it receives. The processing and representation in the brain of signals originating in the body is termed interoception (Craig, 2002; Critchley and Garfinkel, 2017; Feldman Barrett and Simmons, 2015). In addition to direct control of bodily states, interoceptive signals also play a role in the perception of symptoms (Locatelli et al., 2023), a process in which the brain tries to make sense of interoceptive signals by classifying them into meaningful categories with behavioural relevance. The Bayesian brain theory is based on Bayes' theorem (see Figure 1), which describes how to optimally combine noisy data (likelihood) with prior knowledge to estimate a hidden (body) state. Applied to brain function, it suggests that the brain uses implicit a-priori expectations (prior) to interpret sensory signals. These priors are based on general knowledge of body states and how they are influenced by context, which is represented in so-called internal models in the brain. Depending on the quality

and associated reliability of both the sensory input (likelihood) and the prior, the eventual perception of symptoms (posterior) in consciousness can be closer to the sensory input or closer to the prior (Edwards et al., 2012; Knill and Richards, 1996; Pezzulo et al., 2019; Van Den Bergh et al., 2017). Highly reliable but incorrect priors (or very noisy sensory data), could explain persistent and strong breathlessness, even in the absence of underlying impairment of lung function (Faull et al., 2018; Marlow et al., 2019; von Werder et al., 2024).

The Bayesian brain theory has also been applied to explain increased breathlessness ratings despite normal physiology and breathing patterns during a rebreathing challenge in functional breathlessness (Bogaerts et al., 2010), myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) and fibromyalgia (Van Den Houte et al., 2018). Interestingly, breathlessness was only increased compared to healthy controls when participants (unknowingly) breathed room air and sensory input was low. When sensory input was strong due to increasing CO_2 levels during rebreathing, symptoms were similar to those of healthy participants and more strongly correlated with physiological measures (Bogaerts et al., 2010; Van Den Houte et al., 2018). These results point to dysfunctions in the process of symptom generation due to incorrect internal models and thus inadequate priors, especially when the relevant sensory input is low.

In this study, we investigate whether similar differences in breathlessness perception during rebreathing are also present in patients with post-COVID syndrome with intact lung function and no signs of an underlying organic disease. We used the same rebreathing challenge as in these previous studies to perturb the respiratory body state in a controlled way and investigated how this influences the adaptation of the perceptual (breathlessness ratings) and physiological (heart rate and exhaled CO_2) responses, as well as breathing patterns (respiratory rate and tidal volume). A strong association between symptom reports, breathing patterns and physiological measures is indicative of adaptive internal models that can correctly predict sensory signals. Conversely, a decoupling between those measures would indicate the strong influence of incorrect internal models leading to priors that bias symptom perception away from actual sensory input. In additional exploratory analyses, we investigated whether symptom perception during the experiment depends on whether patients are hyperventilating and whether patients experience breathlessness as part of their post-COVID syndrome or not. We hypothesize that, compared to healthy control participants, patients with post-COVID syndrome show:

1. Similar breathing patterns and physiology

2. Increased breathlessness ratings before and after the rebreathing challenge

3. Similar breathlessness ratings during rebreathing, i.e., during a period with a strong respiratory stimulus

4. Similar breathing patterns and reports of breathlessness in the subgroup of patients with and without a history of post-COVID breathlessness

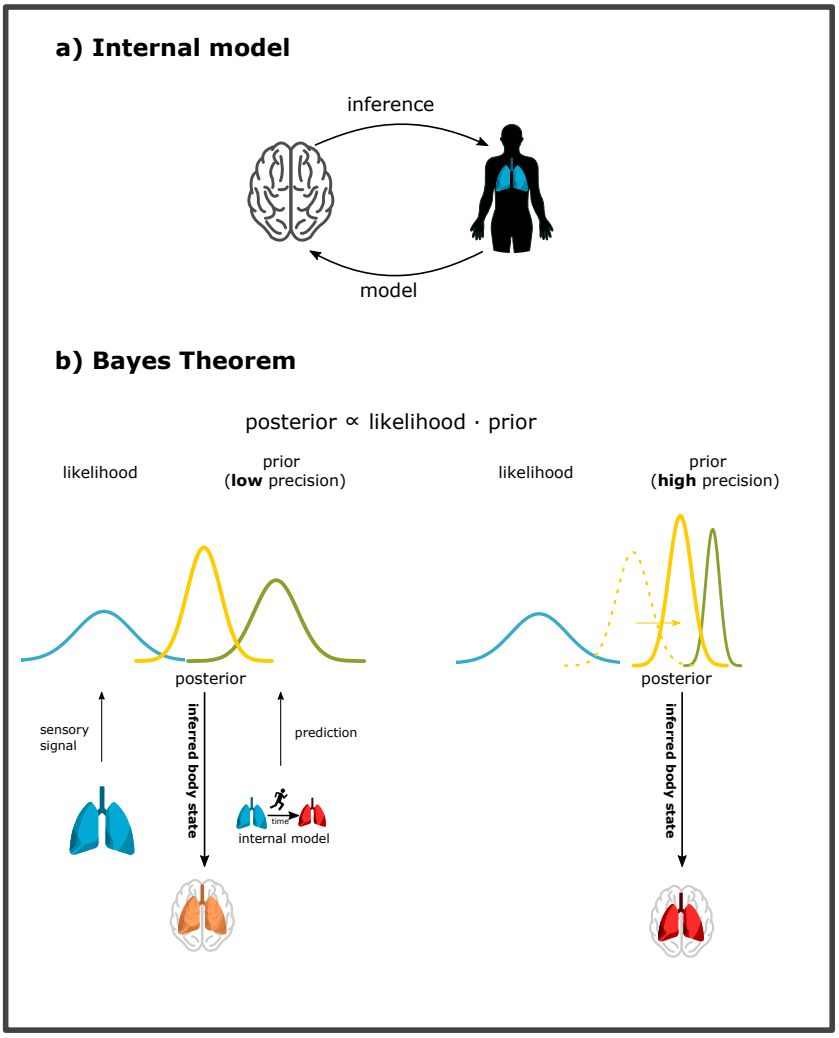


Figure 1: a) Internal model and inference (based on Petzschner et al. (2017)). The brain holds a probabilistic model of how the received respiratory input has been generated. This includes the probabilities of different respiratory body states (prior) and the probabilities to observe the received respiratory input conditioned on the possible respiratory body states (likelihood). By inverting this model, the brain can infer the underlying respiratory state. This inference corresponds to applying Bayes theorem. b) Bayes theorem describes how to optimally combine different sources of noisy data. It is commonly applied to interoception and symptom perception and suggests how the brain should combine noisy sensory (respiratory) data (likelihood) with model-based predictions (a priori knowledge, prior) to yield an optimal estimate of the underlying respiratory body state (posterior). Prior and likelihood are conceived as probability distributions to assign (un)certainty to each of these. The width (i.e., variance) of the likelihood function corresponds to the brain's uncertainty (i.e., the signal's reliability) only based on the sensory signal. The variance of the prior corresponds to the brain's uncertainty of its knowledge about possible body states, before receiving any sensory signals. The variance of the resulting posterior corresponds to the brain's uncertainty after combining the received sensory signal with prior knowledge. The posterior is shifted towards the distribution with less uncertainty (i.e., higher reliability). This means high certainty about the prior can shift the posterior more towards model-based predictions and away from sensory signals.

Methods

The current study is part of the innovative training network ETUDE (Encompassing Training in fUnctional Disorders across Europe; https://etude-itn.eu/), ultimately aiming to improve the understanding of mechanisms, diagnosis, treatment and stigmatization of Functional Disorders (Rosmalen et al., 2021). It was carried out in accordance with the Declaration of Helsinki and was approved by the ethics committee of the Technical University of Munich. All participants provided signed informed consent and received financial compensation of 10€ per hour. We preregistered the study procedure and analysis on the Open Science Framework prior to data collection. It can be accessed under: https://osf.io/5ysn8. Data from five healthy control participants and five patients was previously used in a publication by our lab (von Werder et al., 2024).

Participants

Overall, 56 patients and 53 healthy participants were measured that met all inclusion and none of the exclusion criteria at the time of screening. Of these, 40 patients (M_{age} = 40.7 years, SD_{age} = 11.7 years, 23 women) and 40 healthy control participants (M_{age} = 37.35 years, SD_{age} = 12.55 years, 25 women) were included for final data analysis, see Figure 2 for reasons of exclusion.
All individuals eligible for the current study were at least 18 years old, had sufficient German language skills to understand instructions and questionnaires, and had a previous Sars-CoV-2 infection. Exclusion criteria for both groups were neurological, cardiological or pulmonological impairment, pregnancy and severe episode of major depression, florid psychosis or addiction disorder. All patients had a post-COVID diagnosis from a specialized post-COVID centre at university hospital clinics and were severely affected by fatigue and/or breathlessness for at least 3 months. They were only included if according to the specialized post-COVID centres, no standard clinical tests revealed an explanation of their symptoms. All healthy participants needed to be symptom free for at least 3 months after their last Sars-CoV-2 infection and were excluded if they were suffering from a functional (somatoform or dissociative) disorder.

Study procedure

Measurements went from July 2022 to May 2024. After written informed consent, all individuals performed the rebreathing experiment described below. Then participants filled out questionnaires and a detailed clinical characterization was performed. This was done after the rebreathing experiment as to not interfere with experimental results.

The rebreathing experiment

The experiment was based on the standard rebreathing paradigm (Read, 1967) previously used to investigate breathlessness perception and breathing patterns in various patient

groups and healthy participants (e.g., Bogaerts et al., 2010; Van Den Houte et al., 2018). Individuals wore a nose clip and breathed through a mouthpiece into a breathing circuit. The circuit was designed such that the experimenter could sit behind a visual barrier and let the participant either breathe normal room air or air from the rebreathing bag. Participants were blinded to the actual source of air breathed and its timing and wore headsets so they were unable to hear when a valve switch was performed for the different breathing conditions.
To get accustomed to the breathing circuit and breathlessness rating scale, participants breathed into the circuit and were informed that they are breathing room air for the next 60s. During the last 30s they additionally rated their breathlessness as described below. In the main session, participants were instructed that the CO_2 concentration in inhaled air can change and that this might or might not lead to breathlessness. The exact wording (and an English translation) is available in the Appendix. The rebreathing experiment started with room air for 60s, after which the valve was switched to the rebreathing condition. After 150s the valve was switched back to room air for another 150s. Breathing flow, CO_2 concentration in breathed air and heart rate were measured with a sampling rate of 50Hz.

CO_2 concentration in inhaled and exhaled air was measured with a sampling port at the mouthpiece that was connected to a side stream CO_2 sensor (*Masimo, NomoLine, ISA CO_2*). Respiratory flow was assessed with a heated pneumotachograph (0-400 L/min,*Hans Rudolph*). Heart rate and peripheral oxygen saturation were measured using an oximeter (*Nonin Xpod*) that was attached to the left index finger. Synchronized data recording from all devices and data storage was ensured by using the *SmartLab* Instrumentation system with *Insight Software* from *Hans Rudolph*. A three-way manual control valve (*Hans Rudolph*) allowed switching the source of breathed air between room air and rebreathing. The rebreathing bag was filled with a gas concentration of 5% CO_2 and 95% O_2 (*Carbogen, Linde*). Synchronization between breathlessness ratings and physiological data was evaluated by installing an *Arduino board* that detected mouse clicks and sent this information to the *SmartLab* Instrumentation system.

Questionnaires

Patient Health Questionnaire (PHQ-15): The somatic symptom scale of the Patient Health Questionnaire (Gräfe et al., 2004; Kroenke et al., 2002) asks how bothered participants have been by 15 common somatic symptoms in the past two weeks. Ratings are on a three-point scale (0: not bothered at all, 1: bothered a little, 2: bothered a lot) and global ratings can range from 0 to 30.
Chalder Fatigue Scale (CFQ): The Chalder Fatigue Scale (Chalder et al., 1993; Jackson, 2015) comprises 11 items and measures the extent and severity of fatigue. Questions 1-7 measure physical fatigue and questions 8-11 cognitive fatigue. Ratings are on a four-point scale (0: better than usual, 1: no worse than usual, 2: worse than usual, 3: much worse than usual). The Likert scoring method was applied, so global scores can range from 0 to 33.
Common post-COVID symptoms: All participants were presented with a list of seven

symptoms commonly reported in post-COVID syndrome and were asked to rate which of them they are currently experiencing and the respective level of severity. Ratings are on a four-point scale (0-not present, 1-mild, 2-moderate, 3-severe).
Concurrently perceived breathlessness: During the experiment participants' breathlessness ratings and their timepoints were recorded with a program written in OpenSesame, version 3.3.11 (Mathôt et al., 2012). It presented a scale with every integer from 0 to 100 every 10s. A tone marked the start of a new rating. Next to the scale verbal descriptions of the breathlessness label (as in Bogaerts et al., 2010) were given (0 – no breathlessness, 5 – barely noticeable, 10 – very slight, 20 – slight, 30 – moderate, 40 – rather strong, 50 – strong, 60 – 80 very strong, 90 – very, very strong, 100 – not bearable; translations from German).

Clinical characterization

On the day of the experiment, we performed a detailed clinical characterization to ensure that participants met all inclusion and none of the exclusion criteria. Pulmonary function was assessed in the Department of Occupational Medicine (Ludwig-Maximilians University) using spirometry and diffusion capacity (*Masterscreen PFT, Vyaire*) according to the European Respiratory Society (ERS) clinical guidelines. The Global Lung Function Initiative calculator was used to evaluate the percentage of predicted norm value and percentage of LLN for each participant depending on age, height and sex. All equations were based on Caucasian data. We determined the following parameters: FEV1 – forced expiratory volume in 1 second. FVC – forced vital capacity. DLCO – diffusion capacity for carbon monoxide. KCO – carbon monoxide transfer coefficient. RV - residual volume. VA – alveolar volume. The semi-structured clinical interview for the diagnosis of DSM-5 disorders (SCID-5-CV, Beesdo-Baum et al., 2019) was performed to ensure that none of the exclusion criteria were met. A standardized neurological examination was performed to rule out neurological impairment. The Montreal Cognitive Assessment (MOCA; Nasreddine et al., 2005) was performed to rule out severe neurocognitive impairment. The MOCA assesses different cognitive domains including short-term memory, visuospatial abilities, working memory, attention, language, abstract reasoning, and orientation. Scores can range from 0 to 30. Scores of 26 and above indicate normal cognitive abilities, scores between 6 and 25 indicate at least mild cognitive impairment and scores below 6 severe cognitive impairment.

Missing data and exclusion on day of study

Participants were excluded for data analysis if they showed signs of obstructive lung function on the day of the experiment, i.e., FEV1/FVC was below the lower limit normal (LLN; Pellegrino, 2005), which is the 5th percentile of a healthy, non-smoking reference population. This was the case for one control participant and one patient. In another two control participants and three patients FEV1/FVC was within 2% lower than the LLN. In these cases, a specialized pulmonologist visually inspected the lung function curves and decided that no obstructive lung function impairment was present, and these participants were

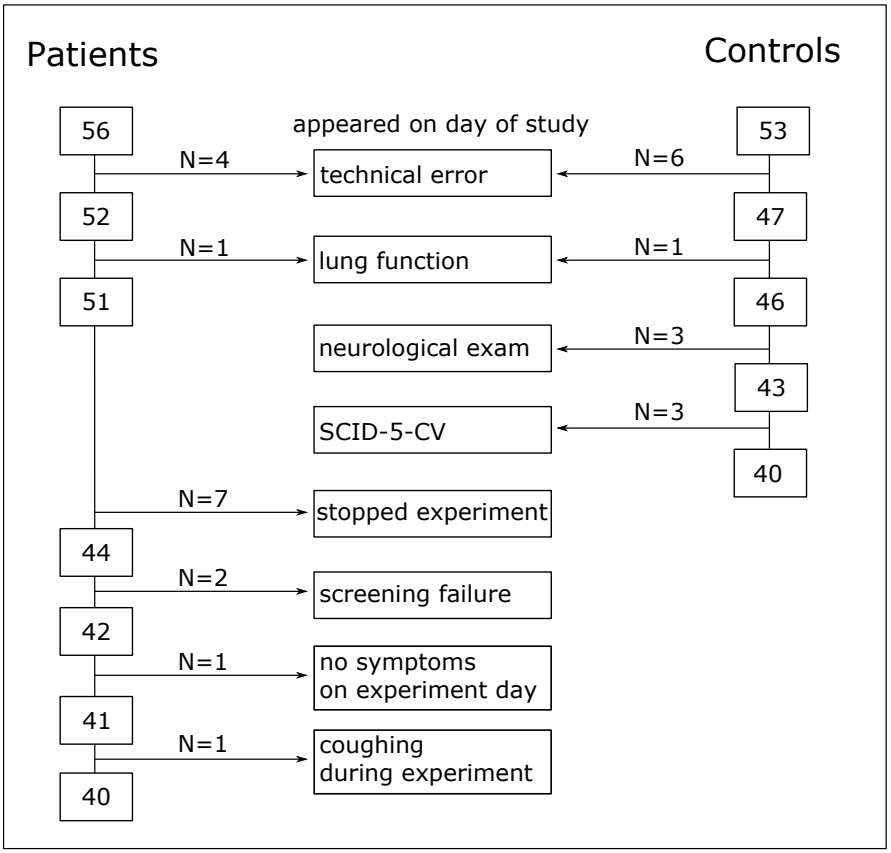


Figure 2: Participants that were excluded from data analysis.

included in the study. For further reasons of exclusion for data analysis after appearance on the day of study, see Figure 2.

Respiratory flow, heart rate and CO2 concentration in breathed air, as well as breathlessness ratings are available for all included participants, except one patient. Due to technical errors, for this patient only CO2 recordings and breathlessness ratings, but not respiratory flow data are available. The CFQ was added after study start to characterize fatigue levels in patients in more detail. At this time point, we had already measured 15 healthy control participants and one patient. The CFQ is thus missing for 15 healthy participants and one patient. However, since this questionnaire only serves to characterize fatigue levels in patients, we still show CFQ scores in the results section. Due to experimenter error, the MOCA is missing for one healthy control participant.

Data processing

Data were processed using Python 3.0. Respiratory flow measurements were normalized to participants' height by dividing the respiratory flow by their height in meters. Breath-by-breath data were obtained by assessing timepoints of in- and exhalation as defined by the

zero crossings of the respiratory flow data. For each breath, the durations of inspiration (T_i) and expiration (T_e) were determined, and the inspiratory and expiratory volumes (V_i and V_e) were calculated by taking the integral of the signal. Respiratory rate (RR) and tidal volume (Vt) were calculated as follows:

$$RR = \frac{60}{T_i + T_e} \tag{1}$$

$$Vt = \frac{V_i + V_e}{2} \tag{2}$$

Fractional end-tidal CO2 ($FetCO_2$) was approximated by taking the maximum exhaled CO_2 concentration in each breath. $FetCO_2$ concentration serves as a proxy for arterial CO_2 concentration (Rentola et al., 2018). We thus captured breathing patterns (RR and Vt) as well as the physiological response (heart rate, FetCO2) which also serves as a proxy of the sensory stimulus for mechano- and chemoreceptors.
The breathlessness ratings were interpolated to match the breath-by-breath data of each participant. Each breath was defined to start with an inhalation that is followed by an exhalation. Breath-by-breath data were then averaged over 10s intervals. The start of the rebreathing phase was defined as the time point of the start of the breath that followed the valve switch. The start of the recovery phase was defined as the time point of the start for the breath that followed the valve switch back to room air. The time point that participants first and last inhaled an increased CO_2 concentration during rebreathing depends on the individual's respiratory rate and time point of the valve switch in the breathing cycle. Thus, although the valve switch occurred at 60s and 210s, the duration of inhaling increased CO_2 concentration during rebreathing was slightly lower for some participants. We thus analysed the first 130s after the rebreathing start to ensure that data is available for all participants. The baseline phase was defined as the 60s before the rebreathing start and the recovery phase as the 150s after recovery start (see Figure 3).

Statistics and reproducibility

Statistical tests were carried out in JASP (Team, 2024). To compare demographic characteristics and questionnaire scores, a Bayesian independent samples t-test (two-sided) was used. To evaluate possible group differences in the rebreathing experiment, we performed a Bayesian repeated-measures ANOVA for each of the different conditions (baseline, rebreathing, recovery) with respectively RR, Vt, FetCO2, heart rate and breathlessness rating as the dependent variable, the between factor group (main analysis: patients versus healthy participants; exploratory analysis: post-COVID with breathlessness versus post-COVID without breathlessness) and the independent within-factor time segment (repeated measures factor). We used a uniform prior over all models. We adopted a Bayesian statistical approach that allows to quantitatively make statements about whether the null or alternative hypothesis are more likely (Peter Rosenfeld and Olson, 2021). The Bayes factor 10 (BF_{10}) quantifies the ratio between the alternative hypothesis given the data and the

null hypothesis given the data. For example, a $BF_{10} = 5$ indicates that the alternative hypothesis is 5 times more likely than the null hypothesis, whereas a $BF_{10} = 1/5$ indicates that the null hypothesis is 5 times more likely. BFs of 1,]1-3],]3-10],]10-30],]30-100] and > 100 are often interpreted as "no", "anecdotal", "moderate", "strong", "very strong", and "extreme evidence" (Lee and Wagenmakers, 2014), or, according to Jeffreys (1961) "not worth more than a bare mention", "substantial", "strong", "very strong" and "decisive evidence". In our interpretation of Bayes Factors, we follow Lee and Wagenmakers (2014). The required sample size for our study was estimated based on the effect sizes of two previous studies using the same rebreathing paradigm (Bogaerts et al., 2010; Van Den Houte et al., 2018). Using G*Power for the power analysis, we obtained a required sample size of 34 participants per group. We included a safety margin and thus measured 40 participants. The detailed sample size calculation can be found in the preregistration (`https://osf.io/5ysn8`).

Exploratory analyses

Since hyperventilation has previously been described as a frequent breathing pattern in patients suffering from post-COVID syndrome (Taverne et al., 2021), we investigated whether this is also the case in our experiment. Since there is currently no gold standard to diagnose dysfunctional breathing (Boulding et al., 2016) nor a specific cut-off defined for hyperventilation, we defined hyperventilation in our study as an FetCO2 level of <3.5%, which is in the range of FetCO2 levels previously shown to cause symptoms in healthy individuals (Rafferty et al., 1992). We subsequently compared the subset of patients that was not hyperventilating to the healthy control group.

We further investigated whether the experience of breathlessness as part of post-COVID syndrome influences the experiences of breathlessness during the experiment. For this purpose, we compared all patients who reported at least mild breathlessness in the COVID symptom questionnaire (see Table 3) with those who reported not suffering from breathlessness. For both exploratory analyses, we used the same Bayesian repeated-measures ANOVA as described above.

Results

Demographic and clinical characteristics

We report on a sample of 40 patients who suffer from post-COVID syndrome without clinical signs of cognitive, neurological or pulmonological impairment and 40 healthy control participants who were matched by age, sex, and body mass index (Table 1 and Appendix Figure 5). The infection that led to post-COVID symptoms was between March 2020 and December 2022. On average patients have suffered for 18.02 months (range: 5 – 36 months) from symptoms at the time of study participation. Patients report very high levels of fatigue as measured with the CFQ and more bodily symptoms than healthy participants as measured with the PHQ-15 (see Table 1). According to the PHQ-15 results, patients are

Table 1: Demographic and clinical characteristics. Chalder Fatigue Scale was available for 39 patients and 25 healthy control participants. Possible scores CFQ (0-33) and PHQ-15 (0-30). BMI – body mass index, CFQ – Chalder Fatigue Scale, PHQ-15 – Patient Health Questionnaire 15

	post-COVID	**healthy controls**	**BF_{10}**
	mean (range)	mean (range)	
Age (years)	40.7 (22-62)	37.35 (24-65)	0.442
Sex (female/male)	23/17	25/15	n.a.
BMI (kg/m^2)	24.13 (18-34)	23.68 (19-35)	0.265
Symptom duration (months)	18.02 (5-36)	n.a.	n.a.
CFQ	25.15 (11-33)	9.96 (2-18)	$3.80*10^{16}$
PHQ-15	12.75 (4-24)	3.3 (0-10)	$1.79*10^{12}$

bothered most by 'Feeling tired or having low energy', 'trouble sleeping' and 'headaches' (see Appendix Figure 6). When asked about current post-COVID symptoms, patients most often reported fatigue, followed by difficulties concentrating, tiredness and dizziness or light-headedness. All patients reported fatigue as one of their post-COVID symptoms and 22 patients reported having breathlessness in addition to their fatigue (see Table 3).

There is no supporting evidence indicating different lung function parameters between healthy control participants and patients, however, there was anecdotal evidence for an increase in DLCO and KCO (see Table 2). It has previously been shown that the odds of experiencing any respiratory symptom decrease the higher the ratio of FEV1/FVC and reaches a minimum at 80% (Torén et al., 2021). All of our participants were above that threshold. None of the included participants has a neurological or severe neurocognitive impairment. Three patients and two healthy participants have MOCA scores below 26, suggesting mild cognitive impairment (see Table 2).

Rebreathing experiment

The results of the rebreathing experiment are visualized in Figure 3 and Table 4.

Baseline

In the baseline phase with room air, reported breathlessness is higher in patients (M_{pat} = 9.0) than in healthy participants ($M_{healthy}$ = 2.8; BF_{10} = 8.029, moderate evidence). There is anecdotal evidence for similar breathing patterns, i.e., respiration rate (BF_{10} = 0.817) and tidal volume (BF_{10} = 0.617) and a similar physiological response, i.e., FetCO2 concentration (BF_{10} = 0.695) and heart rate (BF_{10} = 0.671) in both groups.

Rebreathing

During rebreathing patients report higher breathlessness (M_{pat} = 26.5) than healthy participants ($M_{healthy}$ = 11.1; BF_{10} = 11636, extreme evidence). There is anecdotal evidence

Table 2: Lung function parameters and results from the Montreal Cognitive Assessment (MOCA). % predicted – percentage of predicted norm value based on age, height and sex. % LLN – percentage of lower limit normal. FEV1 – forced expiratory volume in 1 second. FVC – forced vital capacity. DLCO – diffusion capacity for carbon monoxide. KCO – carbon monoxide transfer coefficient. RV- residual volume. VA – alveolar volume.

	post-COVID	**healthy controls**	$\mathbf{BF_{10}}$
	mean (range)	mean (range)	
MOCA	28.26 (23-30)	28.46 (24-30)	n.a.
FEV1/FVC			
% predicted	96.59 (85.50 – 116.29)	97.27 (84.33 – 112.73)	0.255
% LLN	112.04 (98.97 – 134.81)	112.77 (97.61 – 130.22)	0.251
FEV1			
% predicted	99.41 (67.56 – 129.00)	101.18 (73.28 – 124.71)	0.281
%LLN	126.31 (86.17 – 169.65)	128.16 (98.34 – 166.81)	0.261
FVC			
% predicted	102.53 (77.90 – 129.95)	103.59 (79.69 – 131.18)	0.249
%LLN	129.92 (99.26 – 163.75)	130.98 (99.7 – 174.77)	0.242
DLCO			
% predicted	96.33 (67.88 – 130.09)	102.18 (83.19 – 127.08)	1.477
%LLN	123.19 (87.56 – 167.65)	130.18 (105.15 – 160.18)	1.228
KCO			
% predicted	97.35 (75.33 – 127.01)	103.78 (74.10 – 125.00)	1.794
%LLN	124.18 (95.64 – 161.93)	132.20 (98.22 – 160.68)	1.623
RV			
% predicted	104.71 (70.45 – 210.18)	106.69 (65.66 – 179.00)	0.246
%LLN	194.12 (124.37 – 403.79)	203.81 (130.44 – 374.57)	0.307
VA			
% predicted	99.00 (80.89 – 125.10)	99.00 (80.69 – 123.24)	0.232
%LLN	120.67 (99.14 – 153.33)	120.46 (97.93 – 149.87)	0.233

for similar tidal volume (BF_{10} = 0.361) and $FetCO_2$ concentration (BF_{10} = 0.437) and anecdotal evidence for increased respiratory rate (BF_{10} = 2.007) in patients.

Recovery

During recovery with room air, patients report higher breathlessness (M_{pat} = 36.6) than healthy control participants ($M_{healthy}$ = 13.5; BF_{10} = 43662, extreme evidence). There is anecdotal evidence for an increased respiratory rate (BF_{10} = 1.877) and moderate evidence for decreased $FetCO_2$ concentration in patients (BF_{10} = 5.018). Evidence for similar tidal volume (BF_{10} = 0.423) is anecdotal.

Table 3: Prevalence and severity of symptoms commonly reported in post-COVID. Severity was rated on a scale from 0 (not present) to 3 (severe). Mean severity for those participants that reported that the symptom was present. Data is available for 40 patients and 39 healthy control participants.

Symptom	**post-COVID**		**healthy controls**	
	frequency	severity (std)	frequency	severity (std)
fatigue	97.5%	2.36 (0.66)	20.51%	1.25 (0.66)
difficulties concentrating	90.0%	2.06 (0.74)	15.39%	1.00 (0.00)
tiredness	87.5%	2.23 (0.76)	28.21%	1.45 (0.66)
dizziness/light headedness	70.0%	1.39 (0.62)	5.13%	1.00 (0.00)
pain	65.0%	1.62 (0.74)	10.26%	1.25 (0.43)
breathlessness	55.0%	1.64 (0.64)	0.00%	-
loss of taste and/or smell	22.5%	1.89 (0.74)	2.56%	1.00 (0.00)
nausea and/or vomiting	15.0%	1.00 (0.00)	0.00%	-

Exploratory analyses

During the study, eight patients and no healthy control participant were hyperventilating. Of these, two patients were already hyperventilating during the baseline phase with room air and six patients start to hyperventilate only after the rebreathing challenge. When excluding patients that are hyperventilating from the group comparison, all evidence points towards similar breathing patterns (BF_{10}<0.704), while evidence for increased breathlessness during rebreathing and recovery phase remains strong (BF_{10} >126.812) and is anecdotal in the baseline phase (BF_{10} = 1.283).

We further investigated whether experiencing breathlessness as part of post-COVID syndrome leads to higher induced breathlessness perception during the experiment. For almost all phases, evidence for breathing patterns and breathlessness perception points towards similarity between groups and there is anecdotal evidence (BF_{10} = 1.326) for increased breathlessness perception in patients with post-COVID breathlessness in the baseline phase with room air (see Figure 3 on the right and Table 4).

Discussion

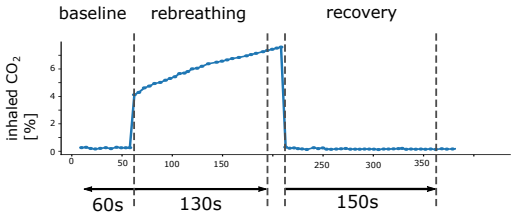
Summary

We used a rebreathing experiment to perturb the respiratory body state in a controlled way. Breathlessness ratings in patients with post-COVID syndrome were increased compared to healthy individuals, while breathing patterns and physiology were similar. During rebreathing and recovery phase, there was no supporting evidence for higher breathlessness ratings in patients that experience breathlessness as part of their post-COVID syndrome and those who do not. 20% of patients hyperventilated during the experiment, however, differences in breathlessness remained when removing these patients from analysis.

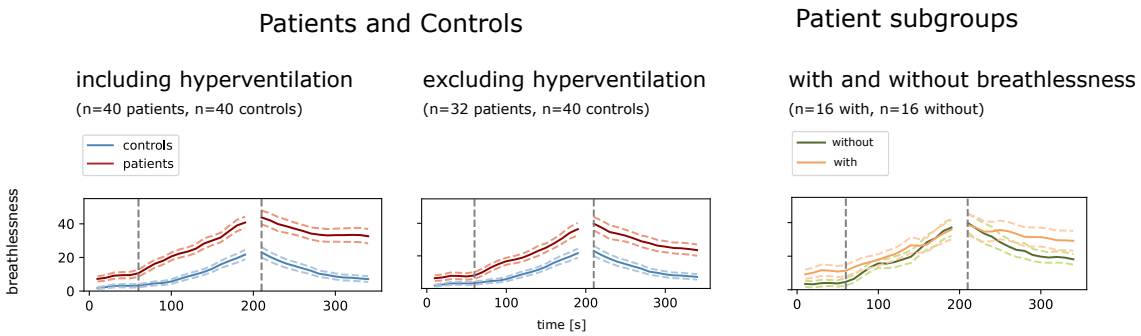
Table 4: Bayes factors (BF_{10}) for different group comparisons.

	Baseline	**Rebreathing**	**Recovery**
Patients versus healthy controls			
Including hyperventilation			
Breathlessness	8.029	11636	43662
Respiration rate	0.817	2.007	1.877
Tidal volume	0.617	0.361	0.423
FetCO2	0.695	0.437	5.018
Heart rate	0.671	0.708	0.776
Excluding hyperventilation			
Breathlessness	1.283	126.812	751.282
Respiration rate	0.562	0.651	0.669
Tidal volume	0.619	0.640	0.478
FetCO2	0.704	0.307	0.480
Heart rate	0.568	0.500	0.531
Patients with versus without breathlessness			
Breathlessness	1.326	0.414	0.618
Respriation rate	0.701	0.605	0.665
Tidal volume	0.664	0.480	0.512
FetCO2	0.689	0.626	0.684
Heart rate	0.797	1.336	1.632

a) Inhaled CO_2 concentration



b) Perception



c) Physiology and breathing patterns

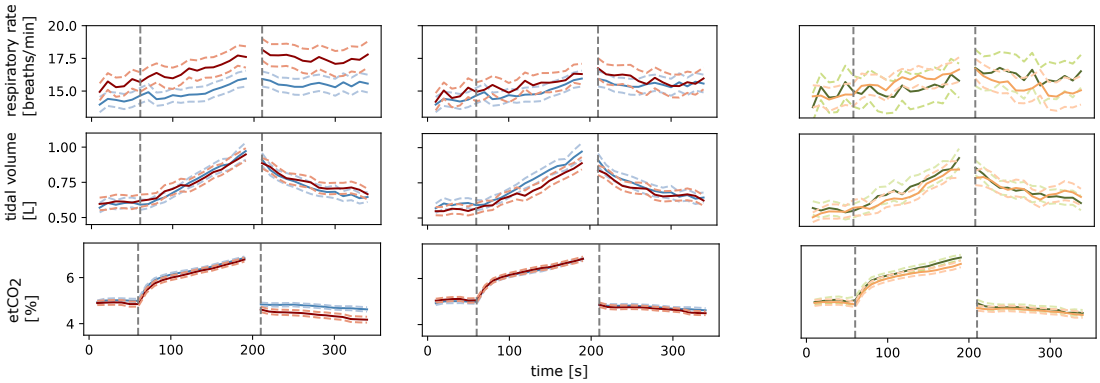


Figure 3: Results rebreathing experiment. a) Exemplary time course of inhaled CO_2 concentration from one individual. First, participants breathe room air, i.e., inhaled CO2 concentration is low. After a valve switch, they rebreathe from a rebreathing bag, initially filled with 5% CO_2 and 95% O_2. This constitutes a strong respiratory stimulus. After 150s the breathing circuit is opened again, and participants breathe room air. The exact rebreathing and recovery start was defined based on the inhaled CO_2 concentration of each individual (see Methods). b) Differences in breathlessness reports for all patients and healthy participants (left), only those that were not hyperventilating (middle) and patients with versus without breathlessness that were not hyperventilating (right). c) Breathing patterns and $FetCO_2$ for all three group comparisons. Solid lines – mean, dashed lines – standard error of the mean.

Intact breathing patterns

Our results are in line with our first hypothesis that stated similar adaptation of respiratory patterns and physiology to the rebreathing challenge in patients and healthy participants. This suggests that patients in our study were able to correctly process sensory signals related to respiration, infer the underlying respiratory body state and plan adaptive breathing patterns. As in several previous studies (El-Medany et al., 2024; Kaye et al., 2022; Sneller et al., 2022), we find intact lung function in patients with post-COVID syndrome. Our results of similar breathing patterns, extend the common finding of intact lung function, by showing that not only mechanical ventilation and gas exchange in the lung are functioning appropriately, but also the sensory-control loop for breathing regulation is intact. It must be mentioned that while in all breathing conditions evidence pointed towards similar breathing patterns and physiology, evidence remained anecdotal. In addition, while most evidence pointed towards similar lung function measures between healthy participants and patients, we also observed anecdotal evidence for decreased lung diffusing capacity (DLCO and KCO) in patients. Our sample size might thus have been too small to detect subtle differences in breathing patterns or lung function. However, it remains questionable whether such small differences could explain the observed large differences in breathlessness ratings in our study.

Dysfunctions in symptom perception

We were further able to confirm our second hypothesis that breathlessness is increased before and after the rebreathing challenge, i.e., during phases with room air. However, we also found strongly increased breathlessness during the rebreathing challenge, i.e., when the respiratory stimulus was very strong. This is against our third hypothesis and not in line with previous results in ME/CFS, fibromyalgia (Van Den Houte et al., 2018) and functional breathlessness (Bogaerts et al., 2010). One possible explanation for the latter divergent result is that the effect of rebreathing on breathlessness ratings is dependent on stimulus strength. While we used the same experimental paradigm as in other studies, $FetCO_2$ levels in our study were lower (mean $FetCO_2$ at end of rebreathing 6.9%) than in these studies (mean $FetCO_2$ at end of rebreathing 8% in Bogaerts et al. (2010)). This could either be due to differences in the technical setup (e.g., different dead space of the breathing circuit) or differences in breathing patterns. Slower and shallower breathing, as already exhibited

during the baseline phase in participants in our study, leads to less CO_2 that is exhaled into the breathing circuit during rebreathing and thus a lower respiratory stimulus intensity. This interpretation is consistent with the results of another study with non-clinical high and low symptom reporters using the same rebreathing paradigm (Walentynowicz et al., 2018). Here, high symptom reporters also reported higher breathlessness during the rebreathing phase than low symptom reporters. Interestingly, in this study, $FetCO_2$ levels were in the same range (mean $FetCO_2$ at end of rebreathing 7.3%) as ours.

Potentially transdiagnostic mechanism

Furthermore, we could partly confirm our fourth hypothesis, i.e., breathlessness ratings are similar in post-COVID patients with and without a history of breathlessness. While breathlessness ratings during baseline were slightly increased in patients with post-COVID breathlessness, our statistical analysis yielded no group differences during rebreathing and recovery. This is in line with previous studies showing increased symptom reporting in different groups of patients regardless of their primary symptoms and suggests a more general dysfunction of symptom processing underlying persistent symptoms across diseases. Context and learned associations play a dominant role in symptom perception. Experimental setups such as the rebreathing experiment in this study and instructions that focus on symptom ratings create a context that activates symptom priors. This might be especially strong in patients and could outweigh symptom- or disease-specific processes, leading to the observed similarities across different studies, diagnoses and symptoms.

Possible computational mechanisms

We explored different computational mechanisms that could explain our observed results. Since breathing control is intact but breathlessness reports increased, one possibility would be the use of different internal models. For example, assuming the same sensory input and its reliability but a higher and more reliable prior for symptom perception than breathing patterns would result in increased breathlessness reports while breathing regulation is within normal limits (see Figure 4A). This would be in line with hierarchically arranged levels of interoceptive respiratory processing, ranging from homeostatic regulation of breathing control to meta-cognitive processes of symptom perception that are connected and share algorithmic similarities but also include different processing steps (Allen et al., 2023). To specifically explain the observed differences in breathlessness ratings, we further tested what kind of prior would lead to the observed results (see Appendix Figure 7). We first considered the effect of a prior for higher breathlessness in patients that is equally reliable as in healthy participants. In this case, breathlessness ratings are already increased during the baseline phase with room air and progressively increase during rebreathing. Thus, the difference in breathlessness ratings persists when the stimulus strength is increased, which is in line with our results. Accordingly, one possible explanation for the observed differences in breathlessness is that patients expect higher levels of breathlessness in the experiment than controls, with both groups being similarly certain about their a-priori

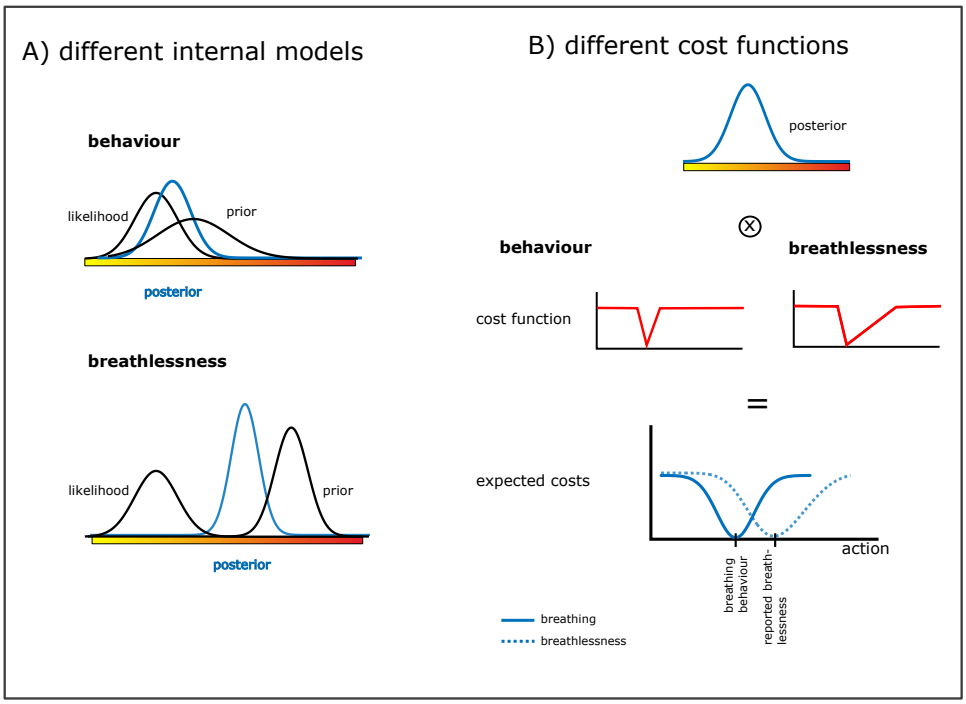


Figure 4: Possible computational mechanisms that could explain increased breathlessness despite normal breathing patterns. A) Different internal models for breathlessness perception and breathing patterns. The same sensory input and its reliability is assumed for breathing patterns and breathlessness perception, represented as the same likelihood function. However, for breathlessness a higher and more reliable prior (i.e., higher mean value and less variance/higher precision) is assumed. According to Bayes theorem, the posterior (blue curve) is a precision-weighted combination of likelihood and prior. Thus, due to the higher and more reliable prior for breathlessness perception than breathing patterns, the resulting posterior is shifted towards higher breathlessness levels, even though sensory input (likelihood) is the same as for breathing patterns. The inferred bodily state (posterior) is thus closer to the actual sensory input in breathing patterns and closer to the prior in symptom perception. While the respiratory state is correctly inferred for breathing patterns, an incorrect internal model, e.g., with a strong weighting of erroneous priors, could lead to strong breathlessness despite an intact respiratory body state. B) Alternatively, the same internal model could be used, yielding the same posterior (top, blue curve) but different cost-functions could be applied to decide on the action that should be taken. Applying a cost function mathematically corresponds to a convolution of the posterior with the cost function. This yields the expected costs (solid line for breathing patterns, dotted line for reported breathlessness) for each possible action and allows to choose the action associated with minimum costs. An action can either be a specific breathing pattern or a symptom report. While breathing patterns and symptoms are outcomes that can be consciously perceived, the decision process involving the application of cost functions (B), or the formation of priors (A), is happening subconsciously.

expectations. To explain the observed breathlessness ratings within the patient group, i.e., between patients with and without a history of breathlessness, we propose that patients with post-COVID breathlessness are more certain about their a-priori expectations of increased breathlessness during the experiment than those patients without post-COVID breathlessness. This would be represented in a similarly high but more reliable prior, which would lead to the observed increased breathlessness ratings during baseline and a decrease of this difference during rebreathing (see Appendix Figure 7). We further explored how different cost functions would influence breathlessness perception and breathing regulation (see Figure 4B). Cost functions are an essential part of Bayesian decision theory. The brain's inference of the underlying body state is represented as the posterior distribution. It describes the probability of the value or category of a bodily state given the current sensory input and the prior knowledge about this state. However, the brain must eventually choose one value from this posterior probability distribution. Cost functions allow to integrate rewards and costs into this decision-making process and thus decide on the action with highest expected reward (or lowest expected cost) given the current bodily state represented by the posterior distribution (Dayan and Daw, 2008; Körding and Wolpert, 2006). This action can either be a specific breathing behaviour or a decision to consciously perceive and report a specific symptom level. Cost functions are task specific and depend on the desired goal. A stronger perceptual response in relation to the underlying body state will lead to an earlier initiation of preventive measures that reduce further bodily stressors. Consequently, it is 'safer' to perceive symptoms that overrepresent the underlying body state. This would be achieved by applying an asymmetric cost function that rewards symptom reports overrepresenting the actual underlying body state and penalizes underrepresenting them. This would be similar to a better-safe-than-sorry strategy that has previously been suggested by Van den Bergh et al. (2021). This explanation assumes the same internal model for respiratory control and symptom perception, but the use of a symmetric cost function for respiratory control and an asymmetric cost function for symptom perception, leading to the observed increased breathlessness ratings despite normal breathing control. Similarly, it can explain the observed differences in breathlessness ratings between patients and healthy participants.

Hyperventilation

While breathing patterns were similar to healthy controls in most patients, 20% of post-COVID patients hyperventilated during the experiment. Recently, carotid body dysfunction has been proposed as a possible cause of hyperventilation in post-COVID syndrome. The carotid body monitors and provides feedback about CO2 levels and changes in blood pH. Dysfunction could, for example, result in an over-reactive breathing response to otherwise normal pH levels (El-Medany et al., 2024). A similar response could be due to dysfunctions in inspiratory muscles that has recently been shown in patients with post-COVID (Hennigs et al., 2022). Pathological dysfunction on the side of the sensor (carotid body) or effector (inspiratory muscles) are a possible explanation for the observed breathing patterns and breathlessness reports in patients that hyperventilated in our experiment

and could lead to erroneous processing of interoceptive respiratory signals. Six out of the eight patients that hyperventilated breathed normally during the baseline phase, and only started to hyperventilate during the recovery phase after the aversive rebreathing stimulus. Because fear of bodily symptoms in response to breathing distress have been shown to alter breathing, also this explanation may account for the observed hyperventilation responses. Stress-related hyperventilation is a type of feedforward regulation (Van Diest et al., 2001) and thus overweighing priors during breathing regulation could play a role in this subgroup. A catastrophic interpretation of interoceptive signals has also been suggested to underlie the observed discordance between physiological measures and symptom reports during a hyperventilation provocation test (Spinhoven et al., 1993). Importantly, the dissociation between breathlessness and breathing patterns in our study remains when removing participants who hyperventilated during the experiment from the analysis.

Internal models

Our experimental results suggest that the cause of heightened symptoms in patients is not directly related to breathing physiology but rather differences in processing and incorporating interoceptive breathing signals into symptom perception due to incorrect internal models or overly cautious cost-functions. It is currently unclear where and how internal models for interoception are represented and maintained in the brain, but there is evidence that brain areas like the anterior insula (Harrison et al., 2021) play an important role. There have been several findings of brain changes concerning the structural as well as functional connectivity in patients with post-COVID (Douaud et al., 2022; Serrano Del Pueblo et al., 2024), some of them pertaining to brain areas that are thought to be involved in interoceptive processing. Pathological changes in these brain areas could lead to problems in correctly maintaining and adapting internal models. Similarly, internal models and cost functions can be adapted by experience. For example, experiencing a persistent immune reaction due to viral reservoirs or social or emotional stress and anxiety, can lead to an adaptation of internal models that assume a high risk for aversive bodily stressors and thus the development of incorrect priors. Anxiety and depression are known risk factors for developing post-COVID symptoms (Tsampasian et al., 2023; Wang et al., 2022) and Harrison et al. (2021) have recently shown a close link between anxiety and respiratory-related interoception that is especially strong at higher levels involving meta-cognitive processes of interoception with different activities in the anterior insula in individuals with low versus high anxiety. Our computational approach provided insights into possible ways how internal model-based prior expectations and cost-functions might be altered. In specific, we have shown that our data can be explained by patients expecting a higher level of breathlessness, however, being equally certain about their prior expectation as healthy participants. Better understanding how exactly priors, i.e., (implicit) symptom expectations, are altered are crucial to develop new and improve existing therapeutical approaches. This is supported by previous studies showing that breathlessness reductions during pulmonary rehabilitation in COPD patients are associated with altered neural processes reflecting learned breathlessness associations (Herigstad et al., 2017). Furthermore,

virtual-reality approaches that alter breathlessness perception by modulating expectations have been proposed to re-align breathlessness with sensory signals (Finnegan et al., 2022) which has implications for exposure based cognitive-behavioural therapies.

Conclusion

In summary, we have provided first evidence that while breathing control is mostly intact, processes in the brain for symptom perception are erroneous in patients with post-COVID syndrome. We have suggested different computational mechanisms that could underlie this erroneous processing in a Bayesian brain framework. This theoretical approach allowed to investigate how prior symptom expectations must be altered to match our experimental data which can guide development of specifically targeted treatments options. Importantly, these priors are mostly implicit and a result of specific brain activity that might be altered due to disease-specific or transdiagnostic processes that are currently not well understood. Our results highlight that in addition to physiological processes in the body, further research could greatly benefit from focusing on interoception and its influence on symptom-related processing in the brain by taking a Bayesian brain perspective.

Data Availability

Anonymized physiological data and breathlessness ratings recorded during the rebreathing experiment as well as lung function parameters, MOCA scores and questionnaire data (PHQ-15, CFQ, prevalence of common post-COVID symptoms, breathlessness ratings in everyday life situations) can be found via the following link: `https://osf.io/vt2j5/?view_only=9c65fd05163249b2b116c750bde43476`

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Author contributions

NL: Initial idea and project initiation. DW, NL, OVdB, SG: Conceptualization. DW, MA: data curation. DW: formal analysis. DN, NL, SG: Funding acquisition. MA, ET, KA, HS, DS, FR, DW, RJ, KB: Investigation and Recruitment. DW, SG, RJ, DN, NL, OVdB: Methodology. DW, MA, NL: Project administration. DN, SG, NL: Resources. DW, FR, SG: Software. SG, NL: Supervision. DW, MA, SG, NL: Validation. DW: Visualization. DW: Writing – original draft. All authors: Writing – review and editing.

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Competing interests

There are no competing interests.

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Appendix

Instruction for rebreathing experiment

German (original)
Im folgenden Experiment atmen sie Luft mit unterschiedlichen CO2 Konzentrationen ein. Das kann zu Atemnot führen, muss aber nicht. Wir messen kontinuierlich ihre physiologischen Atemparamter und bitten Sie alle 10 Sekunden anzugeben, ob Sie Atemnot haben und falls ja, wie stark diese ist. Atemnot kann bei Personen ganz unterschiedliche Empfindungen auslösen. Das kann zum Beispiel das Gefühl sein, nicht genügend Luft zu haben bzw., dass die geatmete Luft nicht ausreicht. Es kann sich in dem Wunsch oder Drang äußern, z.B. an ein Fenster zu gehen und dort frische Luft zu atmen. Es kann auch mit dem Drang verbunden sein, das Mundstück loszulassen und frei oder mehr zu atmen. Ebenso kann sein, dass Sie das Gefühl haben, dass die aktuelle Atmung nicht ausreicht. Atemnot kann auch mit einer gewissen Anstrengung oder Schwierigkeiten bei der Atmung verbunden sein. Diese Empfindungen können auftreten, müssen aber nicht und die Empfindungen können kommen und gehen. Atemnot kann also ganz unterschiedliche Empfindungen auslösen und diese können in unserem Experiment kommen und gehen oder gar nicht auftreten.
English (translation)
In the following experiment, you will breathe air with different CO2 concentrations. This can lead to breathlessness but does not have to. We continuously measure your physiological breathing parameters and ask you to indicate every 10 seconds whether you experience breathlessness and, if so, how strong it is. Breathlessness can trigger very different sensations in people. For example, it can be the feeling of not having enough air or that the air you are breathing is not enough. It can manifest itself in the desire or urge to go to a window and breathe fresh air, for example. It can also be associated with the urge to let go of the mouthpiece and breathe freely or more deeply. You may also feel that your current breathing is not sufficient. Breathlessness may also be associated with a certain effort or difficulty in breathing. These sensations may or may not occur and the sensations may come and go. Breathlessness can therefore trigger very different sensations and these can come and go or not occur at all in our experiment.

Deviations from pre-registered analysis plan

As stated in our pre-registration, our experimental paradigm consisted of the conditions in 5. Since the second rebreathing phase was too short for breathlessness changes to occur and for better comparability with previous studies, we only evaluated data up to the end of the recovery phase in this paper. In our pre-registration we also included a co-variate in the repeated-measures ANOVA. Starting from the rebreathing phase, we planned to add the mean of respective dependent variable (CO_2 concentration, breathlessness rating or breathing flow) over the last 30s of the previous breathing condition as a covariate. However, for this paper we were interested in the difference for each specific breathing condition, independent of baseline levels. We thus decided to not include the co-variate in

the analysis.

Table 5: Experimental phases of the pre-registered paradigm

Breathing condition	Duration
Baseline (room air)	60s
Rebreathing	150s
Recovery (room air)	150s
Cognitive cue (room air)	30s
Second rebreathing	30s

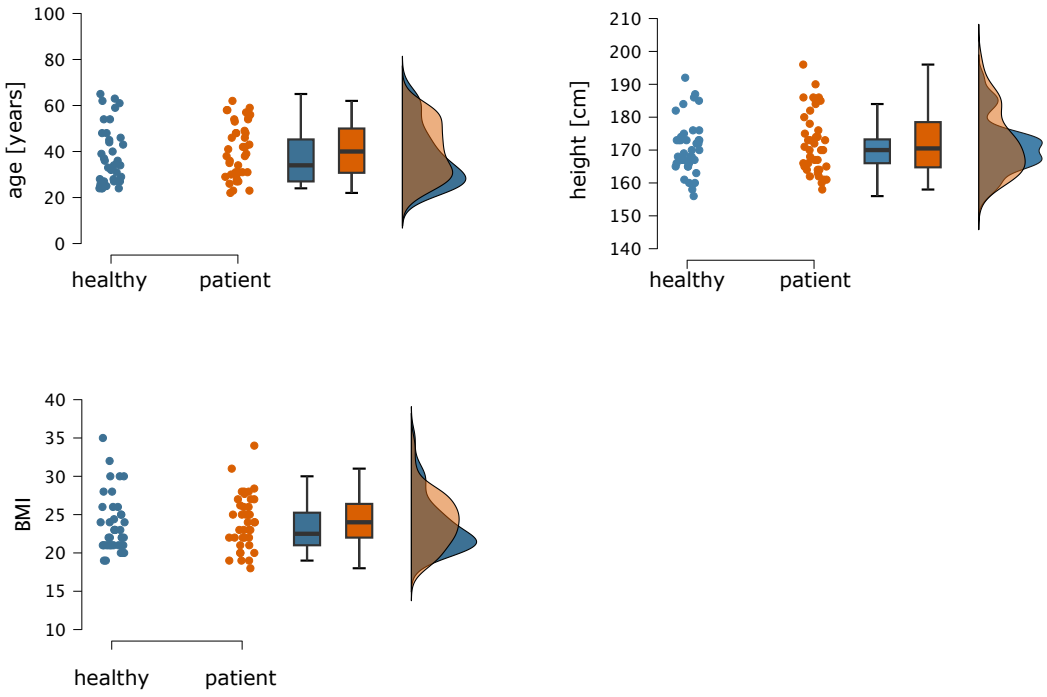
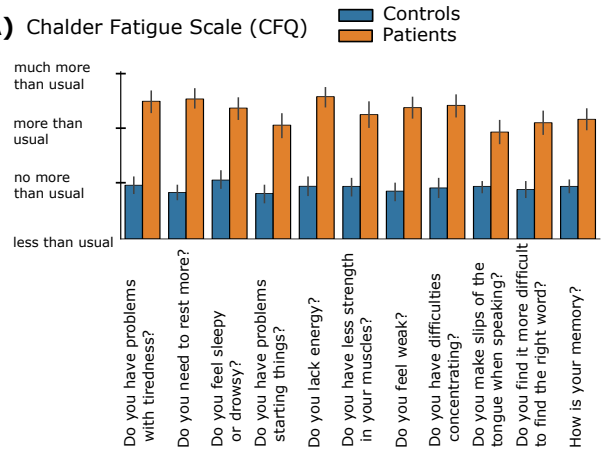
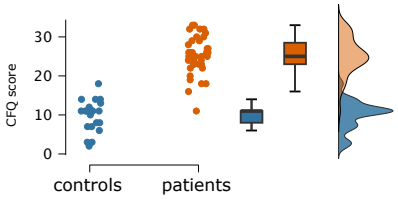


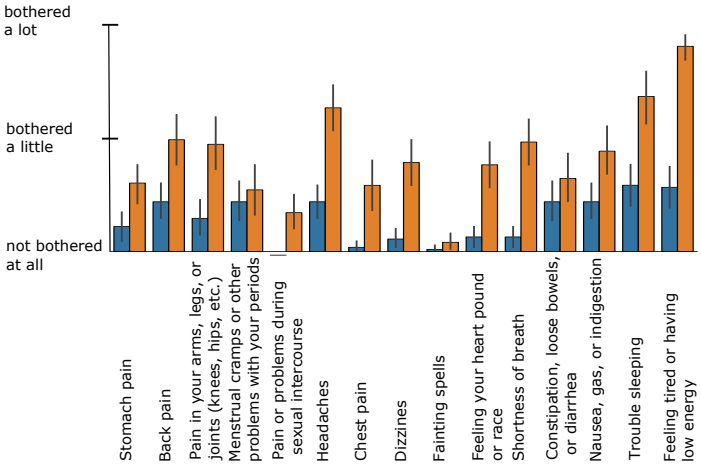
Figure 5: Demographic characteristics of the patient and healthy participant group for age (BF_{10} = 0.442), height (BF_{10} = 0.289) and body mass index (BMI; BF_{10} = 0.265).

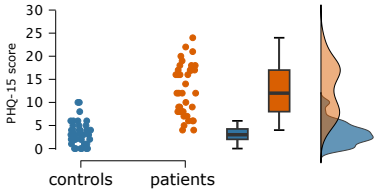
A) Chalder Fatigue Scale (CFQ)





B) Patient Health Questionnaire (PHQ-15)





C) Current symptoms frequently reported in post-COVID syndrome

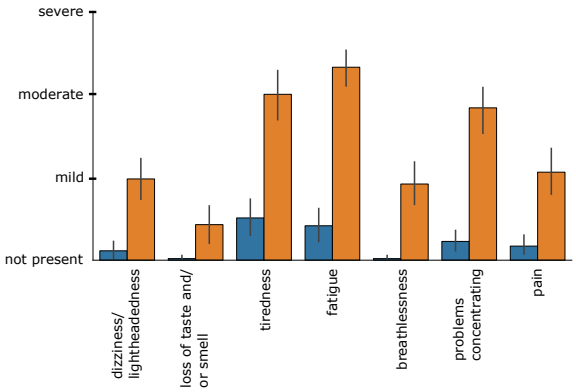


Figure 6: Clinical characteristics. A) Results for Chalder Fatigue Scale (CFQ) for each question (top) and overall group comparison (bottom, BF10 = 3.8*1016). B) Results for Patient Health Questionnaire 15 (PHQ-15) for each question (top) and overall group comparison (bottom, BF10 = 1.79*1012). C) Presence and severity of current symptoms frequently reported in post-COVID syndrome.

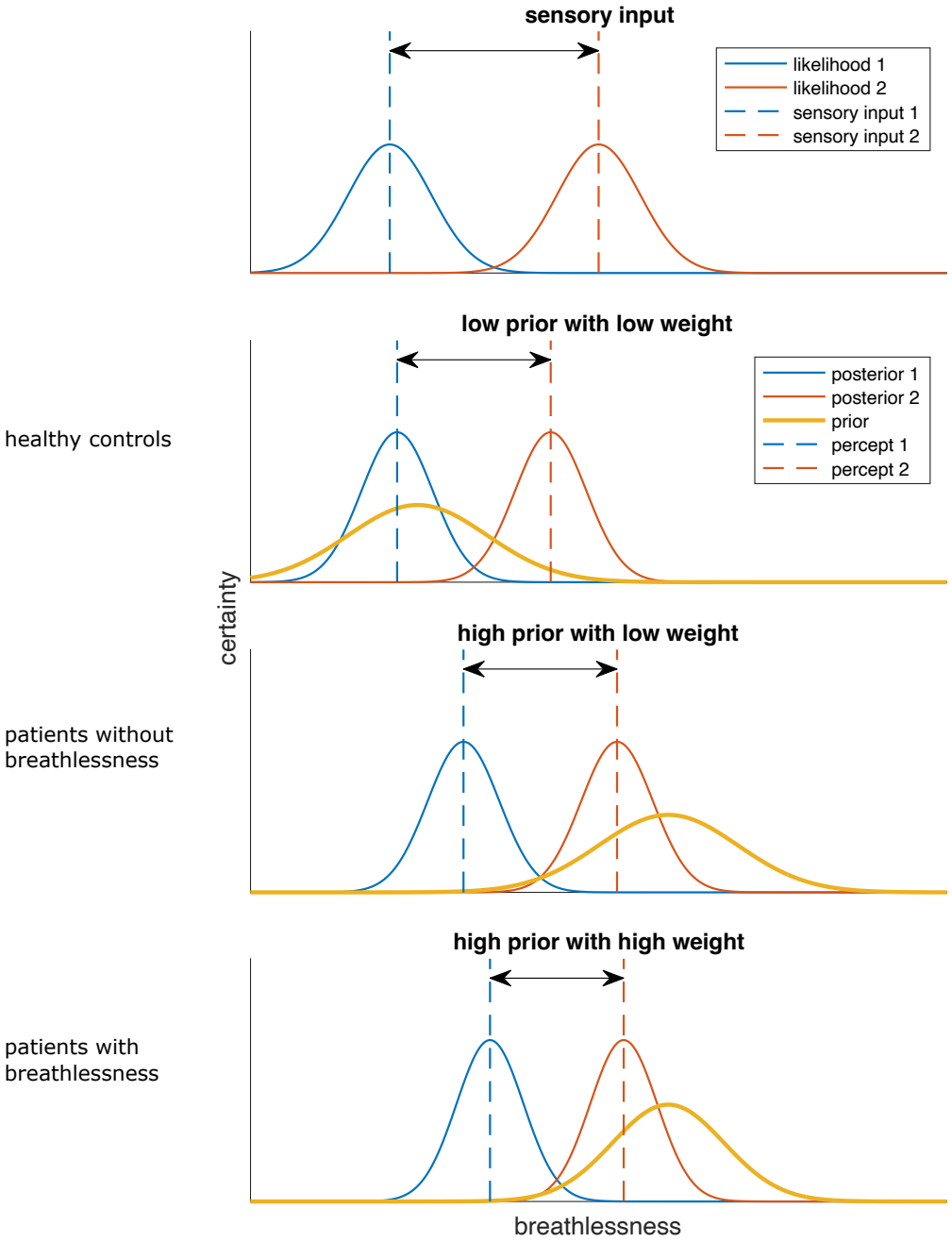


Figure 7: The effect of different priors (i.e., different internal models) on breathlessness reports. Top: During rebreathing sensory input and thus the mean of the likelihood function increases. Since lung function is intact, the same likelihood function is assumed for patients and healthy participants. Second row: The internal model for healthy participants leads to a prior with a low mean to which low weight is assigned (high variance, i.e., low precision of the prior). Thus, healthy participants expect low breathlessness, but rely mostly on sensory input. Third row: Patients without breathlessness assume a higher breathlessness level than healthy participants but are equally certain about their belief. The prior variance is thus the same as in healthy control participants, but the prior is shifted to the right, i.e. higher breathlessness levels. This leads to a shift of the posterior towards higher breathlessness levels than in healthy participants. When the stimulus strength increases (likelihood 2 in the top panel), the shift of the mean of the posterior is equally strong as in healthy participants, i.e., breathlessness differences during rebreathing remain (same length of errors in panel 2 and 3). Bottom: Patients with breathlessness expect an equally high level of breathlessness but are more certain about their belief than patients without breathlessness. This leads to a lower variance, i.e., higher precision of the prior. During phases with low stimulus intensity this will lead to a higher posterior mean, i.e., slightly increased breathlessness reports, however, when stimulus intensity increases (e.g., during rebreathing) breathlessness reports are similar. This is in line with our experimental results.

Chapter 4

A mathematical model of breathlessness processing in the brain

The current chapter encloses the research article with the title 'Post-COVID breathlessness: a mathematical model of respiratory processing in the brain'. The article is published in *European Archives of Psychiatry and Clinical Neuroscience*.

4.1 Summary

We developed a model of respiratory processing in the brain that explains how breathlessness can emerge in the absence of lung function deficits. The model assumes that perceived breathlessness is an estimate of the current respiratory state of the body. This respiratory state depends on the measured CO_2 level in the blood, evolves from the respiratory state in the last breath and takes the respiratory demands in the current context into account. We validated our model by using experimental data from healthy participants performing a rebreathing task.

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ORIGINAL PAPER

Post-COVID breathlessness: a mathematical model of respiratory processing in the brain

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Abstract
Breathlessness is among the most common post-COVID symptoms. In a considerable number of patients, severe breathlessness cannot be explained by peripheral organ impairment. Recent concepts have described how such persistent breathlessness could arise from dysfunctional processing of respiratory information in the brain. In this paper, we present a first quantitative and testable mathematical model of how processing of respiratory-related signals could lead to breathlessness perception. The model is based on recent theories that the brain holds an adaptive and dynamic internal representation of a respiratory state that is based on previous experiences and comprises gas exchange between environment, lung and tissue cells. Perceived breathlessness reflects the brain's estimate of this respiratory state signaling a potentially hazardous disequilibrium in gas exchange. The internal respiratory state evolves from the respiratory state of the last breath, is updated by a sensory measurement of CO_2 concentration, and is dependent on the current activity context. To evaluate our model and thus test the assumed mechanism, we used data from an ongoing rebreathing experiment investigating breathlessness in patients with post-COVID without peripheral organ dysfunction ($N=5$) and healthy control participants without complaints after COVID-19 ($N=5$). Although the observed breathlessness patterns varied extensively between individual participants in the rebreathing experiment, our model shows good performance in replicating these individual, heterogeneous time courses. The model assumes the same underlying processes in the central nervous system in all individuals, i.e., also between patients and healthy control participants, and we hypothesize that differences in breathlessness are explained by different weighting and thus influence of these processes on the final percept. Our model could thus be applied in future studies to provide insight into where in the processing cascade of respiratory signals a deficit is located that leads to (post-COVID) breathlessness. A potential clinical application could be, e.g., the monitoring of effects of pulmonary rehabilitation on respiratory processing in the brain to improve the therapeutic strategies.

Keywords Post-COVID · Breathlessness · Bayesian brain · Respiratory processing · Predictive processing

Nadine Lehnen and Stefan Glasauer contributed equally.

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Introduction

Post-COVID breathlessness

Persistent breathlessness is estimated to affect more than 25% of patients after COVID-19 [1]. While some patients present with impaired lung function and carbon monoxide diffusing capacity [2], others have neither measurable pulmonary [3, 4] nor cardiac impairments [5] despite profound breathlessness. In general, there is only a moderately strong relationship between peripheral organ dysfunction and patients' breathlessness, and a considerable number of patients lack any measurable organic symptom correlate [1]. Recently, concepts based on the processing of respiratory information in the brain have been developed that describe how persistent breathlessness that is not sufficiently explained by organ dysfunction could manifest [6–10]. These concepts highlight that perception of symptoms occurs in the brain, even if the initial cause resides in body periphery, and that symptoms can be just as authentic and disabling when peripheral organs are intact, but information relayed from sensors to the brain is misprocessed. Therefore, investigating how bodily signals are processed in the brain should be an integral part of the search for possible disease mechanisms in addition to the examination of peripheral organ impairments.

A new perspective on breathlessness

The environment around us is constantly changing. To keep the body in homeostasis, the brain must monitor all relevant processes in the body and adjust them as soon as they exceed setpoints such as a certain core temperature, pH or glucose level [11]. In the case of breathing, different receptors signal information about lung mechanics, cardiac function, carbon dioxide (CO_2) concentration and pH levels in the blood. The brain needs to measure and integrate these signals to obtain information about the current respiratory state, i.e., the gas exchange between the environment, lungs, and tissue cells [12, 13]. This involves two problems: (1) Sensory information coming from receptors is inherently noisy which makes sensing of a signal prone to errors. (2) Sensory input always follows an event and consequently is delayed. Therefore, reactive control of bodily states will often be too slow leading to over- or undershooting the desired setpoint, which could, e.g., in the case of pH levels, be life-threatening.

This implies that in many scenarios, reactive control mechanisms will not be sufficient. Conversely, it is crucial that the brain predicts deviations from setpoints in advance and adjusts breathing in anticipation of actual changes, e.g., in pH. To predict future changes of bodily states, the brain needs to form an internal representation that describes how such bodily states evolve over time (see Fig. 1). This internal representation is often called an internal model. It needs to be dynamically adapted based on newly available information. For example, changes such as increased lung ventilation due to training, or decreased lung function due to disease (as in Fig. 1b) need to be incorporated. This means that the internal representation is built from past experiences. Based on these, predictions can be developed (see Fig. 1) to handle noisy measurements and obtain an optimal estimate of the underlying body state [9, 14, 15]. This is comparable to driving on a familiar road at night: even if visibility is poor, our knowledge of how the road is developing improves our perception and makes driving easier. In a similar way, the brain obtains an optimal estimate of the actual underlying body state from the combination of sensory input and prediction. The relative contributions of noisy measurements and predictions (see Fig. 1c) are determined by their relative precision. If sensory input is very noisy and imprecise (like when driving at night and vision is poor), more reliance will be put on predictions (our knowledge of the road), and the resulting estimate is shifted toward these. Thus, predictions will dominate the estimate of the body state (see Fig. 1c). In contrast, if sensory input is precise (driving during the day and good vision), the brain's estimate of the body state will more closely reflect the actual sensory input. The brain's best educated estimate about the underlying body state is thus a combination of predictions based on internal representations and sensory input. This is described by Bayes' Law, a statistical framework that can explain different perceptual phenomena [16, 17] and is often used to model perception [15]. It is important to highlight that the brain's estimate about body states is not necessarily consciously perceivable and that probably a further step is necessary that translates this estimate into conscious perception.

While internal representations are crucial to correctly interpret the noisy information around us and to deal with bodily perturbations in an adequate and timely manner, visual illusions demonstrate that predictions based on internal representations can also misdirect perception. Visual illusions (such as the checkerboard illusion [18]) are often caused by strong predictions that bias our perception, leading to a discordance between the perceived reality and the physical reality. Similar to perception of stimuli arising *outside* the body, internal representations can bias perception of stimuli arising *inside* the body [19]. If the internal representation about the processes causing the respiratory state is defect, measurements will be incorrectly interpreted, and breathlessness could arise even if the sensory input does not signal any abnormalities—just as an optical illusion is perceived and becomes one's own reality despite not corresponding to physical reality. Importantly, even though objective knowledge about the actual physical reality is present, it usually does not 'correct' perception.

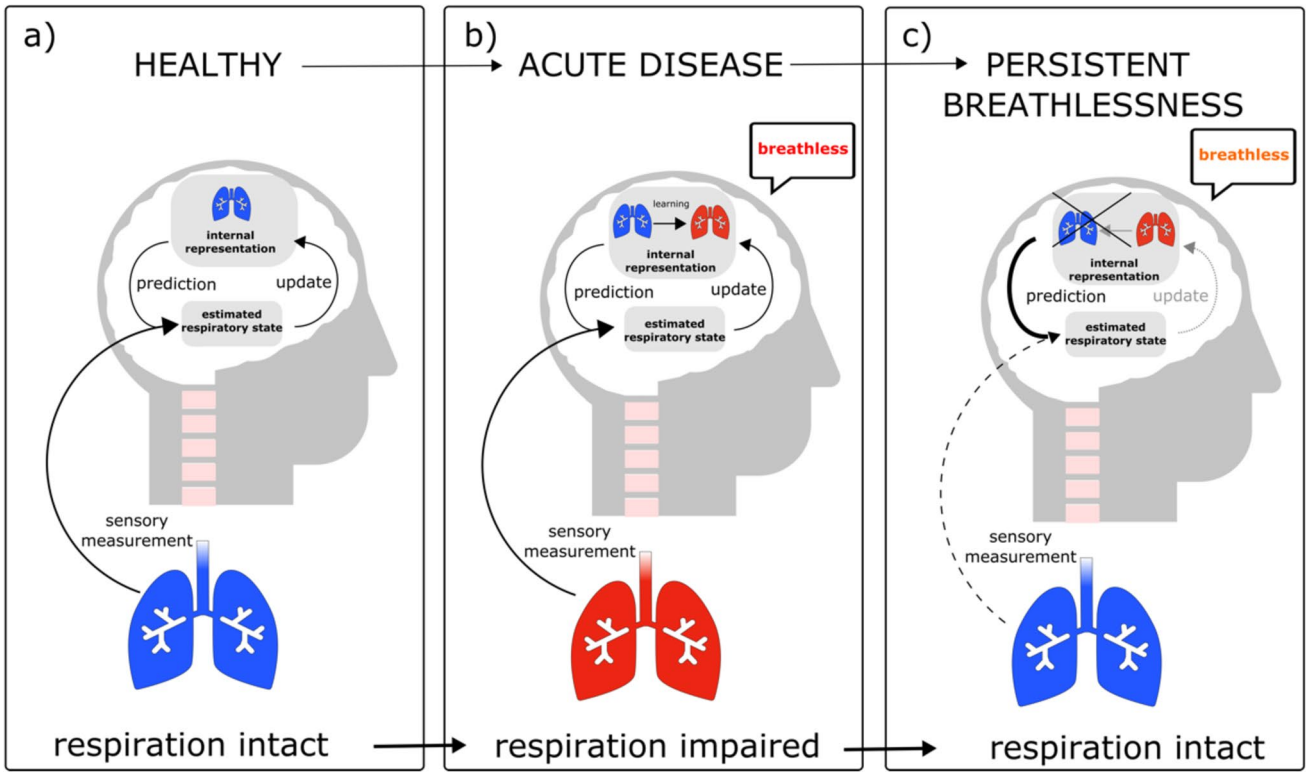

Fig. 1 Development of breathlessness perception. **a–c** The brain holds an internal representation how bodily states evolve over time. Based on this, it can inform predictions about sensory input and use these predictions to optimally estimate the actual sensory input in a noisy environment. The brain's best estimate is thus always a combination between prediction and sensory measurement. Each component can be weighted differently, according to how precise it is (Bayes law). **b** During acute disease, respiration can be impaired, and the internal representation is adapted to this diseased state. **c** When the lung recovers and respiration is intact, but the internal representation not updated, predictions are developed based on an internal representation that still assumes impaired respiration. If sensory input is noisy (dashed line) and predictions assumed to be very precise (thick line), predictions will be weighted more strongly in the estimation process of the respiratory state. Thus, even though sensory input signals intact respiration, inadequate predictions of diseased respiration can bias the estimate toward a respiratory state signaling impaired gas exchange. This can subsequently lead to breathlessness in the absence of any sensory input signaling impaired respiration

At present it is unclear how and where these internal representations are implemented in the brain, although there is some evidence that the insula [20, 21] and cerebellum [22–24] are involved in updating and maintaining internal representations. Here, mathematical models can provide relevant insights by revealing constraints to which the physiological mechanisms must be subjected. Such models implement a quantitative description of assumed internal representations and estimation processes of bodily states. In our model, we assume an internal respiratory state that describes gas exchange between environment, lung and tissue cells. The current internal representation evolves from that of the last breath via updating from sensory measurements of CO_2 concentration in the blood and cerebrospinal fluid. The perceived breathlessness reflects the brain's estimate of this respiratory state signaling a normal versus potentially dangerous disequilibrium in gas exchange.

In the present work, we test the plausibility of this hypothesized mechanism by evaluating whether our model can describe the relationships between individual breathlessness ratings and CO_2 levels measured in a rebreathing experiment.

By writing down our proposed mechanism as a quantitative mathematical model, we render our theory about processing of respiratory information in the brain testable. We hypothesize that breathlessness ratings from a very heterogeneous sample including healthy participants and patients with post-COVID can be simulated by a model that assumes the same underlying processes in all individuals and that differences in breathlessness are explained by different weighting and thus influence of these processes on the final percept.

Methods

The current study is part of the innovative training network ETUDE (Encompassing Training in fUnctional Disorders across Europe; https://etude-itn.eu/), ultimately aiming to improve the understanding of mechanisms, diagnosis, treatment and stigmatization of Functional Disorders [25].

Experimental paradigm

Experimental data were acquired using an experimental paradigm that is a variation of Read's rebreathing method [26] and was previously used to investigate, e.g., medically unexplained breathlessness [27], as well as chronic fatigue and fibromyalgia [28]. Participants breathed through a mouthpiece that was connected to a Y-valve behind a visual barrier. The experimenter was located behind the barrier and could let the participant breathe either room air or air from a rebreathing bag. The rebreathing bag was initially filled with a gas mixture of 5% CO_2 and 95% O_2 (Carbogen, *Linde*). Due to rebreathing from this closed system, the inhaled CO_2 concentration gradually increased leading to hypercapnia and breathlessness.

During the experiment, we recorded CO_2 concentration in breathed air (capnograph, *Hans Rudolph*), peripheral oxygen saturation (pulse oximetry, *Nonin Xpod*) and respiratory flow rate (pneumotachograph, *Hans Rudolph*) with a sampling rate of 50Hz. For this study, we calculated single breath data for CO_2 concentration. End-tidal CO_2 ($etCO_2$) was obtained by taking the maximum CO_2 concentration exhaled in each breath. These single breath data were averaged over 10s intervals. Participants were instructed to rate their breathlessness on a scale from 0 (not at all) to 100 (unbearable) every 10s when an auditory cue was presented. They were informed that they would breathe air with different concentrations of CO_2 and O_2 that can induce either a feeling of breathlessness or no symptoms at all. However, at no point in the experiment, the actual source of breathed air was known to them. The experiment started with a baseline phase, during which participants inhaled room air for 60s. This was followed by a rebreathing phase for 150s and a subsequent recovery phase with room air for another 150s.

Participants

We recruited patients at specialized post-COVID clinics in university hospital settings who presented with post-COVID breathlessness not explained by peripheral cardiorespiratory or neurological impairments. All patients needed to provide a PCR test documenting the initial SARS-CoV-2 infection and had to be suffering from post-COVID symptoms for at least 3 months. Data collection for this rebreathing study is still ongoing, but we consider it worthwhile to inform other researchers on our modeling approach using first results. For evaluating the model, we included data from the first 5 patients (mean age ± standard deviation: 34.2 ± 13.7 years, 4 female). Healthy control participants were recruited through the intranet of the Klinikum rechts der Isar, Technical University Munich, as well as through advertisement (flyers) outside of the clinic. For this study, we included 5 healthy controls participants (mean age ± standard deviation: 35.0 ± 15.5 years, 4 female) who were matched by age and gender to the 5 patients.

On the day of the experiment, lung function tests (spirometry and diffusing capacity for CO) and a standardized neurological examination were performed to rule out any organ impairment on that very day. None of the included participants nor patients showed signs of impairment in these exams. In addition, we clinically characterized all participants using the gold standard for making DSM-5 diagnoses, i.e., the Structured Clinical Interview for DSM-5 disorders (SCID-5-CV). Furthermore, we used the patient health questionnaire (PHQ-15), a well-established tool which asks about the presence and severity of common bodily symptoms [29], and asked participants about the presence and severity of breathlessness in everyday life situations.

The study was designed in line with the Declaration of Helsinki, and the Ethics Committee of the Technical University Munich approved the study protocol prior to conduction. Informed consent was obtained from all individual participants included in the study.

Model description

The brain is not passively waiting and then reacting to sensory input but rather actively predicting sensory input based on its internal representation how certain body states are generated. Accordingly, our main assumption for mathematical modeling is that the brain holds an internal representation of how bodily states related to breathlessness are changing over time and how these changes are linked to sensorily measurable quantities such as CO_2 concentration. In the following, we will refer to the bodily state reflecting the gas exchange between environment, lung and tissue as "internal respiratory state". We assume that perception of breathlessness reflects potentially dangerous levels of this state, like perception of pain reflects damage to the body. Perception of breathlessness thus represents the brain's estimate of a respiratory state indicating disequilibrium in gas exchange that may cause dangerous pH levels in the blood.

To construct our mathematical model of breathlessness perception (see Fig. 2, for the equations see Appendix), we first formulated a hypothesis about the brain's internal representation how the respiratory state will evolve. This internal representation can then be used to form predictions to

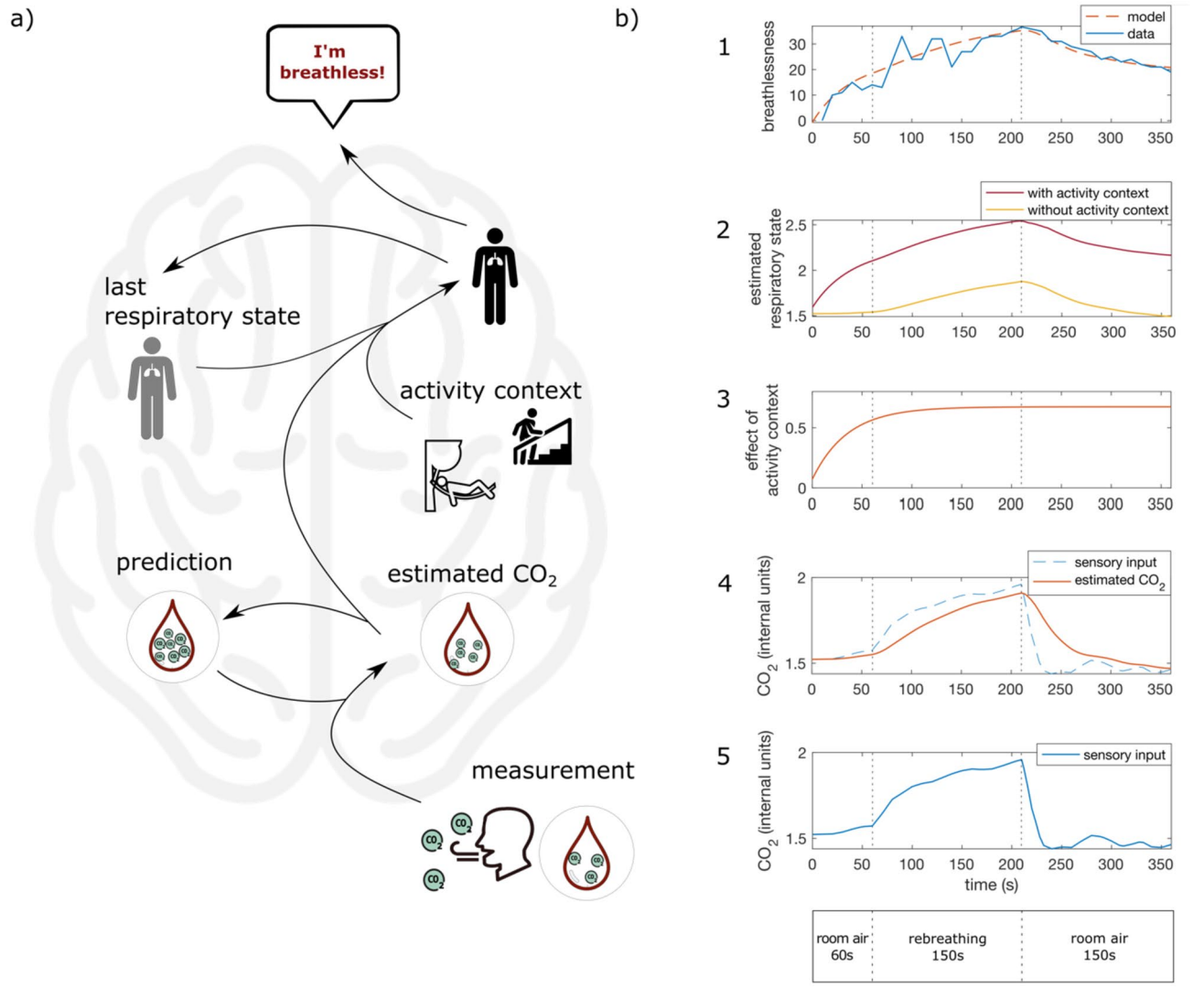

Fig. 2 Model of breathlessness perception (**a**) and a visualization of the different processing steps (**b**). Measurement of CO_2 concentration in the blood and cerebrospinal fluid (bottom, b5) is noisy and error-prone and thus needs to be combined with a prediction to obtain an estimate of the actual underlying CO_2 concentration (orange, solid line in b4). Note that this internal estimate can be different from the actual CO_2 concentration and will be used to update predictions about future measurements. Furthermore, the current activity context plays a role (b3). Walking up a flight of stairs leads to a high activity context, which will increase the respiratory state, while resting evokes a low activity context and a lower respiratory state. Note that while the activity context is constant throughout the simulation, its effect (shown in b3) increases and saturates after about 2 min for this participant. The respiratory state describes the current gas exchange between environment, lung and tissue cells and is not consciously accessible. The respiratory state in the last breath is used to predict the current respiratory state and can be updated by the estimated CO_2 concentration as well as the activity state. How much the estimated CO_2 concentration is taken into account can vary. If the sensory update is taken into account only to a very small extent, the respiratory state is mainly influenced by the prediction based on the last respiratory state and the current activity context. Thus, even though sensory measurements signal an improvement in CO_2 levels (b5, in last phase with room air), the respiratory state signaling imbalances in gas exchange may show minor improvement (b2, in last phase with room air). Finally, the respiratory state needs to be translated into the perception of breathlessness (b1). Breathlessness thus reflects an internal respiratory state that signals a potentially dangerous imbalance in gas exchange

optimally estimate the internal respiratory state that is not directly accessible to the brain. All our following assumptions for the construction of the model are physiologically informed. For simplification, we assume that the respiratory state can be summarized in a single variable. We further assume that the state varies only slowly from one breath to the next and is influenced by the internal CO_2 concentration as well as the current activity context. Walking up a flight of stairs would amount to a high activity context as compared to standing still. Similarly, our rebreathing paradigm can

amount to a high activity context. The activity context thus describes the expected influence of an activity on respiratory demands. Importantly, it can be different between individuals. We chose exhaled CO_2 concentration per breath as the sensory quantity to update the respiratory state since it is experimentally accessible and can be used to approximate arterial CO_2 concentration [30] that is measured by chemoreceptors. Like the internal respiratory state, the exhaled CO_2 concentration is assumed to vary only slowly from one breath to the next. Thus, we hypothesize that the current respiratory state evolves from the respiratory state in the last breath and is updated by the sensory CO_2 state. This process describes the brain's internal representation of how a respiratory state is generated.

For the estimation of the expected respiratory state, the brain needs to combine the measured CO_2 concentration with the internal representation described above. Since measurement of the CO_2 concentration is noisy and error-prone, the brain also needs to estimate the actual CO_2 concentration. For this, the brain forms a prediction based on the internal representation that the CO_2 level changes slowly, but randomly, from one breath to the next. This prediction can be combined with the measured CO_2 concentration to optimally estimate the actual CO_2 concentration. For this estimation process, the framework of Bayes law can be used. It shows that if sensory measurement is precise, the resulting CO_2 estimate will primarily rely on the sensory measurement. However, if sensory uncertainty is high, the estimate will more closely reflect the prediction based on the internal representation. As Kalman Filters are generally applied to estimate states evolving over time from noisy measurements, we used this approach to formulate the Bayesian estimation process (for the equations see Appendix). The five free parameters of this estimator, which are considered to be characteristic for each individual, can be computed from the experimental CO_2 and breathlessness data from each individual participant. They are (1) the ratio of measurement uncertainty and assumed random changes of CO_2 concentration, (2) a weight factor describing how much the CO_2 level influences the respiratory state in every breath, (3) a parameter for the assumed activity context, and (4,5) two scaling parameters for the transformation translating the respiratory state into breathlessness perception (formulated as linear transformation comprising an offset and a gain factor).

The resulting estimated breathlessness states from the estimation model were compared to the time course of the actual breathlessness ratings from participants in the experiment. The free parameters were fitted by minimizing least-squares between actual and estimated breathlessness rating using the in-built MATLAB function *lsqnonlin*.

Model evaluation

To evaluate whether the observed breathlessness ratings could also be explained by a simpler model that assumes that breathlessness is a scaled and shifted version of sensory input, we compared our model to a linear regression model of the following form:

$$b = \beta_0 + \beta_1 * x + \varepsilon$$

with b: breathlessness, $\beta_{0,}$ intercept, β_1: regression slope, x: CO_2 concentration measured in the experiment and ε: error term.

Furthermore, we tested whether simpler versions of our proposed model can explain breathlessness ratings equally well as the full version. Our proposed model describes the respiratory state as depending on the activity context, the respiratory state in the last breath and an estimate of the internal CO_2 level. While sensory input (in this case internal CO_2 level) will likely play a role to some extent in every participant, we kept this component but set up two new model variants where we (1) removed the activity context and (2) in another model removed the dependence on the respiratory state in the last breath.

Performance between the different model versions, i.e., (1) the full model, (2) without activity context and (3) without dependence on the last respiratory state and (4) the linear regression model was compared using Akaike Information Criterion (AIC) which evaluates the quality of a model fit

Table 1 Clinical characterization of participants

	How breathless are you when…			PHQ-15 SCORE
	…at rest	…putting on clothes	…walking up the stairs one floor	
P1	2	5	7	6
P2	1	2	7	16
P3	1	3	8	21
P4	2	2	6	16
P5	0	3	5	17
H1	0	0	0	6
H2	0	0	0	2
H3	0	0	0	0
H4	0	0	1	6
H5	0	0	0	3

Left: Participants were asked how breathless they are in everyday situations. Breathlessness was rated on a scale from 0 (no breathlessness at all) to 9 (extreme breathlessness) in these different situations. Right: PHQ-15 scores of patients (P) and healthy controls (H). PHQ-15 scores of $\geq 5, \geq 10, \geq 15$ represent mild, moderate and severe levels of somatization

Table 2 Diagnoses as obtained from SCID-5-CV interview of all participants. P - patient; H - healthy control participant

Participants	Diagnosis
P1	Major depressive disorder, single episode, unspecified
	Undifferentiated somatoform disorder
P2	Premenstrual dysphoric disorder
	Specific isolated phobias
	Undifferentiated somatoform disorder
P3	Major depressive disorder, single episode, moderate
	Generalized anxiety disorder
	Undifferentiated somatoform disorder
P4	Undifferentiated somatoform disorder
P5	–
H1	Bipolar disorder, in full remission
H2	Major depressive disorder, recurrent, in full remission
H3	–
H4	Specific isolated phobias
H5	–

while also taking into account the number of parameters and thus the risk of overfitting.

Results

Clinical characterization

Table 1 displays the clinical characteristics of all included patients and healthy control participants. These characteristics were not part of the modeling procedure, nor were they considered for statistical analyses to evaluate differences between patients and healthy control participants. Table 2 shows diagnoses of all participants as obtained with the clinical interview for DSM-5 disorders (SCID-5-CV).

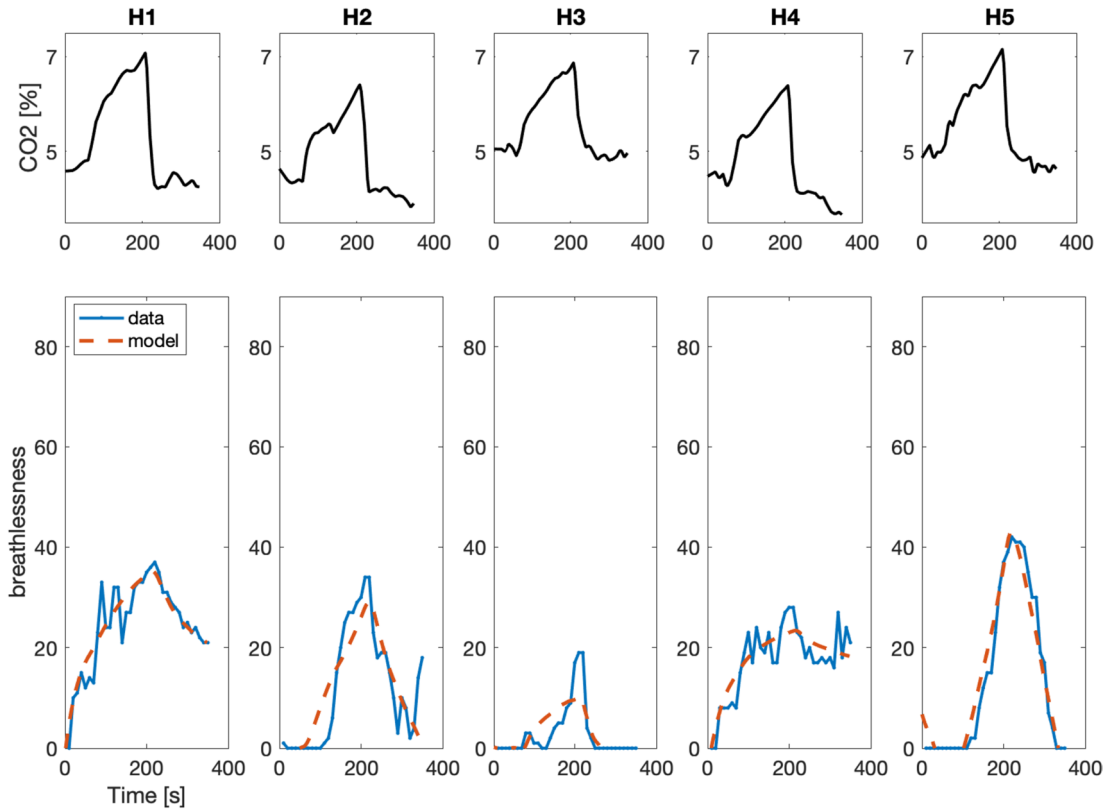

Fig. 3 CO_2 concentration in exhaled breath (**top**) and breathlessness ratings (blue) and model simulation (red dashed) (**bottom**) for individual, healthy control participants (H1: same data as in Fig. 2). Participants rated breathlessness on a visual analog scale from 0 to 100. H - healthy control participant

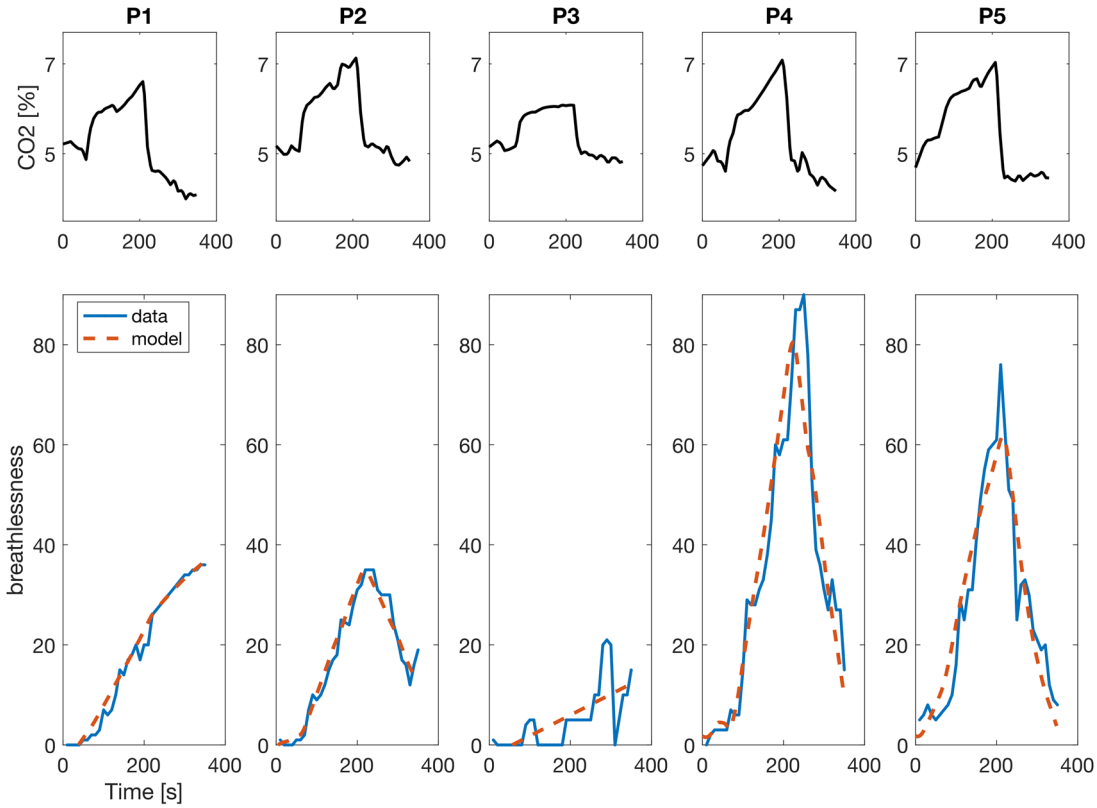

Fig. 4 CO_2 concentration in exhaled breath (**top**) and breathlessness ratings (blue) and model simulation (red dashed) (**bottom**) for individual patients with post-COVID breathlessness. Patients rated breathlessness on a visual analog scale from 0 to 100. P - patient

Modeling results

Although all participants inhaled air with the same CO_2 concentrations, both at baseline and at the beginning of the rebreathing phase, i.e., received a similar sensory stimulus, breathlessness ratings varied considerably between participants (see Figs. 3 and 4). This was true both for the maximum perceived breathlessness and for the development of breathlessness over time. Differences in breathlessness patterns could be observed between the two groups; however, there were also substantial differences between individual patients, as well as between individual healthy participants. While some participants recovered rapidly after the rebreathing phase, i.e., breathlessness decreased back to low ratings, others remained breathless even when they were breathing room air (compare e.g., P1 to P5 in Fig. 4). Despite these very different patterns, our model showed good performance in its capability to replicate the observed time course of individual breathlessness. Using only CO_2 concentration as input, it did not simply mirror this input but was also capable of describing breathlessness ratings that were uncoupled from the actual sensory input. This was for example the case

Table 3 Akaike Information Criterion (AIC) for the full proposed model, variants with either no activity context or no dependence on the respiratory state in the last breath as well as a linear regression model

	P1	P2	P3	P4	P5	H1	H2	H3	H4	H5
Full model	46.53	61.08	113.70	149.02	142.02	91.07	134.31	94.94	98.10	92.08
No activity context	169.85	63.14	117.36	147.06	140.15	117.44	136.27	92.95	120.23	125.55
No dependence on last breath	187.68	70.45	134.45	155.23	149.26	110.34	132.98	92.49	120.21	140.53
Linear Regression	168.39	172.99	121.67	231.73	207.01	147.38	166.25	99.67	136.55	196.09

The lower the AIC, the better the model fit. Green: Lowest AIC, i.e., best model performance, for each participant. P - patient; H - healthy control participant

in P1, where breathlessness increased throughout the experiment and stayed high, even though CO_2 concentration had decreased back to baseline.

Table 3 shows Akaike Information Criterion (AIC) for variants of the proposed model as well as a linear regression model. The lower the AIC, the better the model performance. The diverse breathlessness patterns observed in the experiment were poorly explained by a linear regression model which assumes that breathlessness is a scaled and shifted version of the sensory input, i.e., CO_2 concentration. In none of the participants, it performed better than the full proposed model or variants of it. Similarly, simpler version of our proposed model (1) without activity context and (2) without dependence on the respiratory state in the last breath predicted breathlessness ratings in general less well than the full model. A model variant without the activity context only led to slightly better predictions in 2 out of 10 participants. Similarly, the model variant without dependence on the respiratory state in the last breath only improved model prediction slightly in 2 out of 10 participants. However, in most participants, our full model showed a decisive improvement in model performance when compared to variants of it or the linear regression model.

Discussion

In this work, we provided a quantitative and testable model that describes how respiratory processing leads to breathlessness perception. According to our model, the brain needs to estimate a respiratory state by updating predictions based on the last respiratory state and an estimated CO_2 concentration, while taking the current activity context into account. It showed good performance in describing highly heterogeneous time courses of individual breathlessness ratings obtained in our rebreathing experiment and outperformed other model variants as well as a linear regression model. Since the experimental data demonstrated very diverse breathlessness patterns, this might have required different mechanistic approaches for different subgroups. However, our model equipped with only one underlying mechanism was capable across all of these different, individual breathing patterns. Remarkably, it could also simulate breathlessness when it was uncoupled from the sensory CO_2 stimulus (see P1, Fig. 4). It thereby provides a possible mechanism of how the same CO_2 stimulus can be linked to different breathlessness patterns. Interestingly, only two patients with post-COVID (P4 and P5) developed strong breathlessness in the rebreathing phase. This shows that the patients in this study were not in general more sensitive to respiratory stimuli and thus experienced stronger breathlessness but that likely more complex dysfunctions in respiratory processing played a role that can result in more or less sensitive detection and response to these stimuli.

The parameter values of the model obtained from fitting the model output to experimental data describe how strongly each of the processes formulated in our model influence the final breathlessness percept. While the sample size in this study allowed to test whether the model in general can produce breathlessness ratings that are similar to experimentally obtained ratings, future studies with higher sample sizes are necessary to evaluate possible parameter differences between individuals as well as different groups. The parameters of the model provide specific insight into where in the processing of respiratory information a dysregulation might occur that leads to persistent breathlessness. For example, the internal CO_2 state could be wrongly estimated. This could result from increased uncertainty of CO_2 sensors, which leads to relying more on predictions than actually measured CO_2 concentration. Then, the internal respiratory state would not reflect the actual underlying CO_2 level. Another factor is the activity context, which, if wrongly estimated, might lead to increase of breathlessness even without changes in CO_2 measurement. Our model thus allows to test within the same mechanism how different processes are weighted which could result in (post-COVID) breathlessness even though peripheral organ function is intact, and chemoreceptors signal a balanced gas exchange.

On a general level, the question remains how inadequate internal representations emerge. One possibility (see Fig. 1) could be that during the acute phase of COVID-19, the internal representation had to be adapted to a state of lung disease from viral infection (Fig. 1b). During this time, the adaptation was crucial to maintain homeostasis; however, it needs to be revised back to the healthy body state as soon as the infection resolves. If this does not take place (see Fig. 1c), sensory input signaling an intact lung would be interpreted with an internal representation referring to the diseased state, leading to symptom perception. A failure to update the internal representation could be due, for example, to persistent damage of respiratory chemoreceptive sensors or pathways. Persistent sensory changes in post-COVID have been reported for smell and taste, but also for other sensory inputs [31]. Such damage to respiratory chemoreception could also explain why breathlessness can be decoupled from actual CO_2 level, as found in P1 (see Fig. 4). Furthermore, Sars-CoV-2-related changes in brain structure could play a role. In a longitudinal study comparing MRI scans before and after SARS-CoV-2 infection, Douaud et al. [32] found greater loss of gray matter and increased diffusivity, which is indicative of tissue damage in several brain regions, including the insula. Exploratory analyses have also shown loss of gray matter in the cerebellum. Both brain areas are involved in

breathlessness perception and are assumed to store internal representations and to process prediction errors that arise when sensory input does not match predictions [33–35]. In addition, it is well known that stress [36] and mental health conditions such as anxiety [37, 38] interfere with how bodily signals are processed.

A discordance between symptoms and lung function parameters such as forced expiratory volume (FEV_1) is a well-known phenomenon in respiratory diseases such as asthma [39–41]. However, symptoms decoupled from organ dysfunction are not specific to respiratory diseases but rather can be found in any field of clinical medicine [42]. Experimental approaches have been developed to test altered processing of body signals as a cause of these symptoms. For example, Lehnen et al. [43] developed an experiment that challenges the interaction between sensory input and internal model to study functional dizziness in patients with intact organ function which allowed to detect markers indicating dysfunctional sensorimotor processing [44, 45]. This was transdiagnostically extended to irritable bowel syndrome [46].

Limitations

The fact that our mathematical model could simulate our experimental data does not necessarily mean that it is the only possible model. It is also still greatly simplified. For example, it is unlikely that CO_2 concentration is the only sensory input used to update the respiratory state. Breathing also evokes, e.g., proprioceptive signals that provide information about lung mechanics such as the breathing frequency. In addition, for sudden changes in breathlessness perception that are decoupled from changes in CO_2 concentration (see e.g., P3 & H3), our current model shows poor performance. Here threshold effects could be implemented in future versions of the model to allow simulations of such patterns. Furthermore, the sample size in this study only allowed to show that in general our model can predict different breathlessness patterns but did not allow for analysis of group differences, neither for model parameters nor for experimental data. Despite these limitations, we present our model at this stage of development because it could already describe experimental data very well, especially in view of the small set of parameters needed to describe a complex behavior.

Outlook

Our model enables to test hypotheses about the processing of (post-COVID) breathlessness in the brain. While our hypothesis of how respiratory signals are processed in the brain is so far supported by results, further experimental tests are required to validate, and potentially refine it. Especially in post-COVID patients such as P1, an independent test of respiratory chemoreception could help to answer the question, whether sensory damage, e.g., to the carotid bodies or to central chemoreception [47], may have played a role in maintaining an inadequate internal representation of respiratory state. Another obvious consequence of the hypothesis would be that relief from breathlessness should be possible by readjusting the internal representation so that it adequately reflects a healthy state. One may assume that this already occurs during pulmonary rehabilitation programs, although not explicitly addressed [48]. Here, our model could provide a means to monitor which parameters are improved by rehabilitation. Finally, a possible method of providing improved sensory input is biofeedback, which has recently been suggested for post-COVID treatment of dysregulation of the autonomic system [49]. For example, monitoring the blood oxygenation level or, via transcutaneous CO_2 monitoring, even the CO_2 level, could show patients that their respiratory state is normal despite feeling breathless. Such a cognitive input might have a small effect but could help in gradually readjusting the internal representation.

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Data availability The data used in this study can be found on Open Science Framework (osf.io) via the following link: https://osf.io/srv5z/?view_only=325c37a979f74dc096ab189c9cdf772a.

Declarations

Conflict of interests On behalf of all authors, the corresponding author states that there is no conflict of interest.

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Chapter 5

General discussion

5.1 Key findings

This thesis investigated sensorimotor control and symptom perception in patients with PPS. Our experimental findings revealed sensorimotor dysfunction in patients with functional dizziness and altered symptom perception in patients with post COVID-19 condition that can be attributed to incorrect internal models instead of pathophysiological body states. In chapter 2, we showed that gaze in patients with functional dizziness is only unstable in phases requiring model-based motor planning but not in phases that are sensory reflex-driven. In chapter 3, we demonstrated that while most patients with post-COVID fatigue can correctly adapt breathing patterns to changing stimuli, breathlessness is increased compared to healthy control participants, hinting at dysfunctional internal models specific to symptom perception. In chapter 4, we bridged the gap between theoretical approaches and experimental data by developing a mathematical model that formalizes the hypothesized mechanism of how processing of respiratory signals can lead to breathlessness perception.

5.2 Towards a mechanistic understanding of functional dizziness

We were able to demonstrate that deficits in gaze stabilization in patients with functional dizziness are due to incorrect internal models, however, the exact underlying mechanism remains unclear. Next to gaze instability, several other (sensorimotor) deficits are known in patients with functional dizziness. In the following sections, potential mechanisms that could explain the observed sensorimotor deficits in the eye-head paradigm will be discussed. Then, a possible adaptation of the experimental paradigm to multisensory contexts will be suggested and theories of multisensory integration and Bayesian causal inference introduced. The following section reviews (sensorimotor) dysfunctions in this multisensory framework. Finally, different potential reasons why incorrect internal models could be

immune against updating and their role in further developing and refining treatment approaches for functional dizziness will be discussed.

5.2.1 Sensorimotor deficits in the eye-head paradigm

Gaze stabilization requires correct inference of head inertia as well as a correct forward model to plan and adapt the required compensating eye movement. When gaze has reached the target, the head continues to move which needs to be counteracted by eye movements into the opposite direction to keep gaze stable. If the eyes can completely counteract the head movement, this leads to a counter-rotation (CR) gain of 1. A CR gain close to 1 is observed in healthy participants in the baseline phase of our experiment. When we artificially increased head inertia by placing a helmet with weights on participants' heads, this led to an insufficient counter-rotation of the eye in respect to the head movement and thus a decreased CR gain in healthy participants. In patients with functional dizziness, however, the CR gain was already decreased in the baseline and further worsened in the condition with increased head moment of inertia (see chapter 2).

A possible mechanistic explanation for the decreased CR gain in a Bayesian framework is a down-weighting of vestibular information (likelihood) due to precise, but incorrect prior distributions over head inertia (Lehnen et al., 2018). According to Bayes rule, the inferred state based on the available sensory input (y) is proportional to the likelihood function of the sensory input given the actual body state and the prior describing the probability of this state (x).

$$p(x|y) \propto p(y|x) * p(x) \tag{5.1}$$

Introducing the helmet leads to an increase in head inertia, which cannot be predicted since participants have never seen or worn the helmet before. The prior over head inertia thus does not correctly represent the now increased head inertia. A prior assigning higher probability to lower head inertia than actually present, will lead to an underestimation of head inertia. Consequently, also the overshoot of the head at the end of the gaze shift will be underestimated and thus no sufficient counter-rotation of the eye is planned. This leads to a decreased CR gain in the weighted condition in healthy participants. In patients, a decreased CR gain is observed in the baseline phase and further exacerbated in the weighted condition, suggesting that patients hold an incorrect prior already in natural, unweighted conditions. While our experimental results are well accounted for by an explanatory mechanism that assumes failures in correctly inferring head inertia due to incorrect priors, they could equally well be explained by alternative mechanisms, such as imprecise likelihood functions instead of precise priors. Since different mechanisms can lead to the same observed behaviour, it is inherently difficult to disentangle where a dysfunction is located exactly. What is more, patients with functional dizziness are mostly diagnosed given an exclusion of other pathophysiological processes that could cause the experienced symptoms. This does not necessarily mean that the same mechanism is present in all patients, making it even harder to disentangle mechanistic underpinnings in results from possibly heteroge-

neous patient groups. Here, a combination of modelling approaches and carefully designed experiments might help to gain insight into the exact mechanism as well as to investigate possible differences between individual patients. Such an experimental-computational approach to distinguish between different Bayesian computational mechanisms has, for example, been applied to study autism (Schneebeli et al., 2022).

Next to an incorrect inference model, deficits might also arise due to erroneous forward models that, based on an efference copy, incorrectly predict how the head will move and the associated vestibular input (Lehnen et al., 2018). Eye movements are then planned accordingly, leading to deficient gaze stabilization. Incorrect forward models can also explain previous work in our research group. Lehnen et al. (2019) investigated head oscillations in patients with functional dizziness, bilateral vestibulopathy and cerebellar ataxia.[1] When gaze reaches the target, the head usually overshoots and oscillates around the gaze target. In patients with functional dizziness, these head oscillations were higher than in healthy control participants[2] but not different from patients with organo-structural vestibular deficits, i.e., bilateral vestibular loss and cerebellar ataxia. Whereas in these patients, no vestibular input is available (bilateral vestibular loss) or this input cannot be processed due to damage in the cerebellum (cerebellar ataxia), similarly impaired head control in functional dizziness with intact vestibular function can be explained by incorrect forward models. If head movements and its sensory consequences are incorrectly predicted, only insufficient stabilization by, e.g., the neck muscles, will be initiated which leads to the observed head oscillations.

In summary, internal models incorrectly representing head inertia can explain sensorimotor deficits observed in functional dizziness. Whether this is due to incorrect inference, forward or other internal models, cannot be fully determined based on our experimental results. Since these internal models might be maintained in different brain areas and involve different processing steps, a better understanding of the exact mechanism could help to further elucidate the cause of sensorimotor dysfunctions in functional dizziness.

A limitation that currently hinders translation of our experimental results to clinical contexts is that the current experimental paradigm investigates gaze stability in a context where only vestibular input is available[3]. Usually, gaze stabilization requires correct estimation of head characteristics based on visual, vestibular and proprioceptive sensory input to optimally plan eye movements that can counteract unwanted head movements. As a next step, it is thus essential to conduct the current experiment in conditions where visual input is available which also more closely reflects the experiences of patients in everyday

[1]The data analyzed in this thesis for functional dizziness was part of this larger study which investigated gaze shifts in functional dizziness, bilateral vestibulopathy and cerebellar ataxia.

[2]We have recently replicated the results of increased head oscillations in patients with functional dizziness as compared to healthy participants (Regnath et al., 2024).

[3]Theoretically, also proprioceptive input is available. However, Sağlam and Lehnen (2014) and Wibble and Pansell (2024) have shown that in the absence of visual input, proprioceptive feedback is negligible for adapting eye movements. The eye-head paradigm in this study is conducted in complete darkness and it can thus be assumed that it isolates vestibular processing from other sensory modalities when performing gaze shifts.

life. This will also allow to investigate multisensory integration and the question of whether visual input can improve gaze stability in patients with functional dizziness. In the next section, a Bayesian framework for multisensory integration and Bayesian causal inference will be introduced.

5.2.2 Multisensory integration and Bayesian causal inference

Integrating information from the visual and vestibular system leads to improvements in perceptual and behavioural performance. For example, integrating visual and vestibular signals has been shown to improve heading perception in healthy participants, i.e., the direction of self-movement (Dokka et al., 2015; Gu et al., 2008; Fetsch et al., 2009) and dissociating self-motion from object motion is enhanced when in addition to visual input, vestibular inputs are available (Dokka et al., 2015).
If the cause of sensory signals from the visual (y_{vis}) and vestibular (y_{vest}) system is the same, the posterior over the hidden states (x) that might have caused these signals is proportional to the product of the prior ($p(x)$) over possible states and the likelihood functions of each sensory input (Ma et al., 2023). This can be formulated as follows:

$$p(x|y_{vest}, y_{vis}) \propto p(x)p(y_{vest}|x)p(y_{vis}|x). \tag{5.2}$$

However, sensory information from different modalities should only be combined if it arises from the same underlying (body) state. Thus, the brain must infer whether sensory signals arise from the same cause and should be integrated into one percept or whether they should be segregated and interpreted independently of each other. This inference of the causal relationship of sensory signals can be described by Bayesian causal inference models (Noppeney, 2021; Körding et al., 2007; Acerbi et al., 2018). For two independent measurements (y_{vest} and y_{vis}), the inference of whether a common cause ($C = 1$) or two different causes ($C = 2$) underlie these measurements can be described by Bayes' law:

$$p(C|y_{vest}, y_{vis}) = \frac{p(y_{vest}, y_{vis}|C)p(C)}{p(y_{vest}, y_{vis})} \tag{5.3}$$

As there is noise and it can never be fully determined whether there is one or multiple causes of different sensory signals, the estimates of the true states of each sensory signal are calculated for both causal structures ($C = 1$ and $C = 2$). For the case that both signals share a common cause (i.e., $C = 1$), this happens according to Equation 5.2 and a specified cost function and yields $\hat{x}_{vestvis,C=1}$. For the case that there are different causes, each estimate is calculated independently of the other according to Equation 5.1. This yields $\hat{x}_{vest,C=2}$ and $\hat{x}_{vis,C=2}$. To estimate the hidden state underlying the sensory signals, the estimates for $C = 1$ and $C = 2$ are combined according to a specific decision theory. One strategy involves model averaging, where each estimate is weighted according to the posterior of the causal interaction. Consequently, in the event that there is a greater probability that the two signals have a shared underlying cause, the integrated estimate ($\hat{x}_{vestvis,C=1}$) is weighted more strongly. If both signals are unlikely to share the same

hidden cause, the unimodal estimate receives more weight. The inference of the hidden state underlying the vestibular input when also visual input is available and vice versa, can be formulated as follows (Jones and Noppeney, 2024):

$$\hat{x}_{vest} = P(C = 1|y_{vest}, y_{vis}) * \hat{x}_{vestvis,C=1} + (1 - P(C = 1|y_{vest}, y_{vis})) * \hat{x}_{vest,C=2}. \quad (5.4)$$

$$\hat{x}_{vis} = P(C = 1|y_{vest}, y_{vis}) * \hat{x}_{vestvis,C=1} + (1 - P(C = 1|y_{vest}, y_{vis})) * \hat{x}_{vis,C=2}. \quad (5.5)$$

In summary, multisensory integration involves two parts a) inference of the causal structure causing the sensory signals and b) inference of the hidden (body) states. In the next section, our experimental results and proposed mechanisms for gaze instability in functional dizziness will be discussed in the light of this multisensory Bayesian framework.

5.2.2.1 Gaze (in)stability in multisensory contexts

In the current version of the eye-head paradigm, participants only receive feedback via the vestibular system. Conducting our eye-head paradigm in light conditions would offer a way to study how visual and vestibular information is integrated during gaze stabilization and whether visual input is sufficient to adapt incorrect priors and improve gaze stability. If correctly integrated, adding visual input provides additional feedback that could serve to update incorrect priors over head inertia and thus decrease gaze as well as head instability. This requires that the brain correctly infers the causal structure, i.e., that both sensory signals (vision and vestibular) convey information about the same body state and should be integrated. If the brain cannot correctly integrate this multisensory input, gaze instability should remain, independently of whether visual information is available or not.

If gaze instability remains, visual feedback should signal a drift of the visual environment, i.e., a movement of the retinal image, each time patients perform a gaze shift. The brain needs to infer whether this movement of the retinal image is due to self-movement or movement in the environment, which has implications for, e.g., adjustments of body posture. Several findings suggest that patients with functional dizziness have problems in distinguishing self- from external motion. This will be addressed in the next section.

5.2.2.2 Deficits in distinguishing self-motion from motion in the environment

Am I moving or is the environment moving? Most people will have experienced the train illusion. When sitting in a train at a station and watching another train through the window, a movement of the other train is often perceived as self-motion, i.e., a feeling that one's own train is starting to move. It is usually only after some time that you become aware of this illusion and realise that the train you are in is standing still, while the other train is moving. This subjective feeling of self-motion in the presence of a strong visual stimulus but no actual physical movement is known as vection. It occurs if the brain incorrectly solves ambiguous visual input that could either signal movement of the own body or of objects in the environment. It has been shown that the inability to correctly resolve ambiguity can

lead to maladapted postural control and body sway in healthy participants which can be explained by a Bayesian causal inference model that assumes two competing hypotheses relating to self-motion versus motion of the environment (Dokka et al., 2010).

The effect of vection might be particularly strong in patients with functional dizziness. Chaudhary et al. (2022) instructed patients to fixate letters on a background that changed from low visual complexity to high complexity involving moving stimuli while measuring patients' postural body sway. Patients showed significantly increased body sway in conditions involving complex, and especially moving visual stimuli compared to healthy participants. Incorrectly attributing the observed visual motion in the experimental condition to own body movement, might lead to a feeling of self-motion even though no actual movement is present (vection). This perceived self-movement is then compensated by adjusting body posture, leading to the observed body sway in patients. This also aligns with patients often reporting an exacerbation of their symptoms in contexts with complex visual scenes (Staab et al., 2017), such as during traffic or in crowds of people moving into different directions.

The tendency to attribute motion to one-self instead of the external environment might also be facilitated due to decreased vestibular motion thresholds. When inducing vestibular signals via galvanic stimulation, patients with functional dizziness report a feeling of self-motion already at lower stimulation intensities than healthy participants (Helmchen et al., 2024; Storm et al., 2024). This implicates that even small bodily movements and deficits in postural control that lead to low vestibular input might be capable to induce a feeling of self-motion in patients. This aligns with the finding that the lower this vestibular motion threshold, the higher the difference between perceived postural instability and actual postural instability (Helmchen et al., 2024). Greater perceived postural instability could then lead to stronger adjustments in body posture, further exacerbating actual postural instability, creating a vicious cycle.

Deficits like postural instability, head oscillation and gaze instability lead to constant errors, which should usually update incorrect movement patterns based on maladapted internal models. Since this does not seem to happen, it raises the question of why internal models are so rigid and immune against updating in patients with functional dizziness.

5.2.3 Why are internal models not updated?

When artificially inducing movement errors (e.g., via prism glasses (Harris, 1965) or shifting visual presentations of hand position in virtual reality (Cheng and Sabes, 2007)), healthy participants can usually adapt to these changes by taking error information into account. Persistent sensorimotor dysfunctions described in the last sections generate constant errors that should lead to an adaptation of movement patterns, however this does not seem to happen in patients. Previous work from our lab has tested whether increasing prediction errors by artificially altering head inertia (helmet with weights) can lead to adaptations of internal models, which would manifest in decreased head oscillations over time. While healthy participants can update incorrect models and reduce head oscillations after some trials when head inertia is artificially increased, a reduction is only minimal in patients

with functional dizziness (Lehnen et al., 2019). To investigate whether increasing prediction errors during the weighted condition with helmets has an influence on subsequent movements without the helmet, we added a second unweighted condition after the weighted one. While healthy participants were able to reduce head oscillations from the first to the second unweighted condition, patients failed to do so (Regnath et al., 2024). These results support the theory that patients maintain very rigid internal models which remain resistant to updating, even in the presence of large errors.

Why are incorrect internal models not updated? From a mechanistic Bayesian predictive coding perspective, this could happen if the precision, i.e., reliability, of the prediction errors is assumed to be low relative to the prediction itself. Thus, if patients hold an excessively precise prior that their head inertia is lower than it actually is, while vestibular input is assumed to be extremely noisy and unreliable, prediction errors will not be able to update incorrect internal models.

Furthermore, the arising error might be falsely attributed to a cause other than the own motor system. Movements should only be adapted if the experienced error is relevant to the performed actions. This can be illustrated with the following example. When trying to hit a target with a ball but the ball is heavier than expected, one should update movements related to throwing the ball (e.g., recruit more muscle force) in the next trial. However, if a short and transient increase in wind blows the thrown ball away from its planned trajectory, this should not lead to adaptations of movement patterns in the next trial. Wei and Körding (2009) have suggested that inferring relevance of errors for motor adaptation involves similar mechanisms to Bayesian causal inference (described in subsection 5.2.2). Similarly to the process of deciding whether two sensory inputs should be integrated or separated, the brain needs to infer whether an error is due to an uncontrollable external factor or due to the own motor system (e.g., due to fatigue). The latter case should lead to adaptations of actions, while the former one should not. The authors showed that participants' motor learning in different tasks can be predicted by such a Bayesian causal inference model. How can this be translated to our findings? Head oscillations and gaze instability lead to sensory feedback that should signal an error. The brain has two opposing hypotheses that could cause the observed sensorimotor errors: A) incorrectly inferred head inertia or B) an external cause or noise. If the brain attributed the ensuing error to sensory noise instead of a meaningful signal, it should not update internal models of head inertia. This would reflect a higher threshold of detecting relevant sensory stimuli, equivalent to a heightened just-noticeable difference.

Stress and anxiety might also increase resistance to updating internal models. Both are known to influence how interoceptive signals are processed and lead to decreased adaptation to changing contexts. Harris et al. (2023) have investigated whether anxiety changes the way how participants exert predictive gaze shifts. They used experimental data in the form of predictive gaze locations from a virtual reality sensorimotor paradigm as input to a Markov decision process model to infer the participant's belief about the optimal next gaze position. Using this combination of experimental data and computational modeling, they were able to show that under increased levels of anxiety, individuals update their belief about the predicted gaze position slower than in low-anxiety contexts. They

hypothesized that under anxiety-related uncertainty, individuals refrain from updating sensorimotor patterns and resort to more familiar and established ones. Our experimental paradigm involved particularly large gaze shifts, which are less frequent in everyday life. As a consequence, during the task more extreme motor patterns were required for gaze shifts than usually exerted in everyday life. In addition, our experiment was conducted in complete darkness, and the absence of visual input might have led to increased uncertainty and anxiety. We did not measure anxiety levels in our patient cohort, however, anxiety is a frequent comorbidity in patients with functional dizziness, and psychological distress (anxiety and post-traumatic stress disorder) is estimated to occur in over 40% of patients (Waterston et al., 2021). If anxiety levels were higher in patients than in the control group, this may have resulted in patients exhibiting a tendency to avoid adapting to the more extreme gaze movements required by our experimental paradigm. In addition, anxiety also directly affects sensorimotor processing (Nieuwenhuys and Oudejans, 2012). However, the interaction of anxiety and gaze stabilization in functional dizziness patients warrants further research to better understand their respective influences.

5.2.4 Summary and implications for treatment

In this thesis, we have shown that patients with functional dizziness cannot adequately stabilize gaze at the end of large gaze shifts. We have proposed that gaze instability as well as previously observed head oscillations could be explained in a Bayesian framework where incorrect forward models or precise but incorrect priors of head inertia lead to an underestimation of actual head inertia and as a consequence to maladapted movement patterns. An extension of the current experimental paradigm to conditions where visual feedback is available, would allow to investigate multisensory processing in patients with functional dizziness, and to test whether visual input can update incorrect priors over head inertia. Previous behavioural (Breinbauer et al., 2020; Im et al., 2021; Dieterich and Brandt, 2024; Moaty and Nada, 2023) as well as neuroimaging (Indovina et al., 2021) studies suggest that patients might have difficulties in adequately integrating multisensory input. If this was also the case for gaze stabilization, gaze will remain unstable even in conditions where visual input could provide feedback. This gaze instability should then evoke a visual drift each time patients perform a gaze shift involving eye and head movement. Such a moving retinal image indicates that either the body itself or the environment is in motion. If the visual drift is perceived as self-motion, this might elicit adjustments in body posture aimed at compensating the perceived motion. This could lead to the commonly observed postural instability in patients and could also explain vertigo, i.e., a feeling of self- or surround motion in stationary contexts, which is a common symptom in functional dizziness (Staab et al., 2017). Incorrect internal models seem to be particularly resistant to updating in patients with functional dizziness. This might be due to **i)** low precision of prediction errors **ii)** failures in correctly attributing the cause of errors and/or **iii)** anxiety. How can these findings inform and influence the development of future therapeutic approaches?

i) How can prediction error precision be increased? Whether prediction errors update internal models and resulting predictions depends on the assumed reliability or precision of

the prediction error in respect to the prediction itself. This implies that either reducing the precision of predictions or increasing precision of sensory signals, should lead to an adaptation of incorrect internal models. Attention seems to play an important role in increasing precision of attended signals, while down-weighting those of unattended signals. However, the exact mechanism of how attention modulates perceptual inference and processing of sensory input is still debated (Whiteley and Sahani, 2012). While one account proposes that attention is a way to increase precision of sensory input (Mirza et al., 2019; Feldman and Friston, 2010), others explain attention as acting via priors on the inference process (Chikkerur et al., 2010; Garlichs and Blank, 2024). Mirza et al. (2019) have provided a theoretical formulation of selective attention in an active inference framework. Here, selective attention is described as a way to actively sample only task relevant information by assigning increased certainty to it. Attention is thus a way of increasing the precision of task-relevant sensory information when planning movement behaviour. As a consequence, it may be proposed that actively focusing attention on sensory input could serve as a treatment strategy for reducing the influence of incorrect prior beliefs.

However, this approach warrants caution since too much attention (or on the wrong input) can also exacerbate symptoms. For example, assigning excessively high precision to small body movements might lead to compensating movements which further increase body sway. This is supported by a study showing that when patients engage in dual cognitive tasks and thus attention is shifted away from body signals, objective postural instability is improved (Sprenger et al., 2017; Wuehr et al., 2017). The authors suggested that in baseline conditions an overly strong attention and focus on own body sway could lead to an increased weighting of current sensory input that leads to adaptive movements that would otherwise only be required in more challenging balance situations. When patients are distracted and attention is shifted towards a cognitive task, the attention-driven over-weighting of sensory information is replaced by more automatic adaptations of movement, leading to a decrease in body sway. As a consequence, while learning to direct attention towards vestibular input has the potential to increase precision of these signals and thereby counteracting the effect of incorrect but precise priors, this approach might only be beneficial for some sensory modalities and possibly not for all patients. Whereas our experimental results suggest a down-weighting of sensory input from the vestibular system, processing of sensory signals from other modalities (Powell et al., 2020), and especially vision (Cousins et al., 2014) might already involve a high precision weighting. As a consequence, it will be necessary to first assess how much patients already focus on own body signals and especially also to which signals. Depending on this, either methods should be provided to learn to shift attention away from own body signals or to focus on those that are currently not attended to. Furthermore, this highlights the necessity to improve understanding of potential mechanistic differences between individual patients.

ii) How can failures of error attribution be resolved? Providing explicit online feedback about dysfunctions such as head oscillations and postural instability might help patients to correctly attribute errors to their own movement patterns instead of noise. This is supported by a study by Murillo et al. (2022), who showed patients a video recording of their body sway as well as trajectories of their centre of pressure and gave an explanation

of how postural instability might arise. Following this intervention, patients' perception of postural instability reduced (however, not their actual body sway). Further research is needed to understand how transient these effects are and whether this will over time also affect objectively measured body sway.

iii) Finally, the results from Harris et al. (2023) suggest that reducing anxiety may prove an effective contribution to making internal models more adaptable. Thus, in patients with co-morbid anxiety, the impact of the aforementioned approaches could be enhanced when they are accompanied by treatment aiming at a reduction of anxiety, such as psychotherapy. While the causal relationship between functional dizziness and anxiety is unclear, an early intervention with psychotherapy and pharmacotherapy, especially serotonergic medication, has been shown to reduce dizziness and psychiatric co-morbidities (Scarff and Lippmann, 2023).

5.3 Altered symptom perception in post COVID-19 condition

We demonstrated increased perceived breathlessness in patients with post-COVID, while the objectively measured underlying respiratory body state (physiology and breathing behaviour) was not different from healthy control participants (chapter 3). This indicates intact interoception, i.e., inference of the underlying respiratory state, for adapting breathing behaviour but dysfunctions in the symptom generation process. We proposed two different potential mechanisms that could explain the divergence between breathing behaviour and symptom perception which are in line with our experimental data. One possibility is that there are two separate inference processes about the respiratory state, involving different priors, for controlling breathing behaviour and for generating symptoms. Another possibility is that only a single posterior of the respiratory state is computed but subsequently combined with different cost functions when a specific breathlessness report or breathing behaviour is chosen. Before discussing the potential involvement of altered prior and cost-function in patients with post COVID-19 condition, evidence that the brain is able to form representations of both, prior and cost functions, is reviewed.

5.3.1 Does the brain represent prior and cost functions?

There is evidence for differential representations of likelihood and prior uncertainty in the brain (Vilares et al., 2012) and that information about rewards and costs is encoded (Chen, 2021). However, only recently a study investigated whether the brain forms internal representations of both, prior and cost functions in the same task, and thus is sensitive to changes in either of them. To test whether humans can build and adapt internal models of priors and cost functions, Sohn and Jazayeri (2021) have developed an experimental paradigm involving prior-cost metamers. These prior-cost metamers are different combinations of priors and cost functions that lead to the same action policy. The authors designed a time reproduction task in which they altered reward (cost function) and the rate

of occurrence of stimulus magnitudes (prior) such that each combination was a metamer. Their idea was that an observer that relies on priors and cost functions should see the metamers as two different pairs and should be sensitive to switches in pairs, whereas an implicit, non-Bayesian learner, should only learn the optimal policy and is not able to distinguish between different pairs. During the task they changed the underlying structure of cost and prior covertly and observed whether individuals show signs of relearning this new structure. They simulated data of an optimal observer, i.e., an observer that has full knowledge of the underlying task structure and optimally responds to it. After metamer switches the probability that the human time reproduction data resulted from the ideal-observer model decreased but recovered within around 50 trials. This indicates that humans learn the structure of the novel metamer and, following a period of learning, their response becomes increasingly more similar to the optimal-observer model. Hence, this study provides evidence in favour of the view that humans are sensitive to changes in prior and cost functions and learn their underlying structure. However, such sensitivities to changes in prior and cost function were only present in a time reproduction task but not in a visuomotor rotation task. Thus, further research is needed to understand in which tasks and contexts representations of priors and cost functions are formed.

Computational modeling of the learning rates of prior and cost-function also implied that both processes likely involve different neural systems. The authors highlighted that this is in line with neurobiological accounts of how prior beliefs and cost-functions are learnt. Prior beliefs are thought to be updated when there is a sensory prediction error, i.e., a mismatch between observed and predicted stimuli (Izawa and Shadmehr, 2011). Here, the cerebellum is believed to play an important role (Tseng et al., 2007; Synofzik et al., 2008). Cost functions are assumed to be updated if a mismatch occurs between predicted and actual reward (reward prediction error) and here the dopaminergic system is involved (Watabe-Uchida et al., 2017).

In summary, humans seem to be able to represent and learn different combinations of cost functions and priors, which likely involve distinct neural processing systems. However, evidence for differential representation of priors and cost-functions has only recently been emerging and further studies are needed to understand in which contexts the brain implements these quantities.

5.3.2 Cost functions for breathing behaviour and symptom perception

According to Bayesian Decision Theory, an ideal observer should integrate prior, likelihood and cost function to derive an optimal estimate of an action that minimizes expected loss (or maximizes expected reward). Cost functions for breathing behaviour likely assign high costs for breathing patterns that over- or under-represent the actual underlying respiratory body state, since both will threaten gas exchange and bodily homeostasis. Breathing too slow and shallow does not bring enough oxygen into the body. Next to increased energy expenditure, breathing too fast and deep can lead to hyperventilation and decreased CO_2

concentration in the blood, leading to an increase in pH and respiratory alkalosis. Cost functions for breathing behaviour should thus assign high costs for breathing too fast as well as too slow to keep bodily processes within the narrow range needed for survival.

Reporting or consciously experiencing a symptom also involves a selection process based on the posterior of the inference process. Here, the cost function describes the costs associated with experiencing a specific level of breathlessness. Breathlessness that is too low and under-represents the current respiratory state is dangerous, since respiratory dysfunctions remain unnoticed and no volitional measures can be taken to alleviate it. In contrast, breathlessness that over-represents the underlying body state might in the short term be beneficial, since it motivates behaviour to deal with the current body state and take alleviating and preventing measures. It might thus serve as a warning mechanism and enable timely reactions. However, in the long term considerable costs are associated with experiencing slight deviations in body states as strong symptoms. Such a 'better-safe-than-sorry' theory has previously been suggested to represent a common processing strategy that underlies different mental disorders (Van den Bergh et al. (2021)). However, instead of cost functions, Van den Bergh et al. (2021) formulated this processing heuristics using imprecise likelihood functions and highly precise priors. This again highlights the difficulty of distinguishing between different computational mechanisms. While Sohn and Jazayeri (2021) have provided evidence that humans learn representations of prior and cost functions in the previously described time reproduction experiment, it remains challenging to disentangle the influence of each component.

One potential distinction between priors and cost functions that warrants further research is the idea that cost functions might be more closely related to trait measures. An example of such a trait-like characteristic is a general worry that pathological body states could not be detected, thus favoring perception that overrepresent the actual body state. Priors might then be more closely related to state measures, i.e., the expected symptom level based on the momentary context. The same view can be adopted when interpreting the results from a study by Bogaerts et al. (2005). They measured accuracy of respiratory symptom perception in people with high versus low negative affectivity (NA). NA is a disposition to experience sensations in a negative way and is closely related to trait-anxiety. People with high NA were overall less accurate in reporting respiratory sensations, which worsened even more when the experiment was framed in a negative way, i.e., the possibly arising symptoms were described as distressing versus pleasantly arousing. People with high NA (trait measure) might thus have an altered cost function that leads to general dysfunctions in body awareness, that are further exacerbated by the momentary negative contexts.

This reasoning also suggests that beliefs about the expected severity of symptoms might shape cost-functions, thus playing a crucial role in (post-COVID) symptom emergence. This is supported by a study by Rozenkrantz et al. (2022). The authors showed that the belief about symptom severity at the time point of a hypothetical infection with SARS-CoV-2 can predict the number of symptoms at a time point three to four weeks later. This finding was replicated in a second cohort of participants. In addition, they developed a novel scale measuring an individual's belief of how well their own body can deal with

diseases and used a questionnaire to measure resilience and feeling of control during adverse events. Their experimental data provided evidence that the predictive association between beliefs about severity and number of symptoms was mediated by the belief about their body's capability to fight diseases as well as their perceived resilience to averse situations. Thus, individuals who expect that their symptoms during a hypothetical infection will be more severe, believe that their body is less capable to fight diseases, perceive themselves as less able to handle difficulties, and consequently develop more symptoms.

5.3.3 Limitations

While Bayesian theories of brain function can successfully explain many different behaviours and symptom perception, they are sometimes challenged and critiqued (Bowers and Davis, 2012) since in many cases the underlying model cannot be uniquely determined and models cannot be falsified. As seen above, different combinations of likelihood and prior can lead to the exact same inference and it is inherently difficult to disentangle both processes. This also applies to prior and cost functions. A similar change in behaviour or perception can occur due to a shift in the cost function, while the prior stays constant or vice versa. Furthermore, simpler approaches that do not necessarily require learning and representation of prior, likelihood and cost function in the brain might exist that can explain many behaviours equally well as Bayesian approaches (for a discussion on criticism about Bayesian decision theory see Ma, 2019).

While our experimental results do not allow to distinguish whether increased symptom perception in patients with post-COVID fatigue is due to altered cost functions or prior beliefs, knowledge about the exact underlying mechanism would provide important insights since learning of priors and cost-functions has been suggested to involve different processes and neural systems (Sohn and Jazayeri, 2021). Further studies should thus address the challenging but crucial endeavour to disentangle different plausible mechanistic proposals, necessary to inform the development of more effective therapeutic approaches.

5.3.4 Summary and implications for treatment

Most accounts of symptom perception have focused on incorrect and excessively precise priors, while the role of cost-functions in symptom emergence has so far been largely overlooked. First evidence supports the hypothesis that the brain can form representations of both, priors and cost-functions (Sohn and Jazayeri, 2021). We proposed a possible alteration of cost-functions that can explain increased symptom perception in the presence of normal breathing behaviour. In the framework of Bayesian Decision Theory, cost-functions define how an optimal estimate is chosen from the posterior distribution. Symptom perception can be seen as a decision process of how the belief about underlying body states (i.e., posterior) is brought to conscious awareness. To our knowledge, our study is the first to propose altered cost-functions resulting in symptom perception in the absence of pathophysiological processes.

We have shown a mismatch between symptom perception and the objectively measurable body state in post COVID-19 condition. This characteristic finding has also been demonstrated in fibromyalgia, chronic fatigue (Van Den Houte et al., 2018) and functional breathlessness (Bogaerts et al., 2010). By adopting an explanatory approach previously used for functional disorders, we have demonstrated that the observed mismatch in post COVID-19 condition can be explained by either incorrect priors or cost-functions. This rises the question whether post COVID-19 condition can be seen as a functional disorder. Such a perspective has previously been proposed by some researchers (Teodoro et al., 2023; Joffe and Elliott, 2023; Willis and Chalder, 2021), while others have strongly argued against this hypothesis (Van der Feltz-Cornelis et al., 2023; Davenport et al., 2024). The question is thus highly debated with strong opinions on either side. However, the potential diagnosis of a functional disorder seems to be largely neglected at the moment. A review investigating the presence of functional neurological disorder (FND) in 102 studies about neurological symptoms in patients with post COVID-19 condition found "no evidence [..] that any authors had systematically looked for positive features of FND" (Teodoro et al., 2023).

The Bayesian brain framework describes each perception as dependent on both, (implicit) prior beliefs and sensory input. Depending on various factors and influences, either prior knowledge or sensory input is weighted more strongly. As a consequence, perception always lives on a continuum between both influences. Functional disorders might represent one extreme of this continuum where overly precise priors largely dominate sensory input, leading to symptom perception in the absence of pathological body states (Henningsen et al., 2018a; Van Den Bergh et al., 2017; Petzschner et al., 2017; Lehnen et al., 2018). However, there is no clear cut-off defining where a functional disorder starts. Our experimental results suggest that also in post COVID-19 condition, priors and 'top-down' processing play an important role and can bias perception away from sensory signals. However, it remains unclear where post COVID-19 condition is located on the continuum in respect to functional disorders. Thus, further studies are needed and we do not aim to join a categorical side of the debate whether post COVID-19 condition is a functional disorder. Rather, we would like to point out the benefits of adopting a Bayesian brain perspective and its promising potential in improving treatment and reducing suffering in patients with post COVID-19 condition. This perspective can incorporate a biopsychosocial framework that resolves the outdated dualistic view of symptoms either arising due to psychological *or* biomedical reasons. While it remains important to look for pathophysiological or organo-structural deficits, considering incorrect internal models as a cause of post COVID-19 condition, opens up promising new treatment approaches and highlights that bodily symptoms are reversible and might be treated *via* the brain. For example, Herigstad et al. (2017) have shown that improvements of breathlessness in patients with chronic obstructive pulmonary disease (COPD) over the time course of pulmonary rehabilitation correlated with changes in brain activity related to learnt breathlessness associations. While changes in breathlessness ratings correlated with the stimulus valuation network in the the brain, changes in breathlessness related anxiety correlated with activity in areas involved in attention processing and motor control. They thus demonstrated that improvements of breathlessness

ratings as well as breathlessness-related anxiety during pulmonary rehabilitation might reflect changes in associative learning, rather than actual improvements in lung function. Treatment targeted at a re-evaluation of breathlessness related cues might prove beneficial to reduce symptom burden. Next to pulmonary rehabilitation, they suggested approaches such as breathing exercises and mindfulness (Borge et al., 2014). Further treatment options might include other forms of psychotherapy (Myers et al., 2021), physiotherapy (Nielsen et al., 2015) and neuro-feedback (Orendáčová et al., 2022).

5.4 Conclusion

By adopting a Bayesian brain perspective on two examples of PPS, functional dizziness and post COVID-19 condition, this thesis makes three central contributions. First, we improve the mechanistic understanding by pinpointing deficits in functional dizziness to failures in internal model-based planning and by demonstrating that in most patients with post COVID-19 condition deficits arise in processes specific to symptom perception. In addition, by formulating our theory of how respiratory processing could lead to different levels of breathlessness in a mathematical model, we provided a way to test a specific theory. Second, we provide an explainable model that shifts the perspective on PPS from 'medically unexplained' to 'explained by maladapted internal models'. This offers a way to explain symptoms to patients when no measurable biomarker can be found. Providing an understandable explanation of the underlying disease together with the diagnosis has been shown to be crucial to reduce future health care use and associated costs (Lagrand et al., 2023). This explanation should also entail that internal models are adaptive and incorrect models can be relearnt, thereby highlighting that symptoms are reversible. We hope that this way patients can regain a feeling of control over their health and a positive attitude that suffering can be alleviated. Third, we reduce stigmatization of PPS via an objectively measurable disease marker of functional dizziness alongside further evidence for a theory that explains PPS as arising due to dysfunctions in internal models maintained by the brain. We thereby hope to shift PPS away from 'medically unexplained' towards 'explained by incorrect internal models'.

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Author contributions

Study 1: Unstable Gaze in Functional Dizziness: A Contribution to Understanding the Pathophysiology of Functional Disorders

Authors: Lena Schröder, Dina von Werder, Cecilia Ramaioli, Thomas Wachtler, Peter Henningsen, Stefan Glasauer, Nadine Lehnen

NL designed the study. CR collected the data. LS, **DW**, TW, SG, and NL analyzed the data. LS and **DW** created the figures. LS and NL wrote the initial manuscript. All authors reviewed and edited the manuscript.

My contribution to this publication:
For this publication, I helped analyzing the experimental data in MATLAB and verified existing scripts and results. Together with LS, I created the figures. I interpreted data, reviewed and edited the manuscript and supported LS in the peer review process.

Dr. Lena Schröder
Munich, October 2024

Study 2: Increased breathlessness in post-COVID fatigue despite normal breathing behaviour in a rebreathing challenge

Authors: Dina von Werder, Maria Aubele, Franziska Regnath, Elisabeth Tebbe, Dejan Mladenov, Victoria von Rheinbaben, Elisabeth Hahn, Daniel Schäfer, Katharina Biersack, Kristina Adorjan, Hans C. Stubbe, Katleen Bogaerts, Rudolf A. Jörres, Dennis Nowak, Omer Van den Bergh, Stefan Glasauer, Nadine Lehnen

NL: Initial idea and project initiation. **DW**, NL, OVdB, SG: Conceptualization. **DW**, MA: data curation. **DW**: formal analysis. DN, NL, SG: Funding acquisition. MA, ET, KA, HS, DS, FR, **DW**, RJ, KB: Investigation and Recruitment. **DW**, SG, RJ, DN, NL,

OVdB: Methodology. **DW**, MA, NL: Project administration. DN, SG, NL: Resources. **DW**, FR, SG: Sojware. SG, NL: Supervision. **DW**, MA, SG, NL: ValidaEon. **DW**: Visualization. **DW**: Writing – original draft. All authors: Writing – review and editing

My contribution to this publication:
Together with NL, OVdB and SG, I developed the concept of the study. I wrote the ethics proposal and pre-registration on the Open Science Framework and contributed in acquiring funding. I planned, ordered and was responsible for the experiment setup and maintenance. I coordinated the cooperation with the clinical ambulance and between all institutions involved. I set up and was responsible for data management and storage. I was responsible for project administration and management. Together with co-authors, I was involved in participant screening, recruitment and scheduling, data collection and participant compensation. I performed the data quality checks and wrote all pre-processing and analysis scripts in Python. I performed the statistical analysis in JASP. I generated all visualizations, wrote the original manuscript draft, incorporated co-authors reviews and I am in charge of the peer review process.

Study 3: Post-COVID breathlessness: a mathematical model of respiratory processing in the brain

Authors: Dina von Werder, Franziska Regnath, Daniel Schäfer, Rudolf Jörres, Nadine Lehnen, Stefan Glasauer

Conceptualization: **DW**, RJ,NL, SG; Methodology: **DW**, DS, RJ; Formal analysis and investigation: **DW**, DS, RJ, SG; Writing—original draft preparation: **DW**, SG; Writing—review and editing: **DW**, FR, DS, RJ, NL, SG; Funding acquisition: NL, SG; Supervision: NL, SG.
Together with the co-authors, I conceptualized the study. SG and I developed and evaluated the mathematical model. I was responsible for participant recruitment and screening, data collection, pre-processing and analysis of the experimental data. I performed model fitting to the experimental data and wrote the MATLAB scripts for this step. I generated the visualizations. I drafted the original manuscript. I incorporated co-author reviews and was responsible for the peer-review process.

Prof. Dr. med. Nadine Lehnen
Munich, October 2024