Aetiopathogenesis and Phenomenology of Medically Unexplained Conditions

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Content

List of abbreviations

ACR	American College of Rheumatology
ACTH	Adrenocorticotropic hormone
ANS	Autonomic nervous system
CDC	Centers for Disease Control and Prevention
CFS	Chronic fatigue syndrome
CRH	Corticotropine-releasing hormone
CWP	Chronic widespread pain
DSM	Diagnostic and Statistical Manual of Mental Disorders
FMS	Fibromyalgia syndrome
FSS	Functional somatic syndrome
HLM	Hierarchical linear modelling
HPA	Hypothalamic-pituitary-adrenal
IBS	Irritable bowel syndrome
ICD	International Classification of Diseases
LC	Locus coeruleus
MUS	Medically unexplained symptoms
NA	Noradrenaline
PTSD	Post-traumatic stress disorder
sAA	Salivary alpha-amylase
SAM	Sympatho-adrenomedullary system
SNS	Sympathetic nervous system

1. Introduction

For many of us, experiencing fatigue, muscle pain, or digestive problems is an everyday occurrence. If they are not part of any chronic illness, most of these somatic sensations or complaints are transient, non-disturbing, and do not affect any major aspects of life. On the other hand, there is overwhelming evidence to suggest that in some cases, these complaints grow into a significant problem for the individuals affected and for societies worldwide. In Germany, over 22% of the general population suffers from at least one complaint causing severe impairment over the course of one week (Hiller, Rief, & Brähler, 2006). Ongoing distress or impairment due to these complaints is likely to result in health care visits by affected persons. However, with 36% of patients seeking help from their general practitioner, a clear-cut medical explanation cannot be established (Toft et al., 2005). Consequently, symptoms are designated as “medically unexplained”. The implications of this are manifold. In patients, the initial relief of not having “anything organic” gives way to uncertainty, frustration, and helplessness (Dwamena, Lyles, Frankel, & Smith, 2009), and these feelings are often equally encountered by the treating physicians (Olde Hartman, Hassink-Franke, Lucassen, van Spaendonck, & van Weel, 2009). In some cases, this eventually leads to a referral to different specialised health care services, the choice of which depends on the most debilitating symptom. In specialised hospital clinics (e.g., gastroenterology), patients with MUS make up 52% of new attendees (Nimnuan, Hotopf, & Wessely, 2001). They often undergo multiple, invasive testing, and various treatments are offered, which sometimes inflict iatrogenic harm on patients. One outcome of this exhaustive process may be that patients are provided with a diagnosis of a so-called “functional somatic syndrome” (FSS).

Wessely, Nimnuan, and Sharpe (1999) define a functional somatic symptom as “one that, after appropriate medical assessment, cannot be explained in terms of a conventionally defined medical disease” (p. 936). Barsky and Borus (1999) choose a slightly different wording, stating that FSS “are characterized more by symptoms, suffering, and disability than by disease-specific, demonstrable abnormalities of structure or function” (p. 910). Together, these definitions suggest two main criteria that must be met for a condition to fall into the category of FSS: a) the presence of at least one somatic symptom (positive criterion), and b) the absence of any disease or structural and functional abnormalities that fully account for the somatic symptom(s) (negative criterion). It is important to note that it needs to be ruled out that the presence of symptoms are feigned, and the

absence of a medical explanation should, of course, not be the mere consequence of inadequate or inaccurate diagnostic procedures.

Case definitions for numerous different FSS have been formulated by various expert committees over the past decades (see also 1.1.2.1). A non-exhaustive list of syndromes encompasses conditions such as chronic fatigue syndrome (Fukuda et al., 1994), fibromyalgia syndrome (Wolfe et al., 2010), functional chest pain (Galmiche et al., 2006), functional dyspepsia (Tack et al., 2006), globus (Galmiche et al., 2006), irritable bowel syndrome (Longstreth et al., 2006), multiple chemical sensitivity (Bartha et al., 1999), persistent idiopathic facial pain (International Headache Society, 2004), premenstrual syndrome (World Health Organization, 1992), temporomandibular disorder (Dworkin & LeResche, 1992), and tension-type headache (International Headache Society, 2004). All of these different case definitions share the positive (at least one somatic symptom is present) and negative criterion (no disease fully accounts for the somatic symptoms) of FSS. However, as implied by some of these names (e.g., “irritable bowel syndrome”, “multiple chemical sensitivity”), in each syndrome, specific organ systems are presumably involved in the pathophysiology, or certain circumstances serve as symptom-triggering events. The existence of these case definitions has resulted in numerous lines of research, each focusing on one particular FSS.

1.1 The question of nosology – “one versus many”

The nosology of FSS is inconclusive. As, to date, none of the above-mentioned case definitions have the status of nosological entities, there are currently two approaches to the classification of FSS in Germany and other European countries (see Fig. 1): a) unified as a mental or, more precisely “somatoform disorder”, described in the fifth chapter (F) of the tenth edition of the International Classification of Diseases (ICD-10; World Health Organization, 1992), or b) individually as diseases according to other chapters of the ICD-10. For instance, in clinical practice, chronic fatigue syndrome (CFS) is given the label of neurasthenia (F48.0) or a disease of the nervous system (G93.3). Fibromyalgia syndrome (FMS) is categorized as a persistent somatoform pain disorder (F45.4) or as a disease of the musculoskeletal system and connective tissue (M79.7). Irritable bowel syndrome (IBS) is classified as a somatoform autonomic dysfunction (F45.3) or a disease of the digestive system

(K58). Importantly, the case definitions and ICD-10 diagnoses overlap to varying degrees but cannot be considered as identical.

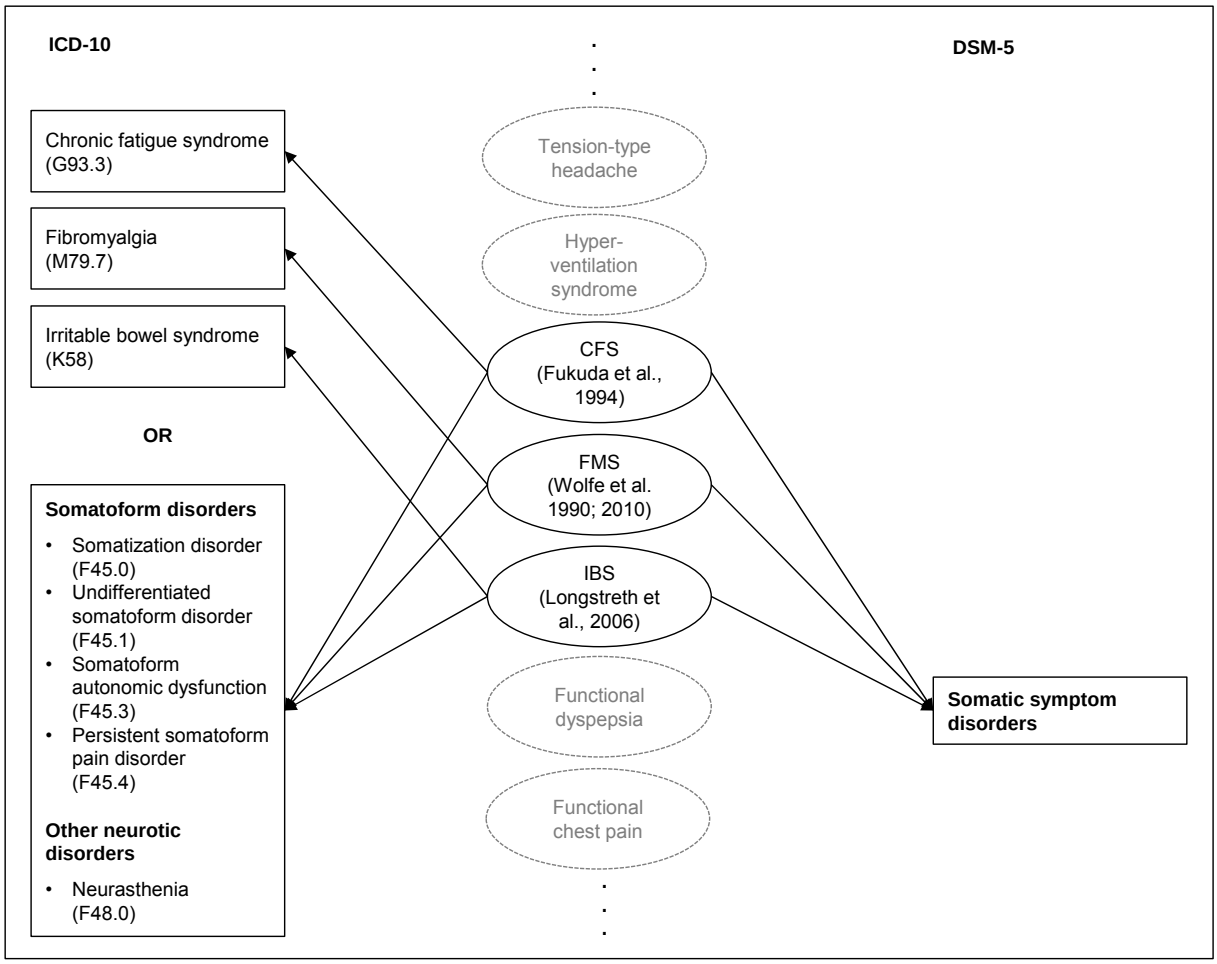

Figure 1 Exemplary classification of the three functional somatic syndromes chronic fatigue syndrome (CFS), fibromyalgia syndrome (FMS), and irritable bowel syndrome (IBS) in terms of the current editions of the International Classification of Diseases (ICD) and the Diagnostic and Statistical Manual of Mental Disorders (DSM)

In the USA, mental disorders are classified within the Diagnostic and Statistical Manual of Mental Disorders (DSM). It is noteworthy that while according to the previous edition of this manual (DSM-IV), a somatoform disorder was, in essence, identical to an ICD-10 somatoform disorder, this changed dramatically with the latest version (DSM-5), which was released in 2013. As with many other diagnostic categories, an intense debate preceded the publication of this DSM-5 chapter. Doubts were raised about the key defining feature of somatoform disorders: medically unexplained symptoms (MUS). Not only was the distinction between MUS and medically explained symptoms found to be unreliable in clinical practice, but it was said to fuel mind-body dualism and make patients feel marginalised (Dimsdale et al., 2013). The second major criticism concerned the number of sub-diagnoses (e.g., somatization disorder, pain disorder), which was deemed “both confusing and

clinically unhelpful" (Dimsdale et al., 2013, p. 224). With the revised category, named "somatic symptom disorder", the distinction between MUS and medically explained symptoms was therefore abolished and sub-diagnoses were merged together. Furthermore, "psychological criteria", such as excessive or disproportionate cognitions, emotions, and behaviour that are dedicated to somatic symptoms, were added (American Psychiatric Association, 2013). However, by questioning the tenet of the previous somatoform disorders (i.e., MUS) and lowering the threshold in terms of the number of somatic symptoms that are required (only one in DSM-5), it attracted harsh criticism, which mainly concerned the potential of over-inclusion and mislabelling of patients with conventionally defined medical diseases and the so-called "worried well" (Frances, 2013; Frances & Chapman, 2013).

It is clear from this short summary of how FSS are classified that their nosology poses both an inter- and intra-disciplinary challenge. The reason for this lies in their current conceptualisation. The most recent conceptual controversy began with a seminal article by Wessely et al. (1999). They argued that conditions such as CFS, FMS, or IBS should not be considered as nosological entities in their own right, since they constitute a mere by-product of medical specialisation. By this, Wessely et al. meant that depending on the specialist to whom the individual patient is referred, he/she will receive a different label for the presented MUS. To give an example: A patient complaining of chronic fatigue, diffuse pain in multiple body sites, and gastrointestinal problems will receive a diagnosis of CFS by an infectious disease specialist, a diagnosis of FMS by a rheumatologist, and a diagnosis of a functional gastrointestinal disorder (e.g., IBS) by a gastroenterologist.

Wessely et al. (1999) presented several arguments to substantiate their hypothesis. For instance, they reported that patients with different FSS all share a history of childhood trauma, and certain pathophysiological alterations, suggesting a common aetiopathogenesis. They also mentioned phenomenological similarities: Patients with an FSS often seem to fulfil case definitions for other, additional FSS (so-called "syndrome overlap"). Moreover, patients with different FSS apparently share other characteristics, such as comorbidity with depression and anxiety disorders, or difficulties in interpersonal interactions, including the patient-doctor relationship. Taken together, Wessely et al. argued in favour of a general FSS, instead of numerous different FSS, and this position has sometimes been referred to as the "lumpers' position". Their article caused quite a stir among patient associations, but also among some researchers (e.g., Goudsmit & Shepherd, 1999; Jason, Taylor, Song, Kennedy, & Johnson, 1999).

The following scientific dispute is best illustrated in an "in debate" article by Wessely and White (2004), which appeared in the British Journal of Psychiatry. In the article, Wessely's position was contradicted by White, who preferred to view CFS, FMS, and IBS as distinct nosological entities (sometimes called "splitters' position"). White claimed that "a general functional somatic syndrome can be consistent only with psychogenesis, since it is difficult to conceive of a pathophysiological mechanism that would be common to all functional somatic syndromes", which he feared would result in "a deteriorating doctor-patient relationship" (both p. 96). He further emphasised that only by scrutinising each FSS separately can advances in the elucidation of aetiopathogenetic mechanisms be made. Another point made by White was that the phenomenological similarities among FSS (i.e., syndrome overlap, comorbidity with depression and anxiety disorders) were a methodological artefact, as patient samples were mostly drawn from specialised health care services, which harbour only the most severely disabled patients, who are likely to have comorbidities.

In sum, the state of research in 2004 was sufficiently inconsistent for two diametrically opposite positions to develop regarding the conceptualisation of FSS. The greatest amount of progress in resolving this ambiguity is likely to be made by a) aetiopathogenetic, and b) phenomenological research, that is, by finding out how FSS develop and by identifying similarities and differences in the way they present. In the following sub-chapters, a selective overview of the state of research since the publication of the article by Wessely et al. (1999) will be given. In the first sub-chapter, a theoretical framework that is able to integrate seemingly different aetiopathogenetic findings belonging to FSS will be presented. The second sub-chapter will focus on relevant phenomenological findings in FSS, such as syndrome overlap and their relationship with depression and anxiety. The main findings, gaps in the literature, and methodological limitations will be summarised after each sub-chapter in order to derive implications for future research.

1.1.1 Aetiopathogenesis – the role of stress

The apparent absence of a medical explanation has created an ever-increasing body of literature on predisposing, precipitating, and perpetuating factors in individual FSS over the past decades. Although in the early days, research was driven by mono-factorial hypotheses involving neurological or immunological causative agents for symptoms, the last two decades have witnessed a shift towards a multi-factorial understanding of each FSS. Current aetiopathogenetic accounts can be sub-divided into

two broader categories: cognitive-behavioural and biologically oriented models (see Witthöft & Hiller, 2010 for a review of the most influential models). While cognitive-behavioural models emphasise the importance of personality characteristics, maladaptive attention and interpretation biases regarding somatic sensations, and avoidance behaviour, biological models give more weight to the role of genes and dysfunctional somatic systems, such as the central nervous system (CNS), the autonomic nervous system (*ANS*), the hypothalamic-pituitary-adrenal (*HPA*) *axis*, and the immune system. The complex aetiopathogenesis of FSS, however, can only be addressed by overcoming the mind-body dualism that is implicitly maintained by these different lines of research.

An important concept that is able to bridge the gap between cognitive-behavioural and biological explanations for any FSS is stress. Figure 2 brings together two influential theories about stress: the cognitive-transactional stress theory by Lazarus (1966) and Lazarus and Folkman (1984) and the allostatic load model by McEwen (1998) and McEwen and Stellar (1993). In a nutshell, the cognitive-transactional stress theory (Lazarus, 1966; Lazarus & Folkman, 1984) posits that stress manifests whenever a stimulus is perceived as stressful (primary appraisal) and the resources to deal with it are interpreted as inadequate (secondary appraisal). Examples of stimuli that are able to elicit stress are *trauma*, *chronic stress*, critical life events, or daily hassles, and these can be understood as "psychosocial stressors". Stress includes a so-called "stress response", which can be described in terms of emotions, behaviour, and biology.

The biological stress response and its role in illnesses, including FSS, are further elaborated by the allostatic load model (McEwen, 1998; McEwen & Stellar, 1993). In this model, stress-responsive biological systems are conceptualised as "allostatic systems", meaning that they enable the body to adequately respond to stress (the term "allostasis" refers to the ability to achieve stability through change). The model claims that the adaptive process of allostasis turns into the maladaptive state of "allostatic load" when stress-responsive systems are chronically hyper- or hypoactive. In other words, allostatic load describes the wear and tear of stress-responsive systems, such as the *ANS* and the *HPA axis*, as a consequence of ongoing stress (e.g. due to *trauma* or *chronic stress*).

The concept of stress seems to allow for the reconciliation of many of what appear at first glance to be numerous incoherent findings on FSS (see Fischer & Nater, 2013 for a more comprehensive review of aetiopathogenetic factors in FSS that are stress related). The most important findings that can be discussed within the framework illustrated below will be briefly reviewed in the

following paragraphs. Both psychosocial stressors and stress-responsive systems that are assumed to play a predisposing, precipitating, and perpetuating role in FSS will be presented. Although not part of this thesis, the potential role of immune functioning in FSS will be briefly mentioned in order to facilitate the overall understanding of assumed pathophysiological mechanisms. The term “MUS” will be used whenever pathophysiological mechanisms are described; the term “FSS” will be used when findings are summarised. Notably, the vast majority of aetiopathogenetic research focuses on CFS, FMS, or IBS rather than on general FSS, but there have been some efforts to summarise these findings on a more general level (i.e., in the form of review articles) as similarities among different FSS have become increasingly apparent.

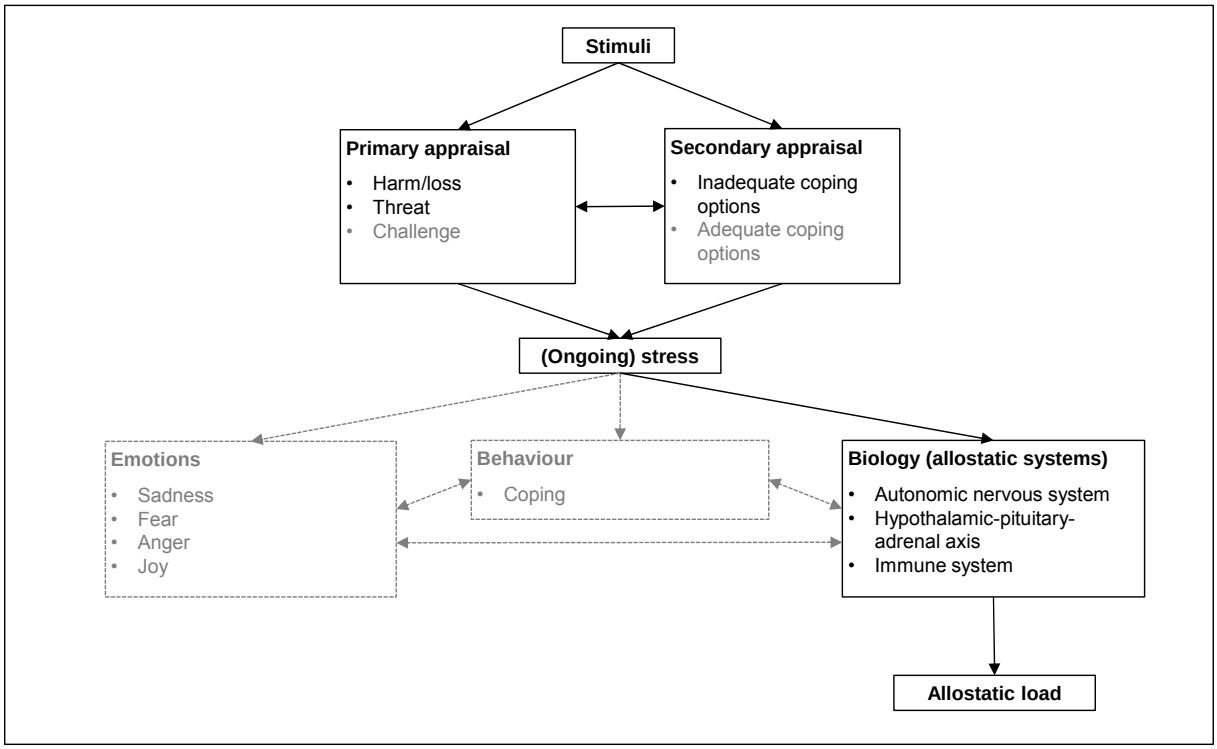

Figure 2 Integrated conceptualisation of stress according to Lazarus and Folkman (1984) and McEwen (1998), grey colour and dotted lines were used for all elements that are not directly relevant to the present thesis

1.1.1.1 Childhood trauma

A traumatic event is the most severe psychosocial stressor that can be experienced by any human being. The DSM-5 (American Psychiatric Association, 2013) defines trauma as “exposure to actual or threatened death, serious injury, or sexual violation” (p. 271), which “causes clinically significant distress or impairment in social, occupational, or other important areas of functioning” (p. 272). If an

event corresponding to this definition occurs during childhood, the term *"childhood trauma"* may be applied. It refers to interpersonal trauma, such as emotional, physical, and sexual abuse, and emotional and physical neglect. According to Bernstein and Fink (1998), these terms are understood as "verbal assaults on a child's sense of worth or well-being" (emotional abuse), "bodily assaults on a child by an older person that pose a risk of, or result in, injury" (physical abuse), "sexual contact or conduct between a child and an older person" (sexual abuse), "failure to provide a child's basic psychological and emotional needs" (emotional neglect), and "failure to provide a child's basic physical needs" (physical neglect; all p. 2). Childhood trauma is usually measured via clinical interviews or questionnaires.

The sequelae of *childhood trauma* are known to be manifold. For instance, there is a burgeoning literature on dysfunctional *stress reactivity* developing from early life events, including persistent changes in stress-responsive systems. More specifically, Heim and Nemeroff (2001) and Heim, Shugart, Craighead, and Nemeroff (2010) have shown that childhood trauma exerts long-term effects on *HPA axis reactivity* in genetically predisposed individuals (see 1.1.1.4). Altered *stress reactivity* may render these individuals more vulnerable to the effects of psychosocial stressors occurring during adulthood. Apart from these biological effects of childhood trauma, specific cognitive schemata seem to evolve from these early life experiences (e.g., self-sacrifice). These schemata are reflected by maladaptive interpersonal behaviour in adulthood (e.g., over-commitment at work). It is conceivable that this behaviour may, in turn, be a source of *chronic stress* (see 1.1.1.2). Taken together, childhood trauma may enhance the probability of experiencing *chronic stress* and of inadequately *reacting* towards it.

The notion of *childhood trauma* as an aetiopathogenetic factor in medically unexplained conditions traces back to Breuer and Freud and their 19th-century studies of "hysteria" (1895/2011). A recent meta-analysis showed that the chance of having an FSS is increased almost threefold in individuals exposed to *childhood trauma* (Afari et al., 2014). Interestingly, although significant methodological heterogeneity across studies was detected by the authors, neither sample type (community vs. other) nor diagnostic approach (clinician-administered vs. self-report) seemed to impact the very robust trauma-FSS relationship. However, studies using non-validated questionnaires consistently reported higher associations than studies using validated questionnaires or interviews, highlighting the importance of using methodologically sound measures for the assessment of

childhood trauma in future studies. There is thus substantial evidence that *childhood trauma* is a predisposing factor of FSS. However, its direct ramifications (e.g., altered *stress reactivity* and *chronic stress*) have rarely been assessed within the same studies. One is therefore left wondering how the transition from experiences of *childhood trauma* to the development of FSS occurs.

1.1.1.2 Chronic stress

Chronic stress is defined in several ways, although a period of prolonged stress is the core feature contained in any definition. *Chronic stress* can be distinguished from acute stress insofar as it is often characterised by a gradual onset, an unforeseeable ending, and embedded within day-to-day life (Schulz, Schlotz, & Becker, 2004). Generally speaking, sources of *chronic stress* are social role conflicts (e.g., between the work and family domain) or unmet personal needs (e.g., recognition). As mentioned above, cognitive schemata that evolved as a result of *childhood trauma* and maladaptive interpersonal behaviour that goes along with it may directly foster experiences of *chronic stress.* A simplified example is a person who learns that affection is dependent on performance (emotional neglect) and later goes on to over-commit at school or work (self-sacrifice). *Chronic stress* is usually measured via questionnaires or by the use of different naturalistic paradigms, such as social isolation, caregiving, or academic stress.

As outlined above, the biological ramifications of *chronic stress* are often subsumed under the term “allostatic load” (McEwen, 1998; McEwen & Stellar, 1993). This term refers to the wear and tear of stress-responsive systems such as the *ANS* and the *HPA axis*. According to Miller, Chen, and Zhou (2007), *chronic stress* is normally accompanied by hyperactivity of the *HPA axis*. However, over time, this initial pattern may turn into one that is characterised by hypo-activity. Importantly, these processes may be influenced by previous exposure to stressors, such as *childhood trauma*, and subsequent alterations in *stress reactivity*. Both hypo-activity of the parasympathetic part of the *ANS* (see 1.1.1.3) and hypocortisolism (see 1.1.1.4) have been directly linked to MUS such as fatigue and pain, suggesting a role for *chronic stress* in their manifestation. In addition, it has often been claimed that somatic sensations created by a state of general arousal (e.g., due to *chronic stress*) are subject to misinterpretation in individuals who go on to develop MUS (Rief & Barsky, 2005). An interesting concept in this context is *somatosensory amplification*, which describes a cognitive style that is

characterised by experiencing somatic sensations as more intense, and evaluating them as more negative (Barsky, Goodson, Lane, & Cleary, 1988; Barsky, Wyshak, & Klerman, 1990). Taken together, it can be hypothesised that *chronic stress* fosters the development of MUS via alterations in stress-responsive systems and cognitive bias.

As with *childhood trauma*, FSS (back then often referred to as "neurasthenia"), were viewed as a consequence of modern life stress as early as in the 19th century (Beard, 1869). We reviewed the literature on different psychosocial stressors in FSS, including *childhood trauma*, *chronic stress*, critical life events (e.g., a viral infection, sudden unemployment), and daily hassles (e.g., being late, having an argument; Nater, Fischer, & Ehlert, 2011). In general, the literature seemed consistent insofar as *childhood trauma* and critical life events were frequently reported by patients with FSS. *Chronic stress* levels, on the other hand, were only investigated by a handful of studies, and the vast majority of these were cross-sectional. Although plausible from an allostatic load model perspective, evidence that *chronic stress* acts as a precipitating or perpetuating factor in FSS currently remains scarce. In other words, it is still unknown whether *chronic stress* precedes the initial manifestation of FSS and aggravates symptoms once they are present, or whether the reverse is the case.

1.1.1.3 Autonomic nervous system

The *ANS* comprises central and peripheral parts, which are referred to as the central autonomic network, and the parasympathetic and sympathetic nervous system (SNS), respectively (Benarroch, 1997; Fischer & Nater, in press). Both afferents and efferents of the *ANS* are involved in vital processes such as the regulation of arousal, pain perception, digestion, and respiration. The parasympathetic system and SNS interact in a complementary fashion to maintain homeostasis. Whenever the body is challenged by an acute stressor, the locus coeruleus/noradrenaline (LC/NA) sympathetic system is activated. Noradrenaline is secreted in specific networks of the CNS and from sympathetic nerve endings in the periphery (sympathetic-neural system). Adrenaline is consequently released from chromaffin cells in the adrenal medulla (sympatho-adrenomedullary system). Both catecholamines produce adjustments in the body to restore homeostasis (e.g., via gluconeogenesis or increasing muscle tension).

Disturbances of the *ANS* may originate from the central or peripheral part of the body and are referred to as “dysautonomias” when they adversely affect health (Goldstein, Robertson, Esler, Straus, & Eisenhofer, 2002). As outlined above, it has been suggested that subtle alterations in *ANS* functioning are stress-related, that is, they develop from experiences of *childhood trauma* or *chronic stress* (see 1.1.1.1 and 1.1.1.2). The LC/NA system is known to regulate arousal and pain perception via descending anti-nociceptive pathways; failure of this system may thus create or enhance MUS such as fatigue or pain (Clauw & Chrousos, 1997; Clauw & Crofford, 2003). Moreover, NA and adrenaline act in concert with cortisol (see 1.1.1.4) to influence immune functioning (see 1.1.1.5), which is most likely relevant to the pathophysiology of MUS. Autonomic markers are often obtained in the periphery. An example is the determination of NA and adrenaline in the peripheral blood stream, or the calculation of heart rate variability. Another, rather novel and easily accessible biomarker that has been suggested to reflect SNS functioning is salivary alpha-amylase (sAA), an enzyme that is secreted by salivary glands and involved in the digestion of starch (Nater & Rohleder, 2009).

As reviewed by others and us (Nater, Fischer, & Ehlert, 2011; Tak & Rosmalen, 2010), in the last two or three decades, research into autonomic alterations in individual FSS has been quite extensive. Both *ANS* activity and *reactivity* have been tested in case-control studies, mostly via indirect parameters (i.e., heart rate variability). There is accumulating evidence of an association between relative parasympathetic hypo-activity and a diagnosis of FSS. This may reflect a state of general hyper-arousal in patients. However, as the parasympathetic system and SNS interact in a synergistic manner, more information about the latter system is needed to be able to draw this conclusion. The literature on autonomic *reactivity* is sparse and inconsistent. There have been attempts to test specific aspects of autonomic functioning in the laboratory; an example is tilt table testing, where patients are being strapped onto a horizontal board and then tilted up in order to evaluate orthostatic responses. However, such paradigms are unable to provoke a stress response as defined above. This is unfortunate, as the identified basal dysfunctions of the *ANS* certainly raise the important question of whether patients with FSS are able to mount adequate autonomic responses when experiencing stress. Clearly, more research is needed to answer this question; even more so, as in the only available meta-analysis on *ANS* functioning in FSS, the overall methodological quality of studies was deemed to be poor (Tak et al., 2009).

1.1.1.4 Hypothalamic-pituitary-adrenal axis

The *HPA axis* stretches from the CNS into the periphery (Chrousos, 2009; Chrousos & Gold, 1992). It serves numerous homeostatic purposes, among which are the coordination of energy expenditure (e.g., gluconeogenesis) and immunological processes (e.g., anti-inflammation). Acute stress poses a threat to homeostasis, leading to the secretion of corticotropin-releasing hormone (CRH) and vasopressin from the paraventricular nucleus of the hypothalamus, which in turn stimulate the release of adrenocorticotropic hormone (ACTH) in the anterior pituitary. The latter hormone is carried through the periphery, and cortisol is secreted from cells in the zona fasciculata in the adrenal cortex to exert its effect on target tissues. Cortisol ultimately engages in a negative feedback loop to suppress central input to the *HPA axis*. As mentioned above, the *HPA axis* closely interlocks with the *ANS* and immune system.

Disturbances of the *HPA axis* may originate in the CNS or periphery, and mostly manifest as either relative hypo- or hyper(re-)activity of cortisol. They are found in the most prevalent diseases and disorders in Western societies (Chrousos, 2009; Chrousos & Gold, 1992), and it has been suggested that some of these more subtle alterations are promoted by experiences of *childhood trauma* or *chronic stress* (see 1.1.1.1 and 1.1.1.2). In the context of MUS, deficiencies of the CRH and LC/NA system (see 1.1.1.3) have been claimed to negatively impact on arousal and pain perception (Fries, Hesse, Hellhammer, & Hellhammer, 2005; Heim, Ehlert, & Hellhammer, 2000). Moreover, the gluconeogenetic, anti-nociceptive, and anti-inflammatory (see 1.1.1.5) effects of cortisol in the periphery may be disturbed and directly contribute to MUS such as fatigue and pain. As the CNS is less accessible than the periphery, levels of total or free cortisol are often determined in individuals' bodily fluids. In the last two decades, the assessment of salivary cortisol has become rather popular, as it is non-invasive and merely reflects the fraction of free (unbound) cortisol that is able to exert its effects on target cells and organs of the body (Hellhammer, Wust, & Kudielka, 2009).

The issue of *HPA axis* functioning in individual FSS has attracted the attention of many researchers over the years, resulting in a plethora of published studies (Nater, Fischer, & Ehlert, 2011; Tak & Rosmalen, 2010). Again, both the activity and *reactivity* of the *HPA axis* have been scrutinised in case-control studies. It is now quite safe to assume that a pattern referred to as relative "hypocortisolism" is prevalent in many different FSS. This pattern describes "a hyporesponsiveness on

different levels of the HPA axis" (Fries et al., 2005, p. 1010) when compared to healthy individuals, including lowered basal levels of cortisol and attenuated *stress reactivity*. A meta-analysis on this topic confirmed this general impression, although the authors found hypocortisolism to be confined to cases with CFS and females with FMS (but not patients with IBS; Tak et al., 2011). Interestingly, however, it seems that the question of whether *HPA axis* functioning is involved in the manifestation of FSS and its symptoms remains unanswered. In other words: Although thinking along the lines of the allostatic load model would imply that *HPA axis* functioning is directly involved in symptoms of FSS, there is barely any correlational evidence to support this notion.

1.1.1.5 Immune system

The immune system consists of an innate and adaptive part (Dhabhar, 2007). Within these two sub-systems, cellular and humoral processes operate to protect the body from external (e.g., bacteria) and internal (e.g., carcinogenic cells) pathogens, and to promote wound healing. Communication between and within the two sub-systems is enabled by cytokines, a large group of different cell-signalling proteins. These are secreted by various cell types including immune cells and are crucial in the regulation of inflammation. Functionally, cytokines can be divided into pro- and anti-inflammatory types, although some are involved in both enhancing and inhibiting inflammation (e.g., interleukin 6, IL-6). Acute stress is known to induce a redistribution of immune cells from lymphoid organs to the peripheral blood and skin and to lead to a short-term increase in circulating inflammatory markers (Dhabhar, 2007; Steptoe, Hamer, & Chida, 2007).

An important stress-related immune dysfunction is referred to as "chronic low-grade inflammation" (Rohleder, 2014). As the term implies, the disturbances manifest as long-term, subtle, systemic inflammation in the absence of any causative pathogens or injuries. Both the *ANS* (see 1.1.1.3) and *HPA axis* (see 1.1.1.4) are able to regulate immune functioning. Although the exact mechanisms of how this occurs are far from being fully understood, Glaser and Kiecolt-Glaser (2005) have highlighted two important interfaces that are relevant to these processes. First, NA that is released from the sympathetic-neural system innervates lymphoid organs. Second, NA, adrenaline, and cortisol all bind to receptors on different cells of the immune system. Given these eminent links, it seems that permanent alterations in catecholamines and cortisol would have implications for immune

cell trafficking and cytokine expression. Taken together, it is tempting to assume that an inability of NA, adrenaline, and cortisol to exert their anti-inflammatory potential results in inflammation, which is well known to be associated with symptoms such as fatigue and pain ("sickness response"; Irwin, 2011). However, as shown above, evidence on the role of *ANS* and *HPA axis* functioning in FSS is still insufficient and requires further investigation.

There is a long history of studying the immune system in FSS. In fact, in the early days of aetiopathogenetic research into FSS, many syndromes were understood as infectious diseases (e.g., CFS was called “chronic mononucleosis”). In the absence of serological abnormalities indicating the presence of, for example, a virus, researchers eventually turned to alternative hypotheses. However, interest in more subtle alterations of immune functioning has been re-awakened in the past two or three decades. Studies in patients with FSS have, for the most part, focused on assessing circulating pro-inflammatory cytokines. Findings from case-control studies generally point to heightened pro-inflammatory activity (Nater, Fischer, & Ehlert, 2011). However, research into the reactivity of the immune system and its potential role in symptoms of FSS is still in its infancy.

1.1.1.6 Conclusion

The framework presented here seems to enable the integration of many factors that have been identified as relevant in research on individual FSS. The reviewed studies provide a sense of how pervasively psychosocial stressors in childhood and adulthood impact on the lives of some of these patients, and point to important mechanisms that may translate the experience of stress into MUS. Based on the presented findings, it may be hypothesised that *childhood trauma* permanently alters an individual’s *reactivity* to *stress* occurring later on in life (e.g., *chronic stress*). Dysfunctional stress-responsive systems, such as the *ANS* and *HPA axis*, may then directly contribute to symptoms of FSS via central and peripheral pathways.

However, several unanswered questions and a series of methodological caveats concerning previous research preclude us from drawing these conclusions. First, the understanding of autonomic *reactivity* has, in general, been lagging. A major problem with this line of research is the choice of laboratory paradigms: Although suitable for testing specific aspects of autonomic functioning, most

paradigms were not appropriate to induce and evaluate stress responses. These studies are thus of limited use in terms of answering the question of whether patients with FSS are characterised by altered autonomic *stress reactivity*. Second, the role of the *HPA axis* (and indeed of the *ANS*) in symptom manifestation is completely under-studied, which is rather surprising given the clinical importance of this question. Third, the multidimensional nature of the stress concept has been neglected by previous research. This has resulted in an incoherent series of (mostly cross-sectional) findings which, as yet, have not been brought together into a comprehensive framework depicting the role of stress in the aetiopathogenesis of FSS.

1.1.2 Phenomenology – syndrome overlap and the role of depression and anxiety

There is a variety of phenomenological findings in FSS. A lot of recent research along these lines has been spurred by the seminal publication of Wessely et al. (1999), in which the authors advocated the conceptualisation of FSS as one general syndrome. All FSS have in common that they are defined by the presence of somatic symptoms (positive criterion) and absence of any structural or functional abnormalities that fully explain these symptoms (negative criterion). However, as emphasised by White (2004), they differ in terms of specific cardinal symptoms that are required by individual case definitions. For instance, the cardinal feature of CFS is fatigue, while FMS is primarily characterised by widespread pain and IBS by abdominal pain.

Beyond symptom overlap, there have been increasing efforts to assess the co-occurrence of FSS (i.e., syndrome overlap) in order to reveal similarities or differences. This was all the more important as most research up to this date suffered from methodological limitations. For instance, syndrome overlap was, for the most part, studied in treatment-seeking (i.e., clinical) samples, which are likely to contain more severe cases of FSS and thus potentially over-estimate the degree of co-occurrence among FSS (so-called “referral bias”). For similar reasons, the comorbidity of FSS with depressive and anxiety disorders was continuously scrutinised. Although similar sample selection problems had occurred in the past (referral bias), the sheer amount of literature rendered the finding of high comorbidity rates much more robust. Over time, the question of temporal order became most pressing, as it promised to provide more insight into the reasons for the high comorbidity that had repeatedly been observed.

Taken together, there is a rapidly growing body of research that is dedicated to the phenomenology of FSS (see Fischer & Nater, 2013 for a more comprehensive review on syndrome overlap and comorbidity of FSS). The most important phenomenological findings will be outlined in the following sub-chapters. First, a brief overview of symptoms belonging to the most recognised FSS, that is, CFS, FMS, and IBS, will be presented, as these syndromes are most relevant to the present thesis. Next, methodologically sound studies on syndrome overlap will be summarised. Finally, current knowledge on the role of depression and anxiety in FSS will be briefly illustrated by means of the most significant studies in the field.

1.1.2.1 Symptoms of CFS, FMS, and IBS

The first case definition of CFS dates back to 1988 (Holmes et al., 1988), but since 1994, studies have relied on its revised version, the so-called “CDC criteria” formulated by a consensus group of the Centers for Disease Control and Prevention (Fukuda et al., 1994). According to this definition, a person is classified as a case with CFS if he/she has persistent or relapsing impairing fatigue of at least six months (but not lifelong) that is not attributable to current exertion and cannot be helped by resting. In addition, four out of eight symptoms that are connected to chronic fatigue are required: cognitive problems (memory, concentration), sore throat, tender glands, muscle pain, multi-joint pain (no swelling or redness), headaches of a new kind, non-restorative sleep, and post-exertional malaise lasting longer than 24 hours. In order to exclude any medical disease, a thorough medical history and a mental and physical examination, including blood testing, is recommended by the guidelines, and a number of exclusionary diseases are listed in the original article. Notably, alternative proposals for the definition of CFS have accumulated during the past two decades, with some proposing different symptoms (e.g., post-exertional malaise) as core features of CFS (Christley, Duffy, & Martin, 2012).

Similar to CFS, controversy was initially invoked by the case definition of FMS (Wolfe, 2010), which was drafted in 1990 by the American College of Rheumatology (ACR; Wolfe et al., 1990). However, most researchers and clinicians eventually embraced the “ACR 1990 criteria”, which required at least three months of pain in all quadrants of the body, axial skeletal pain, and 11 out of 18 tender points upon manual palpation. Contrary to the CFS case definition, no laboratory tests to exclude medical diseases were recommended by the consensus group. In 2010, important changes

were introduced by the ACR (Wolfe et al., 2010). With the new operationalised criteria, symptoms other than pain (i.e., fatigue, cognitive problems, non-restorative sleep, and general somatic symptoms) came into focus, and the tender point examination was abandoned altogether. More specifically, in order to satisfy the new criteria, for at least three months, 7 out of 19 pain sites and a symptom severity score of at least 5 (out of 12) are required. Alternatively, three to six pain sites, combined with a severity score of at least nine suffices to meet the "ACR 2010 criteria".

Finally, the most widely acknowledged case definition for IBS are the "Rome III criteria" (Longstreth et al., 2006), a revised version of original guidelines that date back to 1989 (Thompson, Dotevall, Drossman, Heaton, & Kruis, 1989). The Rome III criteria require an onset of recurrent lower abdominal pain or discomfort at least six months before a diagnosis can be given. Abdominal pain or discomfort is typically experienced on more than three days per month during at least three months, and accompanied by at least two of the following features: it is improved with bowel movement, and its onset is associated with changes in the frequency of stool and with changes in the consistency of stool. The latest version of the Rome criteria distinguishes four subtypes: constipation, diarrhoea, mixed, and un-subtyped. A careful clinical examination including a detailed history, but parsimonious physical examinations and laboratory testing are suggested. The Rome III criteria, although criticised by many, have undoubtedly been adopted by the largest proportion of studies on IBS (Thompson, 2006).

1.1.2.2 Syndrome overlap

Significant overlap between CFS, FMS, IBS, and other FSS has been noted since the beginning of systematic research into these illnesses (see also Aaron & Buchwald, 2001; Rodriguez, Afari, & Buchwald, 2009). However, as mentioned above, these observations were largely based on specialised care patients. A few well-conducted studies have appeared since the one versus many debate article (Wessely & White, 2004). These have identified cases from non-clinical samples, thus eliminating referral bias.

In two of these studies, which were based in the US, CFS was found to co-occur with chronic widespread pain (CWP), the cardinal clinical feature of FMS, to the extent of 16% to 41% (Dansie et

al., 2012; Jason, Taylor, & Kennedy, 2000). The overlap with IBS was found to be 16% (Dansie et al., 2012), while 41% had multiple chemical sensitivity, a syndrome in which seemingly allergic reactions are provoked by various chemical substances (Jason et al., 2000). Chronic widespread pain, in turn, was found to co-occur with CFS in 22% of cases, with IBS in 25% of cases, and with tension-type headache (i.e., bilateral, pressing or tightening pain in the head) in 17% of cases identified from the Swedish Twin Registry (Kato, Sullivan, Evengard, & Pedersen, 2006). In a similar study conducted in the US, a much higher proportion of overlap was found, with 60% of participants with FMS simultaneously having CFS (White, Speechley, Harth, & Ostbye, 2000). In a Norwegian study, the co-occurrence of IBS with FMS was 20% (Vandvik, Lydersen, & Farup, 2006). An Asian study identified 14% of women with IBS as being simultaneously affected by functional dyspepsia, a syndrome that is characterised by pain in the upper abdomen (Lee, Lee, Kim, & Cho, 2009). Data from European communities, on the other hand, suggested a much higher overlap with functional dyspepsia, of 45% to 87% (Agreus, Svardsudd, Nyren, & Tibblin, 1995; Caballero-Plasencia et al., 1999; Hillila, Siivola, & Farkkila, 2007), whereas a US-based study yielded an intermediate proportion of 31% (Koloski, Talley, & Boyce, 2002).

Based on this overview, it seems that the notion of generally high syndrome overlap is questionable. Although at least 20 different FSS are known in the literature, rarely have more than two FSS been examined concomitantly. Moreover, there is a bias as to which FSS were preferably studied together (e.g., CFS and FMS, which already overlap in terms of ancillary symptoms, see 1.1.2.1). Furthermore, there is considerable variation in overlaps across studies (14% to 87%). Although it is conceivable that some inconsistencies are attributable to real differences in prevalence rates (i.e., due to cultural differences), comparisons of studies conducted in the same countries suggest methodological bias. One of the most salient sources of methodological bias may be the diagnostic approach chosen to identify cases with FSS. This is a problem specific to large-scale epidemiological studies on FSS: As comprehensive clinical examinations are not feasible, researchers differ to a great extent in how they operationalise the positive criterion (presence of somatic symptoms) and negative criterion (absence of any disease that fully accounts for the somatic symptoms) of FSS. However, the potential ramifications of this have never been evaluated.

1.1.2.3 The role of depression and anxiety

There is a wealth of studies showing high levels of comorbidity with depressive and anxiety disorders in patients with different FSS (see also Henningsen, Zimmermann, & Sattel, 2003). In population-based studies, 32% of CFS patients were found to have an affective disorder, 29% to 46% an anxiety disorder, and 15% to 18% concomitant PTSD (Nater et al., 2009; Taylor, Jason, & Jahn, 2003). In one study, nineteen percent of cases with FMS were found to have a concomitant major depressive episode, the comorbidity with any anxiety disorder was 12%, and none had PTSD (Raphael, Janal, Nayak, Schwartz, & Gallagher, 2006). The comorbidity of IBS with affective disorders was 40% (Koloski, Boyce, & Talley, 2006), while the comorbidity with anxiety disorders was found to range between 17% and 43% (Koloski et al., 2006; Lee, Wu, et al., 2009).

Although studies on comorbidity rates offer a valuable impression of how frequently patients with FSS are affected by mental disorders, they cannot answer the question of how depression and anxiety relate to FSS. Two studies using 1946 and 1958 British birth cohort data demonstrated that psychopathology through early and mid-adulthood predicted the incidence of CFS at age 42 and 53, respectively (Goodwin, White, Hotopf, Stansfeld, & Clark, 2011; Harvey, Wadsworth, Wessely, & Hotopf, 2008). Similarly, epidemiological data from a Norwegian cohort study established depression and anxiety as prognostic factors for the development of CWP (Mundal, Grawe, Bjorngaard, Linaker, & Fors, 2014), which is in line with findings from similar studies conducted in Great Britain (Gupta et al., 2007; McBeth, Macfarlane, Benjamin, & Silman, 2001). Moreover, both depression and anxiety appeared to be significantly associated with a de novo diagnosis of IBS in two large-scale epidemiological studies (Goodwin, White, Hotopf, Stansfeld, & Clark, 2013; Koloski et al., 2012; Nicholl et al., 2008). In one of these studies, the reversed causation hypothesis (IBS predates depression and anxiety) was simultaneously tested and not confirmed (Koloski et al., 2012).

Taken together, the co-existence of FSS with depressive and anxiety disorders does appear to be quite substantial, although there is some variation across syndromes and studies. There is initial evidence of a temporal precedence of depression and anxiety, although caution is warranted when interpreting these findings, as diagnoses of FSS were often merely established by single-item questions (“Do you have CFS/FMS/IBS?”, “Has your physician ever told you that you have CFS/FMS/IBS?”). These studies therefore need to be interpreted in light of the fact that neither the

positive criterion (presence of somatic symptoms) nor the negative criterion (absence of any disease that fully accounts for the somatic symptoms) of FSS have adequately been accounted for. In general, most studies have again focused on one specific FSS. Obviously, these isolated observations do not allow the conclusion that depression and anxiety are relevant to all kinds of different FSS.

1.1.2.4 Conclusion

In sum, current case definitions suggest that ancillary symptoms of CFS, FMS, and IBS overlap to some extent, while core features are specific to each of these FSS. Syndrome overlap, as summarised above, ranges from 14% to 87%. Comorbidity with depression and anxiety also varies across studies, albeit to a lower extent. There is initial evidence that depression and anxiety temporally precede FSS.

Although the overall knowledge on the phenomenology of FSS has substantially increased in the past 15 years, there are major methodological issues that are likely to account for the observed inconsistencies and are thus worthy of mention. First and foremost, there is a dearth of research examining several FSS at the same time. Although findings from samples consisting of two different FSS are important, in particular, the question of syndrome overlap can only be comprehensively addressed in multiple-syndrome samples. Second, it appears that certain syndromes have preferably been studied concomitantly, while other FSS have been neglected altogether. Unfortunately, the studied syndromes are often the ones that already show considerable symptom overlap (i.e., overlapping case definitions), which renders findings somewhat ambiguous. Third, there is substantial heterogeneity in diagnostic approaches to FSS, meaning that the ways in which the positive and negative criteria of FSS are assessed vary substantially across studies. It seems plausible that this is one of the most important sources of methodological bias, but this hypothesis remains to be tested.

2. Summary and research aim

Functional somatic syndromes are debilitating illnesses that are characterised by the presence of somatic symptoms and the absence of any demonstrable abnormalities of organ structure or function that would allow an attribution to a conventionally defined medical disease. There are numerous case definitions for different FSS, including CFS, FMS, or IBS; however, to date, these do not have the status of nosological entities. The reason for this is that there is no universal consensus on how FSS should best be understood. The most extreme positions are those held by “lumpers”, who advocate the concept of one general FSS, and “splitters”, who are in favour of a concept that distinguishes between specific FSS.

The overall aim of this thesis was to identify similarities and differences of FSS by studying aetiopathogenetic and phenomenological features across a variety of syndromes. Regarding aetiopathogenesis, stress has emerged as an important factor that may be involved in the predisposition, precipitation, and perpetuation of FSS. A psychobiological understanding of stress enables the integration of numerous isolated findings that have accumulated over the years. When taken together, they suggest that childhood trauma and chronic stress contribute to FSS via alterations in stress-responsive somatic systems. However, several important pieces of this puzzle are still missing, and the overall validity of what may be a promising theoretical framework to illustrate the translation of psychosocial stress into FSS awaits empirical confirmation. The first goal of this thesis was therefore to test specific parts of this framework in different patient samples.

Regarding the phenomenology of FSS, research has tried to evaluate the extent of their overlaps (syndrome overlap), and to illuminate their relationship depression and anxiety in order to identify the amount of similarity among syndromes. Unfortunately, the findings are still equivocal: Barely any research has been conducted in samples that allow multiple (i.e., more than two) FSS to be studied at the same time. Furthermore, methodological problems specific to the complex topic of FSS (e.g., divergent diagnostic approaches) may hamper the interpretation of findings in this area. The second goal of this thesis was therefore to provide an in-depth phenomenological account of FSS by studying somatic symptoms and a number of concomitantly measured syndromes in great detail.

A multi-methodological approach, including experimental, ambulatory assessment, and survey research designs, was chosen to answer these research questions. In the first study (Strahler, Fischer, Nater, Ehlert, & Gaab, 2013), we looked at autonomic reactivity to two different laboratory stressors in

patients with CFS. The objective of the second study (Fischer et al., ready to be submitted) was to clarify whether everyday stress and autonomic or HPA axis functioning exacerbate pain in patients with FMS. In the third study (Fischer, Lemmer, Gollwitzer, & Nater, 2014), a multidimensional model concerning the role of stress in FSS in general was tested in a sample of young adults. In the fourth study (Fischer, Gaab, Ehlert, & Nater, 2013), we determined syndrome overlap and predictors of incident FSS. The aim of the fifth study (Fischer & Nater, 2014) was to evaluate the implications of using divergent diagnostic approaches in epidemiological studies on FSS. Finally, in the sixth study (Witthöft, Fischer, Jasper, Rist, & Nater, under revision), we illuminated the latent structure of somatic symptoms and their relationship with depression, anxiety, somatosensory amplification and different FSS.

Four of these studies (I, III, IV, V) were published in 2013 and 2014. One study (VI) is currently under revision, and one study (II) is ready to be submitted. Importantly, results regarding prevalence rates of FSS and comorbidity with mental disorders (see original articles of studies IV and V) have already been presented in my Master thesis and are irrelevant to this doctoral thesis. As they are not part of the present thesis, they will not be summarised in the following chapters.

3. Summary of empirical studies

3.1 Study I

As briefly described in the introduction (1.1.2.1), CFS includes disabling symptoms, such as severe fatigue that is aggravated by exertion, pain, and cognitive symptoms (Fukuda et al., 1994). Patients often make repeated efforts to find organic abnormalities underlying their symptoms, and understandably so. Unfortunately, physicians are rarely able to provide patients with satisfactory explanations as to what the factors underlying the symptoms of CFS are. This is in part due to the fact that, as with all FSS, the exact pathophysiology of CFS is still unknown, but is presumably complex and multifactorial.

There is accumulating evidence to suggest that stress is an important pathophysiological factor in CFS (Nater, Fischer, & Ehlert, 2011). For instance, some symptoms of CFS point to disturbances in stress-responsive systems such as the ANS. Bou-Holaigah et al. (1995) recognised similarities between post-exertional malaise, dizziness, and cognitive problems, and symptoms of neurally mediated hypotension (a so-called “dysautonomia”, see 1.1.1.3). At the same time, in a sample of CFS patients, both the amount of exposure and emotional response to an environmental stressor (Hurricane Andrew) were found to predict clinical relapses and exacerbation of symptoms (Lutgendorf et al., 1995). Taken together, these studies (and many more along these lines) give reason to assume that stressors elicit symptoms of CFS via ANS dysfunctions.

The studies have spurred a variety of research looking at altered autonomic stress reactivity in an effort to better understand CFS. Unfortunately, the literature still has to be considered as inconsistent, and many studies suffer from major shortcomings. For instance, rarely have main effectors of the ANS (e.g., the catecholamines NA and adrenaline) been measured and rarely has autonomic stress reactivity been tested by means of laboratory paradigms that were able to concomitantly stimulate the release of NA and adrenaline. Most importantly, these paradigms often had little in common with the situations which patients with CFS perceive as exacerbating their symptoms (e.g., physical activity).

In study I, we set out to compare autonomic responses to an exercise stressor between patients with CFS and healthy controls. Moreover, we aimed at contrasting the exercise stressor with a pharmacological stressor. This allowed us to distinguish effects of a paradigm that mimics everyday

stressors in the lives of patients with CFS (i.e., physical exertion) from responses to a standardised stimulant of the sympathetic-neural and sympatho-adrenomedullary (SAM) system. We expected to find attenuated autonomic responses in a comparison between patients and controls.

Methods

A German self-help organisation was contacted and informed about our study. Patients interested in participating were carefully screened for positive and negative criteria in accordance with the CDC case definition for CFS (Fukuda et al., 1994). To this end, they were admitted to the research unit of a general hospital and underwent a medical examination and standardised diagnostic interview conducted by a clinical psychologist (Wittchen & Pfister, 1997). Twenty-one patients endorsed the CDC case definition, and were matched with 20 healthy control participants in terms of sex and age.

Both groups participated in two laboratory appointments with at least 48 hrs in between. Both stressors were preceded by a resting period of 45 min after insertion of an intravenous catheter. Cycle ergometry was scheduled at 2 p.m., and started with 50 W (men) and 40 W (women), respectively, with 40 W increments every 3 min. The stressor continued until participants terminated the procedure or until their presumed maximum heart rate (85% 220 bpm - age) was reached. Heart rate (Sport Tester Profi, Polar Instruments, Gross-Gerau, Germany) and perceived exertion (Borg scale; Borg, 1982) were measured every 3 min, and blood was drawn immediately before, and after 10 and 30 min of stressor onset. For the insulin tolerance test, 0.15 U/kg of insulin (H-Insulin, Hoechst, Frankfurt, Germany) was injected at 9.45 a.m. to induce hypoglycaemia. Blood was drawn at baseline, and 20 and 30 min thereafter.

Blood plasma levels of the catecholamines NA and adrenaline were analysed by high-pressure liquid chromatography (detection limit: 0 - 25 pg/ml) at the Laboratory for Stress Monitoring (Göttingen, Germany). For statistical analyses, SPSS 19 was used. Repeated measures ANOVAs were calculated to determine catecholaminergic responses over time. Mean increases in catecholaminergic responses were calculated by subtracting baseline from peak values (10 and 30 min, respectively), and groups were compared by means of univariate ANOVAs.

Results

Our results indicated no significant group differences in peak heart rate and maximum perceived exertion. Both stressors were successful in eliciting an increase in catecholamines. Partly confirming our hypotheses, cycle ergometry resulted in blunted adrenaline (but not NA) response profiles in patients with CFS compared to healthy control participants. Similarly, mean increases in adrenaline (but not NA) were lower in patients. Following the insulin tolerance test, no group differences whatsoever were revealed.

Discussion

Two major findings emerged from study I. First, adrenaline (but not NA) responses to cycle ergometry were dampened in the patient sample. This is in perfect accordance with a previous report by Ottenweller et al. (2001), in which a slightly different protocol was employed to test autonomic reactivity. Second, no differences in response patterns following the insulin injections were present between groups. This resonates well with the observation that the insulin tolerance test did not seem to be able to reveal other adrenal abnormalities (i.e., cortisol secretion) in patients with CFS (Bearn et al., 1995; Gaab et al., 2004).

The exact mechanisms of how patients' inability to mount an adequate autonomic stress response may translate into post-exertional malaise and other symptoms of CFS are poorly understood. Adrenergic receptors are well known to be expressed on numerous tissues and organs of the body, including the cells of the immune system, allowing for catecholamines to modulate various immune processes (Elenkov, Wilder, Chrousos, & Vizi, 2000). In CFS, at least one of these processes, inflammation, has emerged as a pivotal factor that is likely to contribute to the general "influenza-like state" described by patients (Irwin, 2011). It may thus be speculated that the failure of catecholamines to regulate inflammation under conditions of acute stress elicits symptoms of CFS.

To conclude, study I showed attenuated autonomic responses to acute exercise stress in patients with CFS. It is tempting to assume that the identified dysfunction of the ANS plays a key role in the precipitation and exacerbation of CFS symptoms. Future studies are needed to test this assumption, preferably in an ecologically valid setting.

3.2 Study II

Fibromyalgia syndrome is an incapacitating illness that tends to be rather intractable. A follow-up on a cohort of patients yielded only a small fraction of improving cases (Walitt et al., 2011). At the same time, there is evidence from qualitative studies and clinical practice that most patients do not perceive pain, the hallmark symptom of FMS (see also 1.1.2.1), as stable over the course of a day. In fact, there seem to be symptom flares, which make it difficult for patients to plan and go about their activities (Dennis, Larkin, & Derbyshire, 2013). Knowing more about pain-exacerbating factors could be an important first step towards interrupting the perpetuation of FMS.

There is ever-increasing evidence that stress is an important perpetuating factor in patients with FMS (Nater, Fischer, & Ehlert, 2011). In cross-sectional survey studies, chronic stress levels and the amount of daily hassles were shown to be positively correlated with patients' pain severity (e.g., Alok, Das, Agarwal, Salwahan, & Srivastava, 2011; Dailey, Bishop, Russell, & Fletcher, 1990). In addition, stress-responsive systems, such as the ANS and HPA axis, are well known to be involved in central and peripheral pain regulation (Clauw & Chrousos, 1997; Irwin, 2011), and both systems have been shown to be dysfunctional in patients with FMS (Fries et al., 2005; Martinez-Lavin, 2004). Taken together, there is therefore reason to suggest that both everyday stress and dysfunctions of stress-responsive systems could explain pain exacerbations in patients with FMS.

However, there are a number of reasons why previous studies offer only limited insight regarding this assumption. For instance, cross-sectional survey studies in general suffer from recall bias and a lack of ecological validity. In other words, retrospective stress and pain reports are often inaccurate and global measures of these constructs can barely grasp the dynamics of the assumed stress-pain relationship as it unfolds in patients' daily lives. Moreover, virtually no study has investigated whether the ANS and HPA axis are involved in the pain exacerbation in patients with FMS.

The aim of study II was to explore whether and how stress exacerbates pain in the everyday lives of women with FMS. We chose an ambulatory assessment approach to answer this research question as this enables researchers to tap into patients' experiences in their natural habitat. We hypothesised that stress predicts pain and vice versa (i.e., pain itself was assumed to operate as a stressor), and that autonomic and HPA axis activity mediate this relationship. All analyses were run twice: cross-sectionally (momentary analyses), and prospectively (time-lagged analyses).

Methods

Thirty female patients endorsing the Fibromyalgia Research Criteria (Wolfe et al., 2011) were recruited via advertisement in newspapers, general practitioners' and rheumatologists' offices, and self-help organisations. Eligibility was checked on the telephone and during the initial study appointment by means of an interview on mental disorders and a review of the medical history. For inclusion in the study, patients had to be free of any major mental disorder (including a current major depressive episode), and not have any disease which affects autonomic or endocrine functioning.

Patients were introduced to the ambulatory assessment during the initial study appointment. They were required to answer six daily queries on an iPod touch® and simultaneously collect six saliva samples via SaliCaps (IBL, Hamburg, Germany). The measurement time points were prescheduled for 11 a.m., 2 p.m., 6 p.m., and 9 p.m., except for the first assessment, which was to be initiated by the patients themselves directly upon awakening. Momentary stress was measured on a five-point Likert scale (*not at all* to *very much*). Momentary pain was measured on a visual analogue scale (*I am in no pain* to *I am in the most intense pain possible*). A variety of potentially confounding variables (e.g., physical activity, intake of medication) were additionally measured. The assessment period lasted for 14 consecutive days and ended with a final study appointment. Questionnaires on symptoms of FMS, depression, childhood trauma and chronic stress were filled in during the initial and final study appointments.

The activity of sAA, an indicator of the ANS (see 1.1.1.3), was measured using a kinetic colorimetric test (Roche Diagnostics, Mannheim, Germany). Cortisol levels were measured using a commercially available enzyme-linked immunoassay (IBL, Hamburg, Germany). In terms of statistical analyses, descriptive statistics and testing of statistical assumptions were calculated by means of SPSS 21. To test our hypotheses, two-level hierarchical linear modelling (HLM) was performed by means of HLM 7.

Results

Momentary stress predicted momentary pain, even when controlling for physical activity and intake of medication during the past two hours, and time since awakening on level one, and age, number of pain sites, regular intake of medication, childhood trauma, and chronic stress on level two. Within this model, stress alone explained 8% out of the 16% total variance in momentary pain. A similar model including stress reported at the previous measurement time point explained 19% of the variance in momentary pain, and 1% of this was attributable to previous stress alone. The reversed relationship (previous pain on stress) did not prove significant, and nor did momentary associations between sAA and pain. Momentary cortisol was positively linked to momentary pain.

Discussion

Study II yielded two major findings. First, the fact that stress was a meaningful predictor of pain supports the theoretical assumption of stress as a pain-exacerbating factor in patients with FMS. Our study elaborates on previous findings by showing that elevations in stress levels temporally precede elevations in pain levels on the same day, but not vice versa. Second, cortisol, but not sAA, was associated with momentary pain.

Our findings indicate that HPA axis activity may be involved in the exacerbation of pain in FMS. The more cortisol was secreted, the more pain our patients experienced. One way to make sense of this observation is to assume that temporary elevations in individual cortisol output may disturb the CRH system, which is known to be involved in analgesia via descending pathways (Clauw & Chrousos, 1997). This assumption would fit in with the finding that patients with FMS exhibit enhanced negative feedback sensitivity (e.g., Wingenfeld et al., 2007), meaning that their CRH system is hyper-responsive to the inhibitory effects of cortisol. However, as no causality can be implied by our findings, this remains speculative.

To conclude, study II confirmed that stress is an important exacerbating (and thus potentially perpetuating) factor of pain in patients with FMS. The mechanisms underlying this relationship remain to be fully elucidated. Future studies should begin to approach this question by gathering information about the reasons for momentary elevations in patients' stress levels.

3.3 Study III

"Functional somatic syndromes" is an umbrella term for conditions such as CFS, FMS, and IBS. The struggle to understand these puzzling conditions has resulted in thousands of publications on the subject of their aetiopathogenesis. In all three of the above-mentioned conditions, most research has at some point abandoned biological models, which mostly claimed that the observed symptoms were caused by a neurological or immunological process, and turned to psychobiological conceptualisations of FSS. The last decades have witnessed a particular interest in stress and its role in the development of FSS (Nater, Fischer, & Ehlert, 2011; Tak & Rosmalen, 2010).

As outlined in the introduction (see 1.1.1), there is overwhelming evidence that different facets of stress are involved in the predisposition, precipitation, and perpetuation of FSS. Among these are experiences of childhood trauma, stress reactivity (emotional and biological), and chronic stress. An abundant literature now shows that early life stress, such as childhood trauma, is a powerful determinant of stress reactivity throughout life (e.g., Schlotz & Phillips, 2013). At the same time, there is reason to assume that it negatively affects resilience (e.g., Campbell-Sills, Forde, & Stein, 2009), a personality characteristic that promotes adaptation in the face of psychosocial stressors. Each of these factors, that is, experiencing childhood trauma, altered stress reactivity, and low resilience, is in turn known to foster chronic stress (Gonzalez-Ramirez, Garcia-Campayo, & Landero-Hernandez, 2011; Lustyk, Widman, & Becker Lde, 2007; Schlotz, Yim, Zoccola, Jansen, & Schulz, 2011).

However, as is evident from this brief summary, studies on stress in FSS have mostly studied individual facets (e.g., chronic stress in IBS); some have extended this to examine connections between two facets (e.g., altered stress reactivity in patients with CFS as a consequence of childhood trauma). Unfortunately, as of yet, barely any efforts have been made to bring findings from this intriguing line of research together. Moreover, the role of resilience remains completely understudied.

Our aim with study III was to empirically test whether a model integrating multiple facets of stress and resilience is capable of predicting the manifestation of FSS. Based on the outline of predisposition in the preceding paragraph, we expected chronic stress to precipitate and perpetuate FSS. We tested our model cross-sectionally and prospectively in order to be able to establish a temporal order, where stress in its various forms precedes the manifestation of FSS (rather than vice versa).

Methods

Administrators of the major Swiss colleges and universities were contacted and asked for their cooperation. Those who agreed sent out an e-mail to all registered students containing a link to our online survey. The link was additionally posted on websites frequently visited by students. All participants willing to be contacted again were sent a link to an identical follow-up survey six months later. A total of 3054 students (73% female) provided complete data sets at T_0, and 429 complete data sets were received at follow-up (T_1).

Childhood trauma was measured via the Childhood Trauma Questionnaire (Bernstein et al., 2003). An example item is “I felt that someone in my family hated me” (emotional abuse). We relied on the Stress Reactivity Scale (Schulz, Jansen, & Schlotz, 2005) to assess emotional stress reactivity. This instrument refers to situations such as high workload, failure, social evaluation, and anticipation of a psychosocial stressor. Items such as “When I’m wrongly criticised by others…” were answered by choosing a statement completing the sentence. These ranged from “I am normally annoyed for a long time” to “In general, I am hardly annoyed at all”, reflecting different levels of stress reactivity. We adhered to the Resilience Scale (Schumacher, Leppert, Gunzelmann, Strauss, & Brähler, 2005) to measure resilience (e.g., “I usually manage one way or another”). To obtain a measure of chronic stress, the screening version of the Trier Inventory for the Assessment of Chronic Stress (Schulz et al., 2004) was administered. Our items measured excessive demands at work, work and social overload, and chronic worrying during the past three months (e.g., “I do not have enough time to perform my daily tasks”). Finally, FSS were diagnosed by means of the Questionnaire on Functional Somatic Syndromes (Nater, Fischer, Latanzio, Ruoss, & Gaab, 2011). This hierarchical, modular instrument allows for the assessment of 17 different FSS. To answer our research question, we dichotomised all participants into non-cases (*0*) and cases (*1*).

MPlus V7.0 was used for structural equation modelling. Childhood trauma was the latent exogenous variable; stress reactivity, resilience, and chronic stress were latent mediators; and the presence of any FSS was the manifest endogenous variable. A weighted least squares method and a X^2 test, root mean square error of approximation, comparative fit index, and the Tucker-Lewis index were calculated to test whether the covariance matrix of our variables was consistent with our

expectations (Browne & Cudek, 1993; Hu & Bentler, 1999). Indirect effects were tested by the Sobel test (MacKinnon, Lockwood, Hoffman, West, & Sheets, 2002; Sobel, 1982) and a bias-corrected bootstrapping approach by MacKinnon et al. (2004).

Results

Our model proved a good fit with the data structure at T_0 and T_1. Both direct and indirect effects turned out to be significant and coefficients were in the expected directions. However, one path (direct path from childhood trauma to FSS) needed to be removed in both models.

Discussion

In sum, the findings of study III offer an impression of how suffering childhood trauma may transform into FSS by modifying the experience of stress later on in life. Participants who grew up under emotionally hostile, neglectful, and unstable circumstances (childhood trauma) not only showed a pattern of strong stress responses in terms of difficult work and social situations (heightened stress reactivity), but at the same time lower beliefs in their own competence and acceptance of themselves (lowered resilience). As a consequence of this predisposition, they were more prone to experiencing stress in the work and social domain, and to engaging in chronic worrying (chronic stress). This, in turn, precipitated and perpetuated FSS.

Our findings echo evidence on the biological embedding of childhood trauma, that is, its long-term effects on stress-responsive systems that extend into adulthood. An example of this is provided by a study in which patients with IBS and healthy controls were matched in terms of abuse and subsequently underwent the same laboratory stressor (Videlock et al., 2009). In this study, the abused patients with IBS exhibited the most abnormal stress response. Analogous to our study, childhood trauma was thus associated with dysfunctional reactivity in patients when a stressor was being faced.

In conclusion, in study III, we empirically confirmed a model illustrating how different facets of stress interact over the course of developing an FSS. Professionals involved in the treatment of FSS should pay attention to the possibility of childhood trauma. Furthermore, modules enhancing resilience and lowering stress reactivity and chronic stress may enhance treatment outcomes.

3.4 Study IV

As briefly reviewed in the introduction, there is a conceptual debate as to whether or not CFS, FMS, and IBS are, in fact, all expressions of a "general FSS" (Wessely & White, 2004). Wessely et al. (1999) first expressed the view that it was only through medical specialisation that MUS were attributed to specific syndromes. They reached this conclusion by claiming that a variety of symptom characteristics (e.g., overlap in case definitions) and non-symptom characteristics (e.g., high comorbidity with depressive and anxiety disorders) are shared by all FSS.

One of their strongest arguments, however, was that of a substantial co-occurrence of different syndromes (syndrome overlap); in other words, they claimed that a patient with CFS was very likely to suffer from FMS and IBS as well, and vice versa. The first systematic review on the overlap among FSS was published in rapid succession to the seminal article by Wessely et al. (1999). The authors revealed a great amount of overlap within the category of FSS (Aaron & Buchwald, 2001), thus supporting the thesis of Wessely et al.

However, as acknowledged by Aaron and Buchwald (2001), several shortcomings undermine the validity of findings on the overlap among FSS. For instance, one problem is referral bias, that is, the recruitment of participants via specialised care centres (e.g., CFS clinics). As health care-seeking behaviour is known to be associated with various traits (Taylor, Marshall, Mann, & Goldberg, 2012) and states (Hilbert, Martin, Zech, Rauh, & Rief, 2010) in patients with MUS, it becomes clear that these samples cannot reflect the total patient population. Another, even more salient limitation, is the fact that although there are over 20 FSS, rarely have more than two been studied simultaneously. This precludes research from stating that FSS *in general* have high overlaps and can therefore be lumped together.

Our aim with study IV was therefore to investigate overlap among a wide range of FSS in a sample of apparently healthy young adults. In line with previous studies, we assumed that FSS commonly co-occur. However, since a non-clinical sample allowed us to reduce referral bias, we expected fewer individuals to suffer from multiple syndromes at the same time, and overlap rates to be lower. In addition, according to the arguments outlined by Wessely et al. (1999), we hypothesised that the manifestation of any FSS could be predicted by symptom and non-symptom characteristics.

Methods

Apparently healthy students were recruited from major Swiss colleges and universities and asked to participate in the exact same survey twice (six months in between). In total, our data sets encompassed 3054 students (73% female) at T_0, and 429 at follow-up (T_1).

The number of somatic symptoms and consequent impairment in activities of participants' daily lives (symptom characteristics) were measured by the screening part of the Questionnaire on Functional Somatic Syndromes (Nater, Fischer, Latanzio, et al., 2011). This part comprises questions on how frequently 52 different somatic symptoms are experienced. In addition, there are questions on impairment, which refer to all symptoms that are at least frequently present. To obtain a measure of somatisation (another symptom characteristic), that is, how bothered participants were by various somatic symptoms, a subscale of the revised Symptom Check List 90 (Derogatis, 1977) was employed. The frame of reference for all somatic symptoms contained in this instrument was seven days. Depression and anxiety disorders (non-symptom characteristics) were assessed by the Patient Health Questionnaire (Spitzer, Kroenke, & Williams, 1999), which follows DSM-IV criteria (American Psychiatric Association, 2000). Functional somatic syndromes were diagnosed by means of the Questionnaire on Functional Somatic Syndromes (Nater, Fischer, Latanzio, et al., 2011). This hierarchical, modular instrument allows for the assessment of 17 different FSS.

SPSS 20 was used for all statistical analyses. To answer our first research question, the number of diagnoses per person and per FSS category was calculated and presented in absolute and relative numbers. For our second research question, FSS were dichotomised into non-cases (*0*) and cases (*1*), and *t* tests and binary logistic analysis were computed.

Results

Four concomitant FSS were reported by one person, three syndromes by 12 persons (4% of total cases), two syndromes by 49 persons (17%), and one syndrome was reported by 227 persons (79%). Overlap rates mostly did not exceed 10% when we looked at each syndrome separately. For instance, within the functional dyspepsia category, 2% of patients endorsed criteria for temporomandibular disorder, functional chest pain, chronic low back pain, and chronic pelvic pain, respectively, 4% had

premenstrual dysphoric disorder, 7% had hyperventilation syndrome, and 19% had IBS. All symptom and non-symptom characteristics, except for anxiety disorders, predicted the incidence of any FSS six months later. The number of somatic symptoms proved most powerful in this regard.

Discussion

In study IV, two major findings were presented. First, we found that only a minority of participants was affected by several FSS at the same time, and our numbers regarding overlap rates are at odds with other studies. For instance, roughly 40% of functional dyspepsia cases had IBS in one study (compared to barely 20% in our sample; Locke, Zinsmeister, Fett, Melton, & Talley, 2005). Second, we found that a high number of symptoms, symptom impairment, somatisation and depression predicted the manifestation of any FSS six months later. Our findings are in agreement with other prospective studies showing the same factors to be germane to the development of CFS, FMS, and IBS (Forseth, Husby, Gran, & Forre, 1999; Leone et al., 2006; Nicholl et al., 2008). The overall findings can therefore be summarised as low syndrome overlap on the one hand and common risk factors for all syndromes on the other hand.

Our first finding implies that FSS are best regarded as distinct, albeit to some degree comorbid conditions. It points to specific aetiopathogenetic processes that operate in each FSS. Moss-Morris and Spence (2006) found different types of infection to precipitate CFS and IBS, which gave rise to the notion that differential biological mechanisms are involved in each FSS. Our second finding, by contrast, suggests common aetiopathogenetic processes. One might speculate that the identified predictors are indicative of certain cognitive-behavioural mechanisms that are relevant to the development of FSS in general (Witthöft & Hiller, 2010). For instance, a high number of symptoms, and a high amount of symptom impairment and distress, may reflect attentional and interpretative bias regarding somatic perceptions, and a high level of depression may be paralleled by physiological deconditioning through avoidance behaviour.

In conclusion, the findings of study IV point to both specific and common aetiopathogenetic factors in FSS. Our identified predictors provide a possibility for prevention by early detection of individuals at risk of developing an FSS. Futures studies are required to unravel the reasons underlying the apparent inconsistencies in the literature on syndrome overlap.

3.5 Study V

The epidemiological data concerning FSS vary widely. For instance, in a review article on the epidemiology of IBS, prevalence rates ranged from as low as 1% to as high as 45% (Lovell & Ford, 2012). However, there was substantial heterogeneity in the data, which could not be explained by variables such as geographical region, the use of different case definitions, data collection via questionnaires versus interviews, and socio-demographic characteristics. Likewise, the most important review on overlap among FSS revealed that, for example, in patients with FMS, 21% to 80% concurrently had CFS (Aaron & Buchwald, 2001). The diversity of these findings is again striking, and one is left wondering what the underlying causes are.

One explanation that is rather peculiar to research on FSS is emphasised in both reviews: the choice of the diagnostic approach. Inherent in the case definition of any given FSS are two criteria: first, presence of a symptom or constellation of symptoms that is characteristic of the FSS in question (positive criterion), and second, absence of any medical condition that is able to fully account for these symptoms (negative criterion). Both criteria can be checked by asking patients about symptoms, and performing physical examinations and laboratory testing in terms of exclusionary conditions. This two-step procedure is currently considered the *gold standard approach*. However, as epidemiological research is in most instances forced to rely on self-reported data, numerous ways of diagnosing FSS have instead been adopted.

The repercussions of using different diagnostic strategies in research on FSS have rarely been assessed. Based on an empirical comparison, Warren and Clauw (2012) have argued in favour of *symptom-based diagnoses* as opposed to *physician diagnoses*, meaning that people should be asked about each symptom contained in the case definition criteria rather than whether their physician has diagnosed them with syndrome X. However, with the *symptom-based approach*, the negative criterion (see above) is neglected.

We conducted STUDY V in order to compare the *symptom-based approach* with a *symptom-and-exclusion-based approach*. The latter approach combines questions about symptoms with questions about exclusionary conditions as detected by a health care professional. We expected to find substantial decreases in prevalence and overlap rates when following this approach.

Methods

Apparently healthy students were recruited from major Swiss colleges and universities and asked to participate in the exact same survey twice (six months in between). In total, our data set encompassed 3054 students (73% female).

Functional somatic syndromes were diagnosed by means of the Questionnaire on Functional Somatic Syndromes (Nater, Fischer, Latanzio, et al., 2011). This hierarchical, modular instrument allows for the assessment of 17 different FSS. It has three parts that are separated via several algorithms. The first part is the screening part, where 52 somatic symptoms are rated in terms of how often they are experienced. In addition, questions about impairment and the duration of symptoms are asked. The second part is only presented if participants report symptom constellations that point to a certain FSS (e.g., abdominal pain and digestive problems for at least six months in the case of IBS). In this part, case definition criteria (e.g., the Rome III criteria for IBS; Longstreth et al., 2006) are covered. In this study, all participants satisfying any case definition were labelled "*symptom-based cases*". The third part only applies if health care visits were made due to symptoms. Participants were asked about exclusionary conditions that were named by their physician as causes for their symptoms (e.g., ulcerative colitis). The label "*symptom-and-exclusion-based cases*" was given to those stating that no other condition was found that would serve as an explanation for their symptoms.

SPSS 21 was used for all statistical analyses. Prevalence rates and number of diagnoses per person and per FSS were calculated and presented in absolute and/or relative numbers.

Results

There was an up to seven-fold decrease in prevalence rates across all 16 measured FSS when the *symptom-and-exclusion-based approach* was used. Participants with *symptom-based FSS* had one (62% of all cases) to eight (< 1%) concomitant syndromes. Participants with *symptom-and-exclusion-based FSS* had one (79%) to four (< 1%) concomitant syndromes. In the *symptom-based group*, nine other syndromes were present on average. This number was reduced to four in the *symptom-and-exclusion-based group*.

Discussion

Taken together, in study V, the use of medical exclusionary criteria resulted in sizable decreases in the prevalence and overlap of FSS, mirroring data from a previous study on functional gastrointestinal disorders (Koloski et al., 2002). The *symptom-and-exclusion-based approach* seems to "mimic" the two-step *gold standard approach* adequately well, meaning that a comparable proportion of individuals is excluded from an FSS diagnosis due to medical explanations for their symptoms (Perrot, Vicaut, Servant, & Ravaud, 2011; Reyes et al., 2003).

Our study somewhat contradicts the recommendation by Warren and Clauw (2012), who made a case for the *symptom-based approach* to diagnose FSS in epidemiological studies. Based on our findings, it could be argued that their approach bears the risk of mislabelling symptoms (e.g., abdominal pain) as part of an FSS (e.g., IBS) instead of a medical disease (e.g., ulcerative colitis), which ultimately inflates prevalence rates of FSS. This certainly raises the question of whether the common notion of high syndrome overlap is, to some degree, a methodological artefact.

To conclude, study V found the prevalence of FSS and their overlaps to largely depend on the choice of diagnostic approach. Our findings raise concern about the validity of a number of earlier epidemiological findings in the context of FSS. The strict application of case definition criteria, that is, covering both the positive and negative criterion, is strongly encouraged in order to further the accuracy of figures in terms of the prevalence and overlaps of FSS.

3.6 Study VI

As Deary (1999) pointed out, getting a grasp of medically unexplained conditions (i.e., MUS, FSS, or somatoform/somatic symptom disorders) requires a detailed examination of their phenomenology. In the context of FSS, findings so far remain equivocal as to whether the different FSS are the expression of a general syndrome or distinct entities (one vs. many debate; Wessely & White, 2004). However, research along the lines of this question may have been somewhat hampered by its a priori assumption that FSS do exist as described by case definition criteria.

In recent years, another, more unbiased approach to scrutinise the phenomenology of medically unexplained conditions has emerged. Taking one step back, these studies have inquired about the latent structure of *symptoms* rather than describing *syndromes* (i.e., FSS or somatoform/somatic symptom disorders). Four different models have so far been assumed to best represent the variance in bothersome somatic symptoms (Witthöft, Hiller, Loch, & Jasper, 2013). In a comparison of these models, the so-labelled “bi-factor model” proved the best fit for the data. In brief, this model postulates that a general factor and four symptom-specific factors (labelled “fatigue”, “pain”, “gastrointestinal”, and “cardio-respiratory”) account for the variance in bothersome somatic symptoms.

However, the jury is still out on how these factors might best be interpreted and how they relate to existing diagnostic categories such as FSS (construct validity). Other important concepts that are discussed in relation to bothersome somatic symptoms are depression, health anxiety (i.e., the unsubstantiated and disproportionate fear or conviction of suffering from a severe illness), and somatosensory amplification (i.e., the tendency to experience somatic reactions as more intense, and to evaluate them as more negative; Henningsen et al., 2003; Jones, Schettler, Olden, & Crowell, 2004; Schroeder et al., 2012).

STUDY VI was conducted to replicate the bi-factor model and to provide evidence for its construct validity. To this end, depression, health anxiety, and somatosensory amplification were assessed in addition to bothersome somatic symptoms. Based on the available literature, all constructs were expected to strongly relate to the general factor. We also included different FSS in our analyses, which we assumed to be predicted by both the general factor and the symptom-specific factors.

Methods

Two separate samples were recruited to replicate the bi-factor model and to provide evidence for its validity. The first sample consisted of 1604 students (60% females) who had filled in a battery of questionnaires in the waiting area of the office of student enrolment at the University of Muenster. The second sample contained 3053 students (73% women) recruited from major Swiss colleges and universities who had participated in an online survey.

Depression was assessed by the Patient Health Questionnaire (Spitzer et al., 1999), which is in accordance with DSM-IV criteria (American Psychiatric Association, 2000). The Whiteley Index (Pilowsky, 1967) was used to tap into health anxiety, with items such as “Do you worry a lot about your health?”. A measure of somatosensory amplification was obtained by the Somatosensory Amplification Scale (Barsky et al., 1990). An example item is “I can sometimes hear my pulse or my heartbeat throbbing in my ear”. Functional somatic syndromes were diagnosed by means of the Questionnaire on Functional Somatic Syndromes (Nater, Fischer, Latanzio, et al., 2011). This hierarchical, modular instrument allows for the assessment of 17 different FSS. We additionally dichotomised all participants into non-cases (*0*) and cases (*1*). Finally, somatic symptom distress was measured via the Patient Health Questionnaire (Spitzer et al., 1999). With this scale, 13 somatic symptoms are evaluated with respect to how much participants were bothered by each one of them.

MPlus V6.11 was used for confirmatory factor analyses. A weighted least squares method and several fit indices were used to test whether the empirical covariance matrix of our variables was consistent with our expectations. More specifically, a X^2 test, root mean square error of approximation, comparative fit index, and the Tucker-Lewis index were calculated.

Results

The bi-factor model showed an excellent model fit to the data structure of both samples. In the first sample, depression and health anxiety were associated with the general factor and together explained 67% of its variance. In the second sample, depression and somatosensory amplification were again associated with the general factor, explaining 65% of the variance. The general factor, in turn, was

linked to the overall category of FSS. The FSS functional dyspepsia and IBS were each predicted by the general and gastrointestinal factor.

Discussion

Two major findings emerged from study VI. First, the latent structure of bothersome somatic symptoms was composed of a general factor, which was related to depression and health anxiety. Beyond this affective component, the general factor was associated with somatosensory amplification, which may represent cognitive processes specifically involved in medically unexplained conditions. Second, there were four symptom-specific factors that showed strong affiliations with individual FSS. These factors may be interpreted as a sensory component that is unique to each FSS.

The fact that FSS were predicted by both a general and symptom-specific factors has important conceptual implications (one vs. many debate). The finding of a general factor is in line with the notion of shared aetiopathogenetic mechanisms among FSS that are beyond mechanisms underlying depression and health anxiety. The finding of symptom-specific factors favours viewing them as distinct syndromes with unique aetiopathogenetic factors. Taken together, FSS may have to be conceptualised as one *and* many.

Study VI provided evidence for a bi-factor model that best describes the latent structure of bothersome somatic symptoms. This model may enable the reconciliation of contradictory findings in the context of FSS. An important direction for future research will be to discern the aetiopathogenetic mechanisms that are unique to fatigue, pain, gastrointestinal, and cardio-respiratory syndromes.

4. Discussion

4.1 Summary

Studies I to III examined the role of stress as an aetiopathogenetic factor in different FSS. Study I showed that patients with CFS are characterised by attenuated catecholaminergic stress reactivity in response to exercise, which may directly relate to symptoms such as fatigue. Study II complemented these findings in a sample of female patients with FMS by demonstrating that stress and cortisol seem to act as exacerbating factors of pain in the everyday lives of these women. Study III integrated both findings by demonstrating that childhood trauma is associated with heightened stress reactivity and lower resilience, and predicts the manifestation of FSS via chronic stress. Taken together, the findings of studies I to III shed light on important mechanisms translating stress into FSS.

Studies IV to VI studied phenomenological aspects of FSS. Study IV revealed that syndrome overlap was lower than previously shown and that the number of somatic symptoms, impairment due to somatic symptoms, somatisation, and depression predicted the incidence of FSS in general. The findings of study V suggested that a methodological artefact may account for discrepant findings regarding syndrome overlap in the literature: Depending on whether or not exclusionary medical conditions were diagnostically considered, prevalence and overlap rates of FSS were lower and higher, respectively. Study VI showed that the latent structure of bothersome somatic symptoms consisted of a general and four symptom-specific factors (“fatigue”, “pain”, “gastrointestinal”, “cardio-respiratory”). Beyond this, the general factor was related to somatosensory amplification, depression, and health anxiety, while the symptom-specific factors loaded on individual FSS. Taken together, these studies revealed that FSS appear to be one *and* many.

4.2 Integration

The findings of studies I to VI are integrated in Figure 3. Based on the results summarised above, a certain predisposition may be suggested in individuals who later go on to develop a medically unexplained condition (i.e., MUS, an FSS, or a somatoform/somatic symptom disorder). According to Heim and Nemeroff (2001) and Heim et al. (2010), early life events, including *childhood trauma*, program stress-responsive systems (i.e., they alter *stress reactivity*). Furthermore, they impact on certain personality traits (e.g., *resilience) a*nd this predisposition in turn lowers the threshold for

symptoms to be precipitated when encountering psychosocial stressors (e.g., *chronic stress*, *daily hassles*) later on in life. This resonates well with the fact that *chronic stress* is an intermediary between the above-outlined predisposition and the development of medically unexplained conditions (study III).

An important mechanism underlying the translation of psychosocial stressors into medically unexplained conditions is allostatic load. As described by McEwen (1998) and McEwen and Stellar (1993), inadequate biological responses towards repeated bouts of stress foster the wear and tear of the very same systems in the long term and ultimately result in ill health. In fact, patients with a medically unexplained condition show lower autonomic *reactivity* than healthy controls when exposed to acute *stress* (study I) and it may be hypothesised that this directly contributes to symptoms such as fatigue and pain (Clauw & Chrousos, 1997; Heim et al., 2000). Importantly, not only does stress seem to precipitate medically unexplained conditions, but it most likely perpetuates them once they become manifest: Both stress as experienced in everyday life (e.g., *daily hassles*) and *HPA axis* functioning are associated with pain exacerbation on a momentary basis (study II).

The fact that stress is an aetiopathogenetic factor germane to medically unexplained conditions in general fits in well with the observation that a general factor explains a great amount of variance in these conditions (study VI). This factor has strong links to *somatosensory amplification*, which refers to a trait-like tendency to experience somatic reactions as overly intense and negative (Barsky et al., 1988; Barsky et al., 1990). Together with stress, *somatosensory amplification* may be an important factor that governs the development of medically unexplained conditions among predisposed individuals. Barsky and Borus (1999) emphasised two pathways via which somatic sensations may be amplified under conditions of stress: First, some individuals hold beliefs about stress being immediately harmful to health. Second, stress can cause *depression* or *anxiety*, which are both known to enhance the perception of somatic sensations. Indeed, depression and anxiety are linked to medically unexplained conditions in general (studies IV and VI).

Despite these similarities, syndrome overlap is rather modest when case identification is not overly broad (studies IV and V). This points to differential factors in medically unexplained conditions, but current knowledge on this subject is scarce. One study found that gene expression profiles at baseline and after exercise stress differed depending on whether patients had CFS or FMS (Light et al., 2012). Moreover, different types of infections seem to trigger CFS and IBS, respectively (Moss-Morris & Spence, 2006). Another study pointed to differences in the operant learning of pain

sensitisation and habituation between patients with FMS and patients with additional IBS (Becker, Kleinbohl, Baus, & Holzl, 2011). These findings are in accordance with the observation of distinct symptom complexes within the group of medically unexplained conditions (study VI).

In conclusion, it has become clear that the phenomenon of medically unexplained conditions is far too complex to be reduced to a one versus many question. It is possible that both high levels of past or current psychosocial stress and subsequent alterations in stress-responsive systems, and somatosensory amplification constitute endophenotypes that are shared by all medically unexplained conditions (i.e., MUS, different FSS, or somatoform/somatic symptom disorders). If this holds true, the complexes surrounding the core symptoms of fatigue, pain, gastrointestinal problems, or cardio-respiratory difficulties would need to be understood as additional endophenotypes that develop as a consequence of yet to be identified circumstances.

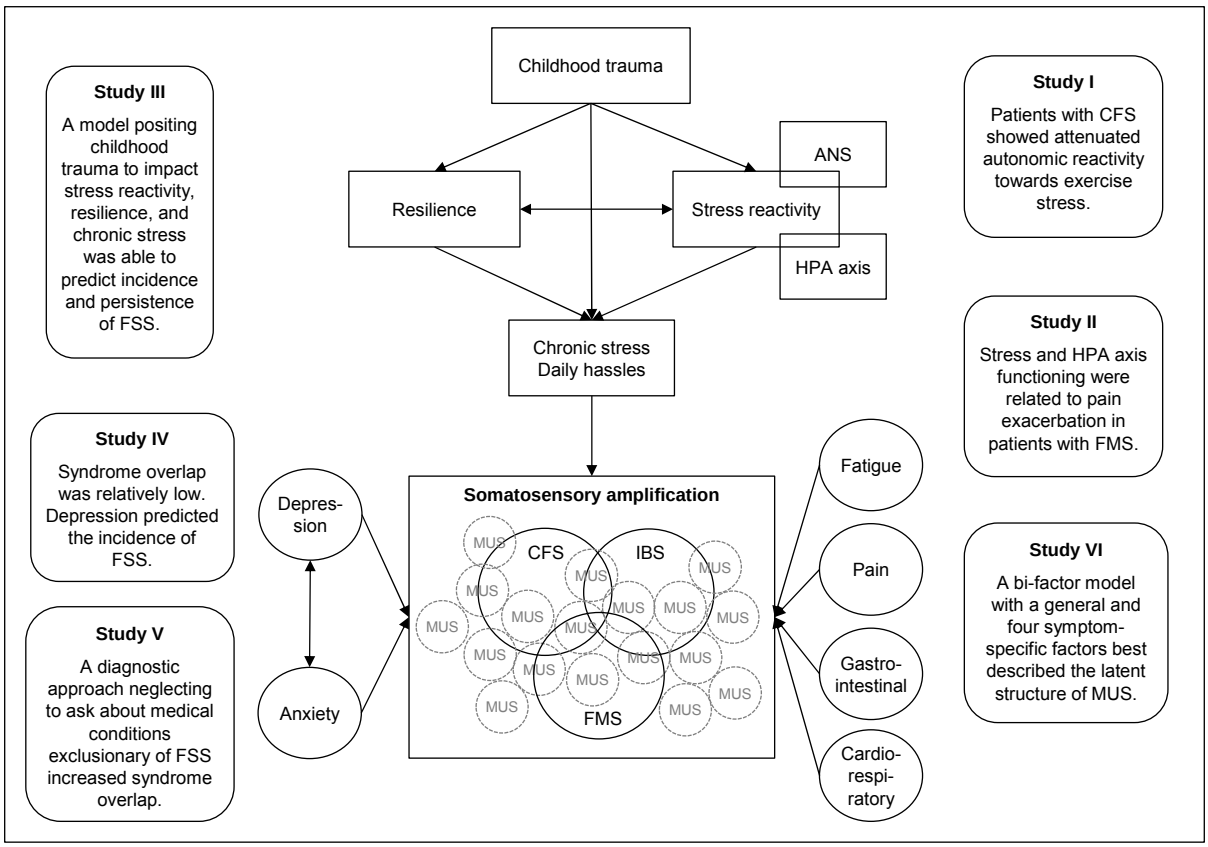

Figure 3 A model positing that individuals who go on to develop a medically unexplained condition (i.e., medically unexplained symptoms, MUS, chronic fatigue syndrome, CFS, fibromyalgia syndrome, FMS, or irritable bowel syndrome, IBS) are characterised by childhood trauma and subsequent alterations in the stress reactivity of the autonomic nervous system (ANS) and hypothalamic-pituitary-adrenal (HPA) axis. Based on this predisposition, chronic stress and daily hassles precipitate and perpetuate these conditions via allostatic load and somatosensory amplification. The four symptom complexes are phenomenological variants of this process that develop as a consequences of yet to be identified circumstances.

4.3 Nosological implications

The findings of the present thesis have two nosological implications. First, the fact that stress and somatosensory amplification are potentially relevant to the aetiopathogenesis of medically unexplained conditions suggests that they are best classified within the realm of mental disorders. Not only would such an approach encourage research to look into other potential commonalities in these patients, but it would help patients to receive adequate treatment. There is increasing evidence that cognitive-behavioural therapy is effective in the treatment of symptoms when techniques to manage stress and deal with somatic sensations are included (e.g., Allen, Woolfolk, Escobar, Gara, & Hamer, 2006; White et al., 2011). Unfortunately, with the ICD-10, clinicians may choose whether to classify a medically unexplained condition as a mental disorder or, for instance, as a disease of the nervous, musculoskeletal, or digestive system. This dualistic approach clouds rather than clarifies the issues at hand by segregating research into completely separate domains (psychiatry/clinical psychology vs. other medical specialities). It is equally doubtful that the treatment of these already complex conditions will be helped by this.

Second, the fact that distinct symptom complexes can be identified among patients with medically unexplained conditions speaks for a classificatory category that acknowledges these phenomenological variants. Defining subcategories within a general category of medically unexplained conditions may be one way to achieve this. These would reflect predominant symptoms (e.g., fatigue, pain, or gastrointestinal problems) and allow for research to investigate differential mechanisms across these variants while still allowing patients to receive adequate treatment. Unfortunately, the recent developments regarding the DSM are in complete disagreement with this idea. As outlined in the introduction, the new category of somatic symptom disorders has abolished its former subcategories and now even includes medically explained conditions such as multiple sclerosis, rheumatoid arthritis, and Crohn's disease (*if* certain psychological characteristics are present). It is evident that any effort to identify differential aetiopathogenetic features of the identified symptom complexes is impossible when adhering to this new categorisation.

Lest the nosological complexity of FSS is to give way to chaos, it is hoped that ICD-11 will avoid following the DSM approach of turning the somatoform disorder category into an amorphous conglomerate of different conditions. A glance at the beta draft that is available online (http://apps.who.int/classifications/icd11/browse/l-m/en) reveals that, although the general dualistic

approach of ICD-10 (see above) is maintained, the current proposal does seem to be more in line with recent research, including the studies that form this thesis. According to the website, the committee has so far settled on the term “bodily distress disorder”. The thus labelled category is composed of three subcategories indicating the degree of severity of the condition (mild, moderate, and severe). This is affirmative of the notion that there seems to be a minority of patients with several concomitant FSS. On the other hand, although fatigue, pain, gastrointestinal symptoms, and respiratory symptoms are listed as the most common symptoms, as yet, there is no explicit mention of different symptoms complexes, even though phenomenological research has found evidence for their existence.

4.4 Conclusion

The current nosology of FSS has created significant confusion by providing multiple options to label and categorise these conditions. This is due to the fact that the conceptualisation of FSS is still subject to debate (one vs. many). The aim of this thesis was to recognise similarities and differences of FSS by a) elucidating specific aspects of their aetiopathogenesis, and b) disclosing their phenomenology in greater detail. Stress was shown to be involved in the predisposition, precipitation, and perpetuation of FSS in different samples of patients. Despite this commonality, syndrome overlap was rather low when the approach to case identification excluded clear-cut medical explanations for somatic symptoms. This apparent discrepancy was reflected by the fact that symptoms pertaining to FSS could best be explained by a general and four symptom-specific factors. Based on the findings of this thesis, the greatest confidence may have to be placed in stating that FSS appear to be one *and* many.

Nosology shapes the way in which we perceive illness. Future attempts at classifying medically unexplained conditions should acknowledge both common and symptom-specific factors in order to foster prolific research. One of the greatest challenges to be faced will be the unravelling of mechanisms behind the four identified symptom-specific factors. Longitudinal studies following up on individuals who have been exposed to early life or chronic stressors will be crucial to answer the question of which factors determine outcome variability. Another promising approach is to compare pathophysiological features across patients with either fatigue, pain, gastrointestinal, or cardio-respiratory symptoms in the laboratory, which would help to foster our understanding of differential factors that are at work in these variants.

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6. Appendix

6.1 Empirical studies

Study I

Strahler, J.*, **Fischer, S.***, Nater, U.M., Ehlert, U. & Gaab, J. (2013). Norepinephrine and epinephrine responses to physiological and pharmacological stimulation in chronic fatigue syndrome. *Biological Psychology, 94*(1), 160-166.

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Norepinephrine and epinephrine responses to physiological and pharmacological stimulation in chronic fatigue syndrome

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ABSTRACT

Chronic fatigue syndrome (CFS) is characterized by fatigue lasting 6 months or longer. CFS has been associated with a disturbed (re-)activity of the autonomic nervous system. However, the sympathetic adrenomedulla (SAM) remains under-examined in CFS. To investigate SAM reactivity, we implemented a submaximal cycle ergometry (ERGO) and a pharmacological test (Insulin Tolerance Test, ITT) in 21 CFS patients and 20 age-, sex-, and BMI-matched controls. Plasma norepinephrine and epinephrine were collected once before and twice after the tests (+10/+20, and +30 min). Lower baseline levels and attenuated responses of epinephrine to the ERGO were found in CFS patients compared to controls, while the groups did not differ in their responses to the ITT. To conclude, we found evidence of altered sympathetic-neural and SAM reactivity in CFS. Exercise stress revealed a subtle catecholaminergic hyporeactivity in CFS patients. It is conceivable that inadequate catecholaminergic responses to physical exertion might contribute to CFS symptoms.

1. Introduction

Chronic fatigue syndrome (CFS) refers to fatigue of more than 6 months duration that cannot be sufficiently explained by any medical or psychiatric condition. According to the Centers for Disease Control and Prevention (CDC) 1994 diagnostic criteria, a number of ancillary symptoms, such as myalgia, memory and concentration problems, and postexertional malaise need to be fulfilled for a diagnosis of CFS (Fukuda et al., 1994). The diagnosis of CFS requires a complete clinical evaluation to exclude any medical or psychiatric cause of symptoms. Prevalence rates range from 0.2% to 2.5% in the general population, with women being more frequently affected than men (Reeves et al., 2007; Reyes et al., 2003). CFS provokes substantial suffering and impairment in patients (Lowry & Pakenham, 2008), leading to a considerable amount of direct (e.g., medical care) and indirect (e.g., lost productivity) costs for society (Lin et al., 2011).

Elucidating pathophysiological mechanisms in any illness is important in identifying targets for treatment. Given the heterogeneity and complexity of CFS, the identification of underlying psychological and physiological mechanisms is still subject to extensive research. A prominent line of research has been dedicated to the role of stress as an etiological and perpetuating factor in CFS (Nater, Fischer, & Ehlert, 2011). On a physiological level, stressors might result in a deregulation of stress-responsive systems, such as the hypothalamic–pituitary–adrenal axis (HPA), the autonomic nervous system (ANS), and the immune system (Danese, Pariante, Caspi, Taylor, & Poulton, 2007; Evans & English, 2002; Heim et al., 2000). It has been suggested that this deregulation contributes to core symptoms of CFS, such as pain and fatigue (Fries, Hesse, Hellhammer, & Hellhammer, 2005; Irwin, 2011; Rief & Barsky, 2005). In accordance with these propositions, symptoms of CFS are exacerbated by psychological (e.g., life events; Lutgendorf et al., 1995) and physiological stress (e.g., exercise; Jammes, Steinberg, Mambrini, Bregeon, & Delliaux, 2005), possibly resulting in postexertional malaise and avoidance behavior often found in these patients (Nater et al., 2006; VanNess, Stevens, Bateman, Stiles, & Snell, 2010).

Due to the observation that conditions characterized by a dysfunctional ANS, such as neurally mediated hypotension or postural orthostatic tachycardia, share prominent clinical features with CFS (e.g., Rowe, Bou-Holaigah, Kan, & Calkins, 1995), several studies have investigated autonomic abnormalities in patients suffering from CFS, yielding inconsistent results (Nater, Heim, & Raison, 2012). Most of this research focused either on the sympathetic neural or the parasympathetic branch of the ANS using indirect measures of autonomic activity such as heart rate or heart rate

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variability. However, power spectrum analysis of heart rate variability as a measure of sympathetic activity is still considered equivocal in terms of the relative contributions of the sympathetic and parasympathetic nervous system (Task Force, 1996). Only few studies have been dedicated to the examination of the sympatho-adrenomedullary (SAM) part of the ANS (Boneva et al., 2007; De Lorenzo, Hargreaves, & Kakkar, 1997; Ottenweller, Sisto, McCarty, & Natelson, 2001; Streeten, Thomas, & Bell, 2000; Timmers et al., 2002), focusing on the release of the catecholamines epinephrine (E), and – to a lower extent (Goldstein, McCarthy, Polinsky, & Kopin, 1983) – norepinephrine (NE) from chromaffin cells in the adrenal medulla. This is somewhat surprising, since catecholamines are the main effectors of the sympathetic nervous system and the SAM system in particular and are therefore intimately related to stress-related pathophysiology (Kvetnansky, Sabban, & Palkovits, 2009). Studies merely assessing baseline levels of catecholamines reported no differences between adult CFS patients and controls (Boneva et al., 2007; De Lorenzo et al., 1997). However, subtle differences in catecholaminergic activity as well as the role of feedback mechanisms might only be revealed during challenges. Three studies employed physiological challenges with adult CFS patients (Ottenweller et al., 2001; Streeten et al., 2000; Timmers et al., 2002), of which two tested the effects of orthostatic stress. Unfortunately, these tests are limited in their ability to elicit both NE and E responses concomitantly (Robertson et al., 1979).

Exercise, on the other hand, increases both sympathetic neural and adrenomedullary activity. In addition, this test bears the advantage of being a critical real-life stressor in CFS and might possibly be related to post-exertional malaise and avoidance behavior in these patients (Jammes et al., 2005; VanNess et al., 2010). A number of studies have used an exercise protocol to test physiological capacity und cardiac function in CFS in the laboratory, yielding inconsistent findings (Gibson, Carroll, Clague, & Edwards, 1993; Montague, Marrie, Klassen, Bewick, & Horacek, 1989; Riley, O'Brien, McCluskey, Bell, & Nicholls, 1990; Sisto et al., 1996; Wallman, Morton, Goodman, & Grove, 2004). However, exercise testing does not only allow for the assessment of physiological capacity but can also be used as a psycho-physiological stressor. This is due to the fact that exercise testing provokes intraindividual processes that might impact motivation and effort (Silver et al., 2002). There is only one published CFS study using (treadmill) exercise as a stressor to challenge the release of catecholamines, showing lower responses of E in CFS compared to healthy controls (Ottenweller et al., 2001). Nothing is known about catecholaminergic responses toward other exercise protocols, such as the frequently used cycle ergometry test (ERGO), in CFS patients.

A far more common approach to study endocrine stress responses involves the use of highly standardized pharmacological protocols. In contrast to exercise testing, these protocols offer an opportunity to minimize the effects of intraindividual processes. A frequently used pharmacological stressor to study the integrity of (hypoglycemia-responsive) endocrine systems in CFS is the Insulin-Tolerance-Test (ITT). The intravenous injection of insulin results in a marked hypoglycemia that provokes a counterregulatory response on the hypothalamic, pituitary and adrenal level, thus constituting a robust stimulus of adrenomedullary catecholamine release (Goldstein, 2010; Pacak, Baffi, Kvetnansky, Goldstein, & Palkovits, 1998). This test has previously been implemented in the study of endocrine dysfunction in CFS, eliciting normal or diminished HPA axis responses in these patients (Bearn et al., 1995; Gaab et al., 2004). Of note, this stimulus does not rely on cognitive-evaluative or affective processes to elicit an adaptive response and is therefore recommended in the study of adrenomedullary function. Currently, nothing is known about the ITT- or hypoglycemia-induced release of NE and E from the adrenal medulla in CFS.

In sum, deregulated stress–responsive systems seem to play a major role in the development and perpetuation of CFS. While there is evidence for a deregulation of the ANS in a subgroup of CFS patients little is known about a possible stress-related deregulation of catecholamines as direct effectors of the sympathetic-neural and SAM system. Moreover, previously used autonomic stress protocols did not show adequate relevance regarding CFS symptomatology.

The aims of this study are therefore to assess the responses of NE and E (outcome variables) to both the ERGO and ITT in male and female CFS patients compared to healthy controls (predictor variables). Employing these two tests will allow us to disentangle different aspects of stress-induced adaptive responses underlying a potentially deregulated stress reactivity in CFS, i.e., its physiological component (as elicited by the ITT) and intraindividual factors, such as cognitive-evaluative and affective processes. Based on the evidence mentioned above, we expect a relative hyporeactivity of both NE and E in CFS patients to the ERGO and the ITT. Due to cognitive-evaluative processes and the subsequent affective response to exercise, we expect that hyporeactivity is even more pronounced in the ERGO condition. In addition, investigating both men and women will enable us to explore sex-related differences in physiological alterations possibly underlying higher CFS prevalence rates in women.

2. Methods

2.1. Subjects

A total of 41 subjects participated in this study. Patients were contacted through a German self-help organization. Interested patients received a postal screening questionnaire, containing all symptoms required by the CDC 1994 definition (Fukuda et al., 1994). Patients fulfilling the symptom requirements in this screening questionnaire were interviewed over the phone and asked for diagnosed medical illnesses and psychiatric disorders. Interested patients were only excluded from participating in the study if they had received a medical or psychiatric diagnosis defined as exclusionary by the CDC 1994 definition (Fukuda et al., 1994). Further selection criteria were acute onset of CFS, between 30 and 50 years of age, no current antidepressive, anxiolytic, antibiotic, antihypertensive, or steroid medication and no medical or psychiatric cause for chronic fatigue using routine laboratory testing and psychiatric interviews. Thus, ten men and 13 women were selected from a cohort of 86 subjects with chronic fatigue syndrome willing to participate in the study. Patients were admitted to the research unit of a general hospital for the duration of one week. All patients were medically examined according to CDC recommendations (Fukuda et al., 1994), and interviewed by a trained psychologist (J.G.) using a computer-aided standardized diagnostic interview (Wittchen & Pfister, 1997) and a semi-structured CFS interview. Two female patients were excluded from the study due to hormone levels indicative of thyroid hypofunction and primary adrenal insufficiency, diagnosed by a blunted cortisol response to Synacthen (Ciba, Wehr, Germany). Patients were matched for age and sex with a total of 20 healthy volunteer controls. Controls were medication-free and underwent comprehensive medical examination for past and current health problems. All subjects provided written informed consent before participation in the study and ethical committee approval for the study was obtained. The study was conducted in accordance with the Declaration of Helsinki. Not all CFS patients underwent both tests; three female patients were unwilling to participate in the ITT, resulting in a sample of 18 patients undergoing the ITT test. Further, not all control subjects were included in both tests; seven controls (three men and four women) did not undergo the ITT. Therefore, four new control subjects (two men and two women) were recruited for this test, resulting in a sample of 17 control subjects participated in the ITT. The newly recruited control subjects did not differ in demographic variables and underwent the same screening and test procedures as the other control subjects while only undergoing the ITT. Patients and controls were not compensated for participating.

2.2. Test protocols

Each subject participated in two laboratory sessions. All subjects arrived 60 min before each test. They were taken into a separate room and an intravenous catheter was inserted and kept patent with a heparin lock. All subjects had to rest for at least 45 min. A baseline blood sample was collected immediately before the respective test began. After the incremental ERGO, starting at 1400 h, all subjects were taken back into their room for further sampling. Subjects who agreed to participate in the ITT reported to the laboratory 48 h after the ERGO. The ITT started at 0945 h. Blood samples for determination of NE and E responses were taken 10 and 30 min (ERGO) and 20 and 30 min (ITT) after the respective test.

2.3. Incremental cycle ergometry test (ERGO)

To test the integrity of catecholaminergic systems during a physiological challenge, a standard cycle ergometry test was used. Notably, the ERGO primarily elicits noradrenergic responses (Dimsdale & Moss, 1980; Robertson et al., 1979). On the day of the ERGO, participants were asked to abstain from caffeine, alcohol, and nicotine. The ERGO started at 50 W for men and 30 W for women, respectively, with 40 W increments every 3 min until the subject was no longer able to continue or until predicted maximum heart rate (85% of 220 bpm – subjects' age). Patients were not verbally encouraged during the test and their heart rate was continuously monitored throughout the test. Subjects were asked to rate perceived exertion using the Borg scale (Borg, 1982).

2.4. Insulin Tolerance Test

The ITT is a standardized pharmacological stressor assessing the integrity of the adrenal hormonal system, thus primarily constituting a potent adrenergic stimulus (Goldstein et al., 1983). Subjects were asked to fast overnight and abstain from caffeine, alcohol, and nicotine. After a 45-min resting period, a baseline sample was taken to measure catecholamines, and an intravenous bolus injection of 0.15 U/kg soluble insulin (H-Insulin, Hoechst, Frankfurt, Germany) was given. Subjects were told that they could request intravenous glucose infusion or oral glucose to reduce symptoms of hypoglycemia. None of the tested subjects received any glucose during the ITT.

2.5. Biochemical analyses

EDTA-treated blood samples were spun immediately at 4 °C and stored at −20 °C until assayed. Plasma samples were analyzed for NE and E by high-pressure liquid chromatography (detection limit: 0–25 pg/ml) at the Laboratory for Stress Monitoring (Goettingen, Germany).

2.6. Heart rate

Heart rate (HR) was determined every 3 min during the incremental ERGO with a heart rate monitor (Sport Tester Profi, Polar Instruments, Gross-Gerau, Germany). Peak HR was defined as the maximal HR achieved during the ERGO session. In the results section, only peak HR will be reported since cardiovascular measures were not the main focus of this report.

2.7. Statistical analysis

Chi square analysis was used to test significant differences in categorical variables; continuous variables were analyzed with ANOVAs. ANOVAs for repeated measures were computed to analyze catecholaminergic responses in the tests. Univariate ANOVAs were utilized to compare increases in catecholamines between groups. Data were tested for normal distribution and homogeneity of variance using Kolmogorov–Smirnov and Levene's test. All reported results were corrected by Greenhouse–Geisser procedure when assumptions of sphericity were violated. Catecholaminergic increases elicited by the stressors were calculated by subtraction of the baseline measurement time point from the respective peak value (10 vs. 30 min). The optimal total sample size of $N = 40$ to detect an expected effect size of 0.35 with a power ≥ 0.90 and $\alpha = 0.05$ was calculated a priori with the statistical software G-Power (Buchner, Faul, & Erdfelder, 1997). For all analyses, significance level was $\alpha = 0.05$. Unless indicated, all results are presented as mean ± standard deviation (SD).

3. Results

3.1. Patients and controls characteristics

Sex ratio as well as mean age did not differ significantly between groups while there was a trend toward a higher body mass index (BMI) in controls (Table 1). Sixteen CFS patients reported an infectious onset of their symptoms. All patients reported an acute onset of their CFS symptoms. Mean duration of symptoms in patients was 63.1 ± 41.5 months, with a range from 17 to 168 months. All patients were drug free for a minimum of one month, while four female subjects in each group used monophasic oral contraceptives. One patient fulfilled criteria for a current episode of major depression. Since the exclusion of these subjects did not alter results, they were included into the following analyses. Seven patients reported a past history of major depression and four reported a past history of anxiety disorder. None of the controls reported any current or lifetime psychiatric disorder.

3.2. Incremental cycle ergometry test (ERGO)

Results of all variables related to the ERGO are reported by sex in Table 1. Groups differed in exercise duration (CFS 10.36 ± 3.66 min vs. controls 12.47 ± 2.75 min; $p = 0.014$) and maximal workload (CFS 171.91 ± 55.46 W vs. controls 199.00 ± 43.76 W; $p = 0.024$), but not regarding peak heart rate (CFS 163.57 ± 17.67 bpm vs. controls 166.75 ± 13.01 bpm; $p = 0.592$) and maximal perceived exertion (Borg scale: CFS 18.00 ± 1.87 vs. controls 18.10 ± 1.17; $p = 0.968$). Men exhibited significantly higher overall levels in all parameters related to the ERGO (all $p < 0.017$), except in peak heart rate ($p = 0.123$). However, no significant group by sex interaction effects emerged (all $p > 0.412$).

Before the ERGO, baseline levels of E were lower in CFS patients ($F(1/36) = 7.01$, $p = 0.012$, $\eta^2 = 0.163$) while there was no difference with regard to baseline levels of NE ($F(1/36) = 0.41$, $p = 0.526$, $\eta^2 = 0.011$). There were non-significant lower baseline E values in women ($F(1/36) = 3.48$, $p = 0.070$). No other effects were significant (all $p > 0.20$). The ERGO protocol induced significant catecholaminergic responses (NE: $F(1.109/41.037) = 202.89$, $p < 0.001$, $\eta^2 = 0.846$; E: $F(1.143/42.283) = 77.46$, $p < 0.001$, $\eta^2 = 0.677$). Since we found differences in exercise duration and maximal workload and a trend toward a difference in BMI, these variables were included as covariates in the following ANOVAs. Baseline levels of E were included as a further covariate into the ANOVAs regarding E.

Patients with CFS showed significantly dampened response profiles to the exercise test with regard to E ($F(1.149/37.931) = 4.85$,

Table 1
Demographic characteristics and cycle ergometry variables.

	Chronic fatigue syndrome ($N = 21$)	Controls ($N = 20$)	Statistics
Females (N [%])	11 (52.4%)	9 (45.0%)	$\chi^2 = 0.22$, $p = 0.636$
Age (years)	36.0 ± 4.6 (range: 29–47)	35.7 ± 4.8 (range: 29–44)	$T = -0.24$, $p = 0.813$
Body mass index (kg/m^2)	22.4 ± 6.8 (range: 17.6–26.3)	24.7 ± 4.7 (range: 18.2–34.6)	$T = 1.95$, $p = 0.058$
Exercise duration (min)	♀ 7.9 ± 2.5 ♂ 13.0 ± 2.8	♀ 10.0 ± 1.6 ♂ 14.5 ± 1.7	$F_{group}(1/37) = 6.60$, $p = 0.014$, $\eta^2 = 0.151$ $F_{sex}(1/37) = 47.82$, $p < 0.001$, $\eta^2 = 0.564$ $F_{group \times sex}(1/37) = 0.27$, $p = 0.609$, $\eta^2 = 0.007$
Maximal workload (W)	♀ 130.0 ± 34.6 ♂ 218.0 ± 31.6	♀ 158.9 ± 26.7 ♂ 231.8 ± 20.9	$F_{group}(1/37) = 5.54$, $p = 0.024$, $\eta^2 = 0.130$ $F_{sex}(1/37) = 78.64$, $p < 0.001$, $\eta^2 = 0.680$ $F_{group \times sex}(1/37) = 0.69$, $p = 0.412$, $\eta^2 = 0.018$
Peak heart rate (bpm)	♀ 159.7 ± 20.5 ♂ 167.8 ± 13.7	♀ 162.8 ± 13.5 ♂ 170.0 ± 12.3	$F_{group}(1/37) = 0.29$, $p = 0.592$, $\eta^2 = 0.008$ $F_{sex}(1/37) = 2.49$, $p = 0.123$, $\eta^2 = 0.063$ $F_{group \times sex}(1/37) = 0.01$, $p = 0.931$, $\eta^2 = 0.000$
BORG (6–20)	♀ 17.4 ± 2.1 ♂ 18.7 ± 1.4	♀ 17.6 ± 0.9 ♂ 18.5 ± 1.2	$F_{group}(1/37) = 0.002$, $p = 0.968$, $\eta^2 = 0.000$ $F_{sex}(1/37) = 6.25$, $p = 0.017$, $\eta^2 = 0.144$ $F_{group \times sex}(1/37) = 0.14$, $p = 0.712$, $\eta^2 = 0.004$

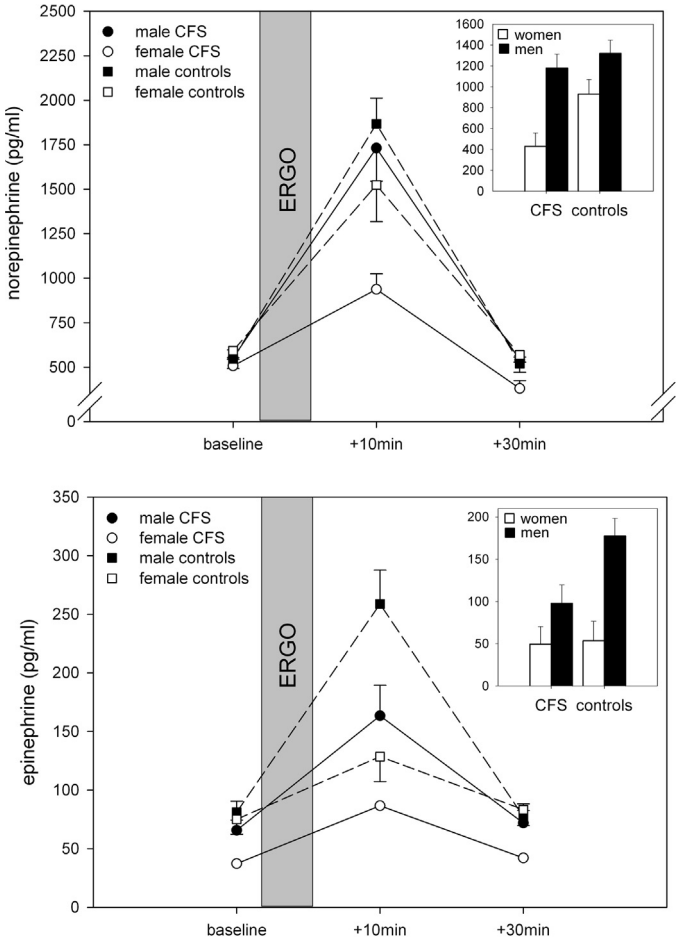

Fig. 1. Catecholamine levels and mean catecholaminergic response during the ERGO with regard to group and sex (mean ± standard error of mean).

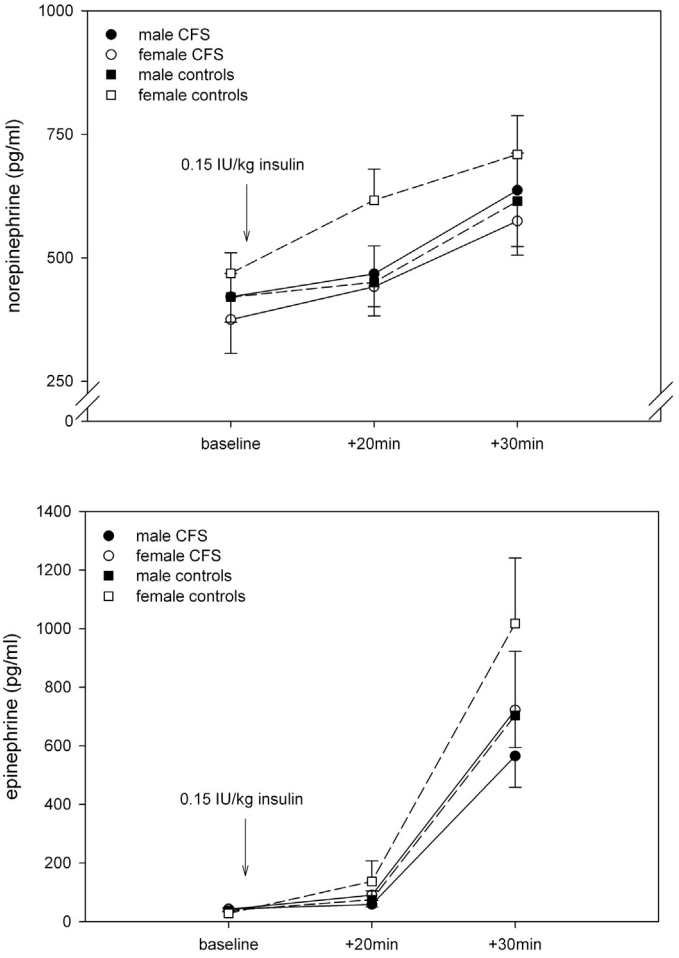

Fig. 2. Catecholamine levels during the ITT with regard to group and sex (mean ± standard error of mean).

$p = 0.029$, $\eta^2 = 0.128$), but not to NE ($F(1.106/37.603) = 2.63$, $p = 0.110$, $\eta^2 = 0.072$) (Fig. 1). A time by sex effect was evident for E ($F(1.149/37.931) = 10.62$, $p = 0.002$, $\eta^2 = 0.243$) as well as a trend toward a significant time by group by sex interaction ($F(1.149/37.931) = 3.24$, $p = 0.075$, $\eta^2 = 0.089$), with no differences between females and less pronounced response profiles in male CFS patients compared to male controls. No time by sex or time by group by sex interaction was shown with regard to NE response profiles (all $p > 0.183$). Both individuals with CFS and healthy controls returned to baseline levels of NE and E within 30 min after the ERGO.

Mean increases of catecholaminergic responses were calculated to examine differences in the magnitude of stress reactivity between groups. Individuals belonging to the CFS group showed lower increases of E ($F(1/33) = 4.56$, $p = 0.040$, $\eta^2 = 0.121$), but not of NE ($F(1/34) = 3.27$, $p = 0.079$, $\eta^2 = 0.088$) compared to healthy controls. Higher mean increases of E were observed in men ($F(1/33) = 9.90$, $p = 0.003$, $\eta^2 = 0.231$) although no group by sex interaction was found ($F(1/33) = 2.35$, $p = 0.135$, $\eta^2 = 0.066$). Regarding NE, no effect of sex or group by sex interaction could be observed (all $p > 0.119$).

3.3. Insulin Tolerance Test

Since we found a trend toward a difference in BMI, this variable was included as a covariate in the following ANOVAs. Prior to the ITT, no group difference in baseline levels of E and NE was evident (E: $F(1/31) = 2.18$, $p = 0.150$, $\eta^2 = 0.066$; NE: $F(1/31) = 0.18$, $p = 0.671$, $\eta^2 = 0.006$). The ITT protocol induced significant changes over time for both analytes (E: $F(1.046/31.375) = 69.56$, $p < 0.001$, $\eta^2 = 0.699$; NE: $F(2/60) = 41.36$, $p < 0.001$, $\eta^2 = 0.580$). Catecholaminergic response profiles to the ITT did not differ between groups (E: $F(1.046/30.322) = 1.68$, $p = 0.206$, $\eta^2 = 0.055$; NE: $F(2/58) = 0.32$, $p = 0.727$, $\eta^2 = 0.011$; see Fig. 2) and no time by sex effects and no triple interaction effects were evident (all $p > 0.239$). Thus, no further analyses were conducted comparing stress reactivity scores between groups.

4. Discussion

To address a possible stress-related deregulation of the sympathetic-neural and SAM system in CFS, we compared catecholaminergic response in CFS patients and healthy controls during a physiological (ERGO) and a pharmacological (ITT) stress test. Both stressors induced increased catecholaminergic activity. During the ERGO, a relative hyporeactivity emerged in CFS patients with regard to E, but not with regard to NE. However, both groups returned to baseline levels of NE and E within 30 min. This indicates that CFS patients are capable of establishing a counterregulatory response to physical exertion, albeit to a lower degree. When exploring possible disparities between men and women, female CFS patients showed non-significantly lower baseline values of E during the ERGO but exhibited similar reactivity profiles compared to female controls. On the other hand, male CFS patients' resting levels were comparable to those of healthy controls, while their exercise-induced E levels were blunted. In contrast to the ERGO, groups did not differ

in their catecholaminergic responses to the ITT. Thus, a relatively normal catecholaminergic secretion could be observed to a standardized pharmacological stimulus. No effect of sex was found in response to this stimulus.

Exercise testing constitutes an ecologically valid stressor in CFS and has so far primarily been used to test physiological capacity and cardiac functioning in these patients. Peak HR has often been included as a dependent variable in these studies, showing attenuated (Gibson et al., 1993; Montague et al., 1989; Sisto et al., 1996; Wallman et al., 2004) or normal (Bazelmans, Bleijenberg, Van Der Meer, & Folgering, 2001; Riley et al., 1990) levels in individuals with CFS. These findings are only partially in accordance with our finding of equal peak HR values between groups. Unfortunately, comparability between studies is severely limited by differing exercise protocols (e.g., cycle ergometery vs. treadmill, submaximal vs. maximal performance testing) and prevents us from drawing conclusions at this time.

This is the first study to assess the catecholaminergic response to a cycle ergometry test in CFS. Our finding of a relative hyporeactivity of E to the ERGO in CFS patients is in line with findings from another study using a treadmill exercise test to examine catecholamines in women with CFS (Ottenweller et al., 2001). Notably, differences in temporal dynamics of NE and E might account for these results. Importantly, in our study, response profiles were attenuated in male CFS patients compared to male controls, while females did not differ. As mentioned above, this difference might be attributed to the differing stress protocols. Moreover, our subjects performed a submaximal test in a sitting posture instead of a maximal exercise test in upright posture, as opposed to the study by Ottenweller et al. (2001), thus enhancing comparability between CFS and healthy control subjects by controlling for the effects of orthostasis and physiological deconditioning. Our finding of a relative catecholaminergic hyporeactivity is not in accordance with other studies implementing protocols testing the effects of orthostatic stress inducing catecholaminergic stress responses in patients with CFS and controls. In contrast to our findings, these tests elicited comparable (Timmers et al., 2002) and excessive catecholaminergic responses (Streeten et al., 2000) in CFS patients. This might be explained by the different physiological processes involved in orthostatic and exercise stress, respectively (blood volume shift vs. energy mobilization), and their ability to stimulate catecholamine release (Goldstein, 1981).

Catecholaminergic responses to the ITT have not been reported in CFS so far. The lack of a difference between CFS patients and controls in responses of NE and E is, however, in line with studies investigating responses of other adrenal hormones (i.e., cortisol) to this stressor (Bearn et al., 1995; Gaab et al., 2004). Therefore, when contrasting both stressors, our results do not support a general dysfunction of the adrenomedullary hormonal system in CFS. Instead, our finding of differential response profiles during the ERGO compared to the ITT points to the role of specific intraindividual processes in patients with CFS regarding physical exertion. Interestingly, psychological stress seems to primarily elicit adrenomedullary responses while physiological stressors favor the release of NE from sympathetic nerve endings (Dimsdale & Moss, 1980). However, since our assessment did not include measures directly addressing both of these putative aspects of the ERGO, this remains purely speculative.

Our result of similar peak HR values in CFS patients and healthy controls despite attenuated stress levels of circulating catecholamines might point to compensatory changes in beta-adrenergic receptor function at the cardiac level. Interestingly, recent research on exercise induced gene expression patterns found elevated amounts of alpha- and beta-adrenergic receptors in peripheral blood mononuclear cells in CFS patients compared to controls (Light, White, Hughen, & Light, 2009; White, Light, Hughen, Vanhaitsma, & Light, 2012), which can be considered reflective of changes in other tissues such as the heart (Mills & Dimsdale, 1993). However, this was not evident during resting conditions (Light et al., 2012; White et al., 2012). This indicates that, during acute stress, lower levels of circulating catecholamines might bind to more sensitive adrenergic receptors resulting in unchanged autonomic reactivity on the cardiac level. Again, this assumption needs to be verified in future studies.

One possibility of how a relative hyporeactivity of catecholamines might be linked to symptoms of CFS is via the immune system. Adrenergic receptors are expressed on various immune cells and organs enabling circulating catecholamines to exert their immunomodulatory effects (Elenkov, Wilder, Chrousos, & Vizi, 2000). During acute stress (e.g., exercise), NE and E favor a shift from a Th1 to a Th2 mediated immune response (Elenkov et al., 2000). It is therefore conceivable that deficiencies in reaching a sufficient catecholaminergic response to re-occurring acute stressors may enhance inflammation, ultimately leading to symptoms of pain and fatigue (Irwin, 2011). When examining the exact mechanisms underlying the interaction between catecholamines and inflammatory processes, the sensitivity of immune cells needs to be taken into account. In a previous study, the capacity of a beta2-adrenergic agonist to inhibit the production of tumor necrosis factor-alpha and to enhance the release of the anti-inflammatory cytokine interleukin-10 was reduced in adolescents suffering from CFS during baseline conditions (Kavelaars, Kuis, Knook, Sinnema, & Heijnen, 2000). Thus, in addition to lower circulating levels of catecholamines, adrenergic receptors on immune cells seem to be less responsive to these signals. However, no study so far has examined the effect of acute stress on the sensitivity of immune cells to adrenergic signaling in CFS. The exact mechanisms that translate acute stress into fatigue are largely unknown and clearly warrant further research.

In our study, limited evidence was found for sex-specific physiological alterations in CFS. Male patients suffering from CFS demonstrated attenuated response profiles of E to the ERGO compared to their female counterparts. However, the lack of significant differences in females could be due to a floor effect. All other analyses failed to show any significant group by sex interaction. To the best of our knowledge, this is the first study examining sex-specific alterations in catecholamines in CFS. Our finding of comparable response profiles in women in both groups on the one hand and attenuated response profiles of E in male CFS patients compared to male controls on the other hand does not explain epidemiological reports of higher CFS prevalence rates in women (Reeves et al., 2007; Reyes et al., 2003). Future studies with larger samples are needed to investigate sex-specific mechanisms in CFS.

This study had several limitations. First, generalization of our results is limited by the fact that we recruited individuals with CFS via self-help organizations, as opposed to identifying representative cases from the general population. Second, as mentioned above, the small sample size does not allow us to draw definite conclusions on sex as a moderator of the catecholaminergic stress response in CFS. Furthermore, it prevented us from determining whether only a subgroup of patients might be affected by catecholaminergic deregulation. Third, we did not assess levels of physical fitness in our sample. Thus, possible differences in physiological capacity might have contributed to the differential catecholaminergic responses observed. By implementing a submaximal as opposed to a maximal exercise protocol, we did however account for these confounding effects to some extent. Also, no information on hormonal status (i.e., menstrual cycle phase, menopause) was available, except for the use of oral contraceptives. However, women using hormonal contraceptives were equally distributed among groups, thus minimizing a possible impact on our findings. Fourth, our limited number of measurement

time points after the ITT prevents us from detecting possible group differences during the recovery period. Fifth, we are not able to determine whether our result of a relative hyporeactivity is due to a diminished release of catecholamines into the circulation or whether metabolism and clearance rate is accelerated. Finally, intraindividual (cognitive-evaluative and affective) processes were not directly measured in this study while clearly deserving more attention.

In sum, our results do not support the notion of altered catecholaminergic reactivity in CFS. Using a highly potent pharmacological stressor of the adrenomedullary system (i.e., the ITT), no differences were apparent between healthy controls and individuals suffering from CFS, indicating the lack of a stress-related endocrine disturbance in this disorder. In contrast, exercise seems to be a highly relevant and potent stressor in CFS, leading to subtle catecholaminergic deregulation in these patients. It is conceivable that inadequate catecholaminergic responses induced by physical exertion might contribute to symptoms (e.g., post-exertional malaise) in CFS patients. Replication of our findings in larger samples is required, especially in shedding light on possible sex-specific physiological alterations in CFS. Further, research on stressor-specific effects (e.g., physical activity vs. psychosocial stress) in the different branches of the ANS in CFS is warranted to examine cognitive and affective contributions to deregulated stress responses.

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Study II

Fischer, S., Doerr, J. M., Strahler, J., Mewes, R., Thieme, K. & Nater, U.M. (ready to be submitted). Stress exacerbates pain in the everyday lives of women with fibromyalgia – the role of cortisol and alpha-amylase.

Stress exacerbates pain in the everyday lives of women with fibromyalgia syndrome – the role of cortisol and alpha-amylase

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Abstract

Objective

Although fibromyalgia syndrome (FMS) is a chronic condition, its cardinal symptom pain is known to fluctuate over the day. Stress has often been claimed to exacerbate pain. However, there is hardly any evidence about whether this is true on a day-to-day basis (or whether it is the other way around). We tested whether and how stress and pain are intertwined in participants with FMS, using an ecologically valid measurement design. We additionally looked into the role of the two major stress-responsive systems, the hypothalamic-pituitary-adrenal axis and autonomic nervous system, as potential mediators of this relationship.

Methods

We conducted an ambulatory assessment study over the course of 14 days. Each day, 32 females with FMS provided six diary entries on momentary stress and pain levels. Saliva samples were collected at the same time points to determine cortisol and alpha-amylase as indicators of stress-responsive systems.

Results

Higher stress at a given measurement time point was associated with higher reported pain levels at the next time point (*UC* = 1.62, *p* = .002), but not vice versa (*UC* < 0.01, *p* = .083). The stress - pain relationship was neither mediated by momentary cortisol nor by alpha-amylase; however, momentary cortisol was independently associated with momentary pain (*UC* = 0.28, *p* = .008).

Conclusion

Stress seems to be a powerful exacerbating factor for pain as experienced by patients with FMS in their everyday lives. Cortisol may be involved in the diurnal fluctuation of pain levels in patients with FMS. Future studies should identify relevant daily stressors in persons with FMS and scrutinize the mechanisms underlying the cortisol – pain relationship.

Fibromyalgia syndrome (FMS) refers to widespread pain of more than three months duration that cannot be sufficiently explained by any medical condition. According to the American College of Rheumatology (ACR) 2010 diagnostic criteria, a number of ancillary symptoms, such as fatigue, waking unrefreshed, and cognitive symptoms often occur in patients (1). Prevalence rates range from 2.1% to 5.3% in the general population, with a female preponderance regarding symptom severity (2, 3). The course of FMS is mostly chronic, with a minority of patients reporting symptom improvements over time (4, 5).

Given the typically chronic course of FMS, the identification of mechanisms underlying its perpetuation is imperative. Although generally stable, symptoms of FMS are known to show diurnal variation (6). In a subgroup of patients with high pain sensitivity, on average, a decline in pain levels was observed from 11 a.m. until the end of each day (7). However, symptom fluctuations are mostly perceived as unpredictable by the individual patient, leaving him/her in emotional distress and incapable of engaging in his/her daily routine (8). Moreover, the planning of daily activities is severely hampered by the fact that the triggers for symptom flares often remain obscure (9).The question thus arises what factors underlie the experience of symptom exacerbation in patients with FMS.

In the past, a case has been made that stress may be an important perpetuating factor in FMS (10). As far as empirical evidence is concerned, a plethora of cross-sectional studies have used questionnaires measuring chronic stress or daily hassles in patients with FMS. In these studies, the magnitude of self-reported stress was linked to pain severity and/or functional impairment (11-14). These findings suggest that stress can indeed exacerbate symptoms in patients with FMS. However, the validity of these findings may be questioned, since a peak- and end-bias in the retrospective reporting of symptoms has been discussed in the pain literature (15), meaning that the most intense and recent pain experience influences reports. Moreover, the generalizability of single occasion measurements in a survey or in the laboratory to real-life processes is limited.

Answering the question on whether stress exacerbates symptoms of FMS demands measuring pain close to the actual experience in a repeated, ecologically valid manner. Ambulatory assessment approaches offer the possibility of addressing all these issues simultaneously (16). Regarding FMS, only one study has approached the named question using such a design (17), finding no association between stress and pain experience. However, this study used aggregated stress and

pain scores. Thus, one could argue that a potential relationship was missed due to information loss as a consequence of data aggregation. In other words, the question on how stress possibly translates into the experience of more intense pain over the day in patients with FMS remains unanswered.

The two major stress-responsive systems might be involved in this process i.e. the hypothalamic-pituitary-adrenal (HPA) axis and the sympathetic nervous system (SNS). Dysregulations of both systems have been hypothesized to contribute to core symptoms of FMS. At the central level, blunted corticotropin-releasing hormone and locus coeruleus/norepinephrine-sympathetic systems are known to interact and enhance pain via descending analgesic pathways (18). Evidence has accumulated for patients with FMS to be characterized by hypocortisolism (19). In terms of the SNS, findings generally point to elevated sympathetic activity and attenuated reactivity in patients with FMS (20). Importantly, both cortisol and catecholamines regulate central and peripheral processes involved in pain sensation, including inflammation (21).

However, although widely assumed in theory, there is hardly any empirical evidence for both systems to operate as exacerbating factors of pain in FMS, at least not on a momentary basis. In fact, only one ambulatory assessment study has examined the relationship between concurrent cortisol activity and pain intensity (22), reporting a positive association within the first hour of awakening, but not later during the day. However, although valuable insight was gained from this study, the measurement period was rather short (two days).

Taken together, research lacks a detailed characterization of the proposed role of stress as an exacerbating factor of pain in real life. Also, while there is ample evidence for a general dysregulation of the HPA axis and SNS in FMS, almost nothing is known about the role of these systems in the daily fluctuations of pain levels.

Therefore, the first aim of the presented study was to examine the relationship between stress and pain in the everyday lives of persons' with FMS. More specifically, we assumed increases in stress to predict increases of pain. However, since high pain levels may themselves act as a stressor in persons with FMS, we additionally tested whether increases in pain preceded increases in stress levels. Secondly, we were interested in examining the role of biological stress markers as mediators of these prospective associations. Based on the evidence mentioned above, we expected 1a) momentary stress to predict momentary pain, 1b) stress reported at the previous measurement time

point to predict momentary pain, and vice versa, 1c), previous-day mean stress levels to predict mean daily pain levels, and vice versa, and 2) momentary and daily activity of the HPA axis and SNS to mediate these assumed associations. Although a female preponderance regarding FMS is not substantiated by more recent epidemiological studies, the severity of symptoms seems to be more pronounced in women, which is why we decided to only include women into our study. As it is hardly feasible to assess central parts of the HPA axis and SNS in an ambulatory assessment study, we decided to measure salivary cortisol and alpha-amylase (sAA) as easily accessible end products of these systems.

Participants and methods

Participants

Interested persons were recruited via advertisements in newspapers, through flyers posted in offices of general physicians and rheumatologists, and via self-help groups. Persons were included if they were female, fluent in German, and between 18 and 65 years of age. In addition, all participants needed to satisfy the Fibromyalgia Research Criteria (23), a modified version of the ACR 2010 diagnostic criteria (1; see below). Exclusion criteria were body mass index (BMI) above 30 kg/m²; pregnancy, breast feeding, or irregular menstruation cycles, current episode of major depression, any major psychiatric disorder (substance abuse within the past two years, lifetime psychotic or bipolar disorder, eating disorder within the past five years), and any non-medicated medical condition known to affect endocrine or autonomic functioning. The total sample consisted of 32 women. All women received 80 Euro for participation. The study was carried out in accordance with the Declaration of Helsinki and was approved by the local ethics committee (Department of Psychology, University of Marburg, Germany). All participants provided written informed consent.

Study protocol

We used an ambulatory assessment design. Participants were pre-screened for eligibility via telephone and informed about the study aims and procedures. Eligibility was confirmed during an initial study appointment and several questionnaires were administered. Participants were then instructed on how to handle an electronic diary device (iPod touch®) to answer several questions at six prompts throughout the day (upon awakening, +30 min, 11 a.m., 2 p.m., 6 p.m., 9 p.m.). Similarly, they were trained in the collection of saliva samples, which had to be collected immediately after

answering the electronic diary questions. Importantly, participants were asked to complete the first entries and provide the first saliva sample immediately upon awakening (before doing anything else). All participants completed a test run in front of the research assistant to ensure that they understood the procedures. They received a manual on how to handle the devices, also including a detail explanation of all items and a telephone number they could call in case of technical problems. The assessments took place over a period of 14 consecutive days. The follow-up appointment consisted of a post-monitoring interview and filling in another set of questionnaires.

Questionnaires on patient characteristics

Detailed medical and gynecological histories were obtained. Participants brought a list of their current medication to the initial study appointment. These documents were checked for compatibility with eligibility criteria.

For FMS diagnosis and assessment of FMS severity, participants were asked in how many of 19 areas they had experienced pain for the last three months (Widespread Pain Index; WPI). The German version of the Regional Pain Scale (24) was utilized to measure pain in each area on a scale from 0 (“no pain”) to 4 (“severe pain”). Furthermore, participants were asked to indicate the level of severity of fatigue, waking unrefreshed, and cognitive symptoms on a scale from 0 (“no problems”) to 3 (“severe problems”) during the past week and the presence (“no” vs. “yes”) of headaches, pain or cramps in the lower abdomen, and depression in the past six months (Symptom Severity Score; SSS). The symptoms had to be present at a similar level for at least three months and the Fibromyalgia Research Criteria were satisfied if the WPI was higher than or equal to 7 and the SSS higher than or equal to 5, or if the WPI was between 3 and 6 and the SSS higher or equal to 9 (23).

The German version of the Patient Health Questionnaire 9 (PHQ-9; 25) was used to screen for major depression and as a measure of depression. We excluded any potential participants reporting depressed mood or anhedonia on “several days” over the past two weeks.

As evidence suggests that childhood abuse and neglect have stress-sensitizing effects (26), the German version of the short Childhood Trauma Questionnaire (CTQ; 27) was administered to all participants. The total score of childhood trauma was calculated by adding up all items. For similar

reasons, chronic stress was measured via the screening version of the Trier Inventory for the Assessment of Chronic Stress (SSCS; 28), and a sum score was computed.

Momentary stress and pain (ambulatory assessment)All items were presented using the application iDialogPad (G. Mutz, University of Cologne, Germany). Momentary stress ("At the moment, I feel stressed") was scored on a five point Likert scale ranging from 0 ("not at all") to 4 ("very much"). Momentary pain was rated on a visual analogue scale (VAS) from 0 to 100 ("At the moment, I am in no pain" vs. "At the moment, I am in the most intense pain possible"). Control questions concerned the amount of physical activity within the last two hours (VAS from 0 to 100; "not at all active" vs. "active a lot"), the participants' eating, drinking, and smoking behavior, and intake of medication (dichotomous variables; 0 "no" vs. 1 "yes").

Momentary cortisol and alpha-amylase (ambulatory assessment)

Saliva samples were collected using the SaliCap® system (IBL, Hamburg, Germany). In brief, participants were asked to collect saliva for two minutes in their mouths and subsequently salivate into a pre-labeled polypropylene tube via a straw. They were told to store saliva samples in their freezers or refrigerators and return them to our laboratory at the follow-up appointment.

All analyses were conducted at our laboratory (Biochemical Laboratory of the Department of Clinical Biopsychology, University of Marburg). Samples were kept frozen at -20°C. Cortisol levels were measured using a commercially available enzyme-linked immunoassay (IBL, Hamburg, Germany). Salivary alpha-amylase activity was measured using a kinetic colorimetric test and reagents from Roche (Roche Diagnostics, Mannheim, Germany). Inter- and intra-assay variance for both assays was below 10%.

We calculated the cortisol (CAR) and alpha-amylase awakening response (AAR) by subtracting the first from the second measurement time point. The CAR refers to a rise in cortisol within 30 to 45 minutes after awakening, while the AAR represents a decline within the same time frame. Both the CAR and AAR have been associated with clinical conditions such as post-traumatic stress disorder and chronic fatigue syndrome (29, 30). In addition, slopes and areas under the curves (AUCs) were computed to measure total daily cortisol output and diurnal dynamics, respectively (31).

Statistical analysis

We used two-level hierarchical linear modeling (HLM 7, Scientific Software International Inc., Lincolnwood, USA) in terms of statistical analyses. Stress, cortisol, sAA, and pain (i.e., all momentary assessments) were considered level one variables. Intake of food and drink, smoking, the amount of physical activity (all within the last two hours), salivary flow rate and time since awakening were treated as potentially confounding variables on level one. On level two, age, BMI, duration of FMS, number of pain sites (WPI), depression (PHQ-9), childhood trauma (CTQ), and chronic stress (SSCS) were included into the analyses (i.e., all participant characteristics). Each analysis was conducted twice: within days (84 momentary assessments per participant) and between days (14 aggregated assessments per participant). For each analysis, a different set of covariates and level two variables was considered relevant; these are reported in the tables of the results section.

Two participants had completely missing iPod touch® data sets due to technical problems and were thus excluded from all analyses. One participant had a slightly higher BMI (31.2) than indicated during the telephone interview, and a review of the medical histories revealed that two participants had inflammatory respiratory diseases and one person had Hashimoto's thyroiditis. However, since this had no impact on our results, we included these participants into all following analyses. All cortisol and sAA data were checked for incompliance with the protocol by the use of electronic time stamps. Incompliance was considered present if the second saliva sample was collected later than 45 minutes after the first sample; for the remaining samples (11 a.m., 2 p.m., 6 p.m., and 9 p.m.), collection later than 60 minutes after the scheduled time point was considered incompliant behavior (32). Consequently, 229 values out of 2'520 were eliminated and treated as missing values.

For the within-day analyses, we omitted the second measurement time point (30 min after awakening) as we intended to test the effects of the CAR and AAR in separate analyses (see below). Calculations of the HLM 7 software were based on 1'885 to 1'966 out of 2'100 data points depending on the model that was being tested (listwise deletion of missing values). For our prospective analyses, we time-lagged the predictor variables stress and pain, respectively. As result of this, the data set was again reduced (deletion of the first entry on each day). In these analyses, 1'541 out of 1'980 possible data points were used by the HLM 7 software.

For the between-day analyses, all missing values regarding salivary cortisol and amylase were replaced before running HLM analysis. This was in order to have enough data for HLM analysis after the calculation of the CAR, AAR, the AUCs, and slopes. A total of 219 (cortisol) and 226 (alpha-amylase) out of 2'520 possible values were replaced by the mean of the respective participant at that time of day. Mean daily stress and pain were only calculated if at least two entries had been made on the respective day. HLM 7 used 413 out of 420 (383 out of 390 in time-lagged analyses) data points for calculations. On level two, five values were replaced with the mean value of the sample.

The Kolmogorov-Smirnov test revealed that a few of the measurement time points of the outcome variables were not normally distributed. We thus relied on coefficients with robust standard errors whenever they differed from unstandardized coefficients (33). Our testing of hypotheses consisted of several steps in accordance with Woltman et al. (33). *Pseudo-R^2* was determined as a means of variance estimation for each predictor in question (34). The following equation was used: $Pseudo\text{-}R^2 = (\sigma^2_{reference\ model} - \sigma^2_{final\ model})/\sigma^2_{reference\ model}$, with the reference model being the final model excluding the specified predictor. Mediation analyses were based on the steps suggested by Kenny and Korchmaros (35, 36). We were specifically interested in testing whether previous stress predicted momentary pain via momentary cortisol and sAA. In addition, we aimed at testing whether previous-day stress predicted daily pain via daily activity of the HPA axis and SNS. Data are presented as mean ± standard deviation (SD). For descriptive purposes, figures are provided using mean and standard error values. Overall level of significance was defined as $p < .05$.

Results

Descriptive data

Participants' mean age was 50.7 years (± 9.9) and their average BMI was 25.2 kg/m^2 (± 2.9). Eight (26.7%) participants were on antidepressants, six (20.0%) on thyroid medication, three (10.0%) took antihypertensives, two (6.7%) took analgesics, and ten (33.3%) took other medication (e.g., omeprazole). They had suffered from widespread pain for 10.2 (± 7.2) years on average, had pain in 11.6 (± 4.0) out of 19 possible sites, and rated their symptoms severity as 8.2 (± 2.0) out of a maximum score of 12. In accordance with our eligibility criteria, participants were only mildly depressed (PHQ-9 score of 8.7 ± 3.8). They had a score of 63.3 (± 24.1 out of a 155 maximum score)

on the CTQ and slightly elevated levels of chronic stress (25.3 ± 7.4) when compared to the general population.

Over the day, momentary stress ranged from 1.1 (± 0.9) to 1.7 (± 1.1) on a scale from 0 to 4, indicating low to medium levels of stress (see Figure 1). The lowest levels were observed at awakening and the highest levels at 2 p.m. In contrast, momentary pain, measured on a scale from 0 to 100, was highest upon awakening (50.1 ± 24.7) and lowest at 2 p.m. (46.3 ± 26.3; see Figure 2).. As can be seen in Figure 3, overall, characteristic daily salivary cortisol and sAA profiles including a CAR and AAR were present in our sample of females with FMS.

Effects of stress on pain

The final models of the stress on pain analyses are reported in Table 1. In line with our expectations, we found a positive association between momentary stress and momentary pain, even when physical activity, the intake of medication, and time since awakening were controlled for (*UC* = 4.60, $p < .001$). This means that the more stress a participant experienced, the higher her concurrent pain ratings. The final intercept as outcome model explained 16% of variance in momentary pain levels (8% was explained by stress alone).

We then explored whether stress reported at the previous measurement time point predicted momentary pain. This association was again positive and statistically significant, even when controlling for the effects of momentary stress, physical activity, intake of medication, and time since awakening (*UC* = 1.62, $p = .002$). This means that the higher a participant's stress level at one time point the more pain she experienced three to four hours later. The final model explained 19% of total momentary pain variance (1% was explained by stress at the previous measurement time point).

Finally, we evaluated whether previous-day mean stress levels were predictive of mean daily pain levels. This association was not significant when mean daily stress levels were controlled for (*UC* = 0.59, $p = .581$), indicating that stress levels on one day had no implications on the pain levels of the following day.

Effects of pain on stress

The final models regarding the effects of pain on stress are reported in Table 2. As we had already found a concurrent relationship between momentary pain and stress (reported above), we directly tested whether pain reported at the previous measurement time point was able to predict momentary stress. This association was not significant when controlling for momentary pain, physical activity, and time since awakening (*UC* < 0.01, *p* = .083). This means that pain at one time point failed to predict stress levels three to four hours later.

Finally, we evaluated whether previous-day mean pain levels predicted mean daily stress levels. The association was non-significant when considering mean daily pain levels (*UC* < 0.01, *p* = .707), indicating that pain levels on one day were independent of stress levels on the next day.

Salivary cortisol as a mediator of the stress on pain association

All models including cortisol are shown in Table 3. Momentary cortisol and momentary pain were correlated when physical activity, intake of medication, and time since awakening were considered (*UC* = 0.28, *p* = .008). This means that the higher a participant's cortisol level, the more intense her concurrent pain experience. Interestingly, a negative interaction term combining cortisol and time since awakening (*UC* < -.01, *p* = .006) indicated that this relationship was reversed with increasing hours. The final model explained 11% of variance in momentary pain levels (2% by cortisol alone). However, as stress was not related to momentary cortisol, no mediation analyses were computed.

Next, we tested whether the CAR, AUC, and slope were predictive of mean daily pain levels. No significant relationships whatsoever became apparent between the CAR (*UC* = - 0.06, *p* = .225), the AUC (*UC* < 0.01, *p* = .101), the slope (*UC* = -82.17, *p* = .152), and mean daily pain levels. This indicates that neither cortisol output nor its diurnal dynamic were associated with same-day pain levels.

Salivary alpha-amylase as a mediator of the effect of stress on pain

We used the same procedures as with cortisol to explore whether alpha-amylase mediated the stress - pain relationship. Momentary sAA was not related to pain when controlling for physical activity, the intake of medication, and time of day (*UC* = -0.01, *p* = .199; Table 4).

Next, we tested whether the same-day AAR, AUC, and slope were predictive of mean pain levels. Again the AAR had no significant impact on mean pain levels (*UC* = < -0.01, *p* = .980), and neither did the AUC (*UC* = < 0.01, *p* = .692) or slope (*UC* = 1.78, *p* = .557). This means that neither sAA output nor its diurnal dynamic were related to same-day pain levels.

Discussion

Three findings emerge from our study: first, we identified stress as a powerful precursor of momentary pain in the everyday lives of participants with FMS. Second, there was no evidence for pain to be similarly predictive of momentary stress. Third, cortisol but not and alpha-amylase impacted on pain on a momentary basis. None of our positive results was mirrored on a more aggregated level (between-day analyses).

Our results replicate and extend the results of various survey studies which suggest that stress may be a perpetuating factor in FMS. However, none of these studies examined stress and pain as they interact over the day. Using an ecologically valid momentary assessment design, we were able to show that stress is in fact an important exacerbating (and thus potentially perpetuating) factor of pain levels in the everyday lives of persons with FMS. Pain, on the other hand, was concurrently linked to stress, but failed to predict it up to several hours later. One explanation for the fact that pain was not equally powerful in eliciting stress is that some of our participants may have been so called ‘adaptive copers’ (37). This subgroup of patients with FMS is characterized by low pain intensity, low impairment, and little comorbidity with mental disorders (38). Our exclusion of major mental disorders including current episodes of major depression may therefore have enhanced the proportion of adaptive copers in our sample. Another explanation is that, instead of stress, pain caused emotional distress (e.g., feeling depressed or anxious), which is conceptually distinct and has been shown in a similar study in patients with FMS (39).

As the corticotropin-releasing hormone and locus coeruleus/norepinephrine-sympathetic systems are involved in regulating pain via descending pathways, and as both systems interact with the immune system, we were interested in whether momentary cortisol and alpha-amylase levels were associated with momentary pain levels. Our findings are in line with McLean et al. (22), who found a positive correlation between cortisol levels within one hour of awakening and pain. One of the most robust findings regarding HPA axis activity in FMS is an altered negative feedback sensitivity, which

seems increased in these patients (40). It is tempting to assume that the corticotropin-releasing hormone system is hyper-responsive to the central effects of cortisol, which, in concert with a hypoactive locus coeruleus/norepinephrine-sympathetic systems system, results in a loss of pain inhibitory effects via descending pathways (19) However, as no causality can be implied by our findings, this remains speculative. Another pathway via which cortisol can affect pain levels is through glucocorticoid receptors on numerous cells of the immune system. In fact, a recent report suggests that monocytes of patients with FMS exhibit reduced glucocorticoid sensitivity (41), meaning that they are not responsive enough to the immune-suppressive effects of circulating cortisol.

Our study offers a number of strengths. First, the ambulatory assessment approach allowed us to explore potential mechanisms underlying FMS as they operate in real life. Second, our two week assessment period with six daily assessments enabled us to study the exacerbation of pain in FMS in great detail and in a repeated fashion. Both ecological validity and reliability of our findings are thus likely to be high. Third, we controlled for a variety of potential confounders of momentary assessments (e.g., intake of medication). Still, several limitations need to be acknowledged. First, male persons were excluded; our findings are therefore not representative for the general population of persons with FMS. Second, we excluded subjects with a current episode of major depression. Although this was necessary to control for effects of depression on cortisol levels, it limits the ecological validity of our findings as the comorbidity of FMS with major depression is rather high (42). Third, an obvious limitation inherent in any ambulatory assessment design is the lack of internal validity. Investigations into the stress - pain relationship under highly controlled conditions are thus an important addition to the findings we present here.

Although our sample size is comparable to or even bigger than similar ambulatory assessment studies in persons with FMS, a replication of our findings is warranted. Furthermore, it would be interesting to identify the exact reasons responsible for elevations in momentary stress levels. Our findings highlight the general importance of stress management interventions in patients with FMS. However, knowing what kind of stressors operate as pain exacerbating factors in these patients would allow for cognitive-behavior therapy to specifically target these stressors and potentially increase its efficacy. Moreover, it is of great importance to further explore the mechanisms responsible for the pain exacerbating effect of stress. To this end, it may be informative to additionally perform event-based

measurements in future ambulatory assessment studies, as this would allow looking into possible alterations in patients' responses as stressors occur.

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Tables

Table 1 Final hierarchical linear models predicting pain by stress, using restricted maximum likelihood; residuals were set free whenever there were significant random effects

	Fixed effects				Random effects			
	UC	*SE*	*t-ratio*	*p*	*SD*	*Variance component*	χ^2	*p*
Momentary stress on pain								
Intercept	47.08	3.27	14.38	< .001	15.57	242.26	1941.13	< .001
Age	0.84	0.26	3.31	.003				
Regular intake of antidepressants	-6.21	4.81	-1.29	.210				
Regular intake of antihypertensives	13.10	5.60	2.34	.029				
Regular intake of analgesics	6.99	5.29	1.32	.200				
Number of pain sites (WPI)	2.12	0.70	3.04	.006				
Childhood trauma (CTQ)	-0.02	0.08	-0.21	.833				
Chronic stress (SSCS)	0.65	0.31	2.07	.051				
Momentary stress	4.60	0.64	7.20	< .001	2.84	8.05	79.59	< .001
Time since awakening	< 0.01	< 0.01	0.58	.569	0.01	< 0.01	104.05	< .001
Physical activity	-0.05	0.02	-2.25	.032	0.10	0.01	91.87	< .001
Intake of medication	5.68	2.81	2.02	.044				

Preceding stress on pain								
Intercept	46.30	3.49	13.28	< .001	16.38	268.34	1743.90	< .001
Age	0.60	0.29	2.07	.050				
Regular intake of antidepressants	-5.13	6.42	-0.80	.433				
Regular intake of antihypertensives	7.45	4.51	1.65	.113				
Regular intake of analgesics	12.62	6.06	2.08	.049				
Number of pain sites (WPI)	1.92	0.74	2.58	.017				
Childhood trauma (CTQ)	-0.05	0.10	-0.55	.591				
Chronic stress (SSCS)	0.94	0.32	2.89	.008				
Momentary stress	4.66	0.67	6.99	< .001	3.14	9.85	77.92	< .001
Preceding stress	1.62	0.53	3.03	.002				
Time since awakening	0.01	< 0.01	3.63	.001	< 0.01	< 0.01	51.52	.006
Physical activity	0.01	0.03	0.45	.657	0.13	0.02	95.80	< .001
Intake of medication	6.70	2.77	2.42	.016				
Previous-day stress on pain								
Intercept	46.94	3.28	14.33	< .001	15.14	229.37	841.02	< .001
Age	0.93	0.28	3.32	.003				
Regular intake of antidepressants	-4.15	7.09	-0.59	.565				

Regular intake of antihypertensives	10.82	7.36	1.47	.156
Regular intake of analgesics	14.42	8.92	1.62	.120
Number of pain sites (WPI)	1.78	0.80	2.22	.037
Childhood trauma (CTQ)	-0.04	0.12	-0.32	.752
Chronic stress (SSCS)	0.94	0.35	2.68	.014
Previous-day stress	0.59	1.07	0.55	.581
Same-day stress	7.34	1.39	5.30	< .001

CTQ = Childhood Trauma Questionnaire, *SD* = standard deviation, *SE* = standard error, SSCS = Screening version of the Trier Inventory for the Assessment of Chronic Stress, *UC* = unstandardized coefficient, WPI = Widespread Pain Index; for all variables, higher values imply a higher level of the respective construct

Table 2 Final hierarchical linear models predicting stress by pain, using restricted maximum likelihood; residuals were set free whenever there were significant random effects

	Fixed effects				Random effects			
	UC	*SE*	*t-ratio*	*p*	*SD*	*Variance component*	χ^2	*p*
Preceding pain on stress								
Intercept	1.52	0.10	14.63	< .001	0.59	0.34	810.05	< .001
Childhood trauma (CTQ)	-0.01	< 0.01	-1.75	.092				
Chronic stress (SSCS)	0.04	0.02	2.54	.017				
Momentary pain	0.02	< 0.01	7.10	< .001	0.01	< 0.01	75.87	< .001
Preceding pain	< 0.01	< 0.01	1.73	.083				
Physical activity	0.01	< 0.01	4.48	< .001	0.01	< 0.01	83.62	< .001
Time since awakening	< -0.01	< 0.01	- 5.70	< .001				
Previous-day pain on stress								
Intercept	1.41	0.10	14.75	< .001	0.54	0.29	529.41	< .001
Childhood trauma (CTQ)	-0.01	< 0.01	-1.90	.068				
Chronic stress (SSCS)	0.04	0.01	2.80	.009				
Previous-day pain	< 0.01	< 0.01	0.38	.707				

Same-day pain	0.02	< 0.01	6.52	< .001

CTQ = Childhood Trauma Questionnaire, *SD* = standard deviation, *SE* = standard error, SSCS = Screening version of the Trier Inventory for the Assessment of Chronic Stress, *UC* = unstandardized coefficient; for all variables, higher values imply a higher level of the respective construct

Table 3 Final hierarchical linear models in terms of cortisol, using restricted maximum likelihood; residuals were set free whenever there were significant random effects

	Fixed effects				Random effects			
	UC	*SE*	*t-ratio*	*p*	*SD*	*Variance component*	χ^2	*p*
Momentary cortisol on pain								
Intercept	47.23	3.44	13.73	< .001	16.18	261.93	1909.29	< .001
Age	1.15	0.27	4.35	< .001				
Regular intake of antidepressants	-7.26	5.22	-1.4	.179				
Regular intake of antihypertensives	14.59	4.65	3.14	.005				
Regular intake of analgesics	4.44	4.12	1.08	.293				
Number of pain sites (WPI)	2.47	0.67	3.67	.001				
Childhood trauma (CTQ)	0.06	0.08	0.84	.411				
Chronic stress (SSCS)	0.88	0.27	3.22	.004				
Momentary cortisol	0.28	0.10	2.87	.008	0.29	0.08	51.44	.006
Time since awakening	0.01	< 0.01	2.92	.007	0.01	< 0.01	76.77	< .001
Momentary cortisol*time since awakening	< -0.01	< 0.01	-2.74	.006				
Physical activity	0.01	0.03	0.32	.749	0.11	0.01	92.94	< .001
Intake of medication	7.52	3.13	2.40	.017				

CAR on pain								
Intercept	46.92	3.24	14.46	< .001	15.01	225.33	743.51	< .001
Age	0.89	0.28	3.16	.005				
Regular intake of antidepressants	-3.68	7.17	-0.51	.613				
Regular intake of antihypertensives	10.47	7.10	1.47	.155				
Regular intake of analgesics	13.76	8.49	1.62	.119				
Number of pain sites (WPI)	1.78	0.80	2.23	.036				
Childhood trauma (CTQ)	-0.04	0.11	-0.40	.694				
Chronic stress (SSCS)	0.96	0.34	2.78	.011				
CAR	-0.06	0.05	-1.22	.225				
AUC (cortisol) on pain								
Intercept	46.93	3.25	14.46	< .001	15.01	225.38	748.82	< .001
Age	0.89	0.28	3.16	.005				
Regular intake of antidepressants	-3.68	7.17	-0.51	.613				
Regular intake of antihypertensives	10.47	7.10	1.47	.155				
Regular intake of analgesics	13.76	8.49	1.62	.119				
Number of pain sites (WPI)	1.78	0.80	2.23	.036				

Childhood trauma (CTQ)	-0.04	0.11	-0.40	.694				
Chronic stress (SSCS)	0.96	0.34	2.78	.011				
AUC	< 0.01	< 0.01	1.64	.101				
Slope (cortisol) on pain								
Intercept	46.93	3.25	14.46	< .001	15.01	225.34	745.25	< .001
Age	0.89	0.28	3.16	.005				
Regular intake of antidepressants	-3.68	7.17	-0.51	.613				
Regular intake of antihypertensives	10.47	7.10	1.57	.155				
Regular intake of analgesics	13.76	8.49	1.62	.119				
Number of pain sites (WPI)	1.78	0.80	2.23	.036				
Childhood trauma (CTQ)	-0.04	0.11	-0.40	.694				
Chronic stress (SSCS)	0.96	0.34	2.78	.011				
Slope	-82.17	57.29	-1.43	.152				

AUC = area under the curve, CAR = cortisol awakening response, CTQ = Childhood Trauma Questionnaire, *SD* = standard deviation, *SE* = standard error, SSCS = Screening version of the Trier Inventory for the Assessment of Chronic Stress, *UC* = unstandardized coefficient, WPI = Widespread Pain Index; for all variables, higher values imply a higher level of the respective construct

Table 4 Final hierarchical linear models in terms of alpha-amylase, using restricted maximum likelihood; residuals were set free whenever there were significant random effects

	Fixed effects				Random effects			
	UC	*SE*	*t-ratio*	*p*	*SD*	*Variance component*	χ^2	*p*
Momentary alpha-amylase on pain								
Intercept	47.10	3.33	14.14	< .001	16.00	255.98	1771.68	< .001
Age	1.10	0.26	4.17	< .001				
Regular intake of antidepressants	- 7.90	5.52	-1.43	.166				
Regular intake of antihypertensives	17.74	6.90	2.57	.017				
Regular intake of analgesics	4.94	6.41	0.77	.449				
Number of pain sites (WPI)	2.14	0.73	2.92	.008				
Childhood trauma (CTQ)	0.04	0.09	0.52	.610				
Chronic stress (SSCS)	0.88	0.30	2.94	.008				
Momentary alpha-amylase	-0.01	0.01	-1.29	.199				
Time since awakening	< -0.01	< 0.01	-0.29	.773	0.01	< 0.01	106.49	< .001
Momentary amylase*time since awakening	0.01	0.01	0.82	.412				
Physical activity	-0.01	0.02	-0.54	.597	0.11	0.01	102.10	< .001
Intake of medication	7.01	3.26	2.15	.032				

AAR on pain								
Intercept	46.93	3.25	14.46	< .001	15.01	225.30	740.09	< .001
Age	0.89	0.28	3.16	.005				
Regular intake of antidepressants	-3.68	7.17	-0.51	.613				
Regular intake of antihypertensives	10.47	7.10	1.47	.155				
Regular intake of analgesics	13.76	8.49	1.62	.119				
Number of pain sites (WPI)	1.78	0.80	2.23	.036				
Childhood trauma (CTQ)	-0.04	0.11	-0.40	.694				
Chronic stress (SSCS)	0.96	0.34	2.78	.011				
AAR	< 0.01	< 0.01	0.03	.980				
AUC (alpha-amylase) on pain								
Intercept	46.93	3.25	14.46	< .001	15.01	225.30	740.25	< .001
Age	0.89	0.28	3.16	.005				
Regular intake of antidepressants	-3.68	7.17	-0.51	.613				
Regular intake of antihypertensives	10.47	7.10	1.47	.155				
Regular intake of analgesics	13.76	8.49	1.62	.119				
Number of pain sites (WPI)	1.78	0.80	2.23	.036				

Childhood trauma (CTQ)	-0.04	0.11	-0.40	.694				
Chronic stress (SSCS)	0.96	0.34	2.78	.011				
AUC	< 0.01	< 0.01	0.40	.692				
Slope (alpha-amylase) on pain								
Intercept	46.93	3.25	14.46	< .001	15.01	225.30	740.71	< .001
Age	0.89	0.28	3.16	.005				
Regular intake of antidepressants	-3.68	7.17	-0.51	.613				
Regular intake of antihypertensives	10.47	7.10	1.47	.155				
Regular intake of analgesics	13.76	8.49	1.62	.119				
Number of pain sites (WPI)	1.78	0.80	2.23	.036				
Childhood trauma (CTQ)	-0.04	0.11	-0.40	.694				
Chronic stress (SSCS)	0.96	0.34	2.78	.011				
Slope	1.78	3.04	0.59	.557				

AAR = alpha-amylase awakening response, AUC = area under the curve, CTQ = Childhood Trauma Questionnaire, *SD* = standard deviation, *SE* = standard error, SSCS = Screening version of the Trier Inventory for the Assessment of Chronic Stress, *UC* = unstandardized coefficient, WPI = Widespread Pain Index; for all variables, higher values imply a higher level of the respective construct

Figure legends

Figure 1 Daily stress profile, averaged across 14 days of measurement (mean ± standard error of mean)

Figure 2 Daily pain profile, averaged across 14 days of measurement (mean ± standard error of mean)

Figure 3 Daily cortisol and alpha-amylase profiles, averaged across 14 days of measurement (mean ± standard error of mean)

Figure 1 Daily stress profile, averaged across 14 days of measurement (mean ± standard error of mean)

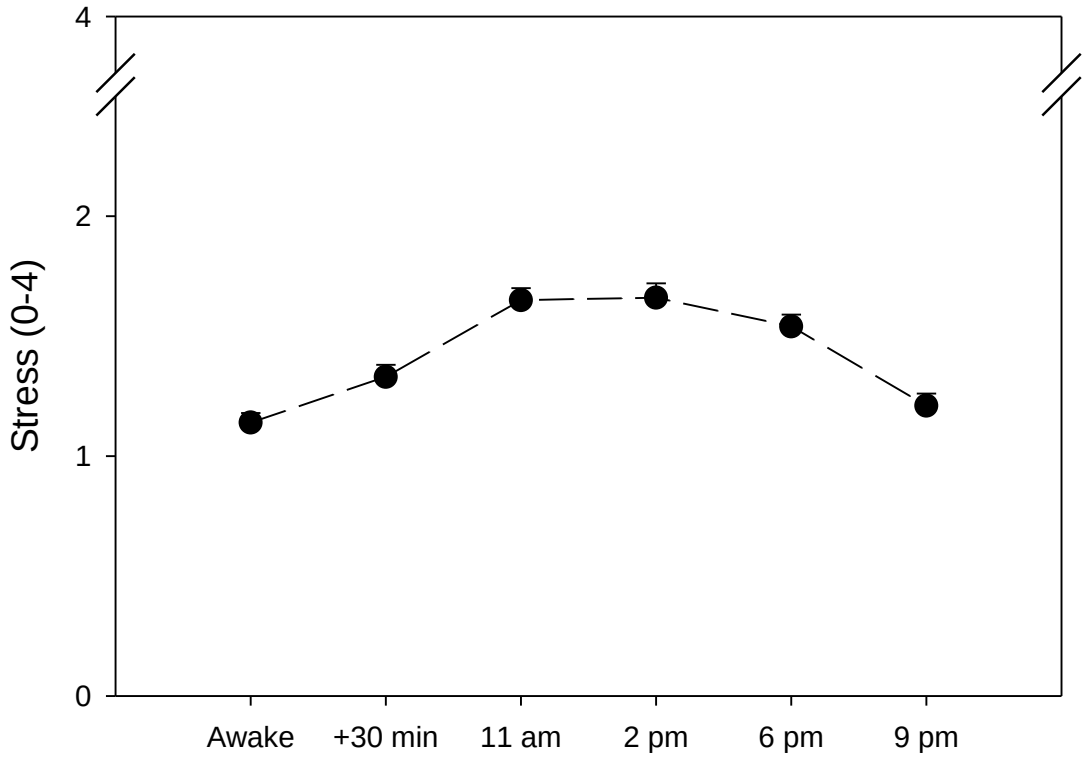


Figure 2 Daily pain profile, averaged across 14 days of measurement (mean ± standard error of mean)

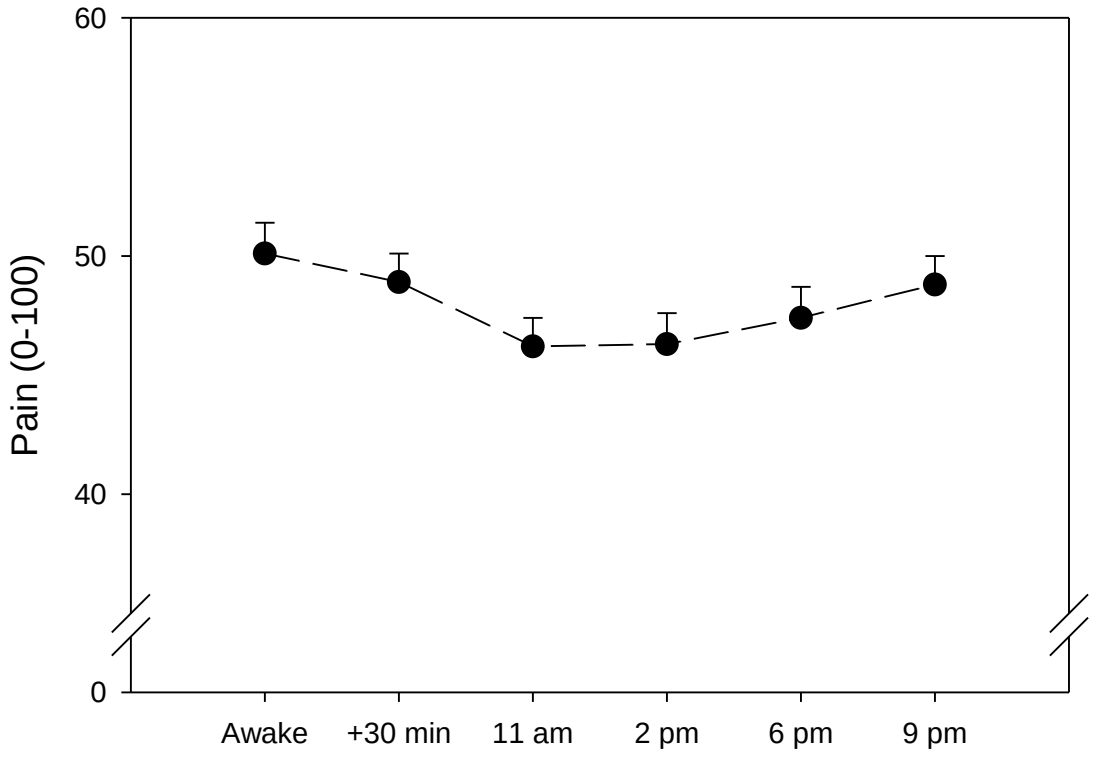
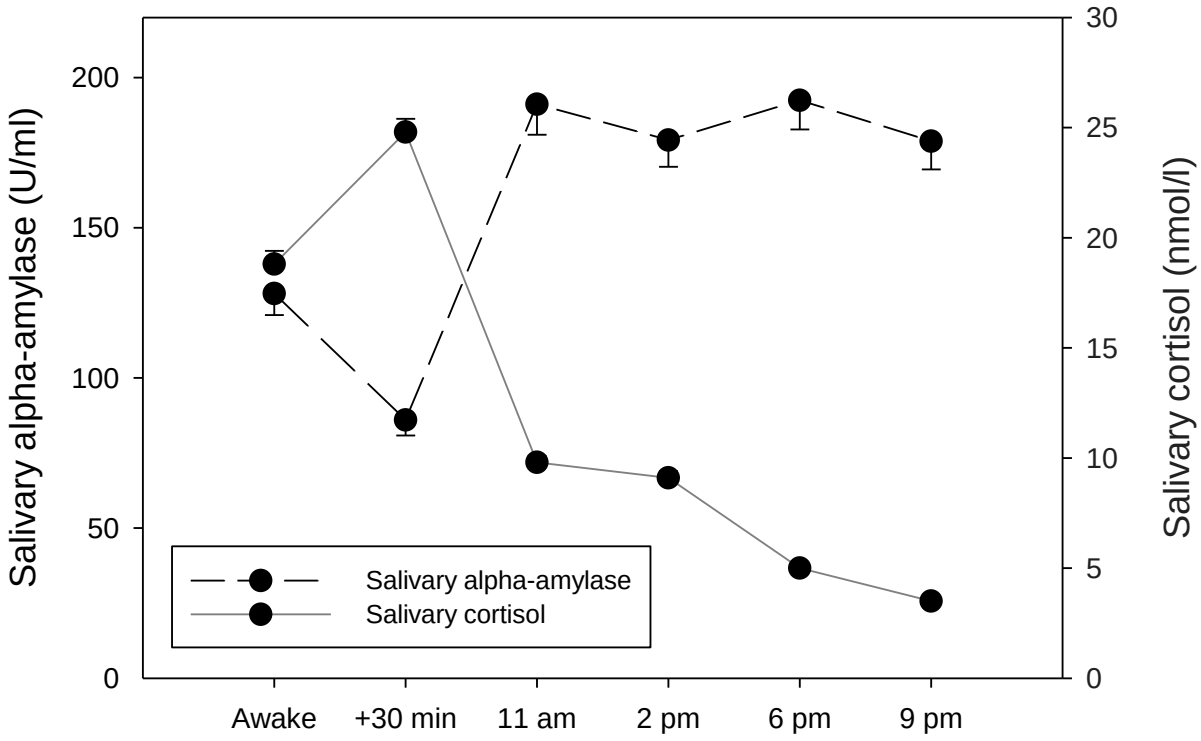


Figure 3 Daily cortisol and alpha-amylase profiles, averaged across 14 days of measurement (mean ± standard error of mean)



Study III

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Stress and Resilience in Functional Somatic Syndromes – A Structural Equation Modeling Approach

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Abstract

Background: Stress has been suggested to play a role in the development and perpetuation of functional somatic syndromes. The mechanisms of how this might occur are not clear.

Purpose: We propose a multi-dimensional stress model which posits that childhood trauma increases adult stress reactivity (i.e., an individual's tendency to respond strongly to stressors) and reduces resilience (e.g., the belief in one's competence). This in turn facilitates the manifestation of functional somatic syndromes via chronic stress. We tested this model cross-sectionally and prospectively.

Methods: Young adults participated in a web survey at two time points. Structural equation modeling was used to test our model. The final sample consisted of 3'054 participants, and 429 of these participated in the follow-up survey.

Results: Our proposed model fit the data in the cross-sectional ($\chi^2(21) = 48.808$, $p<.001$, CFI = .995, TLI = .992, RMSEA = .021, 90% CI [.013.029]) and prospective analyses ($\chi^2(21) = 32.675$, $p<.05$, CFI = .982, TLI = .969, RMSEA = .036, 90% CI [.001.059]).

Discussion: Our findings have several clinical implications, suggesting a role for stress management training in the prevention and treatment of functional somatic syndromes.

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Data Availability: The authors confirm that all data underlying the findings are fully available without restriction.Raw data cannot be made available in the paper, the supplemental files, or a public repository, since the authors' local ethical committee does not allow giving raw data to third parties without the subjects' consent.The readers can contact Susanne Fischer or Urs M. Nater to request an aggregated data file.

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Introduction

The term 'functional somatic syndrome' (FSS) refers to various clusters of somatic symptoms (e.g., fatigue, abdominal or musculoskeletal pain) that cannot be adequately explained by means of modern medicine ('medically unexplained symptoms'). Conditions such as chronic fatigue syndrome, fibromyalgia syndrome, or irritable bowel syndrome represent frequently occurring disorders that fall into this broad category. Functional somatic syndromes as well as medically unexplained symptoms are prevalent in the general population [1–3] and account for a large proportion of health care visits both in primary [4–6] and secondary care [7]. They cause substantial suffering in patients and lead to a considerable amount of direct (e.g., medical care) and indirect (e.g., lost productivity) costs [8–10].

Despite remarkable efforts in attempting to elucidate pathophysiological mechanisms in FSS, the exact determinants and processes underlying these debilitating disorders are still unknown. Current knowledge points to a number of predisposing, precipitating, and perpetuating factors, such as genetic factors [11–13], viral infections [14,15], and alterations of visceral and central sensitivity [16,17]. A prominent line of research has been dedicated to the role of stress in FSS [18], thus conceptualizing FSS as 'stress-related disorders'. The transactional stress theory by Lazarus and Folkman [19] provides a framework encompassing several aspects of the stress concept. According to these authors, stress is understood as a person-environment interaction, involving a potentially threatening stimulus (i.e., a stressor), and a biological and psychological stress response [19]. Importantly, this interaction is mediated by complex appraisal processes within the individual, encompassing an assessment of individual resources to deal with potentially stressful events [19]. As will be outlined in the following paragraphs, there is empirical evidence for all of these theoretical aspects to play a role in FSS.

Events during childhood that are perceived as traumatic (i.e., *childhood traumas*), such as emotional, physical, or sexual abuse [20], are among the most severe stressors and have been reported in a substantial number of FSS patients [21]. Unlike mild to moderate stress, severe early life stress including childhood trauma is well-known to permanently alter the reactivity of biological stress-responsive systems in a negative manner [22]. Simliar to its biological analogue, psychological *stress reactivity*, which is defined as an individual's personal capacity or tendency to respond to stressors [23], seems to be heightened as a consequence of early life

stress. For instance, abnormal birth weight reflecting an adverse prenatal environment was linked to higher levels of psychological stress reactivity as an older adult [24]. In FSS, it has been reported that patients feel more tense or stressed after a laboratory stress test, that is, they show higher levels of psychological stress reactivity [25,26]. Decades of (mostly biological) research have documented the effects of childhood trauma on heightened stress reactivity and subsequent adverse health outcomes [22]. However, no study has ever tested whether a trauma-induced elevation of psychological stress reactivity perpetuates or even favors the development of full-blown FSS. The present study fills this gap.

Apart from the detrimental effects of childhood trauma on stress reactivity, the impact of early life stress unfolds in another fashion: in affecting *resilience*. Initial evidence for a negative association between levels of childhood trauma and resilience exists in healthy individuals [27,28]. Resilience can be defined as a positive personality characteristic that enhances individual adaptation, including the facets of believing in one's personal competence and accepting oneself and one's life [29]. According to the transactional stress theory [19], personality characteristics, such as resilience, largely influence appraisal processes that in turn mediate the stressor-stress response relationship. From this follows that stressors and resilience are intertwined in predicting stress reactivity: an individual with high levels of acceptance of him-/herself is unlikely to lose confidence when being faced with criticsm, and vice versa. Indeed, in an experimental study using a laboratory paradigm to induce pain, healthy individuals scoring high on a resilience scale experienced less stress and even pain after being exposed to a tourniquet procedure [30]. Regarding FSS, research demonstrates comparably low overall scores in associated personality characteristics such as sense of coherence [31] and self-efficacy [32] in these patients. So far, evidence indicates that resilience mediates the effect of childhood trauma on psychological distress in apparenly healthy individuals [33] and Holocaust survivors [34]. However, we are not aware of any studies examining these relationships in FSS patients.

At this point, it remains unclear how experiences of childhood trauma, and (subsequent) alterations in stress reactivity and resilience influence the development of FSS. One possible mediating factor is the occurrence of *chronic stress*. Chronic stress is characterized by recurring episodes of stress that are often related to unsatisfied personal needs [35]. In Lazarus and Folkman's terms [19], experiencing chronic stress may be the result of a negative bias in the appraisal of stimuli, that is, to perceive ambiguous stimuli as a threat [36]. Recent data demonstrating a linkage between early abusive experiences, heightened levels of chronic stress, and premenstrual symptoms suggest a possible origin of these threat appraisals [37]. Similarly, a cross-sectional survey in a non-clinical sample found evidence for a positive relationship between stress reactivity with a measure of chronic stress [38]. Finally, another study conducted in fibromyalgia patients showed that 53% of the variance in chronic stress levels could be explained by self-esteem, self-efficacy, and social support, all of which are known to be associated with resilience [39].

Elevated levels of chronic stress have repeatedly been reported in patients suffering from FSS [40,41]. Several mechanisms by which both traumatic and chronic stress foster the development of FSS are conceivable. At the biological level, traumatic [42] and chronic stress [43] result in the epigenetic modification of genes related to stress-responsive systems. In the long run, this causes dysregulation of the hypothalamic-pituitary axis, the autonomic nervous system, and the immune system [22,44]. Notably, all of these physiological systems seem to be dysregulated in patients suffering from FSS [18] and might exacerbate symptoms like fatigue and pain [45]. From a psychological point of view, medically unexplained symptoms can be regarded as misperceptions and -interpretations of bodily sensations that are generated by stored memory representations [46]. According to Brown [46], these representations can have varied origin. For instance, sensorimotor and emotional concomitants of trauma exposure are an important source for their development [46]. For this reason, experiences of childhood trauma might directly be related to the occurrence of FSS (that are characterized by medically unexplained symptoms). In addition, a recent study found the interaction of stress and the perception of stress as 'dangerous' or 'harmful' to increase reportings of poor health [47]. It is thus likely that chronic stress leads to emotional arousal and accompanying bodily sensations that can be subject to misinterpretation [48].

In sum, FSS seem to be associated with the occurrence of childhood trauma as well as alterations in stress reactivity at the biological and psychological level. Furthermore, chronic stress seems to play an important mediating role in translating these vulnerabilities into FSS. No study has so far targeted multiple aspects of stress (i.e., childhood trauma, stress reactivity, and chronic stress) in a large sample. Thus, the interactions between these variables remain to be specified, and we do not know of any studies that have included measures of resilience in a comprehensive model describing the role of stress in FSS. In the current study, we set out to examine the associations between childhood trauma, stress reactivity, resilience, and chronic stress in FSS in a sample of young adults. Our conceptual model depicting the hypothesized associations is illustrated in Figure 1. In brief, our model posits that the occurrence of childhood trauma takes its toll on stress reactivity and resilience, which in turn facilitate the manifestation of FSS via chronic stress. In addition, we assume that childhood trauma itself is indirectly (via chronic stress) and directly linked to FSS. Importantly, since a temporal order of events and changes in personality characteristics is implied in our model, we wanted to rule out the possibility that stress reactivity, resilience, and chronic stress were merely elevated as a consequence of having an FSS. We thus tested our model not only cross-sectionally, but also prospectively, including its evaluation in new FSS cases. We tested these hypotheses as part of a bigger study [49].

Methods

Sample and procedures

We have previously described how participants for this study were recruited [49]. In brief, German speaking students of Swiss colleges and universities were asked to participate in a web survey on physical and mental well-being (T_0). In addition, the participants were asked if they wished to participate in a follow-up survey, and those who agreed were asked to complete the exact same survey six months later (T_1). This enabled us to evaluate whether experiences of childhood trauma, heightened stress reactivity, and lower resilience were prospectively related to the occurrence of chronic stress six months later and whether this in turn predicted the development (of new) and perpetuation (of existing) FSS.

Ethics statement

The study was conducted in accordance with the Declaration of Helsinki. The web survey design was approved by the ethics committee of the University of Zurich. Written (online) informed consent was obtained from all participants.

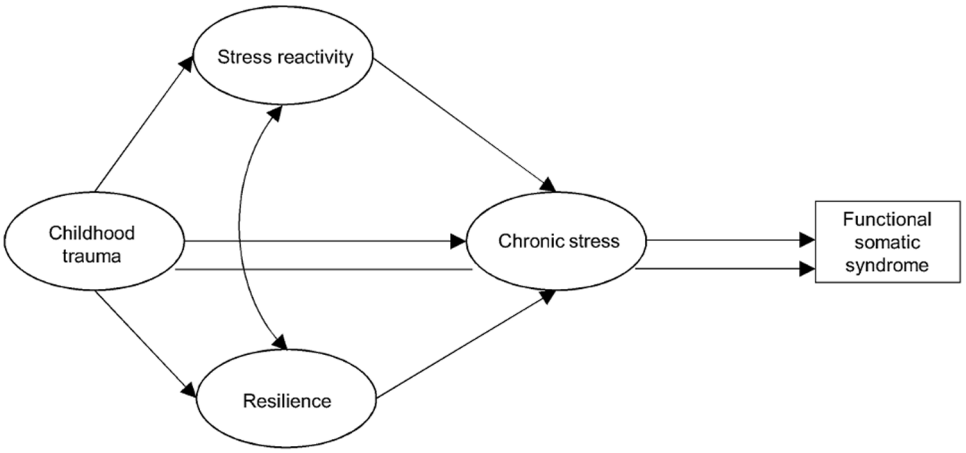

Figure 1. Conceptual model for FSS.
doi:10.1371/journal.pone.0111214.g001

Measures

We decided to shorten each scale in order to reduce the complexity of measurement models of the constructs in terms of the number of parameters to be estimated.

Childhood trauma. To measure childhood abuse and neglect, we used eight items from the German short version of the Childhood Trauma Questionnaire [50] that had the highest factor loadings on the general factor in this sample. The questionnaire consists of six different domains of childhood trauma: emotional abuse, physical abuse, sexual abuse, emotional neglect, physical neglect, and experiences of inconsistency. Of these, only emotional abuse, neglect, and experiences of inconsistency were represented in our eight selected items. An example item is: 'I felt that someone in my family hated me'. Participants rated items on a five point Likert scale from 1 (never) through 5 (very often). A factor analysis (Principal Axis Analysis; PAA) with the eight items signaled a one factor solution (eigen value: 3.91; explained variance: 48.93%). Cronbach's alpha for these items was.88. In addition, participants were classified as having experienced childhood trauma according to recently reported cut-off scores for Germany [51].

Stress reactivity. We selected eight items from the Stress Reactivity Scale [52] to measure stress reactivity that had the highest factor loadings on the general factor. The Stress Reactivity Scale measures general stress reactivity as well as stress reactivity in specific domains (social evaluation, social conflicts, failure, work overload). Moreover, anticipatory stress reactivity, that is, feeling nervous before a previously announced stressor, and prolonged stress reactivity, that is, difficulty relaxing after occurrence of a stressful situation, can be measured with this instrument. Of these, stress reactivity concerning social conflicts and prolonged stress reactivity were the only domains that were not reflected by our choice of items. An exemplary item is: 'When I'm wrongly criticized by others I am normally annoyed for a long time'. Items are rated by marking one out of three statements, leading to a scale ranging from 0 to 2. According to a PAA, a one-factorial structure (eigen value: 3.09; explained variance: 38.65%) underlies the items used in the current study. Internal consistency for these eight items was.83.

Resilience. To obtain a global measure of resilience, we used eight items from the German version of the Resilience Scale [53] with the highest factor loadings. This instrument encompasses aspects of personal competence (e.g., self-esteem) and acceptance of self and life (e.g., flexibility). Items are rated on a seven point Likert scale. An example for an item is: 'I usually manage one way or another'. A PAA with our eight selected items indicated a one factor solution (eigen value: 3.10; explained variance: 38.80%). Internal consistency was.83.

Chronic stress. To measure chronic stress, we used eight items from the screening version of the Trier Inventory for the Assessment of Chronic Stress [35] that had the highest factor loadings. The Trier Inventory for the Assessment of Chronic Stress refers to the past three months, measuring different facets of chronic stress, namely chronic worrying, work and social overload, excessive demands at work, and lack of social recognition on a five point Likert scale. An example item is: 'I do not have enough time to perform my daily tasks'. The eight items used were based on a common factor (eigen value: 4.57; explained variance: 57.09%). Cronbach's alpha was.91.

Functional somatic syndromes. Details on how FSS were diagnosed are reported elsewhere [49]. In brief, we administered a previously developed questionnaire, the Questionnaire on Functional Somatic Syndromes [54]. The German version of this scale is freely available as a Web supplement to the original article (http://content.karger.com/ProdukteDB/miscArchiv/000/333/298/000333298_sm_supplemental_material.pdf). The Questionnaire on Functional Somatic Syndromes consists of three different parts which are connected via several algorithms. First, a screening part encompassing various somatic symptoms was presented. These items represent cardinal symptoms of 17 different FSS. Symptoms were rated according to frequency of occurrence ('never/rarely', 'frequently', 'almost always/always'). Second, if participants reported cardinal symptoms that were characteristic of one FSS (e.g., abdominal pain), additional questions based on diagnostic criteria, e.g., Rome III [55], were presented. Third, those who fulfilled the diagnostic criteria of a specific FSS were surveyed about health care visits (e.g., 'Did you ever visit a doctor about your abdominal pain/changes in bowel movement?'). Participants who responded with 'no' were counted as non-cases. Participants who responded with 'yes' were ultimately directed to a list of items addressing frequent medical exclusionary diagnoses ('What diagnosis did your doctor give you?'). Participants were labeled as having an FSS if they reported that no abnormalities which might account for their symptoms (e.g., an inflammatory bowel disease) had been detected by their physician.

Mental disorders. Details on how the presence of mental disorders was assessed can be found in our previous report [49]. In

brief, we used the German version of the Patient Health Questionnaire [56] to screen for the most common mental disorders, including somatoform syndrome, major depressive syndrome, anxiety syndrome, alcohol syndrome, and bulimia nervosa. All questions and algorithms of the PHQ are guided by DSM-IV criteria [57].

Statistical analyses

We tested our conceptual model (see Figure 1) using a structural equation modeling (SEM) approach. This approach allowed us to evaluate how well our hypothesized relationships between a latent exogeneous variable (childhood trauma), latent mediators (stress reactivity, resilience, and chronic stress), and a manifest dichotomous endogeneous variable (FSS) fit our data. We used item parceling to form our latent variables [58-61]. More specifically, we created two parcels for childhood trauma, stress reactivity, resilience, and chronic stress, with each parcel being based on four items using an item-to-construct balance approach [58–61]. In case of unidimensional constructs (see the results of the PAA) the parceling approach is recommended as a method to reduce the number of variables and to improve the stability of the parameter estimates [58–61]. As in our study FSS was a dichotomous endogenous variable, we used the modified weighted least squares method (WLSMV) for our analysis [62]. To estimate to what extent the empirical covariance matrix of the involved variables could be reproduced by the model, we conducted a χ^2-Test and referred to several fit indices: Comparative fit index (CFI), Tucker-Lewis index (TLI), and root mean square error of approximation (RMSEA). A CFI $\geq$.95, a TLI $\geq$.95 as well as an RMSEA $\leq$.05 signals a good model fit [63,64]. To test the indirect effects for statistical significance, we used the conventional Sobel test [65,66]. Since the Sobel test does, however, rest on the often implausible assumption that both the sampling distribution and indirect effect is normally distributed, we additionally applied the bias-corrected bootstrapping approach as recommended by MacKinnon et al. [67]. The standard errors of the indirect effects and their 95% confidence intervals were estimated based on 1′000 re-samples. In the results section, we report standard errors and *p*-values based on the Sobel Test (see also Table 1 and 2) and confidence intervals stemming from the bootstrapping approach. All analyses were conducted using MPlus V7.

Results

Sample characteristics

A total number of N = 6′206 participants visited the website and about 51% of them finished the survey. After the exclusion of implausible (e.g., survey response duration below 15 minutes) and incomplete datasets, N = 3′054 datasets remained for further analyses. Of these, 2′042 (73.4%) were women and 812 (26.6%) were men and mean age 24.6±5.6 (SD) years. The majority (92.6%) of the participants was not married, and parental household income was almost uniformly distributed across nine predefined categories ranging from less than 3′000 to more than 10′000 Swiss Francs per month (equal intervals across categories). In our sample, physical neglect (24.7%) and emotional abuse (19.4%) were the most prevalent forms of trauma. The prevalence rates of each FSS are reported elsewhere [49]. The most frequently reported FSS were premenstrual syndrome (112 cases or 5%), functional dyspepsia (57 cases or 1.9%), premenstrual dysphoric disorder (34 cases or 1.5%), hyperventilation syndrome (40 cases or 1.3%), and irritable bowel syndrome (39 cases or 1.3%). In our sample, 15.1% had an alcohol syndrome, 9.0% an anxiety syndrome, 8.1% a major depressive syndrome, 6.5% had a somatoform syndrome, and 1.4% had a preliminary diagnosis of bulimia nervosa. Four hundred twenty-nine participants took part in the follow-up survey at T_1, and these participants did not differ from those who chose not to participate with regard to gender, marital status, household income, childhood trauma, stress reactivity, resilience, and chronic stress (data not shown). However, this sub-sample was slightly older (25.6±7.0 vs. 24.4±5.3 years; $t(512.25) = -3.36$, $p = .001$). Of the participants at follow-up, 21 out of 429 (4.9%) had at least one newly developed FSS (incident cases) and 10 out of 48 (20.8%) were stable cases reporting at least one FSS.

Model fit

The first cross-sectional model analyzed included all variables as hypothesized in Figure 1. The model demonstrated good fit statistics ($\chi^2(20) = 50.546$, $p<.001$, CFI = .995, TLI = .991, RMSEA = .022, 90% CI [.015.030]). The χ^2-test was significant for this and the following models, but needs to be interpreted in the context of the large sample size. No significant direct effect of childhood trauma on FSS emerged (Beta = .083, SE(Beta) = .050, $p = .101$). We thus removed this path and repeated our analysis. Our second and final cross-sectional model as depicted in Figure 2 fit our data well ($\chi^2(21) = 48.808$, $p<.001$, CFI = .995, TLI = .992, RMSEA = .021, 90% CI [.013.029]) and did not have a significantly worse fit than the more complex initial model ($\Delta\chi^2 = 1.74$, $\Delta df = 1$, $p = .19$).

In order to evaluate whether our variables were in fact predisposing/precipitating and/or perpetuating factors for FSS, we analyzed our sub-sample of 429 participants that had participated in the follow-up survey. Again, the direct effect of childhood trauma on FSS was non-significant (Beta = .052, SE(Beta) = .064, $p = .410$) and therefore restricted to zero (see Figure 3). As it was the case for the cross-sectional version, this more parsimonious model fitted the data well ($\chi^2(21) = 32.676$, p<.05, CFI = .982, TLI = .969, RMSEA = .036, 90% CI [.001.059]).

Model parameters

All parameter estimates for our cross-sectional and longitudinal analyses are shown in Tables 1 and 2, respectively. In accordance with our proposed conceptual model, childhood trauma had a positive effect on stress reactivity and a negative effect on resilience. Unsurprisingly, the parts of stress reactivity and resilience that could not be accounted for by childhood trauma were negatively related (correlation).

As shown in Tables 1 and 2, our results regarding the direct effects of childhood trauma, stress reactivity, and resilience on chronic stress were also in accordance with our assumptions. Exposure to childhood trauma resulted in more chronic stress at both time points. The same was true regarding stress reactivity, whereas being resilient had an opposite effect. Having suffered from chronic stress during the past three months, in turn, significantly enhanced the probability of having an FSS.

In line with our mediation hypotheses, stress reactivity (Beta = .156, $p <.001$, 95% CI: 0.115, 0.197) had a positive indirect effect on FSS via elevated levels of chronic stress, whereas resilience indirectly lowered the probability of FSS (Beta = −.050, $p<.001$, 95% CI: −0.067. −0.034) via reduced amount of chronic stress (indirect effects; see Table 1). As can be seen in Table 2, this was also true when chronic stress and FSS were measured at T_1 (indirect effect of stress reactivity: Beta = .147, $p <.001$, 95% CI: 0.065, 0.229; indirect effect of resilience: Beta = −.057, $p<.01$, 95% CI: −0.113. −0.001). Moreover, the hypothesized indirect effects of childhood trauma on FSS via chronic stress (Beta = .031,

Table 1. Cross-sectional model direct and indirect effects (standardized coefficients) of variables on chronic stress and FSS (T_0).

	Beta (SE)	*p* value
Measurement Model		
Childhood trauma		
Parcel I	.904 (.014)	<.001
Parcel II	.926 (.014)	<.001
Stress reactivity		
Parcel I	.873 (.009)	<.001
Parcel II	.823 (.009)	<.001
Resilience		
Parcel I	.865 (.008)	<.001
Parcel II	.894 (.008)	<.001
Chronic stress		
Parcel I	.925 (.006)	<.001
Parcel II	.938 (.006)	<.001
Structural Model		
Effect on stress reactivity		
Childhood trauma	.261 (.019)	<.001
Effect on resilience		
Childhood trauma	−.246 (.016)	<.001
Correlation between stress reactivity and resilience	−.489 (0.16)	<.001
Effects on chronic stress		
Direct effects		
Childhood trauma	.116 (.014)	<.001
Stress reactivity	.582 (.016)	<.001
Resilience	−.188 (.016)	<.001
Indirect effects		
Childhood trauma via stress reactivity	.152 (.012)	<.001
Childhood trauma via resilience	.046 (.005)	<.001
Effects on FSS at T_0		
Direct effect		
Chronic stress	.268 (.032)	<.001
Indirect effects		
Childhood trauma via chronic stress	.031 (.005)	<.001
Childhood trauma via reactivity and chronic stress	.041 (.006)	<.001
Childhood trauma via resilience and chronic stress	.012 (.002)	<.001
Stress reactivity via chronic stress	.156 (.019)	<.001
Resilience via chronic stress	−.050 (.007)	<.001

FSS = functional somatic syndromes.
Beta = standardized coefficient.
SE = standard error.
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p <.001, 95% CI:.019,.043), reactivity and chronic stress (Beta = .041, p<.001, 95% CI:.028,.054), as well as via resilience and chronic stress (Beta = .012, p<.001, 95% CI:.008,.017) were significant and in the expected direction. Thus, childhood trauma increased the probability of having an FSS via three indirect routes. The indirect effects of childhood trauma on FSS via chronic stress (Beta = .040, p<.05, 95% CI:.001,.079) and via reactivity and chronic stress (Beta = .029, p<.01, 95% CI:.004,.049) could be replicated in the prospective model (Sobel test and bootstrapping approach). However, the indirect connection via resilience and chronic stress (Beta = .10, p<.05, 95% CI: −.003,.023) was only significant when applying the Sobel test.

Discussion

We set out to examine the role of stress in FSS both cross-sectionally and prospectively. In accordance with our conceptual model, our data show the occurrence of childhood trauma to be significantly related to elevated stress reactivity and attenuated resilience, which in turn predicted the manifestation of FSS via chronic stress. While we observed an indirect effect of childhood trauma on the development and perpetuation of FSS via chronic

Table 2. Longitudinal model direct and indirect effects (standardized coefficients) of variables on chronic stress and FSS (T_1).

	Beta (SE)	*p* value
Measurement Model		
Childhood trauma		
Parcel I	.915 (.039)	<.001
Parcel II	.969 (.041)	<.001
Stress reactivity		
Parcel I	.869 (.026)	<.001
Parcel II	.853 (.026)	<.001
Resilience		
Parcel I	.794 (.028)	<.001
Parcel II	.910 (.031)	<.001
Chronic stress		
Parcel I	.913 (.023)	<.001
Parcel II	.897 (.023)	<.001
Structural Model		
Effect on stress reactivity		
Childhood trauma	.196 (.050)	<.001
Effect on resilience		
Childhood trauma	−.173 (.048)	<.001
Correlation between stress reactivity and resilience	−.545 (0.44)	<.001
Effects on chronic stress		
Direct effects		
Childhood trauma	.117 (.047)	<.05
Stress reactivity	.433 (.053)	<.001
Resilience	−.169 (.053)	<.01
Indirect effects		
Childhood trauma via stress reactivity	.085 (.025)	<.01
Childhood trauma via resilience	.029 (.012)	<.05
Effects on FSS at T_1		
Direct effect		
Chronic stress	.339 (.065)	<.001
Indirect effects		
Childhood trauma via chronic stress	.040 (.018)	<.05
Childhood trauma via reactivity and chronic stress	.029 (.011)	<.01
Childhood trauma via resilience and chronic stress	.010 (.005)	<.05
Stress reactivity via chronic stress	.147 (.036)	<.001
Resilience via chronic stress	−.057 (.021)	<.01

FSS = functional somatic syndromes.
Beta = standardized coefficient.
SE = standard error.
doi:10.1371/journal.pone.0111214.t002

stress, we were not able to show a direct link between traumatic experiences and FSS.

Emotional neglect and abuse were the particluar types of trauma that were indirectly associated with FSS in our sample. These types of childhood trauma resulted from an environment that was perceived as unstable, with caregivers not only failing to meet the child's emotional needs but also showing demeaning and humiliating behavior towards the child [20]. We observed that such experiences were associated with higher stress reactivity and lower resilience in adulthood. More specifically, affected individuals reported elevated habitual levels of stress before important tasks, in response to high workload, social evaluation, and experiences of failure [52]. In addition, they had weaker beliefs in their personal competence and lower levels of acceptance of themselves and their lives [29]. Of note, although stress reactivity and resilience were highly correlated in our sample, they cannot be considered as two sides of the same coin. Rather, they seem to exhibit both overlapping and unique aspects in the stress response context, a finding that is mirrored by recent research suggesting specific neurocircuits to underlie resilience [68]. Interestingly, a recent study showed specific regional patterns of cortical thinning depending on whether participants reported childhood experienc-

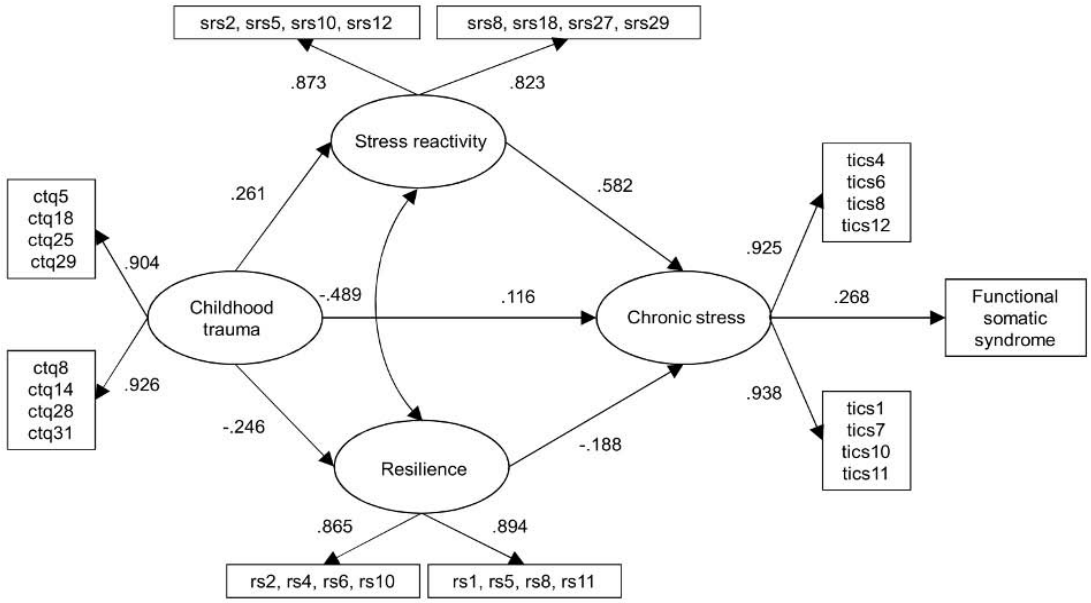

Figure 2. Cross-sectional path analysis model: FSS on chronic stress including standardized path coefficients. ctqx = Childhood Trauma Questionnaire, indicator x. srsx = Stress Reactivity Scale, indicator x. rsx = Resilience Scale, indicator x. ticsx = Trier Inventory for the Assessment of Chronic Stress, indicator x.
doi:10.1371/journal.pone.0111214.g002

es of sexual or emotional abuse [69]. Unlike sexual abuse, cortical thinning was present in regions commonly associated with self-awarness and -evaluation in participants reporting emotional abuse [69]. It is thus conceivable that early adverse stimulation of these brain areas contributes to a vulnerable concept of the self, ultimately resulting in altered stress responses when meeting important tasks or when being subject to social evaluation [69].

These findings fit well with the observation that social-evaluative stressors (like public speaking tasks) are highly effective in eliciting a stress response in FSS patients in the laboratory [25,26]. According to the Lazarus and Folkman framework [19],

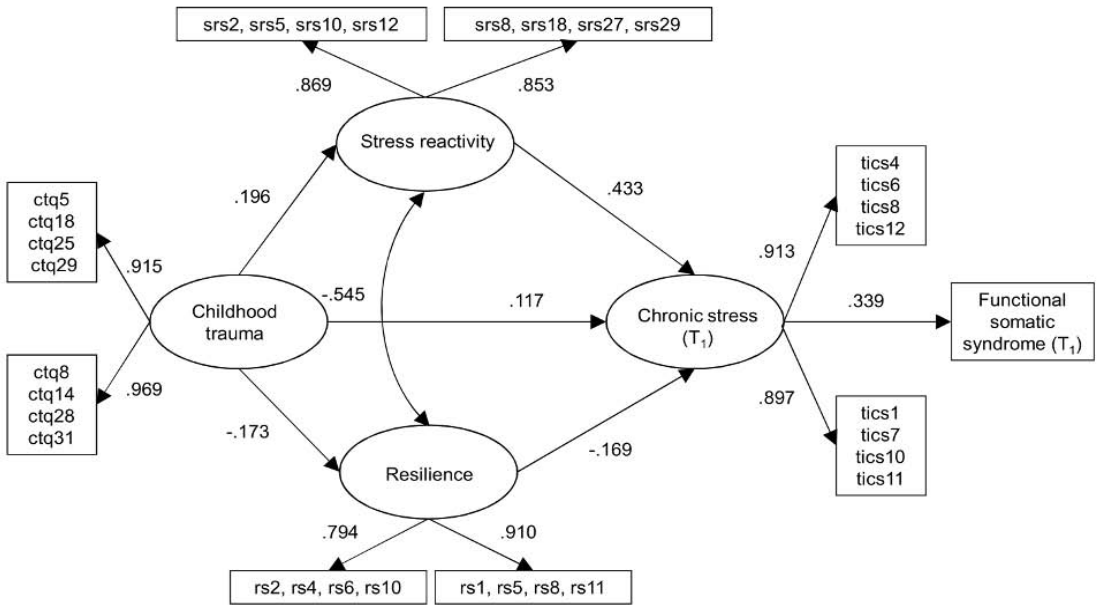

Figure 3. Longitudinal path analysis model: FSS on chronic stress including standardized path coefficients. ctqx = Childhood Trauma Questionnaire (T_0), indicator x. srsx = Stress Reactivity Scale (T_0), indicator x. rsx = Resilience Scale (T_0), indicator x. ticsx = Trier Inventory for the Assessment of Chronic Stress (T_1), indicator x.
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the reason for higher psychological stress responses lies in the appraisal of one's resources as insufficient when encountering a stressor ('secondary appraisal'). Moreover, emotional abuse and neglect and a personality profile that is characterized by high stress reactivity and low resilience seem to render individuals vulnerable to the appraisal of future ambiguous stimuli as a threat [19]. In our sample, these persons were in fact characterized by a high amount of chronic stress at a later timepoint, including worrying and feeling overwhelmed with various kinds of demands. In line with this finding, a study among college students found elevated levels of worry and co-morbidity with generalized anxiety disorder to be characteristic of individuals suffering from irritable bowel syndrome [70]. In our sample, chronic stress was accompanied by the development and perpetuation of FSS. Contrary to our expectations, we did not find a direct effect of experiences of childhood trauma on FSS when all other variables were controlled for. Based on our results, one could thus speculate that for the sensorimotor and emotional concomitants of trauma exposure [46] to translate into FSS, the occurrence of chronic stress as a trigger later on in life is a necessary prerequisite. Regarding the perpetuation of FSS, a recent electronic diary study found stress to predict an increase in functional symptoms in 30% of their participants, thus mirroring our findings in a setting with high ecological validity [71].

Our findings regarding a linkage between childhood trauma and altered stress reactivity in FSS can be discussed in the context of biological findings [72]. For instance, Videlock et al. found traumatic childhood experiences to be related to altered neuroendocrine stress reactivity to a visceral stressor in a sample of irritable bowel syndrome patients [73]. This raises the possibility that our results mirror disturbances at a neuroendocrine level. Importantly, this study utilized an acute stressor in the laboratory as a means of eliciting stress reactivity. However, whether chronic stress outside of the laboratory may serve as an 'opportunity' to translate dysfunctional stress reactivity into FSS has received little attention so far. A recent study conducted in women with fibromyalgia revealed a shorter gestational length (another indicator of early life stress) to be related to altered neuroendocrine stress reactivity, while at the same time 70% of the sample reported severe stress as a triggering event for their symptoms [74]. Unfortunately, the authors did not report to what extent these events were only present in the early life stress/altered stress reactivity group.

This is the first study examining the association between childhood trauma and resilience in FSS patients. It is only in recent years that the neurobiological basis of resilience in humans has begun to be explored [75] and a mere handful of studies have made an effort to approach the subject of resilience integratively, that is, considering both biological and psychological aspects. For instance, a study in patients suffering from posttraumatic stress disorder demonstrated blunted increases in neuropeptide Y (a stress modulating neuropeptide) in response to a pharmacological stimulant of the stress hormone norepinephrine [76]. These findings are intriguing in light of the fact that neuropeptide Y is discussed as a protective factor in stress regulation [75] and high comorbidities with PTSD are present in many patients suffering from FSS [77,78]. However, to what extent this finding applies to patients with FSS remains purely speculative at this point, and both psychological and biological aspects of resilience clearly need to be further scrutinized.

Several limitations need to be taken into account when interpreting our study results. First, the present survey was conducted in a student sample that cannot be considered representative of the general population. Second, our approach of establishing diagnoses of FSS was dependent on the reporting of health care visits, which could potentially lead to an underestimation of prevalence rates. Also, due to the nature of a web-based data collection approach, we were not able to confirm these diagnoses through a physical examination or laboratory assessment in our participants. Third, we relied on retrospective self-reported data to measure childhood trauma. Although the CTQ is a well-validated questionnaire that has been used extensively in research on childhood trauma, we are not able to provide external corroboration of our findings (e.g., by simultaneously asking a family member about childhood trauma occurrence).

In conclusion, we provide a comprehensive view on the role of stress and resilience in the development and perpetuation of various FSS. Large-scale epidemiological studies are warranted to replicate our prospective findings in the general population. Also, while our data suggest stress to be a risk factor that is common to several different FSS, further work is required to confirm our model in samples of specific FSS. Finally, there is an urgent need for integrative research acknowledging both biological and psychological aspects of stress reactivity and resilience in the search for the pathophysiology of FSS.

Our findings have important clinical implications. First, we advocate that attention be paid to the possibility of childhood trauma in FSS patients and affected individuals be offered adequate treatment. Second, given our results, patients with FSS are likely to benefit from interventions reducing stress reactivity (e.g., by learning relaxation techniques) and/or enhancing resilience (e.g., by strengthening individual resources). Finally, due to the observation that the incidence and maintenance of FSS is dependent on chronic stress, a case can be made for psychological therapy as a means of improving stress management strategies.

Author Contributions

Conceived and designed the experiments: SF UMN. Performed the experiments: SF. Analyzed the data: SF GL MG. Contributed reagents/materials/analysis tools: SF GL MG UMN. Wrote the paper: SF GL MG UMN.

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Study IV

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Prevalence, Overlap, and Predictors of Functional Somatic Syndromes in a Student Sample

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Abstract
Background Although at least 20 different functional somatic syndromes (FSS) have been described, and overlaps between individual FSS and a high comorbidity with depressive and anxiety disorders have been suggested, barely any studies have examined a broad array of FSS within one study. Moreover, information on psychosocial risk factors gained from prospective studies is scarce.
Purpose This study aimed to determine prevalence rates, overlap, and comorbidity in 17 FSS and to estimate the influence of psychosocial risk factors on the development of FSS.
Methods In total, 3,054 students (73.4 % women) completed a Web survey containing questions on FSS, comorbidity, and psychosocial risk factors at baseline. Of these, 429 completed the survey again 6 months later.
Results The prevalence of any FSS was 9.5 %, with 227 (78.6 %) subjects fulfilling criteria for only one FSS, 49 (17.0 %) reporting two, and 12 (4.2 %) reporting three syndromes simultaneously. Only one person suffered from four FSS at the same time. "Major depressive syndrome" (15.6 %), "panic syndrome" (4.8 %), and "other anxiety syndromes" (19.7 %) frequently occurred among persons with FSS. Significant predictors of FSS were number of somatic symptoms (OR=1.15), impairment in daily activities (OR=3.17), depression (OR=1.13), and somatization (OR=1.15).
Conclusions Our findings indicate that FSS are common in nonclinical samples. The frequency of overlap and comorbidity in FSS was lower compared with previous research. A consideration of psychosocial risk factors is warranted in the prevention and management of FSS.

Keywords Functional somatic syndromes · Prevalence · Symptom overlap · Comorbidity · Predictors

Introduction

The term "functional somatic syndrome" (FSS) refers to the clinical picture of a particular constellation of somatic symptoms that cannot be adequately explained by any structural or functional abnormality. Syndromes fulfilling this criterion are abundantly prevalent in the general population, accounting for a large proportion of health care visits both in primary [1, 2] and secondary care [3, 4], causing substantial suffering and impairment in patients [5] and leading to a considerable amount of direct (e.g., medical care) and indirect (e.g., lost productivity) costs [6]. Conditions such as chronic fatigue syndrome, fibromyalgia syndrome, or irritable bowel syndrome represent, among many others, frequently occurring examples of FSS. Despite extensive research on FSS, few effective treatment options are available to date.

A critical prerequisite for identifying target populations for treatment programs is the collection of epidemiological data which accurately describe individuals affected by the condition under examination. Prevalence rates from population-based studies for the abovementioned FSS range from 0.2 to 9.4 %

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[7–12]. A characteristic thought to be associated with FSS is gender, with a female preponderance having been consistently reported [7, 8, 10–12], and biological (e.g., endocrine), psychosocial (e.g., traumatic experiences), and sociocultural factors (e.g., health care-seeking behavior) proposed to be responsible for this finding [13, 14]. Furthermore, a low socioeconomic status (SES) seems to be predominant among people suffering from FSS [8, 10, 11]. However, despite growing evidence on such predisposing and precipitating factors in FSS, as yet, no final conclusions can be drawn regarding the exact determinants and processes underlying these debilitating disorders.

Identifying the amount of overlap and comorbidity of FSS might further facilitate our understanding of relevant etiological factors common to all of these syndromes. A considerable overlap has frequently been reported between different FSS on both the symptom and syndrome level [15, 16]. Thus, common pathophysiological mechanisms have been proposed as underlying these syndromes [17–19]. This observation has also led some researchers to question the validity of separate diagnostic entities, interpreting them as mere artifacts of medical specialization [20]. However, samples in these studies were mostly drawn from clinical settings, such as primary, secondary, or tertiary health care, thus rendering them subject to referral bias. Clearly, studies from nonclinical populations are needed in order to generalize findings to all groups of affected individuals. Furthermore, despite considerable evidence on the co-occurrence of FSS, only a small number of studies have looked at more than two syndromes simultaneously (e.g., [21–23]), meaning that the broad spectrum of these disorders is largely neglected.

Similar to studies on overlaps in FSS, investigations of comorbidity have shown a high co-occurrence of depressive and anxiety disorders [24, 25]. However, as mentioned above, further studies recruiting nonclinical populations are needed. In addition, one of the major limitations of previous research in FSS was that only very few studies adopted a prospective study design. Initial attempts to elucidate the temporal order between FSS and comorbid mental disorders have been undertaken, supporting the suggestion of a predisposing role of depression and anxiety in the development of FSS [26–29].

For purposes of etiological research and in order to develop effective prevention strategies, it is essential to identify risk factors in illnesses. Clinical studies in populations at risk (e.g., after an infection) have revealed several psychosocial factors to precede FSS (e.g., number of somatic symptoms, somatization, mental disorders, and illness behavior [30–32]). Similar factors emerged in population-based studies, thus corroborating these findings further [26, 28, 33]. When comparing research on individual FSS, the number of somatic symptoms, the severity of cardinal symptoms, somatization, depression, and anxiety were, apart from gender and age, among the most significant predictors. However, samples recruited from the general population are diverse regarding various variables that have frequently been associated with health (e.g., age, SES, or lifestyle factors). Therefore, an examination of more homogeneous samples might further add to explaining the relationship between psychosocial aspects and FSS.

In sum, research on FSS is in need of epidemiological data on the co-occurrence of more than two FSS. Moreover, nonclinical samples should be investigated in studies on comorbidity in order to prevent selection bias. In addition, more prospective evidence on risk factors in the development of FSS is required. To address these issues, we conducted the current study, which aimed to (1) determine prevalence rates and associated characteristics of FSS in a sample of apparently healthy students, (2) examine the overlap between multiple FSS and comorbidity in a nonclinical sample, and (3) evaluate the impact of relevant psychosocial risk factors on the development of FSS at a later time point. We expected prevalence rates to be comparable to similar studies conducted in student populations. Additionally, we assumed that the overlap and comorbidity would be less extensive in our nonclinical sample. Finally, based on the literature, we hypothesized that the number and severity of somatic symptoms, somatization, as well as depression and anxiety disorders would predict the incidence of any FSS.

Methods

Participants and Procedure

School administrators from public colleges and universities in the German-speaking part of Switzerland were contacted and asked for their assistance in conducting the current study. Potential participants were contacted through cooperating institutions via e-mail and asked to participate in a Web survey on physical and mental well-being (T_0). In addition, a link to the Website was posted on several internet platforms known to be frequently visited by students. Participation was voluntary and all subjects provided electronic informed consent. All procedures were in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki, and the Web survey study design was approved by the local ethics committee. Participants had the chance to win luncheon vouchers and cinema tickets as compensation for their efforts. All subjects were asked if they wished to participate in a follow-up survey and those who agreed were asked to complete the same survey 6 months later (T_1).

Measurements

To assess prevalence rates of FSS, we administered a previously developed questionnaire (Questionnaire on Functional

Somatic Syndromes (FFSS) [34]). The German version of the FFSS is freely available as a Web supplement to the original article (http://content.karger.com/ProdukteDB/miscArchiv/000/333/298/000333298_sm_supplemental_material.pdf). The FFSS consists of three different parts which are connected via several algorithms. First, a screening tool encompassing 52 items on various somatic symptoms was presented. These items represent cardinal symptoms (e.g., abdominal pain) of the most common FSS. Importantly, symptoms are rated according to current frequency of occurrence ("never/rarely," "frequently," and "almost always/always"). A symptom count was calculated by adding up symptoms that were at least frequently present. In addition, the screening tool contains dichotomous questions on functional impairment due to symptoms in different areas (e.g., in daily routine activities), which served as an indicator of symptom severity in this study. Finally, a categorical item on the duration of symptoms (e.g., for at least 3 months) is part of the questionnaire. Second, if participants reported cardinal symptoms that were characteristic of one of 17 FSS (e.g., abdominal pain for at least 3 months), additional questions based on international research diagnostic criteria were presented. These questions allow for a detailed understanding of cardinal and associated complaints, symptom course and fluctuation, functional impairment, and symptom onset regarding each FSS. The following FSS are represented in the questionnaire (either publication on diagnostic criteria or, if no such publication is available, operationalization of the syndrome is mentioned in brackets): tension-type headache and persistent idiopathic facial pain [35], whiplash-associated disorders (pain of at least 6 months' duration that is related to an accident), temporomandibular disorders [36], globus and functional chest pain of presumed esophageal origin [37], functional dyspepsia [38], irritable bowel syndrome [39], chronic low back pain (lower back pain of at least 6 months' duration causing impairment), fibromyalgia syndrome [40], chronic fatigue syndrome [41], multiple chemical sensitivity [42], chronic pelvic pain in men [43] and in women (lower abdominal pain of at least 6 months' duration), premenstrual syndrome [44] and premenstrual dysphoric disorder [45], and hyperventilation syndrome [46]. Third, subjects meeting the minimum of required diagnostic criteria (e.g., recurrent abdominal pain or discomfort on at least 3 days/month in the last 3 months including changes in bowel movement, with symptom onset 6 months previously) were subsequently surveyed about health care visits ("Did you ever see a doctor about your abdominal pain/changes in bowel movement?"). Participants who answered "yes" to this question were ultimately directed to a list of items addressing frequent differential diagnoses ("What diagnosis did your doctor give you?"). Participants were labeled as having FSS (e.g., irritable bowel syndrome) if they reported that no abnormalities had been detected by their doctor which might account for their symptoms (e.g., an inflammatory bowel disease). The FFSS screening tool has good psychometric properties regarding both internal consistency (Cronbach's alpha=0.94) and retest reliability (r=0.80−0.94). No information on external validity is available to date.

Information on comorbidity was obtained by administering the German version of the Patient Health Questionnaire (PHQ [47, 48]). This scale screens for general psychopathology on a symptom and syndrome level. A "somatoform syndrome" was considered to be present if a person reported at least 3 out of 13 somatic symptoms leading to severe impairment during the past 4 weeks. These somatic symptoms (e.g., back pain) are frequently experienced by patients suffering from both somatoform disorders and FSS. Depression was measured along a continuum by adding up nine depression-relevant items. On the other hand, an algorithm allowed for a preliminary diagnosis of a current episode of major depression, labeled "major depressive syndrome." In order to receive this preliminary diagnosis, individuals needed to report at least five out of nine symptoms characteristic of a major depressive episode according to DSM-IV [45], including depressed mood and/or diminished interest or pleasure in activities. Similarly, if between two and four of these symptoms were present, including depressed mood and/or diminished interest or pleasure in activities, criteria for "other depressive syndromes" were seen as fulfilled. Moreover, both syndromes needed to have been present for 2 weeks and the symptoms needed to be present for most of the time. "Panic syndrome" was defined by recurring unexpected panic attacks causing suffering/and or impairment. The definition of a panic attack was in accordance with DSM-IV [45]. "Other anxiety syndromes" were considered as present in an individual if he/she reported feeling nervous, anxious, tense, or worried during the past 4 weeks. Additionally, three out of six symptoms relevant for a diagnosis of a generalized anxiety disorder as described in DSM-IV [45] had to be met. A preliminary diagnosis of "bulimia nervosa" and "binge eating disorder" were present in cases of recurrent episodes of binge eating occurring at least twice a week during the past 3 months. The definition of an episode of binge eating was in accordance with DSM-IV [45]. Furthermore, recurrent compensatory behavior in order to prevent weight gain differentiated a preliminary diagnosis of "bulimia nervosa" from a preliminary diagnosis of "binge eating disorder." Finally, participants were classified as having "alcohol syndrome" if they reported at least one out of five maladaptive alcohol-related behaviors within the last 6 months. As with the remaining syndromes, these questions were guided by the DSM-IV [45] criteria for substance abuse [45].

In addition, all 12 items of the somatization subscale of the German version of the revised Symptom Checklist 90 (SCL-90-R [49, 50]) were administered. Somatization refers to a person's tendency to both frequently experience and report somatic distress [51]. The items in this scale represent somatic symptoms commonly experienced in patients suffering from

somatization disorder (e.g., dizziness and fainting spells), but are rather untypical of common FSS such as premenstrual syndrome, functional dyspepsia, or irritable bowel syndrome. Importantly, symptoms are rated according to the extent to which an individual was bothered by somatic symptoms in the previous 7 days ("not at all" to "extremely"). Therefore, the somatization score calculated based on these items reflected the amount of somatic distress experienced by study participants.

Statistical Analyses

Descriptive statistics (mean, standard deviation, and range) were used to describe participants. Prevalence rates for diagnoses according to well-established criteria and for overlap between FSS, as well as for comorbidity, were calculated in percentages. Student's *t* tests and Chi-square tests were computed for comparisons between FSS noncases and cases at T_0 (cross-sectional analyses), as well as for comparisons between subjects without any diagnosis of FSS at T_0 or T_1 and subjects reporting a newly developed FSS at T_1 (prospective analyses). Odds ratios were calculated for variables that differed significantly between the latter two groups through the use of univariate binary logistic regression analysis. In addition, multivariate binary logistic regression analysis was applied in order to identify the most significant risk factors for newly developed FSS at T_1. The software SPSS 20.0 (SPSS, Chicago, IL) was used and the significance level was set at α=5 % (two tailed).

Results

Sample Characteristics

In total, 6,206 participants visited the survey Website at T_0. A total of 3,054 (49.3 %) students provided full information on gender and age and completed the Web survey, taking a minimum of 15 min (36 min completion time on average). These subjects were considered to have provided reliable data and were thus included in the statistical analyses. Two thousand and forty-two (73.4 %) were women and 812 (26.6 %) were men, and the mean age was 24.6±5.6 (SD) years. The majority (92.6 %) of the subjects was single, and parental household income was almost uniformly distributed across nine predefined categories ranging from less than 3,000 to more than 10,000 Swiss Francs/month (equal intervals across categories). At T_1, 429 students participated in the follow-up survey, and these participants did not differ from those who chose not to participate with regard to gender, marital status, household income, number of somatic symptoms, functional impairment due to symptoms, as well as number of FSS, comorbidity, and somatization according to the SCL-90-R at T_0 (data not shown). However, the subsample was slightly older (25.6±7.0 vs. 24.4±5.3 years; T (512.25)= −3.36, p<0.01) and indicated having suffered from somatic symptoms for longer (52.1 % vs. 44.8 % for more than 1 year; χ^2 (6, N=2,724)=15.78, p<0.05).

Prevalence and Characteristics of FSS

Point prevalence rates of FSS are reported in Table 1. No subjects reported suffering from persistent idiopathic facial pain and no male subjects suffered from chronic pelvic pain; these FSS were therefore excluded from all further analyses. Premenstrual syndrome (5.0 %), functional dyspepsia (1.9 %), and premenstrual dysphoric disorder (1.5 %) were the most frequently reported syndromes.

At least one FSS was reported by 289 (9.5 %) subjects. Within this group, women were significantly over-represented, with prevalence rates of any FSS of 11.6 % (vs. 3.7 % among men; χ^2 (1, N=3,054)=42.96, p<0.001). Subjects belonging to the FSS group reported 12.8±6.8 (vs. 6.5±5.5 in noncases) symptoms on the FFSS. They experienced impairment due to symptoms in various domains such as in their daily routine (31.1 vs. 16.1 % in noncases), in their movements (20.1 vs. 11.2 % in noncases), in educational and/or occupational activities (34.9 vs. 25.2 % in noncases), and 26.3 % (vs. 15.5 % in noncases) felt that their symptoms negatively affected their social lives. More than three quarters (88.9 vs. 27.1 % in noncases) of FSS cases had been suffering from somatic symptoms as measured by the FFSS for more than 1 year. These

Table 1 Prevalence rates of FSS

	Total (n=3,054)	Men (n=812)	Women (n=2,242)
Frequencies of FSS (FFSS; %)			
Tension-type headache	26 (0.9)	6 (0.7)	20 (0.9)
Whiplash associated disorder	11 (0.4)	0 (0.0)	11 (0.5)
Temporomandibular disorder	19 (0.6)	4 (0.5)	15 (0.7)
Chronic low back pain	2 (0.1)	0 (0.0)	2 (0.1)
Fibromyalgia syndrome	2 (0.1)	0 (0.0)	2 (0.1)
Chronic fatigue syndrome	1 (<0.1)	0 (0.0)	1 (<0.1)
Multiple chemical sensitivity	1 (<0.1)	0 (0.0)	1 (<0.1)
Hyperventilation syndrome	40 (1.3)	7 (0.9)	33 (1.5)
Globus	2 (0.1)	1 (0.1)	1 (<0.1)
Functional chest pain	14 (0.5)	6 (0.7)	8 (0.4)
Functional dyspepsia	57 (1.9)	8 (1.0)	49 (2.2)
Irritable bowel syndrome	39 (1.3)	5 (0.6)	34 (1.5)
Chronic pelvic pain	5 (0.2)	n.a.	5 (0.2)
Premenstrual syndrome	112 (5.0)	n.a.	112 (5.0)
Premenstrual dysphoric disorder	34 (1.5)	n.a.	34 (1.5)

FFSS questionnaire on functional somatic syndromes, *FSS* functional somatic syndromes

subjects had an average somatization score of 7.1±5.5 (vs. 3.9±3.9 in noncases) on the SCL-90-R. Cases with FSS differed from noncases in terms of number of symptoms (T (327.62)=−15.19, $p<0.001$), functional impairment in daily routine activities (χ^2 (1, N=2,735)=39.83, $p<0.001$), movement (χ^2 (1, N=2,735)=19.28, $p<0.001$), at school or work (χ^2 (1, N=2,735)=11.93, $p<0.001$), and regarding relationships with others (χ^2 (1, N=2,735)=21.95, $p<0.001$), duration of symptoms (χ^2 (6, N=2,724)=36.90, $p<0.001$), and somatization scores (T (328.67)=−13.46, $p<0.001$).

Overlap

The relative overlap of FSS is reported in Table 2. The number of FSS ranged from one to four, with 227 (78.6 %) subjects fulfilling criteria for only one FSS, 49 (17.0 %) reporting two, and 12 (4.2 %) reporting three syndromes simultaneously. Only one person suffered from four FSS at the same time. The overlap ranged from 0 to 100 %/syndrome, with 3.7±3.0 (out of 15, excluding idiopathic facial pain and chronic pelvic pain in men) co-occurring syndromes on average.

Comorbidity

Comorbidity is reported in Table 3. Cases with any FSS were more frequently affected by mental disorders as assessed by the PHQ. They reported higher prevalence rates of somatoform syndrome (χ^2 (1, N=3,054)=87.53, $p<0.001$), major depressive syndrome (χ^2 (1, N=3,054)=24.35, $p<0.001$), panic syndrome (χ^2 (1, N=3,054)=18.82, $p<0.001$), and other anxiety syndromes (χ^2 (1, N=3,054)=45.18, $p<0.001$), but not of other depressive syndromes (χ^2 (1, N=3,054)=0.001, p=0.970), bulimia nervosa (χ^2 (1, N=3,054)=0.24, p=0.625), binge eating disorder (χ^2 (1, N=3,054)=3.00, p=0.083), or alcohol syndrome (χ^2 (1, N=3,054)=0.02, p=0.901).

Table 3 Comorbidity in FSS

	Non-cases (n=2,765)	Cases (n=289)
Psychopathology (PHQ; %)		
Somatoform syndrome[a]	142 (5.1)	56 (19.4)
Major depressive syndrome[a]	201 (7.3)	45 (15.6)
Other depressive syndromes	241 (8.7)	25 (8.7)
Panic syndrome[a]	38 (1.4)	14 (4.8)
Other anxiety syndromes[a]	217 (7.8)	57 (19.7)
Bulimia nervosa	38 (1.4)	5 (1.7)
Binge eating disorder	15 (0.5)	4 (1.4)
Alcohol syndrome	419 (15.2)	43 (14.9)

FSS functional somatic syndromes, *PHQ* patient health questionnaire

[a] Significant differences between noncases and cases

Table 2 Relative overlap of FSS

	TTH	WAD	TMD	CLBP	FMS	CFS	MCS	HVS	GH	FCP	FD	IBS	CPP	PMS	PMDD
Diagnosis (FFSS)															
TTH	100	0	0	0	0	0	0	0	0	0	0	0	0	3.8	0
WAD	0	100	0	0	0	0	0	0	0	0	0	9.1	0	0	0
TMD	0	0	100	0	0	0	0	5.3	0	5.3	5.3	0	5.3	5.3	5.3
CLBP	0	0	0	100	0	0	0	0	0	0	50.0	0	0	0	0
FMS	0	0	0	0	100	0	0	0	0	0	0	0	0	50.0	50.0
CFS	0	0	0	0	0	100	0	0	0	0	0	0	0	0	0
MCS	0	0	0	0	0	0	100	100	0	0	0	0	0	100	100
HVS	0	0	2.5	0	0	0	2.5	100	0	2.5	10.0	5.0	0	15.0	10.0
GH	0	0	0	0	0	0	0	0	100	0	0	0	0	0	0
FCP	0	0	7.1	0	0	0	0	7.1	0	100	7.1	0	0	0	0
FD	0	0	1.8	1.8	0	0	0	7.0	0	1.8	100	19.3	1.8	7.0	3.5
IBS	0	2.6	0	0	0	0	0	5.1	0	0	28.2	100	5.1	10.3	2.6
CPP	0	0	20.0	0	0	0	0	0	0	0	20.0	40.0	100	0	0
PMS	0.9	0	0.9	0	0.9	0	0.9	5.4	0	0	3.6	3.6	0	100	30.4
PMDD	0	0	2.9	0	2.9	0	2.9	11.8	0	0	5.9	2.9	0	100	100

FFSS questionnaire on functional somatic syndromes, *FSS* functional somatic syndromes, *TTH* tension-type headache, *WAD* whiplash-associated disorders, *TMD* temporomandibular disorders, *CLBP* chronic low back pain, *FMS* fibromyalgia syndrome, *CFS* chronic fatigue syndrome, *MCS* multiple chemical sensitivity, *HVS* hyperventilation syndrome, *GH* globus, *FCP* functional chest pain, *FD* functional dyspepsia, *IBS* irritable bowel syndrome, *CPP* chronic pelvic pain, *PMS* premenstrual syndrome, *PMDD* premenstrual dysphoric disorder

Predictors of FSS Incidence

Findings referring to predictors of newly developed FSS are reported in Table 4. Out of 429 participants, 10 (20.8 %) were stable cases reporting at least one FSS and 21 (4.9 %) had a newly developed FSS after 6 months (i.e., incidence cases). The somatic symptom count according to the FFSS (T (21.04)=−3.20, $p<0.01$), impairment in daily activities (χ^2 (1, N=337)=5.96, $p<0.05$), depression as measured by the PHQ (T (21.13)=−2.06, $p<.05$), and somatization (T (20.74)=−2.38, $p<0.05$) were higher in new cases with FSS at T_1 than in subjects without any diagnosis of FSS at either of the two time points. However, multivariate binary logistic regression calculations revealed the number of somatic syndromes to be the only significant predictor of new FSS occurrence at T_1 (OR=1.1, CI=1.0−1.2, $p<0.05$).

Discussion

The prevalence rate of any FSS was found to lie at nearly one in ten participants (9.5 %), with the majority of subjects (78.6 %) reporting only one syndrome occurring at a time. The mean number of overlapping syndromes was 3.7 out of 15 syndromes. Only somatoform syndrome, major depressive syndrome, panic syndrome, and other anxiety syndromes were more prevalent among cases with any FSS. Finally, significant predictors of FSS incidence at T_1 were number of somatic symptoms, functional impairment in daily activities (as an indicator of symptom severity), as well as depression and somatization at T_0.

In previous studies, frequencies of individual syndromes in the general population were almost consistently higher than in our study [8–12]. However, since we studied a student population, our findings should only be compared with similar samples. When looking at similar samples, the same picture emerges: our results regarding tension-type headache were around 30 times lower compared with prevalence rates of 9.5 to 32.9 % obtained in students in Brazil [52–54], Greece [55], Turkey [56], Oman [57], and Singapore [58]. Premenstrual syndrome in a Nigerian [59], Saudi Arabian [60], Iranian [61], and Pakistani [62] sample, and premenstrual dysphoric disorder in a Brazilian sample [63], two Nigerian samples [64, 65], a Kuwait-based sample [66], and a Pakistani [62] sample were found to be more common in comparison to our study. By contrast, similar patterns of relatively low prevalence rates emerged in student populations regarding other pain conditions, such as temporomandibular disorder in a Swedish sample [67] and fibromyalgia syndrome in a Turkish sample [68], with the latter study additionally reporting relatively few cases with CFS [68]. Comparisons regarding functional gastrointestinal disorders were somewhat mixed, with a German study showing relatively high prevalence rates of irritable bowel syndrome [69], and a Swiss study finding prevalence rates matching our results [70]. Overall, prevalence rates of FSS in Swiss students seem to be relatively low compared with similar study populations in other countries. Our finding of lower prevalence rates compared with studies conducted in the general population might be explained by sample characteristics, such as SES, which is generally very high in Switzerland. Moreover, the present study employed a rather rigorous approach in diagnosing FSS, and this might have contributed to the differing frequencies observed in other student samples. For example, the majority of population-based studies relied on mere self-report of symptoms required for a diagnosis of one specific FSS, while at the same time neglecting to request information on medical illnesses that may account for the reported symptoms.

In this nonclinical study, only a small number of individuals suffered from several FSS simultaneously and rather low levels of overlap among FSS were observed. To our knowledge, no study has yet examined 17 FSS simultaneously. Our finding of only a small proportion of cases reporting several FSS at the same time echoes previous studies on the overlap between four and six different FSS, respectively [21, 22]. Our results regarding the level of overlap, on the other hand, are not entirely in agreement with earlier population-based studies. For example, Jason et al. reported levels of overlap between chronic fatigue syndrome, fibromyalgia syndrome, and multiple chemical sensitivity ranging from 8.9 to 40.6 % [71], and White et al. found 59.5 % of subjects with a fibromyalgia syndrome to be affected by chronic fatigue syndrome [72]. With regard to irritable bowel syndrome, a study by Zondervan et al. showed a substantial overlap with chronic pelvic pain (38.5 % [73]). Sample selection bias might account for these diverging results, as two of the above-cited studies preselected their subjects regarding symptoms of

Table 4 Predictors at T_0 of FSS incidence at T_1

	Non-cases (n=361)	New cases (n=21)	OR (95 % CI)
Mean values and frequencies (SD; %)			
Number of somatic symptoms (FFSS)	6.20 (5.18)	11.71 (7.80)	1.15 (1.04–1.23)
Impairment in daily routine (FFSS)	46 (14.5)	7 (35.0)	3.17 (1.20–8.37)
Depression (PHQ-9)	5.67 (3.94)	8.29 (5.73)	1.13 (1.04–1.24)
Somatization (SCL-90-R)	3.88 (3.76)	7.38 (6.70)	1.15 (1.06–1.24)

FFSS questionnaire on functional somatic syndromes, *FSS* functional somatic syndromes, *PHQ* patient health questionnaire, *SCL* symptom checklist

fatigue and pain. Our findings on the overlap of FSS generally point to specific etiological factors in individual FSS. Nevertheless, a small group of our participants was affected by several FSS at the same time. Interestingly, a recent study confirmed earlier findings of distinct clusters of somatic symptoms by employing latent class analysis in a large sample of twins [74]. However, these authors also found one cluster consisting of individuals reporting multiple symptoms at the same time, which is in line with our results. Another study on FSS in adolescents provided evidence on differential cortisol response patterns in a cluster of gastrointestinal symptoms and headache and one of musculoskeletal pain, dizziness, and overtiredness, respectively, pointing to specific pathophysiological correlates in FSS [75]. In conclusion, further research investigating differential pathophysiological mechanisms in FSS is warranted at this point.

Our findings regarding comorbidity are in line with high levels of depressive and anxiety disorders usually experienced by affected populations [24, 25]. However, as with prevalence rates and levels of overlap, we mostly observed slightly lower proportions of subjects with any comorbid depressive or anxiety disorder compared with previous population-based research [76–78]. Again, this discrepancy might be explained by sample characteristics and/or different diagnostic approaches. Only 19.4 % of our FSS cases concomitantly fulfilled criteria for a somatoform syndrome, which is often considered equivalent to a diagnosis of FSS. This might imply that the current definition of somatoform disorders does not capture the whole spectrum of FSS and is thus in need of a substantial revision (for a comparison of new proposals, see [79]). However, this finding needs to be interpreted with caution since we did not utilize a clinical interview to assess mental disorders. High levels of comorbidity with depressive and anxiety disorders often observed in FSS patients might in part reflect mere symptom overlap (e.g., lack of energy, problems with concentration [80]). On the other hand, a recent population-based study on FSS, major depression, and generalized anxiety disorder identified two latent traits labeled "sensory component" and "affective component" which are common to all of these conditions [81]. Interestingly, these two components seemed to load differentially on FSS and mental disorders, respectively, indicating shared as well as specific pathophysiological mechanisms underlying these conditions.

By employing a prospective study design, the present study showed a predictive quality for the number of somatic symptoms, functional impairment in daily activities (as an indicator of symptom severity), depression, and somatization in FSS. Recruiting a rather homogeneous sample of well-educated young adults automatically limits the influence of some confounders relevant to health (e.g., SES and lifestyle factors). Our first finding is in accordance with an earlier study conducted among women reporting pain, which identified the number of associated symptoms as a major risk factor for later development of chronic widespread pain, which is a typical feature of fibromyalgia syndrome [32]. Moreover, a recent study in patients with glandular fever found an association between number of nonspecific complaints, among other factors, and new onset of chronic fatigue syndrome [30]. Similar to our finding of impairment in daily routine activities being a risk factor for incidence of any FSS at a later time point, Leone et al. [82] found lower levels of physical functioning to precede CFS-like illness among sick-listed employees. Our results are compatible with several prospective studies showing an association between depression and FSS [26–28, 30, 32, 83]. Hallmark symptoms of depression (e.g., social withdrawal, and avoidance behavior) might be associated with aggravation of somatic symptoms due to reducing general fitness levels through physiological deconditioning processes. Similarly, population-based studies showed higher levels of somatization in individuals with later development of chronic widespread pain and irritable bowel syndrome, respectively [28, 29, 33]. Somatization reflects the individual amount of suffering on account of somatic complaints and might thus constitute a "cognitive vulnerability" towards the development of FSS. Notably, our findings on predictors of FSS suggest at least some common psychosocial risk factors in all FSS.

Several limitations need to be taken into account when interpreting our study results. First, the present survey was conducted in a student sample that cannot be considered representative of the general Swiss population, thus limiting the generalizability of our findings. In addition, people with a special interest in health might have been more likely to participate in our study, therefore adding further to the selection bias. Second, our approach of establishing diagnoses of FSS was dependent on the reporting of health care visits, which could potentially lead to an underestimation of prevalence rates. Also, due to the nature of a Web-based data collection approach, we were not able to confirm these diagnoses through a physical examination or laboratory assessment in our subjects. Third, our finding of a somatic symptom count predicting the incidence of any FSS 6 months later might seem trivial at first, as reporting at least one somatic symptom (e.g., abdominal pain) is inherent to any FSS diagnosis (e.g., irritable bowel syndrome). This suggests at least some conceptual overlap in these analyses. However, the fact that subjects experiencing 12 (instead of only six) different somatic symptoms on average had a higher probability of suffering from any FSS 6 months later suggests that nonspecific symptoms (e.g., headaches) were in fact major risk factors for the development of specific syndromes. Also, the somatic symptom count consisted of both medically unexplained and explained symptoms, which further highlights the conceptual difference to FSS diagnoses.

To summarize, our data on 17 FSS in Swiss students represent an important addition to previous epidemiological data. Furthermore, this study complements previous research examining only a small number of FSS simultaneously. In our prospective study, we identified the number of somatic symptoms and functional impairment as valid indicators of clinical relevance in somatic complaints. Most interestingly, while our results on overlap in FSS point to differential etiological factors in the development of individual FSS, a number of psychosocial factors seem to be relevant to all FSS. Thus, future research needs to investigate differential pathophysiological mechanisms and possibly specific psychosocial risk factors by comparing multiple FSS at the same time.

Our findings point to the relevance of a somatic symptom count as a possible red flag for FSS, which could be easily assessed in a primary care setting by, for example, administering a checklist to patients. Furthermore, treatment of FSS should aim at reducing functional impairment due to somatic symptoms. Moreover, the presence of depression might contribute to motivational difficulties with regard to seeking adequate treatment and compliance during therapy. Finally, information on attentional bias and alternative explanations for somatic sensations might be addressed in individuals at risk of FSS. Thus, careful consideration of these variables in the current diagnostic assessment of FSS is warranted and comorbidity with depressive disorders as well as somatization needs to find adequate consideration in the management of FSS.

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Competing Interests The authors declare no competing interests.

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Study V

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Functional somatic syndromes: asking about exclusionary medical conditions results in decreased prevalence and overlap rates

Susanne Fischer* and Urs M Nater

Abstract

Background: The diagnosis of functional somatic syndromes (FSS) requires 1) presence of somatic symptoms, and 2) absence of medical conditions potentially accounting for these symptoms. Due to the limited feasibility of medical examinations, epidemiological research on FSS has neglected to assess the second criterion. Our objective was therefore to evaluate the implications of considering information on exclusionary medical conditions in epidemiological research on FSS.

Methods: A survey among 3'054 students was conducted. We compared prevalence rates and overlap of 17 FSS obtained by: 1) a *symptom-based strategy* and 2) a *symptom-and-exclusion-based strategy* including information on exclusionary medical conditions.

Results: The *symptom-and-exclusion-based strategy* led to a marked decrease in prevalence rates compared to the *symptom-based strategy*. Furthermore, it resulted in fewer individuals who were affected by multiple FSS.

Conclusions: Adding self-reported information on exclusionary medical conditions leads to a significant decrease in the prevalence and overlap of FSS. More rigorous approaches to studying FSS should be adopted.

Keywords: Diagnostic criteria, Epidemiology, Functional somatic syndromes, Overlap, Population-based, Prevalence

Background

The term 'functional somatic syndrome' (FSS) refers to a certain constellation of somatic symptoms that cannot be adequately explained in the context of a known medical condition. Case definitions of the numerous existing FSS therefore each require 1) the presence of at least one characteristic symptom (positive criterion), and 2) the absence of any medical condition that can account for these symptoms (negative criterion). There is a long list of FSS, but among the most prevalent are chronic fatigue syndrome, fibromyalgia syndrome, and irritable bowel syndrome. The diagnostic criteria for FSS are commonly formulated by expert committees; examples are the 1994 Centers for Disease Control and Prevention criteria for chronic fatigue syndrome [1], the Rome III criteria for irritable bowel syndrome (and other functional gastrointestinal disorders) [2], and the 1990 and 2010 American College of Rheumatology criteria for fibromyalgia [3,4].

These diagnostic criteria are used in clinical practice and research settings, where patients are asked about symptoms (positive criterion), medical records are reviewed, and physical examinations and laboratory tests are performed in order to identify medical conditions considered exclusionary for FSS (negative criterion). This two-step approach, which covers the assessment of both criteria inherent in the definition of FSS, is considered the *gold standard* for diagnosing an FSS. However, epidemiological research is challenged by the limited feasibility of reviewing medical records and/or conducting comprehensive medical examinations, and thus often exclusively relies on self-reported information. Several ways of diagnosing FSS have been adopted to deal with this problem: a) asking patients whether they suffer from a (specific) FSS (*self-reported diagnosis*), b) asking patients whether they have ever received an FSS diagnosis by a physician (*physician diagnosis*), or c) providing patients with a list of

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characteristic symptoms in accordance with the diagnostic criteria, but without an assessment of exclusionary factors (*symptom-based diagnosis*). Naturally, the approaches leading to these outcomes differ in their ability to cover both the positive and negative criterion of FSS.

It is conceivable from this comparison that the choice of diagnostic strategy may contribute to diverging study findings. In fact, reviews on the epidemiology of each FSS show a broad range of prevalence rates across studies (e.g., [5-7]). Another epidemiological estimate rather specific to research on FSS is the amount of comorbidity among FSS, i.e., the so-called 'overlap'. With regard to prevalence rates, overlap between FSS has been found to vary substantially [8,9]. Importantly, studies showing high levels of overlap have led some researchers to propose the existence of only one FSS [10]. These so-called 'lumpers' are opposed by other authors, who insist that there are several specific syndromes, and these authors are usually referred to as 'splitters' [11]. Thus, the overlap rates can be considered a key parameter in the so-called 'one vs. many debate'. However, direct evidence on the repercussions of using different diagnostic strategies as a possible reason for the observed discrepancies in prevalence rates and overlap is extremely scarce.

To the best of our knowledge, so far, only one study has directly examined the consequences of using different diagnostic strategies for FSS. In a recent study conducted among female FSS patients and matched controls, Warren and Clauw [12] reported a lack of sensitivity and specificity of *physician diagnoses* (the above-mentioned option b) when compared to *symptom-based diagnoses* (option c). While we fully agree with the authors' conclusion that 'queries of symptoms, not diagnoses, are necessary' (p. 894 in the same article), we believe that merely asking about characteristic symptoms (positive criterion) may result in an overestimation of FSS prevalence (and possibly overlap) rates. In cases in which a thorough medical examination is not feasible (such as in the above-mentioned study designs), we believe it preferable to also obtain self-reported information on medical illnesses considered exclusionary for FSS (negative criterion). In essence, we would argue in favor of a combination of options b) and c) in determining FSS diagnoses in epidemiological studies (*symptom-and-exclusion-based strategy*).

However, the potential impact of this strategy needs to be examined. We aimed to extend the findings reported by Warren and Clauw [12] by comparing two different diagnostic strategies in 17 different FSS in a large, non-clinical sample of young adults. The two strategies were as follows: 1) identifying cases of FSS by means of presenting a list of symptoms that are based on the diagnostic criteria (*symptom-based strategy*), and 2) additionally asking about medical exclusionary criteria (*symptom-and-exclusion-based strategy*). We expected to find 1) a significant decrease in prevalence rates of FSS, and 2) a marked decrease in the extent of overlap between FSS when using the *symptom-and-exclusion-based strategy*. We tested these hypotheses as part of a larger study on the prevalence, overlap, and predictors of FSS [13].

Methods

Participants

The recruitment procedure for participants in this study has been described previously elsewhere [13]. In brief, German-speaking students from 23 Swiss colleges and universities were contacted via e-mail through cooperating school administrators, and asked to participate in a web survey on physical and mental well-being. All procedures were in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki, and the web survey study design was approved by the ethics committee of the Canton of Zurich. Written informed consent was obtained from all participants.

Measurement

We administered a previously developed questionnaire (Questionnaire on Functional Somatic Syndromes; FFSS; [14]). The German version of the FFSS is freely available as a Web supplement to the original article (http://content.karger.com/ProdukteDB/miscArchiv/000/333/298/000333298_sm_supplemental_material.pdf). The FFSS consists of three different parts which are connected via several algorithms. In the first part, a screening section encompassing 52 items on various somatic symptoms was presented. These items represent cardinal symptoms of 17 FSS: Tension-type headache and persistent idiopathic facial pain [15], whiplash-associated disorders (pain of at least 6 months' duration that is related to an accident), temporomandibular disorders [16], globus and functional chest pain of presumed esophageal origin [17], functional dyspepsia [18], irritable bowel syndrome [2], chronic low back pain (lower back pain of at least 6 months' duration causing impairment), fibromyalgia syndrome [3], chronic fatigue syndrome [1], multiple chemical sensitivity [19], chronic pelvic pain in men [20] and in women (lower abdominal pain of at least 6 months' duration), premenstrual syndrome [21] and premenstrual dysphoric disorder [22], and hyperventilation syndrome [23]. The instruction was to rate all current symptoms ('I suffer from the following complaints:') according to frequency of occurrence ('never/rarely', 'frequently', 'almost always/always'). In addition, the screening part contains dichotomous questions on functional impairment due to symptoms in different areas and a categorical item on the duration of symptoms.

In the second part, if participants reported cardinal symptoms that were at least 'frequently' present and

characteristic of one of 17 FSS (e.g., abdominal pain in the case of irritable bowel syndrome), additional questions based on diagnostic criteria (e.g., Rome III) were presented. Our questions were based on the most commonly used diagnostic criteria (all publications containing these criteria can be found in the previous section for each FSS). These questions allowed for a detailed understanding of both cardinal and associated symptoms, symptom course and fluctuation, functional impairment, and symptom onset for each FSS. Participants were labelled as having a *'symptom-based FSS'* if they met the minimum of required positive criteria (e.g., recurrent abdominal pain or discomfort on at least 3 days per month in the last 3 months including changes in bowel movement, with symptom onset at least 6 months previously).

In the third part, those who fulfilled the positive criteria of a specific FSS were subsequently surveyed about health care visits. Importantly, visits related to the previously diagnosed FSS (but not health care visits in general) were of interest at this point (e.g., 'Have you ever visited a doctor about your abdominal pain/changes in bowel movement?'). Participants who responded with 'yes' were ultimately directed to a list of items addressing frequent differential diagnoses ('What diagnosis did your doctor give you regarding your abdominal pain/changes in bowel movement?'). These lists were again based on the diagnostic criteria for each FSS as cited above. If they reported that no abnormalities had been detected by their doctor that might account for their symptoms (e.g., an inflammatory bowel disease), participants were labelled as having a *'symptom-and-exclusion-based FSS'*. The FFSS screening part has good psychometric properties regarding both internal consistency (Cronbach's alpha = 0.94) and retest reliability (r = 0.80 − 0.94).

Prevalence rates and overlap estimations of *symptom-and-exclusion-based FSS* have already been described in our previous report [13].

Results

Participants' characteristics

Our recruitment and data preparation process is visualized in Figure 1. A total number of N = 6'206 participants visited the website and about 51% of them finished the survey. After the exclusion of implausible and incomplete datasets (regarding survey response duration, gender, and age), N = 3'054 datasets remained for further analyses. Out of these 3'054 participants, 2'242 (73.4%) were women and 812 (26.6%) were men. The mean age was 24.6 ± 5.6 (SD) years. Parental household income was almost uniformly distributed across nine predefined categories ranging from less than 3'000 to more than 10'000 Swiss Francs per month (equal intervals across categories).

Prevalence of FSS

As illustrated in Figure 1, about one third of our sample endorsed an FSS when using the *symptom-based strategy*. Half of these participants had embarked upon health care visits because of their symptoms. More than half of the health care visitors were not offered a medical explanation for their symptoms and those were thus labelled *symptom-and-exclusion-based FSS* cases. To compare the impact of our two diagnostic strategies on epidemiological data, we calculated the prevalence rates of 17 FSS according to both strategies. We additionally included the health care visitor data for descriptive purposes. No male participant reported suffering from chronic pelvic pain and thus this FSS was excluded from all analyses. The results are illustrated in Figure 2. The prevalence rates of the premenstrual syndrome, premenstrual dysphoric disorder, and chronic pelvic pain all refer to the female population only. In accordance with our first hypothesis, we observed marked decreases in prevalence rates when using a *symptom-and-exclusion-based approach* to diagnosing FSS.

Overlap between FSS

To evaluate the potential impact of our two diagnostic strategies on the extent of overlap between FSS, we counted the number of FSS per person according to each strategy. The number of *symptom-based FSS* per person ranged from one to eight, with 631 (62.2%) participants reporting only one, 239 (23.6%) reporting two, 92 (9.1%) reporting three, 35 (3.5%) reporting four, 13 (1.3%) reporting five, three (0.2%) reporting six, and one person (0.1%) reporting eight *symptom-based FSS* occurring at the same time. The number of *symptom-and-exclusion-based FSS* ranged from one to four: 227 (78.5%) participants fulfilled criteria for only one, 49 (17.0%) reported two, 12 (4.2%) reported three, and one person (0.3%) reported four *symptom-and-exclusion-based FSS* simultaneously.

We then calculated the number of co-occurring FSS for each strategy separately. Since premenstrual syndrome represents a less severe form of premenstrual dysphoric disorder, the extent of overlap between these syndromes was not evaluated. We first looked at each FSS separately. For instance, within the irritable bowel syndrome group, most people had one additional FSS, but some had up to seven additional syndromes. We did this with every syndrome and computed an average index. Within the *symptom-based FSS* group, 9.2 ± 3.6 different co-occurring syndromes (out of 16) were present on average, whereas individuals with *symptom-and-exclusion-based FSS* fulfilled criteria for an average amount of 3.7 ± 3.0 co-occurring syndromes (out of 15, excluding idiopathic facial pain).

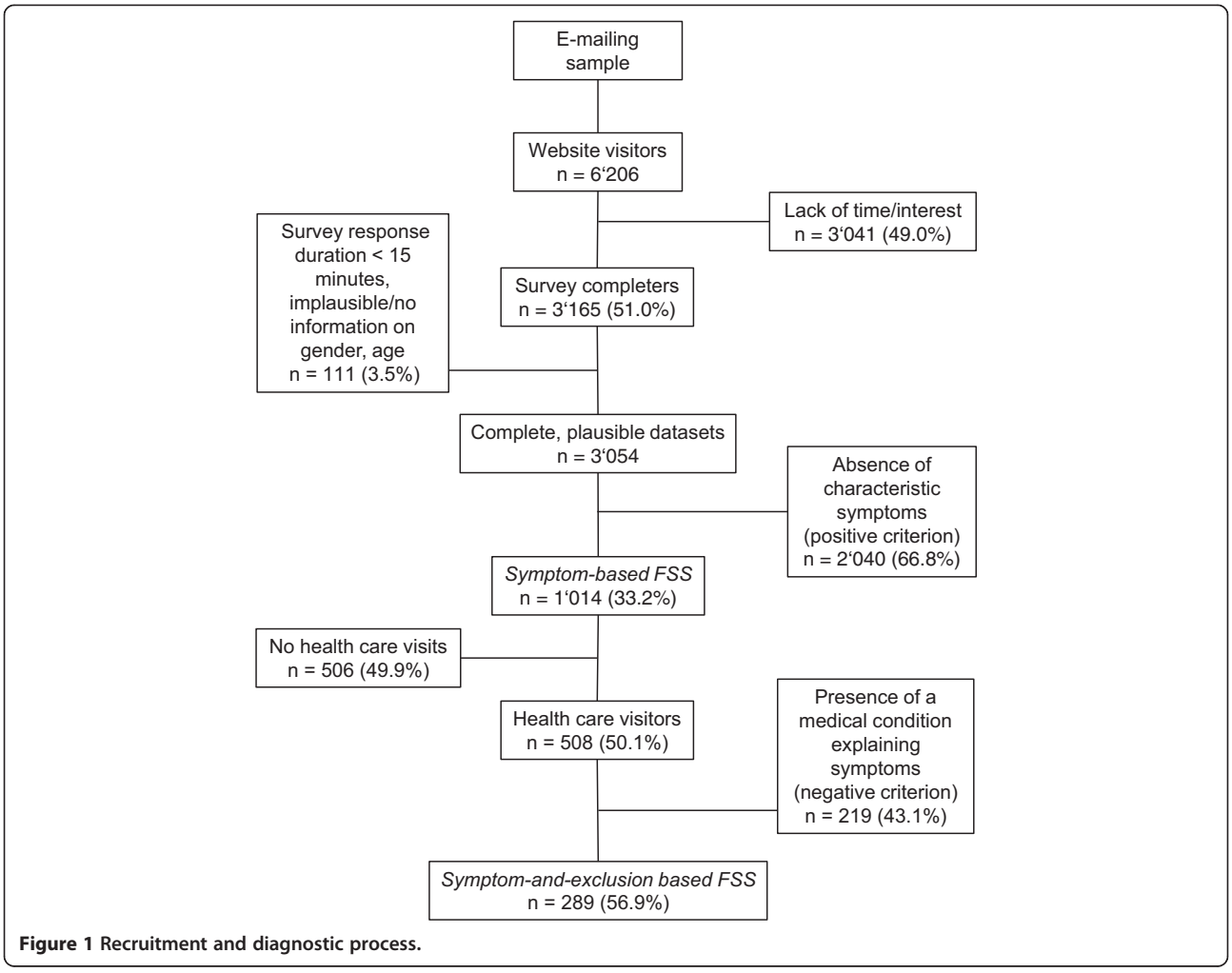

Figure 1 Recruitment and diagnostic process.

Discussion

Summary of study results

In this study, we aimed to evaluate the implications of considering self-reported information on exclusionary medical conditions in epidemiological research on FSS. We compared prevalence rates and overlap of 17 FSS diagnoses obtained by two different diagnostic strategies: a *symptom-based strategy* and a *symptom-and-exclusion-based strategy*. We report two findings that are in accordance with our initial hypotheses: First, the use of medical exclusionary criteria (*symptom-and-exclusion-based strategy*) led to a marked decrease in prevalence rates of FSS when compared to the *symptom-based strategy*. Second, the use of the *symptom-and-exclusion-based strategy* resulted in fewer numbers of individuals who were affected by multiple FSS at the same time. Moreover, it also resulted in fewer overlapping syndromes.

Integration and interpretation of study results

This is the first study to directly examine the impact of adding information on exclusionary medical conditions on the prevalence of FSS. In a recent report, Warren and Clauw [12] found *symptom-based diagnoses* to be superior to *physician diagnoses* of FSS in terms of sensitivity and specificity. While this is an important finding, with both diagnostic and clinical implications, the results of the present study indicate that a *symptom-based strategy* might, in turn, overestimate prevalence rates of FSS. This is most likely due to a participant's incorrect attribution of a somatic symptom (e.g., abdominal pain) to a specific FSS (e.g., irritable bowel syndrome), when, in fact, it is part of a medical illness (e.g., Crohn's disease).

Our finding of a marked decrease in prevalence rates of FSS when considering exclusionary medical conditions is mirrored by other population-based research adopting the *gold standard* procedure, in which patients are first asked about symptoms (positive criterion), followed by physical examinations and laboratory testing (negative criterion). None of these studies explicitly assessed the ramifications of using different diagnostic strategies; however, their detailed reporting of patient screening procedures (e.g., using flow charts) allows the reader to compare the

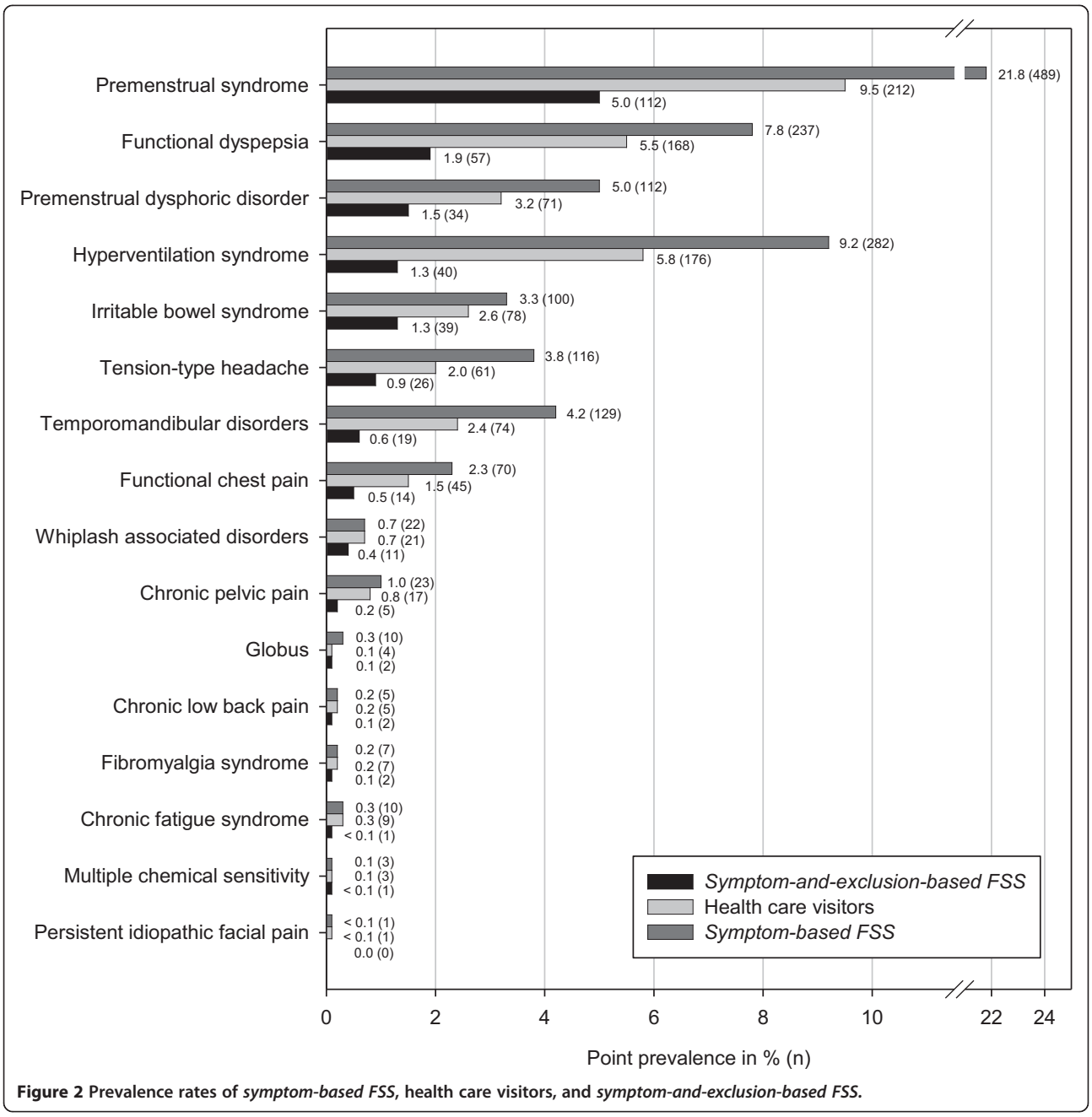

Figure 2 Prevalence rates of *symptom-based FSS*, health care visitors, and *symptom-and-exclusion-based FSS*.

number of participants at each step of this process. For example, before vs. after medical examination by the study investigators, chronic fatigue syndrome was present in 555 vs. 43 individuals in a US-based study [24], and 7.5% vs. 1.6% in a French sample were estimated to have fibromyalgia [25]. Similarly, an in-depth look at the study by Koloski et al. [26], in which an approach comparable to our *symptom-and-exclusion-based strategy* was used in functional gastrointestinal disorders, reveals a more than doubled decrease in prevalence rates before vs. after the exclusion of medical illnesses. This suggests that the use of our *symptom-and-exclusion-based strategy* 'mimics' the diagnostic pathway of epidemiological gold standard studies adequately well. For absolute comparisons of prevalence rates obtained by this strategy with findings of other studies, the interested reader is referred to a previously published article by our group [13].

Based on our findings, we further argue that potential misattribution of somatic symptoms to a specific FSS (instead of a medical illness) artificially inflates the extent of overlap between syndromes. Only a small number of population-based studies have examined overlap between

multiple (i.e., more than two) FSS [27-30]. On the one hand, two of these studies relied either on *physician-based* [27] or on *symptom-based* [28] *diagnoses*. Their finding of a substantial co-occurrence of FSS is in accordance with our finding of more than nine concomitant syndromes in our *symptom-based FSS* group. Interestingly, in one of these studies, the authors argue that their 'results support theories suggesting that medically unexplained conditions share a common etiology' [[27]; p. 818]. This study, as well as our finding of a considerable overlap between *symptom-based diagnoses*, are therefore in favor of the single syndrome hypothesis [lumpers' position; [10]]. On the other hand, in another study, a *symptom-and-exclusion-based strategy* was used for the diagnosis of FSS [30]. After re-analyzing their Swedish Twin Registry data, Kato et al. reported that only 2.8% of their participants were characterized by multiple FSS [30]. This percentage is in line with our finding of 4.5% of participants having at least three *symptom-and-exclusion-based FSS*. Based on their findings, the authors conclude that 'taken together, overlaps among the three functional somatic syndromes were not substantial' (p. 451). This study, as well as our data obtained by using the *symptom-and-exclusion-based strategy*, thus both lend support to the notion of the existence of multiple specific FSS instead of one single syndrome [splitters' position; [11]]. Taken together, study findings regarding the overlap between FSS seem to depend heavily on the selected diagnostic strategy, a finding which has important conceptual ramifications (one vs. many debate). Importantly, to answer the question of overlap, and whether FSS are all expressions of the same underlying phenomenon or discrete diagnoses, a different analysis strategy should be employed [see e.g., [31,32]]. This strategy would ideally combine a factor analysis with latent class analysis. Unfortunately, the hierarchical, modular structure of the herein used FFSS prevented the use of this approach in the current data set.

Study strengths and limitations

A strength of our study lies in our access to a large, non-clinical sample that was free of any healthcare-seeking bias. Nevertheless, a number of limitations need to be taken into account when interpreting our results. First, the present survey was conducted in a student sample, which cannot be considered representative of the general population. However, as outlined above, our findings are in accordance with general population-based studies, indicating potential generalizability at least to some extent. Second, our strategy of establishing diagnoses of FSS was dependent on health care visits. This led to a reduction of our sample size, and could have potentially resulted in an underestimation of 'true' prevalence rates in *symptom-and-exclusion-based FSS*. However, accounting for medical exclusionary conditions is very likely to explain a large proportion of the decrease in prevalence rates, as mirrored by the fact that in 43.1% of cases, a medical explanation for patients' symptoms was provided by a health care professional. Third, due to the nature of a web-based data collection approach, we were unable to confirm our diagnoses through a physical examination or laboratory assessment in our participants (*gold standard* procedure). This might again have led to an underestimation of 'true' prevalence rates in *symptom-and-exclusion-based FSS*, since patients whose symptoms were caused both by an FSS and a medical condition were not counted as FSS cases in this study. In other words, we considered those individuals having a medical condition that explained their symptoms on part as non-cases. Also, some of the exclusionary medical conditions might have been incidental, with the FSS actually causing the symptoms. As illustrated above, our diagnostic strategy does, however, lead to similar decreases in prevalence rates compared to those epidemiological studies using the *gold standard* approach.

Conclusions

To summarize, we were able to show that including information on exclusionary medical conditions leads to a significant decrease in prevalence and overlap rates of FSS. This may call into question the validity of the findings of a number of epidemiological studies on FSS. In a next step, the validity of our *symptom-and-exclusion-based strategy* should be checked in FSS patients that were diagnosed by the *gold standard procedure*. Also, comparisons of prevalence rates as obtained by our approach with prevalence rates of self-reported and physician diagnoses would be of interest. Future studies should adopt more rigorous approaches to the study of FSS, and combine both the positive and negative criterion inherent in their definition. This is likely to enhance the clinical benefit from epidemiological findings on FSS, with the potential to guide diagnostic and, ultimately, treatment decisions.

Abbreviation

FSS: Functional somatic syndromes.

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

SF contributed to the conception and design of the study, analyzed and interpreted the data and provided a first draft of the manuscript. UMN contributed to the conception and design of the study and revised earlier versions of the manuscript. Both authors read and approved the final manuscript.

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Study VI

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Title page with Author Information and Author Note

Clarifying the Latent Structure and Correlates of Somatic Symptom Distress: A Bifactor Model Approach

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Clarifying the Latent Structure and Correlates of Somatic Symptom Distress: A Bifactor Model Approach

Abstract

Distressing somatic symptoms are ubiquitous both in psychopathology and medical conditions. Yet, from a psychometric perspective, the structure and dimensionality of somatic symptom distress is unclear, and little is known about the strengths of associations to other constructs, such as health anxiety or the trait of somatosensory amplification. In order to clarify the latent structure of somatic symptom distress and to explore associations to health anxiety, somatosensory amplification, and functional somatic syndromes, data sets of two samples of college students from Germany (N = 1,520; Study 1) and Switzerland (N = 3,053; Study 2) were investigated with non-parametric confirmatory factor analysis. In Study 1, a bifactor model (with one general and four orthogonal specific symptom factors—gastrointestinal, fatigue, cardio-pulmonary, and pain symptoms) revealed the best model fit. Medium-sized associations were found among latent factors of general somatic symptom distress, health anxiety, and depression. Study 2 demonstrated first evidence for the construct validity of the latent variables within the proposed bifactor structure by observing (a) strong associations between the general somatic symptom distress factor and somatosensory amplification, and (b) significant associations between both the general somatic symptom factor as well as the symptom-specific factors with functional somatic syndromes. The results offer a theoretically and psychometrically plausible model for the latent structure of somatic symptom distress and suggest a distinction between cognitive-affective and sensory aspects of symptom perception. The findings imply that somatic symptom distress is both strongly linked to but also clearly separable from psychopathological constructs (i.e., depression, health anxiety).

Keywords: somatic symptoms; somatic symptom disorder; medically unexplained symptoms (MUS); somatoform disorders; functional somatic syndromes; irritable bowel syndrome (IBS); fibromyalgia syndrome (FMS); bifactor model.

Between two thirds and three quarters of distressing somatic symptoms presented in primary medical care are not fully explainable by current medical knowledge and consequently represent medically unexplained symptoms (MUS; Körber, Frieser, Steinbrecher, & Hiller, 2011). A considerable amount of people with MUS (10-30%) develop chronic and distressing symptom patterns which fulfill the diagnostic criteria of functional somatic syndromes (e.g., fibromyalgia syndrome; Fischer, Gaab, Ehlert, & Nater, 2013) and/or a somatoform disorder according to DSM-IV. For the sake of clarity, we apply the term *somatic symptom distress* in this article. It remains largely unknown which factors contribute to a chronic development of somatic symptom distress. Importantly, the fundamental question of the *latent structure* of somatic symptom distress remains unanswered. According to Deary (1999), solving this question represents one of the crucial prerequisites for explaining aversive somatic symptom experiences which are the core feature of somatoform disorders and functional somatic syndromes. Without exact knowledge regarding the type of latent structure and an adequate measurement model, somatic symptom distress remains poorly specified and research into causes and correlates is hampered. Recent evidence from taxometric analyses suggests that somatic symptom distress should be considered as a continuous construct (e.g., Jasper, Hiller, Bailer, Rist, & Witthöft, 2012). This finding implies that the etiology of chronic somatic symptom distress is indeed most likely a complex and multi-causal process and that the mechanisms are not qualitatively different from the mechanisms of milder variants of transient somatic symptom experiences. Thus, more detailed analyses on the dimensionality of somatic symptom distress are justified. Further knowledge of the factor analytic structure is directly related to the question whether it is reasonable to distinguish among different kinds of somatic symptom distress, in terms of separate diagnoses or different functional somatic syndromes (e.g., fibromyalgia or chronic fatigue syndrome), or whether the similarities among different somatic symptom distress patterns

outweigh their differences (e.g., Wessely, Nimnuan, & Sharpe, 1999). In this latter case, more general and comparatively broad diagnostic terms, as recently proposed with the novel diagnosis of somatic symptom disorder in DSM-5, would be empirically justified.

Previous studies on the structure of somatic symptom distress (e.g., Deary, 1999) mostly relied on three kinds of models: (a) a general factor model, in which the variability of every single item is explained by one latent (general) factor; (b) a correlated factor model consisting of correlated symptom-specific factors; and (c) a hierarchical model in which the variability of symptoms is explained by lower-order symptom-specific factors, and the associations among these latent symptom-specific factors are accounted for by a higher order general factor. Recently, a fourth type of model has been proposed which can be considered as a mixture of the general model and the correlated subfactor approach. In this so called "bifactor" model (Brunner, Nagy, & Wilhelm, 2012), every single symptom is explained by two latent factors: a general factor that is related to every symptom, and a second symptom-specific factor that is related to specific groups of symptoms (e.g., pain symptoms or gastrointestinal symptoms). The different latent factors are orthogonal in this model, i.e., each latent factor explains the unique variability of a given symptom distress level. A bifactor approach was recently proposed to represent the best-fitting measurement model in the realm of somatic symptom distress (Thomas & Locke, 2010; Witthöft, Hiller, Loch, & Jasper, 2013).

Although evidence of the superiority of the bifactor model is growing, data on the construct validity of the proposed latent (general and specific) somatic symptom-distress factors is still missing and it remains unclear, how strongly the different factors relate to other relevant constructs. Health anxiety (i.e., the unsubstantiated and disproportionate fear or conviction to suffer from a severe illness) represents one of the most important related constructs. The relation between health anxiety and somatic symptom distress has long been debated. Currently, two

positions seem to prevail on this issue: The first position considers health anxiety and hypochondriasis as a byproduct of somatic symptom distress (APA, 2013). The second position considers health anxiety as a distinct construct (e.g., Leibbrand, Hiller, & Fichter, 2000), which might even be more strongly related to the realm of anxiety disorders than to somatic symptom distress and related conditions. Beyond health anxiety, the construct of somatosensory amplification has been proposed as an explanatory construct to account for the development and maintenance of both chronic somatic symptom distress and health anxiety (Barsky, Wyshak, & Klerman, 1990). Somatosensory amplification is defined as a trait-like disposition involving the tendency to experience somatic reactions as more intense and to habitually evaluate them as more negative, noxious, and as evidence of a physical disease. Somatosensory amplification as a rather general construct regarding symptom perception, should be strongly related with the general factor of somatic symptom distress within the bifactor model. Finally, little is known about how the different general and specific somatic symptom factors in the bifactor model relate to different functional somatic syndromes.

We will present two studies that aim at testing and validating the latent structure of somatic symptom distress. In the first study, the recently proposed bifactor model will be tested and compared to alternative models (the general factor model, correlated factor model, and the hierarchical model)[1]. In Study 2, we aim at replicating the findings of Study 1 in an independent sample. Furthermore, evidence for the construct validity of the proposed latent variables will be tested by exploring associations to somatosensory amplification and functional somatic syndromes. Specifically, we hypothesize (a) that the general factor reflects the affective component of somatic symptom distress and should therefore reveal the strongest associations to

health anxiety and somatosensory amplification; and (b) that functional somatic syndromes are equally well predicted by the general somatic distress factor and the symptom-specific factors.

Study 1: Method

Participants and Measures

A total of *N* = 1,604 participants completed a set of questionnaires in the years 2004 to 2005 in the waiting area of the Office of Student Enrollment at a German University. They were asked to take part in a study on environment and well-being. Of the participants, 60.1 percent were female and the mean age was *M* = 21.8 (*SD* = 5.81). Most of the participants were university students (83.5%), with chemistry (17.2 %) and economics (11.7%) reported as the most frequent academic majors. The study was approved by the local ethics committee.

Patient Health Questionnaire-15 (PHQ-15; Kroenke, Spitzer, & Williams, 2002). The PHQ represents a continuous self-report measure of somatic symptom distress over the previous four weeks. The PHQ-15 consists of 15 somatic symptoms (e.g., headaches, back pain, dizziness) with three response categories (not bothered at all, bothered a little, or bothered a lot).

The Whitely Index (WI). The WI represents the most prominent self-report measure for a dimensional assessment of health anxiety. It consists of 14 dichotomous items (*"yes"* or *"no"*) and a two dimensional structure (factor 1: health anxiety; factor 2: symptoms and illness convictions; Schwarz et al., 2007).

The Patient Health Questionnaire 9 (PHQ-9). The PHQ-9 (Kroenke, Spitzer, & Williams, 2001) comprises nine four-point items that are based on the criteria for depressive disorders in DSM-IV. The response format ranges from "*not at all"* to *"nearly every day*" and

[1] Some of the models that we compared are nested within one another (i.e., hierarchical model within the bifactor and g-factor model within the bifactor model). This implies that one model may be seen as the extension of the other model. Thus, a g-factor model or a hierarchical model do not necessarily contradict a bifactor model. Rather, they should be seen as extensions that help to model the data structures even better.

the PHQ-9 is regarded as a valid and reliable measure for depression (Kroenke et al., 2001).[2]

Data Analysis

Confirmatory factor analyses were performed with MPlus Version 6.11 (Muthén & Muthén, 2010). The analyses of the measurement models were conducted with the robust mean and variance adjusted weighted least squares (WLSMV) procedure[3]. Because the χ^2 test is sensitive to the sample size and the complexity of the model, we used other descriptive fit measures for the evaluation of the model fit. As an absolute fit index, we chose the RMSEA (Root Mean Square Error of Approximation). Furthermore, the CFI (Comparative Fit Index) and the TLI (Tucker-Lewis Index) are reported as incremental fit indices.

Study 1: Results and Discussion

The latent structure of somatic symptoms in the PHQ-15. Several models were tested on the latent structure of somatic symptom distress: The bifactor model (Figure 1), consisting of a general symptom distress factor and four orthogonal symptom-specific factors (pain-, gastrointestinal-, cardio-pulmonary-, and fatigue-related symptoms) showed an excellent model fit ($\chi^2(54) = 88.38$; $p = .002$; CFI = .992; TLI = .989; RMSEA = .020; 90% CI = .012 –.028). This model fitted the data significantly better than a hierarchical factor model with one higher-order and four lower-order factors (χ^2 (64) = 402.03; $p < .001$; CFI= .926; TLI = .909; RMSEA = .059; 90% CI = .054 –.065; χ^2-difference test: χ^2 (10) = 221.20; $p < .001$). The assumption of a general factor model resulted in rather poor model fit (χ^2 (65) = 900.56; $p < .001$; CFI = .816; TLI = .780; RMSEA = .092; 90% CI = .087 –.097).

[2] Because the PHQ-9 contains two items ("trouble sleeping" and "feeling tired/low energy") that are also part of the PHQ-15, we used only the remaining seven items for the depression score to avoid item overlap.

[3] For model comparisons, we used the DIFFTEST option in MPlus which takes into account that the distribution of the WLSMV based Chi-Square differences is not itself Chi-Square distributed.

Associations between somatic symptoms and health anxiety. To test the strength of associations between the different latent somatic symptom factors derived from the bifactor model and the two facets of health anxiety included in the WI (health anxiety; symptoms and illness convictions), we computed a structural equation model consisting of the PHQ-15 bifactor model and a hierarchical model of the WI consisting of a higher-order factor (general health anxiety) and the two lower-order factors "health anxiety" and "symptoms and illness convictions." The model revealed a good fit to the data (χ^2 (213) = 511.37; p < .001; CFI = .968; TLI = .962; RMSEA = .030; 90% CI = .027 –.034). The health anxiety general factor showed strong associations to the somatic symptom general factor (r = .622; p <.001; *SE* = 0.053). Additionally, weaker but significant associations were observed between the general health anxiety and the cardio-pulmonary symptom factor (r = .264; p =.001; *SE* = 0.077), as well as between the general health anxiety and the gastrointestinal symptom factor (r = .219; p <.001; *SE* = 0.047). Associations between the general health anxiety and the pain symptom factor (r = .067; p =.219; *SE* = 0.054) and the fatigue symptom factor (r = .092; p =.137; *SE* = 0.062) did not reach significance.

Associations among somatic symptoms, health anxiety, and depression. In order to explore the associations of somatic symptom distress and health anxiety with depressive symptoms, we added the PHQ-9 to the previous model. This extended structural equation model again yielded a good model fit (χ^2 (382) = 912.28; p <.001; CFI = .964; TLI = .959; RMSEA = .030; 90% CI = .028 –.033). The latent depressive symptom factor was strongly related to the general somatic symptom-distress factor (r = .615; p <.001; *SE* = 0.046), to the general health anxiety factor (r = .477; p <.001; *SE* = 0.037), and to the fatigue symptom factor (r = .578; p <.001; *SE* = 0.045), but not to the cardio-pulmonary (r = -.039 p =.590; *SE* = 0.073), gastrointestinal (r = .051; p =.196; *SE* = 0.052), or pain symptom factor (r = -.082 p =.064; *SE* =

0.044). These findings suggest that for the somatic symptom distress model, only the general symptom-distress factor and the fatigue factor are significantly associated with depressive symptoms. Specifying a latent regression model in which the PHQ-15 general factor was regressed onto the health anxiety and the depression factor yielded significant latent regression coefficients for both health anxiety (r = .407; p <.001; SE = 0.089) and depression (r = .542; p <.001; SE = 0.061). Together, both constructs account for a total of 67% of explained variance in the general somatic symptom factor. We used the Wald test to compare the strengths of association in this model (H0: the regression weights of health anxiety and depression are of equal size). The Wald test was not significant (p = .333), suggesting that health anxiety and depression represent equally powerful predictors of general somatic symptom distress.

The results of Study 1 showed that a bifactor model offered an excellent model fit and outperformed alternative structural models (e.g., a general factor, or a hierarchical factor model). The findings mean that most of the symptoms covered in the PHQ-15 are determined by one general symptom factor and four symptom-specific factors. Regarding the question of construct validity of the different latent somatic symptom factors, the pattern of associations of the somatic symptom factors with health anxiety and depression revealed a quite clear pattern: Both constructs, health anxiety and depression, had the strongest associations with the general somatic symptom factor. It is important to note that the strengths of associations were about of equal size for both constructs, suggesting that health anxiety is not more closely related to somatic symptom distress than is depression. Regarding the specific somatic symptom factors, a quite different pattern of associations was observed, with depression being significantly related only to the fatigue factor, and health anxiety being significantly related to the cardio-pulmonary as well as the gastrointestinal, but not the pain or fatigue factor. This differential pattern of associations regarding depression and healthy anxiety underlines the validity of the different constructs and

speaks against the notion that the latent factors (both in the somatic symptom bifactor model and the health anxiety and depression model) are just reflections of unspecific negative affectivity. Finding the general somatic symptom-distress factor to be most strongly related to psychological constructs (e.g., health anxiety and depression) confirms previous suggestions (Witthöft et al., 2012) that the general factor might rather represent cognitive-affective facets of symptom perception, whereas the specific factors might include physical and sometimes perhaps organ-specific aspects of sensory symptom experience, which might be more strongly related to specific functional somatic syndromes (e.g., irritable bowel syndrome, fibromyalgia).

Study 2: Method

Participants and Measures

The study was conducted as a web-based survey at a University in Switzerland. Invitations to take part in the study were sent out via administrators of public colleges and universities in the German-speaking part of Switzerland. A link to the survey website was posted on several Internet platforms that are known to be frequently visited by students. The participants were asked to take part in a survey on physical and mental well-being. A total number of N = 6,206 participants visited the website and about 51% of them finished the survey. After the exclusion of implausible datasets (regarding duration, age, etc.) and incomplete SSAS responses, N = 3,053 datasets remained for further analyses. About 73% of the participants were female and the mean age was M = 24.6 (SD = 5.60). About 76% had at least a high school diploma and 22% a university degree; the remaining participants had lower school degrees (22%).

Patient Health Questionnaire 15 (please see the Method section of Study 1).

Somatosensory Amplification Scale (SSAS). The German version of the SSAS (e.g., Jasper et al., 2013) was used, which asks the respondent to what extent each of the 10 items is "characteristic of you in general" (Barsky et al., 1990, p. 325) on a five-point scale from *not at all*

true to *extremely true*. The 10 items mainly ask for uncomfortable bodily sensations, such as Item 5, "Sudden loud noises really bother me" (Barsky et al., 1990, p. 327).

Questionnaire for the Assessment of Functional Somatic Syndromes (FFSS; Nater, Fischer, Latanzio, Ruoss & Gaab, 2011). The FFSS assesses 17 functional somatic syndromes according to their existing research criteria[4].

Data Analysis

Please see the Method section of Study 1 for details.

Study 2: Results and Discussion

The bifactor model of somatic symptoms presented in Study 1 also revealed an excellent fit to the data (χ^2 (54) = 140.04; CFI= .992; TLI = .988; RMSEA = .023; 90% CI = .018 –.028) in Study 2.

Associations between somatic symptoms and somatosensory amplification (SSA). A structural equation model containing the PHQ-15 bifactor model and a general factor measurement model for the SSAS obtained good model fit (χ^2 (211) = 868.94; CFI = .966; TLI = .960; RMSEA = .032; 90% CI = .030 –.034) and a strong association (r = .525; p < .001; *SE* = 0.033) between the general somatic symptom factor and the SSAS. Associations between the SSAS and the specific symptoms factors were of small size (pain: r = .066; *SE* = 0.040; cardio-pulmonary: r = .065; *SE* = 0.050; gastrointestinal: r = .090; *SE* = 0.035; fatigue: r = .076; *SE* = 0.041) and only reached significance for the gastrointestinal symptom factor (p = .009). In order to test for specific associations between SSA and somatic symptom distress beyond depression, we specified a latent regression model in which the PHQ-15 general somatic symptom factor was

[4] (tension-type headache; globus hystericus; whiplash-associated disorders; temporomandibular disorders; persistent idiopathic facial pain; chronic low back pain; fibromyalgia syndrome; chronic fatigue syndrome; multiple chemical sensitivity; irritable bowel syndrome; functional dyspepsia; chronic abacterial prostatitis; chronic pelvic pain; premenstrual syndrome; premenstrual dysphoric disorder; functional chest pain of presumed esophageal origin; hyperventilation syndrome).

regressed onto SSA and the depression factor. Both SSA (r = .400; p < .001; SE = 0.047) and depression (r = .556; p < .001; SE = 0.037) yielded significant latent regression coefficients and accounted for a total of 65% of explained variance in the general somatic symptom factor. Thus, SSA is specifically related to general somatic symptom distress beyond depressive symptoms.

To test possible associations between the different factors of somatic symptom distress and the existence of functional somatic syndromes, we specified a latent regression model in which binary variables that indicated the existence of specific functional somatic syndromes (*e.g. irritable bowel syndrome*) and the existence of any functional somatic syndrome were regressed onto the different somatic symptom-distress factors in the PHQ-15 bifactor model. The model yielded an excellent fit to the data (χ^2 (62) = 168.84; p < .001; CFI = .990; TLI = .986; RMSEA = .024; 90% CI = .019 – .028) and the general somatic symptom-distress factor turned out to be the strongest predictor for the existence of any functional somatic syndrome (r = .487; p < .001; SE=0.046). Among the specific factors, only the gastrointestinal factor significantly contributed to the prediction of functional somatic syndromes. It was the best predictor of the presence of irritable bowel syndrome (r = .83, p < .001; SE=0.109) and significantly predicted the presence of any functional somatic syndrome (r = .18; p < .001; SE=0.051). Overall, 28% of the variability of functional somatic syndromes could be explained by the different somatic symptom factors.

The aims of the second study were to test the validity of the bifactor model of somatic symptom distress proposed in Study 1 by exploring possible associations between the different somatic symptom factors and the trait of SSA, as well as the existence of functional somatic syndromes. As expected, SSA was found to be strongly related to the general somatic symptom-distress factor[5]. Of further note is the observation that none of the specific symptom factors was significantly associated with SSA, suggesting that it might be especially the general symptom-

[5] This association remained significant even after controlling for individual differences in depression.

distress factor that covers cognitive-affective components of symptom perception, as opposed to the specific symptom factors, which might rather represent physiological or sensory aspects related to symptom perception. Regarding the second question, of possible associations between the bifactor model and the existence of functional somatic syndromes, we observed substantial positive associations between the general somatic symptom factor and the existence of any functional somatic syndrome. This finding suggests that somatic symptom distress, as covered in the general factor of the PHQ-15, can be considered as the core feature for functional somatic syndromes.

General Discussion

The primary aims of the two presented studies were to gain a further understanding of the structure of somatic symptom distress and to determine possible associations of the different factors to related constructs, specifically depression, health anxiety, the trait of somatosensory amplification, and specific functional somatic syndromes. In search of a psychometrically adequate and theoretically plausible structural model of somatic symptoms, we were able to replicate the recently proposed bifactor model (Thomas & Locke, 2010; Witthöft et al., 2013). The bifactor approach may also represent an elegant way to reconcile the long-lasting debate about whether qualitatively distinct patterns of somatic symptom distress (i.e., different functional somatic syndromes) exist, or whether the common variance among the different somatic symptom patterns may outweigh their differences (e.g., Wessley et al., 1999). The bifactor model implies that a large proportion of common variance exists between somatic symptoms across diverse organ systems. The observation that the general factor is strongly associated with psychopathological constructs (i.e., health anxiety and depression in Study 1), as well as somatosensory amplification (Study 2) suggests that psychological processes regarding the formation and perception of somatic symptom distress (e.g., Brown, 2004; Witthöft & Hiller,

2010) may represent individual differences in the general somatic symptom-distress factor. In this respect, it appears noteworthy that SSA was specifically (i.e., independently of depression) associated with the general somatic symptom factor, but not with the more specific somatic symptom-distress factors. Because in previous studies SSA has been found to be either unrelated or inversely related to interoceptive accuracy (e.g., Aronson, Barrett, & Quigley, 2001), we assume that the general aspect of symptom distress is not associated with a higher interoceptive ability, but rather with distortions in the processing of interoceptive stimuli leading to the subjective experience of somatic symptom distress. Future studies that experimentally assess interoceptive awareness and interoceptive accuracy are needed to confirm this hypothesis. In contrast to the general factor, which most likely represents a central affective-motivational and evaluative component of symptom perception, the *residual* or *specific* symptom factors most likely reflect sensory-discriminative aspects of symptom perception which are more specific and informative regarding the exact location (i.e., organ system) and type of the respective symptom. This important distinction between an affective and a sensory component of symptom perception has long been recognized in pain research (Fernandez & Turk, 1992) but comparatively neglected in the research on MUS so far. The findings also call into question the novel diagnosis of illness anxiety disorder in DSM-5, which is defined by strong health anxiety in the absence of distressing somatic symptoms. The findings rather endorse the notion to define somatic symptom distress and health anxiety as separate psychometric and diagnostic entities that can co-occur but do not necessarily have to do so.

Limitations. Several limitations of our study have to be considered: First, and perhaps most importantly, the current models are based on samples of college students that are not

representative of the general population[6]. However, previous studies suggest that the bifactor model of somatic symptoms fits the data well also in samples of the general population, as well as in patient samples (Thomas & Locke, 2010; Witthöft et al., 2013). A further limitation represents the internet-based mode of administration. No study has so far demonstrated the psychometric equivalence of the paper-pencil and the internet version of the PHQ-15 as it has been comprehensively done for other psychometric instruments (e.g., Bagby et al., 2014). However, the observation that the described bifactor model was also found in previous paper-pencil administrations of the PHQ-15 in patients' samples and members of the general population (Thomas & Locke, 2010; Witthöft et al., 2013) endorses the notion that the proposed structure is not simply and artifact of the chosen mode of administration. Finally, the presented models are based on self-report data that do not allow for a definite distinction between medially explained and MUS. Analyzes using more elaborate clinician ratings of medically explained vs. unexplained somatic symptom distress may come to different conclusions.

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[6] Although samples of college students are younger and have more years of formal education compared to the general population, a considerable amount of psychopathology (including MUS) has been reported in college students similar to the general population (Bailer, Schwarz, Witthöft, Stübinger, Rist, 2008).

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Figure 1. A bifactor model of somatic symptoms in the PHQ-15 in Study 1 (N = 1,520) with standardized factor loadings (circles represent latent variables, squares refer to manifest variables, single headed arrows represent factor loadings; all factor loading coefficients printed in bold are significant at $p < .05$; error terms of manifest variables not shown)

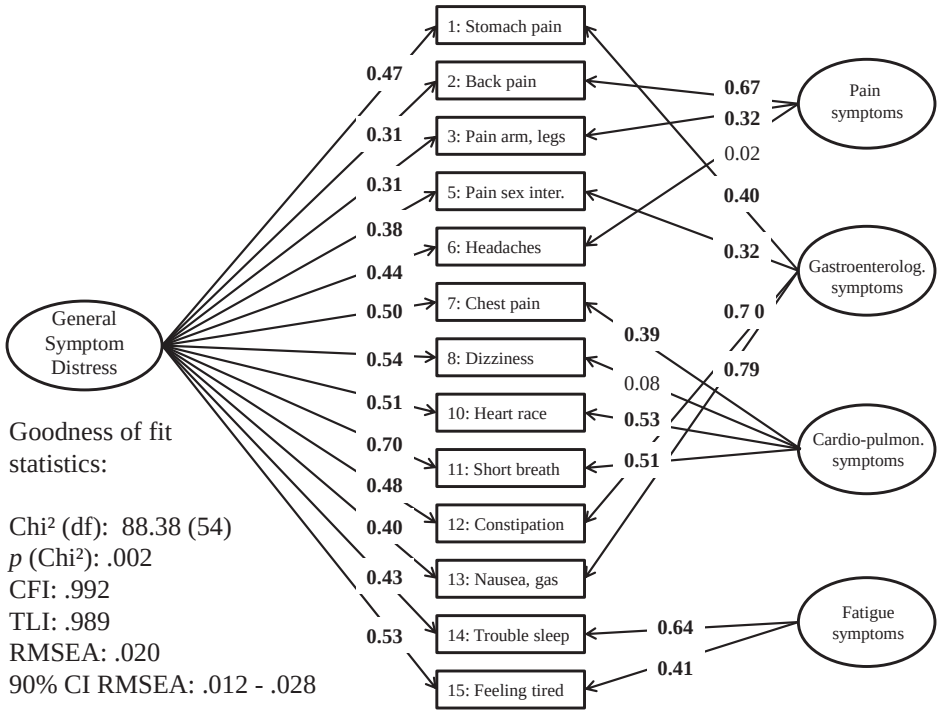
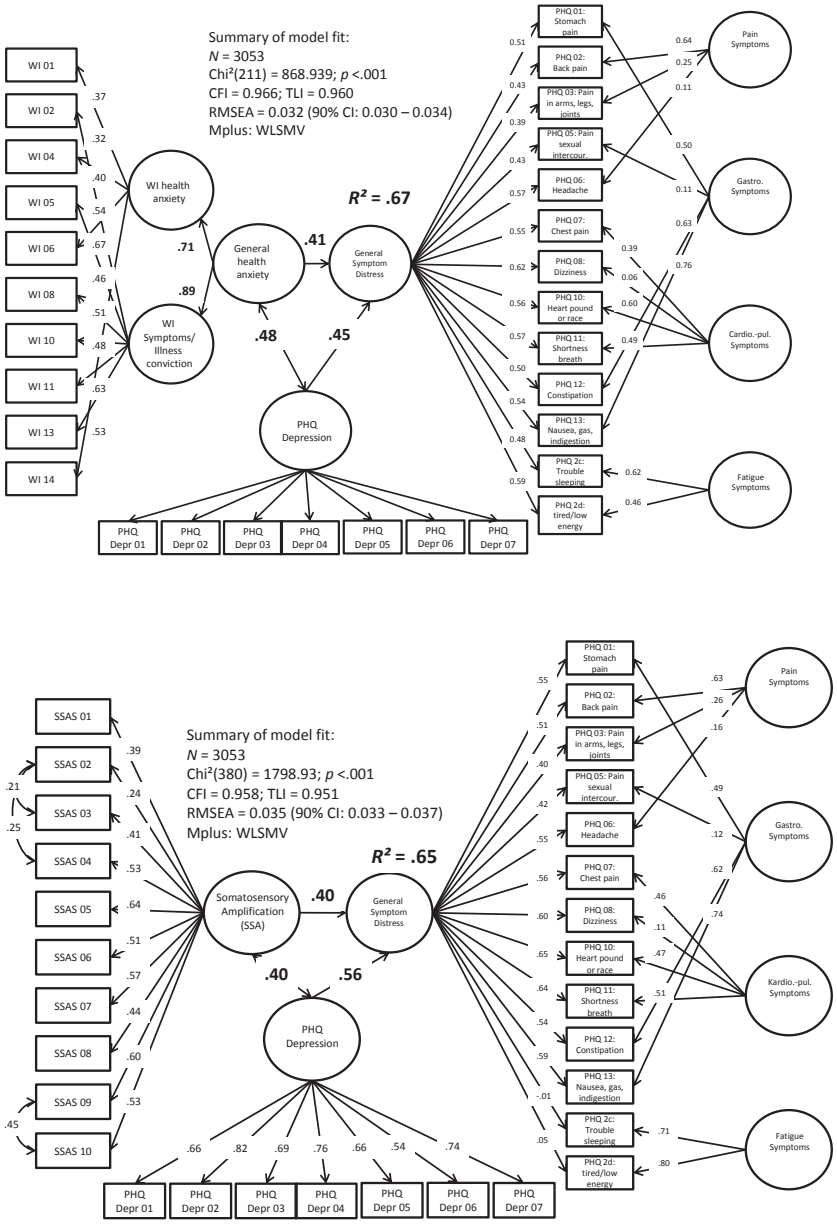


Figure 2. Upper part: Latent regression model for the prediction of somatic symptoms (bifactor model), by health anxiety and depressive symptoms; lower part: SEM for somatic symptoms (bifactor model), somatosensory amplification (SSA), and depression (significant association between SSA and cardio-pulmonary symptoms, r=-.17, p=.034, not shown; all other correlations between SSA factor and symptom-specific factors: $r \leq .09$; circles represent latent variables, squares refer to manifest variables, single headed arrows between manifest and latent variables represent factor loadings; single and double headed arrows between latent variables represent latent regression and correlation paths, respectively).



6.2 Zusammenfassung

Funktionelle somatische Syndrome (FSS) sind definiert durch das Vorhandensein somatischer Symptome bei gleichzeitiger Abwesenheit von strukturellen oder funktionellen Auffälligkeiten, die eine Erklärung der Symptome im Rahmen einer medizinischen Erkrankung nahelegen würden. Es existiert eine Vielzahl an Falldefinitionen für verschiedene FSS. Beispiele sind das das chronische Erschöpfungssyndrom, das Fibromyalgiesyndrom und das Reizdarmsyndrom. Diese Falldefinitionen haben derzeit jedoch nicht den Status nosologischer Entitäten. Der Grund dafür liegt in der unklaren Konzeptualisierung von FSS. Dies kann am besten anhand der so genannten „one-versus-many-Debatte“ illustriert werden: Die Extrempositionen in dieser Debatte sind diejenige der „lumpers“, die ein Verständnis von FSS als ein einziges, generelles Syndrom befürworten, und diejenige der „splitters“, die für eine Aufteilung in verschiedene, distinkte FSS plädieren

Ziel der vorliegenden Dissertation war es, Gemeinsamkeiten und Unterschiede von FSS zu identifizieren, indem ätiopathogenetische und phänomenologische Merkmale bei einer Reihe von Syndromen untersucht wurden. Bezüglich der Ätiopathogenese war insbesondere der Faktor Stress von Interesse. Basierend auf der Literatur wurde ein Rahmenmodell postuliert, das die Rolle von psychobiologischem Stress in der Entstehung und Aufrechterhaltung von FSS illustriert. Spezifische Bestandteile dieses Rahmenmodells sollten empirisch überprüft und integriert werden. Bezüglich der Phänomenologie von FSS sollte eine Vielzahl von Syndromen gleichzeitig erfasst werden, um deren Überlappung untereinander, die Rolle von Depressivität und Ängstlichkeit und die latente Struktur somatischer Symptome zu betrachten. Zur Untersuchung beider Teilfragestellungen wurden verschiedene Patientenstichproben rekrutiert und es kamen unterschiedliche Forschungsdesigns (experimentell, ambulantes Assessment, Befragungen) zum Einsatz.

In der ersten Studie wurde die autonome Stressreaktivität bei Patienten mit einem chronischen Erschöpfungssyndrom untersucht. In Reaktion auf einen körperlich beanspruchenden Stressor (Ergometer) zeigten die Patienten im Vergleich zu einer gesunden Kontrollgruppe eine erniedrigte catecholaminerge Stressreaktion. Die Patienten unterschieden sich von den gesunden Personen nicht hinsichtlich ihrer Reaktion auf einen pharmakologischen Stressor (Insulin-Toleranz-Test).

Das Ziel der zweiten Studie war es, zu klären, ob Stress im Alltag und stress-responsive Systeme, wie das autonome Nervensystem und die Hypothalamus-Hypophysen-Nebennierenrinden-Achse, in die Exazerbation von Schmerzen bei Patienten mit einem Fibromyalgiesyndrom involviert sind. Hierzu wurde ein ambulanter Assessment-Ansatz gewählt. Momentan erlebter Stress sagte die Schmerzintensität mehrere Stunden später vorher. Momentane Cortisolkonzentrationen waren mit momentaner Schmerzintensität assoziiert. Es zeigte sich kein Zusammenhang zwischen der Aktivität von Alpha-Amylase (ein Indikator des autonomen Nervensystems) und der Schmerzintensität.

In der dritten Studie wurde in einer Stichprobe von scheinbar gesunden jungen Erwachsenen ein multidimensionales Modell bezüglich der Rolle von Stress bei FSS getestet. Das Modell postulierte, dass Kindheitstraumata zu einer erhöhten Stressreaktivität führen und gleichzeitig mit geringerer Resilienz (i.e., psychische Widerstandsfähigkeit) verbunden sind. Eine derartige Prädisposition würde dann zu mehr chronischem Stress führen und dieser wäre wiederum auslösend und aufrechterhaltend an der Manifestation von FSS beteiligt. Das theoretisch postulierte Störungsmodell zeigte in quer- und längsschnittlichen Analysen von Befragungsdaten eine gute empirische Passung.

In der vierten Studie wurden im Rahmen einer Befragung Überlappungsraten innerhalb der Kategorie der FSS sowie Prädiktoren für die Inzidenz von FSS sechs Monate später eruiert. Im Gegensatz zu bisherigen Studien erfüllten nur wenige Personen die Kriterien für mehr als ein FSS gleichzeitig. Prädiktoren für die Entwicklung von FSS allgemein waren die Anzahl körperlicher Beschwerden, die damit einhergehende Beeinträchtigung, Somatisierung (i.e., das Ausmaß, indem sich Personen durch somatische Symptome gestört fühlen) und Depressivität.

Das Ziel der fünften Studie war es, die Konsequenzen unterschiedlicher Vorgehensweisen in der Diagnostik von FSS zu evaluieren. Der in der epidemiologischen Forschung häufig verwendete Ansatz der „symptom-based diagnoses“ führte im Vergleich zum Ansatz der „symptom-and-exclusion-based diagnoses“ (der zusätzlich zur Abfrage von somatischen Symptomen auch medizinische Ausschlussdiagnosen berücksichtigt) zu deutlich höheren Prävalenzraten von FSS. Gleichzeitig fanden sich unter Verwendung des ersten Ansatzes höhere Überlappungsraten zwischen einzelnen Syndromen.

In der sechsten Studie (Studie VI) wurde in zwei Stichproben von scheinbar gesunden jungen Erwachsenen die latente Struktur von somatischen Symptomen und deren Bezug zu Depressivität, Ängstlichkeit, somatosensorischer Verstärkung (i.e., ein kognitiver Stil, der mit einer verstärkten Wahrnehmung somatischer Empfindungen einher geht) und verschiedenen FSS näher beleuchtet. Ein Bifaktormodell mit einem generellen Faktor und vier symptomspezifischen Faktoren („fatigue“, „pain“, „gastrointestinal“ und „cardio-respiratory“) beschrieb die latente Struktur von somatischen Symptomen am besten. Der generelle Faktor war mit Depressivität, Ängstlichkeit und somatosensorischer Verstärkung assoziiert. Die symptom-spezifischen Faktoren waren mit verschiedenen FSS assoziiert.

Die Resultate der Studien I bis III zeigen Stress als prädisponierenden, auslösenden und aufrechterhaltenden Faktor bei verschiedenen FSS und weisen auf wichtige Mechanismen hin, die an der Übersetzung von Stress in somatische Symptome beteiligt sind. Trotz dieser Gemeinsamkeit wurden in den Studien IV und V geringe Überlappungsraten zwischen FSS gefunden, sofern medizinische Ausschlussdiagnosen berücksichtigt wurden. Diese scheinbare Diskrepanz spiegelt sich in den Befunden von Studie VI wider, in der ein genereller und vier symptomspezifische Faktoren die latente Struktur von somatischen Symptomen beschrieben. Gemäß der Befunde der vorliegenden Dissertation scheinen FSS „one *and* many“ zu sein. Es ist denkbar, dass ein hohes Ausmaß an Stress während der Kindheit oder im Erwachsenenalter und nachfolgende Veränderungen in stress-responsiven Systemen sowie der kognitive Stil der somatosensorischen Verstärkung Endophänotypen darstellen, die sämtlichen medizinisch unerklärten Beschwerden zugrunde liegen. Falls dies zuträfe, wären die identifizierten symptomspezifischen Faktoren als phänomenologische Varianten dieses Prozesses zu verstehen. Künftige Klassifikationen sollten den gemeinsamen und spezifischen Faktoren Rechnung tragen, um eine adäquate Behandlung und erfolgreiche weitere Erforschung von medizinisch unerklärten Beschwerden zu gewährleisten.

6.3 Curriculum vitae

Personal Information

Name	Susanne Fischer
Address	King's College London Institute of Psychiatry, Psychology and Neuroscience PO74 Affective Disorders 103 Denmark Hill London SE5 8AF United Kingdom

Education

Feb. 2011-present	PhD student Department of Psychology, Clinical Biopsychology, University of Marburg, Marburg, Germany (Supervisor: Prof. U. M. Nater)
Dec. 2010-present	Postgraduate training in Cognitive Behaviour Therapy, Institute for Psychotherapy Marburg (Head: Prof. W. Rief), Marburg
Nov. 2010-Jan. 2011	PhD student Department of Psychology, Clinical Psychology and Psychotherapy, University of Zurich, Zurich, Switzerland (Supervisors: Prof. U. Ehlert, Prof. U. M. Nater)
Oct. 2005-Nov.2010	MSc in Psychology Department of Psychology, Clinical Psychology and Psychotherapy, University of Zurich, Zurich, Switzerland Title of master thesis: "The role of stress in functional somatic symptoms" (Supervisors: Prof. U. Ehlert, Prof. U. M. Nater)
Aug. 98-Jul. 04	Matura (Type B, Latin) Gymnasium in Zurich Oerlikon (CH)
Aug. 93-Jul. 98	Primary School in Boppelsen (CH)

Professional positions

Jan. 2015-present	Visiting Researcher, Psychological Medicine (Prof. A. Cleare), King's College, London, United Kingdom
Feb. 2011-Dec. 2014	Research Fellow, Clinical Biopsychology (Prof. U. M. Nater), University of Marburg, Marburg, Germany
Oct. 2012-Sept. 2014	Executive Assistant to the Board of the International Society of Behavioral Medicine (ISBM)

Nov. 2010-Jan. 2011	Research Fellow, Clinical Psychology and Psychotherapy (Prof. U. Ehlert), University of Zurich, Zurich, Switzerland
Sept. 2008-Jan. 2009	Teaching Assistant, Motivational Psychology (Prof. V. Brandstaetter-Morawietz), University of Zurich, Zurich, Switzerland
Feb.-Aug. 2008	Research Assistant, Clinical Psychology and Psychotherapy (Prof. U. M. Nater), University of Zurich, Zurich, Switzerland
Aug. 2007-Aug. 2008	Research Assistant, Clinical Psychology and Psychotherapy (Dr. R. La Marca), University of Zurich, Zurich, Switzerland

Clinical experience

Feb. 2011-Dec. 2014	Therapist, Outpatient Clinic for Psychological Interventions (Prof. W. Rief), Marburg, Germany
Sept.-Dec. 2009	Centre for Substance Abuse, Psychiatric University Hospital, Zurich, Switzerland
Jun.-Jul. 2009	Cantonal Psychiatric Clinic, Liestal, Switzerland

Teaching experience

Feb. 2011-present	Co-mentoring of six master theses
Feb. 2011-Dec. 2014	Substitutions in courses on depression, post-traumatic stress disorder, stress, fatigue, and sexual dysfunction disorders
Apr.-Jul. 2013	Lectureship in anxiety disorders

Awards and Scholarships

Early Postdoc.Mobility Scholarship, Swiss National Science Foundation, Jan. 2015-Jun. 2016

Travel Award, German Academic Exchange Service (DAAD), 72nd Annual Meeting of the American Psychosomatic Society, San Francisco, CA, USA, 2014

Scholarship, Department of Psychology, University of Marburg, Feb.-Jul. 2014

Research Assistantship (STIBET), German Academic Exchange Service (DAAD), Aug.-Nov. 2012

Travel Award, German Academic Exchange Service (DAAD), 70th Annual Meeting of the American Psychosomatic Society, Athens, Greece, 2012

Ad hoc reviewer for scientific journals

International Journal of Behavioral Medicine

Journal of Psychosomatic Research

Peer-reviewed journal articles

Fischer, S., Doerr, J. M., Strahler, J., Mewes, R. & Nater, U. M. (ready to be submitted). Stress exacerbates pain in the everyday lives of women with fibromyalgia – the role of cortisol and alpha-amylase.

Klaus, K., **Fischer, S.**, Doerr, J. M., Nater, U. M. & Mewes, R. (submitted). Classifying fibromyalgia as a psychiatric disorder? An ambulatory assessment study. *Journal of Pain.*

Witthöft, M., **Fischer, S.**, Jasper, F., Rist, F. & Nater, U. M. (under revision). Clarifying the latent structure and correlates of somatic symptom distress: A bifactor model approach. *Psychological Assessment.*

Skoluda, S., Strahler, J., Schlotz, W., Niederberger, L., Marques, S., **Fischer, S.**, Thoma, M. V., Spoerri, C., Ehlert, U. & Nater, U. M. (2015). Intra-individual psychological and physiological responses to acute laboratory stressors of different intensity. *Psychoneuroendocrinology, 51,* 227-36.

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Fischer, S. & Nater, U. M. (2013). Ätiopathogenetische Faktoren bei funktionellen somatischen Syndromen [Etiopathogenetic factors in functional somatic syndromes]. *Verhaltenstherapie & Verhaltensmedizin, 34*(4)*,* 419-43.

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Strahler, J.*, **Fischer, S.***, Nater, U.M., Ehlert, U. & Gaab, J. (2013). Norepinephrine and epinephrine responses to physiological and pharmacological stimulation in chronic fatigue syndrome. *Biological Psychology, 94*(1), 160-6.

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Nater, U. M., **Fischer, S.** & Ehlert, U. (2011). Stress as a pathophysiological factor in functional somatic syndromes. *Current Psychiatry Reviews, 7*(2), 152-69.

Nater, U. M., **Fischer, S.**, Latanzio, S., Ruoss, D. & Gaab, J. (2011). FFSS - Fragebogen zur Erfassung funktioneller somatischer Syndrome [FFSS - Questionnaire on functional somatic syndromes]. *Verhaltenstherapie, 21*(4), 263-5.

*Shared first authorship

Book chapters

Fischer, S. & Nater, U. M. (in press*). Autonomes Nervensystem [Autonomic nervous system]*. In W. Rief & P. Henningsen (Hrsg.), Psychosomatik und Verhaltensmedizin. Schattauer.

Fischer, S. & Nater, U. M. (in press*). Illness perception and management in chronic fatigue syndrome*. In C. Hudson (Ed.), Chronic fatigue syndrome: Risk factors, management and impact on daily life. Hauppauge, NY: NOVA Science Publishers.

Fischer, S. (2012). *Resilience: Measurement.* In M. D. Gellman & J. R. Turner (Eds.), Encyclopedia of behavioral medicine (pp. 1673-5). New York, NY: Springer.

Published abstracts

Doerr, J. M., Strahler, J., **Fischer, S.** & Nater, U. M. (2014). Acute stress influences momentary pain in women with fibromyalgia. *International Journal of Behavioral Medicine, 21*(Suppl. 1), S134.

Fischer, S., Mewes, R., Strahler, J. & Nater, U. M. (2014). Perceived discrimination induces psychological and physiological stress in immigrants. *International Journal of Behavioral Medicine, 21*(Suppl. 1), S147.

Markert, C., **Fischer, S.** & Nater, U. M. (2014). Stress is associated with diminished sexual interest in a Swiss student population. *International Journal of Behavioral Medicine, 21*(Suppl. 1), S179.

Fischer, S., Mewes, R., Strahler, J., Dieterich, L., Oezcan, O. & Nater, U.M. (2014). Psychobiological validation of a discrimination paradigm in the laboratory. *Psychosomatic Medicine, 76*(3), A-132.

Strahler, J., **Fischer, S.**, Doerr, J.M. & Nater, U.M. (2014). Relationships between momentary stress, neuroendocrine stress markers, and symptoms in patients with fibromyalgia. *Psychosomatic Medicine, 76*(3), A-121.

Fischer, S., Mewes, R., Dieterich, L., Öczan, O. & Nater, U.M. (2013). Psychobiologische Validierung eines Diskriminierungsparadigmas im Labor [Psychobiological validation of a discrimination paradigm in the laboratory]. *Verhaltenstherapie & Verhaltensmedizin, 34*(Suppl. 1), 11-2.

Markert, C., Doerr, J.M., **Fischer, S.**, Tepe, A., Sanchez, L. & Nater, U.M. (2013). Beeinflusst Stress das alltägliche Schmerzerleben von Frauen mit Fibromyalgie [Does stress have an impact on daily pain experiences in women with fibromyalgia]? *Verhaltenstherapie & Verhaltensmedizin, 34*(Suppl. 1), 19.

Fischer, S., Ehlert, U. & Nater, U. M. (2012). Overlap of functional somatic syndromes - findings from a non-clinical sample*. International Journal of Behavioral Medicine, 19*(Suppl. 1), 53.

Markert, C., **Fischer, S.**, Ehlert, U. & Nater, U. M. (2012). Stress and functional gastrointestinal disorders in a non-clinical sample*. International Journal of Behavioral Medicine, 19*(Suppl. 1), 54-5.

Strahler, J., **Fischer, S.**, Nater, U. M., Ehlert, U. & Gaab, J. (2012). Epinephrine and norepinephrine responses to physiological and pharmacological stimulation in chronic fatigue syndrome. *International Journal of Behavioral Medicine, 19*(Suppl. 1), 118-9.

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Nater, U. M., **Fischer, S.** & Ehlert, U. (2012). Intra-individual psychological and physiological responses to acute laboratory stressors of different intensity. *Psychosomatic Medicine, 74*(3), A-81.

Strahler, J., **Fischer, S.**, Nater, U. M., Ehlert, U. & Gaab, J. (2012). Catecholaminergic responses to the insulin tolerance test in chronic fatigue syndrome. *Psychosomatic Medicine, 74*(3), A-84.

Strahler, J., **Fischer, S.** & Kirschbaum, C. (2012). Vital exhaustion is differentially related to daily salivary cortisol in older men and women. *Psychosomatic Medicine, 74*(3), A-30.

Fischer, S., Gaab, J., Ehlert, U. & Nater, U. M. (2011). Prävalenz und Inzidenz von funktionellen somatischen Syndromen- die Rolle von Stress in einer Längsschnittuntersuchung [Prevalence and incidence of functional somatic syndromes - the role of stress in a prospective study], *Verhaltenstherapie, 21*(suppl. 1), 31-2.

Fischer, S., Gaab, J., Ehlert, U. & Nater, U. M. (2011). Prevalence of functional somatic syndromes in an apparently healthy population. *Psychosomatic Medicine, 73*(1), 32.

Conference Presentations

Doerr, J. M., Strahler, J., **Fischer, S.** & Nater, U. M. (2014). Acute stress influences momentary pain in women with fibromyalgia. Talk given at the 13th International Congress of Behavioral Medicine, Groningen, The Netherlands.

Fischer, S., Mewes, R., Strahler, J. & Nater, U. M. (2014). Perceived discrimination induces psychological and physiological stress in immigrants. Talk given at the 13th International Congress of Behavioral Medicine, Groningen, The Netherlands.

Markert, C., **Fischer, S.** & Nater, U. M. (2014). Stress is associated with diminished sexual interest in a Swiss student population. Poster presented at the 13th International Congress of Behavioral Medicine, Groningen, The Netherlands.

Doerr, J. M., **Fischer, S.**, Strahler, J. & Nater, U. M. (2014). Der Effekt von akutem Stress im Alltag auf das Schmerzerleben bei Frauen mit Fibromyalgie [The effect of acute stress in everday life on pain experiences in women with fibromyalgia]. Poster presented at the 32nd Symposium of the Division of Clinical Psychology and Psychotherapy of the German Psychological Society (DGPs), Brunswick, Germany.

Klaus, K., Doerr, J. M., **Fischer, S.**, Nater, U. M. & Mewes, R. (2014). Psychologische Somatisierungssymptome bei Patientinnen mit Fibromyalgie: Eine ambulante Assessement-Studie [Psychological symptoms of somatization in fibromyalgia patientes: an ambulatory assessment study]. Poster presented at the 32nd Symposium of the Division of Clinical Psychology and Psychotherapy of the German Psychological Society (DGPs), Brunswick, Germany.

Markert, C.**, Fischer, S.**, Nater, U.M. (2014). Stress und vermindertes sexuelles Verlangen bei Schweizer Studierenden [Stress and diminished sexual desire in a Swiss student population]. Poster presented at the 32nd Symposium of the Division of Clinical Psychology and Psychotherapy of the German Psychological Society (DGPs), Brunswick, Germany.

Fischer, S., Mewes, R., Strahler, J., Dieterich, L., Oezcan, O. & Nater, U.M. (2014). Psychobiological validation of a discrimination paradigm in the laboratory. Poster presented at the 72nd Annual Meeting of the American Psychosomatic Society, San Francisco, CA, USA.

Strahler, J., **Fischer, S.**, Doerr, J.M. & Nater, U.M. (2014). Relationships between momentary stress, neuroendocrine stress markers, and symptoms in patients with fibromyalgia. Poster presented at the 72nd Annual Meeting of the American Psychosomatic Society, San Francisco, CA, USA.

Fischer, S., Markert, C., Strahler, J. & Nater, U. M. (2013). Differentielle Stressreaktivität bei funktionellen somatischen Syndromen [Differential stress reactivity in functional somatic syndromes]. Talk given at the Young Scientist Retreat of the German Society for Psychophysiology and its Application (DGPA) and the Division of Biological Psychology and Neuropsychology of the German Psychological Society (DGPs), Berlin, Germany.

Fischer, S., Mewes, R., Dieterich, L., Özcan, O. & Nater, U.M. (2013). Psychobiologische Validierung eines Diskriminierungsparadigmas im Labor [Psychobiological validation of a discrimination paradigm

in the laboratory]. Talk given at the 14th Annual Meeting of the German Society for Behavioral Medicine and Behavior Modification (DGVM), Prien am Chiemsee, Germany.

Markert, C., Doerr, J.M., **Fischer, S.**, Tepe, A., Sanchez, L. & Nater, U.M. (2013). Beeinflusst Stress das alltägliche Schmerzerleben von Frauen mit Fibromyalgie [Does stress have an impact on daily pain experiences in women with fibromyalgia]? Talk given at the 14th Annual Meeting of the German Society for Behavioral Medicine and Behavior Modification (DGVM), Prien am Chiemsee, Germany.

Doerr, J.M.*, **Fischer, S.***, Strahler, J. & Nater, U.M. (2013). Stress und Schmerz: Eine psychobiologische Untersuchung im Alltag von Patientinnen mit Fibromyalgie [Stress and pain: A psychobiological approach in the daily life of fibromyalgia patients]. Poster presented at the 15th Annual Meeting of the German Society for Psychological Pain Therapy and Research, Marburg, Germany.

Markert, C., **Fischer, S.**, Strahler, J. & Nater, U.M. (2013). Differentielle Stressreaktivität bei funktionellen somatischen Syndromen [Differential stress reactivity in functional somatic syndromes]. Poster presented at the 15th Annual Meeting of the German Society for Psychological Pain Therapy and Research, Marburg, Germany.

Fischer, S., Nater, U.M., Ehlert, U. & Ditzen, B. (2013). Kindheitstraumata und Stressreaktivität bei Frauen mit prämenstruellem Syndrom [Childhood trauma and stress reactivity in women with premenstrual syndrome]. Poster presented at the 30th Symposium of the Division of Clinical Psychology and Psychotherapy of the German Psychological Society (DGPs), Trier, Germany.

Fischer, S., Ehlert, U. & Nater, U. M. (2012). Overlap of functional somatic syndromes - findings from a non-clinical sample. Poster presented at the 12th International Congress of Behavioral Medicine, Budapest, Hungary.

Markert, C., **Fischer, S.**, Ehlert, U. & Nater, U. M. (2012). Stress and functional gastrointestinal disorders in a non-clinical sample. Poster presented at the 12th International Congress of Behavioral Medicine, Budapest, Hungary.

Strahler, J., **Fischer, S.**, Nater, U. M., Ehlert, U. & Gaab, J. (2012). Epinephrine and norepinephrine responses to physiological and pharmacological stimulation in chronic fatigue syndrome. Talk given at the 12th International Congress of Behavioral Medicine, Budapest, Hungary.

Fischer, S., Ehlert, U. & Nater, U. M. (2012). Stress as a risk factor in chronic fatigue - a prospective study in a Swiss student population. Poster presented at the 70th Annual Meeting of the American Psychosomatic Society, Athens, Greece.

Fischer, S., Strahler, J. & Nater, U. M. (2012). Die Rolle von Stress beim chronischen Erschöpfungssyndrom [The role of stress in chronic fatigue syndrome]. Talk given at the 27th Annual Meeting of the German Society of Behavior Therapy (DGVT), Berlin, Germany.

Nater, U. M., **Fischer, S.** & Ehlert, U. (2012). Intra-individual psychological and physiological responses to acute laboratory stressors of different intensity. Poster presented at the 70th Annual Meeting of the American Psychosomatic Society, Athens, Greece.

Strahler, J., **Fischer, S.**, Nater, U. M., Ehlert, U. & Gaab, J. (2012). Catecholaminergic responses to the insulin tolerance test in chronic fatigue syndrome. Poster presented at the 70th Annual Meeting of the American Psychosomatic Society, Athens, Greece.

Strahler, J., **Fischer, S.** & Kirschbaum, C. (2012). Vital exhaustion is differentially related to daily salivary cortisol in older men and women. Poster presented at the 70th Annual Meeting of the American Psychosomatic Society, Athens, Greece.

Fischer, S., Gaab, J., Ehlert, U. & Nater, U. M. (2011). Prävalenz und Inzidenz von funktionellen somatischen Syndromen - die Rolle von Stress in einer Längsschnittuntersuchung [Prevalence and incidence of functional somatic syndromes - the role of stress in a prospective study]. Talk given at the 13th Annual Meeting of the German Society for Behavioral Medicine and Behavior Modification (DGVM), Luxembourg, Luxembourg.

Fischer, S., Gaab, J., Ehlert, U. & Nater, U. M. (2011). Risikofaktoren bei funktionellen somatischen Syndromen in einer Studierendenstichprobe [Risk factors for functional somatic syndromes in a student sample]. Poster presented at the 29th Symposium of the Division of Clinical Psychology and Psychotherapy of the German Psychological Society (DGPs), Berlin, Germany.

Fischer, S., Gaab, J., Ehlert, U. & Nater, U. M. (2011). Prevalence of functional somatic syndromes in an apparently healthy population. Poster presented at the 69th Annual Meeting of the American Psychosomatic Society, San Antonio, TX, USA.

*Shared first authorship

6.4 Erklärung

Ich versichere, dass ich meine Dissertation

Aetiopathogenesis and Phenomenology of Medically Unexplained Conditions

Selbständig und ohne unerlaubte Hilfe angefertigt und mich dabei keiner anderen als der von mir ausdrücklich bezeichneten Quellen und Hilfen bedient habe. Die Dissertation wurde in der jetzigen oder einer ähnlichen Form noch bei keiner anderen Hochschule eingereicht und hat noch keinen sonstigen Prüfungszwecken gedient.

Marburg, 21. Januar 2015

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Susanne Fischer