Dysfunction of stress responsive systems in somatization
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CHAPTER 1

General introduction

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Chapter 1

CONCEPT OF SOMATIZATION: A CONTINUUM WITH MANY FACES

The purpose of this chapter is to define and describe somatization and its related constructs, to illustrate the clear need for a better understanding of somatization and to provide background information to explain the rationale behind studying the role of stress responsive system dysfunction in relation to somatization. The chapter ends with the main research questions and content of this thesis.

Functional somatic symptoms
Symptoms are in the heart of clinical medicine as a consult with a physician typically starts with the question “what are your complaints?” Physicians structure their differential diagnosis on the constellation of symptoms that a patient presents. A symptom is defined as an aversely perceived internal state (van Wijk & Kolk 1997), such as abdominal pain, fatigue, nausea, dizziness or muscle weakness. Normal physiological fluctuations and pathophysiological processes may trigger interoceptors that generate information about the state and function of organ systems. Most of those somatosensory stimuli remain unconscious but some become conscious and are perceived as a sensation or as a symptom.

Experience of symptoms in the general population is an extremely common phenomenon. In a population survey, 96% reported that they had experienced at least one symptom during the preceding month (Ihlebaek et al. 2002). Symptoms may or may not be accompanied by objective signs of underlying disease such as findings derived from physical examination, blood tests, or diagnostic imaging. When an individual experiences symptoms for which no known organic pathology (i.e., a deviation from the normal condition in a part, organ, or system of the body characterized by an identifiable group of signs or symptoms) can be found, these symptoms are referred to as functional somatic symptoms (FSS). Also when organic pathology is present, symptoms may have a functional component when they are in excess of what would be expected based on objective findings (Kroenke & Rosmalen 2006).

Although the prevalence of FSS in the general population is high, only a minority of people seek medical attention for them (Kroenke & Price 1993, Hiller et al. 2006). Still, FSS are the most common single category of symptoms in primary care and form a substantial part of complaints presented in medical specialties (Kroenke & Mangelsdorf 1989, Katon & Walker 1998, Nimnuan et al. 2001a). Precise estimates are dependent on the population under study and definition of FSS. Typically, a third to half of the presented symptoms remains unexplained in primary care and population based studies, and of this group of FSS, 25% are chronic or recurrent (Kroenke & Rosmalen 2006).

Although a large part of symptoms presented to doctors is functional somatic, it appears that doctors find it difficult to satisfactorily explain this to patients and
reassure that their symptoms are as real as symptoms with a known organic cause (Hartz et al. 2000). Alongside and partly due to those insufficient explanations of doctors, patients experiencing FSS tend to equate the explanation that no organic pathology is found for their symptoms with ‘not real’, ‘simulated’, or ‘imaginary’. Psychosocial and somatic factors are incorrectly believed to be mutually exclusive and symptoms with a known organic pathology are experienced as more legitimate than FSS. Patients often resist clarifications that there is no organic pathology causing their symptoms, or that stress is possibly involved. This is particularly the case when a functional explanation is introduced for the first time after all somatic examinations have failed to provide results that confirm organic disease (Bensing & Verhaak 2006).

Sometimes no clear-cut stressors are present, and moreover, it is difficult to understand why stress would lead to abdominal pain, a feeling of a lump in throat, or muscle weakness. Under the assumption that there must be organic pathology underlying their symptoms, patient might clamp to the diagnostic process and consult many health care providers for the same problem. Consequently, patients with FSS disproportionately use health care resources (Barsky et al. 2005). No uniform intervention or treatment protocol for FSS across primary care, somatic medical specialties and psychiatry is available. FSS cause a large burden in patients experiencing them. FSS are often as disabling in daily life as somatic symptoms with a known organic cause (Kisely et al. 1997). Patient with FSS have a poorer self-rated health than people presenting the same symptoms with a known pathological basis (Frostholm et al. 2007).

In aggregate, FSS form a highly prevalent and clinically important and costly health care issue, which frustrates physicians and dissatisfies patients. Clearly, it is essential to better understand the etiology of FSS.

**Functional somatic disorders**

FSS tend to occur together and result in functional somatic disorders (FSD), syndromes of related complaints with no known organic pathology. Without logical nomenclature based on underlying pathology, FSD are often described by their lead symptoms or implied cause. The main three FSD are chronic fatigue syndrome (CFS), fibromyalgia (FM), and irritable bowel syndrome (IBS). Other examples of FSD include whiplash syndrome, functional dyspepsia, temporomandibular dysfunction, tension-type headache, multiple chemical sensitivity, non-cardiac chest pain, hyperventilation syndrome, reactive hypoglycemia, low back pain, and atypical facial pain. History seems to repeat itself, as new disorders with clusters of FSS continue to be defined. Some diagnoses have only recently been acknowledged as FSD, such as interstitial cystitis and chronic non-bacterial prostatitis; however, this has not been generally accepted yet (Clemens 2008). The introduction of a new FSD is inevitably followed by a search to causal factors, such as exposure to micro-organisms or
chemical agents (Iversen et al. 2007). These steps are similar to the search for an isolated causal factor in CFS, FM, and IBS, that started more than a decade ago and is still proceeding in some research groups.

It is a matter of debate whether all FSD are in fact manifestations of one single disorder, as pursued by the ‘lumpers’, or that FSD cannot be narrowed in a single entity, as argued by the ‘splitters’. FSD overlap in case definition, reported symptoms, and in non-symptom characteristics such as gender, prognosis, and response to treatment (Wessely et al. 1999, Barsky & Borus 1999, Aaron & Buchwald 2001, Fink et al. 2007, Henningsen et al. 2007), supporting the view of the lumpers. The splitters postulate that despite of all the commonalities, the differences between the FSD cannot be ignored. They consider the finding that specific infections and premorbid levels of stress differentially precipitated IBS and CFS supportive for their view (Moss-Morris & Spence 2006). Those two views are not mutually exclusive. Shared factors might underlie general susceptibility for development of any FSD, whereas FSD-specific factors might shape their final manifestation (Aggarwal et al. 2006, Kato et al. 2009). Despite this discussion, it seems generally accepted that FSD have at least a common core, allowing researchers to include different FSD when discussing determinants of the tendency to experience FSS in general.

**Somatoform disorders**

FSS can also be diagnosed on the psychiatric multi-axial diagnostic system of the Diagnostic and Statistical Manual, Fourth Edition (DSM-IV) (American Psychiatric Association 1994). In this classification system, FSS are classified in the category of somatoform disorders, together with conversion disorder, hypochondriasis, and body dysmorphic disorder. Although the latter three diagnoses are categorized under somatoform disorders in DSM-IV, those diagnoses are dissimilar from the FSS count diagnoses and their relationship is debatable (Mayou et al. 2005), and are therefore not considered in this thesis.

In the DSM-IV, FSS are defined as ‘physical complaints not fully explained by a general medical condition, by the direct effects of a substance, or by another mental disorder’. In all somatoform disorders, FSS must cause clinically significant distress or impairment in social, occupational, or other areas of functioning. In contrast to factitious disorder and malingering, the somatic symptoms are not intentional or feigned.

Diagnosis of somatization disorder requires a history of many FSS beginning before the age of 30 years that occur over a period of several years. Each of the following criteria must have been met, with individual FSS occurring at any time point during the course: four pain symptoms, two gastro-intestinal symptoms, one sexual symptom, and one pseudoneurological symptom. Undifferentiated somatoform disorder is characterized by one or more FSS lasting at least six
months with the number of FSS below the threshold for a diagnosis of somatization disorder. The diagnosis of pain disorder is made in patients when pain has existed for at least six months in at least one anatomical site. Psychological factors are judged to play a role in the onset, severity, exacerbation, or maintenance of the pain. DSM-IV does not inform users about the kind of psychological factors and who has to judge whether they play a role. Somatoform disorder not otherwise specified (NOS) codes disorders with FSS that do not meet the criteria for any of the other somatoform disorders. Somatoform disorder NOS can be diagnosed when somatoform symptoms are present but criteria for another somatoform disorder are not met, such as in case of FSS of recent onset or short duration.

While FSS are common, somatization disorder is a very rare diagnosis with an estimated prevalence of 0.03 – 0.84% in the general population (Creed & Barsky 2004). Prevalences of undifferentiated somatoform disorder and somatoform disorder NOS have not been surveyed in the general population, but almost 30% of primary care consulters meet the diagnostic criteria (Fink et al. 1999).

In response to the broadly interpretable definitions of undifferentiated somatization disorder and somatoform disorder NOS in the DSM-IV, researchers have been introducing several new definitions that require a less-restrictive than eight, but variable number of FSS. Examples include Abridged Somatization Disorder (Escobar et al. 1998), Somatization Symptom Index (Escobar et al. 1989), Bodily Distress Disorder (Fink et al. 2007), and Multisomatoform Disorder (Kroenke et al. 1997). Whilst uniformity in classification is lacking, these proposals provide the implicit notion that counting the exact number of FSS seems redundant and somatization is better seen as a continuum. Empirical studies that support such a dimensional model have been published (Katon et al. 1991, Liu et al. 1997, Hiller et al. 2006).

**Somatization**

Historically, somatization is defined as the tendency to communicate emotional distress in physical or bodily terms (Lipowski 1988). This view assumes that emotional distress is involved and unhelpfully underscores dualistic thinking. Somatization is better described as the processes involved in experiencing somatic symptoms not or not conclusively explained by known organic pathology (Lipowski 1988) (i.e., FSS) along a continuum from relatively mild symptoms to severe and disabling disorders (Hiller et al. 2006).

As the etiology of somatization is not understood, it seems logical to maintain neutrality in its nomenclature. No generally accepted definition for somatic symptoms not or not conclusively explained by organic pathology exists. The long list of descriptions, ‘functional somatic symptoms’, ‘medically unexplained symptoms’, ‘symptoms that are difficult to objectify’, ‘inexplicable health
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problems’, ‘somatization symptoms’, ‘symptoms without substrate’, ‘somatoform symptoms’, ‘subjective health complaints’, ‘psychogenic symptoms’, ‘vague symptoms’, and ‘psychosomatic symptoms’ illustrates the ongoing discussion about semantics but also about etiology. Definitions expressing a psychological connotation, such as ‘psychogenic symptoms’ and ‘psychosomatic symptoms’, are preferred by neither researchers or patients. ‘Medically unexplained symptoms’ is regarded honest and neutral by some researchers, however, many patients dislike this term (Stone et al. 2002). Moreover, the term ‘medically unexplained symptoms’ contradicts with a lot of models - more or less supported by research - that provide explanations of symptoms in terms of interacting biological, psychological, and social processes (Brown 2007). As earlier applied, we use the term ‘functional somatic symptoms’ (FSS), since this definition side steps the psychological versus physical dichotomy, is etiologically neutral, and is preferred by patients (Stone et al. 2002).

Alike FSS, disorders with clusters of FSS have parallel classification systems and definitions that are confusing. FSD in somatic medicine, such as CFS, FM, and IBS, suggest specific organic disease and thus highlight specific bodily patterns. Somatoform disorders in psychiatry highlight psychological processes and only count the number of FSS (Mayou & Farmer 2002). Patients may be classified by both a FSD and a somatoform disorder for the same set of FSS (Mayou et al. 2005). In the psychiatric classification system for instance, a patient with musculoskeletal FSS can be diagnosed with a somatoform disorder on axis I as well as with fibromyalgia on axis III. There is a clear need to harmonize the isolated classification systems; nevertheless, there is little agreement on which label is the most appropriate.

In this thesis, somatization is defined as a broad concept. When using the term somatization, we refer to people in the general population presenting with relatively mild FSS, as well as to patients with FSD, and, at the very end of the spectrum, to somatization disorder according to DSM-IV.

Etiology of somatization
Little is known about elementary processes in the physiology of symptom experience. Visceral signals, afferent sensory pathways processing those signals to the central nervous system, and higher-order cognitive processes that are involved before a symptom is reported are largely unexplored (Barsky 2001). Several mechanisms have been proposed to explain somatization. Briefly, those mechanisms can be distinguished in vulnerability factors, triggering factors, and perpetuating factors (Deary et al. 2007).

Vulnerability factors make a person susceptible for somatization and include genetic predisposition (Gillespie et al. 2000), early life experiences with parental illness (Hotopf et al. 1999), early adverse life events such as sexual abuse or
childhood maltreatment (Salmon & Calderbank 1996), and neuroticism or other stress sensitive personality traits (Rosmalen et al. 2007, Turk et al. 2008).

Triggering factors are catalysts for somatization in already vulnerable persons, and include sensitization (Ursin 1997), acute psychological stressors, infections or trauma (Moss-Morris & Spence 2006, Roelofs & Spinhoven 2007), chronic psychosocial stress (van Houdenhove & Egle 2004), and attention processes, such as health anxiety, depression, self-focused attention, or lack of distraction (Pennebaker 1982, Lowe et al. 2008).

Perpetuating factors maintain the somatization process and include a predominant somatic attribution style, dysfunctional health cognitions, and iatrogenic somatic fixation due to diagnostic tests and referrals (Rief et al. 2004). Behavioral processes such as symptom-led activity pattern, dysfunctional coping strategies, and social reinforcement also contribute to perpetuation of somatization (Vercoulen et al. 1997, Kirmayer & Looper 2006).

It has also been hypothesized that FSS are nothing more than somatic representations of anxiety and depressive disorders. Indeed, high rates of comorbidity exist between FSS on the one hand and anxiety and depressive disorders on the other hand (Haug et al. 2004, Lowe et al. 2008). In a study in primary care, however, only 26% of the patients with a somatoform disorder - mainly undifferentiated somatoform disorder - had an anxiety or depressive disorder (Waal de et al. 2004). Furthermore, a meta-analysis indicates that FSD are related to, but certainly not fully dependent on anxiety and depressive disorders (Henningsen et al. 2003).

FSS are not fully explained by any single mechanism and a multifactorial approach is needed. Recent research and theory in this area show complex interactions between physiological, psychological, and social factors in the development and perpetuation of FSS. Many models incorporating those factors have been advanced and all have different features. Importantly, they all share the idea of different levels in the pathway of symptom perception: disturbances in generation, attention, interpretation, and behavioral processes may all account to varying extents in different persons.

Relatively little attention has been paid to underlying biological mechanisms. When appreciating research concerning biological mechanisms, two directions of research can be identified. The first direction concerns brain imaging studies. Structural and functional brain imaging both point to central nervous system alterations in somatization, which are extensively reviewed (Wood 2005). The second direction concerns studies that are indicative of alterations in responsivenes of important bodily stress responsive systems. This thesis will focus on the latter direction of research.
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We will start the next section by outlining the rationale to investigate stress responsive system dysfunction in somatization, followed by a summary of available evidence for this association.

STRESS RESPONSIVE SYSTEM DYSFUNCTION IN SOMATIZATION: AN INCONCLUSIVE AREA OF PSYCHOSOMATIC RESEARCH

The rationale to investigate stress responsive systems in somatization
The first studies investigating stress responsive system function in somatization were published about twenty years ago. A reason to investigate an etiological link between the stress responsive systems and somatization emerges from the potential of those systems to increase symptom experience and perception (Sharpe & Bass 1992). Often, the idea of stress responsive dysfunction as a mediator between psychosocial stress and somatization has been advanced, under the assumptions that psychosocial stress is associated with somatization and that among the long-term effects of psychosocial stress are chronic under- or over activity of the stress responsive systems.

We begin by outlining the rationale for this theory. For each stress responsive system, we will start with a brief description of the most important features, followed by a discussion of potential consequences of dysfunction for symptom experience and available evidence for such dysfunction in somatization. Then, we will discuss limitations of the current evidence and explore alternative pathways.

Psychosocial stress and somatization
To start with the first assumption, an important theory about the etiology of somatization is the chronic stress hypothesis. The chronic stress hypothesis refers to the generally existing idea that stress has part in the development and experience of FSS and FSD. Stress has been defined as environmental demands that individuals appraise as heavily taxing or exceeding their coping abilities (Lazarus & Folkman 1984). This definition clearly indicates that stress comprises two components: the presence of a stressor (i.e., demand from an individual’s environment) and the subjective experience of stress due to the presence of this stressor (i.e., the appraisal that the stressor taxes the coping abilities). The nature of stressors may be predominantly physiological or predominantly psychosocial. Psychosocial stress is the overall name for stressors that have primarily a psychological or social nature. Usually, a distinction is made between major life events, chronic difficulties, and daily hassles. Examples of major life events are death of a spouse or a divorce (Brugha et al. 1985). Examples of chronic difficulties are work overload or permanently living with insufficient financial resources (Hendriks et al. 1990). Examples of daily hassles are losing things and minor family concerns (Kanner et al. 1981). It seems widely accepted that
psychosocial stress impacts on development of symptoms and disorders that are not explained by organic pathology. In the general population, FSS are often referred to as ‘stress-related symptoms’ by laypersons (www.helpguide.org, 2009). Professionals, such as primary care physicians (Wileman et al. 2002) and psychiatrists (see Figure 1) also think that psychosocial stress is the most important etiological factor in FSS. Indeed, virtually all models on the etiology of somatization include forms of psychosocial stress. The question whether psychosocial stress precedes FSD, such as CFS, FM, and IBS, has been answered with a “fairly unequivocal yes” in a narrative review (Deary et al. 2007). Stress sensitive personality traits, premorbid psychosocial stress, also if happened several decades ago, and acute psychosocial stress predict development of CFS (Heim et al. 2006, Kato et al. 2006, Prins et al. 2006), FM (Wolfe & Hawley 1998, Gupta & Silman 2004, van Houdenhove et al. 2005), and IBS (Mayer 2000, Blanchard & Scharff 2002, Folks 2004). Life events also precede different FSD surveyed in the general population (Aggarwal et al. 2006).

Figure 1. Etiology of somatization according to psychiatrists.

Before the start of a symposium on concepts and mechanisms of somatization, 18 psychiatrists and psychiatrists in training were asked to write down which etiological factors they considered important in development of functional somatic symptoms and disorders. Only factors that were reported by at least two psychiatrists are shown.
Stress responsive system dysfunction in somatization
The second assumption is that chronic stress is able to induce alterations in stress responsive system activity. When stress exceeds a certain threshold, it evokes a generalized stress system response. The aim of this response is to restore homeostasis (Chrousos & Gold 1992). The autonomic nervous system, the hypothalamic-pituitary-adrenal axis, and the immune system all serve to protect the body from stress and can therefore be seen as bodily stress responsive systems (McEwen 1998b). When the load of stressors in an individual is too large, when stress responsive systems are chronically addressed, or when the capacity of the stress responsive systems to adjust is diminished, dysfunction of stress responsive systems may develop (Chrousos & Gold 1992). Stress responses are generated by a network of integrative brain structures involving the paraventricular nucleus of the hypothalamus and the amygdala. These structures receive input from visceral and somatic afferents and from cortical structures. This integrative network provides output to the pituitary and to the pontomedullary nuclei, structures that mediate the autonomic and endocrine output to the body. Repeated or prolonged exposure to stress may result in changes in this central stress circuitry. Consequently, these changes may result in stress responsive system alterations.

Autonomic nervous system (ANS)
The ANS is responsible for rapid stress responses, since it reacts within seconds after stimulation. The ANS controls bodily functions such as thermoregulation, breathing, and circulation. It helps maintain homeostasis and coordinates responses to external stimuli. The ANS can be divided in two divisions: the sympathetic and the parasympathetic nervous system. The sympathetic nervous system is frequently referred to as the ‘stress’ or ‘fight or flight’ system, as it has a stimulatory effect on bodily systems and organs that are responsible for quick sensory activity and movement. The sympathetic influence is mediated through the postganglionic release of noradrenalin. Roughly said, the parasympathetic nervous system antagonizes the sympathetic nervous system, since it has ‘rest and digest’ activity. Stimulation of the parasympathetic nervous system results in bradycardia and relaxes many bodily systems and organs through the postganglionic release of acetylcholine. The ANS does not function on its own, but is both anatomically and functionally linked to other parts of the nervous system.

ANS activity is influenced by chronic, repetitive, and acute psychosocial stress (Sloan et al. 1994, Dishman et al. 2000, Schommer et al. 2003). ANS alterations as a result of psychosocial stress would most likely consist of decreased activity of the ‘resting’ parasympathetic nervous system and increased activity of the ‘stress’ sympathetic nervous system. As the ANS innervates several organs, sensation and misinterpretation of peripheral physiological arousal may result in experience of FSS (Sharpe & Bass 1992, Rief & Barsky 2005). Examples of FSS that may result
from misinterpretation of autonomic physiological arousal are functional chest pain in case of increased heart rate, functional abdominal pain in case of decreased gastro-intestinal peristalsis, and functional musculoskeletal pain in case of increased muscle tension.

A widely used proxy for ANS function is heart rate variability (HRV), reflecting interbeat interval fluctuations in heart rate (HR). In an attempt to study sympathetic nervous system activity, studies have often reported power in the low frequency band (HRV-LF), defined at 0.04 - 0.15 Hz. However, the physiological basis is not well understood and HRV-LF certainly does not simply reflect sympathetic activity, although frequently reported as such. Therefore, we here consider only studies reporting on resting PNS activity in the high frequency band (HRV-HF), defined at 0.15 - 0.40 Hz and also referred to as cardiac vagal activity, as this measurement has a clear physiological basis (Berntson et al. 1997).

A narrative review of more than thirty studies suggests that decreased cardiac vagal activity could be associated with presence of the main FSD (i.e., CFS, FM, and IBS), however, findings are not fully consistent (Tak & Rosmalen 2007). When HRV is measured under resting conditions, if there are any significant differences, they point consistently in the direction of decreased cardiac vagal activity in FSD compared to healthy controls. Nevertheless, studies often find no baseline differences between patients with FSD and healthy controls. Although reliability of HRV measurements performed during challenges is generally poorer than when measured at rest (Sandercock et al. 2005b), several strategies to challenge the ANS have been used to provoke HRV responses, such as measurements during standing, tilt table testing, deep breathing, isometric exercise, treadmill walking, thermal stimuli, and mental stress. Also, specific challenges or procedures, such as eating a meal or rectal balloon distention, have been performed in IBS studies. In about half of the studies, no differences after challenge tests are apparent. When significant differences were found compared to healthy controls, cardiac vagal activity was always lower or responsiveness was decreased in FM and CFS, and mostly in IBS. Only one study in IBS found increased cardiac vagal activity in cases compared to controls (Tousignant-Laflamme et al. 2006). Another study specifically looking at IBS symptom groups found that those groups were characterized by different physiological responses to food intake (i.e., an increase in cardiac vagal activity in constipation-predominant IBS and a decrease in cardiac vagal activity in diarrhea-predominant IBS) (Elsenbruch & Orr 2001b). No studies on ANS function in somatization disorder, pain disorder, undifferentiated somatoform disorder, or somatoform disorder NOS have been performed. Furthermore, no studies on the association between ANS function and the extent of FSS in individuals from the general population are available.
Hypothalamic-pituitary-adrenal axis (HPA axis)

In response to several afferent stimuli, the hypothalamus releases corticotrophin-releasing hormone (CRH) and arginin vasopressin (AVP). CRH and AVP synergistically induce release of adrenocorticotropic hormone (ACTH) from the pituitary. ACTH is secreted with a diurnal rhythm superimposed upon the pulses of CRH. The lowest serum ACTH concentrations occur in the early night, whereas the highest ACTH concentrations occur between 0400h a.m. and 0600h a.m. In addition to this diurnal rhythm, ACTH responds to a wide variety of stimuli. ACTH controls the release of cortisol from the adrenal cortex. The diurnal curve of total and free plasma cortisol includes 7 to 13 pulses of cortisol secretion per day. Half of the total daily cortisol is secreted within the major burst before dawn. Cortisol causes negative feedback of its own secretion at several levels, including hippocampus, hypothalamus, and pituitary. The biologically active component of cortisol is the unbound or free fraction and the main biological effects are widespread, including increase of glucose levels and blood pressure, fat metabolism, protein catabolism, breakdown of muscle mass, lowering the activity of the immune system, and altering mood. These biological effects depend on many factors other than blood plasma concentrations, such as sensitivity of glucocorticoid receptors and the presence of other molecules. It is important to realize that the HPA axis does not function on its own, but interacts with many other bodily systems (Niewoehner & Bantle 1998, Genuth 1998).

There are several hypothetical pathways how altered concentrations of corticotrophin-releasing hormone (CRH), adrenocorticotropic hormone (ACTH), and cortisol can be involved in somatization. Firstly, CRH not only modulates the endocrine response, but also influences pain perception. Although acute stress is known to produce analgesia, chronic stress may have the opposite effect, a process mediated by CRH (Clauw & Chrousos 1997, Lariviere & Melzack 2000). Low cortisol concentration may cause widespread pain and fatigue (Heim et al. 2000a, Fries et al. 2005).

In this thesis, the focus is specifically on cortisol, of which secretory patterns can provide a partial window into the activity of the HPA axis. Cortisol can be assessed in blood plasma, saliva, or urine. Measurement can take place at a single time point, but it is generally preferred to collect cortisol several times a day, or during several days (Nicolson 2007). Although there is no gold standard, assessment of cortisol in saliva seems to be the preferred method as it has proven to be a valid and reliable reflection of the respective unbound concentration in blood and has advantages such as stress-free sampling and laboratory independence (Kirschbaum & Hellhammer 1994). Twenty-four hour urinary free cortisol (24-h UFC) excretion is considered a practical index of integrated plasma free cortisol, not influenced by the time of measurement and interpersonal differences in circadian rhythm (Levine et al. 2007).
Although more than sixty HPA axis studies in FSD have been published, they do not exclusively support one separate kind of dysfunction. Narrative reviews conclude that baseline findings on cortisol levels in CFS, FM, and IBS subjects compared to healthy controls are inconsistent: mild hypocortisolism seems the most frequent finding, but normal or increased cortisol levels have also been reported (Mayer et al. 2001, Geenen et al. 2002, Cleare 2003, Tak & Rosmalen 2007).

Dynamic challenges of the HPA axis in FSD have been undertaken, to detect more subtle disturbances and to determine the level of dysfunction in the HPA axis that cause reported cortisol alterations FSD in rest. The HPA axis can be activated by several stressors and findings have been presented on different pharmacological challenges, including the insulin tolerance test, CRH stimulation test, vasopressin infusion, standard ACTH stimulation test (250 µg), low dose ACTH stimulation test (1 µg), and glucagon stimulation test. In addition, cortisol measurements after administration of medication, such as d-fenfluramine, naloxone, and buspirone have been performed. To challenge the HPA axis non-pharmacologically, measurements after procedures to elicit physical or psychological stress have been used, such as auditory stress, food intake stress, exercise stress, thermal stress, rectal balloon distention, sigmoidoscopy, mental tasks, or public speaking. In narrative reviews on HPA axis activity after stress tests, divergent results were reported, without clear evidence for any specific change to the HPA axis. When studies find differences, mostly an impaired or blunted response of the HPA axis has been shown (Cleare 2003, Tanriverdi et al. 2007). One of the theories regarding the underlying cause of hypocortisolism in FSD is that of enhanced negative feedback on the hypothalamus or pituitary. To test this theory, the dexamethasone suppression test is most often used, in which enhanced negative feedback in FSD compared to controls indeed is the main finding (Tak & Rosmalen 2007).

No studies regarding HPA axis activity in somatization disorder, pain disorder, undifferentiated somatoform disorder, or somatoform disorder NOS exist. However, two studies including patients with less strict diagnoses than somatization disorder have been performed. The first study observed no alterations in a range of cortisol measurements in patient with at least eight FSS compared to healthy controls (Rief & Auer 2000). The second study even observed higher basal salivary cortisol concentrations in patients having at least four FSS (when male) or at least six FSS (when female) compared to healthy controls (Rief et al. 1998). In a study making 24-h real-life ambulatory recordings of salivary cortisol in patients with different FSD (such as hyperventilation syndrome and CFS, but also other conditions such as burnout syndrome), no differences compared to healthy controls were found (Houtveen & van Doornen 2007b). In a community study of 41 adults, plasma cortisol levels measured after the dexamethasone suppression test did not predict self-perceived fatigue. No
other studies on HPA axis function and FSS in the general population are available.

**Immune system**

A third important stress responsive system to consider in the etiology of FSS is the immune system. Unlike the ANS and the HPA axis, the immune system is not primarily known as a stress responsive system. The immune system is a complex system known for its protection against pathogens and can be divided into innate and adaptive immunity (Male 2001). Innate immunity is immediate but non-specific, whereas adaptive immunity is specific and recognizes a pathogen. Immune responses are produced primarily by leucocytes and soluble mediators of which there are several different types. Phagocytes, such as monocytes and macrophages, internalize micro-organisms and are a component of the innate immunity. Lymphocytes, such as B cells and T cells, have more specialized functions and are central to adaptive immunity. Cytokines are proteins that enable immune cells to communicate and play an integral role in the initiation, perpetuation and subsequent down regulation of the immune response. Cytokines can be divided into pro-inflammatory cytokines such as interleukin (IL)-1, tumor necrosis factor (TNF)-alpha, and IL-6, and anti-inflammatory cytokines like IL-4 and IL-10 (Male 2001). Production of C-reactive protein (CRP), an acute phase protein in the immune reaction, is induced by pro-inflammatory cytokines. CRP levels may rise rapidly and as much as 1000-fold after an acute inflammatory stimulus (Black et al. 2004). It has been documented that the immune system can become triggered by non-pathogenic, more generic signals, such as psychological stress (Kiecolt-Glaser et al. 2002). A meta-analysis showed that acute stressors are associated with potentially adaptive upregulation of the immune response in a similar pattern for men and women across the life, whereas chronic stressors were associated negative effects on almost all functional measures of the immune system, especially in older adults (Segerstrom & Miller 2004). This meta-analysis did only include few studies on cytokines and none on CRP and chronic stress. In a population-based study of older adults, higher levels of chronic stress were associated with higher concentrations of IL-6 and CRP (Ranjit et al. 2007).

Different pathways may be etiologically involved in the link between the immune system and somatization. Firstly, the immune system may be related to FSS and FSD via sickness behavior, a constellation of non-specific symptoms induced by pro-inflammatory cytokines, such as IL-1, IL-6, and TNF-alpha (Dantzer 2001, Wieseler-Frank et al. 2005). These non-specific sickness behavior symptoms, including fatigue, weakness, malaise, hyperalgesia, and increased focus on own body, are core characteristics of persons having FSS and FSD (Dantzer 2005). Secondly, immune activation may be a marker for activity of the ANS and HPA axis, as both systems closely interact with the immune system (McEwen et al. 1997, Araujo et al. 2006).
A lot of other immunological abnormalities (e.g. T cell quantity and function, B
cell quantity and function) have been identified in several FSD; however, those
abnormalities are rarely replicated. This is illustrated by a critical review of
immunological abnormalities in CFS. No consistent pattern of immunological
abnormalities has been identified, and additionally, the high quality studies where
the ones that demonstrated that cytokine levels in patients were not different
from those in controls (Lyall et al. 2003). Furthermore, a study combining
patients with different FSD did not find differences in pro- and anti-inflammatory
cytokines between somatizers and healthy controls (Houtveen et al. 2007a). In a
less restrictive diagnosis of somatization syndrome, another study found lower
levels of pro-inflammatory cytokine IL-6 in somatization patients compared to
healthy controls (Rief et al. 2001), an unexpected direction based on theory. In
sum, although elevated cytokine levels may induce sickness behavior, they are not
unambiguously being found in somatization. Maybe these conflicting findings are
due to the fact that alterations in central behavior of cytokine, if present, are not
necessarily measurable in the peripheral blood (Dantzer 2001). Therefore, other
immunological biomarkers that reveal stress responsiveness of the immune
system are important to consider.

CRP might be a more integrated and accurate peripheral marker for innate
immune system activation. Although historically long been considered as
clinically irrelevant, minor elevations of CRP (3 - 10 mg/L) have been reported to
be associated with psychosocial stress (McDade et al. 2006). Ultrasensitive
assays can detect CRP in this subclinical range as high-sensitive CRP (hs-CRP).
Thus, elevated hs-CRP does not directly causes generation or sensation of FSS
but rather is a biomarker of immune activation. Of associations of circulating
concentrations of CRP and pro-inflammatory cytokines in subjects of the general
population without active infection, those between IL-6 and CRP have been most
frequently investigated and are generally strongest, with reported significant
correlation coefficients ranging from 0.24 to 0.50 (Ridker et al. 2000, Cesari et al.
et al. 2009). In the study with the strongest correlation between IL-6 and CRP,
which included 901 subjects aged 65 years and older, correlations of CRP with
other investigated cytokines were lower: significant correlations of 0.09 and 0.19
were found for IL-1β and IL-18 respectively, and an non-significant correlation of
0.06 was found for TNF-α (Milaneschi et al. 2009). Indeed, the few available
findings addressing hs-CRP appear more consistent. Patients with FSD have
higher levels of hs-CRP compared to healthy controls (Buchwald et al. 1997,
Spence et al. 2008), although this difference is not always statistically significant,
such as in IBS (Schoepfer et al. 2008). No data about immune function or hs-CRP
in persons experiencing FSS in the general population have been published.
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Methodological problems
Summarizing the available results on the association between the stress responsive systems and somatization, one encounters heterogeneous results. Nevertheless, some specific directions can be distilled from research findings on the ANS and the HPA axis. If associated at all, somatization seems quite consistently characterized by lower cardiac vagal activity and hypocortisolism. However, research focusing on stress responsive system dysfunction and somatization is mainly conducted in small samples derived from clinical settings, which are not representative for all individuals with FSS. The wide variability in assessment of different parameters, particularly when measuring HPA axis or immune system activity, may also contribute to the mixed findings. Furthermore, little attention has been paid to the role of potential confounders, such as body mass index, smoking, physical activity, sleeping problems, psychiatric co-morbidity, concurrent psychosocial stress, and medication use, or potential moderators, such as gender and age (Tak & Rosmalen 2007).

Causality and alternative pathways
It remains unclear whether stress responsive system dysfunction, if present, is causally related to somatization. The temporal relationship between stress responsive system dysfunction and somatization is not well established, because previous studies have generally been cross-sectional. Several pathways should be considered; an overview of these four pathways is shown in Figure 2.

Firstly, alterations in stress responsive systems could induce FSS: the etiological pathway. In this chapter, we have introduced the hypothesis of stress responsive system dysfunction as a causal risk factor in the etiology of somatization. Although this etiological pathway is biologically plausible, preceding and etiologically important stress responsive system dysfunction may also arise from other factors than psychosocial stress, such as genetic predisposition.

Somatization and stress responsive system dysfunction could also share the same etiological determinants, such as stress sensitive personality or psychiatric co-morbidity, and develop parallel in the epiphenomenal pathway. In this pathway, stress responsive system alterations may not cause symptom experience at all and, whereas it may also be a perpetuating factor of symptom experience, and constitute a combination of the consequential and etiological pathway (i.e., perpetuating pathway).

Thirdly, FSS and FSD could induce stress responsive system alterations, for example, due to symptom experience or lifestyle alterations: the consequential or concomitant pathway. In this pathway, stress responsive system alterations may not cause symptom experience at all and, whereas it may also be a perpetuating factor of symptom experience, and constitute a combination of the consequential and etiological pathway (i.e., perpetuating pathway).
Finally, it may be possible that there is no association between stress responsive system dysfunction and FSS and FSD at all. Previous positive findings may be artifacts of methodological shortcomings and publication bias.

**Figure 2.** Four simplified representations of theories about the relationship between stress responsive system dysfunction and somatization.

1. **Etiological pathway:** stress responsive system dysfunction is a cause of developing FSS and FSD

   ![Diagram 1] (Chronic psychosocial stress → Stress responsive system dysfunction → Somatization)

2. **Epiphenomenal pathway:** stress responsive system dysfunction is an unrelated epiphenomena of FSS and FSD

   ![Diagram 2] (Chronic psychosocial stress → Stress responsive system dysfunction → Somatization)

3. **Consequential pathway:** stress responsive system dysfunction develop as a result of FSS and FSD (see dashed arrow for perpetuating pathway)

   ![Diagram 3] (Somatization → (Behavioral) consequences → Stress responsive system dysfunction)

4. **No association between stress responsive system function and FSS and FSD**

   ![Diagram 4] (Stress responsive system dysfunction → Somatization)

*Abbreviations: FSS = functional somatic symptoms, FSD = functional somatic disorders*

We are primarily interested in stress responsive system dysfunction in the etiology of somatization. Accordingly, it is of importance to assess whether stress responsive system dysfunction satisfies the requirements of being a causal risk factor. To assess this, a decision tree for classifying the association between a certain factor and an outcome has been proposed (Kraemer et al. 1997). A risk factor is a measurable characterization of each subject in a specified population...
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that precedes the outcome of interest. A characterization that satisfies all requirements for a risk factor except for precedence is a correlate of the outcome. This is a crucial point, because concomitants or consequences of outcomes are likely more highly correlated with the outcomes than are risk factors. A risk factor that can change spontaneously within a subject (such as age or body mass index) or that can be changed with an intervention is a variable risk factor. A risk factor that cannot be changed (such as genetic predisposition or gender) is a fixed risk marker. The term causal risk factor can only be used when a variable risk factor is manipulable and change the risk of the outcome when it is manipulated (see for a schematic overview Figure 3).

AIMS OF THIS THESIS

Hypotheses
The overall aim of the studies described in this thesis is to test the presence of dysfunction of stress responsive systems in the etiology of somatization. We hypothesize that dysfunctions in stress responsive systems, as characterized by hypofunction of the HPA axis, altered ANS function in the direction of decreased cardiac vagal activity, and increased immune system activation, are shared causal risk factors in the etiology of FSS and the main FSD.

Investigating whether there is a causal role for dysfunction of stress responsive systems in the etiology of somatization is only possible in large cohort studies, a type of design that is uncommon in this research field. Therefore, we started with extracting as much as possible available information from cross-sectional case-control studies by using meta-analysis. This approach is particularly valuable to investigate whether stress responsive system dysfunction is a shared or FSD-specific correlate and which other factors influence their association. Furthermore, we used data from a large longitudinal population-based cohort study to evaluate whether stress responsive system dysfunction is a prospective risk factor for FSS.

Outline
Following this introductory chapter, Chapter 2 focuses on the general principles of performing a meta-analysis, with an emphasis on its specific merits and pitfalls for observational, psychosomatic research. Chapter 3 is a systematic review of methodological quality and meta-analysis of ANS function in FSD. Chapter 4 presents a meta-analysis and meta-regression on HPA axis activity in FSD. Both chapters aim to test whether stress responsive system dysfunction is a shared or FSD-specific factor. Chapter 5 tests the assumption that somatization may be better considered as a continuum instead of requiring FSS in several bodily clusters. Next, we report on the association between ANS function (Chapter 6),
HPA axis activity (Chapter 7), and immune function (Chapter 8) and FSS using prospective measurements in a population-based cohort (Figure 4). Chapter 9 presents an exploratory study on the association between psychosocial stress and stress responsive system function. Finally, in Chapter 10, the main findings will be summarized and integrated with as central question: what is the evidence for a pivotal role of dysfunction of stress responsive systems in somatization?

Figure 3. The process of elucidation of risk factor status for a factor in a population for a particular outcome.
Figure 4. Stress responsive system dysfunction and somatization. Variables in italic represent variables we have measured in the population-based studies in this thesis.

Abbreviations: ANS = autonomic nervous system, HPA axis = hypothalamic-pituitary-adrenal axis, hs-CRP = high-sensitive C-reactive protein, 24 h UFC = 24-hour urinary free cortisol