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Erroneous sensorimotor processing as a transdiagnostic mechanism underlying functional disorders?

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List of abbreviations

APA	American Psychiatric Association
BDD	Bodily Distress Syndrome
BF	Bayes Factor
CNS	Central nervous system
DSM	Diagnostic and Statistical Manual of Mental Disorders
ETUDE	Encompassing Training in fUnctional Disorders across Europe
FD	Functional Disorder
FND	Functional neurological disorder
FSS	Functional somatic symptom(s)/syndrome
ICD	International Classification of Diseases
NHST	Null Hypothesis Statistical Testing
OSF	Open Science Framework
PPPD	Persistent Postural-Perceptual Dizziness
PSS	Persistent somatic symptom(s)
SCID-5-CV	Structured Clinical Interview for DSM-5 Disorders, Clinician Version
SSD	Somatic Symptom Disorder
vHIT	Video head-impulse test
VOR	Vestibulo-ocular reflex
WHO	World Health Organization

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Chapter 1

Project Objectives

Functional disorders (FD) are a significant public health concern commonly encountered in all healthcare settings (e.g., Price & Okai, 2016). Persons with FD often face unique challenges in obtaining a timely diagnosis and adequate treatment, as functional bodily complaints lack a clear organo-structural or biochemical correlate, and underlying pathomechanisms are still poorly understood (Espay et al., 2018; Henningsen, Zipfel, et al., 2018). Alongside, this patient group experiences considerable stigma from the public, their close social circle, and healthcare professionals (Rawlings & Reuber, 2016; Rommelfanger et al., 2017).

The goal of the here presented studies is to improve the mechanistic understanding of FD and to provide an objectively assessable, potentially transdiagnostic marker of FD. More specifically, the research examined whether patients with chronic (functional) pain, functional dizziness, or functional movement disorder exhibit measurable sensorimotor processing deficits during large gaze shifts.

This dissertation project is part of the innovative training network ETUDE (Encompassing Training in fUnctional Disorders across Europe), ultimately aiming to improve the understanding of mechanisms, diagnosis, treatment and stigmatization of FD (Rosmalen et al., 2021).

Introduction to Functional Disorders

People commonly experience mild and transient physical symptoms without a clear root cause, such as headache or fatigue (e.g., Van Der Windt et al., 2008). However, when bodily symptoms become chronic and cause considerable functional impairment, clinical attention is warranted. Functional disorders (FD) describe an umbrella term for persistent somatic symptoms that have typical clinical characteristics but currently cannot be associated to reproducibly observable pathophysiological mechanisms (Rosmalen et al., 2021). FD characterizes a heterogeneous range of symptoms, including motor and sensory disturbances or loss, fatigue, gastrointestinal symptoms, dizziness, or pain, and thus also span many specialist disciplines. The experienced symptoms are burdensome and significantly interfere with the person's ability to participate in personal (e.g., maintain home duties), social (e.g. attending events), or occupational (e.g., loss of productivity) areas of life (American Psychiatric Association [APA], 2022).

The 12-month prevalence rate of FD is estimated to be around 11% (Jacobi et al., 2004). Prevalence rates of FD can vary widely depending on the particular functional symptom (e.g., pain) or syndrome (e.g., irritable bowel syndrome) (Fink et al., 2007; Kroenke, 2003; Petersen et al., 2019), the country or region (Rometsch et al., 2024; Sperber et al., 2021), and the specific medical setting. About one third of all patients present with FD during primary health care consultations (De Waal et al., 2004; Haller et al., 2015; Steinbrecher et al., 2011), and around 15 - 50 % of patients who visit or were referred to specialist practice (Nimnuan, 2000; Ramsay et al., 2023; Reid, 2001; Stone et al., 2010). Generally, women are two to three times more likely to develop FD in their lifetime (Grabe et al., 2003; Lidstone et al., 2022), and people below the age of 65 are most commonly affected (De Waal et al., 2004; Hilderink et al., 2013).

Due to loss of productivity, often delayed diagnosis, inadequate treatment as well as high healthcare utilization (i.e., rehabilitation, repeated hospitalization and diagnostic tests), there is considerable personal and societal cost associated with FD (O'Mahony et al., 2023; Saunders et al., 2020; Tack et al., 2019; Tinazzi, Gandolfi, et al., 2021). For instance, research suggests that health care utilization – and therefore also the associated cost – is increased when patients receive a diagnosis but do not receive an adequate explanation for their symptoms (Lagrand et al., 2023). This shows that accurate diagnosis alone is not sufficient, but that healthcare professionals also need to be able to provide a tangible mechanistic model for the patient's symptom(s).

In more recent years, the gold standard in the diagnosis of FD has shifted from solely excluding known pathophysiological causes to instead identifying positive (i.e., present) markers of FD (APA, 2022). With this, research continues its efforts in closing existing knowledge gaps around the underlying mechanisms of FD and to identify characteristic, measurable (bio-)markers that aid in its diagnosis. Together, the aim is to provide a comprehensive and unifying understanding of FD across clinical disciplines, educational environments, and health care settings (Rosmalen et al., 2021), facilitating interdisciplinary professional health care for patients with FD.

Chapter 2

Theoretical Background

Diagnosis of Functional Disorders

Obtaining a diagnosis is a key step for the patient in receiving access to an appropriate treatment plan and outcome perspectives as well as an explanatory model for their complaints (Kendell & Jablensky, 2003). However, persons who developed FD and are seeking a diagnosis for their symptoms may face multiple challenges along the way. For instance, as patients tend to have frequent contact with the health care system, they are at risk of iatrogenic harm due to at times numerous (invasive) examinations and negative interactions with medical staff (Finkelstein et al., 2021; O'Neal & Baslet, 2018). On average, time until diagnosis spans several years (Butler et al., 2021; Tinazzi, Gandolfi, et al., 2021), and patients eventually face a multitude of available labels while often not receiving an adequate explanation of their diagnosis (e.g., see Stone et al., 2016). Not surprisingly, people with FD often end up frustrated and doubtful of their diagnosis (Burton et al., 2015).

The dualistic mind-body problem & diagnostic classifications

In the 17th century, René Descartes postulated that the mind and body are inherently separate: while the body consists of physical matter, the mind is a nonphysical substance – together composing the human being (Descartes, 1984). Although even Descartes himself seemed to have a more nuanced view of mind-body interactions (see Correll, 2022), the dualistic divide had been incorporated in the medical field at the time. To date, dualistic models are still inherent in our medical systems and curricula, especially when it comes to FD. Within this mind-body perspective, bodily complaints are considered as either having an identifiable "organ-structural" cause explaining the symptoms (i.e. somatic disease), or as being attributable to psychological causes that cannot be treated medically but instead require psychiatric attention (i.e., mental disorder).

This split between "somatic" and psychiatric medicine is also reflected in the plethora of available diagnostic labels for FD. For instance, outdated but still often used

descriptors like "non-organic", "psychogenic", or "conversion" suggest that FD is either entirely rooted in the body's organ structure or a purely psychological condition. In the same way, the contemporary label of FD as a somatoform disorder (ICD-10; World Health Organization [WHO], 2004) may imply that symptoms merely imitate those of "real" neurological or medical conditions (e.g., "[d]issociative convulsions may mimic epileptic seizures very closely", F44.5). Similarly, the (once) popular description of FD symptoms as 'medically unexplained' not only reinforces a sole focus on biological explanations and causes, but also incorrectly conveys that we have no knowledge on the etiology, diagnosis, or treatment of the disorder (e.g., see Edwards et al., 2014; Velazquez-Rodriquez & Fehily, 2023).

The dualistic mind-body gap between somatic and psychiatric health care settings is also represented in current taxonomies. The major classification systems for FD are the current Diagnostic and Statistical Manual of Mental Disorders 5th edition (DSM-V and DSM-V-TR; APA, 2013, 2022) and the International Classification of Diseases 11th edition (ICD-11; WHO, 2021). The current DSM-5 was introduced in 2013 and, with that, replaced the former 4th version, the DSM-IV (APA, 1994, 2000). In contrast, the ICD-11 only came into effect in 2022 and will slowly replace its previous edition (ICD-10; WHO, 2004) over the subsequent years; until then, many countries currently still use ICD-10 codes in practice (e.g., at most 5 more years in Germany). While the DSM classification systems exclusively define mental disorders, the ICD codes all presentations of human disease, including mental disorders. With this, the ICD covers all medical specialties.

Dualistic views around disorders and diseases have coloured the diagnosis of FD. Historically, FD has been a diagnosis of exclusion, i.e., made on the basis of ruling out any "somatic"/"physical"/"organo-structural" disease condition (e.g., multiple sclerosis), disorder (e.g., epilepsy), or impairment (e.g., tissue damage) that explain the full range or severity of the symptom(s). As a result, the assigned FD diagnostic labels instead focus on what the bodily symptom is not (e.g., nonepileptic seizures), or instead label the disorder automatically as psychological (e.g., psychogenic seizures; see also Burke, 2019). This approach bears multiple problems: First, it neglects that "somatic" and functional disorders often co-occur in the same patient (e.g., epileptic and functional seizures comorbid in 22% of patients; Popkirov, Asadi-Pooya, et al., 2019). As a result, co-occurring functional symptoms that closely resemble those of a "somatic" disorder may be missed and left

untreated (Walzl et al., 2022). Second, it leaves room for pejorative explanations and labels (e.g., "pseudoseizures") that may even insinuate feigning or malingering and stigmatize the patient (Smith, 2023). Consequent negative attitudes towards people with FD adds to experiences of feeling invalidated, as their bodily complaints are sometimes construed as wilfully amplified or 'not real' by health professionals and their social circle (Foley et al., 2024; Stone et al., 2016). Third, arriving at an FD diagnosis solely based on excluding any other known disorder or diseases introduces barriers for patients to be confident about their diagnosis. Patients may doubt whether more testing is needed or whether new technologies may find the underlying "physical" cause in the future, remaining sceptical or altogether rejecting current biopsychosocial explanatory models and treatment (O'Neal et al., 2021; Smith, 2023).

As a result, the current diagnostic gold standard for FD has shifted towards clinical assessments based on positive (i.e., present, measurable) signs. To date, the number of valid and reliable positive markers for FD is limited and mostly focused on neurological – versus autonomous or sensory – presentations of FD (for a detailed overview of [validated] positive signs, see Daum et al., 2014; Espay et al., 2018; Stone, 2016a; Stone et al., 2020). The presence of measurable signs can help patients to gain insight and confidence in the accuracy of the diagnosis and the functioning of their bodies, for instance by demonstrating that their body still has the capacity to function under certain circumstances (e.g., automatic movements) and that physical impairment is potentially reversible (Stone, 2016a). Together with the patient, practitioners should demonstrate a positive sign without stigmatizing or putting blame on the patient (e.g., "gotcha!" moment). Furthermore, this should be accompanied by a tangible and individualized explanation of the sign(s) and underlying mechanisms during the consultation, and how it could shape subsequent treatment (MacDuffie et al., 2021; Stone, 2016a). However, positive signs for the diagnosis of FD are still not always assessed in practice (LaFaver et al., 2020), and not yet required or recognized in all professional classification systems currently used for FD.

In the former DSM-IV-TR, FD was covered under axis I ("Mental Health and Substance Use Disorders") in the chapter for somatoform disorders (APA, 2000). Here, sensory and motor symptoms (e.g., impaired balance, weakness, seizures) were coded under the *conversion disorder* category, a term dating back to Sigmund Freud's psychodynamic idea that functional somatic symptoms are the expression (or conversion) of underlying

psychological trauma or conflict (Demartini et al., 2016). In line with this, the bodily symptom(s) had to be associated with a psychological stressor or conflict. FD characterized solely by pain was coded under *pain disorder* (associated with psychological factors and/or a general medical condition), with psychological factors playing a key role in the onset, severity, exacerbation, or maintenance of pain. Importantly, this diagnosis of pain disorder also allowed co-existing medical conditions and with that, at least partly, acknowledged the biopsychosocial nature of chronic pain. Remaining functional symptoms (e.g., fatigue, dizziness, gastrointestinal complaints) were considered as *undifferentiated somatoform disorder*. As part of the somatoform disorders chapter, any distressing bodily symptoms had to occur in the absence of an underlying neurological or medical condition (except for pain), and could also not be fully explained by another psychiatric condition or effects of a substance. These criteria lay out a classical diagnosis of exclusion, in that they only describe what the disorder is *not*. Of note, DSM-IV-TR also explicitly stated that clinicians need to ensure that the presented somatic symptom was not deliberately produced or feigned – with this, insinuating that patients may be malingering, thus opening the door to stigmatization and hampering diagnosis, treatment, and the patient-clinician alliance. Importantly, evidence suggests that feigning or intentional amplification of FD symptoms is likely not a relevant concern in clinical practice (Edwards et al., 2023). Rather, people may unconsciously feel the need to exaggerate their symptoms if their suffering and needs are not being acknowledged (O'Neal et al., 2021).

With the introduction of the DSM-5 (APA, 2013), the multiaxial system has been abandoned and the diagnostic criteria for FD underwent several important changes. The section on somatoform disorders has been renamed to "somatic symptom and related disorders". The label for *conversion disorder* received the addendum of *functional neurological symptom disorder* in parentheses, acknowledging preferences of patient and clinician communities as well as advancements in research on the etiology of FD. For the publication of the most recent text revision, the DSM-5-TR, the terms were reversed, now reading *functional neurological symptom disorder (conversion disorder)* (APA, 2022). In line with the change in name, the focus of the diagnosis moved away from a psychodynamic pathogenesis and dropped the requirement of a recent psychological stressor. Furthermore, FD in the DSM-5 is no longer an (entirely) exclusionary diagnosis. FD symptoms can still co-exist with (but should not be sufficiently explained by) another disorder or disease. In

addition, the DSM-5(-TR) requires that the "symptoms of altered voluntary motor or sensory function" (criterion A) must show "evidence of incompatibility between symptoms and recognized medical or neurological conditions" (criterion B) for the diagnosis of FD (APA 2013, 2022). Notably, patients suffering from common functional symptoms such as pain, fatigue, or autonomic dysfunction (e.g., gastrointestinal disturbances) do not meet criterion A – the former DSM-IV's categories of *undifferentiated somatoform disorder* and *pain disorder* (together with *somatization disorder* and *hypochondriasis*) have been abolished and now all fall under the DMS-5's umbrella term of *somatic symptom disorder*. Apart from this, criterion B should ideally encourage a diagnosis based on characteristic confirmatory features. As such, the absence of any other disease or disorder is neither necessary nor sufficient for the diagnosis of FD. Most clinical positive signs demonstrate an inconsistency between automatic and voluntary performance, such as Hoover's sign for functional leg weakness/paralysis or the entrainment test for functional tremors (for a comprehensive overview, see Aybek & Perez, 2022; Espay et al., 2018). Overall, valid and reliable positive signs, especially for non-motor FD symptoms (e.g., pain, fatigue, dizziness, cognitive symptoms), are few or even entirely lacking, thus diagnosis is still largely based on a lengthy and frustrating process of excluding any possible alternative "organo-structural" diseases or disorders that could explain the symptoms.

While the DSM versions have, by definition, always coded FD as psychiatric conditions, classification of FD in the 10th and 11th version of the ICD and its numerous hierarchical chapters and (sub-)categories (e.g., anatomical sites/organ systems, diseases, injuries, external causes) is less straightforward (WHO, 2004, 2021).

In the ICD-10 (WHO, 2004), FD can be coded under separate categories, *dissociative [conversion] disorders* (F44.-) or *somatoform disorders* (F45.-), in chapter V – "mental and behavioural disorders". FD coded under F44.-, such as functional movement disorders (F44.4; e.g., weakness, involuntary movements) or functional seizures (F44.5), are defined as being associated with a psychological and interpersonal stressor or conflict ("psychogenic origin"). This is reminiscent of the earlier psychodynamic descriptions of FD in the DSM-IV. Furthermore, the functional symptoms cannot co-occur with a "physical or neurological" disorder, but symptoms merely represent how the patient would conceptualize the corresponding "physical illness" (e.g., functional seizures "mimic epileptic seizures"). First, this again purports that FD is a diagnosis of exclusion. Second,

the ICD-10's descriptions of FD include pejorative terms (e.g., "conversion hysteria") and may even imply that symptoms are generated wilfully (e.g., F44.6: symptoms represent "patient's ideas about bodily functions, rather than medical knowledge") – this should be considered in light of the fact that this version of the ICD is currently still widely employed in clinical curricula and practice. FD coded under the category F45.- covers pain and symptoms of autonomic dysfunction (e.g., dizziness, irritable bowel syndrome). In contrast to the dissociative disorders, somatoform disorders can co-occur with another disorder not fully explaining the symptoms. An example for this are pain symptoms, which can be separately coded as persistent somatoform pain disorder (F45.40; emotional or psychosocial in origin) or chronic pain disorder with somatic and psychological factors (F45.41; originally due to a physical cause but exacerbated or maintained by psychological distress). Apart from the ICD-10's psychiatry chapter, FD can also be found in its respective symptom's or syndrome's specialty (sub-)chapters. For instance, functional syndromes such as irritable bowel syndrome can be found in chapter XI "diseases of the digestive system" (K-code) and fibromyalgia in chapter XIII "diseases of the musculoskeletal system and connective tissue" (M-code).

In the newest, 11th version of the ICD (WHO, 2021), FD characterized by motor, sensory, or cognitive symptoms can be found under the subcategory *dissociative neurological symptom disorder* (6B60.-) in chapter 6 – "Mental, behavioural or neurodevelopmental disorders". With this, the ICD has eliminated the outdated term "conversion" from its nomenclature but kept the "dissociative" name in its title. The term "dissociation" has a long history but was first conceptually coined by Pierre Janet to describe the phenomenon of disintegrated psychological function or states of (sub-)consciousness, to be later adopted and developed further by Sigmund Freud for his psychodynamic theory and views on conversion (Hart & Horst, 1989); to date, the term remains part of clinical medicine's nosology. In contrast to DSV-IV and ICD-10, the term "somatoform" has been dropped entirely for this ICD version. In the ICD-11, *dissociative neurological symptom disorder* is described as discontinuity in normal integration of bodily function or inconsistency with other known disorders or diseases. In light of current trends in assigning FD based on positive signs, this description remains vague with regards to abandoning a diagnosis of exclusion. While "discontinuity in normal integration of bodily function" may point towards observable positive signs (e.g., inconsistency between automatic and voluntary

function), "inconsistency with other known disorders or diseases" may suggest that diagnosis is (also) based on clinical features that seem incongruent with other known neurological diseases or disorders (for a critical discussion of "incongruency" as a criterion for FD, see Stone, 2024). In other words, the ICD-11 does not take a clear stance about required present or absent diagnostic signs and criteria for FD.

Apart from that, a psychological stressor is no longer required for a diagnosis but has instead been integrated as part of the etiological biopsychosocial description of FD in the ICD-11 (WHO, 2021). Interestingly, the available symptom specifiers for *dissociative neurological symptom disorder* do not cover some autonomic dysfunctions (e.g., problems with digestion) and other bodily symptoms such as pain or fatigue. One reason for this could be the lack of positive signs in demonstrating inconsistencies between "functional" and "neurological" processes for these symptoms. Similar to the ICD-10, the ICD-11's functional symptoms or syndromes can also be found it their respective medical specialties, such as functional tremor or functional parkinsonism in the neurology section (chapter 8) and functional gastrointestinal syndromes in the gastroenterology section (chapter 13). What is more, chronic (functional) pain in the ICD-11 is no longer coded as a psychiatric or rheumatic disorder, but has now received its own category as an independent symptom entity: Pain, defined as a biopsychosocial phenomenon (e.g., Chronic Pain, MG30).

The ICD allows for double-coding, but typically codes are assigned according to their respective settings (e.g., F-codes in psychiatry), mostly due to administrative and billing purposes (Stone et al., 2014) but also in line with the clinician's specific training (e.g., psychologist versus neurologist; e.g., Pohontsch et al., 2018; Wu et al., 2024). For instance, a patient presenting with functional gastrointestinal disturbances in a psychiatric setting will likely receive the diagnostic ICD-10 code for F45.32 (somatoform autonomic dysfunction: lower gastrointestinal tract; chapter 6), which would be coded as K58.0 or K58.9 (irritable bowel syndrome with or without diarrhea, respectively; chapter 13) in a somatic setting (e.g., gastroenterologist). Similar for the ICD-11, patients with functional dizziness will likely receive a diagnosis of dissociative neurological symptom disorder (with vertigo or dizziness, 6B60.2, chapter 6) from a psychiatrist and a diagnosis of Persistent Postural-Perceptual Dizziness (PPPD, AB32.0, chapter 10) from a neurologist. Perhaps not surprisingly, evidence suggests that not so much the symptom presentation, but rather the practitioner's specialty determines what diagnosis the patient will receive (Noll-Hussong &

Otti, 2015). Sometimes, healthcare providers also refrain from assigning F-/psychiatric codes to avoid potential stigmatization of their patient (Pohontsch et al., 2018). At the same time, this artificial categorization between medical specialties can lead to confusion about diagnostic terms among patients and health care providers alike, and hinders communication as well as sharing of expertise and knowledge across medical disciplines.

Once the diagnosis of FD is recognized, the diagnostic label rarely changes (e.g., due to previously undetected pathological findings; Eikelboom et al., 2016; Stone et al., 2009). However, there seems to be a disbalance in the perception of harm when it comes to possible misdiagnosis – that is, medical professionals seem to be more concerned about missing an "organic" disease, than about incorrectly providing an "organic" diagnosis when the underlying disorder is functional (Espay et al., 2009; Walzl et al., 2019). The latter also carries considerable iatrogenic harm due to negative side-effects of non-indicated medications (e.g., anti-epileptic drugs), delayed appropriate treatment (and possibly resulting chronicity of symptoms), and possible psychological burden (e.g., when wrongly receiving the diagnosis of an incurable and/or fatal disease; Walzl et al., 2022). In fact, misdiagnosis in both directions is about equally likely, albeit rare overall (Walzl et al., 2019). Of note, functional and "biomedical/organo-structural" disorders that induce similar symptoms often co-exist (e.g., functional and epileptic seizures; Kutlubaev et al., 2018).

Lastly, while both the DSM and ICD systems have partly moved away from stigmatizing or dualistic labels suggesting a purely psychological or psychodynamic pathogenesis (e.g., less emphasis on conversion in the DSM-5) or mimicry of 'real' medical conditions (e.g., ICD-11's abolishment of the somatoform label), the term *functional disorder* – which is also the name used throughout this dissertation – is not without criticism either. On the one hand, the term functional disorder is seen as advantageous in that it is agnostic as to whether symptoms are purely 'physical' or 'psychological', but merely describes the patient's level of central nervous system and bodily (dys)function (e.g., see Henningsen et al., 2011). Additionally, research suggests that patients perceive the label *functional disorder* to be less stigmatizing and that health care providers feel more confident in communicating the diagnosis compared to earlier labels such as 'psychogenic' or 'medically unexplained' (Ding & Kanaan, 2016; LaFaver & Hallett, 2014; Stone, 2002). However, 'functional' also has attached history dating back to the 19th century and, for instance, was a term used by

Jean Martin Charcot to describe a dynamic or functional lesion in the brain that was just too small to be detected by the available technology of the time (see Stone, 2016b). Following, Charcot's views had deeply influenced the further development of the psychodynamic theory around 'hysteria' by Janet and Freud (Bogousslavsky, 2011). Over the years, the medical field around 'hysteria' had split into neurology and psychiatry, with the former losing interest in the clinical phenomenon due to a lack of 'organic' findings, and the latter being only consulted rarely by patients as they saw their disorder to be 'neurological' (Stone et al., 2008). Even today, clinicians use the term 'functional' to denote different meanings in communication with patients and colleagues (i.e., dysfunction of the brain, dysfunction of the body, psychiatric disorder, or 'non-organic'; Kanaan et al., 2012).

What about Somatic Symptom Disorder & Bodily Distress Disorder?

Next to the categorization of FD based on the presented bodily symptom(s) and respective positive signs, FD is sometimes diagnosed based on the patient's way of thinking, behaving, or feeling with regard to their symptom(s) – this is especially the case for functional symptoms where objectively measurable markers are missing and the presence and severity of symptoms is solely based on patients' self-report (e.g., pain, nausea, fatigue). For these bodily symptoms, medical exclusion has instead been replaced with psychological inclusion.

In the ICD-10, the phenomenon is defined as *somatization disorder* (F45.0) under somatoform disorders in chapter V – "mental and behavioural disorders", characterized by persistent and recurrent but frequently changing bodily symptoms over a duration of two years at minimum. (The same presentation but at a shorter duration and lesser severity can be coded as *undifferentiated somatoform disorder* [F45.1].) Patients can experience symptoms in any part of their body, but a clear cause can often not be found; frequent medical consultations are typical. The bodily symptoms are burdensome and often chronic, negatively impacting the person's personal, social, and occupational life. In sum, this ICD-10 description covers patients who suffer from multiple functional symptoms that are diagnosed in an exclusionary fashion rather than on the basis of positive signs.

Its successor, the ICD-11 (WHO, 2021), introduced *bodily distress disorder* (BDD) as a new diagnostic label. The disorder is characterized by persistent bodily symptoms that

significantly impact facets of daily life. Patients usually experience multiple bodily symptoms, but seldom also a single symptom (typically pain or fatigue). A specific time frame is not defined, but physical symptoms should be present "on most days for at least several months". Apart from this, the criteria for BDD now also lay out positive affective, behavioural, and cognitive features: "excessive attention directed toward the symptom(s)" (e.g., repeated health-care-seeking behaviour, health anxiety despite reassurance from a clinician, health examinations beyond what is deemed appropriate, dedicating a significant amount of time to the bodily symptom[s]).

In accordance with the ICD-10, the term *somatization disorder* was also used in the DSM-IV(-TR) and categorized under the somatoform disorder chapter (1994, APA, 2000). In comparison, however, the defined criteria were significantly more restrictive (and thus only rarely diagnosed; Creed & Barsky, 2004), such that only patients with chronic, multisymptomatic presentations would meet these criteria. Outlined are a minimum of eight different bodily complaints in the same individual's medical history (past 30 years) – specifically, pain symptoms in four different body sites, two additional gastrointestinal symptoms (excluding [abdominal] pain), one sexual or reproductive symptom (again excluding pain), and one "pseudoneurological" symptom (e.g., seizures, paralysis). Furthermore, the bodily symptoms are either not sufficiently explained by another known 'medical' condition or substance intake (i.e., implying functional symptoms based on a diagnosis of exclusion) *or* related to a known 'medical' condition and cause significant physical, social, or occupational impairment beyond of what would normally be expected. In line with the stigmatizing criteria for the DSM-IV(-TR)'s *conversion disorder*, practitioners must also ensure that the bodily symptoms are not feigned or intentionally generated.

With the reconceptualization of the "somatic symptom and related disorders" chapter in the DSM-5(-TR) (APA, 2013, 2022), the diagnostic categories of somatization disorder, undifferentiated somatoform disorder, pain disorder, and hypochondriasis were abolished, and *somatic symptom disorder* (SSD) as a main diagnosis was added in their place. With this, the 'medical' inexplicability of symptoms was dropped as a prerequisite and a specific number of bodily complaints is no longer required. Instead, the focus in SSD shifted to an inclusion of affective, cognitive and behavioural characteristics. Specifically, the diagnosis can be made for persons experiencing one or more persistent (>6 months) and clinically significant bodily symptom(s) that are accompanied by excessive symptom-

related thoughts (e.g., ruminating about the seriousness of the bodily symptom), feelings (e.g., significant health anxiety), or behaviours (e.g., several hours per day devoted to symptoms).

Taken together, the most current ICD and DSM versions converge in their definition of the diagnostic criteria for SSD/BDD in that the etiology of the experienced bodily symptom(s) is no longer at the centre of these diagnoses. Instead, the presence of psychological and behavioural features is decisive in assigning a diagnosis. Although psychiatric disorders are more common in persons with FD compared to the general population (De Waal et al., 2004; Henningsen & Löwe, 2006), not every person exhibits pathological behavioural, emotional, or cognitive symptoms (Kranick et al., 2011; Macchi et al., 2021; Toft et al., 2005). This means that the labels of SSD/BDD do not apply to all patients with FD. Importantly, the diagnostic labels for SSD/BDD are not reserved for patients suffering from FD only but can be coded for all patients experiencing any persistent somatic symptom(s) – including clearly 'medically explained' symptoms – as long as the criteria for excessive behavioural, cognitive, or emotional responses are met.

Interestingly, the introduction of these diagnostic entities – specifically the removal of an explicit distinction between 'medically explained' and 'unexplained' bodily symptoms – was received critically by some members of the medical community, who feared that the diagnostic criteria were too loosely defined or unfitting to those with 'medical' conditions (Lehmann et al., 2019). For instance, Frances (2013) argued that the diagnosis of SSD or BDD would suddenly also apply to a larger body of people who suffer from 'medical conditions', now labelling them as mentally ill. Perhaps, this reaction is not too surprising considering that psychiatric disorders (including FD) carry inherent stigma, with the idea that patients hold personal responsibility and blame over their illness, are malingering or exaggerating their suffering (Corrigan et al., 2003; Husain et al., 2020; Lauber, 2008; Looper & Kirmayer, 2004; X. L. Mason, 2023; McLoughlin et al., 2024; Sartorius, 2007).

When are responses to physical complaints deemed "excessive"? A cut-off for this is arbitrary and diagnosis solely based on a clinician's judgement of whether or not the patient's psychological and behavioural response to their bodily symptoms is above and beyond of what would normally be expected. This may cast doubt on the legitimacy regarding their suffering (Bransfield & Friedman, 2019); there are concerns that especially women, whose physical suffering has a long history of being underrecognized and deemed

exaggerated or "psychological" (Briones-Vozmediano et al., 2018; Cox et al., 2003; I. Kim et al., 2022; McLoughlin et al., 2023; Newman-Toker et al., 2014; Samulowitz et al., 2018; Werner & Malterud, 2003), may be disproportionally diagnosed with SSD/BDD in an effort to dismiss the severity of their symptoms.

Others have argued that the newer DSM-5 concept of SSD is an improvement to the previous DSM-IV's *somatization disorder*, in that the criteria for SSD do not evolve around feigning/malingering or the medical (in-)explainability of bodily symptoms while acknowledging the patient's suffering (and necessary treatment thereof) beyond the physical symptom(s) (e.g., Rief & Isaac, 2014). Furthermore, diagnostic labels that were perceived as stigmatizing (e.g., somatoform) have been dropped for SSD/BDD and instead been replaced with more etiologically neutral names (Gureje & Reed, 2016).

Summary: Diagnosis

Functional disorder (FD) as an umbrella name for a range of – often overlapping – persistent bodily symptoms is an etiologically neutral and currently largely well accepted term by patients and clinicians. The diagnostic process of FD tends to be a lengthy and at times frustrating process for both patients and clinical practitioners. Reasons for this are manifold, including difficulties in patient-practitioner communication, lack of (mechanistic) explanation for the patient's symptoms, numerous overlapping – and at times stigmatizing – diagnostic labels and criteria, with diagnostic terms and expertise split across medical specialties. Over the years, clinical medicine and its classification systems have (partly) moved away from psychoanalytic explanations, stigmatizing labels, and exclusionary diagnoses. Importantly, the diagnosis of FD should now be made on the basis of positive signs. However, objectively measurable markers for FD are few and largely lacking entirely.

Mechanisms of Functional Disorders

The etiological and mechanistic understanding of FD has markedly evolved over the centuries and has integrated advances from a broad range of fields, including neurology and psychiatry, psychology, neuroscience or sociology. Today, FD is seen as a condition that should be understood within a biopsychosocial framework, where a complex interplay of several factors contribute to the development and maintenance of the disorder. In more recent years, research has focused on elucidating the underlying mechanisms in separate

functional symptoms or FD as a whole, and we have become to understand FD as a current status of 'perceptual dysregulation' in the central nervous system (e.g., Henningsen, Gündel, et al., 2018).

From a Biomedical to a Biopsychosocial Model

In 1977, the psychiatrist and internist George L. Engel published his now influential proposal for the adoption of a biopsychosocial model in medicine, in which he argued for a fundamental and necessary shift in clinical medicine's approach to viewing and treating disease. At the time, Engel (1977) laid out how physicians advocated for a strict biomedical model, according to which only biologically based diseases should be treated within the field of medicine - psychosocial factors found no place in this understanding of disease and should, therefore, belong to a new field outside of medicine, which would deal with psychological, social, and behaviour-based problems. From then on, psychiatry as a field of medicine should either only deal with diseases based on 'natural causes' (i.e. biological, neurochemical, neurophysiological), or be excluded altogether. According to this biomedical view of disease, it was believed that ailments would improve or be completely resolved as soon as its natural causes were treated (A. M. Ludwig, 1975). With this, the biomedical model takes a reductionist position to disease and the patient's experience of being ill.

In contrast to this, Engel (1977) further described that a sole focus on biomedical causes would ignore the complex interactions of biological, psychological, and social factors that are relevant at every stage in the formation and treatment of a disease. This consideration already starts at the initial consultation with the physician, as patients describe and contextualize their complaints in terms of their physical, psychological, social and cultural experience (see also Nunes et al., 2013). What is more, behavioural (e.g., physical activity supporting optimal glucose uptake and insulin receptor formation in diabetes mellitus) and psychosocial factors (e.g., community support, a good patient-practitioner relationship, and trust leading to better acceptance and adherence to insulin therapy) play an integral part in positive treatment progression (see also Miller et al., 2020). Accordingly, Engel (1977) posited that a person will not have recovered completely if only the underlying biochemical dysfunctions have been treated, but psychosocial aspects of the disease have not been adequately addressed.

Since then, much progress has been made to incorporate the biopsychosocial model in medicine's curricula, professional practice, and research (e.g., see Bolton, 2023; Card, 2023; Wade & Halligan, 2017). FD in particular assumes a special role in this framework, as its etiological factors, assumed mechanisms, symptom presentations, diagnostic frameworks, and treatment demands defy dualistic views on disease.

Biopsychosocial formulations of specific functional symptoms and FD as a whole have been extensively reviewed and encompass various predisposing, precipitating, maintaining and perpetuating factors, providing insights as to 'why' FD developed and persists in an individual (Beneitez & Nieto, 2017; Henningsen, Zipfel, et al., 2018; Löwe et al., 2024; Párraga & Castellanos, 2023). For instance, female sex and gender (Janssens et al., 2014; Mewes, 2022), low educational and socioeconomic status (Kingma et al., 2009; Schovsbo et al., 2023), (early) adverse life experiences or trauma (Duncan & Oto, 2008; Paras et al., 2009; Tak et al., 2015), emotional and mood disturbances (e.g., personality disorders, anxiety, depression, negative affectivity, perfectionism; Bonvanie et al., 2015; Janssens et al., 2014; Weisberg, 2000), social factors and environmental stressors (e.g., parental modeling, hostile family environment, employment setting; Palermo & Chambers, 2005; Schanberg et al., 2001; Vanini et al., 2024), previous (chronic) health conditions (O'Connell et al., 2020), and genetic factors (e.g., family history of FD, genetic variation in epigenetic makeup and biological systems; Heim et al., 2009; Janssens et al., 2014; Tak & Rosmalen, 2010) are predisposing factors that generally increase a person's vulnerability to developing FD in the future. In contrast, precipitating factors describe events that commonly trigger the onset of functional bodily symptoms, such as acute infections or injuries (Carstensen et al., 2015; Forestier et al., 2018; Stone et al., 2012), medical interventions (e.g., surgery, vaccine administration; Lim et al., 2022; Pareés et al., 2014), and stressful life events. Notably, however, many persons with FD do not identify (a) precipitating factor(s) for their symptoms (e.g., see Ludwig et al., 2018; Utianski & Duffy, 2022). While triggered bodily symptoms may initially only persist short-term, biopsychosocial factors may maintain and even aggravate the bodily complaints (for an overview, see Löwe et al., 2024). Examples of this include complex interactions between cognitive or emotional (e.g., catastrophizing, alexithymia, negative illness perceptions, deficient/biased attentional processing; Galvez-Sánchez et al., 2021; Kaplan et al., 2013; Steffen et al., 2015; Xiong et al., 2018), perceptual (e.g., somatosensory amplification; Perez et al., 2021), behavioural (e.g., physical inaction, protective posture, fear of falling; Haugstad

et al., 2006; Schlick et al., 2016), and social-environmental factors (e.g., overprotective parenting style, poor living conditions; Bergman et al., 2001; Logan et al., 2012; Wilson et al., 2014) as well as pathophysiological states and reactions (e.g., changes or abnormalities in brain activation and networks thought to be implicated in FD, see Pick et al., 2019; Voon et al., 2016 for an overview) and experiences within the healthcare context (e.g., negative patient-practitioner interactions; Bailey et al., 2024; Burke, 2019). Together, initially transient bodily complaints can develop into chronic and disabling bodily symptoms. At the same time, identifying factors that perpetuate or worsen symptoms can help formulate potential treatment targets. For instance, physical exercise and physiotherapy (e.g., Busch et al., 2007; K. J. Thompson et al., 2015), cognitive-behavioural therapy to address psychosocial and behavioural functioning (e.g., Edelman et al., 2012; Goldstein et al., 2010; Nielsen et al., 2015), and neuromodulatory therapies (e.g., TMS, iTBS; Spagnolo et al., 2021; Taib et al., 2019) have been shown to help alleviate symptoms.

In sum, the biopsychosocial model contrasts traditional biomedical formulations in describing a broad conceptual, multifaceted framework to understand, diagnose, and treat FD, taking into account an individual's psychosocial and biomedical past and present factors and its complex interactions. With this, the assessment, explanation, and management of FD also requires a multidisciplinary approach (e.g., see Chambers et al., 2015; Henningsen, Zipfel, et al., 2018).

Bayesian Brain & Predictive Processing Model

The most recent neurobiological theories see FD as a brain-based disorder stemming from dysregulation in the central nervous system (CNS). In contrast to the broader formulations of the biopsychosocial model, mechanistic models can provide a more detailed understanding of 'how' FD may develop in the first place, and subsequently persist. In the wider field of (computational) neuroscience, the Bayesian Brain hypothesis and the predictive processing – also called predictive coding – model are the currently most influential frameworks. The principles of Bayesian inference and predictive processing have been applied across various fields to explain a wide range of human experience and behaviour, including attention (e.g., C. Thompson et al., 2021), perception, motor control (e.g., Adams et al., 2012, 2013), goal-directed action and reflexes (e.g., Pezzulo et al., 2015), cognition (e.g., Burnston, 2021), vision (e.g., Marić & Domijan, 2022), and general (psycho)pathology (e.g., Barca & Pezzulo, 2020; Linson et al., 2020; Schoeller et al., 2024).

While Bayesian inference provides a computational framework for modelling behaviour based on CNS-based knowledge and sensory input, predictive processing describes neural responses along a hierarchical brain structure with a focus on prediction error minimization. As such, both theories are separate concepts (see figure 1 and 2) but complement each other well, which is why Bayesian theory is often combined with predictive processing accounts to describe a unified model of Bayesian predictive processing (Aitchison & Lengyel, 2017; Harkness & Keshava, 2017). Importantly, this conceptualization of brain function can help explain how persistent and distressing functional symptoms affecting the sensory (e.g., pain) and motor systems (e.g., involuntary movements) can result from normal structures and processes responsible for perception and action.

Bayesian predictive processing accounts do not oppose other prevailing theories and potential explanatory models of FD but can instead well integrate these frameworks. Examples are central sensitization (i.e., increased responsivity to painful stimuli; Woolf, 1983; Woolf et al., 1988), somatosensory amplification (heightened sensitivity to bodily sensations; Barsky, 1992), hypothalamic–pituitary–adrenal axis dysregulation (i.e., hypocortisolism; Tak et al., 2011), the signal-filtering model or gate-control theory (i.e., defective filter system; Melzack & Wall, 1965; Rief & Barsky, 2005), or autonomic nervous system dysfunction theory (e.g., reduction of heart rate variability, but see Tak et al., 2009). For a more thorough discussion of these model, the associated body of evidence as well as and their possible shortcomings, see literature reviews of van Ravenzwaaij and colleagues (2010) or Grover and Kate (2013).

According to Bayesian predictive processing views (e.g., Clark, 2013, 2016, 2018; Edwards et al., 2012; Friston, 2005; Hohwy, 2012, 2013; Lee & Mumford, 2003), perception and action do not represent linear, stimulus-response driven processes or responses with the brain assuming a passive position. Instead, the brain acts as an active organ that constantly generates predictions about the body and the external world. These brain-based predictions or 'priors' are based on so-called internal models, which represent accumulated knowledge, beliefs and expectations about internal (e.g., glucose levels, thirst, body temperature, joint and limb positioning) and external states and causes (e.g., weight of a coffee mug, speed of a thrown ball, reaction of another car driver; e.g., see Hayhoe et

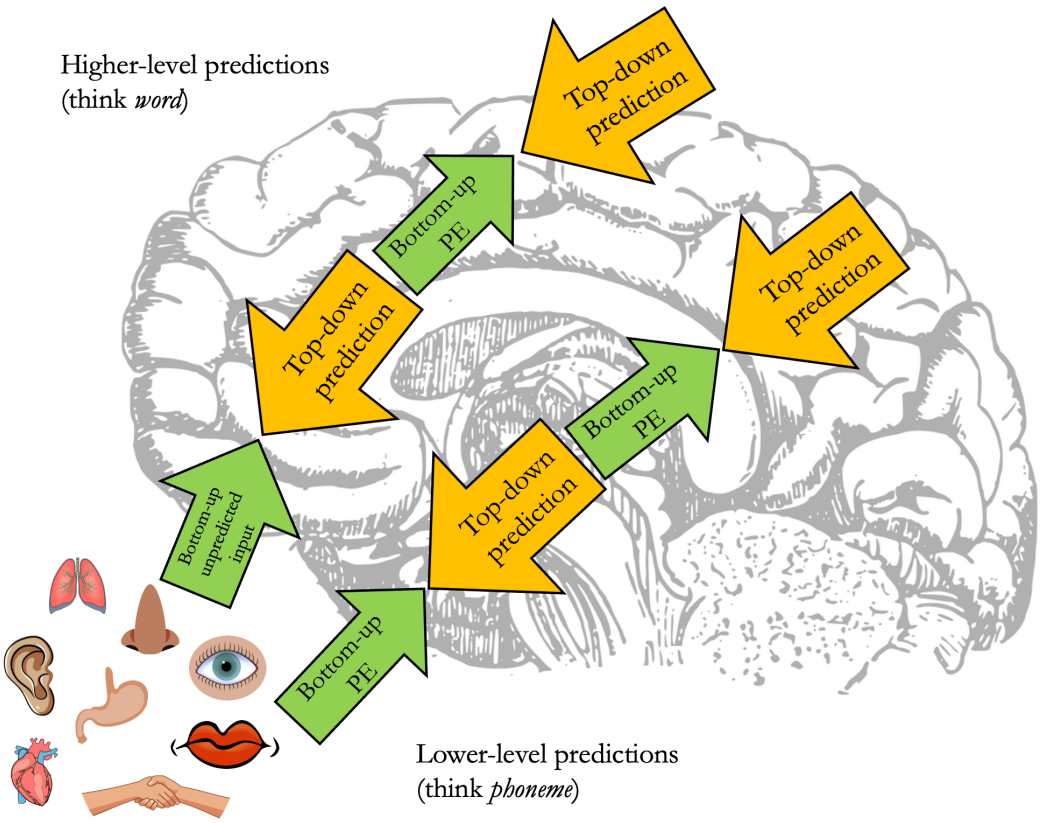

Figure 1. *Predictive Processing Model.* The brain is viewed as a predictive processing device, where top-down predictions meet bottom-up sensory input from the periphery at multiple levels of the cortical hierarchy (Mumford, 1991; Wacongne et al., 2011). This generative structure is thought to be organized along cascading levels of complexity (Blank et al., 2023; Heilbron et al., 2022; Tanaka, 1996), with lower levels of the hierarchy representing concrete, local, and fast-changing features, while higher levels encode more abstract and constant knowledge. Residual prediction errors at one level are propagated to higher levels, where they can be used as learning signals to revise predictions such that discrepancies between top-down information and bottom-up activity are reduced the next time around. Thus, the focus of this generative model rests on prediction error minimization: the goal is that internal models at each level can optimally predict lower-level input, such that the entire structure most accurately represents the causal properties of its body and environment (Hohwy, 2012; Rao & Ballard, 1999). PE = prediction error.

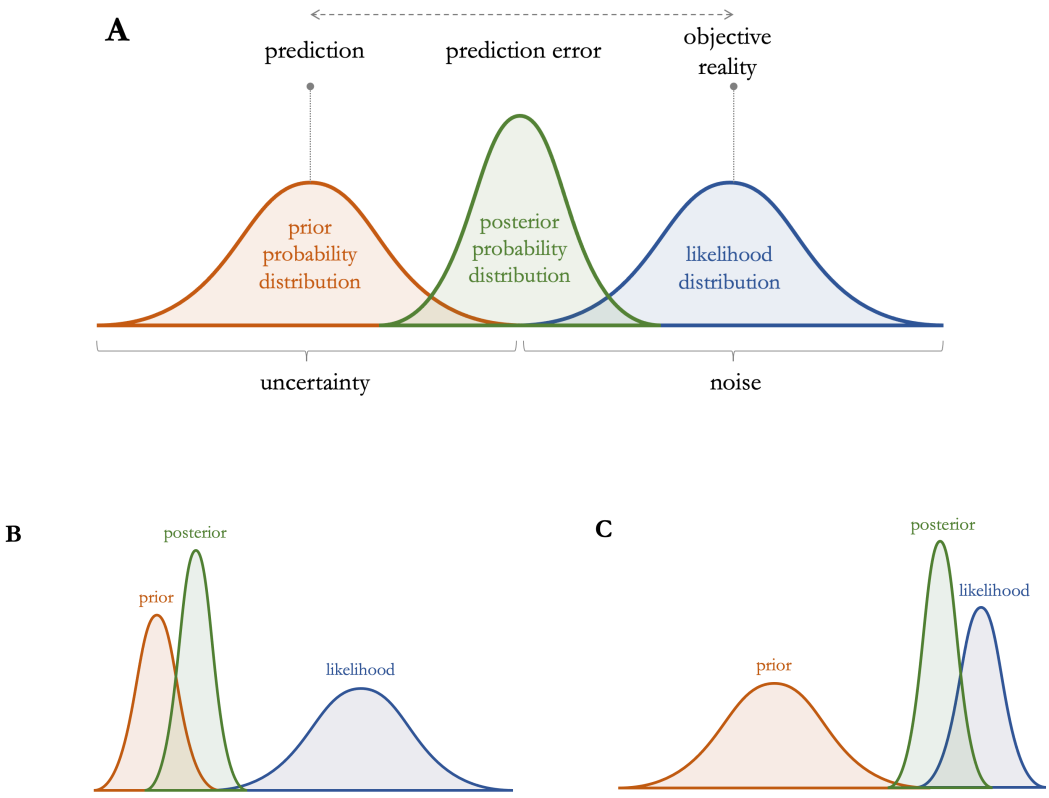

Figure 2. *Bayesian Brain Hypothesis.* (A) The brain is a probabilistic inference machine, constructing external and internal reality (i.e., posterior) by integrating prior knowledge, beliefs, or predictions (i.e., prior) with peripheral sensory input (i.e., likelihood). Both components are weighted by their relative certainty (i.e., precision), with the peak or maximum of the probability distribution reflecting its likely state or cause. Precision refers to the inverse variance or width of the respective distribution (Edwards et al., 2012). (B) When precise (i.e., highly certain) priors meet sensory input with low precision (i.e., unreliable or noisy input), an eventual percept will be dominated by the prior. In this example, a person can perceive a symptom (e.g., prior of there being damage in the body) without any organo-structural correlate that would give rise to it. (C) The opposite scenario is also possible. Here, highly precise sensory input (e.g., knife cuts into skin) can easily override any prior (e.g., a body at rest), shifting the eventual percept close to the incoming peripheral input. Note that Bayesian inference does not only apply to perception, but also to action (Barrett & Simmons, 2015; Singh & Scott, 2003).

al., 2004; Pezzulo et al., 2015; Shadmehr, 2004). Together with the information from internal models and the observed sensory input, the brain constructs perception and controls movement. Internal models are thought to undergo constant adaptation in response to relevant changes in the internal and external environment, specifically when predictions meaningfully deviate from the actual incoming sensory input. This discrepancy is called the prediction error (Egner et al., 2010), signalling unexpected signal ("surprise") and a need for learning (i.e., updating of internal models; Holroyd et al., 2009). Taken together, perception and action always represent a tightly intertwined combination of internal model predictions and actual sensory information. Because of this, constructed perception and actions should be considered as the best possible estimate of actual external and internal states.

The extent to which (and weather at all) learning takes place depends on the precision of the internal model/prior, the incoming sensory signals, and the elicited prediction error. In other words, highly precise priors or internal models are less likely to be updated, while internal models that are deemed less reliable are more likely to be updated when prediction errors arise. Rigid internal models are thought to form in the face of events that are highly relevant to the organism, such as traumatic experiences or acute illness (Dworkin et al., 1992; Garralda, 2011; Lyndon & Corlett, 2020). Such strong internal models require precise, repeated predictions errors to drive learning. When sensory input is considered reliable, resulting prediction errors will be deemed precise and, thus, are more likely to update predictions. In contrast, predictions errors arising from noisy or unreliable sensory evidence are estimated to be imprecise and are more likely to be ignored. However, when internal models are abnormally strong, even reasonably reliable sensory information is much less precise in comparison, therefore shifting the posterior probability distribution towards the pathological prior. Arising prediction errors are deemed equally unimportant, failing to update inflexible internal models and further reinforcing its precision – a vicious circle ensues (e.g., see Edwards et al., 2012).

As an organ enclosed in the skull, the brain has no direct access to the rest of the body or external events in the environment. Instead, the brain has to infer these hidden factors. Thus, the need for a predictive component in perception and action is manifold, especially when perceiving and acting in complex and ever-changing environments and bodies. For one, sensory processing is slow (e.g., when stubbing one's little toe, information

travels slowly and pain is only felt with a short delay), and purely response-driven behaviour would hamper timely and adequate responses in everyday life (e.g., catching a ball) as well as in life-or-death scenarios (e.g., anticipating hazards on the road; Engström et al., 2018; Jackson et al., 2009; Shadmehr, 2004). In addition, in order to maintain homeostasis (e.g., blood glucose levels), the organism needs to engage in goal-directed behaviour (e.g., obtaining food) or regulate autonomic function (e.g., insulin or glucagon release) well in advance (Nave et al., 2022; Pezzulo et al., 2015). What is more, sensory input is often ambiguous and inherently noisy (e.g., random discharges from neurons and receptors; objects in different lightning, orientations, sizes etc.), and any resulting percept or action would be highly error-prone (Gray, 2011). Based on previous knowledge or experiences in a given context, predictions help to obtain a more accurate estimate of the current state of the body or world when faced with ambiguous information. For instance, the intricate involvement of a predictive component becomes apparent when viewing visual illusions (see Figure 3), such as when a stationary image appears to be in motion or when the perceived colour of an object depends on assumed luminance, texture, or angles (Bloj et al., 1999; Brown & Friston, 2012; Weiss et al., 2002). Additionally, by focusing on prediction errors instead of on the entire sensory input in its every detail, the organism can preserve energy and cognitive capacities for other tasks central to thriving and surviving (Den Ouden et al., 2009; Friston, 2009; Koch & Poggio, 1999).

The Bayesian predictive processing account can help explain how FD can both develop in the first place and subsequently be maintained (e.g., see Pezzulo et al., 2019; Von Werder et al., 2024). For example, a person may suffer from acute vestibular neuritis (i.e., inflammation of the vestibular nerves), leading to the experience of imbalance and vertigo – and with this, providing initial sensory input for illness-characterized internal models. Due to the temporarily impaired peripheral vestibular function, internal models are updated accordingly, now incorporating the disease state and changed vestibular input. Because acute disease or impairment of the body is highly relevant to the survival of the organism, internal models are readily adapted to reflect the new circumstances and, therefore, are likely to be strong and rigid (i.e., highly precise). After treatment and complete recovery of the vestibular nerve, the now established highly precise priors or strong internal models representing pathology can be resistant to adaptation. As a result, the person's real-life perception can be almost completely dominated by an illness-related internal model. In line with this theoretical example, a significant portion of patients

suffering from vestibular neuritis go on to develop chronic dizziness or vertigo even though peripheral vestibular function has completely recovered again (e.g., see Arshad et al., 2023).

Perceptual inference, that is, adapting internal models in the face of relevant prediction errors, is one way to minimize surprise. Active inference (Barca & Pezzulo, 2020; Brown et al., 2011; Feldman & Friston, 2010; Pezzulo et al., 2015; Seth & Friston, 2016; Shipp et al., 2013) offers yet another way to reduce prediction errors, particularly by actively modulating what will arrive at the senses such that bottom-up information conforms to top-down predictions. In FD, predictions (e.g., about nociceptive or proprioceptive input) stemming from a (pathologically) precise prior about a bodily state (e.g., pain) or motion (e.g., gut movement, hand tremor) induce predictions errors that can be resolved by

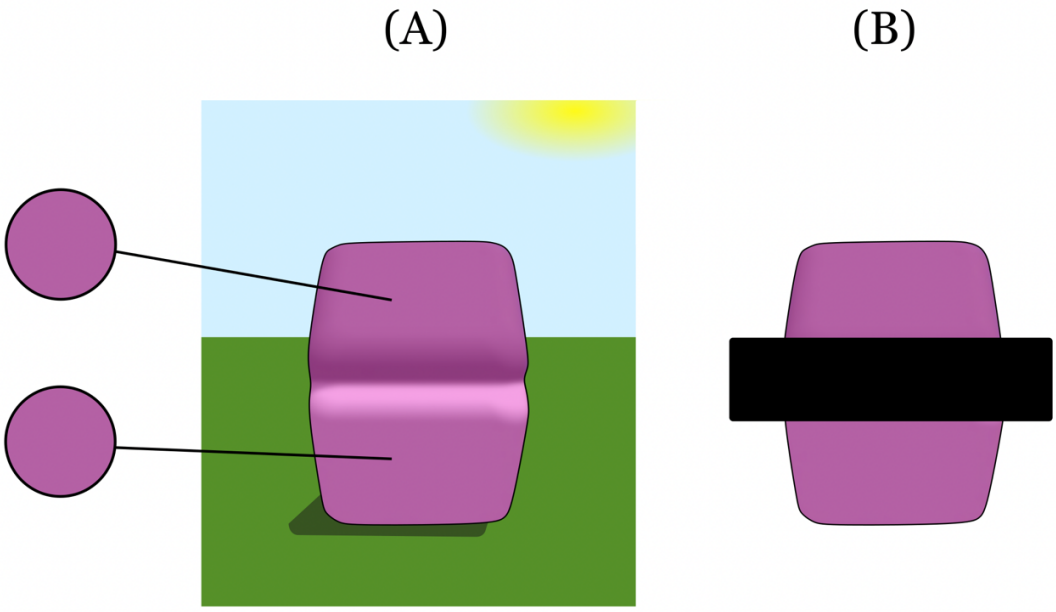

Figure 3. *Cornsweet illusion* (Cornsweet, 1970). The perceived colour of a surface depends on the inferred reflectance values of an object's periphery (e.g., due to contrasts induced by luminance intensity of the object's edges and its surrounding contexts; Purves et al., 1999). (A) The pink colour in the upper panel typically appears darker than in the lower panel. (B) This illusion is resolved when blocking contextual features – both rectangles now appear to be identical in colour. Note that this represents an automatic process in the central nervous system, which is why explicit knowledge of the illusion does not change the perception, akin to symptom perception in functional

(automatically) by altering sensory input to match predictions, for instance by eliciting action via classical reflex arcs at the level of cranial nerve nuclei and spinal cord or by shifts of attention that preferentially sample certain information or modulate prediction error precision (Adams et al., 2012, 2013; Barrett & Simmons, 2015; Eippert et al., 2009; Hechler et al., 2016).

Historically and still to this day, there has been a misconception among some health care practitioners – explicitly or implicitly – that FD symptoms are wilfully produced, feigned, or malingered (Edwards et al., 2023; McLoughlin et al., 2023). Importantly, akin to perceptual inference (e.g., see Henningsen, Gündel, et al., 2018), active inference processes (e.g., engaging reflexes) can function automatically without voluntary control or explicit decisions in the context of FD (Adams et al., 2013; Bourdin et al., 2019; Hodges & Tucker, 2011; Lersch et al., 2023). Similarly, attentional processes that lead to a preferential selection of prior-conforming sensory signals are also thought to operate mostly on an unconscious or automatic level (Edwards et al., 2012; J. Kim et al., 2018; Roelofs et al., 2003). This may also be why patients with FD lack a sense of agency for their symptoms (Baek et al., 2017), such is the case of involuntary limb movements in functional movement disorder. That is, movements initiated through classical reflex arcs may surpass higher-level structures that would give rise to conscious intention of a movement (Ainley et al., 2016; Maselli et al., 2022). Similarly, movement and its generated sensory feedback may not be accurately predicted due to erroneous internal models, and may thus be interpreted as uncontrollable or unpredictable (Chambon et al., 2014; Tinazzi, Marotta, et al., 2021).

Although the ideas of the contemporary Bayesian predictive processing accounts have gained more recent popularity within neuroscientific research, the involvement of 'priors' or predictions in the formation of perception and action has already been described in Helmholtz' (1867) early work on what he called 'unconscious inference': the brain does not directly construct perception from sensory input but takes into account earlier experiences and knowledge in order to create a meaningful and coherent (visual) percept. These ideas of an internal generative model subsequently resurfaced and were further developed in animal research, which also unveiled insights into the respective brain regions responsible for the integration of internal models with sensory input; for instance, Sperry (1950) surgically manipulated the eyes of southern swellfish, blinding one eye and rotating the other eye by 180 degrees. Consequently, he observed an impairment of the fish's

optokinetic reflex, in that the fish kept moving circular in the direction of the self-initiated movement, presumably to "catch up" with the external world's seeming displacement. This demonstrated that the brain can distinguish externally- versus self-generated displacement of the visual image on the retina (i.e., due to movement of the surroundings versus the self) based on so-called 'corollary discharge' – a copy of the self-generated motor command that the brain can account for; a feedback mechanism that was disrupted by the experimental visual inversion. In the same year, von Holst and Mittelstaedt (1950) published their findings on the 'reafference principle', according to which the brain actively estimates sensory feedback ('reafference estimate') based on the motor command's copy, which they termed an 'efference copy'. It allows the brain to anticipate the effects of self-generated movements and, in a comparison, cancel out the reafferent input. This way, sensory reafferent feedback arising from one's own action that matches the respective efference copy is interpreted as self-generated ("I am moving"), while discordant ('exafferent') input is considered to be generated by someone or something else ("The world is moving").

MacKay (1956), and later Barlow (1961), built on these initial findings and further theorized how the sensory (visual) system benefits from a probabilistic neural 'code' to transform sensory information into meaningful representations of the body and world, analogous to an internal model that matches predictions with sensory input and relays prediction errors to change the respective code or model. Around the same time, seminal work by Held and Freedman (in a series of experiments summarized in 1963) extended these lines of thought by investigating feedback mechanisms that proved to be crucial for the flexibility of the (human) central nervous system, specifically the sensorimotor system. For instance, participants viewed through prisms that displaced or distorted their visual field while completing motor tasks, such as drawing or grasping an object with their hand. Importantly, participants were eventually able to fully adapt to the changed conditions when they actively moved the hand by themselves; when the same movements were carried out passively (i.e., the arm was moved by an external agent), no such adaption took place. Thus, the prediction error arising from the mismatch between predicted and actual hand movement was able to drive learning when movements were self-generated, while passive movements failed to produce efference copies and, consequently, prediction errors.

Summing up, the scientific groundwork for the brain as a predictive, generative organ that infers the most likely causes of sensory input and the state of the world and body has been laid many decades ago, but remains highly relevant for understanding a range

of human behaviour and experience – including FD – today. However, the way in which this mechanism is impaired in FD specifically remains an open question for research.

Summary: Mechanisms

The field of medicine has undergone a fundamental shift, away from considering health and disease solely within a biomedical model, on to integrating biological, psychological, behavioural, and social dimensions in understanding the patient as a whole person – as such, health care also requires an interdisciplinary and multiprofessional approach to treatment. Within this biopsychosocial framework, FD is currently best understood as a consequence of dysregulated perceptual or active inference, characterized by erroneous integration of peripheral sensory input with rigid internal models of the body and world.

Chapter 3

Methodology

Overarching Research Questions

Taken together, FD are captured under both separate syndromal or symptom-specific (e.g., PPPD, pain) as well as common (e.g., functional/dissociative neurological symptom disorder) diagnostic labels. To diagnose FD in clinical practice, healthcare practitioners (should) rely on positive signs; however, currently available signs are few and tend to be symptom-specific (e.g., Hoover's sign for functional weakness/paralysis) while a unifying, transdiagnostic marker is missing. In the current body of literature, it has long been theorized that FD may share common underlying mechanisms (e.g., Wessely et al., 1999) – specifically dysregulated sensorimotor processing (Bogaerts et al., 2010; Lehnen et al., 2019; Schröder et al., 2021, 2022; Van Den Houte et al., 2018) – but empirical evidence for an objectively measurable unifying mechanism this is still scarce. Overall, the professional uncertainty and lack of understanding surrounding the diagnostic validity of FD and its underlying mechanistic processes fuels the stigmatization of this already underserved patient group. Therefore, the aim of this dissertation project was three-fold:

Is erroneous sensorimotor processing during large combined eye-head gaze shifts

1) a shared, **transdiagnostic mechanism** underlying FD,
2) an objectively **measurable marker** of FD, and
3) a replicable, **robust phenomenon** in FD?

In order to answer these questions, we employed an eye-head paradigm to measure sensorimotor processing in healthy controls and people who experienced a single functional symptom: chronic (functional) pain, functional movement disorder, or functional dizziness.

Experimental Paradigm & Operationalisation

We employed an eye-head paradigm that is designed to uncover problems in sensorimotor processing – specifically in integrating internal model predictions about movement and the actual sensory feedback generated by the movement – during large combined eye-head gaze shifts. The experimental paradigm is based on Lehnen and colleagues' (2003) study, in which they examined healthy volunteers' motor control during large combined eye-head gaze shifts towards briefly flashing visual targets under normal and increased (2.5-fold) head moment of inertia. Participants completed the task in darkness (i.e., no visual feedback) and wore a modified bike helmet with attached masses for the experimental manipulation. In comparison to unweighted gaze shifts, gaze shifts with the helmet were characterized by markedly slower head velocities and amplitudes (degrees), although they were equally able to reach the target and stabilize the eyes. In a subsequent study (Lehnen et al., 2008), the same group could demonstrate that increasing the head moment of inertia (3.3-fold) experimentally induces a mismatch between the predicted and actual signals arriving at the sensors (e.g., vestibular sensors situated in the inner ear). In other words, the manipulated head characteristics are not yet accounted for in the participant's internal model when predicting vestibular (and proprioceptive) feedback based on the motor command's efference copy. The result are instable head movements, characterized by measurable head oscillations at the end of gaze shifts.

Since then, the eye-head paradigm in general can be considered a well-established setup to measure sensorimotor processing (deficits) under normal and increased head moment of inertia in healthy participants and patients with functional (i.e., functional dizziness, irritable bowel syndrome; see Lehnen et al., 2019; Schröder et al., 2021, 2022) or organo-structural impairments (i.e., cerebellar ataxia, bilateral vestibulopathy; Lehnen et al., 2009b, 2009a; Sağlam et al., 2011, 2014; Sağlam & Lehnen, 2014).

The setup used in the studies included in this dissertation comprises three experimental rounds, starting with 1) a natural, unweighted condition, followed by 2) a weighted condition in which participants' head moment of inertia was increased 3.1-fold and 3) a final natural, unweighted round. Gaze shifts in all experimental rounds were carried out in complete darkness. Participants were seated in front of five target LED lights, positioned to the person's left (at 40° and 35°), center (at 0°, 1m distance to the eyes), and right (at -35° and -45°). We asked participants to naturally direct their gaze – the eyes and the head together – to an LED target when it briefly flashed and to keep gaze in the

remembered target position. The same light would briefly flash again (i.e., control light), which allowed participants to correct gaze position and ensured that the next gaze shift started close to the intended location. During each experimental round, participants performed 52 gaze shifts to a visual target, of which 43 were large (80° or 75°) gaze shifts.

Throughout the experiment, we acquired continuous head velocity and pupil rotation data streams using the EyeSeeCam system's wearable goggles with built-in 3D inertial sensors and videooculography (220 Hz sampling rate; EyeSeeTec GmbH, Munich, Germany), from which we could also derive head and eye position data. In advance, goggles were calibrated to the participant's individual eye and head characteristics using a five-point laser pattern projected at a wall (1.5m distance). For the purpose of the here presented studies, we were interested in head velocity data during large gaze shifts to the target lights. The remaining raw head and eye position data were only inspected visually to ensure that gaze shifts were executed in accordance with the provided instructions (e.g., eyes and head are both moved together), and that data was complete and recorded correctly. Head instability was operationalised as the absolute amplitude of the first negative head velocity peak, normalised by the movement's absolute positive peak velocity – the head oscillation ratio (see figure 4).

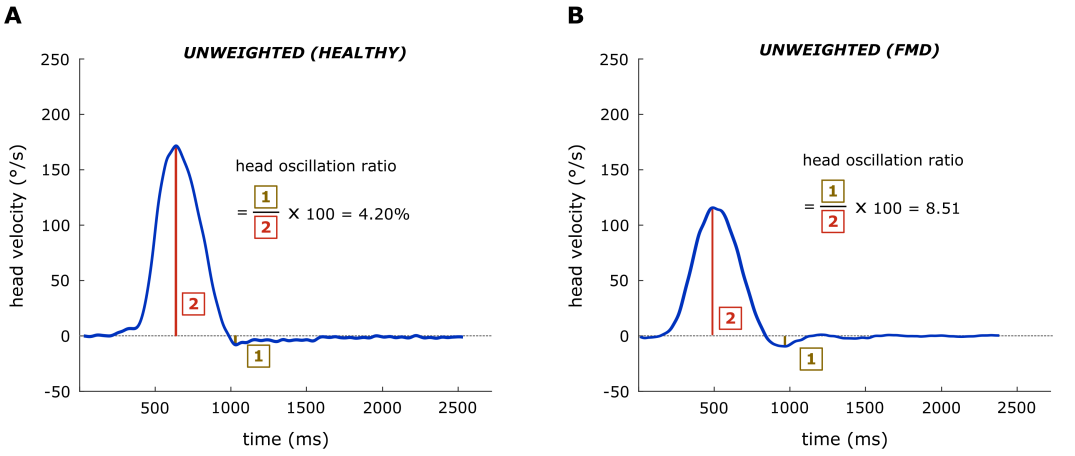

Figure 4. *Illustration of Head Oscillation Ratio.* (A) A participant performed a relatively smooth head movement, characterized by a bell-shaped head velocity profile. (B) Head stability worsens as the head moment of inertia is experimentally increased 3.1-fold, reflected in a larger head oscillation ratio.

Participants

In order to ensure that we were measuring a possible transdiagnostic mechanism and marker, it was important that all patients experienced only a single functional symptom currently and throughout the past three months. Patients were eligible to participate if they met a diagnosis based on the ICD-10's (WHO, 2004) definition for chronic (functional) pain (i.e., persistent chronic [functional] pain disorder, F45.40; or chronic pain disorder with somatic and psychological factors, F45.41), functional movement disorder (i.e., dissociative movement disorder, F44.4), or functional dizziness (i.e., somatoform dizziness, F45.8). Healthy control participants did not suffer from any functional symptom(s), currently or at any time in the past, as to maximize potential differences in underlying sensorimotor processing capacities (i.e., head instability). In addition, patients were excluded from the studies if they currently suffered from another (mental) disorder that dominated the disorder or symptom pattern. Healthy controls were excluded from participation if a mental disorder was currently present. Table 1 summarizes all other in- and exclusion criteria for persons with FD and healthy controls that took part in the here presented studies. We recruited patients from in- and outpatient clinics of the Department of Psychosomatic Medicine and Psychotherapy, and patients with functional movement disorder additionally from the outpatient clinic for movement disorders at the Department of Neurology; healthy control participants via external and internal clinic-wide web- and poster-based announcements at the University Hospital rechts der Isar of the Technical University of Munich, Germany

Table 1. Overview of additional ex- and inclusion criteria applying to both patients and healthy control participants.

Inclusion criteria	≥ 18 years old
Exclusion criteria	Current pregnancy
	Visual acuity < 20% (c.c.) in the better eye
	Deficits that make structured questioning impossible
	Acute complaints of the cervical spine
	Signs of a vestibular, extrapyramidal or cerebellar disorder

Clinical Characterization

We used EyeSeeCam's (EyeSeeTec GmbH, Munich, Germany) video head-impulse test (vHIT) to assess the passively evoked horizontal vestibulo-ocular reflex (VOR), a fast-acting brainstem reflex that keeps the eyes (gaze) stable. Specifically, the vHIT is a test of the horizontal semicircular canals situated in the inner ear. In our experimental context, we assessed function of the right and left horizontal semicircular canals since we only tested the VOR for head shifts in the horizontal plane and were also only interested in measuring horizontal eye-head movements in the experiment (Weber et al., 2009).

While the participant kept their eyes fixated on a centrally positioned target (at 1m distance from the eyes), the experimenter abruptly rotated the participant's head horizontally, such that the direction of the small (10 – 20°, 150-300°/s) movement was unpredictable. The VOR gain represents the eye-head velocity ratio during external perturbations to the head; that is, the VOR gain is 1.0 if the eyes perfectly move in opposition to the head. Particularly, the eyes rotate at (typically nearly) equal velocity in the opposite direction to the head to compensate the passive movement, such that the visual image is stabilized on the retina (McGarvie et al., 2015). For the studies included in this thesis, we regarded a VOR gain of less than 0.79 and the presence of covert (i.e., during head impulse) or overt (i.e., after head impulse) catch-up saccades as indicative of abnormalities in the peripheral vestibular system (in analogy to Blödow et al., 2014; MacDougall et al., 2009; Mossman et al., 2015). The vHIT was always conducted immediately before the eye-head experiment.

In addition, we completed the Structured Clinical Interview for DSM-5 Disorders, Clinician Version (SCID-5-CV, German version; Beesdo-Baum et al., 2019) with all participants. On the one hand, this served to clinically characterize our patient group, since we measured a very specific, relatively small group of patients with especially severe FD. On the other hand, this ensured that we complied with the in- and exclusion criteria for patients as well as healthy control participants with regards to psychiatric comorbidity and severity. The SCID-5-CV was always conducted after the eye-head experiment.

Statistical Analysis

We adopted a Bayesian Sequential Analysis approach for the here presented studies (Schönbrodt et al., 2017), permitting us to collect data successively, if necessary, until we reached a pre-determined threshold of evidence; optional stopping and sequential analysis do not pose a problem in Bayesian statistical tests (see Rouder, 2014). We decided to pre-register an initial sample size for the first rounds of analyses based on an a priori power analysis as well as subsequent incremental data collection rounds. This approach was highly valuable given that our sample consisted of a very unique population (i.e., severe but isolated functional symptom without a relevant organo-structural correlate). This way, we were still able to obtain meaningful effects despite a quite limited population to draw from, and could simultaneously reduce an unnecessary burden of participating in a lengthy and at times challenging study for this vulnerable patient group. In addition, the more general Bayesian approach enabled us to determine the relative evidence for both the alternative and the null hypothesis or model (Peter Rosenfeld & Olson, 2021; Wagenmakers et al., 2018). The Bayes Factor (BF) represents the marginal likelihood ratios of two models, i.e., the change in odds from the prior (i.e., initial belief) to the posterior (i.e., updated belief) in favour of the null or alternative hypothesis in light of new evidence (i.e., after incorporating the data; Kelter, 2021; Wagenmakers et al., 2010). The degree of evidence provided by the obtained BF is generally described in a qualitative way, such that a BF of 1, 1–3, 3–10, 10–30, 30–100, and >100 respectively correspond to no, anecdotal, substantial, strong, very strong, and extreme evidence (Wetzels et al., 2011). The subscripts $_{10}$ (BF_{10}) and $_{01}$ (BF_{01}) denote which model's marginal likelihood (null model H0 versus alternative H1) is in the numerator versus denominator (Quintana & Williams, 2018); this also means that reported BFs can be readily translated into its counterpart, as $BF_{10} = 1/BF_{01}$ and $BF_{01} = 1/BF_{10}$. That is, BF_{01} indicates evidence for the null hypothesis, while BF_{10} implies evidence for the alternative hypothesis. For instance, a BF_{01} of 1 indicates that the data are equally likely to have occurred under the null and alternative hypotheses/models, and a BF_{01} of 5 can be interpreted as substantial relative support in favour of the null hypothesis in comparison to the alternative hypothesis.

Traditional Null Hypothesis Statistical Testing (NHST) relies on data sampling distributions and allows to only reject the null hypothesis (generally at $p < 0.05$) in favour of the alternative hypothesis, but never allows to accept the null hypothesis. By definition, the p-value represents the probability of observing the current or more extreme set of

observations, *given that the null hypothesis is true*. Thus, a non-significant p-value is inherently uninformative: it can either indicate that the null hypothesis is indeed true, or that the study simply lacked power to detect an effect (Marsman et al., 2017). The Type I error (α) corresponds to the false positive error rate (1 out of 20 tests at a chosen α of 0.05), the Type II error (β) rate corresponds to the false negative error rate (i.e., lack of statistical power, 1 – β), that is, failing to reject the null hypothesis when the alternative hypothesis is in fact true (Biau et al., 2010). Due to Type I error occurrence naturally increasing with an Increasing number of hypothesis tests, interim or multiple testing will inevitably make a false positive result more likely if p-values are not corrected for (De Groot, 2014; Stefan & Schönbrodt, 2023). In contrast to a BF, a p-value also does not provide any indication of the magnitude of an effect (Verdam et al., 2014).

Open Science & Good Research Practices

We preregistered all study protocols, power analyses, statistical analysis plans, and research hypotheses on the Open Science Framework (OSF; https://osf.io) prior to any data collection. Analyses that deviated from the *a priori* planned, confirmatory statistical tests were clearly described as *post hoc* or 'exploratory'. All data processing scripts, statistical analysis files, and anonymized raw data are openly accessible to the public via their respective OSF environments. In an effort to increasingly rely on accessible, freely usable, and distributable resources, we mostly used programming languages (i.e., Python; Python Software Foundation, https:// www.python.org; van Rossum & de Boer, 1991) and statistical analysis applications (i.e., JASP; JASP Team, 2023) with an open-source licence. Matlab (The MathWorks Inc., 2022) constitutes an exception, which we used to preprocess raw data and automatically compute initial parameters. We published all scientific articles open-access, in line with the European Commission's Horizon 2020 policy.

Chapter 4

Study 1

Publication Information

Title	Not a general, symptom-unspecific, transdiagnostic marker for functional symptoms: sensorimotor processing of head control is intact in chronic pain
Authors	Franziska Regnath, Katharina Biersack, Nina Jäger, Stefan Glasauer, Nadine Lehnen
Journal	Frontiers in Neurology
DOI	10.3389/fneur.2023.1294702
Citation	Regnath, F., Biersack, K., Jäger, N., Glasauer, S., & Lehnen, N. (2023). Not a general, symptom-unspecific, transdiagnostic marker for functional symptoms: Sensorimotor processing of head control is intact in chronic pain. *Frontiers in Neurology*, *14*, 1294702. https://doi.org/10.3389/fneur.2023.1294702

Individual Contribution

Franziska Regnath (FR) is the first author of this publication. FR preregistered the study. FR performed the experiments and curated the obtained data; she also verified existing Matlab-script to preprocess the raw data, programmed new scripts for data cleaning and preparation (Python), and carried out the statistical analyses JASP. FR was also in charge of project administration and management (i.e., data storage and screening, participant recruitment and screening, scheduling, laboratory supplies, participant compensation, ethics proposals/amendments/extensions). FR created all visualizations, wrote the original manuscript draft, incorporated co-authors' reviews and edits, and was in charge of the peer-review process. FR additionally created the project environment on the Open Science Framework, where she made anonymized raw data and analysis script openly accessible.

Abstract

Introduction: Functional disorders are prevalent in all medical fields and pose a tremendous public health problem, with pain being one of the most common functional symptoms. Understanding the underlying, potentially unifying mechanism in functional (pain) disorders is instrumental in facilitating timely diagnosis, stigma reduction, and adequate treatment options. Neuroscientific models of perception suggest that functional symptoms arise due to dysregulated sensorimotor processing in the central nervous system, with brain-based predictions dominating the eventual percept. Experimental evidence for this transdiagnostic mechanism has been established in various functional symptoms. The goal of the current study was to investigate whether erroneous sensorimotor processing is an underlying transdiagnostic mechanism in chronic (functional) pain. Method: A total of 13 patients with chronic (functional) pain [three patients with chronic (functional) pain disorder, F45.40, ICD-10; 10 patients with chronic pain disorder with somatic and psychological factors, F45.41, ICD-10]; and 15 healthy controls performed large combined eye-head gaze shifts toward visual targets, naturally and with increased head moment of inertia. We simultaneously measured participants' eye and head movements to assess head oscillations at the end of the gaze shift, which are an established indicator of (transdiagnostic) sensorimotor processing deficits of head control. Results: Using a Bayesian analysis protocol, we found that patients with chronic (functional) pain and control participants stabilized their heads equally well (Bayes $Factor_{01}$ = 3.7, Bayes $Factor_{exclusion}$ = 5.23; corresponding to substantial evidence) during all sessions of the experiment. Conclusion: Our results suggest that patients with chronic (functional) pain do not show measurable symptom-unspecific sensorimotor processing deficits. We discuss outcome parameter choice, organ system specificity, and selection of patient diagnoses as possible reasons for this result and recommend future avenues for research.

Chapter 5

Study 2

Publication Information

Title	Experimental evidence for a robust, transdiagnostic marker in functional disorders: Erroneous sensorimotor processing in functional dizziness and functional movement disorder
Authors	Franziska Regnath, Katharina Biersack, Lena Schröder, Marie-Christin Stainer, Dina von Werder, Dominik Pürner, Bernhard Haslinger, Nadine Lehnen
Journal	Journal of Psychosomatic Research
DOI	10.1016/j.jpsychores.2024.111694
Citation	Regnath, F., Biersack, K., Schröder, L., Stainer, M.-C., Von Werder, D., Pürner, D., Haslinger, B., & Lehnen, N. (2024). Experimental evidence for a robust, transdiagnostic marker in functional disorders: Erroneous sensorimotor processing in functional dizziness and functional movement disorder. *Journal of Psychosomatic Research*, 111694. https://doi.org/10.1016/j.jpsychores.2024.111694

Individual Contribution

FR is the first author of this publication. FR wrote the preregistration for the study and created the corresponding project environment on the Open Science Framework, where all anonymized raw data and analysis scripts were made publicly available after publication. FR performed the experiments and collected the data; she also verified existing preprocessing scripts (Matlab), programmed the Python scripts and performed the statistical analyses JASP. FR was responsible for project administration and management (i.e., data storage and screening, participant recruitment and screening, scheduling, laboratory supplies, participant compensation, ethics proposals/amendments/extensions).

FR generated all visualizations, wrote the original manuscript draft, incorporated co-authors' reviews and edits, and was in charge of the peer-review process.

Abstract

Objective: Recent neuroscientific models suggest that functional bodily symptoms can be attributed to perceptual dysregulation in the central nervous system. Evidence for this hypothesis comes from patients with functional dizziness, who exhibit marked sensorimotor processing deficits during eye-head movement planning and execution. Similar findings in eye-head movement planning in patients with irritable bowel syndrome confirmed that these sensorimotor processing deficits represent a shared, transdiagnostic mechanism. We now examine whether erroneous sensorimotor processing is also at play in functional movement disorder. Methods: We measured head movements of 10 patients with functional movement disorder (F44.4, ICD-10), 10 patients with functional dizziness (F45.8, ICD-10), and (respectively) 10 healthy controls during an eye-head experiment, where participants performed large gaze shifts under normal, increased, and again normal head moment of inertia. Head oscillations at the end of the gaze shift served as a well-established marker for sensorimotor processing problems. We calculated Bayesian statistics for comparison. Results: Patients with functional movement disorder (Bayes Factor $(BF)_{10}$ = 5.36, BF_{incl} = 11.16; substantial to strong evidence) as well as patients with functional dizziness (BF_{10} = 2.27, BF_{incl} = 3.56; anecdotal to substantial evidence) showed increased head oscillations compared to healthy controls, indicating marked deficits in planning and executing movement. Conclusion: We replicate earlier experimental findings on erroneous sensorimotor processing in patients with functional dizziness, and show that patients with functional movement disorder show a similar impairment of sensorimotor processing during large gaze shifts. This provides an objectively measurable, transdiagnostic marker for functional disorders, highlighting important implications for diagnosis, treatment, and destigmatization.

Chapter 6

General Discussion

In the present dissertation, the goal was to investigate 1) potential transdiagnostic sensorimotor processing deficits in people with FD (i.e., functional [chronic] pain, functional movement disorder, functional dizziness) compared to healthy controls by employing a well-established eye-head paradigm, 2) to examine whether erroneous sensorimotor processing is an objectively measurable and 3) robust marker in FD. Our experimental work is embedded within the theoretical framework of the Bayesian predictive processing model, which allows us to explain how perception and action arise from an intricate mix of CNS-based internal model predictions and sensory signals from the periphery.

Together with our key results, this chapter will discuss the relevance of our findings within the broader body of scientific research as well as its (clinical) implications for diagnosis, treatment and stigma. It will also present the importance and advantages of open science in supporting reproducibility and transparency in (FD) research, and provide an outlook to possible future research endeavours.

Key findings

Across two studies, we measured participants' head motor control during large combined eye-head gaze shifts towards visual targets under normal, increased (3.1-fold), and again normal head moment of inertia. Head instability at the end of gaze shifts served as a well-established marker of altered sensorimotor processing (see Lehnen et al., 2019; Sağlam et al., 2011; Sağlam & Lehnen, 2014; Schröder et al., 2021, 2022).

Study 1 (Regnath et al., 2023) showed that persons with chronic (functional) pain (F45.40 or F45.41; ICD-10) do not exhibit sensorimotor processing deficits compared to healthy controls, neither during gaze shifts with normal nor with increased head moment of inertia. In other words, our results indicate that patients' head movements were driven by correct internal model predictions. What is more, internal models (e.g., of the head plant) – and subsequently head motor commands across trials – were updated equally well in

patients and healthy control participants when the head characteristics were experimentally altered (i.e.., helmet or goggles).

In study 2 (Regnath et al., 2024), we employed the same experimental paradigm to examine whether previous findings of sensorimotor processing deficits in persons with functional dizziness (F45.8, ICD-10) could be replicated in a new patient sample, and whether erroneous sensorimotor processing is a transdiagnostic mechanism underlying functional movement disorder (F44.4, ICD-10). First, we observed marked head instability in persons with functional dizziness compared to healthy controls during natural and weighted head shifts, similar to earlier results reported by Lehnen and colleagues (2019). Unlike healthy controls, persons with functional dizziness could likely not adapt internal models across experimental trials, including to the slightly increased head moment of inertia that was presumably induced by the measurement goggles also in the two unweighted conditions. Second, persons with functional movement disorder showed more pronounced head instability compared to healthy controls across all experimental conditions, indicating wrong internal model use already during natural head movements. Again, healthy controls clearly learned to adapt internal model predictions to the altered head characteristics (i.e., helmet or goggles); however, our sample was too small to determine whether persons with functional movement disorders also improved head motor control throughout the experiment.

Taken together, we found that erroneous sensorimotor processing, characterized by objectively measurable head oscillations at the end of gaze shifts, is a transdiagnostic mechanism and objectively measurable marker for functional dizziness and functional movement disorder, but not chronic (functional) pain.

Erroneous Sensorimotor Processing as a Common Mechanism Underlying FD

The vast range of FD symptoms have long been considered to be an expression of (a) common underlying mechanism(s) mainly due to the high co-morbidity between functional symptoms (Fink, 2017), thus various general umbrella terms (e.g., functional disorder, FD; functional somatic symptom[s]/syndrome, FSS; persistent somatic symptoms, PSS) have emerged to describe differently presenting (e.g., pain, fatigue, involuntary movements, weakness/paralysis, seizures, dizziness, gut problems) functional bodily complaints

(Burton et al., 2020; Creed et al., 2010; Henningsen, Gündel, et al., 2018; Henningsen, Zipfel, et al., 2018; Löwe et al., 2024). For instance, researchers and clinicians based in the United Kingdom commonly use the abbreviation 'FND' (functional neurological disorder) to describe functional symptoms except for pain and fatigue (Bennett et al., 2021), although the latter are the most often co-occurring bodily symptoms in FD (Butler et al., 2021; Kroenke, 2003). While most clinicians and researchers would agree that all functional symptoms likely share etiological and risk factors (e.g., prior gastrointestinal infection not only specific to IBS; Donnachie et al., 2020), pathophysiological patterns (e.g., brain region activation, connectivity, and anatomical alterations; see Barrett & Simmons, 2015; Bègue et al., 2019; Ito, 2008; Nisticò et al., 2022; Ong et al., 2019; Perez et al., 2015), and underlying mechanisms (e.g., 'perceptual dysregulation'; Henningsen, Gündel, et al., 2018), some studies have identified certain symptom-specific characteristics such as age and type (i.e., sudden versus gradual) of onset, average remission rates (Gelauff & Stone, 2016) and, obviously, the site or affected organ system (Lidstone et al., 2022; Tinazzi, Geroin, et al., 2021; Wessely et al., 1999; Wessely & White, 2004; White, 2010). This debate is also reflected in diagnostic classification systems that code different functional symptoms under both common (e.g., functional dizziness and functional movement disorder under dissociative neurological symptom disorder in ICD-11) and separate symptom or syndrome categories (e.g., Chronic Pain or PPPD in ICD-11). Likewise, treatment recommendations for different functional symptoms largely overlap, with a multimodal stepped care approach being considered the most promising line of treatment (Henningsen, Zipfel, et al., 2018); next to this, there are additional individualized treatment options for specific functional symptoms available (e.g., vestibular rehabilitation for dizziness, motor retraining or physiotherapy for motor symptoms; Espay et al., 2018; Nada et al., 2019; Roenneberg et al., 2019; Schaefert et al., 2014, 2021).

Erroneous sensorimotor processing is one mechanism that has been proposed to underly FD more generally. First empirical evidence for this notion comes from experimental work assessing breathlessness perception in patients with functional dyspnea as the primary complaint before, during, and after a rebreathing challenge (Bogaerts et al., 2010). They found that compared to healthy controls, patients reported significantly more breathlessness when respiratory sensory input was weak (i.e., breathing room air) while measured physiological parameters (i.e., fractional end-tidal CO_2 concentration, minute ventilation) did not reach established symptom-inducing levels or were equal between

groups. In contrast, dyspnea perception was equal between groups when sensory input was strong (i.e., increased CO_2 in the breathed air during the rebreathing phase), with again no differences in physiological parameters. In a subsequent study, the same research group employed the rebreathing paradigm with persons suffering from fibromyalgia or chronic fatigue syndrome to investigate whether similar sensorimotor (respiratory) processing alterations could be found in FD where the primary complaint is unrelated to dyspnea (Van Den Houte et al., 2018). Here, they also found a decoupling effect of breathlessness perception and corresponding physiological parameters: during the rebreathing challenge, both breathlessness perception as well as physiological parameters did not differ between healthy controls and patients. However, in the subsequent recovery phase (i.e., participants breathing normal room air again), patients reported markedly increased and prolonged breathlessness than healthy controls despite equal physiological measures. Presumably, in patients, highly precise sensory input indicating relevant deviations in arterial CO_2 concentration might have activated pathological internal models about breathlessness, which continued to dominate perception when CO_2 concentrations had normalized again (i.e., weak sensory input). Overall, this suggests that in persons with FD – irrespective of the specific symptom (i.e., dyspnea, pain, fatigue) – precise pathological internal model predictions can dominate and bias the percept, especially when paired with imprecise sensory input from the periphery. Using a computational modelling approach, von Werder and colleagues (2024) have shown that a similar mechanism may underly persistent dyspnea in post-COVID syndrome. The results presented in this thesis have also shown that altered sensorimotor processing seems to be a general, transdiagnostic mechanism that can be measured independently of the specific experienced symptom: functional dizziness and functional movement disorder. This was not the case in chronic (functional) pain.

Sensorimotor processing deficits in functional dizziness have previously been shown in a series of studies employing the gaze shift paradigm. Lehnen and colleagues (2019) assessed sensorimotor processing during large gaze shifts in persons with functional dizziness and found that head stability was significantly lower compared to healthy controls already during natural head shifts, which further worsened under increased (3.3-fold) head moment of inertia; notably, the degree of head instability was similar to the eye-head movement impairments measured in persons with bilateral vestibulopathy or cerebellar ataxia, illustrating the severe level of disability experienced also by persons with FD (see also Sağlam et al., 2014); a subsequent study has shown that not only head movements but

also gaze is instable in functional dizziness (Schröder et al., 2021), possibly also reflecting the specific dizziness symptomatology. Of note, these studies provided the first evidence of an objectively measurable marker of erroneous sensorimotor processing in functional dizziness. With the current, replicated results presented as part of this thesis, we have shown that increased head oscillations at the end of gaze shifts are a robust marker of sensorimotor processing deficits in functional dizziness.

Apart from this, there is also evidence for erroneous sensorimotor processing in functional movement disorder, although to date, experiments have only tested symptom-specific deficits. For instance, Lin and colleagues (2020) assessed the so-called 'broken escalator phenomenon' in persons with functional gait disorder, where participants stepped on a mobile sled that either moved or stayed stationary. Gait characteristics as well as subjective experiences were measured, and participants were explicitly aware of whether or not the sled would move. The authors found that compared to healthy controls, patients displayed significantly increased body sway and initially slower gait velocity when first stepping onto the stationary sled. In contrast, when participants walked onto the moving sled in the subsequent condition, no differences between groups could be found. However, when participants stepped onto the stationary sled again in the final experimental round, patients exhibited locomotor after-effects (i.e., trunk sway) significantly longer than did healthy controls; they also persistently reported to feel more anxious and instable throughout all conditions when anticipating stepping onto the sled. The broken escalator phenomenon (see Bronstein et al., 2009) describes a delay in normal motor adaption in the face of conflicting contextual cues, in which people exhibit increased body sway and a faster approach when walking onto a usually moving but now stationary escalator (or sled). This is because the brain's internal model predictions pertaining to the likely sensory input when stepping onto escalators drive initial motor commands, which are normally quickly updated once the stationary condition is incorporated; based on the study by Lin and colleagues (2020), this central process seems to be impaired in persons with functional movement disorder. For the first time, our study demonstrates transdiagnostic sensorimotor processing deficits in persons with functional movement disorder, in that the predominantly experienced symptom was not (only) related to the vestibular system and measured eye-head motor control.

In line with our results on head instability as a transdiagnostic marker in functional movement disorder and functional dizziness, Schröder and colleagues (2022) measured

persons with irritable bowel syndrome using the same gaze shift experiment. Notably, patients did not experience any dizziness three months prior or at the time of measurement (akin to our sample of persons with functional movement disorder) to capture a possible transdiagnostic mechanism. They found that patients were able to stabilize the head equally well as healthy controls when moving in the natural, unweighted condition; however, patients exhibited markedly pronounced head instability compared to controls under increased head moment of inertia, indicating difficulties with flexibly adapting internal models to the changed head properties. These observed sensorimotor processing difficulties could indicate a more general deficit in (sensori-)motor control across the body; that is, in the case of irritable bowel syndrome, this deficit is predominantly expressed as altered gut motility but can also be observed in other, seemingly unaffected, sites or organ systems when challenged (i.e., head motor control). What is more, such a general sensorimotor processing deficits could also represent a possible risk factor for developing additional, non-gastrointestinal symptoms later on (e.g., dizziness) – a pattern that would also fit with the high comorbidity of different functional symptoms observed in clinical practice (Enck et al., 2016; Steinruecke et al., 2024).

In contrast with our hypothesis and earlier results on dysregulated sensorimotor (respiratory) processing in fibromyalgia reported by Van Den Houte and colleagues (2018), we did not find that patients with chronic (functional) pain exhibit sensorimotor deficits. This was somewhat surprising, as disturbances of sensorimotor control in chronic (functional) pain are widely reported in the scientific literature. For instance, patients with chronic functional pain (e.g., in the neck or lower back) have been shown to exhibit suboptimal postural control and slower movements when manoeuvring from a seated into a standing position (and transitioning into a sitting position again), which also maps onto alterations in brain network known to be crucially involved in sensorimotor control (e.g., altered organization and/or structure of the somatosensory cortex, motor cortex, and cerebellum; see Brumagne et al., 2019; Claeys et al., 2011; Kristjansson & Treleaven, 2009; Pijnenburg et al., 2015). Similarly, compared to healthy controls, persons with chronic functional pain show increased postural sway and altered postural control when standing on complex, unstable surfaces (Brumagne et al., 2008), or when visual input is absent and/or vestibular input altered by tilting the head backwards (Mientjes & Frank, 1999). Overall, there is a large overlap of chronic functional pain with deficits in balance and posture (Berenshteyn et al., 2019; Koch & Hänsel, 2019) as well as generally restricted or

suboptimal movement patterns (Carrasco-Vega et al., 2022; Michaelson et al., 2003), thus, a shared mechanism of pain, dizziness, and movement disturbances seems plausible. To date, only few studies have investigated specifically eye-head motor control in people with chronic functional pain. For instance, Grip and colleagues (2009) examined eye-head coordination of persons with chronic whiplash disorder (i.e., mainly functional neck pain) during horizontal gaze shifts and found that, compared to healthy controls, patients demonstrated slowed and reduced range of head motion as well as increased head instability when the head moved independently after only the eyes were first moved to a target location. However, it is difficult to discern whether the suboptimal motor control was specific to the pain symptomatology, as patients also reported suffering from whiplash-related symptoms such as dizziness (not explained by any known organo-structural impairments). A follow-up study from the same research group also reported reduced range and velocity of head rotations, although also not in patients with an isolated chronic functional pain disorder but with other typical whiplash-related functional symptoms such as dizziness, unsteadiness, or blurred vision; their previous findings on head instability during eye-head coordination could not be replicated (Treleaven et al., 2011).

There may be several reasons for why we were not able to measure any pain-related sensorimotor processing deficits in our study. First, it is possible that pain is not a direct result of sensorimotor processing deficits per se, but that persistent sensorimotor processing deficits often lead to pain later on (Hodges & Moseley, 2003; O'Sullivan, 2005). This could also explain the usually high correlation between chronic functional pain and other functional symptoms (with pain developing before, concurrently, and after the onset of functional neurological disorders; see Mason et al., 2023; Steinruecke et al., 2024; Stone & Evans, 2011), including those with erroneous sensorimotor processing in head motor control measured with our paradigm: functional dizziness, functional movement disorder, and irritable bowel syndrome as isolated symptoms or syndromes; in the latter case, (abdominal) pain is even listed as a hallmark symptom. Importantly, the link between altered sensorimotor control and pain could be due to persistent changes in posture (e.g., stiffness) and engaged muscles (e.g., modified behaviour) as well as decreased range, force, and amplitude of movement in an intuitive attempt to decrease pain and a avoid further/repeated injury. However, this could lead to inefficient and suboptimal motor control long-term (Hodges & Tucker, 2011). Second, it is possible that the selected sample was not optimal for measuring (potentially very subtle) sensorimotor processing deficits

with our experimental paradigm. The majority of persons included in the study suffered from chronic pain disorder with somatic and psychological factors (F45.41, ICD-10), i.e., mixed organo-structural and functional causes of pain, as opposed to persistent chronic (functional) pain disorder (F45.40, ICD-10), which would correspond to a 'pure' form of functional pain. Perhaps, a new sample consisting entirely of persons with persistent chronic (functional) pain disorder may produce different results. In addition, it would be worthwhile to conduct our gaze shift experiment with people affected by other functional pain disorders, such as fibromyalgia (akin to the sample employed for Van Den Houte and colleagues' [2018] rebreathing study) or complex regional pain syndrome (see Popkirov and colleagues [2019] for overlaps with functional neurological disorder). Lastly, eye-head motor control assessed with our experimental paradigm may have been too symptom-unspecific to measure alterations of sensorimotor processing in chronic functional pain. In line with previously reported studies, movements focused more "centrally", e.g., on the body's trunk, may be better able to capture various pain symptoms throughout the body. These paradigms may also be more suitable to measure aberrant internal model predictions about proprioceptive input from the entire body; in our eye-head experiment, (neck) proprioceptive estimates and feedback may be less relevant than vestibular in stabilizing the head during active movements (Bizzi et al., 1976; Sağlam et al., 2014).

In future studies, it would be interesting to assess sensorimotor processing in persons with various different functional symptoms using other experimental paradigms, such as grip force experiments. This could provide insight into whether the here measured sensorimotor deficits pertaining to (eye-)head movements can also be found throughout the entire body's motor system. It could also elucidate whether there are symptom-specific components to this deficit, akin to the altered head control in persons with irritable bowel syndrome that could only be observed when the system was challenged. For instance, in a grip force experiment, internal models about the predicted properties of an object (e.g., size, weight, surface friction) play a crucial role in successfully lifting an object with the hand, as any corrective adjustments to grip (i.e., hand and fingers) and load (i.e., arm and shoulder) force in response to unpredicted sensory feedback are delayed by about 100ms (Hermsdörfer et al., 2003; Nowak, 2004). It has been shown that patients with focal hand dystonia exhibit an overshoot in grip force (i.e., gripping too forcefully), indicative of problems in the interaction of internal models (required to anticipate the required force) and sensory input (from mechanoreceptors) processing when grasping and lifting objects

(Nowak & Hermsdörfer, 2006); therefore; it is plausible that persons with functional movement disorder could exhibit more pronounced, symptom-specific deficits when grasping objects than persons with functional dizziness.

Furthermore, it would be interesting to see whether persons who exhibited increased head instability during our experiment also subjectively experienced their movements as instable. Under normal circumstances, large combined eye-head gaze shifts are planned and executed independently of higher-order cognitive systems; however, since head movements were measurably instable, patients may have also consciously noticed that the actual movement deviated from the intended/predicted outcome. Some evidence suggests that interoceptive awareness and accuracy may be impaired in functional movement disorder (e.g., Ricciardi et al., 2016), although with mixed findings (e.g., Millman et al., 2023), and patients may be well aware of their poor interoceptive performance (Ricciardi et al., 2021). In addition, future research could examine whether head stability as measured during our experiment is also consciously experienced as dizziness or as an involuntary, aberrantly generated movement, akin to symptoms in FD.

Apart from sensorimotor processing specifically, the current body of evidence suggests that information processing may dysregulated in FD more generally. Using a temporal resolution task, Sadnicka and colleagues (2020) demonstrated that persons with functional movement disorder exhibit information processing deficits, which was previously also reported in people with Parkinson's disease (Tomassini et al., 2019). In this task, either a single or two in rapid succession occurring (between 1 and 200ms) stimuli are delivered to the finger and participants have to indicate whether they perceived one or two impulses. In comparison to healthy controls, patients had more difficulties in discerning whether one stimulus or two stimuli were delivered and required a longer interval between two successive impulses. In addition, longer response times in patients also reflected increased uncertainty in arriving at a decision. In Bayesian predictive processing terms, this suggests that abnormally precise top-down priors (in part mediated by attentional processes) downgraded (in relation less precise) bottom-up information, affording sensory input less influence on the decision-making process. Importantly, the authors suggest that the measured deficits in information processing and decision-making may also reflect general, symptom-unspecific cognitive difficulties that are often experienced across persons with FD (see Teodoro et al., 2018). Since the brain relies on internal models to successfully

navigate the entire bodily system and generate conscious experience, problems in the interaction of CNS-based predictions and peripheral sensory input will not only become evident as functional bodily symptoms but also in other facets of clinical conditions (Seth & Friston, 2016). Examples are dysregulated interoceptive as well as aberrant attentional and predictive processing in anorexia nervosa (Barca & Pezzulo, 2020), schizophrenia (Nelson et al., 2014; Sterzer et al., 2018), panic disorder (Maisto et al., 2021), anxiety disorders (Domschke et al., 2010), depression (Barrett et al., 2016; Harshaw, 2015), stress- and trauma-related disorders (Kaye & Krystal, 2020), and personality disorders (e.g., Herzog et al., 2022). This could also explain the high comorbidity between functional symptoms and general psychopathology (e.g., De Waal et al., 2004).

Head Oscillation Ratio: A Suitable Marker of Erroneous Sensorimotor Processing and Potential for a Diagnostic Tool

Combined eye-head gaze shifts are well suited for examining the integration of internal model predictions and sensory signals during sensorimotor processing. Based on previous research using the eye-head paradigm, we know that eye and head movement trajectories of a gaze shift can be roughly divided into two "phases": a counterrotation phase and an oscillation phase (see Schröder et al., 2021). That is, after the target light briefly flashed, the participant starts moving the eyes and the head toward the target location. Since eye movements are faster than head movements, the eyes reach the target first while the head continues to move; in order to keep gaze stable on the target, the eyes counterrotate in the opposing direction of the head. Active movements in this 'counterrotation phase' are substantially driven by internal model predictions. Once both the eyes and the head have arrived at the target location, unexpected passive head oscillations can occur (i.e., 'oscillation phase'), which are then counteracted based on sensory input (i.e., VOR); feedforward control does not play a role here. Therefore, investigating gaze stabilization during these two phases allows to further narrow down problems in the interaction of internal model predictions and peripheral input (Lehnen et al., 2009b; see also Sağlam et al., 2014; Sağlam & Lehnen, 2014). Schröder and colleagues (2021) found that persons with functional dizziness showed deficits in stabilizing gaze during the active movement phase driven by internal models: gaze starts to drift as the eyes overshoot the remembered target,

because head movements were incorrectly estimated and therefore not compensated sufficiently by counterrotating eye movements (in both natural and weighted gaze shifts). In contrast, when passive head oscillations could be compensated by eye movements through the sensory input-driven VOR, gaze was stable. This is line with the hypothesis that aberrant CNS-based internal model predictions are the root of functional (dizziness) symptoms, while no peripheral sensorimotor dysfunction can be found during clinical examinations (e.g., intact VOR during head-impulse testing). For instance, for persons with complete bilateral vestibular loss, the pattern is reversed: based on efference copies, eye movements can better compensate the ongoing head movement during active gaze shifts ('counterrotation phase'), but the VOR cannot stabilize gaze against passive head perturbations in the 'oscillation phase' due to absent vestibular afference (Sağlam & Lehnen, 2014).

Similar to gaze stability, head stability at the end of eye-head gaze shifts can be used as an indicator of sensorimotor processing deficits in internal model use and/or sensory input processing (Lehnen et al., 2019). The only disadvantage of using head oscillations as a potential diagnostic parameter is that – unlike gaze (in)stability during a 'counterrotation phase' versus 'oscillation phase' – head instability at the end of gaze shifts cannot provide an indication of *where* sensorimotor processing went wrong: internal model use, sensory input processing, or both could be aberrant. For instance, persons with functional dizziness, persons with complete bilateral vestibular loss, and persons with cerebellar ataxia will all exhibit marked head instability during unweighted and weighted gaze shifts (Lehnen et al., 2019; Sağlam et al., 2014) but the correct diagnosis, underlying pathology, and rehabilitation recommendation will vastly differ between them. Therefore, a diagnostic tool providing an assessment of head stability should be part of a larger test battery.

Apart from this, there are several reasons why head instability is a good candidate parameter for the development of a diagnostic tool. The head oscillation ratio is easily calculated and can sometimes even be seen from raw data alone. An algorithm that automatically determines the average oscillation ratio over successive gaze shift trials could be reasonably incorporated into already existing eye-head tracking tools, such as the measurement goggles used in our current experiments to assess the VOR (via video head-impulse testing) as well as head velocity and position data during the experiment. As such, it may be possible to produce head instability score readouts against healthy norm data immediately after testing to inform next steps during healthcare consultations.

Furthermore, large gaze shifts can be performed by almost all persons and easily measured in most settings; clinicians only require a chair for the person to be seated, an indication of target locations (e.g., small flashing LED lights), and a room that can be darkened (e.g., curtains or shutters). Future studies could assess whether visual feedback during movements meaningfully affects movement stability in this paradigm; if not, practitioners could carry out a potential test without completely darkening the room beforehand. Lastly, assessing head oscillations (rather than gaze instability) at the end of gaze shifts may indicate dysregulated internal model use across FD (i.e., functional dizziness, functional movement disorder, irritable bowel syndrome); it still remains to be determined whether the gaze instability in functional dizziness reported by Schröder and colleagues (2021) can also be transdiagnostically measured in people with other functional symptoms. However, diagnostic tests need to meet certain standards such as specificity (true negative rate) and sensitivity (true positive rate). To this end, larger and more diverse (e.g., age, symptom severity and type, comorbidities) patient as well as healthy control groups would need to be tested to establish more robust and representative results. For instance, in our studies (e.g., see Regnath et al., 2023), few healthy control participants exhibited head instability during both natural and weighted gaze shifts that even exceeded the scores of patients (also reported by Schröder and colleagues [2022]).

The Possible Role of Attention in Motor Control

When interpreting the study findings from our eye-head paradigm, the demands on patients when completing the experiment have to be considered as well, especially because functional symptoms are highly susceptible to the influence of expectations and attentional effects (Huys et al., 2022; McCabe et al., 2005; McIntosh et al., 2017). Since the aim was to study large eye-head gaze shifts, the focus of both the experimenter as well as the patient (or healthy control participant) was on the head, eyes, and their movements: the study information (e.g., measurement of eye and head movements), the experimental setup and procedure in the lab (e.g., measurement goggles, experimental manipulation with the helmet, video head-impulse test, complete darkness and silence during movements), the task instructions (e.g., use the eyes and the head together when shifting gaze, move in a natural way) all shifted attention to these body areas. It is thus possible that, unlike active gaze-shifts in everyday life, the gaze-shifts during our experiment may have been impacted by increased attention to the head, eyes, and vestibular functioning during movement.

Attention (e.g., monitoring the body) plays an important role in both optimizing top-down prediction precision conveyed by deep pyramidal cells and enhancing bottom-up information by modulating the post-synaptic-gain of prediction error units corresponding to activity of superficial pyramidal cells (Adams et al., 2013; Brown et al., 2011; Shipp et al., 2013). An example of attentional effects can be illustrated when persons with a functional tremor are asked to direct attention toward an affected hand (Huys et al., 2020), which typically worsens the symptom (via active inference). In contrast, when attention is diverted away, for example by another simultaneous task (e.g., contralateral finger tapping, cognitive arithmetics), the tremor attenuates. The same effect can be seen in Hoover's sign, where the leg muscles affected by functional weakness cannot be engaged voluntarily but will extend when engaged automatically by flexing the contralateral leg (McWhirter et al., 2011; Ziv et al., 1998). The implications of biased attention also pertain to sensory modalities such as pain (e.g., see Wiech, 2016): for instance, when attention is directed inwards to imprecise interoceptive cues (e.g., sensory noise in the body), pathologically precise internal models are activated and can easily override peripheral signals, leading to distorted symptom perception. Explicitly directed attention can have similar, albeit less severe effects in people not suffering from FD, namely when paying undue attention to normally automatic processes (e.g., focusing on every step when walking, a professional golf player trying to putt; Edwards & Rothwell, 2011) or interoceptive noise (e.g., itching sensations on the skin; Edwards et al., 2012; Holle et al., 2012). These examples again underline that functional symptoms arise from the same 'software infrastructure' in people with and without FD alike.

In the context of our experiment, increased attention to the self (i.e., to the head and eyes) or to specific external cues (i.e., red visual targets) could have impacted gaze-shift movements in at least three ways: As a first possibility, an internal shift of attention to the exact movement of these body regions (e.g., step-by-step motor trajectory) and their impact on vestibular processing (e.g., "Will this make me feel dizzy?") could have impaired automatic performance due to conscious, explicit movement planning – much like "choking under pressure" in professional sports(wo)men (Edwards et al., 2012; Huys et al., 2022; Philippen & Lobinger, 2012). A well-known example of this phenomenon are so-called 'putting yips' in golf playing (Gerland, 2015), which typically occur when the golfer is close to the cup (i.e., circular hole in the ground) and focused on their final put. Instead of a smooth putting movement, the player may experience jerky, rigid, or tremor-like lower-

arm movements when under pressure on a short important put. Speculatively, patients focusing on the exact movement mechanics may experience similar effects (i.e., suboptimal head movements) during our experiment. In this scenario, every-day automatic gaze-shifts may be characterized by more stable and overall smoother head movements than we observed in the experiment, akin to a person who is asked to lift a glass of water with the hand affected by a functional tremor while diverting gaze to a distractor versus while focusing on the hand. Self-focused attention can enhance the precision of bottom-up information (prediction errors) relative to top-down predictions from (presumably) pathological internal models – in other words, attention can boost prediction error precision of the attended field (i.e. bodily sites, sensations, or movements), while simultaneously decreasing precision of input from unattended sites (Allen & Tsakiris, 2018; Feldman & Friston, 2010; Mumford, 1991; Rao, 2005; Smout et al., 2019). Prediction errors that are more precise could possibly drive learning (i.e., update rigid suboptimal internal models) and improve task performance overall compared to prediction errors elicited by every-day head movements. Persons with chronic (functional) pain exhibited improved head stability over the course of gaze-shift trials similar to healthy control participants, although head movements were not unstable to begin with when compared to healthy controls. The same pattern was found in persons with irritable bowel syndrome (Schröder et al., 2022). Whether this learning effect was driven or enhanced by attention and/or by the increase of head inertia – which should both lead to higher prediction error precision – cannot be deduced based on our experimental setup and results. Due to sample size restrictions, we could not conclusively determine whether persons with functional dizziness or functional movement disorder showed learning effects across trials. Self-focused attention may have produced particularly precise prediction errors but may have still failed to update the respective pathologically rigid internal models. From our results alone, we cannot infer the particular attentional and mechanistic process underlying the measured behaviour.

As a second possibility, the study procedures could have also shifted attention away from the self to the overall aim of the task, i.e., to direct gaze at the visual targets. In this case, participants' attention is not primarily drawn to their body but rather focused on the external spatial locations of the five red visual targets in front of them. At least in theory, this should increase the detection of the brief red target lights in the visual periphery while decreasing awareness of other stimuli (e.g., body symptoms, movement trajectories) that

are less relevant to the successful completion of the task (Desimone & Duncan, 1995). Eye-head movements should then be executed more automatically with the help of internal models (for an analogy of the effects of an external versus internal locus of attention on motor performance, see Lohse et al., 2010). On top of this, the lack of visual guidance during gaze-shifts may have additionally increased reliance on automatic movements based on internal models, as limited visual feedback was available for *a priori* contextual movement planning and no visual feedback for online corrections (Pham & Hicheur, 2009; Vaziri et al., 2006). If these internal models are pathological (e.g., wrong head plant), then the resulting movement will still be aberrant. In this scenario, the measured head instability of persons with functional dizziness or functional movement disorder would reflect wrong internal model use, with little influence of explicit movement decisions that might have otherwise worsened head stability further. It is also possible that the shift of attention away from the body and its symptoms could decrease the precision of abnormal internal models that are usually afforded high precision due to misdirected attention in daily life (Edwards et al., 2012); more adequate internal models of movement have now been able to drive action, making head movement more stable in the experimental context. Apart from this, healthy controls as well as participants with chronic (functional) pain simply executed automatic, smooth, active gaze-shifts with the help of correct internal models.

As a third possibility, attention can not only increase the weighting of bottom-up prediction errors but also the precision of internal model priors and its predicted content (Garlichs & Blank, 2024; Spratling, 2008). It follows that under our experimental conditions, internal models pertaining to pathological expectations about instable, involuntary, effortful movements or sensations pertaining to motion (e.g., pain, dizziness) may be more readily retrieved and, simultaneously, sensory(motor) input (and resulting error signals) aligning with these predictions afforded more influence (Barrett & Simmons, 2015; Kok et al., 2012). In this scenario, the aberrant internal models pertaining to head movement planning would exert even more influence than during every-day head shifts, where visual feedback may facilitate movement planning/correction and other distractors help may divert excessive attention from pathological priors. In other words, patients' head movements could be more stable outside our experimental context, because bottom-up sensory input is less likely to be overridden by strong abnormal priors but may instead be incorporated to a larger extent when planning and executing movement. It would be interesting to examine whether sensory(motor) signals in line with pathological priors are

also more likely to be experienced consciously, for instance, as heightened levels of dizziness due to pronounced instable head movements.

Literature suggests that patients with FD are more vulnerable to biased attention, which is reflected in, for instance, increased body scanning or self-monitoring (Delange et al., 2007; Popkirov et al., 2018; Rief et al., 2004). This is also in line with the findings by Pareés and colleagues (2012), who showed that persons with functional tremor significantly overestimate the duration of their tremor presence. Functional tremor occurs or worsens when attention is directed at the affected site, and attenuates or disappears once attention is directed away again; that is, the absence of the tremor is simply not registered when engaging in everyday tasks, but the symptom is always there when attention is automatically or intentionally (e.g., when asked about it during consultation) drawn to it. It is likely that this phenomenon also applies to other functional disorders such as dizziness (Drane et al., 2020; Hallett et al., 2022).

Regarding the general treatment approach of FD, whether attention should be directed towards or away from the self (i.e., to increase the relative impact of bottom-up or top-down information, respectively) may also depend on the particular individual. For instance, persons with functional movement disorder and/or relevant comorbid disorders associated with self-focused attention such as anxiety, depression, or obsessive–compulsive symptoms/personality disorder (Edwards & Rothwell, 2011; Nováková et al., 2023) should perhaps rather shift focus away from overlearned conscious, highly controlled movements towards automatic processes, such as the end result of a movement without focusing on the specific steps in-between (e.g., with the help of distractions; Nielsen et al., 2015). In contrast, a patient with, for example, comorbid alexithymia may also benefit from a shift of attention inwards, such that the increased precision of sensory input may help drive learning and provide an opportunity to adapt aberrant internal models (Harshaw, 2015; Ricciardi et al., 2016).

Taken together, we cannot pinpoint the exact effects of our experimental context on our results; however, it is possible that the added attention on the self (i.e., body sensations/movements; prior expectations) or the external world (i.e., task) had some influence on movement control and head (in)stability. Future studies could investigate whether specific instructions that either shift the participant's focus 1) on the body and its symptoms, 2) explicit movement steps (e.g., "move as smoothly as possible") or 3) that offer distractions from a controlled movement, e.g., by stressing the importance of the

movement end goal (e.g., "look at the target") or by concurrently playing an audiobook, can differentially influence the magnitude of head instability. It would also be interesting to examine whether this relationship is further influenced by psychiatric conditions (e.g., alexithymia, obsessive-compulsive symptoms, anxiety, depression) or the specific functional symptom (e.g., movement disorder versus pain). To assess the external validity of our findings, it could also be worthwhile to assess head instability in more natural contexts, where participant's attention is unlikely to be centered on the specific execution of targeted eye-head gaze shifts.

Implications on Diagnostic Labels of FD

Historically, diagnostic labels of FD have developed from psychoanalytic (e.g., conversion, somatization), antiquated and at times stigmatizing (e.g., hysteria, somatoform) to now more etiologically neutral (e.g., functional) terms. As a next step, professional classification systems could move towards more mechanistically informed labels. In this dissertation, we investigated whether erroneous sensorimotor processing is a transdiagnostic mechanism underlying FD, specifically pain, dizziness, and motor symptoms. At the time, setting, and location of conducting our studies and writing this thesis, the official classification system in place for professionally diagnosing FD is the ICD-10 (WHO, 2004). That is, persons with a chronic functional pain disorder (F45.40 or F45.41) and functional dizziness (F45.8) received a diagnosis from the category of somatoform disorders (F45.-), which covers symptoms of pain and autonomic dysfunction (e.g., also bowel problems). In contrast, persons with functional movement disorder (F44.4) are covered under a different category, i.e., dissociative [conversion] disorders (F44.-).

Based on our results and previous findings from the same experimental paradigm (see Schröder et al., 2022), functional movement disorder (F44.4), functional dizziness (F45.8), and irritable bowel syndrome (F45.32, i.e., somatoform autonomic dysfunction of the lower gastrointestinal tract) share a common underlying mechanism: erroneous sensorimotor processing. However, we obtained evidence that this mechanism is not at play in chronic functional pain (F45.40, F4541). That is, under ICD-10, FD with a shared mechanism can be found in different subchapters (F44.- and F45.-), while FD without a common mechanism – at least not sensorimotor processing deficits in eye-head gaze shifts – can be found in the same subchapter (i.e., F45.-). Interestingly, our findings are (somewhat) reflected in the new version of the ICD. In the ICD-11 (WHO, 2021),

functional dizziness and functional movement disorder are now combined in the subchapter of dissociative neurological symptom disorder (6B60.-), which does not cover pain, fatigue, or gastrointestinal dysfunctions. Instead, chronic (functional) pain has received its own symptom category, Chronic Pain (MG30), which is also line with our mechanistic findings. Only irritable bowel syndrome (F45.32) does not fit the picture, which is now coded separately as a functional gastrointestinal disorder under its own specialty chapter (i.e., diseases of the digestive system [DD91.-]) due to empirical findings on the 'Gut-Brain axis' (see Kennedy, 2014; Mulak & Bonaz, 2004; Ortega et al., 2023). Future research employing the eye-head paradigm could examine whether other functional symptoms included in ICD-11's dissociative neurological symptom disorder, such as functional seizures or functional cognitive deficits, show similar sensorimotor processing difficulties.

Treatment Through Adaption of Aberrant Internal Models?

Across the two studies presented in this dissertation, we showed that persons with functional dizziness and functional movement disorder likely employ aberrant internal models to plan and execute large natural gaze shifts, resulting in mismatched sensory feedback reflected in suboptimal head movements. Despite enhanced prediction errors arising from an experimental increase in the head moment of inertia, persons with functional dizziness likely did not adapt internal models; evidence for a learning effect in persons with functional movement disorder remained inconclusive. Here, we can only speculate about the possible reasons for these findings and factors that may hamper or facilitate sensorimotor learning.

Since our experiments took place in complete darkness, participants were only able to correct movement errors (online) in response to proprioceptive and vestibular input, but not to visual feedback. For instance, research on visuomotor adaption has shown that error corrections after versus during an ongoing movement likely employ separate mechanisms (Shabbott & Sainburg, 2009). The authors further point out that online and inter-trial movement corrections may also depend on different brain areas: patients with impairments of the basal ganglia exhibited impaired online movement correction but intact movement adaptation between trials, while patients with cerebellar ataxia were able to make

in-flight adjustments during an ongoing movement based on visual feedback but could not adapt movement patterns across trials (Day, 1998; M. A. Smith & Shadmehr, 2005); importantly, the cerebellum is implicated in the adaption of internal models and motor commands in response to errors (Nezafat et al., 2001). Relating these findings to FD, patients may not have adapted movement errors across trials but may at least have been able to do so within single trials, especially when visual guidance would have been available. Evidence suggests that motor learning can be facilitated by visual feedback during movement (Körding & Wolpert, 2006; Sarlegna & Sainburg, 2009), since its integration (e.g., with proprioceptive signals) could further reduce sensory noise overall (i.e., increased precision of sensory input). In everyday life, sensory information of all kinds is usually processed and integrated in parallel. For instance, a large combined eye-head gaze shift depends on and elicits feedback from proprioceptive, vestibular, visual sensors (Kristjansson & Treleaven, 2009). Schniepp and colleagues (2014) found that persons with functional dizziness rely heavily on visual feedback when walking. Therefore, it would be interesting to examine a possible added benefit on head stability when gaze-shifts are performed in light, as this would also more closely reflect patients' impairment in everyday life.

What is more, Helmholtz (1867, 1862) reported after-effects of sensorimotor adaptation during his experiments with prism goggles that laterally shifted the visual field. While wearing the glasses, participants were asked to point at an object placed in front of them. Initially, they incorrectly pointed at a location opposite to the optical displacement, but quickly incorporated the error and adapted motor commands to point at the correct location. After participants had removed the glasses and quickly pointed at the object again, they still employed the now adapted motor command and pointed off-target. Only after a few attempts, motor commands were gradually adapted and participants were able to perform correct movements again. Since then, the effect has been robustly replicated and applied to many paradigms (Redding et al., 2005). Notably, these after-effects could also relate to the instable active head movements that we measured immediately after participants were wearing the helmet. This may be akin to the earlier described locomotor after-effect found in people with functional movement disorder when stepping onto a stationary sled that was previously moving (Lin et al., 2020). Here, patients' internal model about the effects of stepping on a moving sled likely has been afforded undue precision and thus continued to dominate motor commands even after the sled remained stationary,

leading to measurably increased body sway and displacement compared to healthy controls. Given that patients' primary (and only) complaint was instable gait, a general fear of falling or the adoption of a 'better safe than sorry' approach (e.g., low risk taking, stiff muscles or posture) in this group is likely ; internal models pertaining to gait or balance disturbances may therefore be readily activated or established. In light of these findings, it is possible that a similar effect occurred in our current study on persons with functional movement disorder (and possibly functional dizziness). Since we did not obtain a (clear) learning effect from the first to the last experimental condition, it is possible that internal models instilled by the experimentally increased head moment of inertia during the weighted condition still biased head motor control during the adjacent natural condition. Future research could investigate whether such locomotor after-effects can also be observed in the eye-head gaze shift paradigm by examining head stability during specific trials rather than averaged across the entire experimental condition. Perhaps, comparing learning effects within (i.e., beginning versus end trials within conditions) rather than between (e.g., first versus second unweighted condition) sessions could reveal learning effects that are otherwise masked by after-effects of the preceding experimental manipulation exaggerating overall head instability scores.

Apart from possible locomotion after-effects, assessing head stability within rather than between sessions could reveal general learning capacities; for instance, patients may simply start and end with more instable head movements than healthy controls overall, reflected in higher average head oscillation ratios across experimental conditions, while the learning rate (i.e., reduction in head oscillations across trials within a session) could still be similar between groups. A series of studies employed the eye-head paradigm in people with cerebellar ataxia, complete bilateral vestibular loss, or functional dizziness and additionally examined learning effects within sessions (Lehnen et al., 2019; Sağlam et al., 2014; Van Den Bergh et al., 2021). (In their study, a second unweighted condition was missing, which precluded the investigation of possible learning effects across sessions.) They found that persons with cerebellar ataxia and persons with functional dizziness were somewhat able to reduce head oscillations throughout trials with the helmet, suggesting that large prediction errors induced by the increased head moment of inertia updated internal models, leading to improved head stability. This was not the case in patients with complete bilateral vestibular loss, possibly due to the lack of vestibular feedback. Based on the study setup,

however, it cannot be determined how long and under what circumstances (e.g., also for movements without the helmet) this adaption lasted.

There is another possible reason why presumably large prediction errors elicited by the helmet's increased head moment of inertia did not drive an update of erroneous internal models: the brain may infer that the resulting head instability was due to a new cause outside of the already established internal models, and thus initiated a separate motor program. For instance, instead of updating internal models about the usual head characteristics, the brain may have constructed a separate internal model about the head characteristics that are at play, e.g., when moving with a mysterious bike helmet during a gaze-shift experiment (e.g., see Erdmann & Mathys, 2022 for an analogous idea on the formation of delusional beliefs). In the here presented studies, we have analysed learning effects across but not within session. It is possible that the newly formed internal models about the "weighted head" were still malleable in response to the elicited prediction errors and that head stability improved across the weighted trials. If so, future studies could examine whether an only slightly increased (<3.1-fold) head moment of inertia – closer to the natural head properties – could activate the inflexible internal models employed during everyday movements, and in this way offer a window for learning when prediction errors arise during active head shifts.

Lastly, it is perhaps not so surprising that we did not obtain clear or any learning effects in patient groups that exhibited sensorimotor processing deficits, i.e., in persons with functional dizziness and functional movement disorder. Affected persons likely also exhibit marked head instability during everyday gaze shifts, which should have elicited multiple prediction errors that had not been correctly incorporated into internal models even before participants had arrived for measurement in our lab. Since patients suffered from severe functional symptoms – many for multiple years – it is arguably reasonable to expect that the few head shifts performed during our experiment, and the few resulting (larger with the helmet) prediction errors, would not suffice to update aberrant internal models.

Stigma: Measurable Markers and Empirically Informed Diagnostic Labels

Stigmatisation has adverse effects on affected people's psychological/emotional, biological, and social well-being, for instance via reduced medication adherence and effectiveness (e.g., Yan et al., 2021), social modulation of symptom intensity (Montoya et al., 2004), feelings of 'othering' and exclusion (McLoughlin et al., 2024), and reduced quality of life (Robson et al., 2018). Unfortunately, research suggests that stigmatization of persons with FD is a structural problem (Treufeldt & Burton, 2024). Patients frequently encounter denial and invalidation of their symptoms (e.g., others believing that their symptoms are exaggerated or faked; Ahern et al., 2009; Åsbring & Närvänen, 2002; Kool et al., 2009), disrespectful communication with health care professionals (Robson & Lian, 2017), as well as negative attitudes and prejudices (e.g., being perceived as "complicated" or "whining", see Hanssen & Rosmalen, 2019). On side of clinicians and health care staff, a lack of knowledge around FD mechanisms, (e.g., due to gaps in curricula; Olde Hartman et al., 2009; Robson & Lian, 2017), few or missing treatment options (Reid et al., 2001), frustrations and difficulties in the patient-practitioner relationship (Matthias et al., 2010), differing knowledge and ideas between practitioners and patients about the explanation of symptoms (Stortenbeker et al., 2020) are common problems and barriers to adequate care.

The type of assigned diagnostic label can impact patients' evaluations of their symptoms and their inferences regarding how others perceive them. For instance, a person suffering from chronic functional pain may form the impression that their pain is not taken seriously or that healthcare providers believe that they exaggerate the severity of their symptoms if they receive the diagnosis of bodily distress disorder (BDD) or somatic symptom disorder (SSD; Katz et al., 2015; Marks & Hunter, 2015) [Autonomic symptoms such as pain cannot be covered under ICD-11's (WHO, 2021) dissociative neurological symptom disorder or DSM-5's (APA, 2022) functional neurological disorder.] In contrast, the patient may feel that their pain is more acknowledged when instead a diagnosis of Chronic Pain (ICD-11; WHO, 2021) is provided. Apart from the patient perspective, research suggests that also health care providers hold negative stereotypes about people diagnosed with FD, BDD, or SSD and evaluate associated medical fields as less favourable or prestigious (Album & Westin, 2008; MacDuffie et al., 2021). Nevertheless, positive behavioural, cognitive, and emotional signs as defined under BDD and SSD require clinical attention and treatment; practitioners should therefore carefully evaluate when behaviour,

cognition, or emotions are 'excessive' in relation to the experienced symptom, regardless of the person's sex or gender and whether or not there is an organo-structural explanation for the suffering (LoBrutto et al., 2024; Rief & Martin, 2014).

Certainly, objective markers validating the presence and severity of bodily symptoms would significantly facilitate a timely and appropriate diagnosis of FD. In the studies presented as part of this dissertation, we have provided an objectively measurable marker of an underlying mechanism for functional dizziness and functional movement disorder. It remains to be seen whether it is possible to derive any indication about the severity of symptoms based on this marker (e.g., larger head oscillation ratio corresponding to more severe symptoms). However, erroneous sensorimotor processing was not a transdiagnostic mechanism in chronic (functional) pain; to date, there is no readily available objectively measurable marker to capture the presence or severity of (chronic functional) pain. Healthcare practitioners need to rely on the affected person's self-report to indicate the intensity of pain, and patients in turn need to rely on health care practitioners to trust their reports. For instance, research has shown that women's pain is less likely to be taken seriously than men's pain (Guzikevits et al., 2024), and women's physical complaints are less likely to be thoroughly investigated compared to men's (Ballering et al., 2021).

What is more, we have provided evidence of an objectively measurable marker indicating dysregulation of an automatic information processing mechanism embedded within the central nervous system. For one, this offers clinicians an opportunity to engage in empathetic and informed conversation with the patient and to confidently explain the underlying reason for their symptoms; an appropriate explanation for an assigned diagnosis has been shown to significantly aid in treatment adherence and outcome (Stone et al., 2016). Furthermore, patients may be less likely to have their symptoms dismissed (e.g., see Braksmajer, 2018) if an objectively measurable marker can substantiate the presence of their suffering. This would also aid in assigning a swift and accurate diagnosis, as clinicians do not have to rely on unvalidated und unreliable signs (e.g., taking "bizarre" or stereotypical symptom presentations as an indication of FD; Hallett et al., 2022; Raine et al., 2004). Potentially, measurable signs of FD could improve the patient-practitioner relationship, as symptoms are less likely to be dismissed, patients' suffering is legitimatized, and clinicians may be better able to highlight potential treatment targets (Battin et al., 2022). Lastly, providing evidence for a measurable, transdiagnostic mechanism underlying FD could also improve the content and presence of FD in educational programs and curricula

that are training the current and next generation of clinicians across medical fields (Salmon, 2007; Yon et al., 2015).

Robust Science in FD: Preregistration, Replication, and Open Science

As with all areas of science, good research practices are an integral part of ethical FD research and in upholding the credibility, robustness, and transparency of findings. In the studies included in this dissertation, we have therefore incorporated three fundamental aspects of best practices: preregistration, replication, and open science.

Preregistration is one way to reduce so-called 'researcher degrees of freedom' (Simmons et al., 2011; Wicherts et al., 2016), a term that describes the many possibilities researchers have in (unconsciously) influencing the presence/absence, direction, and size of effects as well as the conclusions drawn from them. For instance, because we *a priori* registered our exact hypotheses and statistical analyses, the here presented results bear a lower probability of "B-hacking", analogous to "p-hacking" in null-hypothesis statistical testing, i.e., when researchers (also implicitly) try out multiple analyses and only report those with large or meaningful BFs. B-/p-hacking can lead to incorrect or inflated effect sizes in the scientific literature (Stefan & Schönbrodt, 2023). In addition, it is also tempting to report post-hoc exploratory analyses as confirmatory, a practice known as HARKing ("hypothesizing after the results are known"; Kerr, 1998), which increases the chances of obtaining a result that can later not be reproduced (for a detailed explanation, see Rubin, 2017b). The analogy of "the garden of forking paths" has often been used to describe the multiple decision points that researchers face along the conduction and evaluation of a study (e.g., data exclusion and transformation, post-hoc testing), unaware of how their choices may be influenced by unconscious biases and affect outcome inferences (Gelman & Loken, 2013; Rubin, 2017a).

Apart from this, we have also replicated the study by Lehnen and colleagues (2019), who were the first to report measurable sensorimotor processing deficits in functional dizziness. This study laid the groundwork for our subsequent work on measurable markers across FD; therefore, it was important to examine whether the results are actually reliable. Replications increase confidence in research findings, can assess the generalizability of findings (e.g., across populations, settings, analyses), and overall ensures that science can

self-correct (Singh, 2003). Unfortunately, replication studies receive less funding and rewards by institutions and publishers, and are still seen as less exiting and worthwhile than "original" research (Nosek et al., 2012; Nosek & Errington, 2020). This is particularly concerning given that only about 60% of findings published in high-ranking journals can be replicated, and if so, effects sizes are on average only half as large (Camerer et al., 2018; Open Science Collaboration, 2015). In our replication study (see Regnath et al., 2024), we therefore increased the target sample size *a priori* based on a power analysis and obtained anecdotal evidence that the size of head oscillation ratios measured did not differ from the data of Lehnen and colleagues (2019); the overall effect could be successfully replicated.

In addition, our Bayesian statistical approach allowed us to also quantify evidence for the null hypothesis. Studies producing p-values that do not reach chosen significance thresholds often end up unpublished, a common phenomenon termed the 'file drawer problem': researchers are less likely to write and submit an article on null or negative results and journals are less likely to publish them, because they are traditionally deemed "uninteresting" by both publishers and the broader scientific community (Muradchanian et al., 2023; Rosenthal, 1979). This can lead to a skewed body of evidence, with potentially considerable implications (e.g., medication efficacy; Kozlov, 2024). What is more, non-significant p-values do not allow for any conclusions as to whether the null hypothesis is indeed true or the sample just too small, even though this is sometimes incorrectly concluded even in published peer-review articles (Greenland et al., 2016; Muradchanian et al., 2024); BFs can somewhat counteract this problem, as they can provide evidence as to whether the effect is present, absent, or inconclusive (Freuli et al., 2023; Haucke et al., 2021). Nevertheless, it is important that also negative (or 'null') results are written up and published, such that multiple other researchers do not waste limited resources in repeatedly testing the same hypothesis (Echevarría et al., 2021). Negative results are also crucial in shaping and falsifying existing theories (Matosin et al., 2014). In our study (see Regnath et al., 2023), we showed that persons with chronic functional pain do not exhibit increased head stability during large gaze shifts; this findings pointed us towards possible other patient groups, experimental setups, and theoretical implications for shared mechanisms in FD.

Lastly, we also engaged in open science practices such as providing transparent insight and/or free access to our employed methods, data, analysis scripts and files. This allows for replication and validity tests of analyses and entire experiments (Wagenmakers

et al., 2021). What is more, articles that are published open-access allow the general public as well as other researchers (especially those in already less privileged regions) to read about mostly publicly-funded scientific insights. As a consequence, freely accessible articles are also cited more often (Piwowar et al., 2018). Considering that we were able to acquire data from a unique patient population with a specialized measurement system and setup, our open materials are highly valuable to researchers who do not have access to a clinical setting or the methodology used but who would like to examine the data in a different light (e.g., gaze analyses, learning effects) or verify our analyses.

Limitations

This dissertation can provide insight into the 'how' questions, e.g., how can one experience a bodily symptom without the corresponding peripheral input, and how can we objectively measure the effect of aberrant internal models? However, based on our experimental design and findings, we cannot address the question of 'why' FD develops in the first place, and sometimes persists despite multidisciplinary and individualized treatment (Aybek & Perez, 2022; Espay et al., 2018). Both the biopsychosocial as well as the, already more specific, Bayesian predictive processing model are quite broad perspectives that also reflect the complexity of the development, maintenance, and remission of FD. For instance, our results give no indication about the influence of – for example – triggering events, cognitive and emotional factors, or metacognitive beliefs on the chronicity of FD and the associated sensorimotor processing capabilities. Likewise, in evaluating our findings in light of the Bayesian predictive processing model, we cannot pinpoint exactly why and where the measured sensorimotor processing deficits arise (i.e., suboptimal motor behaviour). For instance, processing impairments could arise due to faulty efference copies, aberrant formation of predictions or content of internal models, mistakes in the calculation of resulting prediction errors, or any interaction between these factors. We also cannot say to what extent dysfunctional internal models or impairments in peripheral organs or sensors contribute to our measured effect – both in our study as well as in clinical practice, this will most probably be different for every individual person. In the here presented studies, patients underwent thorough clinical investigations, both prior to and on the day of measurement. As such, we can fairly confidently say that peripheral damage cannot (entirely) explain the measured sensorimotor processing deficits.

Another limitation is that we were only able to measure rather small patient samples. This was mainly the case because we recruited persons with FD and healthy controls at two extremes of a spectrum. On the one hand, patients suffered from a severe, isolated (i.e., to measure possible transdiagnostic effects) functional bodily symptom without any relevant organo-structural comorbidities – both characteristics are rarely encountered in clinical practice (olde Hartman et al., 2004; Petersen et al., 2018, 2020). On the other hand, healthy controls were excluded if they suffered from any functional symptom(s) in the past or present, and also when we obtained an indication of a psychiatric disorder during the clinical interview; that is, our healthy control sample was likely "more healthy" than the average non-FD population. Due to comparing two extreme groups, the measured sensorimotor processing deficits are likely larger than would be obtained in a normal clinical setting. Additionally, employing small samples always runs the risk of measuring effects that are not representative of their respective population. Both aspects should be taken into account when, for instance, developing a corresponding diagnostic tool. Nevertheless, as a proof of concept, the here presented studies have (robustly) demonstrated that functional dizziness and functional movement disorder, but not chronic functional pain, are an expression of a shared underlying mechanism.

Furthermore, we recruited mostly from psychosomatic in- and out-patient units, where patients also tend to suffer from psychiatric comorbidities (e.g., affective disorders, somatic symptom disorder, personality disorders). Patients recruited from the department of neurology foremost presented there because of their bodily complaints but where subsequently referred to the psychosomatic treatment setting as well. That is, also this patient sample (i.e., functional movement disorder) suffered from psychiatric comorbidities, possibly more so than the average FD population (not all persons with FD have psychiatric comorbidities, see Steinbrecher et al., 2011; Tinazzi et al., 2020). Lehnen and colleagues (2019) recruited from a specialized vertigo center where psychiatric comorbidities are likely not as prevalent compared to a psychosomatic setting. Nevertheless, we were able to replicate their obtained results, which suggests that the effect can be found in patients with and without additional psychiatric burden.

Conclusion

In this dissertation, two studies were presented that examined a potentially unifying, transdiagnostic and objectively measurable marker underlying FD, specifically chronic

functional pain, functional dizziness, and functional movement disorder. We found that erroneous sensorimotor processing, characterized by head instability at the end of large combined eye-head gaze shifts, is a shared mechanism underlying functional dizziness and functional movement disorder, but not chronic functional pain. With this, our findings provide a potential diagnostic marker that could substantially improve the general understanding of FD, inform diagnostic labels and support a swift diagnosis, and pinpoint potential treatment targets for this underserved patient group. Overall, we hope that these new insights can also help reduce the stigma that persons with FD frequently face.

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Appendix

Manuscript Study 1

Regnath, F., Biersack, K., Jäger, N., Glasauer, S., & Lehnen, N. (2023). Not a general, symptom-unspecific, transdiagnostic marker for functional symptoms: Sensorimotor processing of head control is intact in chronic pain. *Frontiers in Neurology*, *14*, 1294702. https://doi.org/10.3389/fneur.2023.1294702

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Not a general, symptom-unspecific, transdiagnostic marker for functional symptoms: sensorimotor processing of head control is intact in chronic pain

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Introduction: Functional disorders are prevalent in all medical fields and pose a tremendous public health problem, with pain being one of the most common functional symptoms. Understanding the underlying, potentially unifying mechanism in functional (pain) disorders is instrumental in facilitating timely diagnosis, stigma reduction, and adequate treatment options. Neuroscientific models of perception suggest that functional symptoms arise due to dysregulated sensorimotor processing in the central nervous system, with brain-based predictions dominating the eventual percept. Experimental evidence for this transdiagnostic mechanism has been established in various functional symptoms. The goal of the current study was to investigate whether erroneous sensorimotor processing is an underlying transdiagnostic mechanism in chronic (functional) pain.

Method: A total of 13 patients with chronic (functional) pain [three patients with chronic (functional) pain disorder, F45.40, ICD-10; 10 patients with chronic pain disorder with somatic and psychological factors, F45.41, ICD-10]; and 15 healthy controls performed large combined eye-head gaze shifts toward visual targets, naturally and with increased head moment of inertia. We simultaneously measured participants' eye and head movements to assess head oscillations at the end of the gaze shift, which are an established indicator of (transdiagnostic) sensorimotor processing deficits of head control.

Results: Using a Bayesian analysis protocol, we found that patients with chronic (functional) pain and control participants stabilized their heads equally well (Bayes Factor $_{01}$ = 3.7, Bayes Factor $_{exclusion}$ = 5.23; corresponding to substantial evidence) during all sessions of the experiment.

Conclusion: Our results suggest that patients with chronic (functional) pain do not show measurable symptom-unspecific sensorimotor processing deficits.

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We discuss outcome parameter choice, organ system specificity, and selection of patient diagnoses as possible reasons for this result and recommend future avenues for research.

KEYWORDS

somatoform, pain, functional disorder, predictive processing, perceptual dysregulation, bodily distress disorder, motor control, gaze shift

Introduction

Chronic functional pain disorders are common, with worldwide prevalence estimates ranging to ∼20% (1–4). Generally defined as pain without a structural origin (e.g., tissue damage) that could *sufficiently* explain the symptoms, functional pain is often used as an umbrella term for a range of pain phenomena, ranging from a single symptom (e.g., neck pain) to separately defined syndromes such as fibromyalgia or complex regional pain syndrome (5). In contrast to nociceptive pain (i.e., pain due to nociceptor activation) or neuropathic pain (i.e., pain due to nerve damage) affecting the structure of the body, nociplastic or functional pain—as the name already suggests—is concerned with the (dys)function of the organism: due to their symptoms, affected persons are considerably impaired in many facets of everyday functioning (e.g., physical activity, mental wellbeing, and social participation) (6), sometimes even more so compared to patients with nociceptive or neuropathic pain (7, 8). Importantly, simply relieving any (remaining) underlying structural impairment will not lead to a remission of functional pain symptoms (9). Instead, the treatment of functional pain requires a collaborative, patient-centered, multimodal approach (6, 10, 11). To date, treatment for functional pain (and functional disorders in general) is at times inadequate (12–14) and efficacy rather low (15), as the disorder commonly takes on a chronic course. Functional pain inflicts a high burden of disability, reduces quality of life, and incurs considerable individual and societal healthcare costs (12, 16).

Current neuroscientific models suggest that all symptom experience, including pain, is the result of an inferential process in the central nervous system (CNS) (17–22). At the same time, this view can also explain how pain can persist even after the initial, acute injury has fully resolved. According to Bayesian and predictive processing models of brain function, pain experience is generated from a complex interplay between "top-down" CNS-based predictions and "bottom-up" sensory input from peripheral nociceptors (23, 24). This contrasts with the Cartesian view, where pain is solely driven by nociceptive input—however, sensory processing is slow and input is often noisy, such that any response could be delayed or inadequate. To this end, the brain acts as an active agent by constantly drawing predictions about events in the body and the world, and comparing them to the actual sensory input arriving at the senses. This way, the brain only needs to process the discrepancy between the predicted and actual input—also called prediction error—thereby allowing for timely and adaptive responses. Ideally, relevant prediction errors serve to update the CNS-based internal model of the body and world, leading to more accurate predictions in the future. Importantly, top-down and bottom-up inputs are not randomly combined but weighted by their precision (or, in other words, reliability) when forming the percept. For instance, in the case of chronic (functional) pain, internal model predictions are thought to adapt during the acute illness state, as pain is a warning signal indicating actual or potential harm to the body. As structural damage slowly recovers, the brain fails to re-adapt to the healthy state, and the top-down predictions, now incorrect but still regarded as highly relevant (i.e., precise), override bottom-up input. As a result, one feels pain without an accompanying structural deficit (22, 25). Taken together, the experience of pain always arises from a combination of descending predictions and ascending input from the periphery. This also means that pain experience can be almost completely dominated by CNS-based predictions or information coming from the senses, and their relative contribution can change over time (e.g., predictions tend to dominate as acute pain becomes chronic). Importantly, the affected individual cannot discern to what extent the eventual percept was impacted by top-down or bottom-up input—the pain experience is real regardless.

Notably, this inferential process is thought to be dysregulated in functional disorders more generally (18, 20, 26–29). Functional disorders commonly co-occur, suggesting that different functional symptom presentations may share a common underlying mechanism (30–33). In fact, chronic (functional) pain may be one of the most frequent complaints co-occurring with another functional symptom (34–36). For instance, patients with functional dyspnea and healthy controls were covertly exposed to differing levels of CO_2 as part of an experimental study using a rebreathing paradigm. Interestingly, patients reported more intense and prolonged dyspnea than objective measurements of arterial CO_2 would suggest. In line with the predictive processing account of symptom perception, this effect was especially apparent when strong top-down predictions met relatively weak bottom-up peripheral input (37). Using the same paradigm, Van Den Houte et al. showed a similar decoupling of measured physiological responses and noted breathlessness in patients with fibromyalgia and/or chronic fatigue syndrome, where dyspnea is not a predominant symptom. Again, dysregulation in symptom perception was apparent when top-down predictions about breathlessness were strong but simultaneous bottom-up inputs were weak (i.e., normalizing CO_2 levels), providing evidence for a general symptom-unspecific mechanism in functional disorders (38).

More experimental evidence for a shared mechanism in functional disorders comes from studies employing an eye-head paradigm, in which participants' eye and head movements are measured during large gaze shifts. Lehnen et al. compared

the head stability of patients with functional dizziness and patients with structural deficits (i.e., cerebellar ataxia or complete bilateral vestibulopathy) during combined eye-head movements (39). Remarkably, all patient groups showed similar deficiencies in head motor control during both natural head movements and movements with experimentally increased head moment of inertia. The mechanism behind these initial findings was further narrowed down in a follow-up study (39), which investigated gaze stabilization in the patient group with functional dizziness: while gaze stabilization was intact during a phase where gaze was stabilized through sensory feedback mechanisms only, gaze was unstable when stabilization was dependent on correct movement planning (i.e., prediction). Together, this suggests that motor control in patients with functional dizziness may depend on excessively strong but incorrect internal model predictions, resulting in head and gaze instability due to erroneous planning of gaze shifts. To identify whether similar deficiencies in sensorimotor processing can be found more generally across functional disorders, patients with irritable bowel syndrome (IBS) performed gaze shifts in the same experimental paradigm (40). While patients' heads were stable during natural gaze shifts, patients with IBS exhibited larger head instability than healthy controls during gaze shifts with experimentally increased head moment of inertia. The results showed that patients had greater difficulties in flexibly adapting top-down predictions to the new head characteristics, pointing toward dysregulated sensorimotor processing as a symptom-unspecific, transdiagnostic mechanism in functional disorders.

Therefore, the current study examined whether erroneous sensorimotor processing is an underlying mechanism in functional pain. To this end, we measured the head stability of 13 patients with functional pain and 15 healthy controls during a gaze shift experiment, where participants performed large combined eye-head movements naturally and under an increased head moment of inertia. In line with previous studies, we hypothesized that patients exhibit larger head oscillations (i.e., instability) than controls when directing their gaze to the targets.

Materials and methods

This project is part of the innovative training network ETUDE [(41); Encompassing Training in functional Disorders across Europe; https://etude-itn.eu/], ultimately aiming to improve the understanding of mechanisms, diagnosis, treatment, and stigmatization of functional disorders.

The current study was reviewed and approved by the ethics committee of the Technical University of Munich and was carried out in accordance with the Declaration of Helsinki. We preregistered the study on the Open Science Framework prior to any data collection. The preregistration, as well as (raw) data, analysis scripts, and files, can be openly accessed under: https://osf.io/smchp/.

All participants provided signed informed consent before any data were collected and were free to withdraw from study participation at any time. Participants received financial compensation of 10€ per hour.

Sample

A total of 15 healthy participants (M_{age} = 46.33, SD_{age} = 15.42, nine men, six women) and 15 patients (M_{age} = 47.60, SD_{age} = 12.65, six men, nine women) with persistent chronic (functional) pain disorder [F45.40, ICD-10; World Health Organization (WHO), (42); three participants] or chronic pain disorder with somatic and psychological factors [F45.41, ICD-10; WHO (42); 12 participants] took part in the study. Patients were closely age- (BF_{01} = 2.84) and gender-matched (X^2 = 0.417; BF_{01} = 1.47) to healthy controls. Healthy control participants, as well as patients, were not eligible to participate if they were under the age of 18 years, had a neurological disorder (in particular peripheral or central vestibular impairment), corrected vision of <20% on the better eye, a hearing impairment that would not allow for experimental instruction or completion of a structural interview, acute problems of the cervical spine that would significantly prohibit the execution of head movements, or a known pregnancy. In addition, healthy controls were excluded from participation if they had a current or a history of a functional disorder or a current acute psychiatric disorder; patients were excluded if they had another functional disorder or a psychiatric disorder explaining the somatic symptoms.

Healthy controls were recruited via external and internal clinic-wide web- and poster-based announcements at the Klinikum rechts der Isar of the Technical University of Munich, Germany. Patients were recruited at the inpatient and outpatient clinics of the Department of Psychosomatic Medicine and Psychotherapy, Klinikum rechts der Isar of the Technical University of Munich, Germany.

We estimated the sample size with a power analysis based on a pilot study, which applied the same experimental paradigm to patients with functional dizziness (39). The study obtained a large significant group difference (partial η^2 = 0.62, f = 1.27) in head oscillations between functional dizziness patients and healthy controls. Considering that the current study aimed to measure a transdiagnostic, symptom-unspecific mechanism, we expected a somewhat smaller group effect compared to the functional dizziness study. Assuming at least a large group effect (f = 0.5), the *a priori* sample size estimation using G*Power (43) yielded a minimum sample size of nine participants per group (α = 0.05, β = 0.8). Considering a margin of safety, we included 10 persons per group for the first round of data collection. Using a Sequential Bayes Factor design (44), we calculated a Bayesian repeated-measures ANOVA until the predetermined threshold of evidence (i.e., Bayes Factor > 3) was attained. This approach allows for flexible sampling plans and stopping rules and, thus, optimal allocation of limited resources, given our strictly defined patient sample [e.g., see (17, 45)]. We defined an *a priori* sample of 10 participants per group, which would be followed by sequential data collection of five additional participants per group at each analysis round until reaching the minimum target Bayes Factor. In the current study, one additional recruitment round was required after the initial sample, resulting in a total sample of 15 participants per group.

On the day of the experiment, all participants were clinically characterized to ensure that all *a priori*-defined study inclusion

criteria were met. We conducted structured clinical interviews [SCID-5-CV, German version, (46)] to assess possible psychiatric diagnoses according to the DSM-5. We used the EyeSeeCam (EyeSeeTec GmbH, Munich, Germany) video head impulse test to examine the vestibular-ocular reflex (VOR) gain for the vertical canals by rapidly moving the participant's head in the 45-degree planes while the person maintained visual fixation on a centrally positioned LED in front of them. The ideal gain of the VOR is 1.0, meaning that head movement is optimally compensated by eye rotation in the opposite direction, thereby stabilizing gaze. We considered a deficit of the passively evoked VOR at a gain of < 0.79 (47, 48), together with re-fixation saccades, as a pathology affecting the vestibular organ located within the inner ear.

Experimental procedure

All participants were naïve to the purpose of the experiment.

During the experiment, participants wore EyeSeeCam goggles, which simultaneously recorded head movements (recorded via 3D inertial sensors) and the left eye's movements (captured via video-oculography) in the horizontal plane in real-time at a sampling rate of 220 Hz with the EyeSeeCam measuring system (EyeSeeTec GmbH, Munich, Germany). Before starting the experimental task, we calibrated the goggles to participants' eye characteristics using horizontally and vertically aligned 5-point laser dots to ensure accurate recording.

In total, participants successively completed three experimental rounds (Figure 1): first, an unweighted condition, while only wearing the measurement goggles; second, a weighted condition, where participants were wearing the measurement googles as well as a helmet with eccentrically placed masses that increased the head moment of inertia by 3.1-fold; finally, again an unweighted condition identical to the first round.

While seated in front of five red LED lights,[1] the participants' task was to make combined eye-head gaze shifts toward a briefly flashing (one at a time) LED target and to keep their gaze on the target until the next light flashed. We explicitly instructed participants to use both eyes and head when directing their gaze, as they would when naturally looking around the room. In addition, we asked subjects to only shift their gaze when the next target flashed and to refrain from already moving in anticipation in case they had detected a pattern in the flashing of the LED lights. When participants completed the second weighted experimental round, we hid the helmet from the participant's view until the experiment was completed. The experimenter introduced the helmet as a bike helmet and gave no further information on its characteristics (e.g., weight, shape, and modifications). In addition, we instructed participants not to move their heads until the experimental session started again. That way, participants were not able to adapt to the new head characteristics before performing the first gaze shift while wearing the helmet.

Participants completed the task in complete darkness; target LED lights were only flashed briefly (<0.1 s), so participants' executed gaze shifts were not reliant on visual input. In total, participants carried out 52 gaze shifts, of which 43 were large (i.e., 75° or 80°) gaze shifts. Figure 2 demonstrates the LED sequence and illustrates an example.

Eye-head paradigm: feedforward and feedback

Measuring head oscillations as an outcome of sensorimotor processing during active head movements, such as those performed in this eye-head experiment, allowed us to examine the interaction of internal model predictions and processing of sensory signals from the peripheral body.

When visual[2] (e.g., receptors located in the eye), proprioceptive (e.g., neurons in the neck muscles), and vestibular (i.e., semicircular canals and otoliths located in the inner ear) systems sense a movement (e.g., rotation and acceleration of the head), this sensory information is sent to the brain for further processing. For passive head movements (e.g., when driving on a bumpy road), movements of the head are unexpected and, therefore, no predictions about the sensory consequences can be formed *a priori*—any perturbations to the head must be processed in the brain, and resolved *a posteriori* based on sensory input. However, for active head movements, the brain also generates *a priori* predictions of how an active movement will impact the sensory organs (i.e., a reafference estimate based on the efference copy of the motor command). This way, when the planned, actual movement is executed, only information that deviates from this prediction—the mismatch between reafference and reafference estimate (i.e., the prediction error)—needs to be processed further in the brain and can be used as feedback about the executed movement. This allows for efficient (i.e., only prediction errors are processed), timely (i.e., prepared motion rather than stimulus-response), and more accurate (e.g., taking into account past experiences and context) movements [e.g., see (49–53)].

For instance, active head motor commands based on an inaccurate internal model of the head biomechanics will result in a suboptimal head movement (e.g., head oscillation), inducing prediction errors that are ideally used as feedback to update the central nervous system-based internal representation of the head. With the eye-head paradigm employed in the current study, we are able to experimentally induce a mismatch between the internal model of the head plant and the new head characteristics by placing a weighted helmet on the participant's head: the increased head moment of inertia (3.1-fold) is not yet represented in the

1 Of note, we forgot to move one patient closer to the target lights after assessing vestibular function at 1.5 m away from the central light. Thus, this patient was seated further away (1.5 m) from the target lights during the first unweighted session but was moved to the correct distance (1 m) for subsequent sessions. Furthermore, another patient performed gaze shifts at 1.5 m throughout all three sessions due to experimenter error. We retained both patients for statistical analysis because we did not expect this to meaningfully affect our primary outcome, as being seated further away only slightly reduces gaze shift amplitude, and head oscillation ratios are normalized by peak velocity.

2 Note that visual feedback did not play a (major) role in executing gaze shifts for the presented measurements, as the experiment took place in complete darkness.

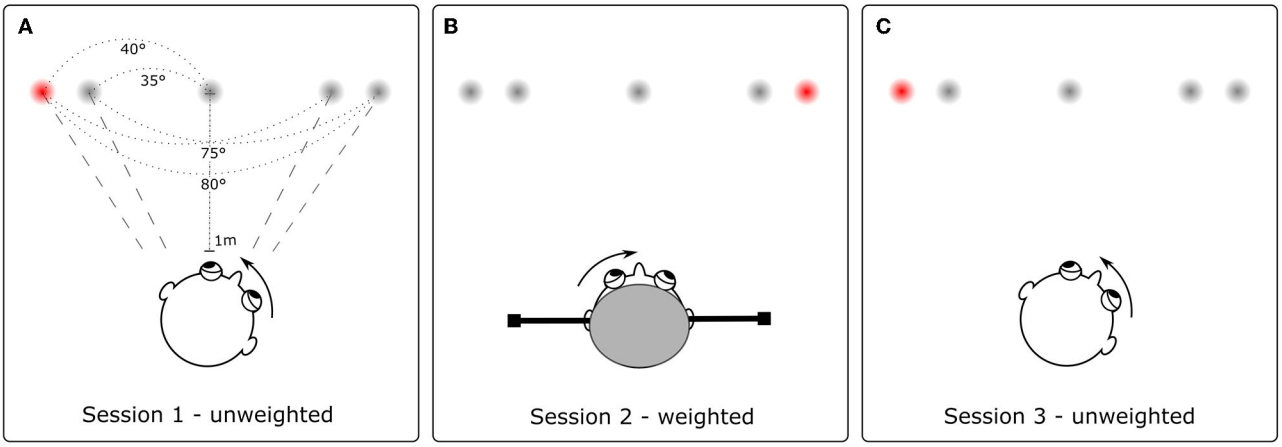

FIGURE 1
Experimental conditions. Participants performed 43 large (i.e., 75° or 80° amplitude) gaze shifts toward a red target light: first in a natural, unweighted condition **(A)**, followed by a weighted condition **(B)** with an increased head moment of inertia, and finally again in an unweighted condition **(C)**. In the weighted condition **(B)**, participants were required to flexibly adapt to the new head characteristics to optimize head stability during gaze shifts. Including two unweighted conditions at the beginning **(A)** and end **(C)** of the experiment allowed us to explore potential learning effects over time.

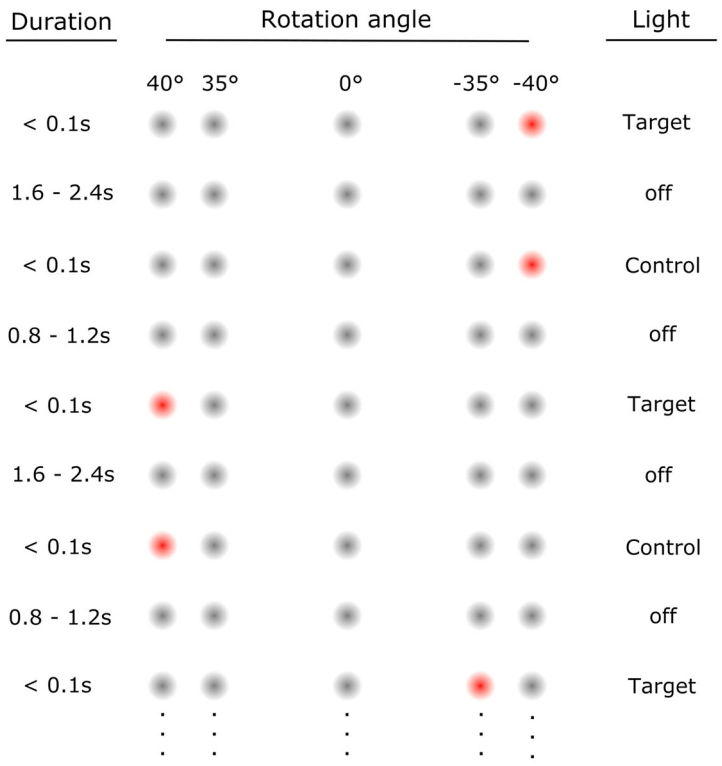

FIGURE 2
Illustration of LED sequence in the experiment. Each target light (flash <0.1 s) was followed by a control light, which briefly flashed (<0.1 s) in the same location to allow participants to correct their gaze if needed. Target light and control light were separated by an inter-trial interval (ITI, 1.6–2.4 s lights off). This ensured that subjects were more likely to start out at the intended position before the next target flashed. The control light was followed by an ITI (0.8–1.2 s lights off), after which the next target lit up. Overall, ITIs were randomized to avoid anticipatory movements toward the next predicted target. We express the amplitude of the required rotation to each light in degrees. With the center LED corresponding to 0°, negative angles represent clockwise rotations and positive angles rotations in the counterclockwise direction in the horizontal plane. Thus, targets lit up in the following sequence: 0° 0° −40° 40° −40° 40° −35° 40° −40° 40° −35° 40° −40° 35° 0° −40° 40° −40° 35° −40° 40° −40° 35° −40° 40° −35° 40° −35° 40° −40° 35° −40° 35° −35° 40° −35° 35° −40° 40° −35° 35° −40° 40° −35° 35° −40° 40° −40° 40° −35° 40° −40° 0°. Control lights are not specially indicated here but always lit up after the target light in the same position. Note that the first central light at 0° was continuously illuminated for 10 s, as it served as a reference for the initial head position for later data processing.

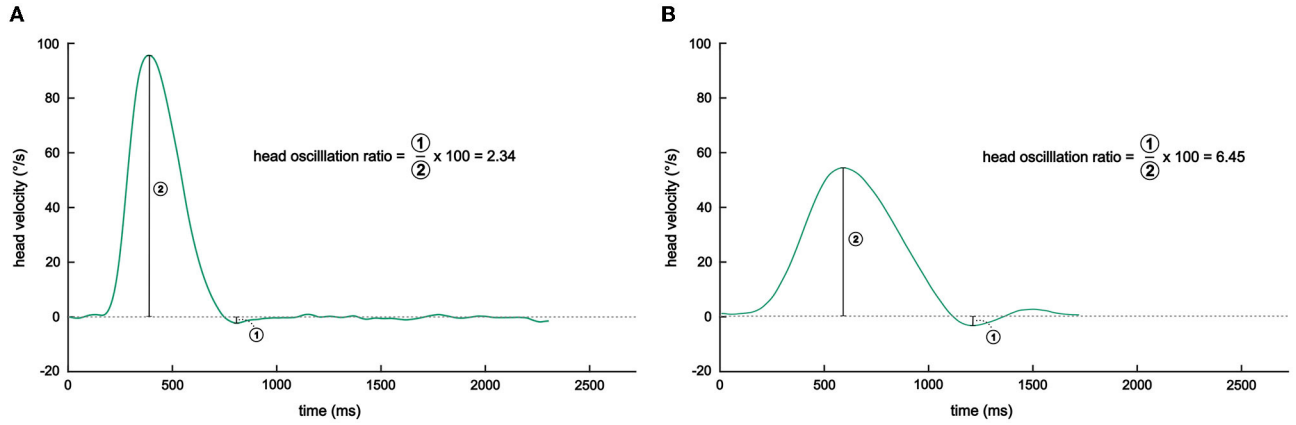

FIGURE 3
Illustration of head oscillation ratio calculation. Shown are representative raw head velocity traces of a patient during a gaze shift in the **(A)** unweighted (session 1) and **(B)** weighted sessions. Note how the head oscillation (i.e., the undershoot in relation to the peak head velocity) is markedly increased when the participant performed the gaze shift while wearing the helmet, reflecting a mismatch in the planned and actual head movement.

internal model, leading to measurably increased head oscillations. The resulting prediction errors should then serve to update the model to the new head properties, resulting in more accurate head movements over the course of these trials (39, 54–57).

Data analysis

Data (pre-)processing

We used MATLAB (58) to preprocess raw data, and Python programming language [(59); Python Software Foundation, https://www.python.org/] to manually inspect and, if required, correct automatically detected events in the data and prepare data for subsequent analysis. Finally, we used the statistical software program JASP (60) to conduct statistical tests. All analysis scripts can be accessed at: https://osf.io/smchp/.

During data preprocessing, we applied a 20-Hz Gaussian low pass filter to continuous, raw eye pupil and raw head position (in deg) and velocity (in deg/s) data streams. Head velocity data were directly obtained from recordings of the 3D inertial sensors, head position was derived from numerical temporal integration of head velocity, and eye position in the horizontal plane was computed from pupil rotation recordings. We then separated the continuous data streams into 52 trials, such that one trial corresponds to one horizontal eye-head gaze shift toward the target light: target LED onset denoted the start of the trial, and control light onset denoted the end of the trial period. For subsequent analysis, we only considered gaze shifts with a target gaze amplitude of 75° or 80°, which resulted in 43 trials per session (i.e., 1—unweighted, 2—weighted, and 3—unweighted) per participant. We *a priori* determined the head oscillation ratio as the primary outcome variable of this study, defined as the absolute ratio of the first positive head velocity peak and the first subsequent negative peak of head velocity [in analogy to (39, 61)]—this way, oscillations are normalized by peak velocity in a given trial (see Figure 3). To this end, head peak velocity, the subsequent first zero crossing (i.e., where head velocity first reaches zero and becomes negative), the absolute minimum peak of the first undershoot (where the head momentarily comes to a halt and then moves backward), and the second zero crossing (i.e., head velocity reaches zero again and then becomes positive) were initially automatically detected and the head oscillation ratio of each trial computed.

Next, we manually inspected each trial and corrected any automatic detection errors. Automatic detection usually failed when participants moved their gaze too early (i.e., in anticipation of the next target flash) or initialized movement too late. Therefore, if participants shifted their gaze too early, we extended the trial window to also include the period between the prior control light and target onset. Similarly, if participants shifted their gaze too late, we extended the window to also consider the movement after the control light had already flashed. We excluded the trial if peak head velocity and/or undershoot could (still) not be determined with certainty. This way, we were able to minimize data loss and include as many gaze shifts as possible in our analyses. On average, patients moved too early in 1.3% (SD = 2.4%) of trials and too late in 4.4% (SD = 4.6%) of trials, whereas 1.5% (SD = 2.5%) of trials had to be excluded because we could not determine all parameters necessary to compute the head oscillation ratio. Healthy control participants, on average, moved too early in 0.3% (SD = 0.5%) of trials and too late in 5.1% (SD = 5.4%) of trials, and 1.7% (SD = 2.5%) of trials had to be excluded from further analysis.

Following, we excluded all trials with a gaze amplitude of <40°, computed as the sum of head position and eye position in the horizontal plane. For trials with gaze shifts that were executed too early or too late, we also considered the extended movement window when calculating gaze amplitude. Overall, we excluded (on average) 6.7% (SD = 6.0%) of trials per patient and 4.7% (SD = 2.0%) of trials per control participant because gaze shifts were too small. Furthermore, within each participant's session, we excluded trials with a head oscillation ratio that was more than two standard deviations below or above the average head oscillation ratio. Consequently, we removed, on average, 4.1% (SD = 1.1%) and 4.9% (SD = 1.0%) of trials per patient and healthy control

participant, respectively. Overall, this resulted in, on average, 38.54 trials (SD = 2.03) in the first session (unweighted 1), 38.08 trials (SD = 3.2) in the second session (weighted), and 39.00 trials (SD = 2.16) in the third session (unweighted 2) to be included for patients; for participants in the control group, we could include 38.77 trials (SD = 1.64) for the first session (unweighted 1), 38.92 trials (SD = 1.8) for the second session (weighted), and 39.08 trials (SD = 1.38) for the third session (unweighted 2), on average. Note that the reported percentages of anticipated/delayed gaze shifts and trial exclusions (oscillation ratio undetermined, gaze amplitude $<40^{\circ}$, outliers) pertain to all included participants in the final analysis round.

Finally, we re-calculated the mean head oscillation ratio with the remaining trials per session (i.e., unweighted 1—weighted—unweighted 2) and per participant to be entered for subsequent statistical analysis.

Statistical analysis

We employed a mixed design, where each participant completed all three sessions successively but belonged to one of two groups. Therefore, for statistical analyses, we performed a Bayesian repeated-measures (RM) ANOVA, where the variable session was the within-subjects factor (three levels: 1—unweighted, 2—weighted, and 3—unweighted) and group (two levels: patient and healthy control) was the between-subjects factor, with the oscillation ratio as the dependent variable.

Unlike the more traditional null hypothesis significance testing (NHST) approach, the employed Bayesian statistical approach allowed us to examine the relative evidence for both the null (i.e., absence of a group and/or session effect) and alternative hypothesis (i.e., presence of a group and/or session effect). More specifically, the Bayes Factor (BF) quantifies the graded strength of statistical evidence for a specific model or effect, where BF subscripts—BF_{01} or BF_{10}–indicate support for the null hypothesis and the alternative hypothesis, respectively. We use quantitative labels as described in Wagenmakers et al. (62) to interpret the evidential strength: BFs of 1, 1–3, 3–10, 10–30, 30–100, and >100 classify no, anecdotal, substantial, strong, very strong, and extreme evidence, respectively. For instance, a BF_{01} of 4 would denote that the data are four times as likely to have occurred under the null than under the alternative hypothesis, thus representing substantial support for the null hypothesis vs. the alternative hypothesis. For model comparisons, we report the BF for the model of interest compared to a null model only including the subject; for analysis of effects, we report the $BF_{inclusion}$ (or $BF_{exclusion}$) that reflects the evidential strength of all models containing a particular effect compared to all models without the effect. This analysis plan was preregistered and can be accessed at: https://osf.io/me4zc/.

Results

For the first interim analysis ($n_{patient}$ = 10, $n_{control}$ = 10), two patients had to be excluded from the analysis because they did not follow the experimenter's instructions: one patient only performed gaze shifts in anticipation of the target light, while another patient already moved the eyes to the expected position of the next target before also moving the head once the target finally flashed. Thus, we calculated a Bayesian RM ANOVA with the remaining eight patients and 10 healthy control participants, which revealed anecdotal (BF_{01} = 2.80, $BF_{exclusion}$ = 2.63) evidence for no differences in the head oscillation ratio between patients and controls across all three sessions. Analyses revealed that our experimental manipulation of increasing the head moment of inertia (i.e., a mismatch between predicted and actual sensory feedback) was successful, as all participants exhibited larger head oscillations during the weighted session (BF_{10} = 2.211e+11, $BF_{inclusion}$ = 1.706e+11, extreme evidence) than during both unweighted sessions. In addition, *post-hoc* analyses revealed a learning effect from the first unweighted to the second unweighted session: irrespective of group membership ($BF_{01,U}$ = 3.27), participants were able to reduce head oscillations over the course of the experiment ($BF_{10,U}$ = 31.74).

For the second analysis round, we recruited five additional participants per group and performed statistical analyses in line with round 1. With a sample of 15 healthy controls and 13 patients (two patients were excluded during round 1), the Bayesian RM ANOVA yielded substantial (BF_{01} = 3.7, $BF_{exclusion}$ = 5.23) evidence for the absence of a group difference in head oscillations (Figure 4). Again, the experimental manipulation of experimentally inducing a mismatch between old and new head characteristics by increasing participants' head moment of inertia was successful: we obtained extreme (BF_{10} = 2.684e+15, $BF_{inclusion}$ = 2.729e+14) evidence that participants exhibited increased head oscillations when wearing the helmet. Matching the analysis in round one, *post-hoc* analyses also indicated extreme ($BF_{10,U}$ = 3,215.99) evidence for a learning effect: participants reduced head oscillations from the first to the second unweighted session, regardless of group affiliation ($BF_{01,U}$ = 4.38).

Overall, the analyses of round two were in line with the results obtained in round one (i.e., in terms of direction of effects) but were larger in the magnitude of evidential strength. Since we crossed the *a priori*-defined mark of substantial evidence ($BF_{01/10} > 3$), we terminated data collection with this round. Table 1 provides a brief overview of head oscillation values within sessions and groups in this final round.

Finally, of all 13 included patients in the final analysis round, 61.5% reported pain in the leg/knee/foot region, 46.2% in their spine, 38.5% in the head/face area, 30.8% in the neck, 30.8% in the arms/hands, 15.4% in the shoulder, 7.7% in the abdomen, 7.7% in the genital area, and 7.7% in the pelvis. Note that the majority of patients experienced pain in more than one body area. Since patients were recruited from in- and outpatient units for severe functional disorders, they were suffering from chronic (functional) pain that significantly interfered with and limited their personal, social, and occupational lives. That is, 30.8% reported being unable to work, while 38.5% were still employed but experienced substantial impairment at work, and 69.2% felt that they could not fully partake in their everyday personal (e.g., hobbies, grocery shopping, and clothing themselves) and social lives (e.g., meeting friends) due to their symptoms. Table 2 summarizes the onset, frequency, and characteristics of pain symptoms described by

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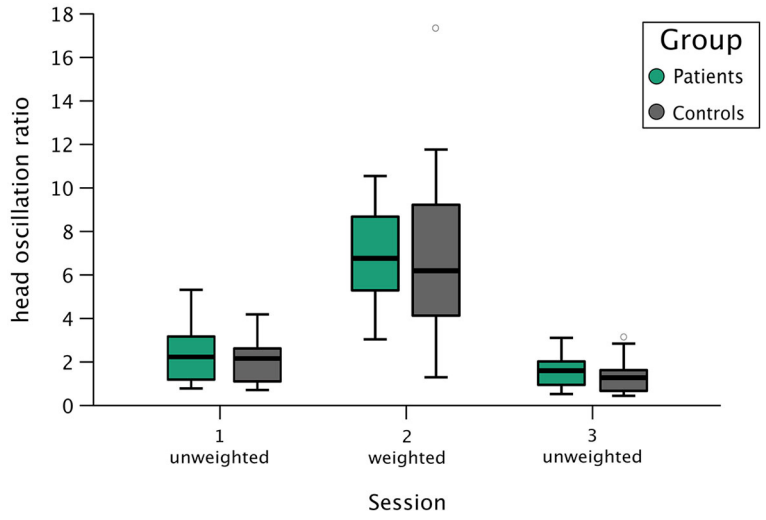

FIGURE 4
Group results of head oscillation ratios during all three experimental sessions. This box plot shows group results for patients (boxes in green) and healthy controls (boxes in gray) during session 1 (unweighted), session 2 (weighted—with helmet), and session 3 (unweighted). The y-axis depicts the head oscillation ratio, where a larger value corresponds to larger head oscillations at the end of the combined eye-head gaze shift. Each box represents the interquartile range (IQR), delineating the lower (25th percentile) and upper (75th percentile) quartile, with the vertical line depicting the group's median head oscillation ratio during the respective session. The boxes' whiskers correspond to the most extreme data point within 1.5 times the IQR from the lower and upper quartiles. Observations exceeding this range are marked as a gray circle, representing a healthy control participant in the weighted condition and a different control participant in the second unweighted condition.

TABLE 1 Descriptive statistics of head oscillation ratios for patients ($n = 13$) and healthy controls ($n = 15$) during each experimental session.

	Session 1 (unweighted)		Session 2 (weighted)		Session 3 (unweighted)	
	Patients	Controls	Patients	Controls	Patients	Controls
Mean	2.35	2.12	6.79	7.04	1.53	1.42
SD	1.39	1.20	2.27	4.29	0.76	0.88

TABLE 2 Descriptive summary of onset, frequency, duration, and characteristics of pain symptoms as reported by patients ($n = 13$).

Patient	Onset (in years)	Frequency (days per week)	Duration (in hours)	Characteristics
P1	4	/[a]	/[a]	Stinging, pressing
P2	9	7	variable[b]	Stinging, cold
P3	19	7	16–24	Stinging, prickly, rubbing
P4	1	7	16–24	Burning, itching, pulling
P5	7	Not daily[b]	21	Stinging
P6	7	2–3	2–3	Throbbing, shooting, burning
P7	30	2–3	0.1–24	Dull, pressing, stinging
P8	3	7	16–24	Shooting, stinging, burning
P9	25	3–4	16–24	Stinging, pressing
P10	6	7	16–24	Dull, pressing, throbbing
P11	14	7	24	Dull, stinging, pulling, throbbing
P12	3	7	16–24	Stinging, sore, pulling
P13	8	7	24	Burning, stinging

[a]Information was not collected at measurement.
[b]Participant could not give a definitive answer, or symptoms were too variable to report a pattern.

TABLE 3 Overview of medication (active ingredient) intake of participants in the patient ($n = 13$) and control ($n = 15$) group.

Subject	Medication (dose, intake frequency)
P1	Denosumab (60 mg, every 6 months)
P2	Pregabalin (75 mg, 1x day), Duloxetine (60 mg, 1x day)
P3	Novaminsulfon (500 mg, 3x day; double if necessary), Venlafaxine (225 mg, 1x day), Metformin (500 mg, 2x day), Atorvastatin (40 mg, 1x day), Pramipexol (0.35 mg, 1x day), Macrogol (13.125 mg, 2x day)
P4	Lacosamid (100 mg, 2x day), Lamotrigin (25 mg, 1x day)
P5	Statin (no information on dosis, 1x day)
P6	Penicillin (1.5 Mega IE, 2x day), Tapendadol (100 mg, 2x day)
P7	Atorvastatin (20 mg, 1x day), Ibuprofen (if necessary), CBD-oil (if necessary), sumatriptan (if necessary)
P8	Tilidine (50 mg, 1x day), Pregabalin (5x 100 mg, 2x day)
P9	Salmeterol xinafoate and Fluticason 17-proprionate (if necessary), Ibuprofen (if necessary)
P10	Acetylsalicylic acid (250 mg, if neccessary), Paracematol (250 mg, if necessary), Amitriptyline (12.5 mg, 1x day)
P11	Gabapentin (500 mg, 3x day), Pantoprazole (20 mg, 1x day), Magnesiumoxide, heavy (250 mg, 1x day), Celecobix (100 mg, if necessary), Ibuprofen (800 mg, if neccessary)
P12	Amitriptylin (6x 45.3 mg, 1x day)
P13	Pregabalin (330 mg, 2x day), Duloxetine (33.7 mg, 1x day), Acetylsalicylic acid (100 mg, 1x day), Rosuvastatin (20.8 mg, 1x day), Pantoprazole (20 mg, 1x day), Tamsulosin (0.4 mg, 1x day)
C5	Exemestan (25 mg, 1x day)
C6	Olmesartan (20 mg, 1x day), Amlodipine (5 mg, 1x day)
C7	Levothyroxine (no information on dosage)
C11	Levothyroxine (88 µg, 1x day)
C12	Valsartan (no information on dosage), Salbutamol (spray, 2x day)
C14	Levothyroxine (no information on dosage)

P1–P13 denotes patients, while C5–14 denotes healthy controls. In this table, we only listed healthy controls who reported medication intake; the remaining nine healthy control participants (i.e., C1–4, C8–10, C13, C15) took no medication at the time of measurement.

patients, and Table 3 provides an overview of the medication taken at the time of measurement by patients and healthy controls.

Discussion

The goal of this study was to experimentally examine whether erroneous sensorimotor processing is a transdiagnostic mechanism underlying chronic (functional) pain. To this end, we measured head stability in a group of 13 patients with functional pain and 15 healthy controls when they performed large gaze shifts naturally, with experimentally increased head moment of inertia, and again naturally. Contrary to our hypothesis, we found that head stability during all three sessions did not differ between patients and healthy control participants. This suggests that sensorimotor processing was intact in our chronic (functional) pain patient group.

In addition, we found that both patients and healthy controls were able to reduce head oscillations from the first unweighted (pre-weight) to the second unweighted (post-weight) session. Presumably, the weight of the measurement goggles had already induced a slight increase in the head moment of inertia, leading to a mismatch in predicted and actual head movement characteristics. As a result, head oscillations were slightly increased toward the beginning of the experiment, and both groups were equally able to adjust their internal model predictions to the altered head characteristics throughout the experiment. Possibly, the even stronger prediction errors evoked during the weighted condition were (additionally) driving this CNS-based learning process. A similar learning effect was already observed in an earlier study with patients suffering from IBS ($n = 7$), which employed the same paradigm (40).

Altered sensorimotor processing in pain

In light of the predictive processing model, pain experience is not solely the product of nociceptor activation but rather represents the final product of a complex interplay of CNS-based internal model predictions and peripheral input. Any mismatch between the expected and actual sensory feedback produces a prediction error, which should prompt an update of the internal model. However, the brain may categorize an underlying inconsistency as potential bodily damage or injury and consequently generate the perception of pain as a protective warning signal. Pain may be a consequence of erroneous sensorimotor processing, but at the same time, it is also a cause: an individual suffering from chronic pain may restrict interaction with the environment (e.g., because of mental exhaustion and stiffness) and may be required to adapt existing motor control patterns (e.g., compensate for a painful leg). In turn, this can lead to additional strain and pain (e.g., due to avoidance of movement) or movement that constantly produces prediction errors (e.g., due to irregularities in new movement strategies). In fact, a broad range of functional pain conditions are closely linked to altered sensorimotor processing and, more specifically, adaptations in motor control and planning [(63–65), for a comprehensive review, see (66)]. This view is corroborated by neuroscientific evidence suggesting that dysregulated sensorimotor processing in functional pain is associated with altered neural representation in the brain [see (67) for an overview, (68–70)]. For instance, adaptions in the primary somatosensory cortex after exercise therapy have been linked to reductions in pain intensity in CRPS (71). Therefore, we expected to be able to measure such processing deficits in our movement-based experiment, where sensorimotor processing was specifically challenged.

Head instability as a transdiagnostic marker of erroneous sensorimotor processing in functional disorders

Prior research employing this paradigm has observed increased head oscillations already during natural, unweighted gaze shifts (i.e., while only wearing the measurement goggles) in patients with functional dizziness (39), indicating that head properties were not represented accurately in the central nervous system-based internal model and were also not sufficiently updated despite prediction

errors resulting from the suboptimal, oscillating head movement. Notably, the patients' experienced symptoms could—at least in part—be an expression of similar head instability in everyday life since head oscillations fit well with the reported dizziness symptomatology. Similarly, Schröder et al. (40) measured increased head oscillations in patients with irritable bowel syndrome (IBS; $n = 7$) and observed increased head oscillations only during gaze shifts with increased head moment of inertia, suggesting that resulting prediction errors did not sufficiently update the internal model at the same rate as it did in healthy controls. The lack of increased head oscillations in both natural sessions fits well with the fact that patients with IBS did not experience any dizziness symptoms. However, the observed pronounced head oscillations in the weighted session point toward a general, transdiagnostic sensorimotor processing deficit in this patient population. Thus, IBS may be understood as a sensorimotor processing disorder, where motor control is not only impaired symptom-specifically (e.g., gut motility) but perhaps also more generally throughout the body (e.g., head control). This is also more in line with the structural makeup of the brain, which is not divided into entirely separate motor regions for each body part (e.g., gut vs. head) but rather coordinates movement throughout the whole body within a complex motor network (72).

In sum, we suggest that these earlier findings may point toward a transdiagnostic, symptom-unspecific sensorimotor processing deficit in functional disorders more generally, which can be unraveled when challenged experimentally within the presented eye-head paradigm: by increasing the head moment of inertia (3.1-fold) with our helmet, we are able to introduce a very specific perturbation to the sensorimotor system that produces a definite prediction error and erroneous movement (i.e., head oscillation), which can be compared to an optimal response (i.e., smooth head movement). Importantly, the observed difficulty in dealing with perturbation could be a general problem in functional disorders and possibly represent a vulnerability for developing additional functional symptoms in the future (e.g., dizziness)—a phenomenon that is also commonly seen in clinical practice [e.g., (73, 74)]. Therefore, to extend this line of research, the current study examined whether a similar symptom-independent sensorimotor processing deficit may also be present in chronic (functional) pain. Although the presented negative results refute the presence of a similar transdiagnostic marker in this patient group, they are an important contribution to the current body of evidence, as negative or null results often remain unpublished, leading to a bias in the available literature (75, 76).

Erroneous sensorimotor processing: not a measurable marker in chronic (functional) pain

In the following section, we outline three possible reasons for the obtained negative result of this study.

First, head stability as a marker of sensorimotor processing deficits may not be the appropriate parameter to measure a transdiagnostic mechanism in functional pain. For example, some experimental paradigms directly measure altered pain perception in functional pain syndromes [e.g., thermal grill illusion; (77)]. However, to reveal a potentially unifying, transdiagnostic mechanisms in functional disorders generally and functional pain specifically, experimental setups that examine performance in symptom-unrelated modalities are necessary. For instance, Cost et al. (78) showed that patients with fibromyalgia exhibited significant disturbances in balance and gait compared to healthy control participants. However, these objective measurements also matched patients' subjective reports on motor impairment in everyday life and thus did not provide insight into kinematic parameters as a transdiagnostic marker in functional (pain) disorders [see also (79)]. To the best of our knowledge, so far, only two studies (38, 40) have provided direct experimental evidence of a symptom-unspecific, objectively measurable transdiagnostic marker of erroneous sensorimotor processing in functional (pain) disorders and have been discussed earlier in more detail.

Second, pain symptomatology may simply be too far removed from the organ systems involving vestibular processing and (eye-head) motor control to measure any underlying transdiagnostic mechanism.[3] Although plausible, this still raises the question of why we were able to measure processing deficits in IBS ($n = 7$) (40) with the same paradigm, where the affected organ systems seem similarly far removed from those challenged in the experiment. Furthermore, diagnostic criteria of IBS include pain (associated with defecation or stool frequency/appearance) as a hallmark symptom (42, 80, 81). Similar to functional pain, pain in the context of IBS also seems to be, at least in part, a result of dysregulated processing in the CNS (80, 82–85). However, it is possible that the measured transdiagnostic sensorimotor processing deficits observed in the IBS sample are independent of the pain symptomatology and are instead a marker of other gastrointestinal symptoms in IBS, such as intestinal motor abnormalities and excessive contractile activity (86–89). Unlike patients with IBS, pain in the current sample was not focused on abdominal pain only but could differ widely in site and spread. In sum, patients with functional pain may not exhibit an all-encompassing deficit in adapting internal models but may instead experience dysregulated adaption more restricted to symptom-specific internal models (e.g., those concerned with potential damage in the body).

Third, patients were eligible to participate if they had been diagnosed with either persistent chronic (functional) pain disorder [F45.40, ICD-10, (42)] or chronic pain disorder with somatic and psychological factors [F45.41, ICD-10, (42)]. Notably, F45.41 was the predominant diagnosis, with 10 out of 13 included patients in our analysis. Although both labels outline the diagnosis as persistent pain not *sufficiently* explained by an underlying structural impairment, a diagnosis of F45.40 posits that psychosocial stress factors play a major role in the onset, severity, exacerbation, or maintenance of pain symptoms, while F45.41 requires structural processes (e.g., damaged tissue) to cause the initial pain complaint, with psychosocial factors subsequently contributing to pain intensity, exacerbation, or maintenance (90).

3 For instance, next to the symptom modalities (e.g., pain vs. dizziness) that tend to arise from different organ systems, the affected site of pain in all included patients did not always revolve around the body areas involved in performing large gaze movements: 38.5% suffered from pain in the head area, 30.8% from pain in the neck, and 15.4% from pain in the shoulder region.

In other words, patients with an F45.41 diagnosis can suffer from pain that is a result of structural impairment *as well as* centrally mediated (functional) processes *simultaneously*. That is, most patients in the current sample may suffer from pain that stems, to a larger part, from an underlying structural impairment and, perhaps to a lesser extent, from an underlying functional CNS-processing impairment. In contrast, earlier studies using the same paradigm found measurable head instability in dizziness ($n = 8$) (61) and IBS (40) patients ($n = 7$), where extensive neurological or gastrointestinal workups did not reveal any comorbid organic-structural impairment. Taken together, our experimental paradigm may not have been sensitive enough to capture possible minor, transdiagnostic, sensorimotor processing deficits in the current functional pain sample.

Limitations

The findings of the present study should be interpreted in light of the following limitations. First, our sample size is relatively small, which may limit the generalization of the obtained effects. The reason for the small number of participants is the nature of our patient sample: only patients with an isolated functional pain disorder were eligible to participate since our goal was to measure a possible transdiagnostic marker. This severely limited the selection of patients, as comorbidity among functional symptoms is the rule rather than the exception (73, 74, 91). Moreover, it is important to note that a similarly small sample size was able to detect such sensorimotor deficits in patients with IBS [(40); seven patients]. In addition, we recruited patients from a specialized institution for functional disorders, which makes it likely that patients suffered from more severe forms of functional pain and additional psychiatric disorders than is typical for this population. Finally, because we selected patients only based on diagnostic labels (i.e., F45.40 or F45.41), the affected region (e.g., head vs. foot) and spread (e.g., isolated body part vs. whole body) of pain differed considerably among participants. However, we did not expect these factors to meaningfully impact sensorimotor processing in the context of our experiment, especially because we aimed to measure sensorimotor processing deficits as a more general, transdiagnostic mechanism.

Future research and hypotheses

The current study adds a valuable contribution to the current body of evidence, as experimental studies on transdiagnostic mechanisms in functional disorders are generally scarce (41). Future research could focus on re-evaluating head stability in the context of the employed eye-head paradigm as a marker to measure transdiagnostic mechanisms in functional (pain) disorders. Calculating the oscillation ratio based on head velocity traces has proven to be an adequate marker of erroneous sensorimotor processing (39, 40, 54–56), but different head velocity parameters (e.g., area under curve and skewness) may be worth validating in subsequent studies. Furthermore, in line with earlier studies on optimal control of head movements in the eye-head paradigm (92), computational modeling could be applied to further narrow down the interplay of CNS-based prediction and sensory input in functional pain. In addition, we recommend analyzing the gaze stability[4] of patients with functional pain during natural and weighted gaze shifts, akin to the previous study on patients with functional dizziness (61). For instance, it may be possible that eye movements do not sufficiently counteract the ongoing head movement [i.e., suboptimal motor planning (92)] and thus still reveal sensorimotor processing deficits that cannot be seen in head stability alone.

When examining possible transdiagnostic mechanisms underlying functional (pain) disorders, future studies could also employ different experimental paradigms (e.g., with a measurement modality slightly closer to the modality of pain) or the same eye-head paradigm with a different patient sample. That is, the eye-head paradigm might reveal processing deficits if patients suffering from other functional pain syndromes are measured. For instance, fibromyalgia may be a suitable choice, as earlier studies have already shown transdiagnostic markers in patients with this diagnosis [i.e., dysregulated breathing perception (38)]. Alternatively, it would be interesting to test patients with other functional disorders (e.g., functional movement disorder) with the eye-head paradigm, where the affected organ system is tied closer to the vestibular system or (eye-head) motor control in general. Complex regional pain syndrome might be another candidate for testing, as pain regions are clearly defined and limited, and top-down pain-regulating mechanisms are known to play an important role (93).

Data availability statement

Raw data supporting the conclusions of this article are available under https://osf.io/smchp/.

Ethics statement

The studies involving humans were approved by Ethics Committee of the Technical University of Munich. The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study.

Author contributions

FR: Data curation, Formal analysis, Investigation, Methodology, Project administration, Software, Validation, Visualization, Writing – original draft, Writing – review and editing. KB: Investigation, Project administration, Validation, Writing – review and editing. SG: Methodology, Supervision, Validation, Writing – review and editing. NL: Conceptualization, Funding acquisition, Methodology, Project administration, Resources, Supervision, Validation, Writing – review and editing.

4 The present data allow analysis of gaze stability and can be openly accessed under the link provided in the data availability statement of this manuscript.

NJ: Investigation, Project administration, Validation, Writing – review & editing.

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Conflict of interest

NL is a shareholder and was a paid consultant to EyeSeeTec GmbH. SG is a shareholder of EyeSeeTec GmbH.

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

Publisher's note

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Manuscript Study 2

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Experimental evidence for a robust, transdiagnostic marker in functional disorders: Erroneous sensorimotor processing in functional dizziness and functional movement disorder

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ABSTRACT

Objective: Recent neuroscientific models suggest that functional bodily symptoms can be attributed to perceptual dysregulation in the central nervous system. Evidence for this hypothesis comes from patients with functional dizziness, who exhibit marked sensorimotor processing deficits during eye-head movement planning and execution. Similar findings in eye-head movement planning in patients with irritable bowel syndrome confirmed that these sensorimotor processing deficits represent a shared, transdiagnostic mechanism. We now examine whether erroneous sensorimotor processing is also at play in functional movement disorder.

Methods: We measured head movements of 10 patients with functional movement disorder (F44.4, ICD-10), 10 patients with functional dizziness (F45.8, ICD-10), and (respectively) 10 healthy controls during an eye-head experiment, where participants performed large gaze shifts under normal, increased, and again normal head moment of inertia. Head oscillations at the end of the gaze shift served as a well-established marker for sensorimotor processing problems. We calculated Bayesian statistics for comparison.

Results: Patients with functional movement disorder (*Bayes Factor (BF)*$_{10}$ = 5.36, BF_{incl} = 11.16; substantial to strong evidence) as well as patients with functional dizziness (BF_{10} = 2.27, BF_{incl} = 3.56; anecdotal to substantial evidence) showed increased head oscillations compared to healthy controls, indicating marked deficits in planning and executing movement.

Conclusion: We replicate earlier experimental findings on erroneous sensorimotor processing in patients with functional dizziness, and show that patients with functional movement disorder show a similar impairment of sensorimotor processing during large gaze shifts. This provides an objectively measurable, transdiagnostic marker for functional disorders, highlighting important implications for diagnosis, treatment, and de-stigmatization.

1. Introduction

Functional disorders represent one of the most commonly seen bodily complaints in primary, specialist, and emergency health care settings [1–4] and are associated with significant disability and reduced quality of life [5,6]. Accurate diagnosis is often delayed by many years [7,8], introducing iatrogenic harm and impeding timely and adequate treatment [9–11]. Overall, the prognosis of functional disorders is rather poor [12]. Although functional symptoms can present in varied modalities (e.g., bowel symptoms, dizziness, paresis, pain), they commonly co-occur, suggesting a shared pathogenesis [10,13]. This is also reflected in current classification systems, which define functional disorders

Abbreviations: FD, functional dizziness; FMD, functional movement disorder; IBS, irritable bowel syndrome; PE, prediction error.

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under a common diagnostic term regardless of the specific bodily symptom(s) [14,15]. To date, however, we still largely lack an understanding of a potentially unifying, transdiagnostic mechanism underlying different functional symptoms, disorders, or syndromes [16,17], which would aid in identifying more positive diagnostic signs and effective treatment targets.

Current explanatory models view functional disorders as a consequence of perceptual dysregulation in the central nervous system. In this predictive processing framework, the brain actively generates predictions about sensory activity, which are then compared to the actual sensorimotor input [18–23]. For instance, executing gaze shifts requires intact interplay of brain-based internal model predictions about sensory consequences of the movement as well as processing of sensory input from peripheral sensors (Fig. 1). If a component is erroneous or fails altogether, this deficit can be measured, e.g., as increased head instability (oscillation) at the end of a combined eye-head gaze shift [24–26].

Lehnen and colleagues [25] measured head stability of healthy controls and patients with functional dizziness (FD) in a gaze-shift experiment, where participants performed large eye-head movements towards visual targets under natural and with experimentally increased head moment of inertia. They found that patients' heads markedly oscillated both in the natural condition and with weighted head characteristics. This suggests sensorimotor processing deficits in functional dizziness: patients' internal models (e.g., of the head plant) were incorrect and not updated despite prediction errors arising from the suboptimal movement's consequences, leading to a mismatch between input from bodily sensors and internal models of sensory input. This mismatch, which can also be measured in unstable gaze movements [27], is consistent with patients' reports of perceived instability in functional dizziness. In order to investigate whether sensorimotor processing is also deficient in other functional disorders, research from our lab employed the same gaze-shift paradigm in patients with irritable bowel syndrome (IBS) [28]. Patients with IBS showed similar deficits only when head characteristics were altered experimentally, revealing more subtle deficits of head control that could likely reflect dysregulation of the entire body's sensorimotor system, but possibly more attenuated than the affected modality (e.g. gut motility). During natural gaze shifts, IBS patients' head movements were not different from healthy controls, consistent with the lack of dizziness symptoms in this patient group.

Additional experimental evidence for erroneous sensorimotor processing as a symptom-independent, transdiagnostic mechanism underlying functional disorders also comes from a rebreathing paradigm, where patients with functional dyspnea, fibromyalgia, or chronic fatigue syndrome have been shown to perceive prolonged breathlessness despite already normalized physiological parameters [29,30]. This likely arises due to erroneous sensorimotor (respiratory) signal processing, where relatively weak sensory input (i.e., normal CO_2 levels) is overridden by strong internal models of respiratory distress. Computational modelling approaches suggest that the same or similar mechanism may be at play in post-COVID [31].

Therefore, the aim of the current study was twofold: First, we examined whether the head instability observed earlier by Lehnen and colleagues [25] could be replicated in a new sample of patients with FD, applying the same experimental paradigm. Second, we investigated whether similar sensorimotor processing deficits could be measured transdiagnostically in patients with functional movement disorder (FMD).

2. Material and methods

This project is part of the innovative training network ETUDE (Encompassing Training in functional Disorders across Europe; https://etude-itn.eu/; [32]), ultimately aiming to improve the understanding of mechanisms, diagnosis, treatment, and stigmatization of functional disorders.

The ethics committee of the Technical University of Munich reviewed and approved the current study, which was carried out in accordance with the Declaration of Helsinki. All participants provided signed informed consent and received financial compensation of 10€ per hour.

We preregistered the entire study procedure and analysis on the Open Science Framework prior to any data collection, which – together with the (raw) data, analysis scripts and files – can be openly accessed under https://osf.io/jcyk7/.

2.1. Sample

2.1.1. Sample characteristics

Patient and healthy control groups were closely age- and gender-matched.

To investigate possible transdiagnostic effects, we measured 10 patients with functional movement disorder (FMD; dissociative movement disorder, F44.4, ICD-10 [33]; $M_{age} = 40.10$ years, $SD_{age} = 15.05$ years; 5 men, 5 women), matched with 10 healthy controls ($M_{age} = 41.20$ years, $SD_{age} = 15.85$ years, $BF_{01} = 2.50$; 5 men, 5 women, $BF_{01} = 1.98$). Table 1 provides a detailed summary of patients' symptoms; note that FMD symptoms were not restricted to gait disturbances but considerably varied in location and type (e.g., involuntary absence versus presence of movement).

To examine the robustness of earlier findings from eight patients with FD ($M_{age} = 35$ years, $SD_{age} = 13$ years; 5 women, 3 males) reported in Lehnen and colleagues [25], we measured another 10 patients with FD (somatoform dizziness, F45.8, ICD-10 [33]; $M_{age} = 51.70$ years, $SD_{age} = 9.66$ years; 4 men, 6 women) and 10 matching healthy control participants ($M_{age} = 51.50$ years, $SD_{age} = 10.61$ years, $BF_{01} = 2.52$; 6 men, 4 women, $BF_{01} = 1.38$).[1] Note that the patients measured in Lehnen and colleagues [25] were overall younger than patients with FD recruited for this study, $t(16) = 3.13$, $p < 0.006$. A retrospective assessment of reported symptoms revealed that 8 out of the 10 patients also met diagnostic criteria for Persistent Postural-Perceptual Dizziness (PPPD, AB32.0) [14].

All participants eligible for the current study were at least 18 years old, had no neurological disorder (including central vestibular impairment, peripheral vestibular impairment), had no hearing impairment that would impede a structured interview or correct instructions for the experiment, had (corrected) vision of at least 20% on the better eye, experienced no acute problems of the cervical spine that would have substantially interfered with the execution of gaze shifts (e.g., due to pain, restricted mobility), and were not pregnant. Furthermore, patients were not eligible to participate if they suffered from more than one functional disorder or a psychiatric disorder explaining the bodily symptoms. Healthy participants must not have a history of or suffer from (a) current functional disorder(s), or a current acute psychiatric disorder.

We recruited patients from the in- and outpatient clinics of the Department of Psychosomatic Medicine and Psychotherapy as well as the outpatient clinic for movement disorders at the Department of Neurology, and healthy participants via external and internal clinic-wide web- and poster-based announcements at the University Hospital rechts der Isar of the Technical University of Munich, Germany.

2.1.2. Sample size estimation

Prior to data collection, we determined the minimum required sample size with a power analysis based on the study by Lehnen and colleagues [25], who employed the same experimental paradigm and

[1] We recruited additional healthy participants in order to match the overall older FD patient group. As a result, the healthy comparison group for patients with FD consists of six persons identical to the control group for FMD and four new persons.

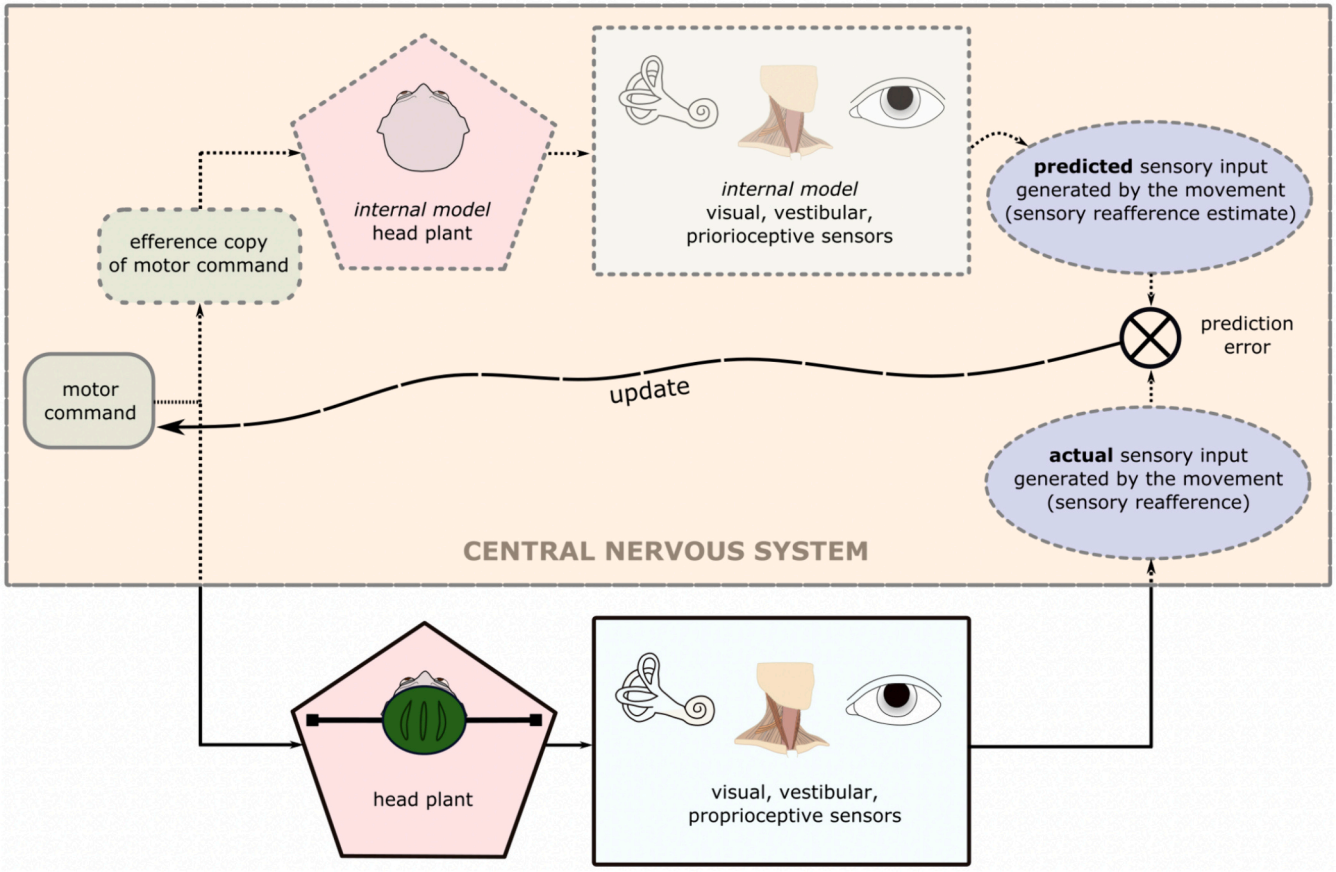

Fig. 1. *Example of motor command updating and execution during a weighted combined eye-head gaze shift.* When experimentally manipulating the participant's head characteristics by placing a helmet with eccentrically attached masses to each side, the now increased head moment of inertia is not yet incorporated in the brain's internal model of the head plant. Consequently, after a subsequent head shift, predictions about sensory input will deviate from the actual sensory input elicited by the executed head movement: the motor command is suboptimal for the current head properties, reflected in an unstable head movement (oscillations). The resulting prediction error should (ideally) serve to update brain-based internal models and motor commands, leading to smoother head movements during subsequent gaze shifts.

obtained a large significant difference in head oscillations between patients with FD and healthy controls (*partial* $\eta^2 = 0.62$, $f = 1.27$). However, since we aimed to measure a possible transdiagnostic mechanism, we expected to measure a slightly smaller effect in patients with FMD. Another goal was to examine whether the effect obtained by Lehnen and colleagues [25] would replicate in a new sample of patients with FD. However, effect sizes of close replication studies – especially when samples sizes are small – are notoriously smaller [34,35], therefore we also expected a somewhat smaller group effect for the current study ($f = 0.5$). As a result, using the software program G*Power [36], we estimated a required sample size of nine participants per group ($\alpha = 0.05$, $\beta = 0.8$). Including a safety margin of one participant per group, we arrived at an a priori sample size of 10 participants per group.

2.2. Materials

2.2.1. Clinical characterization

We assessed the vestibular-ocular reflex (VOR) gain for the vertical canals using the EyeSeeCam (EyeSeeTec GmbH, Munich, Germany) video head impulse test (vHIT) to assure structural intactness of participant's vestibular system. During the vHIT, the participant is asked to keep their eyes focused on a centrally positioned target, while the experimenter quickly and unexpectedly moves the participant's head to the left or right side (10–20° at 150-300 ms head velocity). When the participant's eyes keep fixation on the target (i.e., compensate the passively evoked head movement at the same velocity), the VOR is 1.0; a VOR of <0.79 [37–39] and the presence of re-fixation saccades were considered as vestibular dysfunction. We did not perform a vHIT for one patient with functional movement disorder, because they anticipated potential distress to their neck due to the sudden passive head movements required for the exam. For this patient, we instead ruled out any relevant vestibular disorders via comprehensive neurological exams. Prior to the measurements, we ensured that this patient was comfortable and unrestricted (e.g., due to pain) in performing active gaze shifts required for the experiment.

In addition, we conducted the structured clinical interview for DSM-5 disorders (SCID-5-CV, German version, [40]) to capture psychiatric diagnoses.

2.2.2. Experimental setup and procedure

In line with the methodology in Lehnen et al. [25], we employed an eye-head paradigm that allowed us to examine participants' eye and head motor control during large gaze shifts. Using EyeSeeCam goggles and its measuring system (EyeSeeTec GmbH, Munich, Germany), we simultaneously measured horizontal movements of the head and the left eye via 3D inertial sensors and video-oculography (220 Hz), respectively, throughout the experiment. Goggles were calibrated to each individual's eye characteristics with a 5-point laser prior to the start of the experiment. We asked participants to direct their gaze towards a red target light, which would only flash briefly. Importantly, we instructed to move eyes and head together, as when shifting gaze naturally from one object to another, and to then maintain gaze in the target position until the next light flashed. Participants completed three adjacent experimental rounds (see Fig. 2), each time performing 52 gaze shifts in

Table 1
Description of patients' functional movement disorder symptoms.

Patient	Onset (in years)	frequency (days per week)	duration (hours per day)	body region	symptom
P1	10	7	22	whole body, focused on the upper body	trembling, twitching, involuntary movements
P2	0.9	7	24	whole body ("head to toe")	twitching
P3	0.7	7	variable[a]	eyes	involuntary movements of the eyes and eyelids
P4	2	7	24	legs	weakness of both legs, unsteady gait
P5	0.75	7	4–16	face	tensioned upper lip area, difficulties swallowing, loss of tongue control, involuntary movements of the lower jaw
P6	1.25	7	16	neck	functional torsion of the neck muscles
P7	0.3	7	16	neck, head	functional torsion of the neck muscles, head tremor
P8	3	7	1–16	feet, legs, hands, shoulders	foot rotated inwards, leg cramps, unsteady gait, tremor of the upper body, involuntary movements of the hands, raised shoulders
P9	3	7	variable[a]	hands, legs	trembling of hands and legs, hand numbness and cramps, leg weakness
P10	0.7	7	24	legs	weakness of both legs, unsteady gait

[a] patient had difficulty in estimating symptom duration.

total, of which 43 were large (i.e., 75° or 80°). For the weighted round, participants were unaware of the characteristics or purpose of the helmet, and were requested to keep the head still until the session started, preventing premature adaptation to the altered head characteristics. All participants were naïve to the purpose of the research or the hypotheses tested.

2.3. Study setup comparison: current study versus Lehnen et al. (2019)

Although both studies relied on the same rationale for their experimental paradigm, there were slight differences between the setups. First, the current paradigm introduced control lights between target flashes as well as generally longer intertrial intervals. Fig. 3 illustrates an exemplary light sequence of the current and Lehnen et al.'s [25] study. Second, we introduced a third experimental round, in which participants performed unweighted gaze shifts again. This allowed us to investigate possible learning effects in head motor control across time and experimental conditions. Lastly, the helmet of the current setup induced a slightly lower head moment of inertia (3.1-fold) compared to the helmet used in Lehnen et al. [25] (3.3-fold).

2.3.1. Data (pre-)processing

We preprocessed raw data and automatically detected initial parameters in Matlab [41]. Subsequent manual inspection and, if required, correction as well as data cleaning for statistical analyses was performed with Python [42] (see: https://osf.io/jcyk7/).

For data preprocessing, we acquired head velocity data from the EyeSeeCam's 3D inertial sensors, which we integrated over time to compute head position data; eye position data was calculated from the obtained pupil rotation recordings. We filtered raw eye and head velocity (degrees per second) and position (in degrees) data streams with a 20 Hz low-pass Gaussian filter. Next, we separated the data into 52 trials per session, each trial corresponding to one gaze shift from target light onset to control light onset. Only gaze shifts with a targeted 75° or 80° gaze amplitude were considered for further analysis. The head oscillation ratio was our primary outcome variable (for calculation, see Fig. 4); necessary parameters (i.e., peak and undershoot head velocity) were detected automatically in this first step. Subsequently, we inspected each trial manually and corrected missed or inaccurately detected indices where necessary (see Table 2, and Appendix for detailed description).

The experimental setup from Lehnen and colleagues [25] did not include control lights, which would have allowed us to extend trials to the time window before the target light flashed (for anticipated gaze shifts) and up until the target control light flashed (for delayed movements). Therefore, in this re-analyzed FD data, we did not consider an extended timeframe in case of anticipated or delayed movements. Notably, according to our trial exclusion criteria, this would leave only very few trials for two participants in particular. We therefore decided to include additional exploratory analyses with and without these two patients, as well as an analysis of all patients' gaze shifts including those

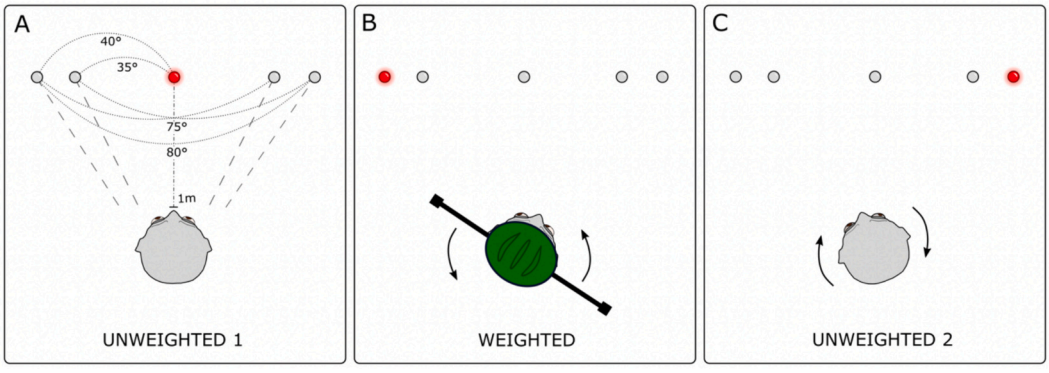

Fig. 2. *Visualization of experimental setup.* Participants were seated in front of a centrally (0°) positioned LED, with two LEDs placed to the left (at 35° and 40°) and two LEDs to the right side (at −35° and − 40°). Participants moved their gaze in three experimental sessions: first in a natural, unweighted condition (A); subsequently in a weighted condition (B) while wearing a helmet that increased the head moment of inertia 3.1-fold by means of two eccentrically attached masses; and lastly, in an unweighted condition (C) again. Participants wore measurement goggles attached to the head throughout all three sessions.

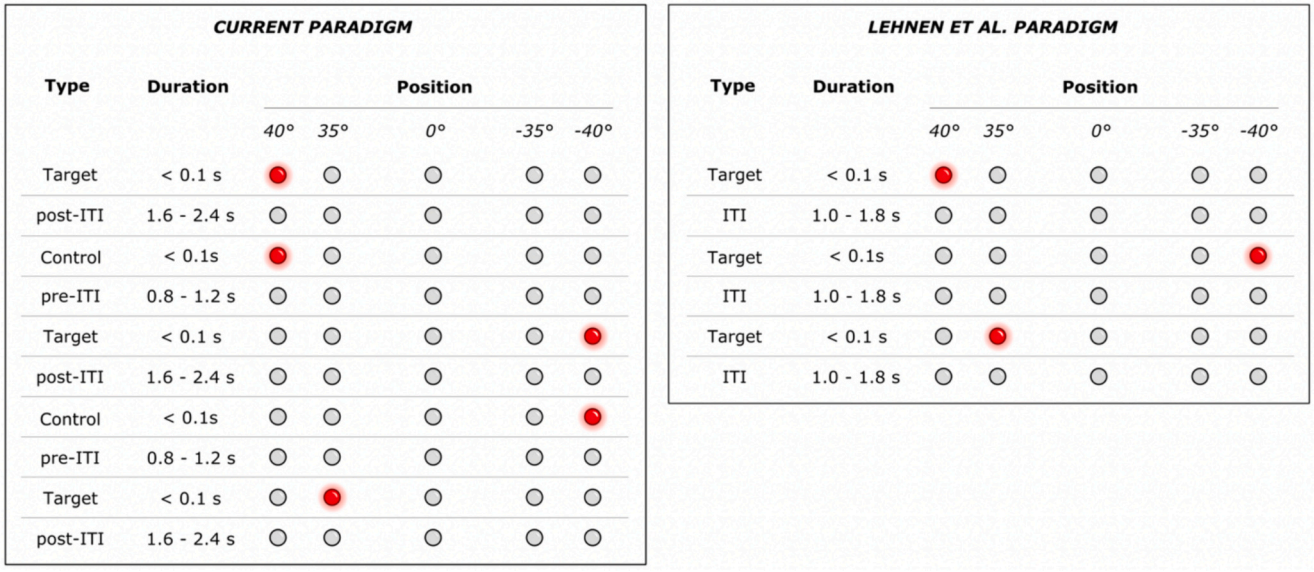

Fig. 3. *Comparison of the LED setup employed in the current study (left) and in Lehnen* et al. [25] *(right) during the eye-head paradigm.* Note that we introduced control lights for the current study, which allowed participants to correct their gaze position after the initial eye-head shift towards the target. This way, participants were more likely to start out at the correct position for the next gaze shift, ensuring that the next executed gaze amplitude was large enough (>40°). The length of intertrial-intervals (ITI) was randomized in both paradigms to avoid preparatory movements; however, the possible length of the interval differed between studies, see post- and pre-ITI (left) versus ITI (right).

smaller than 40° (in analogy to Lehnen et al. [25]) in the Appendix, to illustrate the robustness of our results.

2.4. Statistical analysis

In contrast to the more traditionally adopted null hypothesis testing approach, where a *p*-value >0.05 can arise due to a true null effect or simply due to a lack of power (Type II error), we adopted a Bayesian statistical approach. The Bayes factor (*BF*), denoted by subscripts BF_{10}/$BF_{inclusion}$ and BF_{01}/$BF_{exclusion}$, quantifies the ratio likelihoods of the data/models (i.e., relative statistical evidence) under both the alternative *as well as* the null hypothesis, respectively [43]. *BF*s of 1, 1–3, 3–10, 10–30, 30–100, and > 100 are generally classified as (respectively) no, anecdotal, substantial, strong, very strong, and extreme evidence [44]. For instance, a BF_{10} of 5 is interpreted as substantial evidence for the alternative hypothesis, i.e., the obtained data is 5 times more likely to have occurred under the alternative model.

We carried out statistical tests in JASP [45], all output can be accessed under https://osf.io/jcyk7/. We performed mixed 2 or 3 (Session: unweighted1 – weighted [– unweighted2]; within-subjects factor) x 2 (Group: patient versus healthy control/patient; between-subjects factor) Bayesian RM-ANOVAs with the head oscillation ratio as the dependent variable for group difference analyses and Bayesian independent *t*-tests (one-sided) for post-hoc analyses.

3. Results

3.1. Transdiagnostic effects: functional movement disorder versus healthy controls

Patients with FMD showed more pronounced head oscillations compared to healthy controls (BF_{10} = 5.36, substantial evidence; BF_{incl} = 11.16, strong evidence for main model/effect *group*), visualized in Fig. 5. This was the case in all three sessions ($BF_{10,unweighted1}$ = 10.98, strong evidence; $BF_{10,weighted}$ = 4.51, substantial evidence; $BF_{10,unweighted2}$ = 17.77, strong evidence). With extreme evidence for a main effect *session*, increasing the head moment of inertia 3.1-fold consistently led to increased head oscillations from the first unweighted session to the weighted session across both groups (BF_{10} = 103.71), which decreased again when the helmet was removed for the second unweighted session (BF_{10} = 34,296.59). An exploration of possible learning effects over sessions revealed with strong evidence ($BF_{10,U}$ = 29.89) that healthy controls reduced their head oscillations from the first unweighted to the second unweighted session, while evidence for a similar effect in patients remained anecdotal ($BF_{10,U}$ = 1.19).

3.2. Symptom-specific effects: functional dizziness versus healthy controls

Patients with FD exhibited larger head oscillations than healthy control participants (BF_{10} = 2.27, BF_{incl} = 3.56, anecdotal to substantial evidence for the main effect/model *group*; Fig. 6), replicating earlier findings reported in Lehnen et al. [25]. Indeed, post-hoc analyses suggest that head oscillations of patients were larger throughout all three sessions, i.e. in the first unweighted session (BF_{10} = 4.33, substantial evidence), the weighted session (BF_{10} = 3.79, substantial evidence), and the second unweighted session (BF_{10} = 2.38, anecdotal evidence). Across groups, head oscillations increased when the head moment of inertia was increased 3.1-fold (BF_{10} = 238.19, extreme evidence) and decreased again once the helmet was taken off (BF_{10} = 1288.91, extreme evidence). In addition, we explored possible learning effects across sessions: while healthy controls decreased their head oscillations from the first unweighted to the second unweighted session ($BF_{10,U}$ = 41.05, strong evidence), patients with FD likely did not improve head stability over the course of the experiment ($BF_{01,U}$ = 2.64, anecdotal evidence).

3.3. Head oscillations in functional dizziness: "old" versus "new" data

We compared head stability between patients with FD reported in Lehnen et al. [25] (*n* = 8) and patients with FD collected for the current study (*n* = 10). With anecdotal evidence (BF_{01} = 1.97, BF_{excl} = 1.59, main effect/model *group*), the results indicate that patients in both samples exhibited similarly elevated head oscillations (Fig. 7). Post-hoc analyses suggest that the patient groups likely did not differ in the size of head oscillations during both the unweighted (BF_{01} = 1.87, anecdotal evidence) and weighted session (BF_{01} = 1.60, anecdotal evidence).

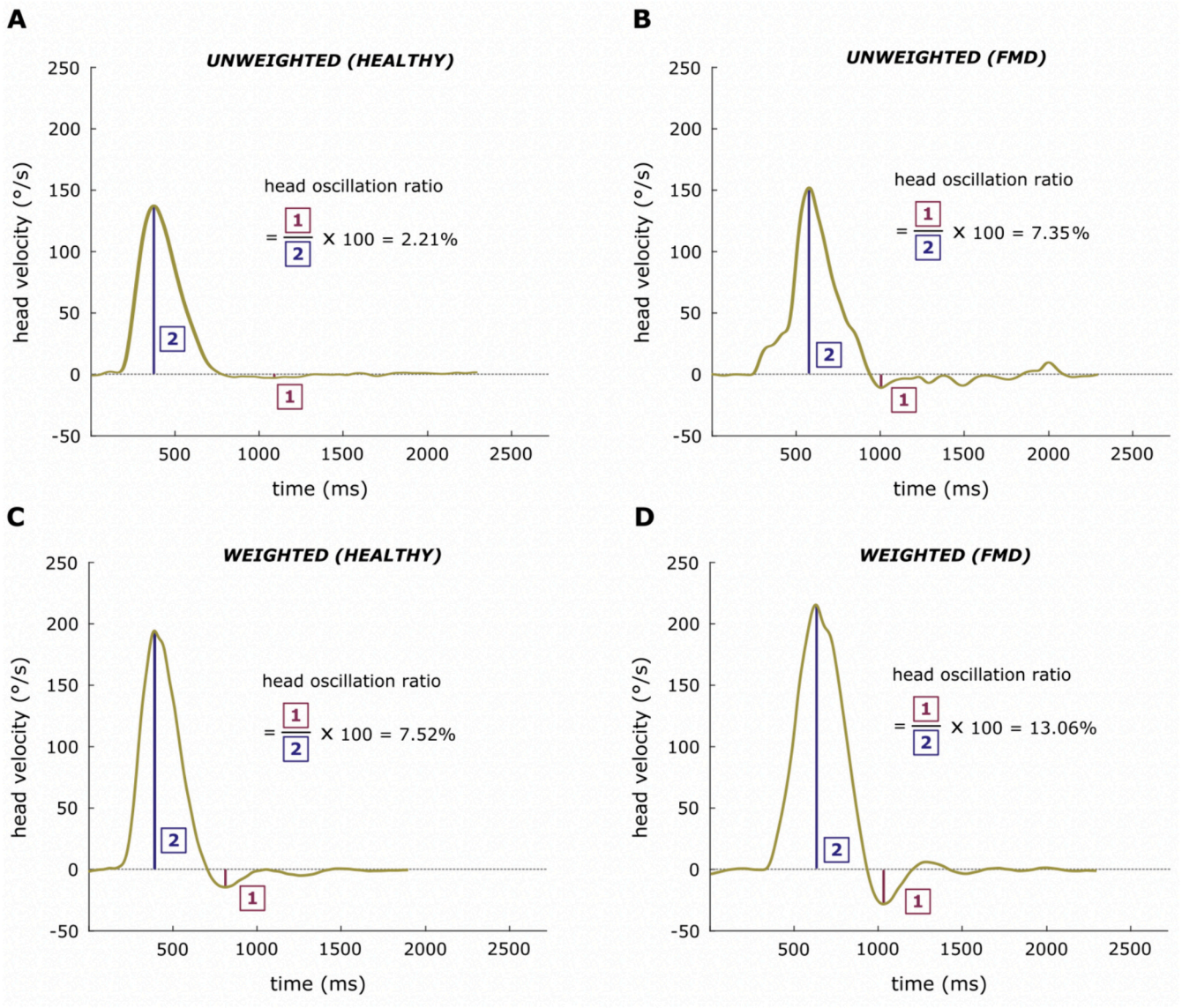

Fig. 4. *Calculation of head oscillation ratio as a marker of erroneous sensorimotor processing.* Illustrated are representative examples of head velocity traces from a healthy control participant (A, C) and a patient (B, D) with functional movement disorder (FMD) during a natural, unweighted and a weighted gaze shift (respectively). The head oscillation ratio is computed by dividing the absolute minimum of the first undershoot (i.e., after head velocity first reaches zero and before it crosses the zero line again) by the first absolute maximum (i.e., peak head velocity, before velocity first reaches zero), multiplied by 100. This way, we normalize the size of the undershoot by the movement's peak velocity. Note how the healthy participant performs a smooth head movement in the natural condition (A), while we can already observe a visible undershoot in the patient's movement (B), indicating a prediction error in the planned and executed head movement. When wearing the helmet, this difference in head stability between the healthy control (C) and the patient (D) is even more pronounced. FMD = functional movement disorder.

Table 2
Overview of trial categorization and exclusion during data processing per group.

	Overall trials (%)					Number of remaining trials		
Group	Anticipated	Delayed	Excluded	Amplitude <40°	Outliers	UW1	W	UW2
FMD	2.6	7.2	4.2	10.8	4.1	34.60 (6.80)	36.30 (2.54)	35.90 (4.58)
FD (new)	1.7	2.5	1.0	7.3	5.0	36.90 (2.89)	38.00 (2.16)	37.80 (2.82)
FD (old)	n.a.	n.a.	22.4	28.3	3.5	26.75 (13.47)	24.00 (12.83)	n.a.
HC-FMD	0.5	4.4	0.9	5.4	5.3	37.70 (1.34)	38.80 (1.69)	38.30 (1.42)
HC-FD	0.2	5.3	1.5	4.6	4.8	38.50 (1.65)	39.00 (2.00)	38.10 (2.69)

FMD = patients with functional movement disorder. FD (new) = patients with functional dizziness in the current study. FD (old) = patients with functional dizziness in Lehnen et al.'s [25] study, reanalyzed here. HC-FMD = healthy control group for patients with functional movement disorder. HC-FD = healthy control group for patients with functional dizziness. UW1 = first unweighted condition (session 1). W = weighted condition (session 2). UW2 = second unweighted condition (session 3). n.a. = not applicable. Values represent the mean percentage or number of trials across all three experimental sessions, standard deviations are reported in brackets where applicable.

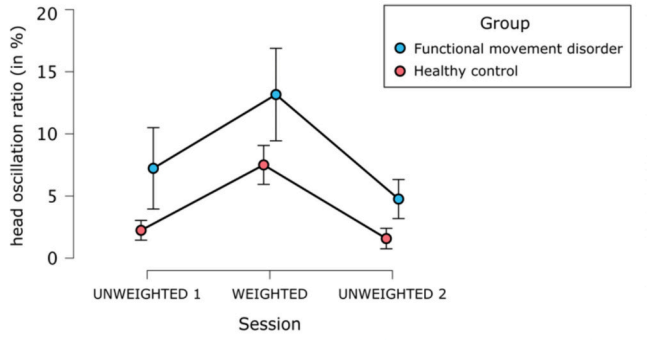

Fig. 5. Illustration of group differences (mean, standard deviation) in head oscillations between patients with functional movement disorder (n = 10, blue) and healthy controls (n = 10, red) throughout the three experimental sessions. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

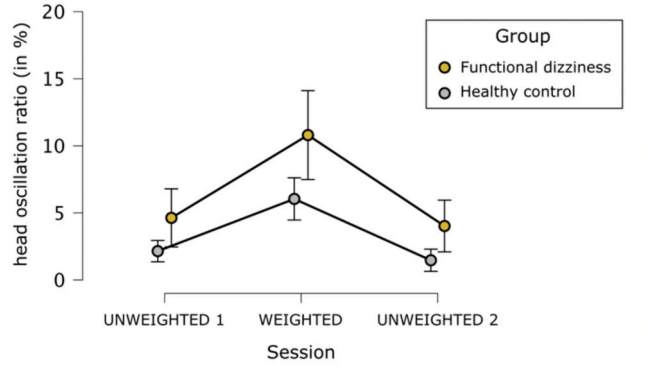

Fig. 6. Depiction of the mean head oscillation ratio of patients with functional dizziness (n = 10, yellow) and healthy controls (n = 10, grey) across experimental sessions. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

3.4. FMD versus FD

We obtained anecdotal evidence for the main model group (BF_{01} = 2.01) and the main effect group (BF_{excl} = 1.95), i.e. that patients with FD and patients with FMD did not differ in the size of head oscillations across sessions (Fig. 8).

4. Discussion

The current study investigated sensorimotor processing of patients with either functional dizziness (FD) or functional movement disorder (FMD) during large combined eye-head gaze shifts under normal and increased head moment of inertia. We found marked sensorimotor processing deficits in both patient samples when compared to healthy controls. Patients from both groups already showed pronounced head instability during natural, unweighted head shifts towards visual targets, which further worsened when the head moment of inertia was experimentally increased. Therefore, we (1) successfully replicated earlier findings of sensorimotor processing deficits in a new sample of patients with FD and (2) provided additional evidence of a transdiagnostic mechanism underlying FMD.

More specifically, our results suggest that patients with FD or FMD already exhibit a mismatch between predicted and actual head movements in both unweighted conditions, reflected in increased head

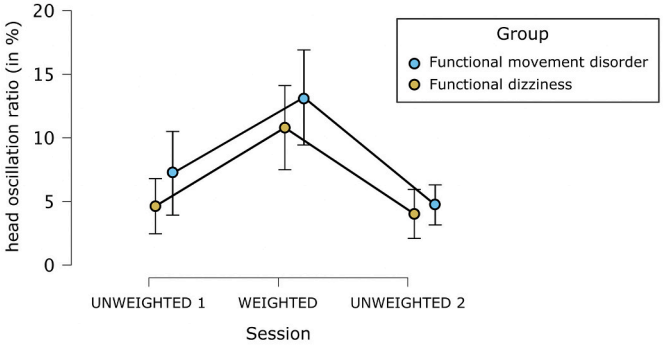

Fig. 8. Comparison of head instability between patients with functional dizziness (FD; n = 10, yellow) and patients with functional movement disorder (FMD; n = 10, blue). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

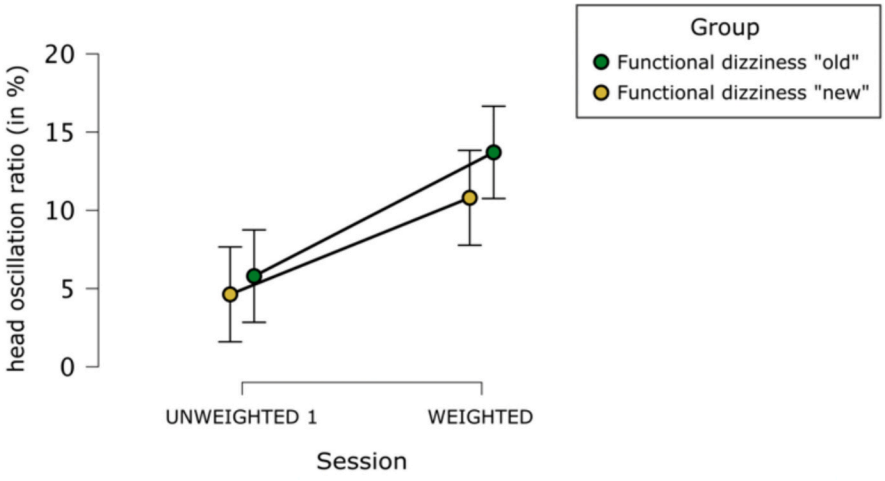

Fig. 7. Comparison of head instability between the "old" sample of patients with functional dizziness as reported by Lehnen et al. [25] (n = 8, green) and the "new" sample of patients with functional dizziness measured for the current study (n = 10, yellow). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

oscillations at the end of gaze shifts. Notably, it is plausible that patients experience similar head instability not only in the lab, but also in everyday life. Importantly, this discrepancy should elicit a prediction error (PE), prompting updates to internal models (e.g., of the head) and subsequently improved motor commands. Experimentally altering the head moment of inertia with our helmet intensifies this PE, potentially driving overall learning. We obtained anecdotal evidence that patients could not clearly improve head stability over the three sessions, while healthy controls clearly reduced head oscillations from the first to the second unweighted session. Similarly, compared to controls, patients struggled to sufficiently adapt internal models when wearing the helmet. Taken together, this suggests that (some, see [46]) functional disorders may be regarded as disorders of sensorimotor control, where optimal planning of movement (e.g., gaze shift, bowel movement, limb control) is compromised, likely due to erroneous brain-based internal models of the body [25,27,28].

4.1. Implications

Our findings have several implications for diagnosis, mechanisms, treatment, and stigma of functional disorders.

First, our results provide an objectively measurable marker of perceptual dysregulation in functional disorders, potentially suitable for the development of a diagnostic instrument. This would aid the diagnosis of functional disorders by supporting a rule-in diagnosis based on positive signs. To this end, future research should validate and generalize our results in larger and more diverse patient populations.

Second, our findings indicate that functional disorders, irrespective of the specific bodily symptom and diagnostic categories (i.e., F45.8 in somatoform disorders and F44.4 dissociative disorders in ICD-10 [33]), share a common underlying mechanism. This also supports the notion of lumping different functional symptoms (e.g., dizziness, paresis, tremor) under one diagnostic umbrella label, as it is – at least in part – done in the most recent classification systems (i.e., "functional neurological symptom disorder" in DSM-5 [15], "dissociative neurological symptom disorder" in ICD-11 [14]).

Third, we highlight a potential treatment target for functional disorders. The transdiagnostic sensorimotor processing deficits now demonstrated in FD (here and earlier [25,27]), FMD, and previously also in IBS [28] (but not in functional pain [46]) point towards a general central dysregulation affecting sensorimotor control, where internal model representations of the body are erroneous and not updated appropriately. By precisely increasing the head moment of inertia, we aimed to induce a sufficiently relevant prediction error under controlled experimental conditions, allowing for a gradual update of CNS-based internal models. This only led to clear improvements of head stability in healthy controls, while learning effects in patients were either too small to detect due to small sample size, or non-existent. Interestingly, patients with IBS were indeed able to reduce head oscillations during unweighted gaze shifts throughout the three sessions in an earlier study employing the same paradigm, with a similarly small sample [28]. This suggests that patients with functional symptoms directly affecting motor control of the head/eyes and other extremities are already too severely impaired for such a short intervention to show any relevant improvement. Future research could therefore investigate how internal models are updated more adaptively and explore suitable interventions that precisely target the underlying mechanism.

Fourth, we pinpoint that dysfunction arises from fundamental, automatic, objectively measurable processes in the central nervous system (CNS) and not from explicit expectations or conscious decisions. The observed head control deficits show a distinct movement pattern that cannot be displayed intentionally ("malingering" or "feigning"): the measured head oscillations are not only consistent within (i.e., weighted versus unweighted movements) and across (e.g., within the same symptom category) individuals, but also between studies (i.e., current and Lehnen et al. 2019). This is in line with findings from other experimental studies showing that functional symptoms are a product of automatic, involuntary processes in the CNS (for a review, see [47]). Persons with functional disorders frequently face stigma from health-care providers, family, and wider society due to a general lack of measurable biomarkers as well as poor knowledge and misconceptions about underlying mechanisms [48–51]. We hope that our findings can contribute to de-stigmatization for this patient population.

4.2. Differences in paradigms

For this study, we modified the experimental paradigm to improve data quality and task adherence.

The helmet used for our experimental manipulation induced a lower head moment of inertia, which can be expected to lead to smaller head oscillations in the weighted condition due to the smaller discrepancy between the natural and manipulated head characteristics. Although this seems to be reflected in the obtained mean effects, a group difference in this session remained statistically inconclusive.

Comparing results with Lehnen et al.'s [25] study, participants in our study had more time between gaze shifts due to the addition of control lights. This alteration positively affected data quality, with fewer gaze shifts below the cut-off amplitude compared to Lehnen et al.'s [25] sample (7.3% versus 28.3%). Additionally, a higher number of trials had to be excluded altogether in Lehnen et al.'s [25] sample because we could not determine the head oscillation ratio (22.4% versus 1.0% - mostly because participants had not finished the movement before the next target already flashed). Despite these changes, we successfully replicated the earlier obtained effect reported by Lehnen et al. [25]. Therefore, future studies employing the eye-head paradigm should apply the current LED setup, as this setup may be more suitable for complete and good quality data acquisition, especially when aiming to examine a patient group with high illness burden (e.g., impaired mobility in a severe functional disorder).

4.3. Limitations and future research

The findings of this study are limited by relatively small sample sizes per group ($n = 10$, based on an a-priori power analysis). The reason for this were strict in- and exclusion criteria required to examine a transdiagnostic mechanism: patients were required 1) to suffer only from one functional symptom at a time (e.g., functional gait disturbance but no dizziness) 2) that currently cannot be associated with reproducibly observable pathophysiological mechanisms [32]. Both criteria are very common among patients with functional disorders [16,52,53], which drastically reduces the number of eligible patients available. Notably, the effects observed here are large, enabling us to reach conclusive results even with small samples (see [25,28,46]). Outside the registered primary aim of this study, we explored possible learning effects. Our sample sizes were insufficient for this.

Furthermore, we initially assumed that the measured head (and gaze [27]) instability in FD would represent the experienced dizziness symptomatology. However, we measured head instability of a similar magnitude in patients with FMD (and IBS [28]), even though they did not experience any dizziness or vertigo. Future studies should examine whether the eyes overshoot the target as well; if the eyes instead compensate the suboptimal head movement sufficiently, gaze could still be stable overall – this could also explain the lack of dizziness in patients with FMD.

5. Conclusion

In sum, we demonstrated that sensorimotor processing deficits, characterized by head instability during large gaze shifts, can be robustly, objectively, and transdiagnostically measured in patients with functional disorders. Our findings point towards a general impairment of sensorimotor control irrespective of the experienced bodily symptom

and highlight a promising mechanism to inform treatment targets, diagnostic tools, and stigma reduction.

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CRediT authorship contribution statement

Franziska Regnath: Writing – review & editing, Writing – original draft, Visualization, Validation, Software, Project administration, Methodology, Investigation, Formal analysis, Data curation. **Katharina Biersack:** Writing – review & editing, Validation, Investigation. **Lena Schröder:** Writing – review & editing, Validation, Methodology, Investigation. **Marie-Christin Stainer:** Writing – review & editing, Investigation. **Dina von Werder:** Writing – review & editing, Validation, Methodology, Investigation. **Dominik Pürner:** Writing – review & editing. **Bernhard Haslinger:** Resources. **Nadine Lehnen:** Writing – review & editing, Validation, Supervision, Resources, Project administration, Methodology, Investigation, Funding acquisition, Conceptualization.

Declaration of competing interest

All authors have completed the Unified Competing Interest form at http://www.icmje.org/coi_disclosure.pdf and declare that NL is founding member and a paid consultant of EyeSeeTec GmbH makers of the goggles used, and BH has had relations with Ipsen Pharma GmbH and AbbVie Deutschland GmbH & Co. KG in the past 3 years that could be perceived to constitute a conflict of interest. All other authors have no competing interest to report..

Data availability

Anonymized raw data is openly accessible online under https://osf.io/jcyk7/.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jpsychores.2024.111694.

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