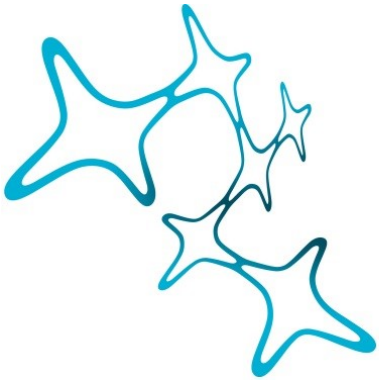
Erroneous Sensorimotor Processing in Functional Disorders

Evidence From Gaze Motor Control of Functional Dizziness and Irritable Bowel Patients

Lena Schröder



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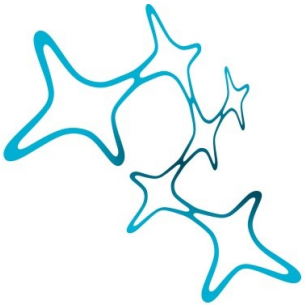

Graduate School of
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Abstract

Patients with functional disorders suffer from persistent somatic symptoms that are insufficiently explained by an organic dysfunction. Such symptoms are common in medicine and can be strongly debilitating for the affected persons. Yet, our current understanding about the underlying pathophysiology is still sparse, challenging diagnosis and therapy in this underserved patient group. A recently evolved theoretical framework based on the concept of predictive processing describes the emergence and manifestation of functional disorders as a consequence of processing deficits in the central nervous system. Here, prior knowledge and expectations are thought to bias sensory signal processing towards a pathological direction, so that emerging symptom percepts are uncoupled from organ functioning and corresponding sensory input. As so far, empirical evidence confirming this theory is still sparse, the aim of the current thesis was to experimentally investigate the role of expectations in sensorimotor processing of patients with functional disorders.

For this purpose, patients with functional dizziness and irritable bowel syndrome (IBS), i.e., functional gastrointestinal symptoms, were investigated in a gaze shift paradigm. In this paradigm, eye-head gaze shifts are performed under normal head properties and with increased head moment of inertia. The experimental perturbation induces a mismatch between the intended and executed head movement, so that the expected and actual sensory consequences of the head movement do not match. Adaptation to this new context allows conclusions about a correct use of expectations and sensory input during sensorimotor processing.

Study 1 investigated patients with functional dizziness and a healthy control group in the gaze shift paradigm. Sensorimotor processing was analyzed by assessing head oscillations. They arise when the increased head moment of inertia is not (yet) incorporated in internal models of the head and accounted for in motor planning. Head oscillations were higher in patients with functional dizziness than in the healthy control group, indicating sensorimotor processing deficits that prevent adaptation to the altered head properties. Such deficits were already found, to a smaller extent, in the natural condition. By reanalyzing data from patients with organic dizziness performing the same experiment, i.e., bilateral vestibulopathy and cerebellar ataxia, no difference could be found between the height of head oscillations in these patient groups and in functional dizziness, demonstrating similar impairment.

In study 2, gaze stability of patients with functional dizziness and a healthy control group was analyzed during gaze shifts in the paradigm described above. Patients showed impaired gaze stability during a distinct epoch of the large gaze shift, in which gaze was stabilized against active head movements. In this epoch, information from motor planning and internal models can be used additionally to ongoing sensory input to stabilize gaze. In contrast, during another epoch of the gaze shift, in which gaze was stabilized against passive, unexpected head movements by using sensory input alone, gaze stabilization was intact. These results further revealed sensorimotor processing deficits in functional dizziness, this time in the functionally relevant parameter of the task, i.e., gaze. Here, processing deficits arise due to an incorrect use of expectations. They were already present in the natural condition, and further pronounced with increased head moment of inertia.

The third study investigated patients with IBS and a healthy control group in the gaze shift paradigm to look for generalized, symptom-unspecific processing deficits that manifest across organ systems. Patients with IBS showed difficulties in adapting to the new context of increased head moment of inertia, reflected in increased head oscillations. These

results point at transdiagnostic processing deficits. As head oscillations in patients with IBS were smaller than in patients with functional dizziness, these processing alterations might represent a risk factor for developing further functional symptoms rather than representing a measurable correlate of pathophysiology.

Together, the findings of the presented studies provide evidence for the predictive processing account of functional disorders, pointing at incorrect expectations that bias sensorimotor processing and impair adaptation in the gaze shift paradigm. Identifying measurable pathophysiological correlates (study 1 and 2) and unifying deficits across symptom modalities (study 3) enhances our understanding of functional disorders and has the potential to improve diagnosis and therapy in this patient group.

Chapter 1

General Introduction: Understanding Functional Disorders

In medicine, we often face somatic symptoms, e.g., pain, dizziness, diarrhea, palpitations or fatigue, that are insufficiently explained by organic dysfunction (Henningsen, Zipfel, & Herzog, 2007). Such symptoms are also called "functional symptoms", as the supposed dysfunction does not lie in the organ structure, but in the function of the affected body region. Although functional disorders are very common (Haller, Cramer, Lauche, & Dobos, 2015) and cause a considerable amount of distress and disability, we are still lacking a pathophysiological mechanism that contributes to a better understanding of the emergence and manifestation of its symptoms. Recent efforts have addressed this issue: In the light of predictive processing, functional symptoms can be understood as a consequence of erroneous sensorimotor processing in the central nervous system. Here, wrong internal expectations are assumed to bias the processing of sensory signals towards a pathological direction [e.g., (Henningsen et al., 2018)]. But so far, little work has been done to test this hypothesis with empirical data from patients.

In brief, the present dissertation project aimed to study sensorimotor processing to experimentally investigate the predictive processing account of functional disorders. A well-known experimental paradigm from the field of gaze motor control was used that is suitable for detecting deviations in the interaction of internal expectations and (vestibular)

sensory input in gaze sensorimotor processing (Sağlam & Lehnen, 2014; Sağlam, Glasauer, & Lehnen, 2014). The paradigm was applied to patients with functional dizziness and head oscillations (study 1) as well as gaze stability (study 2) were investigated. In a second step, the gaze motor control paradigm was extended to patients with irritable bowel syndrome (IBS), i.e., functional bowel complaints (study 3), to test for generalized effects across symptom modalities.

The following chapter provides the theoretical background for the current thesis. In the first section, functional disorders will be introduced by elaborating on general remarks, nomenclature, and diagnostics as well as previous pathophysiological models. In a second step, a modern framework for understanding functional disorders – the predictive processing framework – will be presented, together with implications for and evidence from functional disorders. In the third section, the experimental approach as well as the investigated samples will be introduced. At last, research goals and hypotheses will be presented.

1.1 Characteristics of Functional Disorders

Functional disorders are characterized by persistent somatic symptoms that are insufficiently explained by organic dysfunction, as assessed in clinical examination and diagnostic tests. Such symptoms can emerge in many different body regions or organ systems, and often, more than one symptom can be found in a single patient (Henningsen et al., 2007). Functional symptoms are common: At general practitioners, about 26 to 40% of all the symptoms patients present with are thought to be of functional nature (Haller et al., 2015), and the lifetime prevalence of functional disorders is around 16% (Jacobi et al., 2014). The symptoms lead to a considerable burden for the affected persons and result in distress and disability as well as high societal and economic costs (Hiller, Fichter, & Rief, 2003; Konnopka et al., 2012; Wortman et al., 2018). Many of the affected patients also suffer from a comorbid depression or anxiety disorder (Fröhlich, Jacobi, & Wittchen, 2006; Kohlmann et al., 2016; De Vroege, Timmermans, Kop, & Van Der Feltz-Cornelis, 2018). This goes hand in hand with impaired quality of life (Liao, Ma, Lin, & Huang, 2019), which is often even worse than in patients with corresponding organic diseases (Carson et al., 2011; Vroegop, Dijkgraaf, & Vermeulen, 2013). Nevertheless, there is a huge discrepancy between the patients' reported disability and distress resulting from the symptoms and the unobtrusive diagnostic tests and medical examinations. This demonstrates the need for identifying a (measurable) pathophysiological mechanism that can facilitate diagnosis and, in the long run, therapy in this underserved patient group (Murray, Toussaint, Althaus, & Löwe, 2016).

1.1.1 Nomenclature and Diagnosis

There are many different notions that are used to describe physical symptoms without corresponding organic causes, and even diagnoses and corresponding criteria differ from area to area (Sharpe & Carson, 2001). The concepts lie between a medical and psychological understanding of what is causing these symptoms, and they reflect the disagreement about the underlying causes from the past until today. At general practitioners, for example, such

symptoms have been called “medically unexplained symptoms”, while at medical specialists, the term “functional symptoms” or “functional syndromes” is most commonly used (Toussaint & Herzog, 2020). Different medical disciplines have even come up with their own diagnoses and corresponding criteria for certain symptoms or symptom groups, such as “irritable bowel syndrome” for functional bowel complaints in gastroenterology (Lacy & Patel, 2017) or “persistent postural perceptual dizziness” for functional dizziness in neurology and otology (Staab et al., 2017). Psychological/psychiatric areas formerly referred to “psychogenic” symptoms, and are using the labels “somatoform” or “dissociative” in the current diagnostic system of Europe, the International Statistical Classification of Diseases and Related Health Problems [ICD-10 (World Health Organization, 2004)]. All terms come with different connotations and can lead to discontent at both sides, the patients as well as their caretakers (Sharpe & Carson, 2001; Mayou, Kirmayer, Simon, Kroenke, & Sharpe, 2005; Kirmayer & Sartorius, 2007; Marks & Hunter, 2015).

For the purpose of the current thesis, the term “functional (somatic) symptoms" or "functional (somatic) disorders” is used. It relates to an assumed impairment in the function, instead of the structure of an organ system and is therefore a relatively neutral, descriptive label for physical symptoms that are insufficiently explained by organic dysfunction. By doing so, it is intended to use this terminology as inclusive as possible, and the proposed mechanisms might be transferable to many other labels and diagnoses. It is also used consistently throughout the presented studies. The diagnosis used for study inclusion with its respective criteria depended on their clinical setting and are referred to in the methods section of the accompanying studies.

1.1.2 Pathophysiological Models

Over the past decades, several theoretical models were postulated which present mechanisms or predispositions that might play a role in the emergence and manifestation of functional disorders (Van Ravenzwaaij et al., 2011). In line with the variety of terminol-

ogy, the models either focus on pure physiological or psychological factors or a combination of both. The somatosensory amplification model (Barsky, 1992), as an example for a psychological model, postulates that patients with functional disorders direct their attention to arising physical sensations. Together with dysfunctional attributions of the sensations (e.g., "something is wrong"), the perception of such physical symptoms might be enhanced, maintaining a vicious cycle. Similarly, the filter model (Rief & Barsky, 2005) postulates that somatic signals are enhanced by altered neuronal filter capacity, for example, due to selective attentional processes. Nevertheless, both models cannot explain how physical symptoms emerge in the first place and how the enhancement of those by maladaptive cognitions or attentional processes is implemented in the brain. The endocrine dysregulation theory, a rather physiological model, suggests altered activity of the hypothalamic-pituitary-adrenal (HPA) axis, leading to a modified stress response that influences the occurrence of physical symptoms (Rief, Shaw, & Fichter, 1998; Heim, Ehlert, & Hellhammer, 2000; Rief & Auer, 2000). This model also has shortcomings, as evidence concerning cortisol levels are still inconclusive and the mechanisms behind the relation of HPA-axis-activity and the emergence and manifestation of functional symptoms are unclear (Rief & Barsky, 2005). As a fourth example, the sensitivity theory focuses on predisposing factors (personality traits like neuroticism and negative affectivity or early childhood abuse) that put affected persons at more risk to develop functional symptoms in the future (Waller & Scheidt, 2006; Buffington, 2009). But how this might be linked to functional disorders in a mechanistic way remains still unknown. Further explanatory models are the "sensitization theory", "immune system sensitization theory", "illness behavior theory" as well as the "autonomic nervous system dysfunction theory", which – due to the limited scope of the current thesis – will not be explained in detail and are described elsewhere [see (Van Ravenzwaaij et al., 2011)].

Recently, a more comprehensive theoretical framework was postulated to explain functional disorders: The "perceptual dysregulation" theory focuses on the mechanisms of information processing, i.e., how functional symptoms emerge and manifest in the brain (Edwards,

Adams, Brown, Pareés, & Friston, 2012; Van den Bergh, Witthöft, Petersen, & Brown, 2017; Henningsen et al., 2018). It is derived from the predictive processing framework of normal brain function [e.g., (Mumford, 1992; Rao & Ballard, 1999; Friston, 2005; Friston & Stephan, 2007)] and the proposed mechanisms are linked to neurobiological features of the brain. In this recent approach, many aspects of old theoretical assumptions on the mechanisms behind functional disorders are included, while at the same time, their explanatory shortcomings are reduced, as will be explained later. Bringing together physiological, psychological and social processes in a neurocognitive framework (Smith, Weihs, Alkozei, Killgore, & Lane, 2019), the new concept is in line with a comprehensive biopsychosocial understanding of symptom emergence and manifestation (Engel, 1977, 1980). In the following section, the principles of predictive processing in general as well as its application to symptom emergence and manifestation in functional disorders will be discussed in more detail.

1.2 Principles of Predictive Processing

Predictive Processing [e.g., (Srinivasan, Laughlin, & Dubs, 1982; Mumford, 1992; Rao, 1999; Rao & Ballard, 1999; Friston, 2002, 2003, 2005; Friston & Stephan, 2007) is a neurobiologically consistent, theoretical framework that explains information processing in the brain for perception, action, and probably also higher order cognitive functions in a computational, unifying manner (Wiese & Metzinger, 2017). Its central idea goes back to von Helmholtz (1867), who stated that perception is not only a passive processing of sensory signals, but that percepts are also shaped by prior knowledge. Within predictive processing, the brain can be seen as a "hypothesis testing machine" (Hohwy, 2013), constantly generating predictions about the causes of incoming sensory information from the environment and the body. These predictions are formed *a priori*, i.e., before the actual sensory information is entering the central nervous system (CNS) to prepare the organism for future stimuli and to avoid surprise [or "free energy", for detailed description about the "free energy principle" see (Friston, 2005, 2009; Friston & Stephan, 2007)]. Predictions

are derived from hierarchical, CNS-internal models that are based on previous experiences and reflect the learnt causal relationships in the world (Friston, 2003; Shams & Beierholm, 2010; Wiese & Metzinger, 2017). They are processed top-down in the CNS. Together with the actual sensory information elicited by current stimuli, which are processed bottom-up, the predictions determine the emerging percept. Both are closely intertwined, already on low hierarchical layers in the brain, so that the conscious percept is a product of both without conscious knowledge about how much of the percept was determined by actual sensory stimulation or priorly learned knowledge (Pollen, 1999).

Bayesian inference offers one possibility to explain how predictions and sensory input are computed and combined with each other [e.g., (Friston, 2002, 2003, 2005; Geisler & Kersten, 2002; Knill & Pouget, 2004; Körding & Wolpert, 2006; Aitchison & Lengyel, 2017). It considers the uncertainty of predictions and sensory input by understanding both as probability distributions, where many different prediction or input values receive a certain probability. Each probability distribution has an estimated value (maximum of the distribution), which is the most likely prediction or cause for sensory input, as well as a particular certainty (width of the distribution, see Figure 1.1) that indicates how likely alternative values are. The probability distribution for the prediction is also called *prior*. *Likelihood* relates to the probability distribution generated by sensory input and indicates how likely a certain cause is for generating neuronal activity. The product of both probability distributions results in the *posterior* probability that reflects the processing of sensory information in the CNS and determines the emerging percept. Also, the comparison of sensory activation and prediction leads to a prediction error that indicates the amount of mismatch between the two estimated values of the probability distributions.

Minimizing the prediction error is a goal humans are constantly pursuing to achieve good adaptation to different environmental conditions and needs [e.g., (Friston, 2005; Friston, Daunizeau, Kilner, & Kiebel, 2010; Friston & Stephan, 2007; A. K. Seth, Suzuki, & Critchley, 2012; A. K. Seth, 2013; A. Seth, 2014; Wiese & Metzinger, 2017)]. This can be achieved

in two different ways: First, the error signal can be used to drive learning in the CNS, i.e., adaptation of internal models. For this *perceptual inference* process, based on the *posterior* probability, internal models are updated respectively. Second, by moving the body, seeking certain environments or regulating body states, sensory input can be collected that conforms to the prediction, which is why this process is called *active inference*. For the learning processes during *perceptual inference*, estimation values of the *prior* and *likelihood* are weighted with their certainty [also: precision; (Friston & Stephan, 2007; Feldman & Friston, 2010; Hohwy, 2012)]. If the neuronal data from sensory activation is precise, i.e., noise is low, and the prediction about the sensory activation is imprecise, i.e., uncertainty is high, the posterior distribution will shift towards the sensory activation. Otherwise, a precise prediction paired with noisy or imprecise sensory information will shift the posterior probability towards itself, resulting in a *posterior* probability which is closer to the prediction. In other words, the greater the precision of the *likelihood* or the *prior* is, the greater their influence on the *posterior* probability will be. This mechanism is additionally modulated by attention, because attention serves to optimize precision (Friston & Stephan, 2007; Hohwy, 2012).

1.2.1 Predictive Processing in Functional Disorders

The interplay between predictions and sensory input in predictive processing needs to be highly flexible in order to orient oneself in and adapt to a constantly changing environment. When driving a well-known route in foggy weather, for example, it is more advantageous to rely on the precise prediction [knowledge about the route, after (Clark, 2013)] in order to drive the route safely and without mistakes. Instead, when driving an unknown route while having good sight, it is more advantageous to rely on the precise sensory input. If this well-tuned system is out of balance, it can lead to unadjusted behavior and disease. In schizophrenia, for example, hallucinations and delusions are thought to result from sensory signals that are weighted abnormally strong and induce learning very quickly, so that even

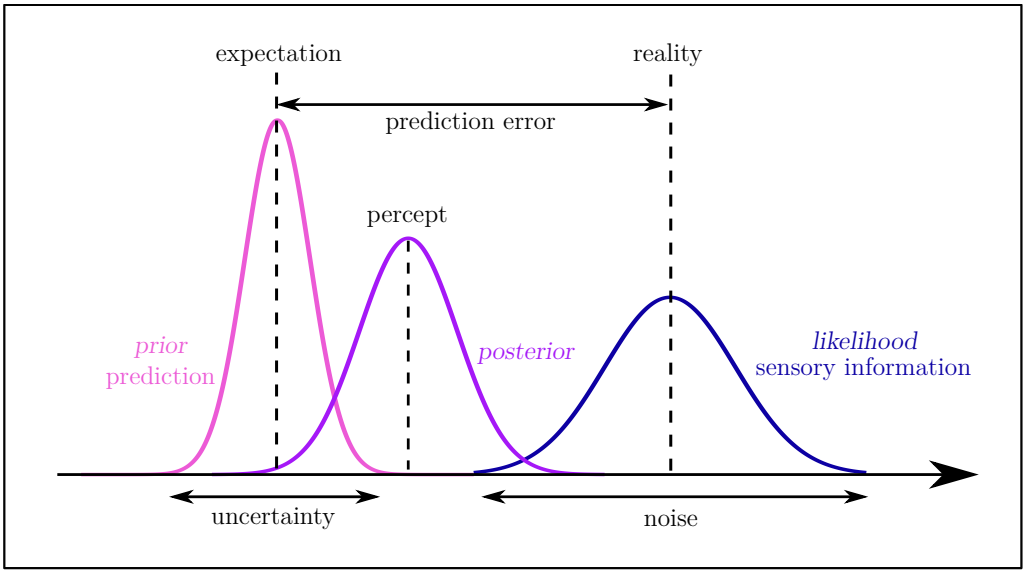

Figure 1.1: **Illustration of Bayesian inference for predictive processing.** Displayed are exemplary probability distributions with their respective properties and interactions within Bayesian inference for predictive processing [adapted from Yanagisawa et al. (2019)]. The combination of the probability distribution of the prediction (*prior*) as well as the sensory information (*likelihood*) determines the *posterior* probability. Its estimation value constitutes the emerging percept. The discrepancy between expectation and reality, i.e., the estimation values of the *prior* and *likelihood*, respectively, represents the prediction error. The precision of prediction and sensory information is the inverse variance of their probability distributions. Variance is also called uncertainty for the *prior* and noise for the *likelihood*.

trivial or irrelevant signals get captured in internal models (Allen, Aleman, & McGuire, 2007; Stephan, Friston, & Frith, 2009; Nazimek, Hunter, & Woodruff, 2012; Shergill et al., 2014). Then, at higher hierarchical levels, highly precise priors manifest that incorporate altered sensory processing in an explanatory nature, maintaining delusional beliefs [(Friston, 2005; Ćurčić-Blake et al., 2013; Schmack et al., 2013; Powers, Mathys, & Corlett, 2017; Cassidy et al., 2018); for a detailed review, see (Sterzer et al., 2018)]. In autism, affected people are thought to put more weight on sensory information (Ewbank et al., 2017; Lawson, Mathys, & Rees, 2017; Palmer, Lawson, & Hohwy, 2017; Tam et al., 2017; Millin et al., 2018), while at the same time showing imprecise higher order priors (Palmer, Paton, Kirkovski, Enticott, & Hohwy, 2015; Thillay et al., 2016; Grisoni et al., 2019), explaining problems in contextual learning and prioritizing of information.

In a similar fashion, the predictive processing approach was recently applied to explain the mechanisms behind the emergence and manifestation of functional disorders (Edwards et al., 2012; Van den Bergh et al., 2017; Henningsen et al., 2018; Pezzulo, Maisto, Barca, & Van den Bergh, 2019; Maisto, Barca, Van den Bergh, & Pezzulo, 2021). It is postulated that highly precise, but false predictions bias the processing of sensory signals towards a pathological direction. In detail, internal models that include illness-related assumptions can lead to a prediction anticipating pathological body states. On a conscious level, such assumptions would correspond to beliefs like "I feel dizzy" or "my chest hurts", but as stated before, their content as well as their influence on the perception of body signals is mostly inaccessible to consciousness. Together with sensory input that signals "normal" but ambiguous body states due to noise or random fluctuations, the resulting *posterior* probability will be closer to the rigid prediction than to the imprecise sensory input, reinforcing the faulty *prior* without actual body pathology verifying it. Over time, this reinforcement can make the *prior* stronger, and symptom experience more and more independent from somatic input (Henningsen et al., 2018).

This process is similar to the emergence of visual illusions [e.g., (Gregory, 1968, 1997a; Coren & Girgus, 1978; Eagleman, 2001)], where sensory information is overruled by overly precise *priors*, for example, the perception of a convex faces in the hollow face illusion when the presented face is actually concave (Hill & Bruce, 1993; Gregory, 1997a, 1997b). Here, the experience of thousands of convex faces seen throughout the life span overrules sensory information of light and shadow that signals a concave face, leading to a percept that is very close to the precise prediction. Functional symptoms can therefore be understood as "somatic illusions", although the emerging percept is experienced as "real" or "true" as organically caused somatic symptoms.

Besides influencing perceptual inference, a highly precise prediction that erroneously anticipates body pathology can also result in active changes of body states. When paired with

relatively weak or imprecise interoceptive signals, such *priors* can drive body regulations, e.g., autonomic reflexes or hormonal modulations, changing the actual interoceptive state to conform to the prediction. This way, harmless body states become threatening due to "dyshomoeostatic" regulations that do not follow homoeostatic principles anymore but rather serve as confirmation for false but strong predictions (Henningsen et al., 2018).

Compared to old pathophysiological models of functional disorders, the predictive processing account can theoretically overcome the obstacle of explaining how somatic symptoms emerge in the first place by embedding prior knowledge in the perceptual process per se. It also provides legitimation for the patients' symptoms experience, as percepts are always "real", independent of how much they are confirmed by sensory input. Additionally, older approaches can be nicely embedded within this new theoretical framework without being completely rejected. For example, the process of somatosensory amplification by dysfunctional cognitions is embedded within the influence of prior knowledge and beliefs on prediction formation, although it presents one special case within the theoretical framework (Henningsen et al., 2018), where many more processes and interactions can lead to symptom perception. Similarly, the effect of selective attention in the filter theory presents only a part of the whole concept, reflected by the modulatory effect of attention on precision. Increased body focus in predictive processing terms will lead to an abnormal enhancement of sensory signals, which can be captured best by a prediction that anticipates body pathology. This amplification of interoceptive activation can be understood as a self-fulfilling prophecy: The anticipation of strong sensory signals leads to a stronger experience of relatively weak sensory activation, and interoceptive noise can be inferred and experienced as a symptom (Van den Bergh et al., 2017).

In sum, the predictive processing framework offers a tempting approach to explain the mechanisms behind the emergence and manifestation of functional disorders. Nevertheless, it comes with great explanatory power and cannot easily be falsified (Harkness, 2015). Therefore, it needs critical evaluation and combination with empirical findings on mecha-

nisms in the brain to estimate its impact on information processing and symptom emergence in functional disorders and ultimately usability of such a framework to aid diagnostics and treatment.

1.2.2 Empirical Findings in Healthy Controls and Functional Patients

So far, little work has been done that investigates the mechanisms behind the emergence and manifestation of functional disorders from a predictive processing perspective. One of the first studies vividly demonstrating the discrepancy between perception and actual body states was performed by Pareés et al. (2012). They investigated the duration and severity of symptoms in patients with functional tremor, compared to patients with organic tremor, collecting objective (actigraphy) as well as subjective (self-reports) data over five days. Patients with functional tremor reported more tremor occurrence than patients with organic tremor (84% vs. 58%), even though their actual amount of tremor, as measured with actigraphy, was lower (4% vs. 25%). Another study (Bogaerts et al., 2010) showed that patients with functional dyspnea (breathlessness) reported longer symptom perception after experimentally induction of respiratory distress, uncoupled from sensory input. The same group could demonstrate that these alterations can be also found in patients with chronic fatigue syndrome and fibromyalgia (Van Den Houte et al., 2018), indicating biased perceptual processes across different organ systems. Perepelkina, Romanov, Arina, Volel, and Nikolaeva (2019) found reduced strength of the rubber-hand-illusion (RHI) in patients with functional disorders, indicating that the integration of multisensory information is disrupted in this patient group. The same effect was found for healthy controls when split up into high and low symptom reporters, with high symptom reporters showing a reduced response to the RHI (Miles, Poliakoff, & Brown, 2011). Further studies with healthy controls demonstrated that symptom-like somatic illusions could be induced by experimentally altering somatic expectations [e.g., (Iodice, Porciello, Bufalari, Barca, & Pezzulo, 2019; Bräscher, Sütterlin, Scheuren, Van den Bergh, & Witthöft, 2020; Wolters, Harzem, Witthöft, Gerlach, & Pohl, 2020). Nevertheless, none of these studies has inves-

tigated how modified bottom-up sensory information or top-down expectations influence information processing in the brain by looking at measurable physiological alterations that reflect these processes. Therefore, the aim of the present thesis was to close this gap, using an experimental approach that is suitable for detecting deficits in sensory activation or expectation processing. The approach and the associated mechanisms in the brain will be described in the following section in more detail.

1.3 Empirically Testing Predictive Processing in Functional Disorders

One convenient possibility to investigate the interplay of internal expectations and sensory input is studying motor control. In this field, the idea that top-down influences drive sensorimotor processing is not new, but has already been described by Sperry (1950) and in the reafference principle by von Holst and Mittelstaedt (1950). In short, copies of motor commands (*efference copies*) are used to expect the sensory consequences generated by movements (*reafference estimates*), these expectations then modify the incoming sensory information (*reafference*). In such research fields, where top-down influences have received decades of attention and study efforts, many well-studied systems have evolved, under which the gaze motor control system represents one example [e.g., (Guitton, Douglas, & Volle, 1984; Laurutis & Robinson, 1986; Tomlinson & Bahra, 1986; Guitton & Volle, 1987; Tomlinson, 1990; Hengstenberg, 1991; Guitton, 1992; Lefèvre, Bottemanne, & Roucoux, 1992; Tweed, Haslwanter, & Fetter, 1998)]. Using such a well-known system to study predictive processing in functional disorders has the great advantage that many steps of information processing are already known and can be directly linked to underlying physiological processes, for example, the contribution of sensory input like the vestibulo-ocular reflex (VOR) during eye-head gaze shifts (Lefèvre et al., 1992). Furthermore, the results of sensorimotor processing are reflected in motor outputs, which are visible and measurable.

To investigate the account of internal expectations and sensory input in functional disor-

ders, a gaze shift paradigm was applied. During the experimental task, subjects perform large gaze shifts towards briefly flashed visual targets by naturally engaging combined eye and head movements [first described in Lehnen (2006)]. This specific paradigm was first used to study head motor control under external perturbations in healthy controls (Lehnen, 2006; Lehnen, Büttner, & Glasauer, 2008), was further used to model eye, head and gaze dynamics during head free gaze shifts (Sağlam, Lehnen, & Glasauer, 2011) and was applied to investigate vestibular and cerebellar contribution to head motor control, gaze optimality and stability by looking at data from neurological patients (Lehnen, Büttner, & Glasauer, 2009b; Sağlam & Lehnen, 2014; Sağlam et al., 2014). In line with the reafference principle (von Holst & Mittelstaedt, 1950), the paradigm makes use of the fact that for a gaze shift engaging eye and head movements, both, bottom-up information from vestibular sensors as well as top-down efference copy processing to predict the sensory consequences of movements guide head and gaze motor control. The way how specific parameters indicate deficient sensorimotor processing will be described below.

1.3.1 Parameter 1: Oscillation Ratio

As a first approach towards studying sensorimotor processing in functional disorders, participants' head characteristics were experimentally altered during large eye-head gaze shifts towards visual targets. This was done by placing a helmet with eccentrically placed masses on both sides on participants' heads, which increased the head moment of inertia to the 3.3-fold. Altering the head mechanics leads to involuntary head oscillations at the end of a head movement, as long as the altered characteristics are not yet reflected in internal models and expectations (Peng, Hain, & Peterson, 1996; Tangorra, Jones, & Hunter, 2003), as shown by Lehnen (2006) and Lehnen et al. (2008). Thus, head oscillations represent a measurable physiological marker for the mismatch (prediction error) between the executed movement together with its actual sensory consequences and the internal models that plan and expect (predict) the outcome of head movements.

Studies from patients that either cannot process vestibular information (complete bilateral vestibulopathy) or have difficulties in updating internal models and forming correct expectations (cerebellar ataxia) further validate the significance of sensory input and expectations during large gaze shifts with altered head characteristics: Both patient groups displayed more pronounced head oscillations than a healthy control group (Lehnen et al., 2009b; Sağlam et al., 2014), indicating that sensory input processing as well as prediction formation is crucial for sensorimotor processing, especially when adaptation to new situations is needed. Evaluating head oscillations therefore represents a first indicator for a general problem in the interaction between vestibular input and expectations in head movement processing and was investigated in study 1 and study 3 of the current thesis.

1.3.2 Parameter 2: Gaze Stability

Studying gaze stability is also suitable for investigating sensorimotor processing in functional disorders and furthermore represents the functionally relevant parameter of the task that is worth to be investigated. During a large eye-head gaze shift towards a briefly flashed visual target, movements follow a typical sequence that includes two stabilization epochs (Sağlam & Lehnen, 2014). First, after eye and head have jointly moved towards the remembered target, a counter-rotation epoch begins, where the eyes compensate the ongoing active head movement towards the target by a counter-rotation to keep gaze stable at the target position. Second, after final gaze position is achieved, the eyes stabilize gaze against small, involuntary head oscillations in this so-called oscillation epoch. Both epochs differ with respect to the presence of head movement expectations: During the counter-rotation epoch, the head movement is of active nature, so that motor commands, internal models and expectations can be used to stabilize gaze, in addition to ongoing sensory input. In contrast, during the oscillation epoch, head movements are involuntary and of passive nature, so that no internal expectations are present, and stabilization is only driven by sensory input.

Data from neurological patients empirically support the presence of internal expectations during the counter-rotation but not the oscillation epoch, as patients without vestibular input (complete bilateral vestibulopathy) were able to stabilize gaze in the counter-rotation epoch to some extent, while almost no stabilization occurred during the oscillation epoch (Sağlam & Lehnen, 2014). Thus, comparing gaze stabilization in those two stabilization epochs might reveal further difficulties in sensorimotor processing, while now being able to localize the possible processing deficit in the sense of predictive processing. This was investigated in study 2 of the current thesis.

1.3.3 Patients with Functional Dizziness - a Suitable Sample

As the vestibular modality is essential for sensorimotor processing during large eye-head gaze shifts (Lehnen et al., 2009b; Lehnen, Büttner, & Glasauer, 2009a; Sağlam & Lehnen, 2014; Sağlam et al., 2014), patients with functional dizziness represent a suitable sample to study the interplay between expectations and sensory input within the gaze shift paradigm. Patients with functional dizziness can experience different types of vestibular-like symptoms (Dieterich & Staab, 2017), for example, distorted or false movement perception (vertigo), unsteadiness or postural imbalance as well as disrupted spatial orientation [dizziness, see classification of vestibular disorders of the Bárány Society: Bisdorff, Von Brevern, Lempert, and Newman-Toker (2009); Bisdorff, Staab, and Newman-Toker (2015)]. Alongside, with a lifetime prevalence of 30%, dizziness represents a common complaint in the general population (Neuhauser, 2009), and in 20-50% of dizziness cases, symptoms can be categorized as functional (Staab & Ruckenstein, 2007; Stone et al., 2010). Dizziness often comes along with psychiatric comorbidities (Eckhardt-Henn, Breuer, Thomalske, Hoffmann, & Hopf, 2003; Wiltink et al., 2009; Lahmann et al., 2015) and leads to impaired health related quality of life (Cheng et al., 2012; Ten Voorde, van der Zaag-Loonen, & van Leeuwen, 2012; Weidt et al., 2014), increased utilization of health care services (Wiltink et al., 2009) and health-care and economic costs (Saber Tehrani et al., 2013). Being both, widespread and burdensome, studying functional dizziness is not only suitable for the pre-

sented paradigm, but also important from a medical and societal point of view. In the present thesis, patients functional dizziness have been the investigated population of study 1 and 2.

1.3.4 Patients with IBS - an Extended Sample

Besides looking at symptom-specific alterations in sensorimotor processing of functional disorders, it may also be fruitful to investigate overarching processing deficits across different organ systems. As stated before, often, more than one functional symptom occurs in a single patient (Henningsen et al., 2007). In the current European diagnostic classification system ICD-10 (World Health Organization, 2004), for example, the diagnosis of a somatization disorder requires at least six symptoms affecting two or more organ systems. Indeed, this diagnosis is not rare, but occurs in up to 5% of the general population (Haller et al., 2015). When it comes to explaining the emergence and manifestation of functional disorders, it is therefore possible to also think of a general, symptom-unspecific CNS-processing deficit that put patients at risk for developing more than one symptom at the same time.

Patients with IBS represent a further patient group that was studied for the purpose of the present thesis (study 3). With symptoms occurring in the lower gastrointestinal system, the affected organ system is far away from eye-head motor control and the vestibular system investigated in the gaze shift paradigm. IBS describes a set of functional bowel symptoms, i.e., abdominal discomfort or pain, bloating as well as irregularities in stool frequency and form, for which no structural correlate can be found that explains the occurrence of the symptoms (Enck et al., 2016). Besides, it affects around 11% of the population (Lovell & Ford, 2012) and therefore represents one of the most common functional syndromes. Similarly to other functional diseases, in patients with IBS, comorbidity with psychiatric disorders like depression and anxiety is increased (Zamani, Alizadeh-Tabari, & Zamani, 2019) and health related quality of life is impaired (Whitehead, Burnett, Cook, & Taub,

1996; Hahn, Yan, & Strassels, 1999; Gralnek, Hays, Kilbourne, Naliboff, & Mayer, 2000; El-Serag, Olden, & Bjorkman, 2002).

1.4 Research Goals and Research Questions

The overarching goal of this dissertation was to investigate the predictive processing account of functional disorders (Edwards et al., 2012; Van den Bergh et al., 2017; Henningsen et al., 2018; Pezzulo et al., 2019) by studying the interplay between CNS-internal expectations and sensory input during sensorimotor information processing in the brain. The general hypothesis was that functional symptoms result from erroneous sensorimotor processing in the brain, with overly precise but wrong internal expectations biasing information processing. This was tested by applying a well-known gaze shift paradigm (Lehnen, 2006; Lehnen et al., 2008, 2009b, 2009a; Sağlam et al., 2011; Sağlam & Lehnen, 2014; Sağlam et al., 2014), which is able to make difficulties in sensorimotor processing visible by affecting different parameters of motor output, to patients with functional disorders.
Initially, patients suffering from functional dizziness were investigated with this gaze shift paradigm. In a first step, head oscillations were studied with and without increased head moment of inertia, with the following research question and hypothesis guiding the investigation:

1) Do patients with functional dizziness display enlarged head oscillations during large eye-head gaze shifts with increased head moment of inertia?

According to the hypothesis of predictive processing, patients with functional dizziness were assumed to display larger head oscillations than healthy controls, as increased head oscillations constitute a marker for the incongruency of expectations and sensory input in head sensorimotor processing (see section 1.3.1).

In a second step, the functionally relevant parameter of the gaze shift paradigm, gaze stability, was assessed in patients with functional dizziness. The following question and hypothesis were examined:

2) Do patients with functional dizziness show deficits in expectation-driven gaze stabilization, in contrast to sensory-driven gaze stabilization?

Patients with functional dizziness were expected to display impaired gaze stabilization during a stabilization epoch where internal models and expectation are used for gaze stbilization (see section 1.3.2), like hypothesized in the predictive processing account of functional disorders. In contrast, patients with functional dizziness were expected to display intact sensory-driven gaze stabilization, in line with the unobtrusive clinical results found in this patient group.

Furthermore, the gaze shift paradigm was applied to another patient group of the field of functional disorders to test for general, symptom-unspecific processing deficits that might be manifested across symptoms. For this purpose, patient with IBS were examined who suffer from symptoms not linked to gaze motor control. Again, head oscillations were assessed to investigate the following research questions and hypothesis:

3) Are the hypothesized processing deficits in functional disorders, reflected in increased head oscillations (see section 1.3.1), symptom-specific or do they manifest across different organ systems, presenting more generally disrupted processing mechanisms?

Assuming a general, symptom-unspecific deficit in sensorimotor processing across patients with different somatic symptoms, irritable bowel patients were expected to show increased head oscillations, compared to a healthy control group.

Chapter 2

Deficient Head Motor Control in Functional Dizziness: Experimental Evidence of Central Sensory-Motor Dysfunction in Persistent Physical Symptoms

The current chapter encloses a research article entitled *Deficient Head Motor Control in Functional Dizziness: Experimental Evidence of Central Sensory-Motor Dysfunction in Persistent Physical Symptoms*. Here, research results show increased head oscillations as a first measurable marker that distinguishes patients with functional dizziness patients from healthy controls. As increased head oscillations indicate disrupted sensorimotor processing, this finding provides first experimental evidence for processing deficits in functional disorders. The article was published in *Progress in Brain Research* in 2019.

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CHAPTER

30

Deficient head motor control in functional dizziness: Experimental evidence of central sensory-motor dysfunction in persistent physical symptoms

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Abstract

Understanding the mechanisms of symptoms that are insufficiently explained by organic dysfunction remains challenging. Recently, it has been proposed that such "functional symptoms" are based on erroneous sensory processing in the central nervous system (CNS), with internal expectations dominating sensory inputs.

In a pilot study, we used a head motor control set-up to assess the interplay between sensory input and expectation on the example of patients with functional dizziness. Eight patients and 11 age-matched healthy controls performed large active eye-head gaze shifts towards visual targets in the natural situation and with the head moment of inertia 3.3-fold increased. The latter induces head oscillations and the expected sensory outcome of the movement, estimated in the CNS, does not match the actual sensory input. Head oscillations were assessed in patients and in healthy subjects and compared to prior results from patients with organic disease (vestibular loss and cerebellar ataxia). Head oscillations in patients with functional dizziness were

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different from those of healthy subjects ($F(1,17) = 27.26$, $P < 0.001$, partial $\eta^2 = 0.62$), and similar to those of patients with cerebellar ataxia, and with vestibular loss ($F(2,19) = 0.56$, $P = 0.58$). Even in the natural, unweighted, condition, head oscillations were higher in functional dizziness patients than in healthy subjects ($P = 0.001$). Since an extensive work-up failed to demonstrate any explanatory peripheral vestibular, motor, or cerebellar organic dysfunction, these motor control deficits are a first indication of erroneous interplay between expectations and sensory input in the CNS that could account for persistent physical symptoms.

Keywords

Functional dizziness, Bodily distress, Somatic symptom disorder, Perceptual dysregulation, Predictive coding, Somatoform

1 Introduction

Patients with persistent physical symptoms that are unexplained by conventional clinical evaluations and tests present an enduring challenge to their caregivers. Their bodily complaints, like chest pain, bowel irritation, fatigue or dizziness can emerge from different body regions (Henningsen et al., 2018b), are very common in medicine (Carson et al., 2000; Fink et al., 2004, 2005; Haller et al., 2015; Reid et al., 2001), greatly impair functioning and quality of life (Carson et al., 2011), and present a huge social and economic burden (Hiller et al., 2003; Konnopka et al., 2012; Wortman et al., 2018). However, despite the extensive and repetitive work-ups characteristic for this patient group (Den Boeft et al., 2016; Fink et al., 1999; Hansen et al., 2002), symptoms are insufficiently explained by organic dysfunction. A recent concept, which is based on the predictive coding model of brain function (Friston, 2005; Mumford, 1992; Rao and Ballard, 1999; Srinivasan et al., 1982), understands persistent physical symptoms as a result of erroneous sensory processing in the central nervous system, with expectations (prior beliefs) dominating perceptual inference (Edwards et al., 2012; Henningsen et al., 2018a; Van den Bergh et al., 2017). This hypothesis is neurobiologically consistent, but so far, has not been experimentally tested. Here, to test this hypothesis, we apply a framework based on mathematical modeling and analysis of the head motor system (Fig. 1, experimental litmus test first described in Lehnen et al., 2018a).

Head movements as part of large eye-head gaze shifts to visual targets are a well characterized example to study the interaction between expectation and sensory input (Goldberg and Cullen, 2011; Guitton, 1992). Discrepancies between expectations and sensory input, i.e., prediction errors, are used to update motor commands, and alter actions, so that the resulting input conforms to the predictions (Wolpert et al., 1998). This can be experimentally tested by mechanically altering head characteristics (cats: Guitton et al., 1984; monkeys: Tomlinson, 1990; Tomlinson and Bahra, 1986; healthy humans: Guitton and Volle, 1987; Laurutis and Robinson, 1986). Increasing the head moment of inertia in healthy humans, for example, leads

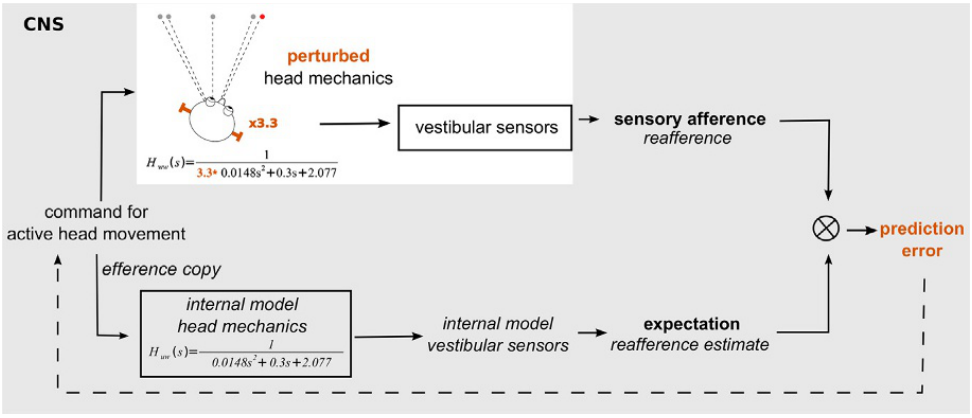

FIG. 1

Simplified scheme of head motor control underlying the experimental approach. In this experiment, subjects performed horizontal large combined active eye-head gaze shifts towards visual targets. After a set of gaze shifts in the natural condition, head mechanics were perturbed by a helmet with eccentrically attached masses 3.3-fold increasing the head moment of inertia (weighted condition, drawing, H_{ww}—head with weight—transfer function of the modified head plant indicated in Laplace notation (Peng et al., 1996; Tangorra et al., 2003)). The sensory input resulting from the head movement during the gaze shift (reafference) is measured by vestibular sensors. In the weighted condition, the reafference does not match the expected sensory outcome of the movement (reafference estimate) formed in the central nervous system (CNS, gray background). This is because the reafference estimate is based on a CNS-internal model of the head mechanics (H_{uw}—head unweighted—transfer function of the head plant in the natural situation) formed before the head moment of inertia was increased. The difference between expectation and sensory afference, i.e., the prediction error, can be exploited to update CNS-internal models, motor commands, and actions, so that the resulting input conforms to the predictions.

to unwanted head oscillations, which, using the prediction error to adapt the internal models to the altered head mechanics, can be reduced over trials (Lehnen, 2006; Lehnen et al., 2008; Sağlam et al., 2011). Both intact sensory afference and the ability to adapt internal models are essential to reduce unwanted head oscillations when the head moment of inertia is increased: patients with chronic complete bilateral vestibular loss (missing vestibular afference) do not reduce head oscillations, and cerebellar ataxia patients (who have deficits in forming internal models) only reduce oscillations to some extent (Lehnen et al., 2009a,b; Sağlam et al., 2014; Sağlam and Lehnen, 2014).

Here, we apply this well characterized set-up to patients who suffer from functional dizziness, a very common persistent physical symptom (Brandt et al., 2015; Dieterich and Eckhardt-Henn, 2004; Eckhardt-Henn et al., 2009; Feuerecker et al., 2015). Following the hypothesis that persistent physical symptoms are based on erroneous sensory processing in CNS, with expectations dominating perception, these patients would feel dizzy because they put too much trust into pathological

prior beliefs used to interpret sensory input. Translated into head motor control, we expect these patients to be more reliant on their existing internal models and therefore more resistant to sensory driven updating (prediction error). This would be reflected in deficient head motor control, which should resemble that of patients with organic disease affecting the interplay between sensory input and expectations like vestibular loss, or cerebellar ataxia.

2 Materials and methods

2.1 Subjects

In a prospective pilot study, 8 patients with functional dizziness (aged 35 ± 13 years, mean $\pm$ standard deviation (SD), 5 females) who presented with permanent symptoms to a tertiary vertigo/dizziness center, and 11 age- and gender-matched healthy volunteers (32 ± 6 years, mean $\pm$ SD, 6 females) participated in the study.

A comprehensive neurological history and exam (including neuro-otological and neuro-ophthalmological assessments), neuro-otological and neuro-ophthalmological work-ups (including caloric irrigation, video head impulse testing and subjective visual vertical), as well as MRI scans of the brain did not reveal any organic dysfunction that could sufficiently explain the patients' symptoms. Healthy subjects had no history of balance disorders and a normal neurological exam.

The experimental procedure was approved by the Ethics Committee of the Medical Faculty of the Ludwig-Maximilians-University and was in accordance with the Declaration of Helsinki. All subjects gave their informed consent prior to participation and were free to withdraw from the experiment at any time.

2.2 Experimental procedure

2.2.1 Video head impulse test and head impulse testing device function test

In addition to the clinical work-up, vestibular function during passive head movements was assessed with the video head impulse test (vHIT, in analogy to Bartl et al., 2009). Also, dynamic vision during passive head motion was measured with the Head Impulse Testing Device—Functional Test (HITD-FT, also called functional head impulse test (Ramat et al., 2012; Versino et al., 2014), procedure described in Ramaioli et al. (2014).

2.2.2 Altering head mechanics during eye-head gaze shifts to visual targets

The experimental set-up was designed in analogy to Lehnen (2006). Subjects performed 52 horizontal gaze shifts (combination of eye and head movements) in complete darkness to visual targets flashed in a frontal plane before them and situated 35 and 40 degrees to the left and right. Subjects were asked to keep gaze position

until the next visual target was flashed. In order to prevent visual feedback, targets were flashed for <100 ms. The interval between two subsequent visual targets (1–1.8 s) and subsequent target eccentricity (35, 40, 70, 75 or 80 degrees) were randomly assigned to prevent anticipation. The experiment was repeated twice: once in the natural, unweighted, condition, and then with the head moment of inertia 3.3-times increased by means of a helmet with eccentrically placed masses (weighted condition, Lehnen, 2006; drawing in Fig. 1). All subjects and patients were naïve with respect to this experiment. During the experiment, eye movements were recorded by video-oculography of the left eye and head movements by inertial sensors (EyeSeeCam system with a sampling rate of 220 Hz, in analogy to Bartl et al., 2009).

2.3 Data analysis

Data were analyzed offline using MATLAB® (MathWorks, Natick, MA) and IBM SPSS Statistics.

2.3.1 Video head impulse test and head impulse testing device function test

In analogy to Lehnen et al. (2018b), the vHIT gain was computed as the ratio of median eye and head velocity in a 10 ms-window between 55 and 65 ms after head impulse start (head velocity exceeding 20 degree/s), and the HITD-FT score was calculated as the rate of correct answers in all trials.

2.3.2 Altering head mechanics during eye-head gaze shifts to visual targets

Active head movements as part of the gaze shifts were analyzed in the natural and in the weighted condition. Head velocity was derived from the inertial sensors and low-pass filtered with a Gaussian filter with a cut-off frequency of 20 Hz. For each trial, i.e., a single gaze shift towards the visual target, head movements were considered in a time window of 1.6 s starting 45 ms before visual target onset. Only movements corresponding to gaze shifts of 75 and 80 degrees were considered in the analysis. Head start was defined as head velocity reaching 6 degree/s, the head movement ended when head velocity crossed 6 degree/s again. In analogy to Sağlam et al. (2014), the head oscillation ratio was assessed as the absolute ratio of the first negative and positive peaks of head velocity (in percent, see inset in Fig. 2). Detection errors could be corrected manually. If head oscillations fell outside 2 SD from the mean of all trials of one subject or patient in one condition (unweighted/weighted), the trial was removed from the analysis. After removing outliers, 31 ± 4 (mean ± SD) and 25 ± 7 trials were considered for each subject in the unweighted condition and 26 ± 8 and 22 ± 8 trials in the weighted condition for healthy subjects and for patients with functional dizziness, respectively.

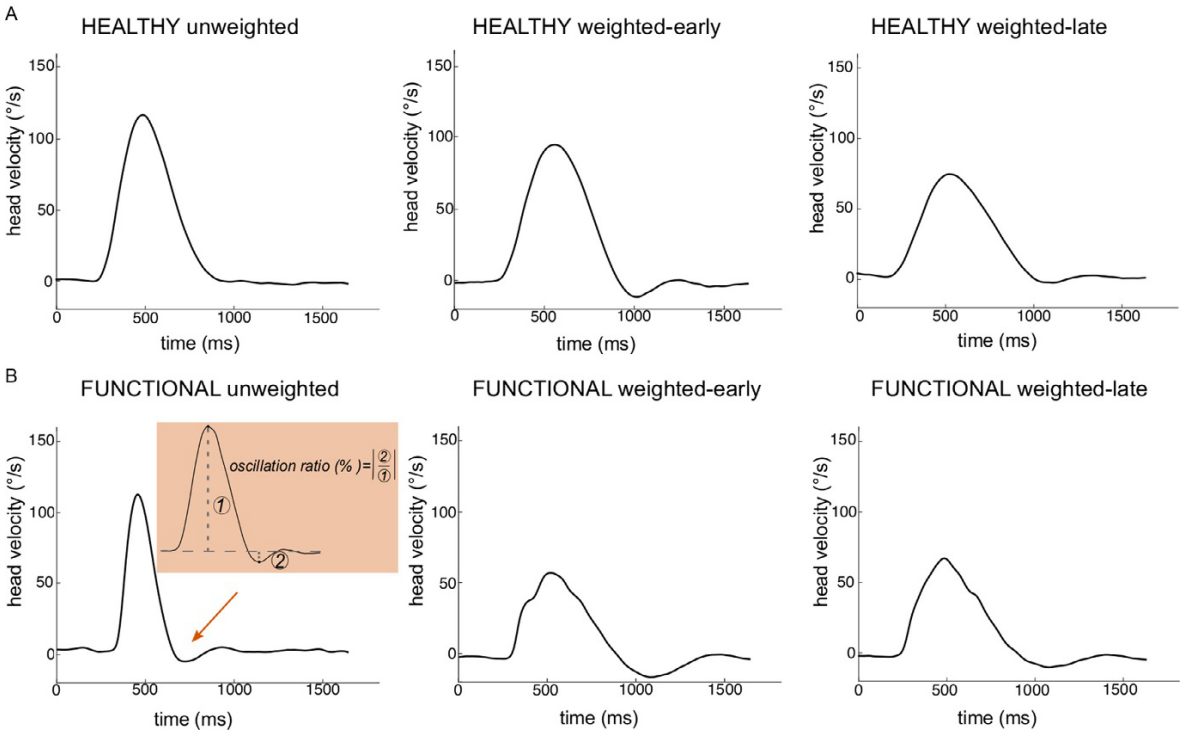

FIG. 2

See legend on opposite page.

2.3.3 Comparison to previously acquired data from patients with chronic vestibular loss and cerebellar ataxia

For comparison, data reported in Sağlam et al. (2014) were reanalyzed in the same way as the data from the functional dizziness patients and healthy subjects of the present study. In Sağlam et al. (2014), 10 healthy subjects (aged 40 ± 6 years, mean $\pm$ SD, 1 female), 9 patients with cerebellar ataxia (aged 57 ± 13 years, 6 females) and 5 patients with chronic vestibular loss (aged 45 ± 7 years, 3 females) participated. In the reanalysis of this data, after outlier analysis, 35 ± 3 (mean $\pm$ SD) and 33 ± 5 trials were considered for healthy subjects, 34 ± 2 and 34 ± 2 trials for patients with cerebellar ataxia and 31 ± 3 and 33 ± 6 trials for patients with chronic vestibular loss, for the unweighted and weighted condition, respectively. A repeated measures analysis of variance (rmANOVA, significance level $P < 0.05$) on head oscillation ratio revealed no difference between the healthy subjects from Sağlam et al. (2014) and the healthy control group investigated for the current pilot study ($F(1,19) = 1.1$, $P = 0.33$), validating following comparisons between the patient groups from Sağlam et al. (2014) and the functional dizziness patients.

2.4 Statistical analysis

Normality was assessed by Kolmogorov-Smirnov testing ($P < 0.05$). Head impulse gains during vHIT and HITD-FT scores for movements to the left and to the right were pooled as there was no side difference (dependent samples t-test, $P > 0.05$). A one-way multivariate analysis of variance (MANOVA, $P < 0.05$) was conducted to compare differences in head impulse gains and HITD-FT scores between groups (healthy subjects and patients with functional dizziness).

Differences in head oscillation ratios within three conditions (*unweighted* and *weighted*—split up into *weighted-early* (first 10) and *weighted-late* (last 33) trials) and between the groups (healthy subjects, patients with functional dizziness) were

FIG. 2

Head velocity traces from a healthy subject and a patient with functional dizziness. Representative head velocity traces during an active gaze shift following a 75 degrees target step from a healthy subject (A) and from a patient with functional dizziness (B) in the natural condition (unweighted, left), for the first 10 trials with increased head moment of inertia (weighted-early, middle) and for the last 33 trials with weight (weighted-late, right). The healthy subject performed a smooth head movement without oscillation in the unweighted condition. In contrast, the patient showed head oscillations (note how head velocity undershoots the zero-line, arrow). Inset: to quantify head oscillations, the oscillation ratio was computed as the absolute ratio of the first negative (2) and positive (1) peaks of head velocity. Increasing the head moment of inertia led to head oscillations, more accentuated in the patient. Over the course of the experiment with increased head moment of inertia, both the patient with functional dizziness as well as the healthy participant could reduce head oscillations.

assessed by rmANOVA ($P < 0.05$, Greenhouse-Geisser correction for violation of sphericity). After a significant interaction, a post-hoc independent *t*-test was calculated to determine differences between groups in the unweighted condition as well as a rmANOVA with subsequent post-hoc Bonferroni tests to compare within factors (*unweighted/weighted-early/weighted-late*) in functional dizziness patients.

Differences between the patient groups (functional dizziness patients and patients with cerebellar ataxia and chronic vestibular loss from Sağlam et al. (2014)) for all three conditions (within factor: *unweighted/weighted-early/weighted-late*) were analyzed with a rmANOVA.

3 Results

3.1 Video head impulse test and head impulse testing device function test

Patients with functional dizziness had intact vestibular function, assessed during passive head movements. Their head impulse gain ($F(1,17) = 0.13$, $P = 0.73$) and HITD-FT responses ($F(1,17) = 1.3$, $P = 0.27$) were not different from those of healthy subjects. Head impulse gains and HITD-FT scores were 1.00 ± 0.06 (mean $\pm$ SD) and $97 \pm 5\%$ for healthy subjects and 0.99 ± 0.1 and $99 \pm 2\%$ for patients with functional dizziness, respectively.

3.2 Altering head mechanics during eye-head gaze shifts to visual targets

Fig. 2 shows representative head velocity profiles from a healthy subject (top panels) and from a patient with functional dizziness (bottom). In the natural, unweighted, condition, the healthy subject performed smooth active head movements without oscillations. In contrast, in the patient with functional dizziness, there was marked head oscillation (note how head velocity undershoots the zero line). Increasing the head moment of inertia (weighted-early condition) led to head oscillations in the healthy subject, and increased head oscillations in the patient with functional dizziness. Head oscillations decreased in both the healthy subject and the functional dizziness patient after several trials with weight (weighted-late condition). This response was true for all subjects and patients. Mean head oscillation ratios (reported as mean $\pm$ standard error of the mean (SEM) in percent) for healthy subjects were 2.33 ± 0.1 for the unweighted and 8.51 ± 0.97 and 6.27 ± 0.33 for the weighted-early and -late condition, respectively. Patients with functional dizziness had head oscillation ratios of 6.02 ± 0.46 (unweighted), 13.17 ± 1.72 (weighted-early) and 11.41 ± 0.58 (weighted-late).

RmANOVA (within-factor *unweighted/weighted-early/weighted-late*) revealed significant differences in head oscillations between patients with functional dizziness and healthy subjects ($F(1,17) = 27.26$, $P < 0.001$, partial $\eta^2 = 0.62$) for the different conditions ($F(1.45,12.36) = 97.42$, corrected $P < 0.001$, partial $\eta^2 = 0.85$)

with a significant interaction ($F(1.45,24.72) = 4.28$, corrected $P = 0.036$, partial $\eta^2 = 0.2$). Functional dizziness patients had higher head oscillations than healthy subjects already in the unweighted condition (post-hoc t-test, $P < 0.001$). Increasing the head moment of inertia increased head oscillations in the functional patients (rmANOVA, $F(1.18,4.12) = 44.42$, corrected $P < 0.001$, partial $\eta^2 = 0.86$, post-hoc Bonferroni $P = 0.001$). Head oscillations decreased in these patients in the course of the gaze shifts with weight (see Fig. 3 for a time course of head oscillations with weight, post-hoc Bonferroni $P = 0.001$).

3.3 Comparison to previously acquired data from patients with chronic vestibular loss and cerebellar ataxia

Whilst different from the healthy subjects, the behavior of the functional dizziness patients was not different from that of the patients with cerebellar ataxia, and of the patients with chronic vestibular loss (reanalyzed from Sağlam et al. (2014); rmANOVA between factor: $F(2,19) = 0.56$, $P = 0.58$, no interaction $F(1.45,27.55) = 1.03$, $P = 0.39$). Head oscillation ratios were $2.09 \pm 0.09/8.8 \pm 0.5/4.84 \pm 0.21$ for the healthy subjects from the Sağlam et al. (2014) study, $3.27 \pm 0.20/16.61 \pm 1.26/11.13 \pm 0.45$ for the patients with cerebellar ataxia and $5.03 \pm 0.26/15.48 \pm 1.64/16.64 \pm 0.68$ for the patients with chronic vestibular loss (unweighted/weighted-early/weighted-late).

4 Discussion

This pilot study reveals a striking deficit in head motor control in patients with functional dizziness, which bears similarities to that of patients with cerebellar ataxia and to that of patients with severe peripheral vestibular disease (chronic bilateral vestibular de-afferentation). Knowing that an extensive work-up failed to demonstrate any explanatory peripheral vestibular, pyramidal or extrapyramidal motor or cerebellar organic dysfunction, and following the logic of expectation- and sensory-input-dependent motor control (Fig. 1), these motor control deficits are a first indication of erroneous sensory-motor processing in the central nervous system.

Already in the natural, unweighted condition, patients with functional dizziness display increased head oscillations, strikingly similar to patients without any vestibular input (bilateral vestibular loss). As the problem does not lie in peripheral sensory-motor functions, this indicates that patients have difficulties optimizing head motor commands, e.g., to match the commands to the actual mechanical head characteristics, which change over time (through weight gain or alterations in muscle stiffness). Increasing the head moment of inertia and experimentally inducing an incongruence between expected sensory consequences of the head movement and the actual vestibular input further unravels these difficulties. This leads to pronounced head oscillations in the patients with functional dizziness, similar to patients with chronic vestibular loss or cerebellar ataxia, reflecting a problem in the CNS pathway using sensory input to calculate prediction errors and update internal models

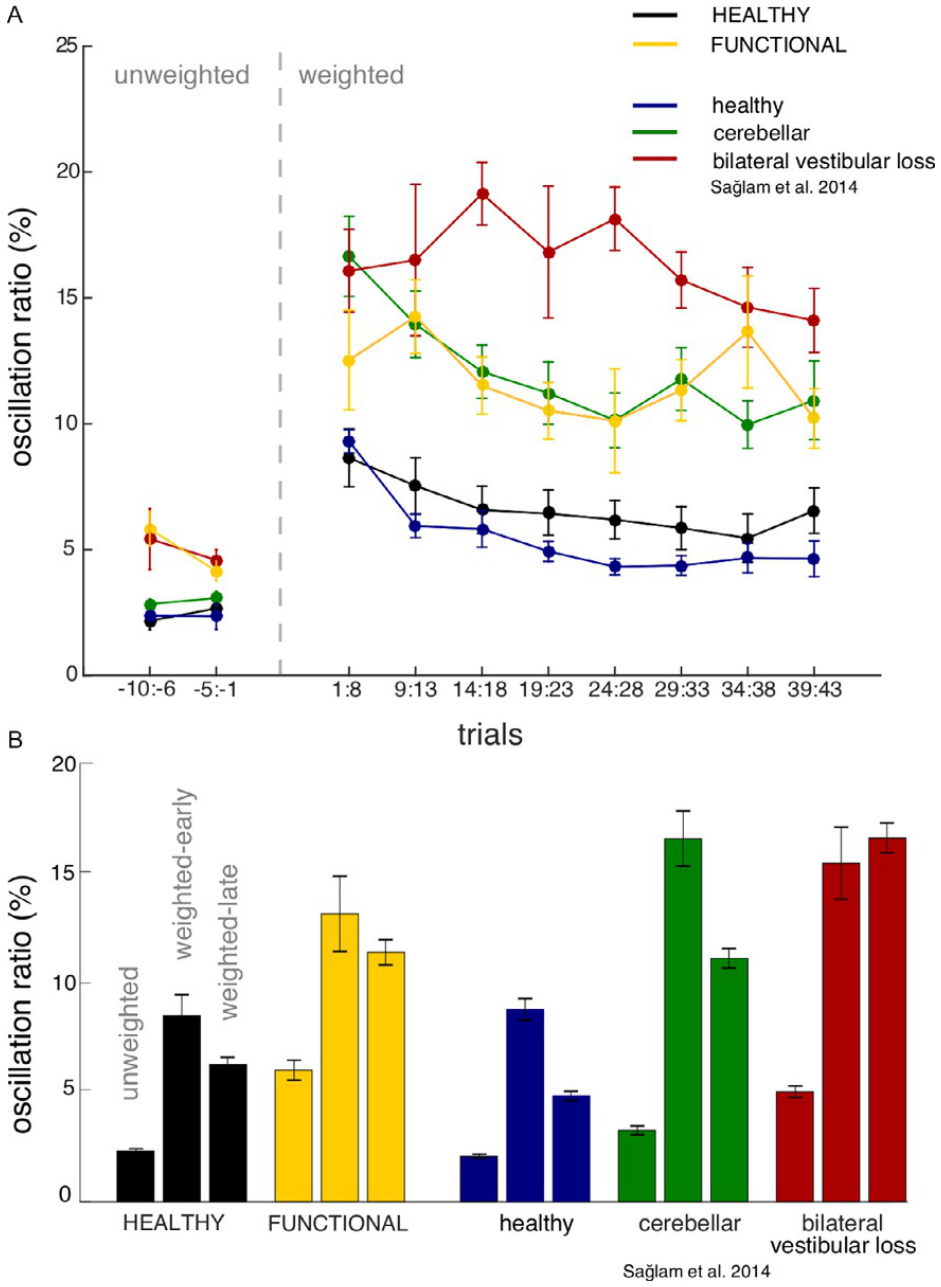

FIG. 3

Group results for head oscillations. (A) Time course of head oscillations over gaze shifts (each dot represents the average of the oscillation ratios over the trials (gaze shifts) indicated on the *x*-axis). Head oscillation ratios (means and SEM) for patients with functional dizziness (FUNCTIONAL, yellow) were different from healthy subjects (HEALTHY, black). They were not different from cerebellar ataxia (green) and chronic bilateral vestibular loss (red) patients

(Continued)

and motor commands (Fig. 1). From our results, we cannot conclude where in this pathway the problem arises. The similarities to patients with chronic vestibular loss and to patients with cerebellar ataxia point towards a pathology related to the interaction between expectation due to motor planning and sensory input. Patients with chronic vestibular loss cannot access essential sensory vestibular input (Sağlam et al., 2014), whereas cerebellar ataxia patients have difficulties forming internal models (Bastian, 2006; Wolpert et al., 1998) to predict the sensory consequences of action (Izawa et al., 2012; Synofzik et al., 2008; Tseng et al., 2007) and are even discussed to have difficulties more generally in prediction, also regarding purely sensory domains (Baumann et al., 2015; Roth et al., 2013; Therrien and Bastian, 2015). The fact that, in the weighted condition, patients with functional dizziness can decrease unwanted head oscillations to some extent is similar to cerebellar ataxia patients, and differentiates them from patients with chronic vestibular loss, who fail to optimize head motor commands and cannot decrease head oscillations (Sağlam et al., 2014).

Although its exact mechanism remains to be determined, the central sensorymotor dysfunction we find in functional dizziness patients is compatible with the recent hypothesis that persistent physical symptoms are based on perceptual dysregulation (Edwards et al., 2012; Henningsen et al., 2018a; Van den Bergh et al., 2017). In this framework, symptoms in patients with functional dizziness are thought to arise because patients are overly reliant on priorly formed but inaccurate expectations that explain the sensory input as dysfunctional. In analogy, head oscillations in this study's natural, unweighted and weighted conditions would arise because functional dizziness patients stuck to priorly formed internal models and insufficiently incorporated natural or experimental changes to the mechanical head characteristics. It is important, however, to note that patients with functional dizziness reduce head oscillations in the weighted condition and thus seem to be able to update motor commands based on sensory input. On the other hand, they display marked oscillations in the natural condition, where, if they were similarly able to update motor commands, they would have had the opportunity to do so over the thousands of eye-head gaze shifts they had performed in natural life. Thus, the ability to use sensory input might be context-dependent. In a Bayesian decision making or causal

(the healthy subjects from this prior study are denoted in blue). In the unweighted condition (last 10 trials are displayed, labeled with negative numbers on the *x*-axis), functional dizziness patients displayed increased head oscillations, similar to patients with chronic bilateral vestibular loss. Healthy subjects, functional dizziness patients, and cerebellar ataxia patients (to some extent) could reduce head oscillations in the course of several gaze shift with weight. (B) Mean and SEM of head oscillation ratios for all trials in the unweighted (left bar) and weighted condition, split up into weighted-early (first ten trials, middle bar) and weighted-late (last 33 trials, right bar) summarizing the effects for group and condition. *Data reanalyzed from Sağlam, M., Glasauer, S., Lehnen, N., 2014. Vestibular and cerebellar contribution to gaze optimality. Brain 137, 1080–1094. https://doi.org/10.1093/brain/awu006.*

inference sense, an interpretation of these results might also be that patients—though able to use sensory information to update internal models and motor commands and reduce head oscillations—have a higher tolerance for error, i.e., the threshold for activating adaptation is higher. In our experiment, when the head moment of inertia is increased, the resulting prediction error seems to be deemed relevant enough to be used for updating to some extent, the one in the natural condition not.

Changes in neuro-physiologically measurable head movement parameters like head oscillation ratio might bridge the gap between the symptoms patients suffer from and the absence of any measurable organic dysfunction. The measurable instability in the natural situation nicely reflects patient reports of feeling—not unlike patients with vestibular loss, or with cerebellar ataxia—instable and "wobbly," in particular when walking, and lends neuro-physiological legitimation to the patients' reports. Experimental similarities to patients with severe organic disease, such as cerebellar ataxia and vestibular loss, reflect similarities in symptom severity reporting (where functional dizziness patients sometimes exceed patients with organic vestibular deficits, (Best et al., 2006)), disability, as well as in participation and quality of life impairments (Eckhardt-Henn et al., 2003; Lahmann et al., 2015; Tschan et al., 2010).

With the limitations inherent to a pilot approach, this study thus provides a first glimpse into the mechanism underlying functional dizziness as an important example of persistent physical symptom. Its results support the notion that dysfunctions in the CNS interaction between sensory input and expectations about the sensory consequences of one's own actions play a role in the emergence and manifestation of these symptoms. This first answer to the "how question" of the underlying mechanism does, of course, not include an answer to the etiology question, i.e., why these inference failures manifest. Similarly, it remains to bee seen how specific the changes in head motor control are to persistent physical symptoms, as supposed to anxiety or mood disorders, for example. Nevertheless, the measurable alterations in head motor control have the potential for improving positive diagnosis, patient education, and further treatment in this patient group where diagnosis is difficult and often contested, and prognosis is rather poor (van Leeuwen and van der Zaag-Loonen, 2012).

Conflict of interest

N.L. is a shareholder and was a paid consultant to EyeSeeTec GmbH. S.G. is a shareholder of EyeSeeTec GmbH. C.R. was an employee of EyeSeeTec GmbH. L.S. and P.H. 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.

Author contribution

N.L. did study conception; C.R. collected the data; N.L., L.S., S.G., and C.R. analyzed and interpreted the data; N.L., L.S., and C.R. drafted the initial manuscript; N.L., L.S., P.H., S.G., and C.R. revised the manuscript. All authors have read and approved the final manuscript.

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Data availability statement

The datasets generated for this study are available on request to the corresponding author.

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Chapter 3

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

The current chapter encloses a research article entitled *Unstable Gaze in Functional Dizziness: A Contribution to Understanding the Pathophysiology of Functional Disorders*. The study demonstrates gaze instability in functional dizziness patients during a stabilization epoch of large gaze shifts, in which internal expectations are used to stabilize gaze, but intact gaze stabilization during a purely sensory-driven stabilization epoch. These research findings identify an incorrect use of internal expectations during sensorimotor processing as central to gaze instability, and provide evidence for the predictive processing hypothesis of functional disorders. The article was published in Frontiers in Neuroscience in 2021.

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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.

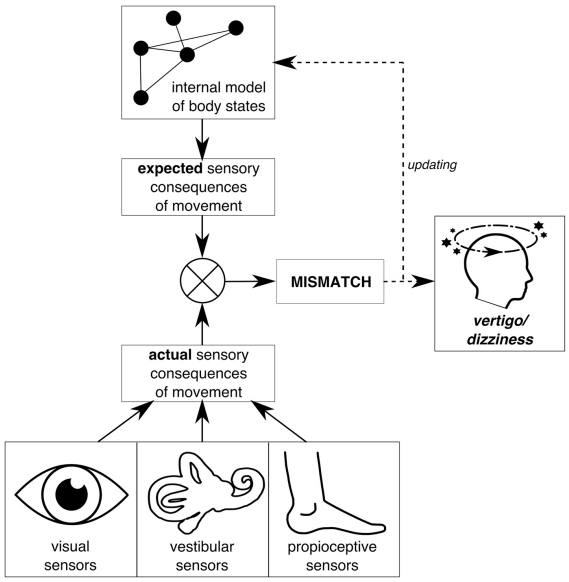

FIGURE 1 | Schematic illustration of symptom emergence in the predictive coding framework on the example of vertigo/dizziness. Predictive coding understands perception as a constant interplay between incoming sensory information and internal expectations about such sensory input. In balance perception, 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.

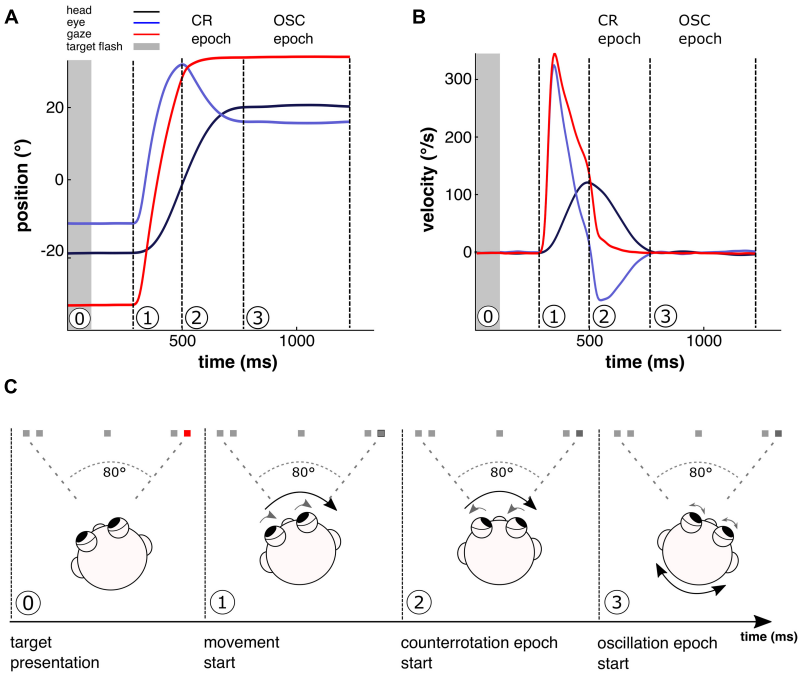

FIGURE 2 | Movement sequence over the course of a single 80° gaze shift. Shown are position **(A)** and velocity traces **(B)** of experimentally recorded eye and head movements during one exemplary 80° gaze shift as well as computed gaze movement. Gaze, i.e., the position of the eyes in space, is composed 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

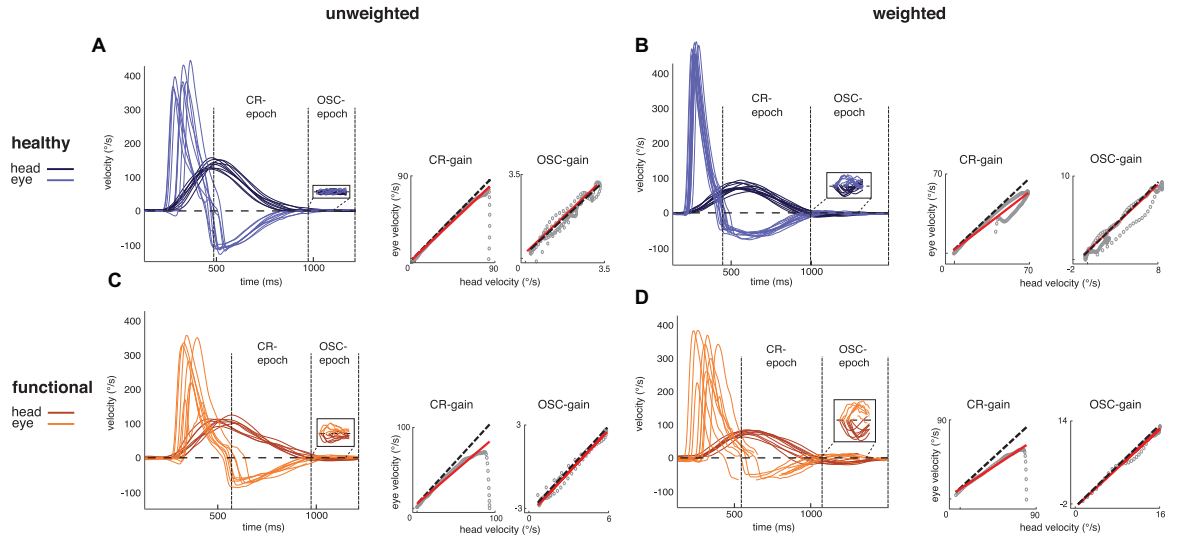

FIGURE 3 | Filtered raw data of experimental movement recordings with illustrated gain computation. **(A–D** left) Shown are representative eye (light) and head (dark) velocity traces of one typical healthy subject **(A,B)** and one typical functional patient **(C,D)** for the unweighted (natural, **A,C**) 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.

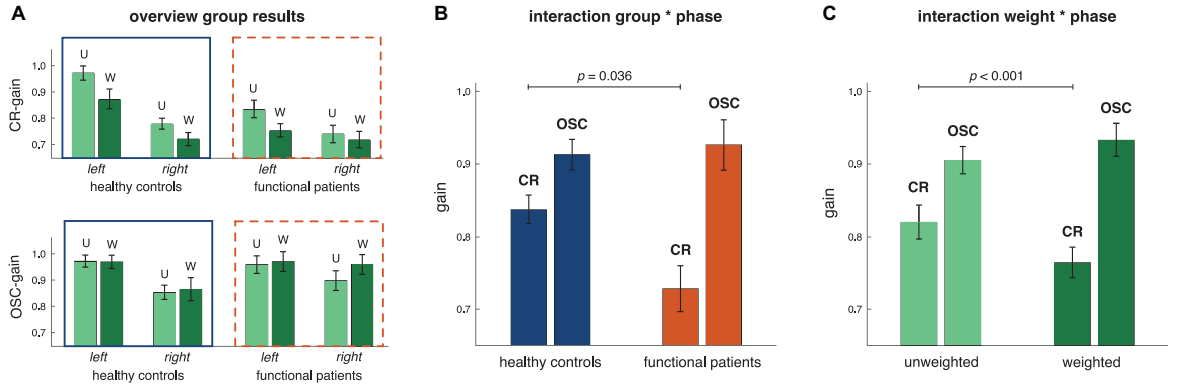

FIGURE 4 | Results of group analysis (controls n = 11, patients n = 8). **(A)** Shown are gaze gains (mean and SEM) for all factor steps of the rmANOVA, i.e., gains to the left vs. right side (within-factor *side*, left group vs. right group of bars), unweighted (U) vs. weighted (W, within-factor *weight*, 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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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 4

Altered Sensorimotor Processing in Irritable Bowel Syndrome: Evidence for a Transdiagnostic Pathomechanism in Functional Somatic Disorders

The current chapter encloses a research article entitled *Altered Sensorimotor Processing in Irritable Bowel Syndrome: Evidence for a Symptom-Unspecific Pathomechanism in Functional Disorders*. The study shows head sensorimotor processing deficits of IBS patients during gaze shifts with experimentally altered head characteristics, reflected by increased head oscillations. These processing alterations reflect deficits in adapting to the new context of increased head moment of inertia, possibly due to an incorrect use of internal expectations. Importantly, these deficits were demonstrated for signal processing outside the affected body region, pointing at general, symptom-unspecific processing deficits in functional disorders. The article was published in Frontiers in Neuroscience in 2022.

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Altered sensorimotor processing in irritable bowel syndrome: Evidence for a transdiagnostic pathomechanism in functional somatic disorders

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Objective: A recent hypothesis suggests that functional somatic symptoms are due to altered information processing in the brain, with rigid expectations biasing sensorimotor signal processing. First experimental results confirmed such altered processing within the affected symptom modality, e.g., deficient eye-head coordination in patients with functional dizziness. Studies in patients with functional somatic symptoms looking at general, trans-symptomatic processing deficits are sparse. Here, we investigate sensorimotor processing during eye-head gaze shifts in irritable bowel syndrome (IBS) to test whether processing deficits exist across symptom modalities.

Methods: Study participants were seven patients suffering from IBS and seven age- and gender-matched healthy controls who performed large gaze shifts toward visual targets. Participants performed combined eye-head gaze shifts in the natural condition and with experimentally increased head moment of inertia. Head oscillations as a marker for sensorimotor processing deficits were assessed. Bayes statistics was used to assess evidence for the presence or absence of processing differences between IBS patients and healthy controls.

Results: With the head moment of inertia increased, IBS patients displayed more pronounced head oscillations than healthy controls (Bayes Factor $_{10}$ = 56.4, corresponding to strong evidence).

Conclusion: Patients with IBS show sensorimotor processing deficits, reflected by increased head oscillations during large gaze shifts to visual

targets. In particular, patients with IBS have difficulties to adapt to the context of altered head moment of inertia. Our results suggest general transdiagnostic processing deficits in functional somatic disorders.

KEYWORDS

irritable bowel syndrome (IBS), functional somatic disorders, somatoform disorders, predictive processing, transdiagnostic mechanism, gaze shift

Introduction

Recently, it was hypothesized that functional somatic symptoms, i.e., debilitating physical symptoms in the absence of a sufficiently explaining organic deficit, emerge, and manifest as a result of erroneous sensorimotor processing (Edwards et al., 2012; Van den Bergh et al., 2017; Henningsen et al., 2018; Pezzulo et al., 2019). This theory is based on predictive processing, a neurobiological framework describing normal brain function (Srinivasan et al., 1982; Mumford, 1992; Rao and Ballard, 1999; Friston, 2002; Knill and Pouget, 2004; Aitchison and Lengyel, 2017). The brain constantly manages situations in which sensory input is ambiguous or noisy ("perceptual problem," first described in von Helmholtz, 1867) by integrating prior knowledge that anticipates sensory information into the perceptual process. Expectations derived from central nervous system (CNS)-internal models representing learned causal relationships in the world and within the body are tightly interwoven with information provided by body sensors already at low hierarchical levels in the brain (Shams and Beierholm, 2010; Hohwy, 2013). This leads to perceptions and actions that always include the product of both, prior knowledge and sensory input. Adaptive behavior in a rapidly changing environment is only possible when this interaction is highly flexible: new situations require more focus on sensory input, as prior knowledge about the situation is still lacking, while during well-known situations, it is beneficial to rely on (successfully acquired) knowledge from the past rather than considering each sensory fluctuation (Clark, 2013; Rauss and Pourtois, 2013). In the case of functional somatic symptoms, it is now assumed that this fine-tuned information processing system is out of balance, so that rigid expectations dominate sensory input during sensorimotor processing, leading to symptom perception (Edwards et al., 2012; Van den Bergh et al., 2017; Henningsen et al., 2018; Pezzulo et al., 2019).

There is experimental evidence for such processing deficits in functional somatic symptoms and disorders (Bogaerts et al., 2010; Van Den Houte et al., 2017; Lehnen et al., 2019; Schröder et al., 2021). In an eye-head coordination paradigm (first described in Lehnen, 2006), patients with functional dizziness showed poorer head motor control compared to healthy controls. Patients displayed stronger head oscillations at the end of a gaze shift, reflecting adaptation deficits in sensorimotor processing, possibly due to incorrect internal expectations (Lehnen et al., 2019). Another study found that gaze movements are also unstable during such large gaze shifts in patients with functional dizziness (Schröder et al., 2021). This was only observed in situations where prior knowledge and sensory information interacted with each other, not during purely sensory-driven stabilization. Taken together, these two studies provide evidence for erroneous internal model/expectation use in sensorimotor processing in functional dizziness. Here, erroneous processing is directly linked to the symptom modality, i.e., the vestibular system for gaze motor control. Similarly, Bogaerts et al. (2010) investigated perception of breathlessness in patients with functional dyspnea and healthy controls. After experimental induction of breathlessness by increasing the carbon dioxide (CO_2) concentration in the inhaled air, patients reported sustained breathlessness even after CO_2 levels had normalized again. Symptom perception was uncoupled from sensory input and was explained by the influence of prior knowledge altering sensorimotor processing within the perceptual process.

Interestingly, in the described re-breathing paradigm, characteristic alterations in symptom perception were not only found in patients with functional dyspnea, but also for patients with other functional somatic disorders, i.e., fibromyalgia and chronic fatigue syndrome (Van Den Houte et al., 2018). This raises the question whether there are generally transdiagnostic alterations in sensorimotor processing in all functional somatic disorders. To explore this research question in more depth, we applied the gaze shift paradigm, which had previously revealed processing deficits in functional dizziness, to patients with irritable bowel syndrome (IBS). So far, no experimental studies have demonstrated sensorimotor processing deficits in patients with IBS. With its symptoms

Abbreviations: CO_2, Carbon dioxide; IBS, Irritable Bowel Syndrome; ICD-10, 10th version of the International Statistical Classification of Diseases and Related Health Problems; DSM-5, Diagnostic and Statistical Manual of Mental Disorders, Version 5; SCID-5-CV, Structural Clinical Interview for DSM-5—Clinician Version; vHIT, video-assisted Head Impulse Test; LED, Light Emitting Diode; rmANOVA, repeated measures Analysis of Variance; BF, Bayes Factor.

arising predominantly in the lower gastrointestinal tract, the clinically relevant symptoms of IBS may not directly be linked to the gaze motor control system and therefore suitable to study general sensorimotor processing deficits across organ systems. The gaze shift paradigm investigates head oscillations during gaze shifts under increased head moment of inertia as a marker for sensorimotor processing deficits. This has been demonstrated in patients with functional dizziness (Lehnen et al., 2019), patients with cerebellar ataxia (Sağlam et al., 2014), and patients with bilateral vestibulopathy (Lehnen et al., 2009; Sağlam et al., 2014). Importantly, these studies show that within one single head movement, both, correct vestibular processing as well as intact feedforward prediction are necessary to reduce head oscillations under increased head moment of inertia. This is different from predictability in motor learning. In line with the findings from Van Den Houte et al. (2018), we assumed that general symptom-unspecific processing deficits are present in functional somatic disorders. Specifically, we hypothesized that when experimentally subjected to increased head moment of inertia, patients with IBS will show higher head oscillations than healthy controls.

Materials and methods

Participants

For this experimental study, seven patients suffering from IBS [age 33 ± 11, mean and standard deviation (SD), 4 women] and seven age- and gender-matched healthy controls (age 33 ± 13, mean and SD, 4 women) were included. *A priori* sample size estimation in a power analysis ($\alpha = 0.05$, $\beta = 0.8$) based on group differences in our previous studies on functional dizziness (partial $\eta^2 = 0.62$, Lehnen et al., 2019) revealed three participants required for each group. Due to this small number, we increased sample size gradually and used Bayesian statistics that allows for stopping testing when data gives sufficient support for the hypothesis (Wagenmakers et al., 2012; Rouder, 2014).

Patients were recruited from a specialized outpatient clinic for Neurogastroenterology and Motility of the University Hospital Zurich as well as the in- and outpatient clinic of the Department of Psychosomatic Medicine and Psychotherapy of the University Hospital of the Technical University Munich. All patients fulfilled the diagnostic criteria of somatoform autonomic dysfunction of the lower gastrointestinal tract according to ICD-10, which was the inclusion diagnosis (F45.32, World Health Organization, 2004). After Rome IV criteria (Rome Foundation, 2016), six patients fulfilled the diagnosis of an IBS, one patient had functional constipation. After S3-guidelines, all patients had IBS (Layer et al., 2021; for a detailed description of the clinical characteristics of this patient group, see **Table 1**). Importantly, for all patients, previous gastrointestinal workups including a colonoscopy did not reveal any organ pathology accounting for the patients' symptoms. Patients did not have any other persisting somatic symptoms corresponding to a somatic symptom disorder, as assessed with the structural clinical interview for DSM-5 on the day of the study (German version of the SCID-5-CV; Beesdo-Baum et al., 2019).

Healthy controls were recruited from the staff of the University Hospital of the Technical University Munich as well as the staff of medical practices and student groups around Munich. On the day of study conduction, they did not fulfill the criteria of a psychiatric disorder according to the German version of the SCID-5-CV (Beesdo-Baum et al., 2019), and, in particular, did not report any current or previous persisting somatic symptoms of functional nature.

All participants had no history of balance disorders. Additionally, to test for an intact vestibular system on the day of study conduction, we performed a video-assisted head impulse test (vHIT) after the vHIT manual of EyeSeeCam (EyeSeeTec GmbH, Munich, Germany), which was normal in patients as well as healthy controls.

The study was designed in line with the Declaration of Helsinki (version from 2008). The Ethics Committee of the Technical University Munich approved the study protocol prior to study conduction. The Ethics Commission of the Kanton Zurich stated that no additional approval was necessary, as study and data responsibility was in Munich alone. All participants provided written informed consent and received a compensation of 10€ per hour.

The current study is part of the innovative training network ETUDE (Encompassing Training in functional Disorders across Europe; https://etude-itn.eu/; see Rosmalen et al., 2021), ultimately aiming to improve the understanding of mechanisms, diagnosis, treatment and stigmatization of Functional Disorders.

Experimental task

Participants were seated in front of a desk, where five light emitting diodes (LEDs) were placed at eye level in the vertical plane. In the horizontal plane, one LED was placed in front of participant's head, two LEDs were placed on each side, left, and right, in 70 and 83 cm distance to the central LED. Then, the seating position was adjusted so that the distance from participant's eyes to the central LED amounted to 1 m. In consequence, from the participant's perspective, gaze shifts toward flashing LEDs corresponded to 0°, 35°, 70°, 75°, and 80° amplitude. During one experimental round, target light was presented 52 times, requiring 52 gaze shifts in total. It is important to note that the target was off during gaze movement

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TABLE 1 Description of patients' characteristics.

	Symptom occurrence			Symptom types					
Patient	Onset (years)	Frequency (days/week)	Duration (hours)	Abdominal pain	Cramps	Diarrhea	Obstipation	Bloating	Flatulence
1	4	7	12	x		x		x	
2	6	3	0.5–24	x	x	x		x	x
3	1	7	6	x		x		x	x
4	10	7	24		x	x		x	x
5	5	3	5–8	x	x		x		
6	4	3	24	x				x	
7	2	7	3		(x)	(x)	x	x	x

The table provides an overview about symptom criteria of included patients with IBS. Symptom onset describes how many years ago the symptoms first appeared, symptom frequency describes how often symptoms occur on average during the week and duration describes the average time of symptom presence during the day. The type of reported abdominal symptoms by each patient is also shown.

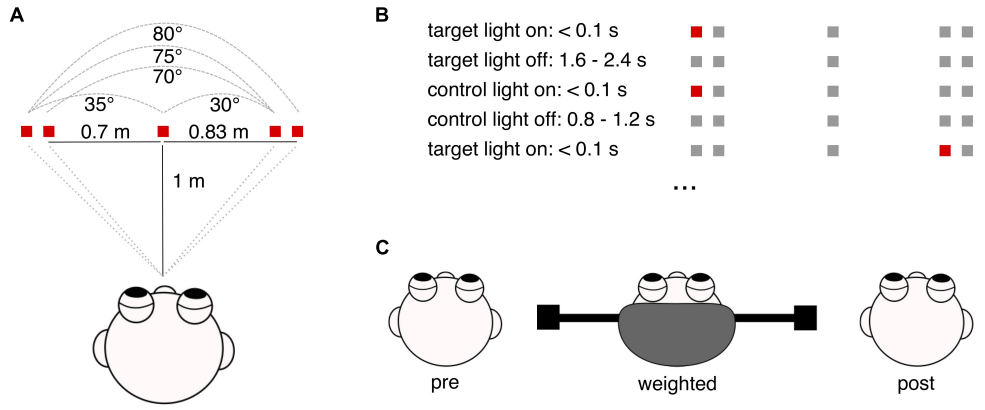

FIGURE 1
Graphical illustration of the experimental paradigm. **(A)** Shown is the experimental setup in the horizontal plane, with the distances of LEDs to each other and to the participant's middle head position as well as the resulting gaze shift amplitudes. **(B)** Depiction of the experimental paradigm. For illustration of the experimental timing, an exemplary sequence of target and control lights is presented. Each trial, i.e., one gaze shift towards the target, starts with target flash for less than 0.1 s. This is followed by a sequence of 1.6–2.4 s where the target light is off again. During this period, i.e., without visual input, participants perform a gaze shift towards the target. Then, a control light is flashed at target position, also for less than 0.1 s. In the following period of 0.8–1.2 s, with the control light being off, participants can adjust final gaze position depending on the feedback they received by the control light. The next target flash presents the start of the next trial, requiring another gaze shift (here, the gaze shift amounts to 75°). In total, participants performed 52 gaze shifts. **(C)** Depicted is the order of the three experimental rounds: pre, weighted and post-condition. The drawing illustrates the construction of the experimental helmet, with masses being attached eccentrically at each side.

to avoid instantaneous visual feedback. To achieve this, LEDs were flashed in complete darkness for less than 0.1 s. The time interval between the light flashes (1.6–2.4 s) as well as their order were randomized to prevent anticipation.

We instructed participants to direct their gaze to the flashing LEDs in a natural manner, using combined eye-head movements. Once final gaze position was achieved, participants were asked to hold their gaze stable until the next target was flashed. To ensure that participants hold final gaze position, after the actual gaze shift, a control light was flashed at target position, with a 0.8–1.2 s time window before the next target light appeared (Figure 1). Participants were told that they may use the second flash as feedback to adjust gaze position.

Participants performed three rounds of this experimental task. First, 52 gaze shifts were performed in the natural condition (pre). Then, we increased participants' head moment of inertia to the 3.1-fold by using a specially designed helmet with eccentrically placed masses on the left and right side. After executing all 52 gaze shifts with the helmet (weighted), participants completed a third round of the experiment without the helmet again (post). All participants had no experience in wearing the helmet and were naïve to the experimental hypotheses.

We recorded participants' eye and head movements with the EyeSeeCam measuring system (EyeSeeTec GmbH, Munich, Germany). The system uses video-oculography to track eye

movements and 3D inertial sensors to track head movements with a sampling rate of 220 Hz. The camera was adjusted to record movements of the left eye, the inertial sensors were attached between both eyes in the middle of the forehead.

Data analysis

Data analysis was conducted offline using MATLAB (MathWorks, Natick, MA, United States). To investigate head movements as part of large horizontal gaze shifts toward visual targets, head velocity in the horizontal plane was obtained from the 3D inertial sensor recordings of the EyeSeeTec measuring system. Head data was then filtered with a 20 Hz Gaussian low pass filter. To estimate the amplitude of the whole eye-head gaze shift, head velocity was further integrated over time to estimate head position. Eye position in the horizontal plane was computed from pupil rotation vectors and was also filtered with a 20 Hz Gaussian low pass filter. Gaze position in space was then computed as the sum of the eye and head position, as eye position was measured in relation to the head and head position was measured in relation to space. Subsequently, the continuous filtered eye, head, and gaze data streams were cut into single trials, so that each movement sequence corresponded to one gaze shift. Trial start was defined as the onset of the target light, trial end was defined as the onset of the control light. Head movements were analyzed during the actual gaze shift period toward the target; possible small corrections of gaze position after presenting the control light were not evaluated in this analysis. Of all 52 gaze shifts, only gaze shifts with a target amplitude of 75° or 80° were considered for the analysis, resulting in 43 valid trials. Furthermore, only gaze shifts with an executed amplitude of at least 40° were included in the analysis.

For each trial, head oscillations were assessed according to Lehnen et al. (2019) and computed as the first undershoot of head velocity at the end of the active head movement toward the target, normalized by peak velocity of the head movement. This was implemented by detecting the maximum of head velocity during the whole trial and the minimum of head velocity between the first zero crossing (head velocity undershoots and becomes negative) and the second zero crossing (head velocity becomes positive again, the first oscillation is terminated). The absolute value of the undershoot was then divided by peak head velocity. Head oscillations were detected automatically and, in case detection errors were identified during visual inspection, were corrected manually. In total, in 5% of healthy controls' gaze shifts and 10% of the patients' gaze shifts, detected maxima and minima were corrected. Only trials where the peak head velocity as well as the velocity of the undershoot could be detected were considered for the analysis.

In case of a predictive response, i.e., participants performed the gaze shift before the target light was flashed, the movement window before the actual target light presentation was included into the analysis (on average 3.3% of the gaze shifts for patients and 0.5% for healthy controls). This was done to include as many gaze shifts as possible. Similarly, if a gaze shift was executed delayed, i.e., when head oscillation was not terminated before the control light was presented, the movement window after the target light window was added to the analyzed movement sequence, affecting 6.2% of the trials for patients and 3.3% of the trials for healthy controls.

Head oscillations were computed for each of the three experimental rounds (pre, weighted, and post condition). In a subsequent outlier analysis, head oscillations outside the range of 2 SDs from the mean of the respective subject and condition were removed from the analysis. On average, for every experimental round 36 ± 5, 36 ± 9, and 36 ± 6 of the 43 trials per condition were considered for the IBS patients and 38 ± 4, 40 ± 1, and 40 ± 2 for the healthy control group for the three experimental conditions pre, weighted and post, respectively.

Statistical analysis

Data were analyzed offline using MATLAB (MathWorks, Natick, MA, United States) and JASP (JASP Team, 2019, Version 0.15).[1] Mean values of head oscillations were computed for each participant and each condition. Shapiro Wilk test was used to test for normality assumption in all groups and conditions, with a significance level of $p = 0.05$. For hypothesis testing, a Bayes repeated measures ANOVA (rmANOVA) was computed to test for differences in head oscillation between patients with IBS and healthy controls (between-factor *group*) for the three experimental rounds (pre, weighted, post; within-factor *weight*). For *post hoc* comparisons, Bayesian dependent and independent *t*-tests were computed. Bayesian statistics was used because of its possibilities to find evidence for the null hypothesis (Rouder et al., 2007; Wagenmakers, 2007), and to evaluate evidence during accumulation so that testing can be stopped when sufficient support for a hypothesis is given (Wagenmakers et al., 2012; Rouder, 2014).

In a Bayes rmANOVA, all measuring factors as well as their combinations and interactions are considered as models to explain the dataset (see e.g., Wagenmakers et al., 2018; van Doorn et al., 2021). Before testing, the models are assigned with the same prior probability, so that all models are equally likely before seeing the data. In our scenario, with one repeated measures factor and one group factor, there are five possible models to explain the data (*weight*, *group*, *weight* + *group*, *weight* + *group* + *weight*group*, null model), so each model receives a prior probability of 0.2. Then, using Bayes statistics, the posterior probability is computed, indicating how likely a model is given the data. The model which fits best to the data receives the greatest proportion of posterior probability.

1 https://jasp-stats.org

Therefore, the posterior probability provides the most relevant output in terms of evaluating evidence of models/effects. To compare models, a Bayes Factor (BF) is computed that shows the ratio between the posterior probabilities of two models. For hypothesis testing, the posterior probability of a model is typically compared to the null model (BF_{10}). BF_{10} indicates how many times the model explains the data better than the null model. A BF_{10} of 1 shows that the posterior probability of the null model and the model are the same, so no evidence for the presence or the absence of an effect is given. With increasing BF_{10}, it becomes more and more likely that an effect is present. Conventions evaluate a BF_{10} between 1 and 3 as anecdotal evidence, between 3 and 10 as moderate evidence, between 10 and 100 as strong evidence, and above 100 as extreme evidence for the presence of an effect (Wagenmakers et al., 2018). Importantly, as the null model is assigned with a posterior probability, the BF_{10} can also show evidence for the absence of an effect (Rouder et al., 2007; Wagenmakers, 2007). BF_{10} between 1/3 and 1 is evaluated as anecdotal evidence, between 1/3 and 1/10 as moderate evidence, between 1/10 and 1/100 as strong evidence and below 1/100 as extreme evidence in favor of the null hypothesis.

For comparability with our previous studies, we also computed a frequentist rmANOVA to assess differences in head oscillations over the three experimental rounds (pre, weighted, post; within-factor *weight*) and between patients with IBS and healthy controls (between-factor *group*). For *post hoc* comparisons, dependent and independent *t*-tests with Bonferroni corrected α-levels were computed.

Results

Group analysis with a Bayesian rmANOVA revealed that the model which included the factor *weight*, the factor *group* as well as their interaction was most likely given the data (*weight* + *group* + *weight***group*: $BF_{10} = 3.4*10^{10}$, corresponding to an extreme effect). To look at the contribution of each factor to explain the data, effect sizes were computed. They estimate the likelihood of models in which the factor was included in comparison to models in which the factor was excluded. The BF for inclusion (BF_{incl}) of the factor *weight* was $2.9*10^{10}$, BF_{incl} for *group* was 7 and BF_{incl} for the *weight***group* interaction was 5.4, demonstrating extreme evidence for *weight* and moderate evidence for *group* and their interaction.

Post hoc testing for group differences revealed that with strong evidence (BF_{10} = 56.4), patients had higher head oscillations in the weighted condition than healthy controls (see **Table 2** for mean head oscillation values and **Figure 2** for head velocity traces of all participants in the weighted condition). With anecdotal evidence (BF_{10} = 0.6), groups did not differ in the pre-condition (see **Figure 3** for representative head movements over all three conditions). In the post-condition, no evidence was found for or against a group difference in head oscillations (BF_{10} = 1). We conducted further *post-hoc* tests to reveal potential differences in head oscillations between the three experimental conditions. With extreme (patients: BF_{10} = 208.1) and moderate (controls: BF_{10} = 5.1) evidence, increasing the head moment of inertia increased head oscillations. There was also extreme evidence that head oscillations decreased again after the weights had been removed (patients: BF_{10} = 443.2; controls: BF_{10} = 162.6). Importantly, with moderate evidence, head oscillations were smaller in the post- than in the pre-condition, but only in patients (BF_{10} = 5.8), not in controls (BF_{10} = 0.7).

TABLE 2 Head oscillation values.

	Condition		
Group	**Pre**	**Weighted**	**Post**
Patients	4.1 ± 0.66	10.4 ± 0.45	2.6 ± 0.56
Controls	2.9 ± 0.99	6.9 ± 0.56	1.6 ± 0.16

Shown are all mean head oscillation values in percent with the standard error of the mean (SEM) for all experimental conditions (within factor *weight*) for patients as well as controls (between factor *group*).

One healthy control showed extremely high head oscillations in the pre-condition (**Figure 4**), with a value ranging > 2 *SD* above participants' mean value. Excluding this participant did not alter the direction of study results, as the model *weight* + *group* + *weight***group* was still the most likely model given the data ($BF_{10} = 8.4 \times 10^{12}$). However, effect sizes became notably larger for the two factors (*weight*: $BF_{incl} = 4 \times 10^{12}$; *group*: BF_{incl} = 45.1) and their interaction (BF_{incl} = 8.7). In *post hoc* testing, the head oscillation difference between patients and healthy controls in the pre-condition additionally showed moderate evidence (BF_{10} = 4), possibly because of the small inertia alterations the goggles create themselves. Differences between the pre- and the weighted condition in healthy controls altered from moderate to strong evidence (BF_{10} = 32.8).

Due to technical issues, few of the experimental rounds were performed without the control light being present (patient one: all three sessions; patient four: pre-session), using the design of our previous studies (e.g., Lehnen et al., 2019). When excluding these patients from the analysis, the results did not change (best model: *weight* + *group* + *weight*× *group*; $BF_{10} = 1.1 \times 10^{8}$), although, due to smaller sample size, BF and effect sizes became smaller when excluding these patients.

For comparability with previous studies, we also computed a frequentist rmANOVA. Results showed a significant main factor weight [$F_{(2,\ 24)} = 73.7$; $p < 0.001$; partial $\eta^2 = 0.69$] and a significant main factor group [$F_{(1,\ 12)} = 10.3$; $p = 0.007$; partial $\eta^2 = 0.08$]. That is, both patients and healthy controls had higher head oscillations in the weighted condition and, overall, patients had higher head oscillations than controls. The interaction *weight*× *group* did not reach statistical significance

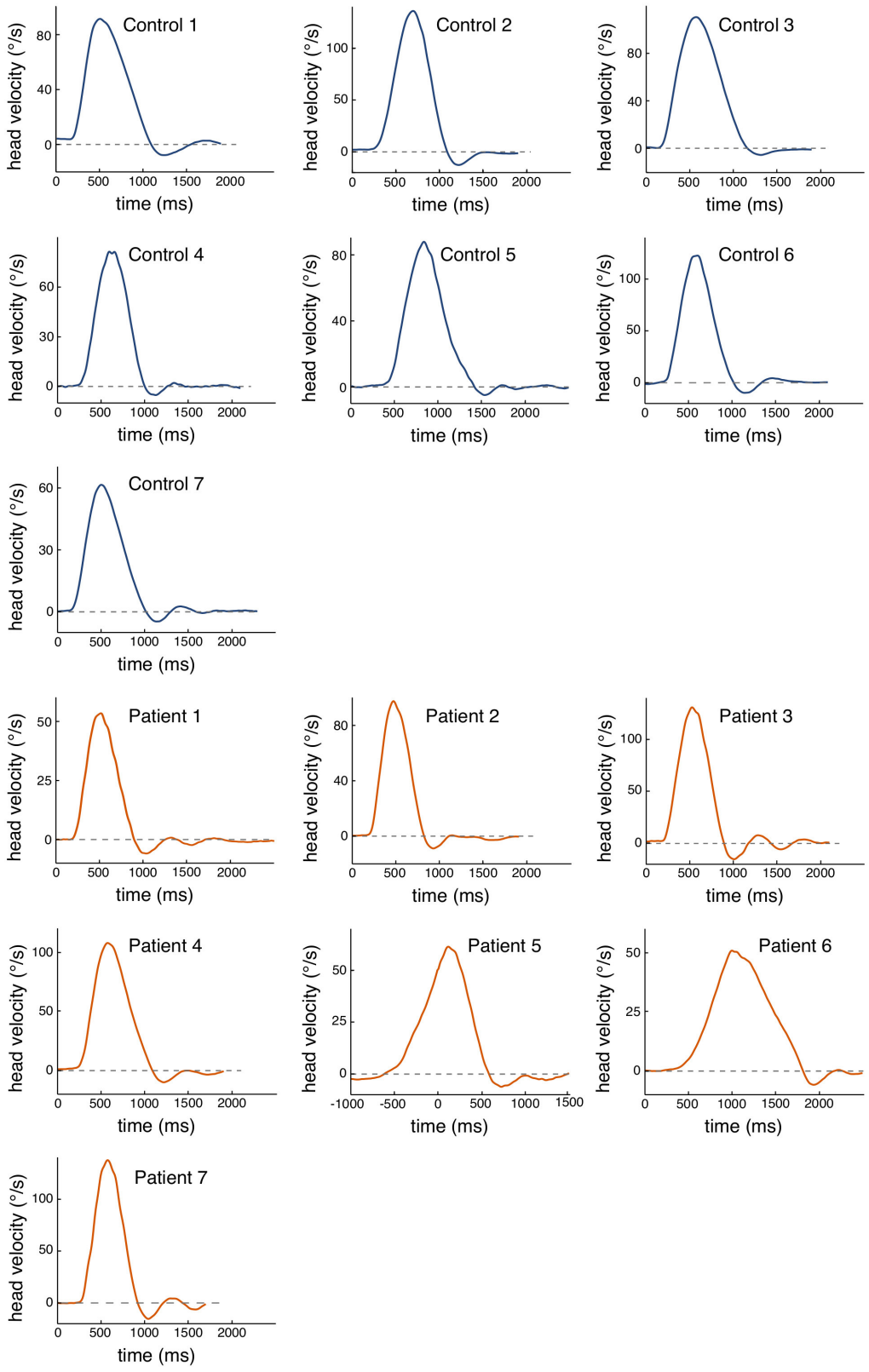

FIGURE 2
Raw data of head velocity profiles for each participant for the weighted condition. The traces represent one head movement toward the target with an oscillation and peak head velocity value that represents the mean of the respective subject. Blue traces are exemplary movements for healthy controls, orange traces show movements for each IBS patient. The dashed line represents the zero line.

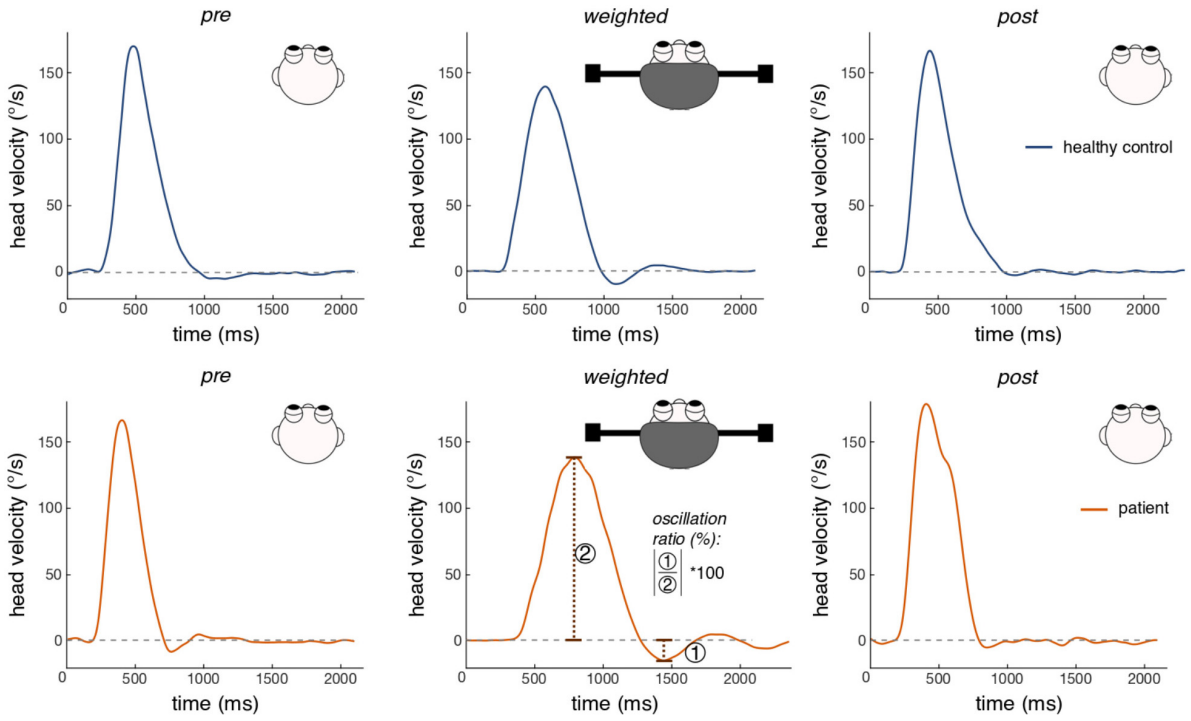

FIGURE 3
Exemplary head movements of one healthy participant and one patient for each experimental condition. Shown are head velocity profiles of one gaze shift toward a flashing visual target in 75° horizontal distance. Blue traces are exemplary movements of a healthy participant, orange traces are exemplary movements of one patient. Traces were selected to illustrate mean head oscillation values of healthy controls and patients with IBS in each of the three conditions. The dashed line indicates a head velocity value of zero. Head oscillations are defined as the minimal value of head velocity under the zero line (undershoot), normalized by peak head velocity (see the velocity trace of the patient for the weighted condition for an illustration of head oscillation computation). Both participants showed increased head oscillations in the weighted condition, which was more pronounced in the patient.

[$F_{(2,\ 24)} = 3.1$; $p = 0.062$]. Both groups displayed higher head oscillations in the weighted condition compared to the pre-condition ($p < 0.001$) and the post-condition ($p < 0.001$), while there was no evidence for differences in head oscillations between the pre- and the post-condition ($p = 0.057$). In line with the Bayesian analysis, excluding the healthy control with a mean oscillation value of 2 SD above the group's mean altered the study results. In addition to the main effects [*weight*: $F_{(2,\ 24)} = 119$; $p < 0.001$; partial $\eta^2 = 0.74$; *group*: $F_{(1,\ 17)} = 20.8$; $p < 0.001$; partial $\eta^2 = 0.11$], the *weight*group* interaction became significant [$F_{(2,\ 24)} = 3.6$; $p = 0.04$; partial $\eta^2 = 0.02$]. In the weighted condition, patients had increased head oscillations compared to healthy controls ($p < 0.001$). This was not the case for the pre- ($p = 0.086$) and post-condition ($p = 1$).

Discussion

We found experimental evidence for a general transdiagnostic processing deficit in patients with IBS, who showed poorer head motor control, reflected by increased head oscillations during gaze shifts with increased head moment of inertia, compared with healthy controls. Altering the head mechanics, e.g., by increasing the head moment of inertia, introduces a mismatch between the intended and executed head movement, so that the actual sensory consequences of the head movement do not match expectations. This mismatch becomes visible in poorer head motor control, reflected by involuntary head oscillations at the end of a head movement, as head alterations are not yet incorporated in internal models of the head for sensorimotor planning. Similar to previous studies (Lehnen, 2006; Lehnen et al., 2008, 2009, 2019; Sağlam et al., 2011, 2014), in the present study, increased head inertia led to higher head oscillations in all participants. Notably, during gaze shifts under increased head moment of inertia, head oscillations of patients with IBS were more pronounced than in the healthy control group, indicating processing deficits in patients with functional somatic symptoms reaching beyond a "normal" reaction to altered head properties.

Predictive processing theory in functional somatic disorders states that persisting somatic symptoms emerge and manifest due to altered sensorimotor processing. That is, rigid expectations dominate sensory input, so that the perception of body signals becomes more and more independent from actual

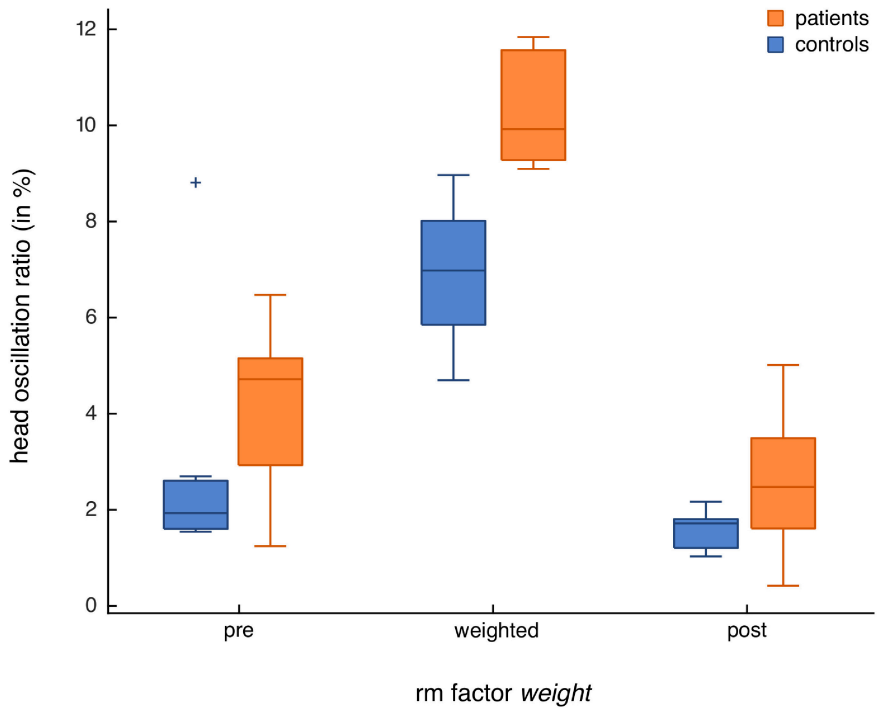

FIGURE 4
Head oscillations of healthy controls (n = 7) and patients with IBS (n = 7) for all three experimental conditions. Shown are boxplots for the repeated measures (rm) factor *weight*, with a separate box for each condition (pre, weighted, post). Results for patients are shown in orange and those for healthy controls in blue. Note the outlier in the healthy control group in the natural condition that was > 2 SD above the participants' mean.

body states (Edwards et al., 2012; Van den Bergh et al., 2017; Henningsen et al., 2018; Pezzulo et al., 2019). In the present study, the use of such rigid expectations could explain poorer head motor control in patients with IBS under increased head inertia. The altered head properties constitute a new context that requires the use of sensory input to adapt expectations to these alterations and subsequently reduce head oscillations. If, as hypothesized, patients rely too much on expectations during sensorimotor processing, this would impair such flexible adaptation processes. Sensory signals would not be sufficiently used to "tell" the brain what is going wrong in head motor control, and, as a consequence, head oscillations would remain increased during gaze shifts under increased head inertia. In contrast, healthy controls can use sensory input to reduce head oscillations.

Increased head oscillations as a marker for impaired sensorimotor processing have also been demonstrated in patients with functional dizziness (Lehnen et al., 2019), a patient group with symptoms directly linked to gaze motor control. However, processing deficits were clearly stronger in the functional dizziness group than in patients with IBS when comparing effect sizes (effect sizes for differences to healthy controls in functional dizziness: partial η^2 = 0.62; IBS: partial η^2 = 0.08). This indicates that erroneous sensorimotor processing is stronger in the impaired modality, possibly playing a central role in symptom emergence and manifestation. However, as the present results show, the processing of sensorimotor signals in patients with other functional somatic symptoms (here: patients with functional gastrointestinal symptoms) is also affected in an attenuated way. These alterations might not be strong enough to present a measurable correlate for already manifested symptoms, as none of our patients with IBS reported signs of dizziness, but they may display a general impairment, putting patients at risk for developing new symptoms. Further studies investigating additional patient groups with different somatic symptom localizations should be conducted to support this speculation. Whereas measuring more patients for generalizability is certainly warranted, it is worthwhile to mention the astonishing power of the current results, reflected in an *a priori* sample size estimation of three in the affected modality and moderate to strong evidence for transdiagnostic effects with a sample size of seven.

Experimental studies specifically focusing on the interplay between expectations and sensory input within interoceptive processing of patients with IBS are still lacking. Nevertheless, many studies have investigated interoception in the gut. Patients with IBS report non-painful and painful stimuli earlier when

stimulus strength is continuously increased (e.g., Ritchie, 1973; Mertz et al., 1995; Whitehead and Palsson, 1998; Verne et al., 2001; Bouin et al., 2002; Azpiroz et al., 2007; Barbara et al., 2011). This effect increases with symptom severity (Posserud et al., 2007; Simrén et al., 2018). In predictive processing, such earlier stimulus reports can be explained by overly reliant stimulus expectations that lower the stimulus strength needed for perception. Importantly, perceptual alterations in patients with IBS have also been demonstrated for other, non-visceral body locations: patients show altered responses in perceiving electrical, cold or heat stimulation of the skin on hands and feet (Bouin et al., 2001; Verne et al., 2001; Iovino et al., 2006; Zhou et al., 2010). These results are in line with our experimental findings, pointing at general, to symptom-unspecific processing alterations in patients with IBS. However, such rather subjective read-outs like reports of perceptual changes are not directly linked to the mostly unconscious perceptual processing steps in the brain and only represent a small proportion of the underlying mechanisms, i.e., the final perception. Also, such reports can underly cognitive and motivational biases that are known from research on decision making (Kahneman et al., 1982; Gilovich et al., 2002). By using a behavioral read-out that is less prone to cognitive strategies, we overcame these obstacles, providing novel evidence for altered sensorimotor processes in this group of patients with functional symptoms. These results are shown for a completely different brain circuitry, i.e., head motor control, where experimental alterations can be directly linked to information processing steps in the brain.

Interestingly, patients with IBS were able to reduce head oscillations in the post-condition, compared to the pre-condition. This difference was not found in healthy controls. A possible explanation may be that, in the pre-condition, head oscillations of healthy controls are so minor that the vestibular input generated by these oscillations is too small to drive further updating of the head plant representation in the brain. In contrast, the reduction of head oscillations in patients with IBS from pre- to post-condition could present a learning process, in which patients are able to factor in their (stronger) sensory feedback to adjust head motor planning and reduce oscillations. Such learning processes could be either driven by sufficient repetitions of experimental rounds. Alternatively, it could be that increasing the head moment of inertia provokes stronger error signals (oscillations), which enable patients with IBS to make sensory-driven updates to CNS-models and associated expectations in the weighted and subsequent post-condition. Future analysis should focus on analyzing head learning strategies in IBS patients, e.g., the effects of serial dependencies (Zimmermann, 2021). Although the exact mechanisms remain to be determined, experimental alterations like increasing the head moment of inertia might provide a promising therapeutic approach to train the flexibility of the brain when processing sensorimotor signals in different contexts. This might counteract the proposed pathophysiology in which patients over-rely on expectations vs. sensory input (Edwards et al., 2012; Van den Bergh et al., 2017; Henningsen et al., 2018; Pezzulo et al., 2019), and potentially contribute to a reduction in symptoms. Although, for IBS patients, we feel that to reduce gastrointestinal symptoms, training target should be the affected modality.

Of course, studying sensorimotor processing like in the present study constitutes one of many possible ways to look at pathophysiological mechanisms in IBS in a rather specialized, neuroscientific framework. For instance, there is also impressive research on the role of gut mucosa, inflammatory and immune processes (Enck et al., 2016) in an attempt to capture more thoroughly the pathophysiology in IBS and related functional gastrointestinal symptoms. However, looking at central processing of body signals in IBS and functional somatic disorders in general is promising, as it provides a unifying framework for the emergence and manifestation of many different types of somatic symptoms across functional somatic disorders. This helps to define functional somatic disorders with positive diagnostic criteria, based on measurable correlates of functional somatic symptoms. Furthermore, sensorimotor processing deficits can exist and be measured in a dimensional way, demonstrating graded effects in patients with functional dizziness or IBS and might therefore strengthen a dimensional understanding of pathophysiology. Nevertheless, it remains to be seen how alterations in sensorimotor processing affect patients' subjective experience and which factors determine the manifestation of a symptom.

In summary, our results provide evidence for a general, symptom-unspecific, transdiagnostic central processing deficit in functional somatic disorders. In a gaze shift paradigm, patients with IBS showed more pronounced head oscillations during eye head gaze shifts toward visual targets under increased head moment of inertia than healthy controls. This was similar to patients with functional dizziness, but less pronounced (Lehnen et al., 2019). These findings indicate an impaired interplay between expectations and sensory input in sensorimotor processing across functional somatic symptoms and supports the predictive processing account of functional somatic disorders (Edwards et al., 2012; Van den Bergh et al., 2017; Henningsen et al., 2018; Pezzulo et al., 2019). Moreover, these findings contribute to a unified and dimensional understanding of the pathophysiology of functional somatic symptoms and disorders and might help in developing further diagnostic and treatment approaches in this patient group.

Data availability statement

The original contributions presented in this study are publicly available and can be accessed on the manuscript's Open Science Framework (OSF) webpage under the following link: https://osf.io/cnu36/.

Ethics statement

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

Author contributions

LS, SW, RvK, and NL designed the study. JH and DP gave input on IBS specifics. LS, FR, and AH collected the data. LS, FR, AH, SG, and NL analyzed and interpreted the data. LS created the figures and wrote the initial manuscript. All authors revised the manuscript critically for important intellectual content and gave final approval of the version to be published.

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Conflict of interest

Authors NL and SG were shareholders to EyeSeeTec GmbH. Author NL was paid consultant to 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.

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Chapter 5

General Discussion

Although functional disorders are very widespread and lead to great suffering and disability, little is known about the mechanisms that contribute to the emergence and manifestation of its persisting body symptoms. The current thesis therefore aimed at investigating the pathological mechanisms behind functional disorders by specifically focussing on the interplay of CNS-internal expectations and sensory input during sensorimotor information processing in the brain. Following the predictive processing account of functional disorders, processing alterations are central to symptom emergence and manifestation. The processing of internal expectations and sensory input was studied in two patient groups with functional disorders, functional dizziness and IBS, by using an experimental design from the field of gaze motor control.

The following section presents the general discussion of the current thesis. In a first step, a summary of the study results will be provided, and the theoretical contribution of the studies will be discussed. In a second step, study implications will be presented, with special attention to clinical considerations.

5.1 Key Findings and their Theoretical Contribution

To study the interplay between CNS-internal expectations and sensory input in sensorimotor processing in functional disorders, three different studies have been performed. The first study, *Deficient Head Motor Control in Functional Dizziness: Experimental Evidence of Central Sensory-Motor Dysfunction in Persistent Physical Symptoms*, investigated head sensorimotor processing during gaze shifts with experimental alteration of head properties in patients with functional dizziness. The study explored the core hypothesis that patients with functional dizziness display poorer head motor control under increased head moment of inertia, reflected by stronger head oscillations.

The second study, *Unstable Gaze in Functional Dizziness: A Contribution to Understanding the Pathophysiology of Functional Disorders*, investigated gaze stability in patients with functional dizziness during two distinct epochs of large gaze shifts that differ with respect to internal expectation contribution to gaze stability. Gaze was expected to be unstable in patients with functional dizziness, but only during a stabilization epoch where expectations can be used to stabilize gaze, not during purely sensory driven stabilization.

The third study, *Altered Sensorimotor Processing in Irritable Bowel Syndrome: Evidence for a Tansdiagnostic Pathomechanism in Functional Somatic Disorders*, investigated patients with IBS in the gaze shift paradigm to study head motor control in another patient group with functional symptoms. It was tested whether IBS patients, like patients with functional dizziness, show stronger head oscillations during increased head moment of inertia, indicating symptom-unspecific processing alterations in functional disorders.

5.1.1 Impaired Head Motor Control in Functional Dizziness

During large eye head gaze shifts towards briefly flashed visual targets, patients with functional dizziness displayed poorer head motor control than a healthy control group, reflected in increased involuntary head oscillations at the end of the head movement towards the

target (Lehnen, Schröder, Henningsen, Glasauer, & Ramaioli, 2019). Increased head oscillations were already present in the natural condition, where gaze shifts were performed without experimental alterations, and were further pronounced under experimentally increased head moment of inertia. However, over the course of gaze shifts with increased head inertia, patients with functional dizziness were able to reduce head oscillations to some extent. Importantly, head motor control deficits of functional dizziness patients were similar to deficits of patients with structural impairments, i.e., patients with bilateral vestibulopathy that cannot process any vestibular input, and patients with cerebellar ataxia, which have difficulties in adapting internal models for expectation generation [(Sağlam et al., 2014); reanalyzed in Lehnen et al. (2019)].

5.1.2 Unstable Gaze in Functional Dizziness

In functional dizziness patients, additional to head motor control deficits, eye-head coordination of large gaze shifts was significantly impaired, resulting in gaze instability (Schröder et al., 2021) This deficit was only presented during gaze stabilization against active head movements that were part of the gaze shift towards the target. Here, internal models, motor commands and efference copies are available to expect the sensory consequences of the movement and can be used, together with sensory feedback, to stabilize gaze. In contrast, purely sensory driven gaze stabilization against passive head movements was not affected. These results are in line with the unobtrusive diagnostic tests and examinations, indicating a structurally intact vestibular system in this patient group that can elicit compensatory eye movements to counteract unexpected head movements in a sensory driven manner. However, when internal models were involved in gaze stabilization, gaze was not stable, but drifting. Importantly, during increased head moment of inertia, gaze instability was worse than during gaze shifts in the natural condition. This effect could also be found in the healthy control group. However, healthy controls overall displayed better gaze stabilization than patients with functional dizziness.

5.1.3 A Broader Image of Functional Dizziness

The results of both studies demonstrate sensorimotor processing alterations in patients with functional dizziness that affect head (study 1) as well as gaze stability (study 2) during large eye-head gaze shifts. Both findings can be explained by an erroneous interplay of internal expectations and sensory information, i.e., mainly vestibular input in the gaze shift paradigm. Altering the head properties by mechanically increasing the head moment of inertia is the key manipulation of the studies above. In this scenario, the intended head movement does not match the actual head movement under perturbation. The helmet therefore introduces a mismatch, or prediction error, between expectations that are based on normal head properties and the sensory consequences elicited by movements with increased head moment of inertia. To adapt to the new context of altered head inertia, sensory input and expectations have to be integrated in a meaningful manner, i.e., the error signal, provided by the mismatch between predictions and sensory input, should be used to drive internal model adaptation. In both studies, patients with functional dizziness present difficulties with this adaptation process, either showing poorer head motor control or less compensatory eye movements for gaze stabilization during active head movements, compared to a healthy control group.

By showing increased head oscillations in patients with functional dizziness in study 1, such measurable processing deficits were demonstrated for the first time. As both, vestibular processing as well as expectation formation are important to adapt to the altered head properties this experiment (Lehnen et al., 2009b; Sağlam et al., 2014), it could not be concluded where in this interplay processing deficits arise. Nevertheless, due to the qualitative similarity of head motor control of patients with functional dizziness and patients with cerebellar ataxia, it can be speculated that both patient groups might have similar impairments, i.e., difficulties in internal model adaptation and expectation formation. The numerous diagnostic tests that revealed a structurally intact vestibular system in the investigated patient group with functional dizziness further support this idea. Study 2

confirmed sensorimotor processing deficits in functional dizziness and provided additional insights about the site of the interplay between expectations and sensory input where these deficits arise. Gaze instability only occurred during active head movements, during which expectations can be used for gaze stabilization, but not during passive head movements, during which sensory information drives gaze stabilization. This points at a wrong internal model and expectation use as the site where processing deficits arise. Additionally, in the second study, movement instability was demonstrated for the functionally relevant parameter of this task, i.e., gaze, underlying the importance of the measured alteration for the pathology of functional dizziness.

Together, these findings from patients with functional dizziness provide evidence for the predictive processing theory of functional disorders (Edwards et al., 2012; Van den Bergh et al., 2017; Henningsen et al., 2018; Pezzulo et al., 2019), that assumes patients with functional disorders to rely on overly precise, but wrong predictions or expectations used to explain sensory input. Such an over-reliance on expectations during sensorimotor processing could explain higher head oscillations in functional dizziness patients in study 1, as patients would stick to the head model of normal head properties after the head moment of inertia was increased, preventing adaptation. However, because of a larger error signal during increased head oscillations in the weighted condition, error signals might be strong enough to drive learning and adaptation, as head oscillations could be decreased to some extent. Similarly, relying on a wrong internal model of the head during gaze stabilization can explain insufficient compensatory eye movements to counteract active head movements in study 2. Importantly, in both studies, sensorimotor processing deficits where not only found during gaze shifts with altered head properties, but also during the natural condition. This could reflect incorrect internal model use and expectation formation already in the natural condition, where patients experience symptoms in everyday life, and not only during experimental situations that require adaptation to new head properties.

The studies presented above are the first investigations looking at combined eye head

movements under experimentally altered head characteristics in patients with functional dizziness. Findings from imaging studies support the conclusion that central processing alterations exist in this patient group [see Indovina et al. (2021) for a detailed review]. More specifically, structural alterations were found for brain areas involved in multimodal vestibular processing, i.e., a decrease in grey matter volume (Wurthmann et al., 2017; Popp et al., 2018), cortical thickness (Popp et al., 2018) and cortical volume (Nigro et al., 2019) in the multimodal vestibular cortex. Furthermore, studies demonstrated reduced brain activity in functional dizziness for the vestibular processing network during resting state (Na et al., 2019) as well as in response to auditory (Indovina et al., 2015) and visual motion stimuli (Riccelli et al., 2017). Consistent with these findings, patients with functional dizziness displayed reduced functional connectivity within the multimodal vestibular network, too (Indovina et al., 2015; Van Ombergen et al., 2017; Lee et al., 2018; Popp et al., 2018; Li et al., 2020a, 2020b) and a special role of the cerebellar network was highlighted, reporting altered cerebellar activity during moving vs. static visual scenes (Huber, Flanagin, Popp, zu Eulenburg, & Dieterich, 2020). Brain alterations from imaging studies fit the idea that central processing of sensorimotor signals is altered in functional dizziness and arise in important pathways for multimodal vestibular processing. However, it is difficult to understand the impact of differences in structure, function or connectivity on perception and behavior in patients with functional dizziness. Identifying measurable physiological parameters like poorer head motor control or gaze stability in study 1 and 2 of the current thesis therefore provides important value for explaining the pathophysiological mechanisms of functional dizziness, as their occurrence can be linked to erroneous processing and impairs motor performance. Furthermore, these measurable parameters fit patients' feeling of instability and the perception of involuntary movement, although it remains to be determined whether this theoretical link holds true after replication of study findings with increased sample sizes in further studies.

There are few recent experimental studies focusing on eye and head movements during whole body balance or movement tasks in functional dizziness (Penkava, Bardins, Brandt,

Wuehr, & Huppert, 2020; Aharoni, Lubetzky, Arie, & Krasovsky, 2021; Lubetzky, Aharoni, Arie, & Krasovsky, 2021). Lubetzky et al. (2021) found increased head sway of functional dizziness patients during a balance task with low visual stimulation using a virtual reality system. This effect diminished with increased visual load as well as additional cognitive load, i.e., distracting patients with a subtraction task. These results match findings from posturography in functional dizziness patients, reporting increased body sway in this patient group (Krafczyk, Schlamp, Dieterich, Haberhauer, & Brandt, 1999) that decreased with increasing cognitive load (Querner, Krafczyk, Dieterich, & Brandt, 2000). Another study (Aharoni et al., 2021) found no differences in head kinematics between functional dizziness patients and healthy controls during a fast walking task in virtual visual environments of different complexity, but head movement kinematics decreased with increasing trait anxiety in patients, possibly reflecting a "high risk" movement strategy. Penkava et al. (2020) report altered eye movement patterns in functional dizziness during walking in a complex environment, with gaze movements directed more downward to the ground and horizontal fixations, possibly to search for auxiliary means. Of course, such findings are not directly comparable to the study results comprising functional dizziness presented in this thesis, as they focus on visual, vestibular, and proprioceptive integration and movement strategies in more complex, realistic environments. In contrast, the gaze motor control approach specifically reduces complexity of sensory integration by only focusing on vestibular processing within the head and gaze motor control system to identify basic processing alterations that are mostly inaccessible to consciousness and therefore not influenced by cognitive strategies. Nevertheless, studies finding alterations in eye and head kinematics highlight the importance of these parameters in understanding the pathophysiology of functional dizziness and might be integrated into a bigger picture someday.

5.1.4 Impaired Head Motor Control in IBS

In the gaze shift paradigm, patients with IBS also showed increased head oscillations compared to a healthy control group, indicating head motor control deficits (Schröder et

al., 2022). Importantly, this deficit was only present during gaze shifts with increased head moment of inertia, not during the pre and post condition, where gaze shifts were performed without altered head properties. Compared to patients with functional dizziness, head motor control of patients with IBS was less impaired. Interestingly, patients with IBS were able to reduce head oscillations after the experimental head perturbation was removed. Here, head oscillations were smaller than in the first condition under normal head properties.

5.1.5 Transdiagnostic Processing Deficits in Functional Disorders

Poorer head motor control in patients with IBS, reflected in increased head oscillations under experimentally altered head moment of inertia, indicates sensorimotor processing deficits like in patients with functional dizziness (study 1). Similarly, these deficits arise because patients have difficulties with adapting to the new head properties, which is due to an impaired processing of expectations or sensory input during eye-head gaze shifts (Sağlam et al., 2014; Lehnen et al., 2019). As processing alterations now have been demonstrated for a second patient group with functional symptoms, the results support the assumption that the underlying mechanism of functional somatic disorders is the same for all types of symptoms, emphasizing the role of predictive processing as a unifying framework across functional symptoms. Like in functional dizziness, deficient sensorimotor processing provides evidence for the predictive processing account, with patients putting too much trust on expectations during sensorimotor processing (Edwards et al., 2012; Van den Bergh et al., 2017; Henningsen et al., 2018; Pezzulo et al., 2019), affecting error-driven updating of internal models and expectations in the experiment.

So far, this is the first study demonstrating sensorimotor processing deficits in IBS that are based on an erroneous interplay between expectations and sensory input. Alterations in head sensorimotor processing are somewhat surprising, since patients with IBS have symptoms in the lower gastrointestinal tract, far away from gaze motor control. However,

it may be possible that such alterations reflect a transdiagnostic processing deficit, i.e., a general deficit that exist across different disorders of functional nature, independent of its symptoms. In medicine, it is often observed that patients present with more than one symptom or syndrome without corresponding organic cause (Olde Hartman, Lucassen, van de Lisdonk, Bor, & van Weel, 2004; Henningsen et al., 2007) and multiple symptoms of functional nature are core criteria to the somatization disorder or the undifferentiated somatoform disorder (World Health Organization, 2004), a common diagnosis (Haller et al., 2015). A general, symptom-unspecific processing deficit that exists across signal processing of different body regions might explain this high comorbidity of functional symptoms. Against this background, the processing deficits of patients with IBS shown by study 3 might not indicate a measurable correlate of pathophysiology but might present a risk factor for these patients for developing further symptoms. The fact that none of the patients with IBS reported dizziness complaints during the months before study conduction supports this assumption. Also, head sensorimotor processing was smaller in patients with IBS than in patients with functional dizziness, possibly indicating two deficits of different strength on a continuum. To validate this speculation of a transdiagnostic mechanism, further studies should investigate eye-head gaze sensorimotor processing in further patient groups. Also, it remains to be determined how such measurable processing alterations can be linked to conscious perception, i.e., whether patients perceive the results of such processing alterations.

5.2 Implications and Conclusions

The findings of the current thesis demonstrate an impaired interplay of expectation and sensory input in perceptual processing, and they are the first that specifically showed sensorimotor processing deficits in functional dizziness and IBS. The results therefore provide significant insights into the pathological mechanisms behind functional disorders, but further validation in future studies is tremendously important. Future studies should address replications of the findings presented above and should also investigate the predictive pro-

cessing account in more types of functional disorders. Here, it would not only be important to examine similar parameters in multiple patient groups that differ with respect to the body region where symptoms arise, but also to develop new experiments that are able to study the interplay between expectations and sensory input in sensory or sensorimotor processing within the affected modality. For example, patients with functional cardiac symptoms could perform an exercise task, with correct or false cardiac feedback provided by an electrocardiogram, thereby manipulating expectations of participants about their own heartbeat. Perceptual processing could not only be assessed by asking patients about their perception, but also by using a more objective outcome parameter, e.g., the heartbeat evoked potential (Pollatos & Schandry, 2004; Coll, Hobson, Bird, & Murphy, 2021) in the electroencephalogram.

The predictive processing idea describes the emergence and manifestation of functional symptoms in a rather cognitive framework that is mainly based on information processing. It represents one way of understanding functional symptoms but might not exclude alternative explanations, which also holds true for the findings presented in this thesis. Likewise, it offers a possibility to understand how functional symptoms emerge and manifest, but not necessarily why (Henningsen et al., 2018). To be able to grasp the whole etiology of functional disorders, further studies are needed that investigate how certain risk factors affect sensorimotor processing. For IBS, for example, impressive research is looking at the role of inflammatory processes and gut mucosa (Enck et al., 2016; Kelly et al., 2015). It is important to integrate such research fields into more comprehensive models of pathological mechanisms, as they can provide the missing link to answer the why-question of etiology and validate the clinical appearance of functional disorders. This was not yet considered in the studies of the present thesis, as the mail goal was to provide a "proof of concept" for the basic mechanism of processing deficits in functional disorders. As a next step, the impact of covariates like age and sex/gender on sensorimotor processing could be examined in experimental studies like the gaze shift paradigm. From an epidemiologic point of view, especially sex would be a variable of interest, as functional disorders are more common in

women than in men and gender therefore provides a risk factor in developing persisting somatic symptoms (Wool & Barsky, 1994; Kroenke & Spitzer, 1998; Creed & Barsky, 2004).

The presented studies have multiple implications that can improve patient care in the short and long run. First, they demonstrate clearly measurable processing alterations in functional disorders that constitute an important step towards a positive definition of these disorders. So far, in the current European diagnostic system ICD-10, functional or somatoform disorders are a diagnosis of exclusion, for which somatic causes of symptoms must be ruled out first. This leaves room for doubts on patients' as well as caretakers' side about a possible overlooking of causes and typically leads to multiple diagnostic procedures, a vicious cycle of patient-physician-interaction and a prolonged period until the right diagnosis is made (Murray et al., 2016). A trend towards positive signs in functional disorders can already be observed in neurology (Stone, Burton, & Carson, 2020), and positive psychological signs for functional disorders have been incorporated in the diagnostic criteria of the current American diagnostic system [Diagnostic and Statistical Manual of Mental Disorders, DSM-5; (American Psychological Association, 2013)] and of the future European diagnostic system [ICD-11 (Gureje & Reed, 2016)]. By identifying measurable correlates of functional disorders that are linked to the underlying pathophysiology, diagnostic procedures can be improved and the time until final diagnosis is made can be shortened.

Second, a measurable marker can provide legitimation for the patients' symptoms and therefore reduce stigma. Due to the lack of understanding about functional disorders and the unobtrusive diagnostic tests and medical examinations, patients are often not taken seriously with their suffering. Knowledge about the pathophysiology of functional symptoms and the demonstration of measurable alterations might relief patients and reassure them in their perception and experience of symptoms.

Third, the presented study results and their contribution to understanding the pathophys-

iology of functional disorders has the potential to improve therapeutic approaches. For example, this can be done by implementing the gained knowledge into a psychoeducational intervention for patients, an important intervention in medicine. Moreover, sensorimotor processing deficits can be directly addressed by adaptation and movement trainings. In functional dizziness, for example, we see a reduction in head oscillations over the course of gaze shifts with increased head moment of inertia (Lehnen et al., 2019). Experimental manipulations of the head properties could therefore serve as training situations, where – due to stronger error signals – patients might be able to adapt their internal models and gain flexibility. First studies show that vestibular rehabilitation training, that also includes head and trunk movements, can improve impairment in patients with functional dizziness (Thompson, Goetting, Staab, & Shepard, 2015; Popkirov, Stone, & Holle-Lee, 2018; Nada, Ibraheem, & Hassaan, 2019).

Fourth, the present results not only contribute to a paradigm shift in medicine towards positive signs and swift diagnosis of functional disorders, but also integrate functional symptoms into a dimensional understanding of somatic symptoms (Van den Bergh et al., 2017; Henningsen et al., 2018; Lehnen et al., 2022), independent of their pathological origin. In predictive processing, symptom perceptions arising from a deficit in peripheral dysfunction or from CNS processing deficits can be the same, meaning that the degree to which perception is actually verified by organic pathology is not important for the experience of symptoms. For example, in the gaze shift paradigm, poorer head motor control in functional dizziness did not differ from head motor control deficits in patients with structural deficits (Lehnen et al., 2019), and all patient groups experienced persisting dizziness. This knowledge can contribute to a dimensional understanding of somatic symptoms, with varying degrees of organic or processing deficits contributing to pathology, rather than categorizing them into distinct subgroups (organic vs. functional), in which many patients are left out. Of course, in future studies, processing deficits should be investigated in patients that experience symptoms with mixed organic and functional origin, as in the current thesis, to exclude confounding effects, only patients without measurable organpathology were

examined. But such a unifying understanding, as provided by the predictive processing framework, could help patients with debilitating symptoms of each type to feel understood and to receive appropriate treatment (Sharpe & Carson, 2001).

Last, a deeper understanding of the pathophysiology behind functional disorders could also help to improve the understanding of recently emerged disorders, like post-COVID. Here, so far, no clear pathophysiological correlates could be identified that sufficiently explain patients' persisting and debilitating symptoms (Froidure et al., 2021; Townsend et al., 2021; Sneller et al., 2022; Staudt et al., 2022), allowing to hypothesize altered perceptual processing in persisting symptoms after COVID-19 (Shalev, 2021; Hentsch et al., 2022). The gaze shift paradigm described in the current thesis, for example, could be used to assess processing deficits as a possible pathophysiological mechanism behind persisting dizziness in post-COVID. Bridging the gap between the mechanisms behind functional disorders and post-COVID might provide a possibility to transfer advantages of understanding and diagnosis to a further patient group and can facilitate appropriate treatment offers.

In summary, the findings of the current thesis provide a new perspective on the pathophysiology of functional disorders by pointing at processing deficits in affected patients that arise due to an incorrect use of expectations during sensorimotor processing. As evidence is still sparse, in future studies, careful evaluation and validation of this understanding is needed. Nevertheless, these pathophysiological contributions come with manifold implications and opportunities for clinical practice and have the potential to improve understanding, diagnosis, and treatment in patients with functional disorders.

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List of Publications

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Schröder, L., Regnath, F., Glasauer, S., Hackenberg, A., Hente, J., Weilenmann, S., Pohl, D., von Känel, R., & Lehnen, N. (2022). Altered sensorimotor processing in irritable bowel syndrome: Evidence for a transdiagnostic pathomechanism in functional somatic disorders. *Frontiers in Neuroscience, 16*, 1-12. doi:10.3389/fnins.2022.1029126

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Eidesstattliche Versicherung/Affidavit

Hiermit versichere ich an Eides statt, dass ich die vorliegende Dissertation *Erroneous Sensorimotor Processing in Functional Disorders - Evidence from Gaze Motor Control of Functional Dizziness and Irritable Bowel Patients* selbstständig angefertigt habe, mich außer der angegebenen keiner weiteren Hilfsmittel bedient und alle Erkenntnisse, die aus dem Schrifttum ganz oder annähernd übernommen sind, als solche kenntlich gemacht und nach ihrer Herkunft unter Bezeichnung der Fundstelle einzeln nachgewiesen habe.

I hereby confirm that the dissertation *Erroneous Sensorimotor Processing in Functional Disorders - Evidence from Gaze Motor Control of Functional Dizziness and Irritable Bowel Patients* is the result of my own work and that I have only used sources or materials listed and specified in the dissertation.

Munich, 6th of July 2022 Lena Schröder

Declaration of Author Contributions

Deficient Head Motor Control in Functional Dizziness: Experimental Evidence of Central Sensory-Motor Dysfunction in Persistent Physical Symptoms

Authors: Nadine Lehnen, Lena Schröder, Peter Henningsen, Stefan Glasauer, Cecilia Ramaioli

The author of this thesis (**LS**) is the second author of this research article. Together with NL, who designed the study, and CR, who collected the data, **LS** analyzed and interpreted the data and drafted the initial manuscript. **LS** and CR created the figures. All authors have revised the manuscript and approved the final version.

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

The author of this thesis (**LS**) is the first author of this research article. **LS** analyzed and interpreted the data, created the figures, and wrote the initial manuscript. DvW assisted with data analysis and figure design. CR collected the data, NL designed the study. TW,

SG and NL supervised data analysis and revised the initial manuscript. All authors reviewed and edited the manuscript and approved the final version.

Altered Sensorimotor Processing in Irritable Bowel Syndrome: Evidence for a Tansdiagnostic Pathomechanism in Functional Somatic Disorders

Authors: Lena Schröder, Franziska Regnath, Stefan Glasauer, Anna Hackenberg, Juliane Hente, Sonja Weilenmann, Daniel Pohl, Roland von Känel, Nadine Lehnen

The author of this thesis (**LS**) is the first author of this research article. **LS** designed the study together with SW, RvK and NL. **LS**, JH and DP recruited the patients, **LS** collected the data with help from FR and AH. **LS** analysed and interpreted the data with help from FR and AH under supervision of SG and NL. **LS** created the figures and wrote the initial manuscript. All authors revised the manuscript critically for important intellectual content.

Munich, 6th of July 2022

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