Kerstin Suarez

Stress in Functional Gastrointestinal Disorders: An approach to the Identification of Specific Psychobiological Markers

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CONTENTS:

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ABSTRACT

The present thesis aimed at determining the role of psychosocial stress in functional gastrointestinal disorders (FGID). In a first study, the association between self-reported gastrointestinal symptoms and perceived stress, operationalized by a well-established multidimensional approach, was investigated. In the second study, we examined the functionality of the most prominent endocrine stress system – the hypothalamus-pituitary-adrenal (HPA) axis – in a sample of women with irritable bowel syndrome (a particular FGID).

Data 1

Background & Aims: Functional gastrointestinal disorders (FGID) are common in the general population. Despite their relevance in public health care, the etiology of FGID remains essentially unknown. Stress has been suggested as a central pathophysiological factor in FGID. However, most previous studies in FGID neglected the multidimensional characteristics of stress. The aims of the present study were: a) to determine the prevalence of FGID in a sample of apparently healthy students, and b) to determine the association of stress and FGID.

Methods: An Internet-based study was conducted in university students. The prevalence rates of 21 different FGID were assessed according to Rome II criteria. Stress variables (subjective experience of chronic stress, individual coping strategies, and dispositional stress reactivity) were measured.

Results: 668 subjects provided complete data sets (66% women, mean age 24.3 years). 64.2% reported at least one FGID. Symptoms of FGID were significantly predicted by increased levels of perceived chronic stress, dispositional stress reactivity, and use of maladaptive coping strategies.

Conclusion: FGID seem to be common in apparently healthy young individuals. The strong relationship between chronic stress, increased stress reactivity, and maladaptive coping in individuals suffering from FGID indicates that stress-reducing interventions may be beneficial in such persons.

Data 2

Background & Aims: Stress has been considered as an important pathophysiological factor in IBS. The physiological mechanisms between stress and gut disturbances, however, are not completely understood. Therefore, the current study aimed to compare IBS patients and controls with respect to (a) their diurnal HPA axis activity and (b) their psychobiological response to a psychosocial stressor.

Methods: Basal and stimulated HPA axis activity was assessed in fifty-seven women with IBS and twenty matched healthy controls. Patients were diagnosed according to the Rome III criteria and assigned to IBS-D, IBS-C or IBS-M. Psychiatric comorbidity was assessed using a clinical interview. Salivary morning cortisol and diurnal profile were obtained and a standardized psychosocial stress test (TSST) was applied. Cortisol and ACTH were measured before and within one hour following the stressor.

Results: Subjects with IBS and controls showed intact circadian rhythmicity of the HPA axis. However, a subgroup of IBS patients (IBS-D) exhibited substantially heightened cortisol at awakening and nearly no morning increase. In response to the TSST, women with IBS exhibited significantly blunted cortisol and slightly attenuated ACTH secretion compared to controls. In the recovery period, ACTH levels were significantly lower in IBS patients than in healthy subjects. In contrast to the biological findings, women with IBS perceived higher general and situation-specific stress susceptibility.

Conclusions: Enhanced morning cortisol in IBS-D may indicate an association between basal HPA axis activity and predominant bowel habit. The downregulated HPA axis reactivity in IBS patients following the TSST suggests a downregulated sensitivity of the endocrine system. Conversely, psychological stress measures were increased overall in the IBS group and suggest heightened stress susceptibility.

TABLES

FIGURES

ACRONYMS

ANOVA= Analysis of variance

ANS= Autonomic nervous system

CNS= Central nervous system

CTQ= Childhood Trauma Questionnaire

CRH= Corticotrophin-Releasing Hormone

EMS= Emotional motor system

ENS= Enteric nervous system

GERD= Gastroesophageal reflux disease

HAD= Hospital Anxiety and Depression Scale

HPA axis= Hypothalamus-pituitary-adrenal axis

IBD= Inflammatory bowel diseases

IBS= Irritable bowel syndrome

FGID= Functional gastrointestinal disorders

PI-IBS= Postinfectious IBS

PSS= Perceived Stress Scale

PTSD= Posttraumatic Stress Disorder

PVN= Paraventricular nucleus

SIBO= Small intestinal bacterial overgrowth

SOMS= Screening for Somatoform Symptoms

SRS= Stress Reactivity Scale

SEM= Standard Error of the Mean Values

TICS= Trier Inventory for the Assessment of Chronic Stress

TSST= Trier Social Stress Test

1. Introduction

"The way to a man's heart is through his stomach" and "scare the pants off someone" are just two of the commonly used expressions in our everyday language suggesting a close association between psychological conditions and digestive functions. Scientific testing of this assumption was first conducted at the beginning of the 19th century by William Beaumont. During the last decades, psychological factors, and in particular stress, have been increasingly implicated in the etiological model of chronic gastrointestinal conditions.

Functional gastrointestinal disorders (FGID), in particular the irritable bowel syndrome (IBS)[1], are the most common conditions resulting in patient visits to primary care physicians and to gastroenterologists. Patients with FGID exhibit a high prevalence of psychiatric comorbidity, psychosocial stress and often show maladaptive illness behavior. For these reasons, FGID have been associated with substantial socioeconomic and individual burden. Although the etiology of FGID remains poorly understood, numerous investigations provide evidence for a crucial role of stress in the etiopathology and in the clinical outcome of these diseases. The influence of acute laboratory stress on bowel functions including motility, secretion and visceral perception is well established in animals and humans. However, stress-induced alterations of gastrointestinal functions have been suggested to be more pronounced in individuals with FGID. Additional evidence for a contributing role of stress in FGID comes from studies linking gastrointestinal symptoms with subjective reports of perceived stress. A variety of "stressors" such as early life stress, acute life-threatening or traumatic events, but also chronic stress in the form of daily hassles and sustained psychosocial stress, have been associated with FGID. It has been postulated that in predisposed individuals, chronic stress modifies the responsiveness and the feedback mechanisms of regulatory psychophysiological systems. The long-term consequences of such alterations are a variety of somatic and psychological symptoms.

[1] IBS is the most expensively investigated FGID. Therefore, the majority of the citations will refer to studies in IBS patients.

Although previous findings provide evidence of stress-induced gut disturbances and psychosocial stress has been associated with the onset and maintenance of FGID, the physiological mechanisms linking stress and gut remain poorly understood. As one mediator of the brain-gut interaction, the hypothalamus-pituitary-adrenal axis – a prominent biological stress system – has been proposed.

The present thesis about Stress in Functional Gastrointestinal Disorders: An Approach to the Identification of Specific Psychobiological Markers includes the three following main parts: A theoretical background, two empirical studies, and a general discussion. The theoretical background consists of information about definition, diagnostic criteria, epidemiology and characteristics of FGID, in particular IBS (chapter I). Following this, current research opinion about etiological factors of FGID in general and IBS in particular will be highlighted (chapter II), and subsequently, the two empirical studies will be presented. The first study aimed at determining the association between functional gastrointestinal symptoms and stress perception in a sample of apparently healthy students. The second study, by contrast, focuses on IBS patients and examines the basal as well as the stimulated hypothalamus-pituitary-adrenal (HPA) axis activity. Finally, a general discussion will embed our current findings in the theoretical background, limitations of the studies will be discussed, and an overview of future research directions will be given.

2. Functional gastrointestinal disorders (FGID)

The following paragraphs will give an overview regarding the definition and the diagnostic criteria of FGID in general and IBS in particular. Moreover, the differentiation between FGID and other somatic syndromes will be discussed. Following this, epidemiological facts and current knowledge about the course of illness will be presented. Finally, important characteristics in FGID including sex/gender differences, health care seeking, illness impact, personality traits and comorbidity will be outlined.

2.1. Definition and diagnostic criteria of FGID

The term 'functional gastrointestinal disorder' (FGID) describes heterogeneous combinations of chronic or recurrent gastrointestinal symptoms, which cannot be fully explained by structural or biochemical abnormalities. In most FGID, physiological markers have not yet been identified, or the cause-effect relationship between the abnormality and the symptom is not clear (Corazziari, 2004). Despite differences in location and symptom patterns, FGID share similarities with regard to their psychophysiological characteristics and the approach to patient care (Drossman et al. 2002). The term of "functional" is somewhat misleading, since current definitions of FGID do not necessarily exclude all organic pathologies but those that cause specific FGID symptoms. For instance, a person suffering from colonic diverticula or gallstones can simultaneously be diagnosed with a FGID (Corazziari, 2004). So far, methodological problems such as measurable biological markers of gastrointestinal functions or a lack of non-invasive access to the gastrointestinal tract have impeded current investigations in terms of detecting subtle structural or biochemical alterations.

In the absence of specific biological markers, FGID can merely be identified by symptoms and their assignment to a positive symptom-based diagnosis. As a consequence, the criteria of FGID represent a consensus opinion of investigators based on clinical assessment and limited information about pathophysiological mechanisms (Corazziari, 2004). In order to overcome classification heterogeneity, a group of experts met in 1989 for the first congress of "Rome working teams to develop diagnostic criteria". Internationally recognized researchers in this field provided the first multinational consensus, the so-called "Rome criteria" (Drossman et al. 2002). Over the last two decades, the Rome working group has modified and established their classification system worldwide. The first update (Rome II) was published in 1999

(Thompson et al. 1999, Drossman et al. 2000), the third version in April 2006 (Drossman, 2006). Reasonable sensitivity and specificity were proved for Rome I (Whitehead et al. 2003, Vanner et al. 1999), and validation data for Rome II are beginning to emerge (Kwan et al. 2003). The current version, the Rome III criteria, contains 28 adult and 17 pediatric FGID (TABLE 1), ranging from the esophagus to the anorectum (Drossman, 2007).

The adult diagnoses are divided into six major domains based on five anatomical regions: oesophageal (category A), gastroduodenal (category B), bowel (category C), biliary (category E), anorectal (category F), and additionally the category of functional abdominal pain syndrome (category D). Each of these domains includes several disorders. For instance, category C contains: irritable bowel syndrome (C1), functional bloating (C2), functional constipation (C3), and functional diarrhea (C4). Most FGID are characterized by a common set of multiple symptoms rather than a single disease entity. However, some conditions are defined by one single symptom (i.e. functional bloating, functional chest pain). The assignment to symptom-based subgroups allows the identification of individuals presenting homogeneous symptom complexes. To separate chronic gastrointestinal conditions from transient gut symptoms, the Rome III includes strict time criteria: symptoms have to have been present on 3 days per month during the last 3 months and they must have occurred for the first time 6 months prior to diagnosis. In pathophysiological studies or clinical trials, the recommended time criterion for symptom occurrence is > 2 days a week (Longstreth et al. 2006).

The principle changes from Rome II to Rome III guidelines lie in (1) the less restrictive timeframe for diagnosis, (2) the revision of the IBS subtype classification, (3) the removal of functional abdominal pain as a separate category, (4) the displacement of rumination from category A to category B, (5) the adaptation of functional dyspepsia criteria, (6) the more restrictive criteria for category E, (7) and finally the creation of two pediatric categories (Drossman, 2006).

The distinction of FGID in clinical practice is not always clear, and the classification is often arbitrary (e.g. IBS versus functional constipation) (Longstreth et al. 2006). In contrast to psychiatric classification systems (APA, 2000), the nosological approach of the Rome consensus does not take into account the subjective impact on quality of life and individual

impairment as a consequence of the disease (Talley, 2008). The symptom severity reported by individuals with FGID ranges from minimal to substantial.

TABLE 1: ROME III CLASSIFICATION OF THE FUNCTIONAL GASTROINTESTINAL DISORDERS (FGID) IN ADULTS

category A: Functional oesophageal disorders
A1 Functional heartburn
A2 Functional chest pain of presumed oesophageal origin
A3 Functional dysphagia
A4 Globus
category B: Functional gastroduodenal disorders
B1 Functional dyspepsia
B1a Postprandial distress syndrome (PDS)
B1b Epigastric pain syndrome (EPS)
B2 Belching disorders
B2a Aerophagia
B2b Unspecified excessive belching
B3 Nausea and vomiting disorders
B3a Chronic idiopathic nausea (CIN)
B3b Functional vomiting
B3c Cyclic vomiting syndrome (CVS)
B4 Rumination syndrome in adults
category C: Functional bowel disorders
C1. Irritable bowel syndrome (IBS)
C2. Functional bloating
C3. Functional constipation
C4. Functional diarrhoea
C5. Unspecified functional bowel disorder
category D: Functional abdominal pain syndrome (FAPS)

category E: Functional gallbladder and sphincter of oddi (SO) disorders
E1 Functional gallbladder disorder
E2 Functional biliary SO disorder
E3 Functional pancreatic SO disorder
category F: Functional anorectal disorders
F1 Functional fecal incontinence
F2 Functional anorectal pain
F2a1 Chronic proctalgia
F2a2 Unspecified functional anorectal pain
F2b Proctalgia fugax
F3 Functional defecation disorders
F3a Dyssynergic defecation
F3b Inadequate defecatory propulsion

2.1.1. A prevalent FGID: The Irritable Bowel Syndrome (IBS)

The irritable bowel syndrome is one of the most extensively studied FGID. IBS is characterized by abdominal pain or discomfort that is relieved by defecation or is associated with a change in stool frequency or stool appearance in the absence of structural disease (Drossman, 1994). Like other FGID, IBS was for a long time considered a diagnosis of exclusion. The first proposal of a positive symptom list to diagnose IBS was made by Manning (1978), and included six gastrointestinal symptoms: (1) pain relieved by defecation, (2) looser stools at onset, (3) more frequent stools at pain onset, (4) visible abdominal distension, (5) passage of mucus, and (6) feeling of incomplete rectal emptying. Several studies reported high degrees of sensitivity (58%-81%) and specificity (67%-87%) of the Manning criteria (Talley et al. 1990 & 2002). However, since the implementation of the Rome criteria, IBS has been increasingly diagnosed according to this modern classification system. So far, no consensus has been achieved regarding which diagnostic system, or which version of the Rome criteria, more accurately estimates IBS prevalence in the general population (Thompson et al. 2000) and is more sensitive to detect IBS cases in clinical practice (Chey et al. 2002, Kwan et al. 2003). The Rome II criteria were implemented to

simplify the Rome I criteria, but they have been shown to be more restrictive and limited in capturing fluctuating symptoms (Boyce et al. 2000, Williams et al. 2006). Despite growing empirical acceptance of the Rome classification, many clinicians believe the criteria to be too restrictive and suggest a broader definition of IBS in clinical practice (Van Zanten, 2002, Brandt et al. 2002). A comparison between the IBS diagnostic criteria according to Manning, and the Rome I, Rome II and Rome III is presented in TABLE 2. It is noteworthy that pain was often reported to be one of the most common symptoms in IBS, although there is no consensus as to whether it is a sine qua non for IBS diagnosis. Substantial variation has been observed with respect to the extent of reported pain, with twice as many patients classifying their symptoms as abdominal discomfort than as pain (Sach et al. 2002).

The ongoing modification of the Rome criteria led to the consequence that previous investigations used heterogeneous diagnostic criteria. Therefore, the comparison and interpretations of available data is impeded. Saito et al. (2003) found a two- to fivefold variation comparing several IBS diagnostic criteria in the same sample. Similarly, in a large epidemiological survey, a substantial variance was observed between the IBS diagnoses: Manning (6.5%), Rome I (4.2%) and Rome II (2.9%) (Hungin et al. 2003). This finding of low concordance rates was confirmed by further studies (Yale et al. 2008, Anastasiou et al. 2008).

TABLE 2: COMPARISON OF DIAGNOSTIC CRITERIA FOR IBS

Manning Criteria	**Rome I**	**Rome II**	**Rome III**
Abdominal pain with 2 or more of the following: 1. Abdominal pain relieved by defecation; *and/or* 2. Abdominal pain onset associated with more frequent stools; *and/or* 3. Abdominal pain associated with looser stools; *and/or* 4. Abdominal distension or bloating; *and/or* 5. Feeling of incomplete defecation; *and/or* 6. Mucus in stools	continuous or recurrent: 1. Abdominal pain, relieved with defecation, or associated with a change in frequency or consistency of stool *and/or* 2. Disturbed defecation (two or more of): a) Altered stool frequency b) Altered stool form (hard or loose/watery) c) Altered stool passage (straining or urgency, feeling of incomplete evacuation) d) passage of mucus usually with: 3. Bloating or feeling or abdominal distension	At least *12 weeks* or more, which need not be consecutive, in the preceding *12 months*, of abdominal discomfort or pain that has 2 out of 3 features: 1. Relieved by defecation 2. Onset associated with a change in frequency of stool 3. Onset associated with a change in form (appearance) of stool *Symptoms that cumulatively support the diagnosis of IBS:* 1. Abnormal stool frequency (may be defined as greater than 3 bowel movements per day and less than 3 bowel movements per week); 2. Abnormal stool form (lumpy/hard or loose/watery stool); 3. Abnormal stool passage (straining, urgency, or feeling of incomplete evacuation); 4. Passage of mucus; 5. Bloating or feeling of abdominal distension.	Recurrent abdominal pain or discomfort at least *3 days per month* in the last *3 months* (*onset at least 6 months prior to diagnosis*) associated with *2 or more* of the following: 1. Improvement with defecation 2. Onset associated with a change in frequency of stool 3. Onset associated with a change in form (appearance) of stool

Since the implementation of Rome II subtype, the differentiation of IBS into predominant diarrhea (IBS-D) or predominant constipation (IBS-C) is possible. The assignment process according to Rome II is based on complex criteria (see TABLE 3) and therefore difficult to use in practice.

TABLE 3: IBS subtypes according to Rome II versus Rome III

ROME II	ROME III
IBS-D: diarrhoea-predominant IBS **IBS-C:** constipation-predominant IBS	**IBS-D:** IBS with diarrhoea **IBS-C:** IBS with constipation **IBS-M:** mixed IBS **IBS-U:** unspecific IBS
IBS-D: one or more of b, d or f and none of a, c, or e; *or* 2 or more of b, d, or f, and one of a or e **IBS-C:** one or more of a, c or e and none of b, d or f; *or* two or more of a, c or e, and 1 of b, d or f	**Classification based on Bristol Stool Form Scale** Loose or watery stools ≥25% and hard or lumpy stool <25% of bowel movements → **IBS-D** Hard or lumpy stools ≥25% and loose or watery stools <25% of bowel movements → **IBS-C** Hard or lumpy stools ≥25% and loose or watery stools ≥25% of bowel movements → **IBS-M** Insufficient abnormality of stool consistency to meet criteria IBS-D, C or M → **IBS-U**
Combination of stool frequency, stool form and the absence or presence of defecation straining or urgency a. Fewer than three bowel movements a week b. More than three bowel movements a day c. Hard or lumpy stools d. Loose or watery stools e. Straining during a bowel movement f. Urgency g. Feeling of incomplete bowel movement h. Passing mucus during a bowel movement i. Abdominal fullness, bloating or swelling	

Moreover, current findings suggest that subtype classification is most reliable according to the stool form rather than the stool frequency as it is used in Rome II (Ragnarsson & Bodemar, 1999; Mearin et al. 2003). For this reason, the subtype assignment in Rome III is simplified using only the stool form as a criterion. Due to the finding that the majority of the patients (63%) were not assignable to either constipation or diarrhea predominant (Hungin et al. 2003, Drossman et al. 2005), the implementation of a new subtype category with alternating symptoms (IBS-M) was proposed. Hence, Rome III includes four IBS subtypes: IBS-C, IBD-D, IBS-M and IBS-U (Drossman, 2006). The latter contains those cases which are not assignable to one of the other three categories. Subtype criteria according to Rome II and Rome III, respectively, are listed in TABLE 3.

Prior to the official term IBS-M according to the Rome III criteria, study participants with mixed or alternating bowel habit were classified as IBS-A using heterogeneous definitions (Mearin et al. 2003, Tillisch et al. 2005a). IBS subtype assignment is primarily important in the decision of treatment and in recruitment for clinical trials (Kellow, 2001, Lembo & Fink, 2002). Nevertheless, it has to be kept in mind that subtype distribution differs substantially between the different diagnostic criteria (Guilera et al. 2005). The concordance between Rome II and Rome III subtype assignment has been documented to lie at 50% (Ersryd et al. 2007) to 87% (Dorn et al. 2009). The graph depicted below (FIGURE 1) illustrates subtype assignment according to Rome III. Longitudinal surveys have confirmed the stability of IBS diagnosis over 10 years, whereas less than 7% of the patients developed organic diseases (Adeniji et al. 2004, Locke, 2003).

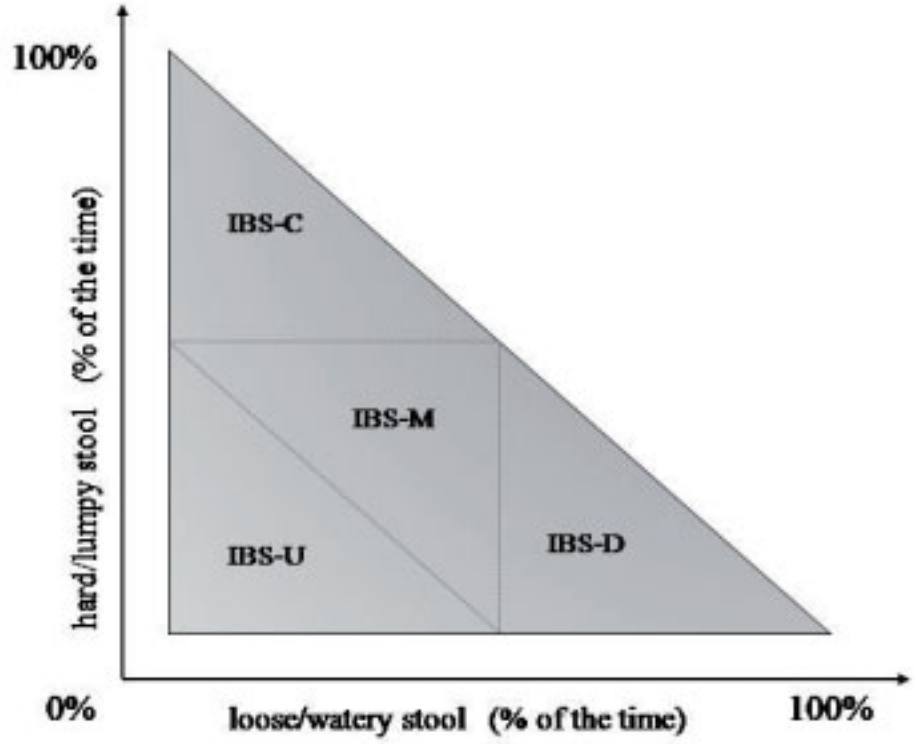

FIGURE 1: DISPLAY OF THE IBS SUBTYPES ACCORDING TO BOWEL FORM (ADAPTED FROM LONGSTRETH ET AL., 2006)

The Rome guidelines provide a positive predictive value of 98%. Hence, only a small number of medical tests are recommended to confirm the IBS diagnosis (Olden, 2002). The usefulness of additional medical tests is determined by individual factors such as age, duration and severity of symptoms, psychosocial factors, and family history of gastrointestinal diseases (Longstreth & Drossman, 2005). If patients consult with their physician regarding typical IBS symptoms in the absence of alarm features such as fever, rectal bleeding, weight loss, anemia, abdominal mass or history of organic bowel disease, unnecessary testing may be costly and even harmful (Brandt et al. 2002, Lembo et al. 2002, Cash et al. 2002). In addition to standard laboratory tests (i.e. cell blood count, chemistry panel and erythrocyte sedimentation rate), the application of sigmoidoscopy or colonoscopy is suggested in some cases. Stool examination for occult blood, leukocytes, or ova and parasites where they are endemic may be indicated. In contrast, routine rectal biopsy and abdominal ultrasonography usually are not. To confirm carbohydrate malabsorption, an H_2 breath test is indicated (Keller et al. 2005). However, in some patients, the symptoms resist

despite strict diet, and some subjects with medically proven lactose intolerance digest lactose with negligible symptoms (Suarez et al. 1995, Ladas et al. 2000). Testing for celiac disease is only indicated by clinical features (O'Leary et al. 2002). In summary, the value of diagnostic procedures in patients fulfilling positive IBS criteria in the absence of alarm symptoms is not established, and current data suggest that additional tests such as negative colonoscopy do not improve reassurance or quality of life in these patients (Hamm et al. 1999, Spiegel et al. 2005).

2.2. Differentiation between FGID and other functional somatic syndromes

There is a high overlap between different FGID. Moreover, FGID share characteristics with other functional somatic syndromes (FSS). The coincidence of FGID and FSS has given rise to the question of "one or many?" and was the origin of a controversial discussion (Wessely et al. 1999). The intention of this dispute is to prove or disprove the independency of *somatoform disorders* in the International Classification of Disease (ICD-10, WHO, Dilling et al. 1999), *somatization disorders* in the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV, APA, 1994), and specific *somatic syndromes* including FGID, fibromyalgia, and chronic fatigue syndrome (CFS). Wessely et al. (1999) advance the view that medical sub-specialization rather than individual symptoms determine the diagnosis. In line with this hypothesis of only one FSS is the increasing evidence that "somatosensory amplification" (Barsky & Wyshak, 1990) – defined as a dysfunctional pattern of interoception, cognition, emotion, and behavior resulting in negative affect and dysfunctional illness management – is present in all types of FSS. Moreover, a high correlation between FGID and the DSM-IV somatization score has been reported (Hiller et al. 2001).

As yet, no agreement has been reached regarding whether FGID are part of a general FSS or whether they represent an independent diagnostic category (Hiller et al. 2001, Henningsen et al. 2007, Enck et al., 2008). While Hiller et al. (2001) propose that FGID should be regarded as part of general somatization (Hiller et al. 2001), other authors consider FGID as independent, and interpret coincidence with other physical or mental disorders as comorbidity (Blewett et al. 1996, Henningsen & Herzog, 2008). The latter point of view is supported by findings of factor analyses suggesting that IBS and functional somatic syndromes should be

classified as independent diseases even though they share some characteristics (Robbins et al. 1997, Zaman et al. 2001, Jones et al. 2001).

2.3. Epidemiology and course of illness in FGID

FGID are widely represented and affect between 35-70% of the adult population (Drossman et al., 1993, Koloski et al., 2002, Halder et al., 2007), with a female preponderance in most of the disorders (Lembo et al. 2009) and a high overlap with each other (Locke et al. 2005). They have a substantial impact on public health and induce high socioeconomic burden through direct (e.g. health care) and indirect (e.g. absenteeism) costs (Dean et al. 2005, Maxion-Bergemann et al. 2006, Nyrop et al. 2007).

Estimates of incidence have varied between 2.6 % to 16 % between several follow-up surveys (Talley et al. 1992, Garcia Rodriguez et al. 2000, Halder et al. 2007). The large variance in estimated prevalence rates has been attributed to heterogeneous diagnostic criteria or population characteristics (see chapter 2.1). Most studies have focused on IBS, which is found in up to 20% of the general population (Drossman et al., 1994b), although the majority of epidemiological surveys suggest a mean prevalence of 10% (Cremonini & Talley, 2005). Functional dyspepsia, a FGID of the upper gastrointestinal tract, affects 10-15% of the general population (El-Serag et al. 2004). Similar prevalences of FGID have been reported in different geographical regions (Drossman et al. 2002, Cremonini & Talley, 2005).

Most FGID are inversely related to age: Globus, rumination, functional chest pain, functional dyspepsia, aerophagia, functional vomiting, IBS, functional bloating, functional diarrhea as well as anorectal pain are more prevalent in younger individuals (review in Chang et al. 2006b). For instance, Hungin et al. (2003) reported decreasing IBS prevalence with respect to age: 18-34 years: 12.2%, 35-54 years: 9.9%, ≥ 55 years: 7%). By contrast, dysphagia, functional disorders of the biliary tract, functional constipation and fecal incontinence have been associated with higher age.

A prospective cohort study found stable prevalence rates of FGID over time (Halder et al. 2007). However, substantial transitions among the FGID categories were observed, indicating that individual symptom disappearance is more related to symptom changes than to remission. Up to 30% of individuals with IBS develop another FGID during follow-up

(Agreus et al. 2001, Halder et al. 2007). Furthermore, previous findings have provided evidence that IBS subtypes are highly unstable, and about 75% of the patients classified as IBS-C, IBS-D or IBS-M change their subtype at least once over a period of one year (Drossman et al. 2005). Most changes occur from/to IBS-M or IBS-U, with only 14% switching between the categories IBS-C and IBS-D (Garrigues et al. 2007).

2.4. Sex and gender differences in FGID

Gender generally refers to a person's non-biological aspects of being female or male, whereas sex describes biological characteristics of women and men (Wizeman & Pardue, 2001). Given that these two terms are often difficult to separate in bio-psycho-social studies, gender will be used in this work as the more inclusive term, taking into account interactions between biology and environment.

As mentioned above, most FGID show a female preponderance. Women more often report IBS, functional constipation, bloating, abdominal pain or pelvic floor dysfunction, whereas no differences have been found between men and women in terms of functional esophageal and gastroduodenal disorders (Chang et al. 2006b). Studies investigating IBS patients have documented a female preponderance in non-pain-associated symptoms such as constipation and bloating but no difference in the female-to-male ratios for pain related symptoms (Corney & Stanton 1990, Simrén et al. 2001).

Gender differences in FGID are not limited to epidemiology. There is evidence that gastrointestinal symptoms are influenced by the menstrual cycle, since increased symptom severity has been observed during late luteal and early menses phases (Heitkemper et al. 2003, Whitehead et al. 1990). Further gender differences have been found for visceral perception and gastrointestinal motility. One explanation for differences between men and women is given by the theory of gender role socialization, suggesting that socialization has an important impact on women's perception of health. According to this approach, gender role concerns such as shame from losing control of bodily functions, ambition of physical attractiveness and pleasing others at the expense of one's own needs were shown to be more fundamental in women than in men (Toner et al. 2000).

2.5. Validated characteristics of individuals with FGID

Individuals with FGID have to deal with recurrent and unpredictable symptoms of uncertain etiology (Royer, 1998, Talley, 2008). Therefore, they often experience a lower quality of life, report restriction and reduced functioning in daily life activities, uncontrollability of the disease, emotional distress and social stigma (Bertram et al. 2001, Milwaukee, 2002). The following sections will summarize current research opinions about health care seeking, quality of life and personality factors in individuals with FGID.

2.5.1. Health Care Seeking and Illness Behavior

FGID have been reported to be one of the most common reasons to consult a general practitioner or a specialist (Everhart & Renault, 1991, Drossman et al. 2002, Sykes et al. 2003). In North America, functional abdominal pain, constipation, dyspepsia and IBS were even in the top six categories of the annual national medical survey (Shaheen et al. 2006). Interestingly, in patients with FGID, and particularly IBS, higher rates of abdominal surgery such as hysterectomy (OR: 1.7), cholecystectomy (OR: 2.09), and appendectomy (OR: 1.45) have been observed compared to the general population or patients with inflammatory bowel diseases (IBD) (Burns, 1986, Kennedy & Jones, 2000, Hasler & Schoenfeld, 2003, Longstreth & Yao, 2004). Hulisz (2004) has suggested that these interventions result from a misinterpretation of gastrointestinal symptoms and has emphasized the importance of an accurate diagnostic process in individuals presenting with gastrointestinal symptoms.

Considerable use of medical care including drug prescription per year has been observed in patients with FGID compared to subjects without FGID (Longstreth et al. 2003, Leong et al. 2003). Patients with FGID use at least three forms of therapy, but only 30% estimate their therapies as effective or satisfactory (Gore et al. 2002). However, health care seeking in FGID does not seem to be restricted to gastrointestinal complaints (Lu et al. 2003, Vandvik et al. 2006, Hillilä et al. 2007). Drossman et al. (1993) reported three times as many physician visits from extragastrointestinal symptoms in IBS patients compared to matched controls. As a consequence, substantial economic costs emerge (Martin et al. 2001, Levy et al. 2001b, Sandler et al. 2002). Compared to the general population, IBS patients have been shown to produce 49% higher medical expenses, to have more absenteeism and 21% reduced work productivity (Dean et al. 2005, Maxion-Bergemann et al. 2006). It is noteworthy that in the

USA, the total annual costs of approximately $US 30 billion are comparable to the expenses of other chronic diseases such as asthma and hypertension (Hulisz, 2004). The economic impact of FGID other than IBS has been studied to a lesser extent (Agreus & Borgquist, 2002).

Despite the high prevalence of FGID in clinical practice, it has been suggested that only a small proportion (25%) of subjects with FGID seek medical care (Talley et al. 1992 & 1997, El-Serag et al. 2004). Individuals suffering from comparable symptoms who do not seek medical care are called non-consulters or non-patients. Previous studies have evaluated potential psychosocial differences between consulters and non-consulters, which may predict the health care seeking behavior (Whitehead et al. 1982, Drossman et al. 1988). More physician visits, medication prescriptions, work absenteeism and a number of symptoms have been found in consulters compared to non-consulters (Eisen et al. 2000, Lu et al. 2003, Vandvik et al. 2006, Hillilä et al. 2007). However, other surveys merely identified an association between symptom intensity and health care seeking (Talley at al. 1997, Icks et al. 2002,). Moreover, psychiatric comorbidity and psychosocial stress have been reported to be similar in IBS consulters and non-consulters (Kanazawa et al. 2004, Hillilä et al. 2007). Therefore, it might be assumed that health care seeking is primarily associated with gastrointestinal symptoms rather than psychiatric conditions.

2.5.2. Personal impact and quality of life

Since FGID are often chronic or recurrent states, the personal impact is substantial (Bertram et al. 2001). In IBS patients, 50% report illness duration of about 10 years and for 16%, this figure even lies at approximately 21 to 30 years (Silk, 2001). Moreover, 57% experience symptoms daily, whereas 12-39% consider their IBS symptoms to be very severe or painful (Lembo et al. 1999, Milwaukee, 2002). Thus, it is not surprising that lower levels of physical and psychological quality of life have been observed in several FGID (Talley et al. 1995, Koloski et al. 2000, El-Serag et al. 2002 & 2003, Mikocka-Walus et al. 2008). Patients with IBS report even poorer quality of life than individuals with chronic conditions such as diabetes, migraine or asthma (Frank et al. 2002, Jones et al. 2007). The impairment due to FGID seems to be comparable to organic diseases (El-Serag et al. 2002). Numerous surveys have documented the negative impact of FGID on daily activities, social life, work and

leisure time, not least due to restrictions in diet, reduced ability to travel or sexual dysfunction (Drossman et al. 1993, Hahn et al. 1999, Wells et al. 1997, Fass et al. 1998, Gralnek et al. 2000, Hungin et al. 2002). Moreover, an association between reduced quality of life and somatic and psychiatric comorbidity has been reported (Vandvik et al. 2004a, Halder et al. 2004).

2.5.3. Personality traits

Higher levels of neuroticism, conscientiousness, hostility and trait anxiety as well as lower levels of openness and agreeableness have been observed in patients with FGID compared to healthy individuals or patients with organic bowel diseases (Dinan et al. 1991, Drossman et al. 1999, Tanum et al. 2001, Farnam et al. 2008). Furthermore, IBS has been associated with high social desirability, hypochondriac beliefs, disease phobia and bodily preoccupation (Toner et al. 1990 & 1992, Gomborone et al. 1995). By contrast, Katon et al. (2001) found no difference in neuroticism between IBS patients and patients with organic diseases. Another personality trait which has been associated with FGID is alexithymia, which is defined as "the paucity of fantasy and the limited ability to identify and verbally express emotions" (Bagby & Taylor, 1997). The alexithymia concept was originally derived from clinical observations in psychosomatic diseases. Strong associations between alexithymia and several FSS, including FGID, have been reported (Porcelli et al. 1999). In conclusion, although some common personality traits in patients with FGID have been identified, the findings remain inconsistent and no personality profile specific to FGID has been empirically verified.

2.5.4. Comorbidity in FGID

Patients with FGID often present a wide range of somatic and psychiatric comorbidity (Markowitz et al. 2001). These multiple and overlapping symptoms impede the diagnostic process, and FGID are initially often misdiagnosed. The following sections will summarize the most common gastrointestinal, extraintestinal and psychiatric comorbidity in FGID.

2.5.4.1. Psychiatric comorbidity

Individuals with FGID show high prevalence rates of current or prior psychiatric comorbidity, with anxiety disorders and depression being the most common (Walker et al. 1995, Lee et al. 2000, Garankani, 2003). In patients from tertiary care centers, the

coincidence between FGID and psychiatric diagnosis has been reported to be up to 90% (Drossman et al. 1999, Whitehead et al. 2002). By contrast, surveys in the general population have found psychiatric disorders in 18 to 50 % of IBS patients (Walker et al. 1992, Vandvik et al. 2006, Hillilä et al. 2007). In a large survey, the prevalence of psychiatric comorbidity was three times higher in IBS patients than in matched controls: anxiety (15.5% vs. 5.75%), panic disorder (3.85% vs. 1.3%) and depression (30.5% vs. 16.2%) (Whitehead et al. 2007). Data regarding differences between IBS subtypes with respect to psychiatric comorbidity are limited. Few studies have provided evidence for an association between anxiety and IBS-D (Si et al. 2004, Sugaya et al. 2008). The coincidence of psychiatric disorders and FGID has been shown to be not gender specific, or only minimally so (Corney & Stanton 1990, Blewett et al. 1996, Lee et al. 2001, Fock et al. 2001). Vandvik et al. (2006) suggested that reduced health status and illness behavior is predicted by somatic and psychiatric comorbidity. By contrast, other work groups have disproved this hypothesis (Talley et al. 1997, Hu et al. 2002, Hillilä et al. 2007, Whitehead et al. 2007). Hence, the causality between psychiatric illness and FGID is still open.

2.5.4.2. Somatic comorbidity

High coincidence and a considerable fluctuation of intestinal and extraintestinal symptoms have been observed in patients with FGID (Agreus et al. 1995, Markowitz, 2001). Numerous studies have reported a substantial overlap among FGID. For instance, 40-80% of IBS patients suffer from functional dyspepsia (Stanghellini et al. 2002, Talley et al. 2003, Hillilä et al., 2007) or gastrooesophageal reflux disease (GERD) (Nastaskin et al. 2006). In dyspeptic patients, up to 50% met criteria for IBS (Talley & Piper, 1985, Talley et al. 1993, Crean et al. 1994) or GERD (Talley et al. 1992, Agreus et al. 1995). IBS has been associated with the development of fecal incontinence (Boreham et al. 2001).

Although according to the Rome criteria, the occurrence of organic gastrointestinal diseases exclude FGID diagnosis, in some patients with FGID, the coexistence of an organic and a functional gastrointestinal disorder might be observed (Drossman et al. 2002). For instance, inflammatory bowel diseases (IBD) are characterized by recurrent inflammatory episodes combined with long-standing remission episodes without active inflammation. Occurrence of IBS-like symptoms during IBD remission phases may be attributed to coexistent IBS (Simrén

et al. 2002). A recent study reported an 80% overlap between IBD and FGID (Mikocka-Walus, 2008). Similarly, the coexistence of FGID, lactose and fructose intolerance (Choi et al. 2003, Fernandez-Banares et al. 1993) and celiac disease (O'Leary et al. 2002) has been observed. In summary, organic diseases of the digestive tract do not always exclude FGID diagnosis in clinical practice. However, empirical studies should clearly distinguish between the two conditions.

Furthermore, a wide range of extra-gastrointestinal symptoms such as headache, backache, asthma, sleep disturbances, fatigue and genitourinary symptoms have been observed in FGID (Kennedy et al. 1998, Aggarwal et al. 2006, Hillilä et al. 2007, Jones et al. 2007, Lembo et al. 2009). Chronic headache has been found in 23-60% and back pain in 28-81% of patients with FGID (Whorwell et al. 1986, Maxton et al. 1991, Azpiroz et al. 2000, Jones et al. 2001, Cole et al. 2006). A medical database survey revealed that IBS patients showed higher incidence rates for 64 of 76 (84%) somatic diagnoses compared to controls (Whitehead et al. 2007). Furthermore, a high coexistence has been reported between FGID and other FSS including fibromyalgia (26-65%), chronic pelvic pain (50%), chronic fatigue (51%) and temporomeandibular joint pain (16-64%) (Triadafilopoulos et al. 1991, Sperber et al. 1999a, Zondervan et al. 1999, Aaron et al. 2000, Aggarwal et al. 2006). The coexistence of somatic symptoms has been associated with increased gastrointestinal symptom severity (Longstreth et al. 2005).

Numerous studies have documented high prevalences of urogenital problems such as dyspareunia, bladder dysfunction, cystitis, premenstrual syndrome, and dysmenorrhea in women with IBS (Whorwell et al. 1986, Franics et al. 1997, Alagiri, 1997, Jones et al. 2001, Williams et al. 2004). Furthermore, an association between FGID and menstrual cycle has been suggested, since gastrointestinal symptoms worsen during menses (Houghton et al. 2002, Heitkemper et al. 2003). Sleep disturbances are present in one third of individuals with IBS, compared to only 10% of healthy controls (Nyhlin et al. 1993, Vandvik et al. 2004), and the examination of objective sleep parameters has identified altered sleep architecture in these patients (Kumar et al. 1992, Orr et al. 1997).

In conclusion, the comparison of findings regarding somatic comorbidity in FGID is impeded by broad heterogeneity of the data. This variance can be attributed to methodology or study

samples. However, it can be concluded that somatic comorbidity is a common feature in FGID, and particularly well established in IBS. The fact that there is a high coincidence with numerous somatic conditions gave rise to the idea of shared non-organ-specific pathophysiological mechanisms such as the dysfunction of regulatory physiological systems (chapter 3.7). Whitehead et al. (2002) suggested that high comorbidity is the consequence of general somatization (chapter 2.5.4) in such patients. Other authors focused on maladaptive coping as a common underlying factor in the pathogenesis of different somatic syndromes (Zaman et al. 1990, Jones et al. 2001). However, the association between FGID and other somatic disorders remains to be clarified (Whitehead et al. 2007).

3. Etiological factors of FGID

The pathogenesis of FGID is not completely understood. The focus of etiological research has changed substantially over the past half century. Initially, the emphasis was on end organ disturbances (motility and compliance) and psychological factors (personality and psychiatric diseases). Subsequently, the focus of interest mainly moved to visceral perception (hypersensitivity) and the autonomic nervous system (ANS). Although all of these approaches have documented interesting findings, they were unable to deliver a satisfactory pathophysiological model for FGID. However, it has become evident that a reductionistical etiological view will not be fruitful. Therefore, current research has shifted from unidirectional approaches to a multidimensional model which integrates several etiological aspects and centers on neuroenteric dysregulation in the brain-gut communication (Talley, 2008). For instance, according to this view, altered motility is no longer seen as an isolated organic problem, but rather as the result of dysfunctional reciprocal communication in the brain-gut connectivity. Stress has been proposed to play a crucial role in the modulation of the brain-gut interaction, and stress-related physiological systems have been suggested to provide the physiological link. Although the evidence for shared pathophysiological mechanisms has been provided, the extent to which FGID exhibit common etiology is insufficiently verified (Cremonini & Talley, 2004). However, most current studies have investigated pathophysiological factors in IBS patients. For this reason, and given that the empirical study II of the current thesis is conducted in subjects with IBS, the overview presented below will mainly refer to IBS studies.

The broad spectrum of etiological factors and their integration into a bio-psycho-social model will be outlined below.

3.1. Gastrointestinal (dys-) motility

The idea of disturbed motility patterns is probably the oldest empirical approach in the etiological research of FGID. Based on his observation of altered motility in IBS patients during interviews concerning personal life events Almy, (1951) postulated the "*motility hypothesis",* indicating an association between negative emotions and colonic motility. Over

the decades, numerous attempts have been made to identify IBS- specific motility patterns. Diarrhea and abdominal pain have been associated with a heightened number of fast propagating colonic contractions, and constipation has been related to slow transit with decreased propagating contractions (Whitehead et al. 1980, Garnett, 1999, Muller-Lissner et al. 1999). Moreover, altered intestinal motility has been observed following the administration of several provocative stimuli (chapter 3.6.2).

Altered motility has also been reported in other FGID. For instance, Kawakami et al. (1995) demonstrated gastric dysmotility in patients with functional dyspepsia. Although basal and stimulated motility disturbances seem to be prevalent in FGID (25-75%), no consensus has been reached regarding motility patterns that are specific to FGID or IBS, respectively. Therefore, the usefulness of motility as a diagnostic marker has not been verified (Muller-Lissner et al. 1997, Drossman et al. 2002a). However, the fact that altered motility has been found in several FGID led to the assumption that neuromuscular dysfunction might be a pathophysiological factor of all FGID (Nastaskin et al. 2006).

3.2. Inflammation and postinfectious IBS (PI-IBS)

The traditional concept postulating FGID as a disease without biological correlates has been contradicted by recent findings which identified subtle biochemical alterations in such patients (Spiller, 2003). At least a subset of individuals with IBS (25%) seems to develop their symptoms after enteric infection such as *Salmonella* or *Shigella* gastroenteritis (Talley & Spiller, 2002, Dunlop et al. 2003a/b, Marshall et al. 2006). Mearin et al. (2005) documented an eightfold increased risk of developing postinfectious IBS (PI-IBS) after gastroenteritis.

There is accumulating evidence for subtle inflammation (Chadwick et al. 2002) and immune activation in IBS, including lymphocyte and mast cell infiltration in the colon (Barbara et al. 2007, Guilarte et al. 2007), increased intraepithelial CD3+ and natural killer cells (Spiller at al. 2000), higher mucosal interleukin 1β mRNA expression (Gwee et al. 2003), higher TNF-α, IL-6 and IL1β levels (Dinan et al. 2006, Liebregts et al. 2007) and altered peripheral cytokine profiles (O'Mahony et al. 2005). In functional dyspepsia, duodenal *eosinophilia* has been reported (Talley et al. 2007). Interestingly, not only subjects with PI-IBS but also IBS patients without previous infection exhibited increased numbers of T lymphocytes (Dunlop et

al. 2003). Following stimulation, a recent study assessing cellular and humoral immune response in FGID found increased IL-5 and IL-13 as well as reduced IL-10 and IL-12 levels in patients with IBS, functional dyspepsia, and non–cardiac chest pain compared to healthy controls (Kindt et al. 2009). It is noteworthy that all of the above-mentioned findings are subtle, and would be considered as "normal" by conventional histological criteria (Talley & Spiller, 2002). Underlying mechanisms in the development of PI-IBS may be colonic changes such as altered gut permeability, an increased number of enterochromaffin cells and hyperalgesic state due to inflammatory stimuli (Mach, 2004). Numerous risk factors of PI-IBS have been postulated, including age, sex, and severity and duration of the infection (Neal et al. 1997, Dunlop et al. 2003, Barbara et al. 2002 & 2007). Interestingly, an association has been reported between the antecedent stress experience and the development of PI-IBS (see chapter 3.6.4) (Gwee et al. 1999, Spence & Moss-Morris 2007).

Another novel approach is the idea of small intestinal bacterial overgrowth (SIBO), defined by an increased population of bacteria in the intestine, which cause fermentation and gas (Pimentel et al. 2000). However, its contribution to etiology is unknown, since recent findings have reported a high variance of SIBO- positive IBS patients (11-84%) due to methodological problems (Pimentel et al. 2003 & 2005, Harris et al. 2005).

In summary, there is growing evidence for an involvement of the immune system in at least a subset of FGID patients. The development of PI-IBS has been suggested to be a pathogen-induced prolonged neuroendocrine dysfunction resulting in altered visceral perception, motility disturbances and subtle inflammation in predisposed individuals (Collins et al. 1999, Kindt et al. 2009). Recent studies have postulated an interaction between intestinal immune activity and the activity of the hypothalamus-pituitary-adrenal (HPA) axis (Mayer et al. 2002, Dinan et al. 2006).

3.3. Visceral hypersensitivity

An etiological core concept of FGID is the assumption of visceral hypersensitivity. In the following sections, basic principles of somatic and visceral pain perception will be imparted, followed by a short overview of current findings concerning visceral hypersensitivity in FGID.

3.3.1. Pain perception

Usually, pain is associated with actual or potential tissue damages described as unpleasant sensory and emotional experience (Wilhelmsen, 2000). Within the gut wall, specified pain receptors transfer - when mechanically activated - visceral signals via spinal afferents to the midbrain, thalamus and cortex (Melzak & Wall, 1965). Pain characteristics such as location and intensity are then processed by the somatosensory cortex and modulated by the limbic system. The latter can influence pain perception via descending regulatory pathways (Drossman et al. 2002). According to the gate control theory, incoming visceral information is modulated by inhibitory pathways, which send directly and indirectly, via the amygdale, efferent signals to the brainstem (Melzack & Wall, 1998). From there, inhibition signals are forwarded to the dorsal horn of the spinal cord, where the incoming pain signals are presynaptically inhibited (Jones et al. 2006a). In summary, pain perception has to be regarded as a plastic process, integrating sensory, emotional, behavioral and cognitive aspects. Abnormal processing of afferent sensory information and therefore increased perception is termed as hypersensitivity.

3.3.2. Visceral perception in FGID

The association between altered visceral perception and FGID is well established (Hu & Talley, 1996). Previous studies have reported increased visceral sensitivity in several FGID, including functional chest pain (Paterson et al. 1995), functional dyspepsia (Mearin et al. 1991, Tack et al. 2001, Corsetti et al. 2004) and IBS (Ritchie, 1973, Mertz et al. 1995, Munakata et al. 1997, Naliboff et al. 1997, Bouin et al. 2002, Delvaux, 2002). Moreover, it has been postulated that the lower perception thresholds in FGID are not site-specific, since visceral hypersensitivity has been observed over the entire digestive tract, including the esophagus, stomach, duodenum, ileum, colon and rectum (Trimble et al. 1995, Zighelbolm et al. 1995, Evans et al. 1996, Holtmann et al. 1997, Rossel et al. 1999). In contrast, Bouin et al. (2004) reported that patients with gastric symptoms exhibited gastric but not colonic hypersensitivity. Visceral hypersensitivity in FGID does not seem to be stimulus-specific; hence, heightened perception has been observed in response to mechanical, thermal or electrical stimulation (Rossel et al. 1999, Li et al. 2004).

Previously, visceral hypersensitivity was interpreted as a physiological dysfunction (Mayer & Gebhart, 1994, Camilleri et al. 2001, Azpiroz, 2002). More recent findings have indicated that visceral perception is strongly associated with cognitive processing. Therefore, it has been hypothesized that the tendency to report gastrointestinal perceptions rather than increased neurosensory sensitivity affects visceral perception (chapter 3.7.2). This assumption was tested by a study by Dorn et al. (2007). Subjects with IBS and healthy controls underwent stepwise and randomized colonic distension and were instructed to rate pain and urge. Interestingly, IBS patients exhibited increased colonic sensitivity during the stepwise protocol, but not during randomized distensions. Similar results have been documented with respect to esophageal sensitivity in patients with non-cardiac chest pain (Bradley et al. 1993). Both findings indicate that hypervigilance to gastrointestinal stimuli in subjects with FGID led to increased pain perception. Recent findings from neuroimaging studies confirmed this hypothesis, since cerebral activation to actual and anticipated rectosigmoid distension were observed to be similar in these patients (Chang, 2005, Naliboff et al. 2001 & 2006). Furthermore, it has been reported that patients with FGID are disposed to interpret even normal visceral sensations as more negative than healthy individuals (Kellow et al. 1991, Gomborone et al 1993, Serra et al. 2001). In turn, negative attribution of visceral sensation has been suggested to intensify the person's interoception, and a vicious cycle is established (Barsky, 1992, Gibbs-Gallagher et al. 2001).

Pain perception is influenced by non-neurosensory factors such as placebo, emotion, distraction and attention (Clark, 1974). Therefore, the focus of the patient's attention modifies visceral processing. Anxiety of pain may lead to attention towards somatic processes, thus increasing it, while anxiety of something else is associated with distraction, which decreases pain perception (Melzak & Wall, 1965). In line with this assumption, Gibbs-Gallagher et al. (2001) found heightened attention to gastrointestinal sensation words in IBS patients during a recall task. The authors hypothesized that this finding is the result of a selective attention process triggered by cognitive schemata about gut-related sensations. Differences in regional brain responses during pain perception have been verified by fMRI studies (Naliboff et al. 2001, Mertz et al. 2000, Schwetz et al. 2003). Mayer et al. (2005) reported enhanced activation in "pain areas" during colonic balloon distension in IBS patients compared to IBD patients and controls.

The observation of a high overlap between FGID and other pain syndromes gave rise to the idea of general (visceral and somatic) hyperalgesia, which might reflect a common pathophysiological mechanism in such patients (Verne et al. 2001, Rodrigues et al. 2005). However, this assumption has been contradicted by several studies documenting somatic hypoalgesia in individuals with IBS (Cook et al. 1987, Whitehead & Palsson 1998, Chang et al. 2000, Iovino et al. 2006).

In conclusion, recent findings provide evidence for visceral hypersensitivity and somatic hypoalgesia in patients with FGID. However, high inter-individual variability in perception thresholds impedes the use of visceral hypersensitivity as a biological marker (Kendall et al. 1990, Whitehead & Palsson, 1998). The exact mechanism of visceral hypersensitivity in FGID needs further investigation. To date, several factors, such as altered cerebral processing, activation of silent nociceptors, spinal hyperexcitability, and neuronal changes (neuroplasticity) have been discussed as important factors contributing to enhanced visceral perception (Mach, 2004, Anand et al. 2007). Interestingly visceral hypersensitivity to rectal distensions can be induced by exogenous CRH infusion (Lembo et al. 1996, Nozu & Kudaira, 2006), indicating an association between the endocrinological stress system and gastrointestinal perception (see chapter 3.7.3). Furthermore, stress has been shown to alter visceral perception (Accarino et al. 1997, Fukudo et al. 1998, Dickhaus et al. 2003, Posserud et al. 2004).

3.4. Genetics

Whorwell et al. (1986) reported first of all that 33% of the IBS patients in their sample had a positive family history, compared to only 2% in the control group. Subsequent studies confirmed this finding, and postulated that the risk of developing IBS is increased twofold in subjects with a positive family history (Kanazawa et al. 2004, Falk, 2003, Locke et al. 2000a). However, Levy et al. (2001a) found that dizygotic twins are more likely to have a mother with IBS than a co-twin with IBS. Since dizygotic twins share the same genetic material as one another and with their parents, the authors suggested that social learning is at least as strong a predictor of IBS as genetic influence. The substantial role of environmental contribution has been confirmed by other studies (Whitehead et al. 1994, Levy et al. 2004).

Evidence for a “purely” genetic contribution has been provided by twin studies, which found that IBS is twice as prevalent in monozygotic twins as in dizygotic twins (Morris-Yates et al. 1998, Bengtson et al. 2006). In contrast, three methodologically equivalent investigations have reported similar concordance rates between monozygotic and dizygotic twins, thus suggesting low to zero genetic liability (Lembo et al. 2001 & 2009, Mohammed et al. 2002). In summary, current results from family and twin studies report heterogeneous results. However, Saito et al. (2005) call for a stronger contribution of environmental factors in the etiology of FGID.

A modern approach to investigate the genetic determination of FGID is the direct measurement of DNA sequences. Recent findings have reported an association between FGID and selected gene polymorphism including IL-10 (Barbara et al. 2002), G-protein GNb3 (Holtmann et al. 2004), alpha adrenoceptor (Kim et al. 2004), and serotonin reuptake transporter (SERT) (Camilleri, 2004). The role of serotonin (5-hydroxytryptamine [5-HT]) has been extensively studied, since it represents a predominant signaling molecule in the enteric nervous system (ENS, chapter 3.7.1) and modulates the interplay between ENS and the effector systems as well as the communication between ENS and CNS (Gershon, 2003 & 2005). Serotonin release controls peristalsis and sensory relays (Talley, 2001). Excess serotonin is removed by the serotonin transporter (SERT) molecule (Chen et al. 1998). Abnormal serotonin regulation has been found in IBS (Miwa et al. 2001, Chen et al. 2001, Coates et al. 2004, Dunlop et al. 2005). Moreover, several studies focused on polymorphism in the promoter region of the SERT gene. However, recent data regarding SERT polymorphism in IBS are contradictory (Pata et al. 2002, Yeo et al. 2004, Camilleri, 2004, Lee et al. 2004), and again, SERT polymorphism might be not specific to FGID, as it has also been associated with other disorders including fibromyalgia, depression or anxiety (Offenbaecher et al. 1999, Cohen et al. 2002, Lesch et al. 1996). In summary, serotonin is a central mediator in the complex interplay between gastrointestinal musculature, ENS, ANS, HPA and CNS. Dysfunction of serotonin signaling may result in altered gastrointestinal motility, secretion and visceral sensitivity.

Despite these promising indications, conclusive evidence for a genetic basis of FGID has not been established (Lembo et al. 2009). Nonetheless, the contribution of genetics in the etiology and manifestation of FGID needs further exploration.

3.5. Lifestyle factors

Several lifestyle factors have been associated with FGID. “Unhealthy habits” including smoking, high alcohol consumption, lack of exercise and unbalanced diet have been discussed as symptom-provoking (Drossman et al. 2002, Heizer et al. 2009). However, there is a lack of empirical evidence regarding the etiological relevance of these factors. Few studies have confirmed the negative influence of high alcohol consumption and smoking (Parry et al. 2005, Halder et al. 2006). Moreover, physical activity has been reported to be higher in healthy controls than in women with IBS (Lustyk et al. 2001). Patients with FGID often claim that specific nutrients cause their symptoms. In line with this assumption, one study was able to document a significant symptom improvement when patients excluded food to which they had IgG antibodies (Atkinson et al. 2004). However, so far, the benefit of specific diets is empirically not well established.

3.6. Stress

Stress – defined as a threat to an organism’s homeostasis – has been suggested to contribute to symptom onset and symptom severity in individuals with FGID (Drossman et al. 2002). Although stress-induced bowel disturbances can be observed in most individuals, patients with FGID have been hypothesized to be particularly susceptible and show heightened reactivity to stress (Mayer et al. 2001). Furthermore, stress has been associated with altered symptom perception, illness behavior, and health outcome (Drossman et al. 1982 & 1999, Xiong, 2004). Given that stress is a broad concept, its operationalization has been heterogeneous. Discussions surrounding the role of stress in the etiology of FGID are contentious. Some authors consider that stress has a more exacerbating and maintaining character (Barbara et al. 2004, Drossman et al. 1998), whereas others suggest that it plays a primary role in the development of FGID (Mayer et al. 2002, Chang et al. 2006a). In the following sections, current research opinion about stress in FGID will be outlined. However, first, a short digression will provide an overview of the most important stress theories. Subsequently, empirical evidence regarding stress-induced gut disturbances will be presented. Finally, the role of stress – divided into (1) chronic stress, (2) life events, (3) abuse experience and (4) coping abilities – in FGID will be discussed.

3.6.1. Digression: Theoretical stress concepts

In everyday parlance, “stress” is used as an unspecific term that helps to explain the innumerable bodily and psychological complaints of unknown origin (Pohlmann & Becker, 2006). For a better understanding of stress as a scientific term, a short digression will outline the most prominent theoretical stress concepts. The main purpose of stress research is to elucidate the organism’s adaptation to challenging environmental conditions (Monroe, 2008). While a short-term psychobiological response to a stressor ensures an organism’s survival by mobilizing energy, various health problems are assumed to be the consequences of sustained stress experience.

W.B. Cannon was a pioneer in the field of stress research. In 1915, he coined the term “fight or flight” and postulated that each stress response is an unspecific and uniform pattern of physiological processes. In 1932, Cannon developed the concept of homeostasis, describing an organism’s physiological capacity to maintain the internal milieu through compensatory mechanisms to equilibrate environmental changes. Many vital functions, including digestion, are balanced through homeostatic control. Several years later, Selye (1950) introduced his conceptualization of the “general adaptation syndrome”, which describes stress in terms of external events that excite certain biological distress responses. He postulated the activation of the hypothalamus-pituitary-adrenal (HPS) axis as an adaptive reaction to physical stressors. Furthermore, he distinguished short-term stress reactions from the development of a pathological state caused by chronic stress. Therefore, Seyle (1936) presented a 3-phasic process model involving an alarm, a resistance and an exhaustion phase. In the first phase, the organism is activated to deal with the threatening situation and to regain its homeostasis. A non-specific activation of biological stress systems is triggered. During the resistance phase, the organism is still in a state of heightened arousal, and adaptive mechanisms are intensified. With enduring threat, the adaptive capacity becomes increasingly depleted, homeostasis can no longer be maintained, and the organism enters into the final phase of exhaustion. In the case of chronic stress, neuroendocrine disturbances and dysregulation of the biological stress systems (see chapter 3.7.3) can be observed. Long-term consequences are morphological and functional changes of organic systems. Both Cannon and Selye described reaction-oriented stress theories, proposing non-specific and uniform stress reactions. The observation that

some stressful events provoke a stress response in some individuals but not in others initiated the development of extended theories (Mason, 1986 & 1975).

The most meaningful example of such an expanded viewpoint is probably the "Transaction Theory of Stress" by Lazarus and co-workers. This approach describes stress as a longitudinal, interactive and dynamic process ("transaction") between an organism and its environmental demands, taking into consideration the individual's appraisal of demands and resources (Lazarus, 1966; Lazarus & Cohen, 1978; Lazarus & Launier, 1978; Lazarus & Folkman, 1984). The original concept has been modified over several years. In the most recent version, the authors define stress as "a particular relationship between the person and the environment that is appraised by the person as taxing or exceeding his or her resources and endangering his or her well-being" (Lazarus & Folkman, 1984) and suggest therefore that stress results from an ongoing interaction process between the individual and his or her environment. According to the transactional model, the cognitive process consists of a primary and a secondary appraisal (see FIGURE 2). During the primary appraisal, a situation is considered as relevant or irrelevant, with the former being distinguished as benign or stressful. The secondary appraisal describes the consideration of alternative solutions and perceived coping abilities as well as consequences of a potential action. Coping resources can be categorized as emotion-focused or problem-focused (Folkman, 1997). While the former contain more passive and avoidant strategies, the latter are characterized by active problem solving. However, considerable differences can be observed between individuals concerning stress appraisal and coping, even when they are exposed to the same stressor, with some individuals tending to respond more strongly to stressful situations than others. This phenomenon is recognized by the concept of inter-individual (dispositional) stress reactivity (Schulz et al. 2005), which describes a trait-like disadvantageous pattern that predisposes a person to respond with an immediate, intense, and long-lasting stress response. In summary, stress can be real (i.e. life-threatening or noxious) or anticipated, arise from internal or external stimuli, is appraised with respect to disposable coping strategies and accompanied by several psychophysiological correlates. Consequently, the individual stress reaction might be attenuated or enhanced through personal appraisal (Kanner et al. 1981). Thus, stress is understood as the result of a *subjective* cognitive appraisal process, resulting in an emotional, behavioral, and physiological stress response. Therefore, a stressor is not defined by its

objective intensity alone, but rather by the subjective appraisal, i.e. the subjectively perceived experience of stress.

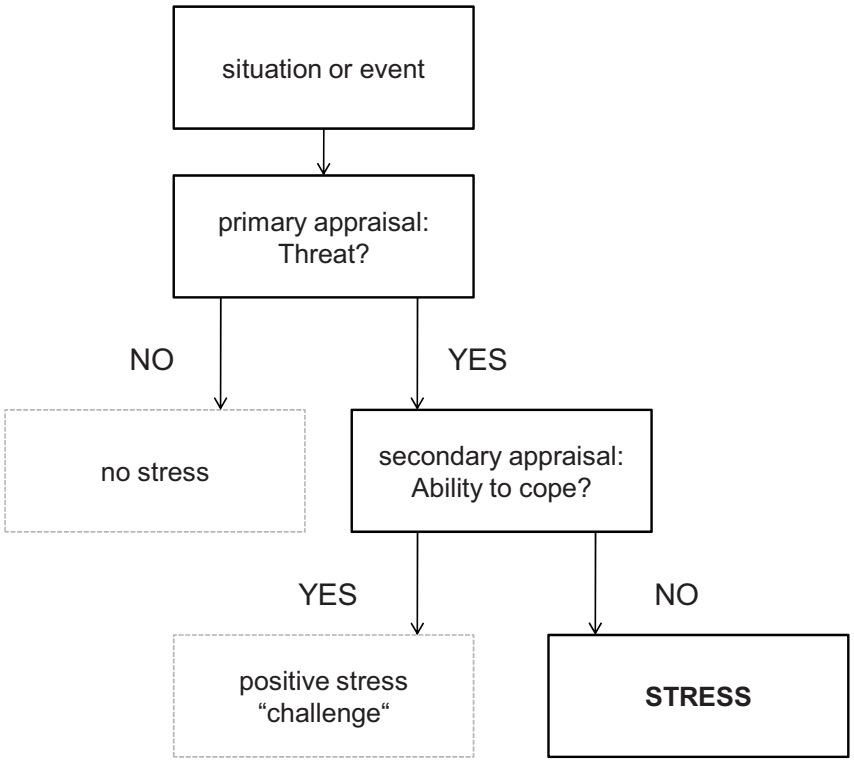

FIGURE 2: TRANSACTIONAL STRESS MODEL BY LAZARUS & FOLKMAN (1984)

Another important concept was introduced by McEwen’s (1998) “allostasis” and “allostatic load”. Similarly to homeostasis, allostasis describes the effort of the body to maintain internal stability, but it encompasses a broader concept and involves whole-organism mechanisms (McEwen & Wingfield, 2003). Furthermore, McEwen emphasized that adaptation to acute stress is essential for the internal regulation (allostasis) and is not generally harmful. The process of achieving internal stability triggers a cascade, which involves the activation of hormonal stress systems such as the HPA axis. Under normal circumstances (adaptive short-term activation), these systems promote an organism’s adaptation and recovery is provided after cessation of the stressor. Allostatic load, in turn, refers to the maladaptive consequences of a sustained activation of primary regulatory systems over time, and therefore describes the long-term burden resulting from repeated strain. Thus, McEwen suggested that chronic

exposure to neural and neuroendocrine activity is reflected by sustained overstraining or underactivity of the allostatic systems (allostatic load) and ultimately contributes to organ damage and disease (McEwen, 1998, McEwen et al. 1993). McEwen's concept provides a potential explanatory approach for a range of pathological mental and physical conditions (De Kloet et al. 2005). Although the core of the concept is the effect of stress on physiological processes, it also accounts for psychological factors, proposing that cognitive processes moderate the stress response and explain the existence of interindividual differences (McEwen, 2007 & 2008).

To draw a conclusion from the above-described theories, one may summarize that the term stress describes the organism's adaptation regarding the most basic biological functions mediated by complex neuropsychophysiological processes. Chronic strain and maladaptive coping show alterations of physiological regulatory systems (e.g. HPA axis) and contribute to the development of psychological and somatic symptoms.

3.6.2. Effects of acute stress on the gastrointestinal tract

Healthy individuals often report abdominal pain and bowel disturbances in times of psychological stress (Drossman et al. 1982). This observation was further explored by numerous studies in animals and humans which have revealed that stress is able to induce bowel disturbances such as altered motility, secretion or pain perception. In these experiments, mainly two classes of stressors have been applied: physical (cold, electric stimulation) or psychological (noise, tasks, emotion induction). While the first is primarily based on reflex circuits, the latter involves cognitive processes such as appraisal of the stressor (Enck et al. 1992). Beaumont (1833) was probably the first to document the association between negative emotion and digestive functions through his examination of an open stomach fistula in an injured soldier. Almy is regarded as a pioneer in the field of gastrointestinal psychophysiology, as he conducted several experiments investigating the effects of laboratory stress on numerous colonic parameters (Almy & Tulin 1947, Almy et al. 1951). The following sections will summarize current knowledge about the effects of experimental stress on the digestive tract.

Previous findings have provided evidence for substantial cerebral control of esophageal functions by vagal pathways (Ayres et al. 1989, Rossiter et al. 1990, Penagini et al. 1992). Stress has been shown to increase esophageal contractions, upper esophageal sphincter pressure and swallowing rates (Stacher et al. 1979a/b, Fonagy & Calloway, 1986, Cook et al. 1987, Anderson et al. 1989, Mittal et al. 1994). Similarly, numerous studies have demonstrated the influence of stress on gastric motility and emptying in several animal species and humans (Koo et al. 1985, Diop et al. 1991, Enck et al. 1992). Psychological, physiological and pharmacological (including CRH) stress was found to decrease gastric emptying in mammalians (Koo et al. 1985, Gue et al. 1989, Garrick et al. 1987, Kacker et al. 1999). In contrast, other studies have reported accelerated gastric emptying following stress exposure (Koo et al. 1985, Gué et al. 1987a/b, Ishiguchi et al. 2003). However, Gué et al. (1990) showed that stress-induced gastric emptying is modulated by many factors such as animal species, the type of stressor or test meal, and measurement technique. In humans, decreased gastric motility has been found after psychological stress (Holtmann & Enck 1991), whereas following physical stress, decreased gastric emptying has been observed (Stanghellini et al. 1983, Camilleri et al. 1984, Fone et al. 1990). Empirical evidence indicates that gastric functions are modulated by the brain via efferent vagal pathways from the dorsal motor nucleus and the medullary raphe nuclei (Heymann-Mönnikes et al. 1991, Garrick et al. 1992, Ishiguchi, 2000 & 2001). In summary, stress response of the upper gut is mediated via efferent pathways from several cerebral regions and is characterized by increased esophageal and inhibited gastric activity (Enck et al. 1992).

The influence of stress on intestinal motility can be assessed recording the intestinal pressure or the transit time of a test meal. Studies in rodents have provided contradictory results. Previous studies have shown that the application of cold stress and the injection of CRH trigger increased intestinal transit, whereas CRH antagonists abolish this effect (Gué et al. 1987, Diop et al. 1991). In contrast, other workgroups have reported delayed transit (Lenz et al. 1987, Williams et al. 1988) or no alteration (Gué et al. 1987, Barone et al. 1990) in response to stress. In humans, psychological and physical stressors have been shown to alter small bowel motility and transit time (Mc Rae et al. 1982, Valori et al. 1986).

The effect of stress on the colon is well investigated. As early as 1934, Hall published his observation regarding the association of the emotional state and the defecation behavior in

rats. Further experiments provided support for this relationship and created the generally accepted opinion that stress accelerates colonic transit in animals (Enck et al. 1992). In humans, both increased motility (Narducci et al. 1985, Welgan et al. 1985 & 2000) and no effect have been observed (Sarna et al. 1982, Welgan et al. 1988) in response to physical and psychological stimulation. However, the understanding of the neuroendocrine control linking stress and colon functions remains poorly understood. Numerous chemicals, including CRH, seem to have a stimulatory or inhibitory effect on colonic motility (Porreca & Burks, 1983, Greenwood et al. 1995, Osinski et al. 1999, Mönnikes et al. 2000a/b). For instance, intracerebroventricular injection of CRH enhances colonic motility and decreases colonic transit time, whereas the exogenous administration of a CRH antagonist abolished this effect (Williams et al. 1987a/b, Mönnikes et al. 1992 & 1993, Sagami et al. 2004). Hence, the HPA axis has been discussed as a potential mediator of stress-induced colonic motility.

Furthermore, several studies have provided evidence for stress-induced modulation of visceral perception. In healthy volunteers, both increased (Ford et al. 1995) and attenuated (Accarino et al. 1997) visceral thresholds during a psychological stress task have been reported. Accarino et al. (1997) assumed that their cognitive stressor acted as a distractor and therefore diminished visceral sensitivity. Furthermore, it has been reported that stress-induced abdominal symptoms lasted significantly longer in IBS patients than in healthy controls (Fukudo et al. 1998). Interestingly, the administration of a non-selective CRH antagonist reduced the pain threshold for rectal distension in healthy controls but not in IBS patients (Sagami et al. 2004). In line with this finding, Dickhaus et al. (2003) reported altered modulation of visceral perception in IBS patients compared to controls.

In conclusion, previous research has provided overwhelming evidence that experimental stress influences digestive functions through the activation of stress-related biological systems including the HPA axis. Mediated by the release of CRH, excitatory effects on the esophagus and colon and mainly inhibitory effects on the stomach and the small intestine have been observed. However, numerous factors including type, duration and intensity of stressor as well as individual characteristics have been shown to modulate this association. Finally, it has to be considered that the above-mentioned studies investigated the effect of acute stress and that repetitive or sustained stress exposure might exhibit different effects on the gut (Wittmann et al. 1990).

3.6.3. Chronic stress and daily life stress in patients with FGID

The relationship between sustained life stress and the development and maintenance of FGID has been investigated mainly in IBS patients. Previous studies have reported higher chronic stress levels, more work-related stress and an increased number of daily hassles in individuals with IBS compared to healthy controls or patients with organic diseases (Creed et al. 1988, Levy et al. 1997, Bennett et al. 1998, Kanazawa et al. 2001, Faresjö et al. 2007). Both symptom severity and symptom onset have been associated with the experience of stress (Levy et al. 1997, Bennett et al. 1998, Walker et al. 2001, Blanchard et al. 2008). Furthermore, it has been suggested that chronic stress has an adverse effect on general health status and illness outcome in such patients (Whitehead et al. 1992). Even in apparently healthy students, an increased prevalence of IBS symptoms has been found in individuals with high chronic stress compared to those with low stress levels (Son et al. 2009).

Moreover, chronic life stress has been suggested to be a predictor for future gastrointestinal symptom intensity (Bennett et al. 1998). Since most findings were based on a retrospective design, no causal inferences can be drawn. Longitudinal surveys have supported a reciprocal relationship between stress and gastrointestinal symptoms in that the experience of ongoing stress might have an impact on symptoms, and conversely, the experience of symptoms might exacerbate subjective stress (Dancey et al. 1995, Levy et al. 1997, Jarrett et al. 1998, Hertig et al. 2007, Blanchard et al. 2008). It seems, though, that stress has a stronger influence on symptoms than the other way round (Dancey et al. 1995). In line with this notion, in a recent study, subjective stress experience was considered as the most predictive factor for developing IBS (Blanchard et al. 2008). This finding suggests that the experience of stress augments gastrointestinal symptoms, and the subjective evaluation of the stressor plays a crucial role in this process. In contrast, a prospective and methodologically elaborated study by Suls et al. (1994) documented that the best indicators of gastrointestinal symptoms are current or prior symptoms, and no consistent effect of prior or concurrent stress on subsequent gastrointestinal symptoms was found.

3.6.4. Life events in patients with FGID

Several studies reported more negative and threatening major life events in FGID patients than in patients with organic diseases (Mendeloff, 1970, Craig & Brown, 1984, Corney & Stanton, 1990) or in asymptomatic controls (Blanchard et al. 1986, Lee et al. 2000, Pinto et al. 2000, Locke et al. 2004). In contrast, some other work groups did not confirm this association (Ford et al. 1987, Schwarz et al. 1993, Levy et al. 1997). In either case, these studies were predominantly retrospective in nature and the causality between the stressful event and the onset or maintenance of FGID could not be verified (Chitkara et al. 2008). Only few prospective studies have examined the influence of life events on FGID. The observed association between life events and subsequent bowel symptoms in IBS patients suggests that stressors might have a maintaining function (Whitehead et al. 1992 & 1996). Similarly, Naliboff et al. (2004) reported that the presence of a stressor significantly predicted the increase in FGID symptoms during the following months. It has not yet been verified whether negative life events are also associated with the onset of FGID.

3.6.5. Abuse experience in patients with FGID

Abuse has received a high level of attention in FGID research. Numerous studies in different countries found high rates (30-56%) of physical, emotional and sexual childhood or adulthood abuse in patients with FGID (Drossman et al. 1990, 1995, 1996 & 1999, Walker et al. 1993, Leroi et al. 1995, Delvaux et al. 1997, Ali et al. 2000, Heitkemper et al. 2001, Koloski et al. 2005). Furthermore, strong associations have been observed between a history of abuse and symptom severity, work absenteeism, somatic and psychiatric comorbidity, health care seeking, reduced daily functioning and worse outcome of FGID (Drossman et al. 1995 & 1996, Creed, 1999). However, abuse does not seem to be specific to FGID, with similar prevalence rates having been found in patients with other FSS such as fibromyalgia, chronic fatigue syndrome, chronic pelvic pain and temporomandibular joint disorder (Leroi et al. 1995, Walker et al. 1993). Altered brain functions (chapter 3.8) have been suggested to mediate the link between abuse experience and symptom severity in FGID (Ringel et al. 2003).

3.6.6. Coping in patients with FGID

Coping is defined as individual effort to deal with internal and external demands (Lazarus & Folkman, 1984, see chapter 3.6.1). The ability to cope with a stressful situation is essential for individual health and well-being, in contrast to ineffective coping strategies, which might lead to somatic or psychological illness. Considerable differences have been observed between individuals with respect to stress appraisal and coping strategies even when exposed to the same stressor (Dickerson & Kemeny, 2004, Kudielka et al. 2009), with some individuals tending to respond more strongly to stressful situations than others. A stimulus (e.g. abdominal sensation) activates a person's cognitive schema, which in turn determines the individual coping behavior. Thus, a subject presenting with dysfunctional schemata ("Abdominal discomfort is always threatening and a sign of a serious organic disease!") shows different coping behavior (health care seeking) and emotional reactions than a person without such thoughts (Wilhelmsen, 2000).

In several FGID including functional dyspepsia, functional constipation and IBS, dysfunctional coping strategies have been observed (Lee et al. 2000, Cheng, 2000). For instance, Ali et al. (2000) reported significantly higher "self-blame"[2] and "self-silencing"[3] in women with IBS compared to women with IBD. In functional dyspepsia, more symptom monitoring and confronting coping styles were reported (Cheng et al., 2003). Furthermore, a low Sense of Coherence (SOC)[4] – an indicator of low coping ability – has been reported in IBS patients (Sperber et al. 1999b).

In summary, the findings discussed above provide strong evidence for an association between FGID and several types of psychological stress including negative life events, abuse experience, chronic stress and reduced coping abilities. Notably, in most studies examining stress, only quantitative parameters (e.g. intensity, number) were measured, rather than carrying out a subjective evaluation of the stressor itself (i.e. how stressful an individual considers a certain experience to be). This appears to contradict modern stress research, which has repeatedly shown that the subjective evaluation of stress as threatening is crucial in terms of its subsequent effect on health (chapter 3.6.1). Furthermore, the importance of

[2] Tendency to accept responsibility for negative life events.
[3] Cognitive schemata that leads to the devaluation of one's own thoughts and beliefs.
[4] Construct that measures the degree to which a person appraises her environment as comprehensible and manageable (Antonovsky, 1979).

individual ability to cope with stressful situations has been posited. Therefore, the evaluation of the role of stress in FGID should be based on a multidimensional stress model considering several aspects of subjective stress appraisal and inter-individual stress response (i.e. stress reactivity).

3.7. The Brain-Gut Axis

It is clear from the sections presented above that previous research has provided evidence for numerous pathophysiological factors of FGID that are not mutually exclusive. Hence, the assumption of a multidetermined etiology, resulting in a dysregulated brain-gut interaction, has become increasingly accepted (Mayer & Collins, 2002). In the following paragraphs, after providing some basic information about the enteric nervous system and its connectivity to the central nervous system (CNS), the role of the brain-gut axis in FGID will be discussed by means of recent findings.

3.7.1. The enteric nervous system (ENS)

Gut functions such as motility, secretion and visceral perception are regulated by neurons, among which the enteric nervous system (ENS) plays the most important role. The ENS contains about 100 million afferent and efferent neurons of distinct categories, which are embedded in the mucosa of the digestive organ (Holzer et al. 2001). Normal gut functions are autonomously regulated by the ENS and underlie the modulating influence of the CNS, the autonomic nervous system (ANS) and the hypothalamus-pituitary-adrenal (HPA) axis. This autonomy, as well as the neuronal complexity of the ENS, led to terms such as “little brain” or “second brain” (Gershon et al. 2003). Core functions of the ENS are digestion and maintenance of the intestinal barrier (enteric immunity).

3.7.2. The brain-gut (CNS-ENS) connection

The gut (ENS) and the brain (CNS) are highly integrated and communicate in a bidirectional manner, whereas the ANS and the HPA axis hold a mediating function. This bidirectional interplay is termed as the brain-gut axis. Brain-gut interactions modulate digestive processes, in health and disease. Signals from the CNS, the ANS and the HPA axis optimize digestive functions regarding the organism’s overall state (e.g. sleep, stress), whereas bottom-up information (ENS to CNS) plays a major role in reflex regulation and modulates mood states

(Rogers et al. 1995). The crucial role of the CNS is supported by the observations that motility disturbances in FGID disappear during sleep, arousal enhances propagating intestinal contractions, FGID are associated with altered encephalographic sleep patterns, and the regional cerebral activity differs during gastrointestinal distension (Mayer et al. 2001).

Communication between the CNS and the ENS involves neural pathways as well as immune and endocrine mechanisms (Jones et al. 2006a). Neuroenteric transmission of information within the ENS and the brain is controlled by transmitters such as acetylcholin, serotonin, cholecystokinin, substance P, vasointestinal peptide and CRH (Drossman, 2002). The brain receives inputs from the periphery (e.g. sensory sources including smell, taste, somatic and visceral sensation), which influence reflex regulation and affective state (Drossman et al. 2002). Notably, 90% of the connectivity between gut and brain are afferent pathways, thus the “little brain” is feeding the “big brain” with a magnitude of visceral information. These inputs are modified by cognition, memory and emotions. Under normal conditions, ascending information is filtered by a protection mechanism and therefore remains unconscious to a substantial degree. Within the CNS, some limbic and paralimbic structures, which have been termed by Mayer et al. (2001) as the “emotional motor system” (EMS), can be regarded as locus of gut control. The EMS includes the amygdale, medial thalamus, hypothalamus, anterior cingulate cortex and prefrontal cortex. The hypothalamus regulates autonomic and neuroendocrine processes and controls the physiological homeostasis of the organism, whereas the amygdale plays an important role in affect regulation. Therefore, it is not surprising that negative affect (e.g. stress and anxiety) influences the perception of gut-related stimuli (Keogh et al. 2001). After processing and integrating incoming sensory information in the CNS, efferent pathways trigger alterations in motility, gastrointestinal secretion and blood flow or enteric immunity (Mach, 2004). Thus, a dysfunction of the brain-gut connectivity should be seen as a dysregulation in functions rather than a disease of single structures (see FIGURE 3).

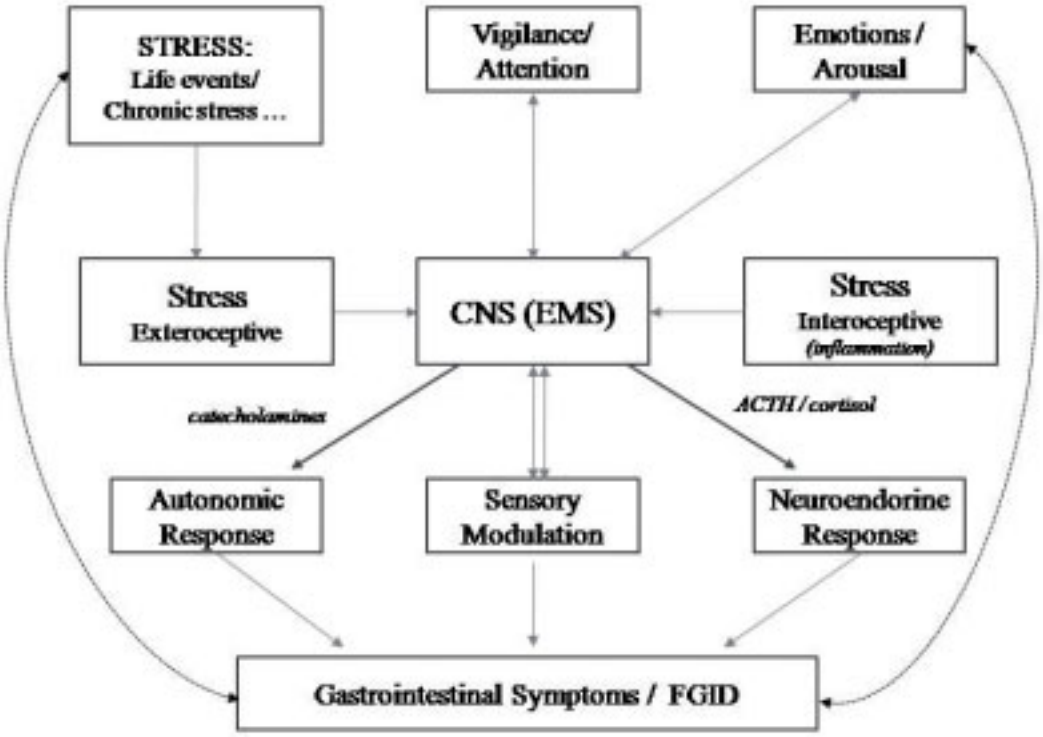

FIGURE 3: INTERPLAY BETWEEN THE STRUCTURES OF THE BRAIN-GUT- AXIS (ADAPTED FROM MAYER ET AL., 2001)

It has been suggested that biological stress systems including the autonomic nervous system (ANS) and the hypothalamus-pituitary-adrenal (HPA) axis are mediators of the brain-gut communication (see chapter 3.7.3, Mayer & Collins, 2002).

In conclusion, different lines of research suggest that symptoms of the FGID result from dysregulation of the brain-gut axis (Drossman, 1994). Alterations at any level can lead to gastrointestinal symptoms and emotional distress. Previous studies provided evidence for disturbed motility, heightened visceral sensitivity and increased levels of psychosocial stress in patients with FGID. Although it has been suggested that stress plays a mediating role in the brain-gut interaction, few data are available regarding the most prominent hormonal stress system, the HPA axis, in patients with FGID. Since these studies have mainly been conducted in IBS patients, in the following, current research opinion about HPA axis activity in IBS will be summarized.

3.7.3. An important mediator of the brain-gut axis: The hypothalamus-pituitary-adrenal (HPA) axis

In order to provide a better understanding of neuroendocrinological mechanisms linking the brain-gut interaction, the following paragraph will outline basic information about the HPA axis, followed by an overview of current findings regarding HPA axis activity in IBS patients.

3.7.3.1. Structures and function of the HPA axis

The HPA axis is a regulatory system of the organism linking the central nervous system via endocrine signaling with the periphery (Tsigos & Chrousos 2002). A stressful event affects the HPA axis and triggers the "endocrine cascade" through the release of three key hormones: (1) CRH secretion in the paraventricular nucleus (PVN) of the hypothalamus into the hypophyseal portal system is increased, (2) within seconds, the release of pituitary adrenocorticotropin hormone (ACTH) is stimulated, and (3) finally triggers, via the blood stream, glucocorticoid secretion (i.e. cortisol in humans) from the adrenal cortex (Sapolsky et al. 2000). Stress hormones then bind on glucocorticoid receptors (90-95%) and on mineralocorticoid receptors or erythrocytes (DeRijk et al. 2002); only a small proportion is unbound and biologically active (Kirschbaum & Hellhammer, 1999 & 2007). Parallel to the activation of the HPA axis, the initiation of several negative feedback loops protects the system from a spillover (Miller & O'Callaghan, 2002). ACTH inhibits further CRH release through inhibitory feedback from the pituitary glands to the PVN of the hypothalamus, and similarly, cortisol attenuates ACTH and CRH through negative feedback from the adrenal cortex to the pituitary and the PVN, respectively. CRH release is under excitatory input from the amygdale and inhibitory control from the hippocampus and mediates autonomic, immune, behavioral and visceral responses (Owens & Nemeroff, 1991). Conversely, HPA axis functioning is influenced by inputs from several cortical areas, the ANS and the immune system (Birbaumer & Schmidt, 2003, McEwen, 2007). To date, two CRH receptors with distinct distribution and pharmacological specificity have been identified. CRH_1 has been suggested to mediate anxiety-related behavior (Liebsch et al. 1999), while CRH_2 mainly contributes to physiological system regulation (i.e. feeding, recovery) (Coste et al., 2000).

Numerous biological and psychological factors lead to intra- and interindividual variability in the HPA reactivity in response to stress (Kudielka et al. 2003 & 2009). Age, sex, pharmaceuticals, and lifestyle factors (e.g. smoking, alcohol) have been shown to influence basal and stimulated HPA axis activity (Smyth et al. 1997, Clow et al 2004). For instance, men exhibit a more pronounced cortisol increase (200-400%) in response to a psychological stressor compared to women (50-100%) (Kirschbaum et al. 1992), and hormonal contraceptives are associated with general attenuation of cortisol activity (Kirschbaum et al. 1999, Wust et al. 2000). Notably, in terms of FGID research, low glucose levels are associated with an inhibition of glucocorticoid responsiveness (Gonzalez-Bono et al. 2002).

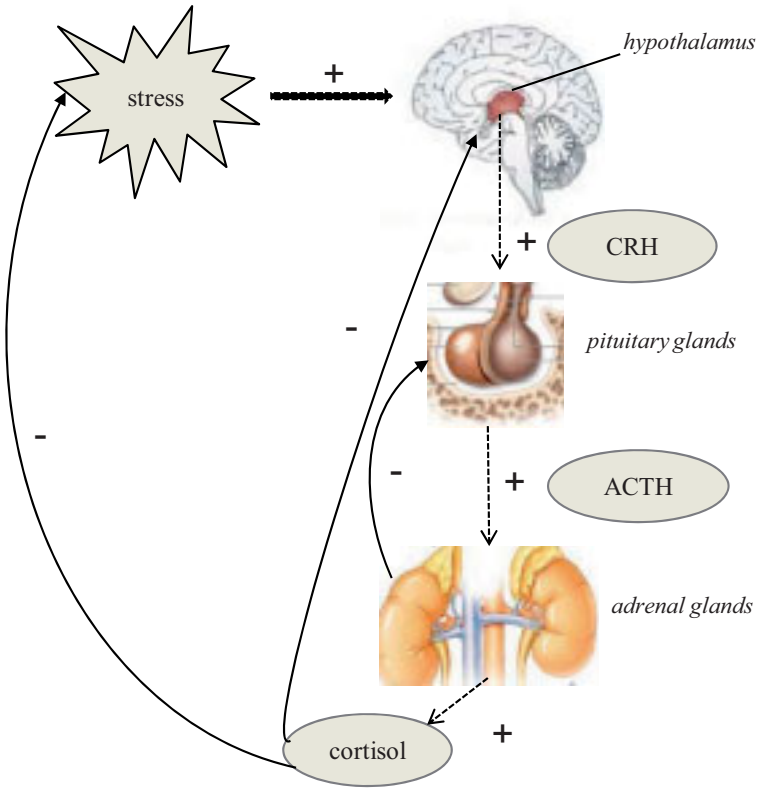

FIGURE 4: THE HYPOTHALAMUS-PITUITARY-ADRENAL (HPA) AXIS

Besides the mediating function in the organism's adaptation to stress, the HPA axis underlies a stable diurnal and circadian rhythm. Cortisol levels rise within the first half hour after awakening (50-160%) and decline thereafter over the course of the day to reach a minimal value at midnight (Edwards et al. 2001). The existence of a stress-independent circadian

rhythm implies that the HPA axis and its endocrine parameters are more than exclusively stress indicators (Sapolsky et al. 2000). Indeed, the HPA axis is responsible for the balance of numerous bodily functions and plays a substantial role in immunological processes (Horn et al. 2005). Recent data suggest that the brain-gut communication is partly mediated by the HPA axis, and its peptides may be responsible for stress-induced bowel dysfunctions (Taché et al. 2001).

The activity of the HPA axis can be determined by the assessment of its key hormones through conventional radioimmunoassay. By contrast, CRH and ACTH are only detectable in plasma, and cerebrospinal fluid cortisol can be measured in several bodily liquids. High correlations (r=0.71-0.96) between salivary and plasmatic cortisol have been documented (Kirschbaum & Hellhammer, 1994 & 2000, Harris et al. 1990). Moreover, several practical advantages (non-invasive sampling, room temperature storage) favor the assessment of salivary cortisol.

3.7.3.2. HPA axis dysregulation in IBS

It has become evident from the above discussed issues that stress plays an important role in the etiology of FGID, respectively IBS. Stress-induced gut disturbances have been documented by a multitude of previous studies (chapter 3.6.2), and a high prevalence of perceived psychosocial stress, abuse experience and critical life events has been observed in individuals with FGID (chapters 3.6.3 - 3.6.6). Moreover, stress has been associated with the onset, exacerbation and severity of gastrointestinal symptoms (Gwee et al. 1999, Hertig et al. 2007, Spence & Moss-Morris, 2007, Blanchard et al. 2008). Nonetheless, the physiological mechanisms linking stress and bowel functions remain poorly understood. The hypothalamus-pituitary-adrenal (HPA) axis has been proposed as one mediator of the brain-gut interaction (Mayer & Collins, 2002). During the past decade, a dozen studies have investigated the HPA axis in IBS patients, one of which additionally included subjects with functional dyspepsia.

Recent findings regarding basal and stimulated HPA axis activity in IBS patients provide conflicting results and are summarized in TABLE 4.

TABLE 4: CURRENT FINDINGS ON BASAL AND STIMULATED HPA AXIS ACTIVITY IN PATIENTS WITH IBS

authors	IBS/ controls	subgroups	psychiatric comorbidity	intervention	result
Böhmelt et al. 2005	Rome 30 / 24	10 IBS 15 IBS/FD 5 FD	assessed by expert interview (DIA-X)	none (diurnal profile) CRH infusion dexamethasone test	↓cortisol ↓cortisol, ↓ACTH →cortisol
Chang et al. 2009	Rome II 41 / 25 10 / 10	9 IBS-C 15 IBS-D 17 IBS-A 10 IBS-D	excluded by expert interview (SCID) 41% fibromyalgia	diurnal profile sigmoidoscopy	↓ ACTH, ↑*(cortisol)* ↑*(cortisol)*, →ACTH
Dickhaus et al. 2003	Rome II 15 / 14	11 IBS-D 4 IBS-C/A	excluded by non-specified screening	rectal distention after dichotomous listening*	→ACTH, →cortisol
Dinan et al. 2006	Rome II 21 / 21 27 / 27	10 IBS-C 36 IBS-D 30 IBS-A	excluded by mental state examination	ovine CRH infusion dexamethasone test	↑ACTH, ↑cortisol →cortisol
Elsenbruch et al. 2001	Rome 24 / 20	12 IBS-C 12IBS-D/A	excluded by personal interview	meal Stroop test (computer)*	↑cortisol (IBS-D) →cortisol
Elsenbruch et al. 2004	Rome 15/15	15IBS-D/A	excluded by personal interview	meal	→cortisol
Elsenbruch et al. 2006	Rome II 17 / 12	2 IBS-C 15IBS-D/A	excluded by non-specified personal interview	public speaking (8:30 am)	→ACTH, →cortisol
Eriksson et al. 2008	Rome II 80 / 21	16 IBS-C 30 IBS-D 34 IBS-A	excluded, non-specified	no stimulation	↑*(cortisol) (am)*
Fukudo et al. 1998	Rome 10 / 10		-	human CRH infusion	↑ ACTH, →cortisol
Heitkemper et al. 1996	Rome 48 / 25	9 IBS-C 5 IBS-D 35 IBS-A	-	no stimulation	↑cortisol (pm)
Patacchioli et al. 2001	55 / 28 Manning	-	-	no stimulation	↑cortisol (am) ↓cortisol (pm)
Posserud et al. 2004	18 / 22 Rome II	7 IBS-C 5 IBS-D 6 IBS-A	-	rectal distension & mental stress **	↑ CRF, ↑ ACTH, → cortisol

FD = functional dyspepsia, *(trend) =p>0.05and p<0.09,*

*stressor did not elicit hormonal stress response in both groups, **stressor did not elicit hormonal stress response in controls

Only two of the studies have assessed the circadian rhythmicity of cortisol (Böhmelt et al. 2005, Chang et al. 2009). While one work group (Chang et al. 2009) reported slightly increased plasma cortisol and blunted ACTH levels over a period of 24 hours, another found attenuated diurnal salivary cortisol secretion (Böhmelt et al. 2005). However, both confirmed intact diurnal HPA axis fluctuation in IBS patients. Studies that determined unstimulated cortisol levels with single-point measures either documented higher morning cortisol (Heitkemper et al. 1996, Patacchioli et al. 2001) and lower evening cortisol in IBS patients or found no differences between IBS and controls (Eriksson et al. 2008).

Studies investigating stimulated HPA axis activity in IBS patients have revealed similarly inconsistent results. Some workgroups have reported increased ACTH and/or cortisol secretion following mental stress and rectal distension (Posserud et al. 2004, Chang et al. 2009) or following CRH infusion in subjects with IBS (Fukudo et al. 1998, Dinan et al. 2006), and have interpreted these findings as HPA axis hyperreactivity. In contrast, Böhmelt et al. (2005) observed attenuated ACTH and cortisol secretion after CRH injection and suggested adrenal insufficiency in FGID. And finally, some investigators have reported no differences between IBS and controls concerning HPA axis activity (Elsenbruch et al. 2001, 2004 & 2006, Dickhaus et al. 2003). However, in two of these studies, the stressor did not induce an endocrine stress response in both groups. The association between HPA axis activity and predominant bowel patterns (IBS subtype) is not yet well examined. One study reported a significant difference between IBS-D and IBS-C patients in terms of their postprandial cortisol increase (Elsenbruch et al. 2001).

The contradictory nature of these findings might be explained by numerous confounding variables including methodology and population characteristics. Despite the fact that the HPA axis is considered to be a highly dynamic system, many studies have only obtained a small number of physiological samples. Moreover, the amount of attention paid to confounding factors has varied considerably among different studies. One of the most important confounding factors is psychiatric comorbidity, since the association between psychiatric disorders and HPA axis dysregulation is well established (see chapter 4). Nevertheless, only two work groups (Böhmelt et al. 2005, Chang et al. 2009) assessed psychopathology and trauma experience by adopting an appropriate methodology.

3.8. Integration: A Bio-Psycho-Social model

Previous research focused mainly on single factors that might contribute to the pathogenesis of FGID and assumed linear, causal relationships according to the dualistic biomedical model (Wilhelmsen, 2000). Although numerous studies provided evidence for pathophysiological mechanisms in FGID, no specific and unique etiological factor has yet been identified. For instance, symptoms of pain are not always correlated with increased gut contractility, and the perception of visceral sensations can be modified by cerebral processing (Drossman, 1994). Therefore, a more integrative scientific position has been developed over the past years and suggests that FGID are best viewed as multi-determined diseases resulting in a dysregulated brain-gut interaction. Therefore Engel's (1977) bio-psycho-social model – a modern interpretation of the holistic theory – offers an appropriate approach to conceptualize the etiology of FGID (see FIGURE 5). In this model, illness results from the interaction of biological, psychological and social sub-systems rather than from a single etiological factor.

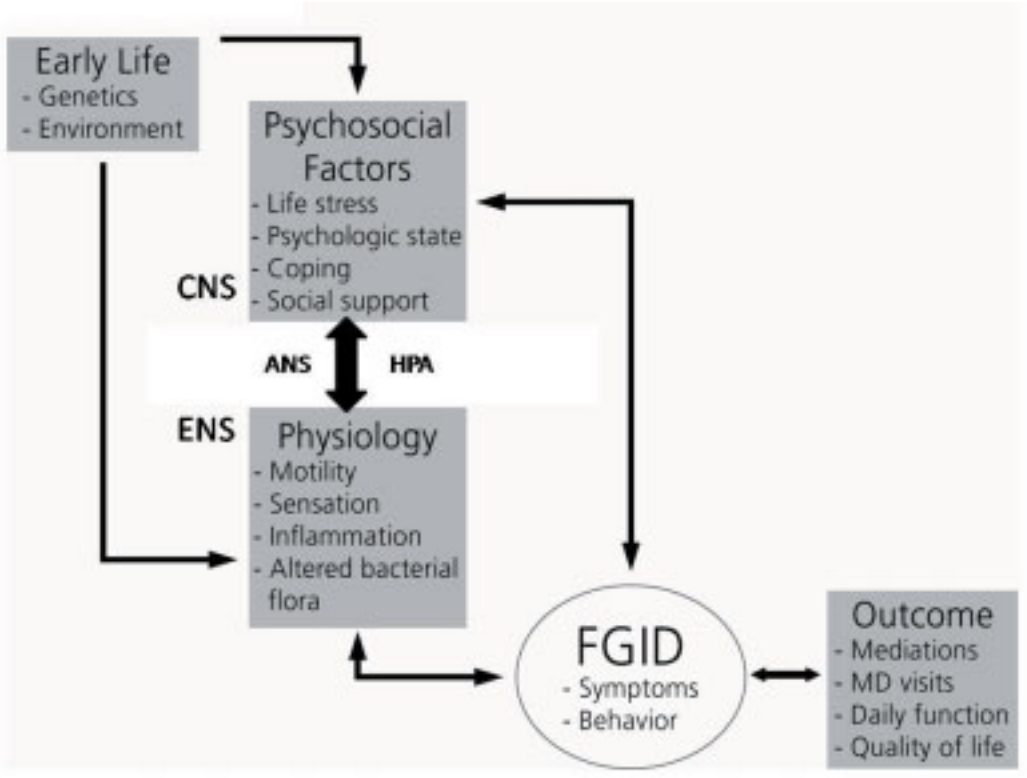

FIGURE 5: THE BIO-PSYHO-SOCIAL MODEL OF FGID (ADAPTED FROM LONGSTRETH ET AL. 2006)

As summarized in the previous sections, a growing body of research underlines the interrelatedness of emotional state, psychological and biological disposition, previous stress experience, visceral processing and gastrointestinal symptoms. The basis of the bio-psycho-social model in FGID is formed by the relationship between stress and gut functions, whereas symptoms are seen as an outcome of temporary or irreversible alterations in the physiological response to various stressors (Jones et al. 2007). Biological stress systems such as the HPA axis represent the physiological link between stress perception and bowel. Individual vulnerability to develop a FGID is determined by genetic predisposition and early life stress, while subsequent stress exposure triggers or exacerbates gastrointestinal symptoms. Finally, conditioning processes play a central role in the maintenance of the disorder (Spence & Moss-Morris, 2007).

4. HPA axis dysregulation in stress-related disorders

HPA axis dysregulation is not specific to IBS and has been associated with numerous clinical populations (Ehlert et al. 2001, Heim et al. 2000a), with early life stress, and chronic ongoing stress (Heim et al. 2008, Kudielka et al. 2006a/b, 2009). It has been hypothesized that HPA axis dysfunction predisposes the individual to heightened stress sensitivity and thereby increases the likelihood of disease onset (Gunnar & Quevedo, 2007). Well established is the hyporeactivity of the HPA axis in posttraumatic stress disorder, resulting in chronic hypocortisolism (Mason et al. 1986, Yehuda et al. 1991, 1995 & 2001, Gill et al. 2008) and hypercortisolism in patients with mood disorders, particularly major depression (Trestman et al. 1995, Holsboer, 2001, Gillespie & Nemeroff, 2005). One of the major problems in clinical practice is the high overlap between different disorders. For instance, anxiety is a common symptom in depression, and patients with primarily somatoform complaints often report mood disturbances (Roy-Burne et al. 2000). HPA axis dysregulation was shown to differ between unimorbid and multimorbid patients (Young et al. 2004). As depression, somatoform and anxiety disorders have been associated with inappropriate adaptation to stress, HPA axis dysregulation and / or ANS dysfunction, they are viewed as stress-related disorders (De Kloet et al. 2005).

Current consensus suggests that HPA axis dysregulations in anxiety disorders are nonexistent or subtle, and reflect altered responses to certain kinds of stress rather than a basal dysfunction (Ehlert, 2001). It has been postulated that the stress responses of anxiety patients vary according to the affinity of the stressor with symptom-provoking stimuli, for instance social evaluation may trigger a stronger stress response in individuals with social phobia (Abelson et al. 2007). Thus, subtle hypercortisolism is probably triggered by differences in CRH secretion or altered CRH receptor signaling following stimulus-specific stress provocation (Risbrough & Stein, 2006). However, symptom patterns and illness severity might modulate HPA activity in anxiety patients.

HPA axis activity in depression is well investigated. Recent data provide evidence for increased basal cortisol levels in about 80% of individuals with major depression (Thomson & Craighead, 2008). Furthermore, non-suppression of cortisol secretion after dexamethasone administration was observed in several studies, indicating reduced feedback sensitivity in such patients (Pariante & Lightman, 2008). In response to CRH infusion and to psychological

stimulation, depressive individuals show blunted ACTH and normal cortisol response (Nemeroff et al. 1996, Holsboer et al. 1985, Heim et al. 2001). Coincidence of basal hypercortisolism and increased cortisol response to ACTH administration was interpreted as hypersensitivity of the adrenal glands (Ströhle & Holsboer, 2003). This assumption was supported by the finding of regular cortisol response despite blunted ACTH secretion following CRH stimulation and an enlarged adrenal size during depression (Rubin et al. 1995). Notably, HPA axis dysregulation was even found after symptom remission (Ahrens et al. 2008).

In numerous FSS such as chronic fatigue (Van Houdenhove et al. 2009, Van den Ede et al. 2007), chronic back pain (Geiss et al. 1997), fibromyalgia (Tanriverdi et al. 2007), chronic pelvic pain (Ehlert et al. 1999, Heim et al. 1997), evidence for HPA axis hypofunction characterized by lower basal cortisol levels and attenuated endocrine response following stimulation has been observed. Thus, it could be suggested that hypocortisolism reflects a common feature of functional somatic conditions without concurrent depression.

Given that psychiatric comorbidity is present in 40%-70% of all patients with FGID (see chapter 2.5.4.1), the exclusion of such patients beforehand when conducting a study in IBS patients might reduce external validity. In addition, current psychiatric comorbidity should be excluded using an appropriate procedure in order to prevent underdiagnosis of previous chronic or recurrent conditions (Ehlert et al. 2001). Previous findings indicate that HPA axis dysregulation might persist after symptom remission in recurrent depression (Ahrens et al. 2008). Therefore, the assessment of current and previous psychiatric comorbidity based on the use of validated and standardized methods (i.e. structured clinical interview) might be the most appropriate approach.

5. Study idea and hypothesis

Study I: The above discussed findings provide strong evidence for a crucial role of psychological stress in the onset and the maintenance of FGID. Factors such as the experience of "negative life events" or "chronic ongoing stress" have been associated with FGID. However, most of these studies focused on single aspects of stress, despite modern stress research advancing the opinion that stress is best viewed as multidimensional phenomenon. Moreover, individual stress appraisal has often been neglected using a quantitative methodology (i.e. number and intensity of objective stressors). Therefore, we conducted an investigation following the well-established and validated transactional stress model by Lazarus & Folkman (1984). According to this model, stress is defined as the result of subjective appraisal of a given situation or stimuli. The present study aimed at determining the relationship between FGID and stress based on a multidimensional stress model considering inter-individual stress reactivity and perception of coping abilities. For this purpose, an Internet-based study was conducted in apparently healthy university students (n=668). The occurrence of FGID was assessed using a validated self-report measure according to the Rome II criteria. Furthermore, specific questionnaires on subjective experience of chronic stress, individual coping strategies, and dispositional stress reactivity were applied.

Study II: The second project was planned to examine the biological link between stress and functional bowel symptoms. Previous studies have suggested that the HPA axis – a prominent hormonal stress system – mediates brain-gut interaction and therefore might be responsible for stress-induced gastrointestinal symptoms. However, only a few studies have investigated HPA axis activity in FGID and current findings are inconclusive. All of these studies were conducted in subjects with IBS, whereas one study additionally included some patients with functional dyspepsia. Generally, the influence of psychiatric comorbidity and trauma experience – which have also been associated with HPA axis disturbances (see chapter 4) – was not assessed using an appropriate methodology. Moreover, the association between HPA axis activity and predominant bowel patterns (IBS subtype) is yet not well investigated. Therefore, the second aim of the present thesis was to explore basal and stimulated HPA axis activity in IBS patients, while taking into account current or lifetime comorbidity and predominant bowel habit. To this aim, a study setting with IBS patients and healthy controls

undergoing an acute psychosocial stress task was planned. HPA axis activity was determined by repeated measures of salivary cortisol and plasma ACTH levels. In addition, we collected psychometric data and assessed unstimulated cortisol (morning and diurnal) profiles during a separate day at home.

6. EMPIRICAL STUDY I: "Psychological stress and self-reported functional gastrointestinal disorders"[5]

6.1. Introduction

Functional gastrointestinal disorders (FGID) represent variable and heterogeneous combinations of chronic or recurrent symptoms attributed to the gastrointestinal tract, which cannot be explained by any structural or biochemical abnormalities. To provide consistent diagnostic criteria of FGID, the use of the validated Rome criteria is recommended (Thompson et al. 1999, Drossman et al. 2006). Population-based surveys estimate the prevalence for individual FGID as lying between 35% and 70% (Drossman et al. 1993, Thompson et al. 2002, Koloski et al. 2002, Halder et al. 2007), with a considerable overlap between disorders (Agreus et al. 1995, Hungin et al. 2003, Locke et al. 2005). The wide range in prevalence rates may be mostly attributed to varying methodological strategies (diagnostic criteria, recruitment, data sampling) or sample characteristics (lifestyle, ethnicity, social class) that were used in previous studies (Drossman et al. 2002, Corazziari, 2004, Talley, 2008). Several studies showed a female preponderance in the prevalence for most FGID (Drossman et al. 1993, Corazziari, 2004, Chang et al. 2006b).

To date, the etiology of FGID remains essentially unknown, but recent investigations propose a multi-causal pathophysiology which includes a variety of biological and psychological factors (Mayer & Collins, 2002). Stress has been suggested as a central factor in the development and maintenance of FGID. As a multi-faceted phenomenon, stress results in a multitude of psychological and physiological processes that may precipitate, exacerbate, and perpetuate physiological symptom (McEwen, 1998). Therefore, stressors are also postulated to evoke gastrointestinal symptoms through alteration of intestinal function mediated by the autonomic nervous system, the hypothalamic-pituitary-adrenal axis, and the immune system (Pinto et al. 2000).

Numerous studies have investigated the role of psychological stress in FGID. Variables such as the experience of distinct "life events" (e.g. accident, job loss) or "chronic ongoing stress"

[5] submitted for publication

(e.g. daily hassles, workload) have been examined in individuals with FGID. It is evident from the literature, however, that most studies have focused on single aspects of stress.

Studies assessing life events found more negative and threatening major life events in FGID than in patients with organic diseases (Mendeloff et al. 1970, Craig & Brown, 1984, Corney & Stanton, 1990) or asymptomatic controls (Mendeloff et al. 1970, Blanchard et al. 1986, Drossman et al. 1988, Pinto et al. 2000, Locke et al. 2004). However, there are some reports that were unable to document an increased number of major life events in FGID patients compared to patients with organic diseases or healthy controls (Ford et al. 1987, Schwarz et al. 1993, Levy et al. 1997). In either case, these studies were retrospective in nature, and it was not possible to evaluate causality between stressful events and the onset or maintenance of FGID. Chronic ongoing stress in FGID has mostly been investigated in subjects with IBS only. Substantially more daily and work-related stress (Faresjö et al. 2007) was found in individuals with IBS compared to controls. On the other hand, a higher prevalence rate for IBS was found in individuals who reported high chronic stress levels compared to individuals with low stress levels (Son et al. 2009). Studies implementing a longitudinal design support a reciprocal relationship between stress and gastrointestinal symptoms: experience of chronic stress might impact symptom manifestation and exacerbation, while experience of symptoms might also have an impact on subjective stress levels (Dancey et al. 1995, Jarett et al. 1998, Faresjö et al. 2007, Hertig et al. 2007, Blanchard et al. 2008).

Interestingly, in most studies examining life events or chronic ongoing stress, only quantitative parameters (e.g. intensity, number) were measured instead of a subjective evaluation of the stressor itself (i.e. how stressful an individual considers a certain experience to be). This appears to contradict modern stress research, which has repeatedly shown that the subjective evaluation of stress as threatening is crucial in terms of its subsequent effect on health (Lazarus & Folkman, 1984, Dickerson & Kemeny, 2004, Monroe, 2008). In line with this notion, *subjective* stress experience has been considered as the most predictive factor for a change to IBS in a recent study (Blanchard et al. 2008). This finding suggests that the experience of stress may augment gastrointestinal symptoms, and the *subjective* evaluation of the stressor plays a crucial role in this process.

Therefore, in our approach, we follow the well-established and validated transactional stress model by Lazarus (Lazarus & Folkman, 1984). According to this model, stress in a given situation is understood as the result of a *subjective* cognitive appraisal process, resulting in an emotional, behavioral, and physiological stress response. Thus, a stressor is not defined by its objective intensity alone, but rather by the subjective appraisal, i.e. the subjectively perceived experience of stress. Furthermore, the model also posits the importance of individual ability to cope with stressful situations. Considerable differences can be observed among individuals concerning stress appraisal and coping even when exposed to the same stressor, with some individuals tending to respond more strongly to stressful situations than others. This phenomenon is recognized by the concept of inter-individual (dispositional) stress reactivity (Schulz et al. 2005), which describes a trait-like disadvantageous pattern that predisposes a person to respond with an immediate, intense, and long-lasting stress response.

In sum, most previous research on the role of stress in FGID has focused on quantitative measures of life stressors. However, modern stress theory posits that stress is a multidimensional phenomenon. To the best of our knowledge, no study has yet evaluated the role of stress and FGID based upon a multidimensional stress model. To address this gap in the current knowledge of the relationship between stress and FGID, we conducted a study that served two aims: a) to assess prevalence rates of FGID, and b) to examine associations of FGID with subjective experience of chronic stress, coping strategies, as well as inter-individual stress reactivity, in a sample of apparently healthy students.

6.2. Methods

6.2.1. Subjects and data collection procedure

Potential participants were contacted by email using the electronic mailing lists of two Zurich-based universities (University of Zurich and Federal Institute of Technology). Email recipients were asked to enroll online for a survey on stress and bodily symptoms. In order to ensure higher participation rates, cinema tickets and a dining coupon were raffled off (Bosnjak et al. 2003). To guarantee anonymity, participants were automatically sent an individual username, a password, and an Internet link to the survey. For the survey, a database (mySQL) on a web server was implemented. Psychometric data and subjects' characteristics were saved separately. All data were imported via Open Database

Connectivity (ODBC), which supports both mySQL and the statistical software package SPSS (SPSS, Chicago, Illinois) for Windows. In a pilot study, a minimum time requirement of 30 minutes to complete all questions was determined. Therefore, subjects performing substantially faster were excluded. By pressing the "continue" button, completed data were automatically transferred into the database. For every page, all questions had to be answered to ensure complete data sets. At the end of the survey, subjects were given the possibility to comment on the questionnaire and they were asked if they would like to receive further information on the results. Clinical contact information was provided in case responding to stress or symptom-related questions resulted in acute psychological problems. All subjects participated voluntarily in the study and provided written informed consent.

6.2.2. Psychological measurement instruments

The complete online survey contained 241 items. The first section was covered by questions addressing sociodemographic and health-related variables. Subjects reporting specific organic diseases (e.g. inflammatory bowel diseases or diabetes) were excluded from calculation for prevalence rates of FGID. In addition, the following questionnaires about stress, coping, and FGID were included:

FGID were assessed by the *Gastro-Questionnaire*, containing a total of 27 items (Leibbrand et al. 2002). Each item has to be rated with regard to the frequency and the subjective distress produced by the specific symptom. On the basis of the responses, 21 categories of FGID according to the Rome II criteria can be assessed.

Perceived chronic stress during the past 12 months was assessed using the Trier Inventory for the Assessment of Chronic Stress (TICS, Schulz et al. 2004). The TICS is a 57-item self-report instrument measuring eight types of perceived chronic stress: (1) Work Overload, (2) Social Overload, (3) Overextended at Work, (4) Lack of Social Recognition, (5) Work Discontent, (6) Social Tension, (7) Pressure to Succeed, (8) Social Isolation. For each item, the frequency of a stressful experience in the last year has to be indicated on a five-point rating scale, ranging from never to very often.

The short version of the *Multidimensional Coping Inventory* (SVF-78, Janke et al. 2002) was used to assess the trait aspects of coping with everyday stressors. The SVF-78 measures

coping strategies independent of time and situation. Coping styles can be categorized into positive and negative coping strategies.

Inter-individual stress reactivity was assessed by the Stress Reactivity Scale (SRS, Schulz et al. 2005) The SRS indicates general stress reactivity as well as stress reactivity in specific domains, such as Social Conflicts, Social Evaluation, Failure at Work, and Workload. Furthermore, two scales assess stress reactivity before and after stressful events.

6.2.3. Statistical analyses

Prevalence rates for diagnoses according to Rome II criteria were calculated in percentages. Data were tested for normal distribution and homogeneity of variance using a Kolmogorov-Smirnov and Levene´s test before statistical procedures were applied. Student's t-tests were computed for comparison of the scale means of the questionnaires. The association between stress variables and gastrointestinal symptoms was calculated using stepwise general linear regression analysis. For all statistical analyses, SPSS 16.0 (SPSS, Chicago, Illinois) was used. The significance level was $\alpha = 5\%$ (two-tailed).

6.3. Results

6.3.1. Subjects' characteristics

A total of 673 individuals completed the survey. After exclusion of individuals suffering from organic diseases related to the gastrointestinal tract (4.6%) a sample size of 668 subjects (66% women and 34% men, mean age 24.3 years) was available for analyses. All participants were university students, thus highly comparable with regard to their education level.

6.3.2. Prevalence of FGID

Prevalence rates of individual FGID are reported in TABLE 5. 429 participants (64.2%) fulfilled the Rome II criteria for at least one FGID. The number of syndromes ranged from 1 to 6. On average, each participant reported having 3.1 (SD: 3.2) gastrointestinal symptoms, although 154 (21.3%) of all participants did not report any gastrointestinal symptoms at all.

TABLE 5: PREVALENCE RATES OF FGID

	absolute cases	**%**
Globus	15	2.2
Functional chest pain	13	1.9
Functional heartburn	9	1.3
Functional dysphagia	8	1.2
Unspecified functional esophageal diso	97	14.5
Functional dyspepsia (ulcer-like)	56	8.4
Functional dyspepsia (dysmotility-like)	35	5.2
Functional dyspepsia (reflux-like)	22	3.3
Functional dyspepsia (unspecified)	45	6.7
Aerophagia	46	6.9
Irritable bowel syndrome	27	4.0
Irritable bowel syndrome – diarrhea predominant	14	2.1
Irritable bowel syndrome – constipation predominant	14	2.1
Functional constipation	6	0.9
Functional diarrhea	3	0.4
Functional abdominal bloating	264	39.5
Unspecified functional bowel disorder	79	11.8
Chronic functional abdominal pain	65	9.7
Functional incontinence	43	6.4
Levator syndrome	10	1.5
Proctalgia fugax	2	0.3

6.3.3. Subjective stress and inter-individual stress reactivity

TABLE 6 displays mean comparisons for all scales of the stress questionnaires between participants fulfilling criteria for no vs. at least one FGID. As is evident from this analysis, the two groups differ significantly in all but one stress factor (positive coping).

TABLE 6: MEAN COMPARISONS FOR STRESS SCALES FOR FGID (NO VS. AT LEAST ONE) IN THE PAST 12 MONTHS

	Mean (SD) FGID 0 (n=239)	**Mean (SD) FGID at least 1 (n=429)**	***t***	***p***
TICS Work overload	14.5 (5.7)	17.5 (6.7)	-6.0	<0.001
TICS Social overload	6.5 (4.2)	7.5 (4.5)	-2.9	<0.01
TICS Pressure to succeed	15.1 (5.2)	16.9 (5.5)	-4.1	<0.001
TICS Work discontent	9.9 (4.8)	12.1 (5.4)	-5.4	<0.001
TICS Overextended at work	6.7 (4.3)	8.4 (4.6)	-4.7	<0.001
TICS Lack of social recognition	4.3 (3.3)	5.0 (3.1)	-3.0	<0.01
TICS Social tension	4.6 (3.6)	5.5 (4.2)	-3.2	<0.01
TICS Social isolation	7.4 (5.4)	9.0 (5.6)	-3.7	<0.001
SRS Workload	3.1 (2.2)	4.3 (2.4)	-6.2	<0.001
SRS Social conflicts	9.2 (2.5)	10.3 (2.4)	-5.5	<0.001
SRS Social evaluation	6.5 (2.3)	7.5 (2.3)	-5.7	<0.001
SRS Failure at work	10.2 (1.9)	11.1 (2.0)	-5.5	<0.001
SRS Stress reactivity before stressors	6.2 (1.7)	6.8 (1.8)	-4.4	<0.001
SRS Stress reactivity after stressors	5.2 (1.8)	6.1 (2.1)	-5.8	<0.001
SVF Positive coping	12.7 (2.7)	12.5 (2.4)	1.3	0.199
SVF Negative coping	9.3 (3.6)	12.0 (4.0)	-8.8	<0.001

TICS: Trier Chronic Stress Inventory; SRS: Stress Reactivity Scales; SVF: Multidimensional Coping Inventory

Subsequently, all stress-related variables were included in a stepwise regression analysis, with sex and age as additional predictors. As outcome variable, the number of functional gastrointestinal symptoms was chosen. TABLE 7 shows the significant predictor variables.

TABLE 7: STEPWISE MULTIPLE LINEAR REGRESSION ANALYSIS PREDICTOR VARIABLES OF NUMBER OF FGI SYMPTOMS IN THE PAST 12 MONTHS (N=673)

	Explained variance*	**Standardized beta**	***t***	***p***
TICS Workload	0.124	0.15	3.8	<0.001
SVF Negative coping	0.181	0.14	3.5	0.001
TICS Work discontent	0.200	0.15	4.0	<0.001
Sex	0.220	-0.13	-3.8	<0.001
SRS Stress reactivity after stressors	0.235	0.15	3.8	<0.001
TICS Social overload	0.244	0.11	3.0	<0.01

adj. $R^2 = 0.244$; $F(6, 661) = 36.9$; $p < 0.001$, * adjusted R^2

6.4. Discussion

The current study aimed at determining the prevalence of self-reported FGID and the relationship between stress and symptoms of FGID in a homogenous sample of apparently healthy young volunteers, utilizing an internet-based survey. The assessment of stress was based on a multidimensional theoretical model of stress including the measurement of chronic stress, coping strategies, as well as inter-individual stress reactivity. This is the first study incorporating comprehensive assessment of stress in a sample of healthy subjects and individuals reporting FGID.

We found that nearly two thirds (64.2%) of the participants fulfilled the Rome II criteria for at least one FGID. This finding is similar to other surveys reporting such high prevalence rates in the general population (Barbezat et al. 2004, Corazziari, 2004, Chang et al. 2006b, Talley, 2008). Studies evaluating prevalence in student samples indicate that about 50% suffer from one FGID or more (Norton et al. 1999), with IBS being the most commonly reported (5-26%) (Norton et al. 1999, Tan et al. 2003, Hazlett-Stevens et al. 2003, Kim et al. 2005, Son et al. 2009).

Group comparisons between individuals with and without gastrointestinal symptoms revealed significant differences concerning chronic stress, stress reactivity, and negative coping. Furthermore, female sex, work-load, work discontent, social overload, negative coping, and

increased stress reactivity were identified as main predictors for the occurrence of functional gastrointestinal symptoms.

Not surprisingly, female sex was a significant predictor for the number of functional gastrointestinal symptoms. This finding is in line with several other reports investigating FGID prevalence rates in different populations (Han et al. 2006, Andrews et al. 2005, Blanchard et al. 2008). Previous studies show sex differences in visceral perception and physiological response to visceral stimuli in specific FGID, such as IBS, which might explain the female preponderance in prevalence rates (Ragnarsson et al. 1999, Tillisch et al. 2005, Chang et al. 2006a). In contrast, not much is known regarding sex differences in terms of psychosocial factors (i.e. psychopathology, sexual abuse, gender role socialization) (Chang et al. 2006b). In our sample, significantly higher scores for all stress scales were found in women compared to men with and without FGID (data not shown). This result may indicate that stress is a mediator variable for female preponderance in FGID.

Moreover, our findings revealed an association between (self-reported) gastrointestinal symptoms and work-related stress. The perception of work-related stress has been associated with an increased risk of suffering from somatic symptoms (Krantz et al. 2005). Our finding in a student-only sample is in line with the hypothesis that perceived stress caused by high study demands contributes to the prevalence of IBS in high-school students (Son et al. 2009). Furthermore, both low control of work planning as well as low control of working pace were shown to correlate with an increased prevalence of IBS within the general population (Faresjö et al. 2007). We were able to corroborate the importance of work-related stress and extend this finding to other FGID.

Our finding of a relationship between increased stress in social relationships and higher prevalence of FGID is supported by a growing body of research highlighting the importance of interpersonal stress in IBS and functional abdominal pain (Creed et al. 1988, Guthrie et al. 1991 & 2003, Benett et al. 2002, Lackner et al. 2005). Previous studies reported a substantial lack of interpersonal support both in FGID patients and in FGID sufferers in the general population (Herschbach et al. 1999, Jones et al. 2006b). Indeed, long-lasting interpersonal stress increased the risk of IBS incidence after an acute enteric infection (Gwee et al. 1999). Moreover, higher social desirability (Toner et al. 1992) and an interpersonal profile

characterized by difficulties with assertiveness and social inhibition (Lackner et al. 2005) was found in IBS patients and may indicate a tendency towards interpersonal conflict avoidance. Overall, these findings suggest higher emotional stress due to perceived interaction difficulties in individuals suffering from FGID.

In the present study, we found an association between the tendency to use negative coping strategies and FGID. This result is supported by recent studies which reported significantly less planful problem solving, less task-oriented coping, less positive reappraisal and more escape-avoidance or more negative coping strategies in FGID sufferers (Xiong et al. 2004, Jones et al. 2006b, Tominaga et al. 2007, Seres et al. 2008). In a longitudinal study, the use of maladaptive coping strategies in combination with a decreased symptom-related self-efficacy revealed an adverse effect on future health outcome in women with gastrointestinal disorders (Drossman et al. 2000). However, the exact role of coping in FGID remains to be clarified, since there is some evidence that coping strategies may serve as a mediating factor between illness representation and health outcome rather than playing a primary role in the etiology of FGID (Rutter et al. 2002).

To our knowledge, no previous study has investigated inter-individual stress reactivity and FGID. We were able to show an insufficient ability to recover from a stressor in individuals with FGID. In this context, it is interesting to consider that studies in patients with FGID showed evidence for the effectiveness of therapies aimed at reducing psychosocial stress (e.g. relaxation, cognitive-behavioral interventions), and therefore may support the hypothesis that such individuals lack adequate strategies to recover from a stressor (Blanchard et al. 1993, Drossman et al. 2003, Guthrie et al. 2003, Toner et al. 2005, Moser, 2007, Kearney et al. 2008). Clearly, further research is warranted in this area.

Despite various advantages of web-based data collection (e.g. access to a broad and homogeneous population, rapid data collection, convenience for participants, anonymity, cost effectiveness), there are some limitations to this approach. Compared to the conventional paper-and-pencil methodology, generally lower response rates are observed. Our study sample was drawn from the two major universities in Zurich and was therefore not wholly representative of the general young adult population in Switzerland. Furthermore, the voluntary nature of study participation may lead to a self-selection bias. In addition, the

cross-sectional design of the present study does not allow for a causal interpretation of our results. Although high correlations between diagnosis from questionnaires and from physical examination have been reported (Talley et al. 1990), web-based symptom assessment makes access to detailed clinical information impossible, and therefore objective FGID diagnoses could not be verified. Finally, the present study did not include specific questionnaires to assess psychopathology (i.e. depression or anxiety). Given the well-documented association between FGID and psychopathology (Whitehead et al. 2002, Mussell et al. 2008), future studies on stress and FGID should include detailed assessment of psychiatric symptoms.

Our results might inform clinical practice. Therapeutic interventions specifically targeting stress management strategies (i.e. coping styles) could be of great benefit for a group of individuals with FGID suffering from high stress levels. Such specific interventions may not only decrease psychosocial distress, but might concomitantly reduce functional gastrointestinal symptoms.

In conclusion, this is the first study to identify a significant relationship between FGID and stress based upon the consideration of a multi-dimension stress model. Future investigations are required to explore the association between stress and FGID in the general population as well as in patient samples and to elaborate on longitudinal relationships between stress and FGID.

7. EMPIRICAL STUDY II: "Altered psychobiological stress responsiveness in women with irritable bowel syndrome"[6]

7.1. Introduction

The irritable bowel syndrome (IBS) is the most extensively examined functional disorder of the lower gastrointestinal tract (Drossman et al. 2002). IBS affects 10-20% of the Western population (Drosman et al. 1993, Koloski et al., 2002, Hungin et al. 2003) and is associated with substantial socioeconomic burden (Eisen et al. 2000, Hungin et al. 2003, Maxion-Bergeman et al. 2006, Talley, 2008). Current research provides evidence for numerous pathophysiological factors in the etiology of IBS that are not mutually exclusive (Mayer & Collins, 2002, Schwetz et al. 2003, Chang, 2006). The assumption of a multidetermined etiology, resulting in a dysregulated brain-gut interaction, has therefore become increasingly recognized (Wilhelmsen, 2000, Mayer et al. 2001, Jones et al. 2006a), and stress is assumed to play a prominent mediating role in the brain-gut communication (Mayer & Collins, 2002).

Stress-induced gut disturbances have been documented by a large number of previous studies. Altered gastrointestinal functions (i.e. motility, secretion or visceral perception) have been observed following pharmacological, physical or psychological stress exposure in animals and humans (Mayer et al. 2001, Enck & Holtmann 1991, Holtmann & Enck, 1992, Fukudo et al. 1998, Taché et al. 2005). At the same time, numerous studies have reported higher prevalence of perceived psychosocial stress, history of abuse (Drossman et al. 1995 & 1996, Delvaux, 1997, Heitkemper et al. 2001), and critical life events (Craig & Brown, 1984, Drossman et al. 1988 & 1999, Pinto et al. 2000, Locke et al. 2004) in individuals with IBS compared to healthy controls or patients with organic diseases. Moreover, stress has been associated with subsequent bowel symptom exacerbation and severity (Dancey et al. 1995, Jarrett et al. 1998, Hertig et al. 2007, Blanchard et al. 2008). One study actually proposed stress as a risk factor for the development of IBS after an acute gastroenteritis (Gwee et al. 1999).

[6] submitted for publication

Although previous findings provide evidence that (1) experimental stress induces bowel disturbances and that (2) psychosocial stress plays a crucial role in the onset and maintenance of IBS, the physiological mechanisms linking stress and bowel functions are not yet completely understood. The biological stress systems including the autonomic nervous system (ANS) and the hypothalamus-pituitary-adrenal (HPA) axis have been proposed as mediators of the brain-gut communication (Mayer & Collins, 2002, Manabe et al. 2009). While a considerable amount of studies have investigated ANS alterations in IBS patients, relatively few have focused on the HPA axis (Chang, 2006). Current data on basal and stimulated HPA axis activity in IBS patients provide conflicting results and are summarized in TABLE 4 (chapter 3.7.3.2). Only two of these studies have assessed the circadian rhythmicity of cortisol (Böhmelt et al. 2005, Chang et al. 2009). While one work group (Chang et al. 2009) reported slightly increased plasma cortisol and blunted ACTH levels over a period of 24 hours, attenuated diurnal salivary cortisol secretion was found by another (Böhmelt et al. 2005). However, both studies confirmed regular diurnal HPA axis fluctuation in IBS patients. Studies that determined unstimulated cortisol levels with single-point measures have either documented higher morning cortisol levels (Heitkemper et al. 1996, Patacchioli et al. 2001, Ehlert et al. 2005) and lower evening cortisol levels in IBS patients (Patacchioli et al. 2001) or have found no difference between IBS and controls (Eriksson et al. 2008). Studies investigating stimulated HPA axis activity in IBS patients have revealed similarly inconsistent results. For example, increased ACTH and/or cortisol secretion following mental stress and rectal distension (Chang et al. 2009, Posserud et al. 2004) or following CRH infusion was observed in subjects with IBS (Fukudo et al. 1998, Dinan et al. 2006). These findings have been interpreted as HPA axis hyperreactivity. Böhmelt et al. (2005), however, observed attenuated ACTH and cortisol secretion after CRH injection and suggested adrenal insufficiency in IBS. And finally, some investigators have reported no differences between IBS and controls concerning HPA axis activity (Elsenbruch et al. 2001, 2004 & 2006, Dickhaus et al. 2003). Notably, two of these studies reported that neither the patients nor the control group showed an endocrine response following the stress exposure (Elsenbruch et al. 2001, Dickhaus et al. 2003). Interestingly, the association between HPA axis activity and predominant bowel patterns (IBS subtype) is yet not well examined, although one of the previous studies reported a significant difference between IBS-D and IBS-C patients with respect to their postprandial cortisol increase (Elsenbruch & Orr, 2001).

The contradictory nature of the above-mentioned findings might be explained by numerous confounding variables, including methodology and population characteristics. Despite the fact that the HPA axis is considered to be a highly dynamic system, many studies have only obtained a small number of physiological samples. Moreover, the amount of attention paid to confounding factors (e.g. sex, glucocorticoid intake, menstrual cycle, substance abuse, comorbidity) has varied considerably between different studies (Kirschbaum et al. 1999, Lee et al. 2001, Chang, 2006). One of the most important confounding factors is psychiatric comorbidity. Although the association between psychiatric disorders and HPA axis dysregulation is well established (Heim et al. 2000 & 2008, Ehlert et al. 2001), only two work groups (Böhmelt et al. 2005, Chang et al. 2009) have assessed psychopathology and trauma experience by adopting an appropriate methodology.

Given the fact that psychiatric comorbidity is present in 40%-70% of all IBS patients (Whitehead et al. 2002, Guthrie et al. 2003, Jones et al. 2006c, Hillilä et al. 2007), the exclusion of such patients beforehand might reduce external validity. In addition, if current psychiatric comorbidity is excluded through the adoption of a non-validated methodology, current and in particular previous or chronic conditions such as recurrent depression might be underdiagnosed (Ehlert et al. 2001). However, findings indicate that HPA axis dysregulation might persist after symptom remission (Ahrens et al. 2008). The assessment of current and previous psychiatric comorbidity based on the use of validated and standardized methods (i.e. structured clinical interview) might therefore be an appropriate approach.

In conclusion, despite conflicting results, current findings propose that HPA axis dysregulation is present in at least a subset of IBS patients. So far, only one study has examined the psychobiological stress response to a psychosocial stressor in IBS patients. Furthermore, the influence of psychiatric comorbidity, psychological stress perception and predominant bowel symptoms (IBS subtype) on the HPA axis (re-) activity is not completely understood. Therefore, the present paper aims at determining basal and stimulated HPA axis activity in IBS patients while taking current or lifetime comorbidity and predominant bowel habit into account.

7.2. Methods

The research protocol was approved by the Ethics Committee of the Canton of Zurich, Switzerland, and was carried out in accordance with the Declaration of Helsinki principles.

7.2.1. Subject Recruitment and Screening

IBS patients were recruited from the Department of Gastroenterology and Hepatology at the University Hospital Zurich, from the Department of Gastroenterology at the Clinic Stephanshorn St. Gallen and by public advertisement. All patients had been diagnosed with IBS at least three months prior to entering in the study. Appropriate procedures to exclude organic diseases were performed when not sufficiently recent or were inconclusive. Asymptomatic control subjects were recruited by public advertisement and matched with respect to age, oral contraceptives, educational level and marital status. Major criteria for eligibility were verified by a short telephone screening. Subjects were excluded if they reported any of the following: pre- or postmenopausal status, smoking, body mass index > 30, previous gastrointestinal surgery, inflammatory bowel disease, lactose intolerance, celiac disease, diabetes, use of psychotropic substances, intake of glucocorticoids.

Subsequently, a validated and computer-based diagnostic interview, the Composite International Clinical Interview according to DSM-IV (DIA-X, Wittchen & Pfister, 1997, APA, 2000) was conducted by a trained psychologist to assess current and/or previous psychopathology. To keep confounding factors low, subjects were excluded if they met criteria for eating disorders, post posttraumatic stress disorder (PTSD), substance abuse, psychosis or bipolar affective disorders. Moreover, in many of these diseases, bowel symptoms might be regarded as an epiphenomenon of the illness or the pharmacological treatment rather than an independent condition. The broadest categories of comorbid psychopathology in IBS, anxiety disorders and depression (i.e. major depression, dysthymia, panic disorder, agoraphobia, generalized anxiety disorder, specific phobia and social phobia), were included if subjects were free from psychopharmacological treatment. HPA axis activity differs according to gender (Kirschbaum et al. 1999), and due to the small sample size of male subjects (n=13), we decided to conduct psychobiological analyses only in women. Furthermore, IBS-U (n=4) patients reported atypical symptoms with low intensity and were also excluded. The recruitment process is depicted in FIGURE 6.

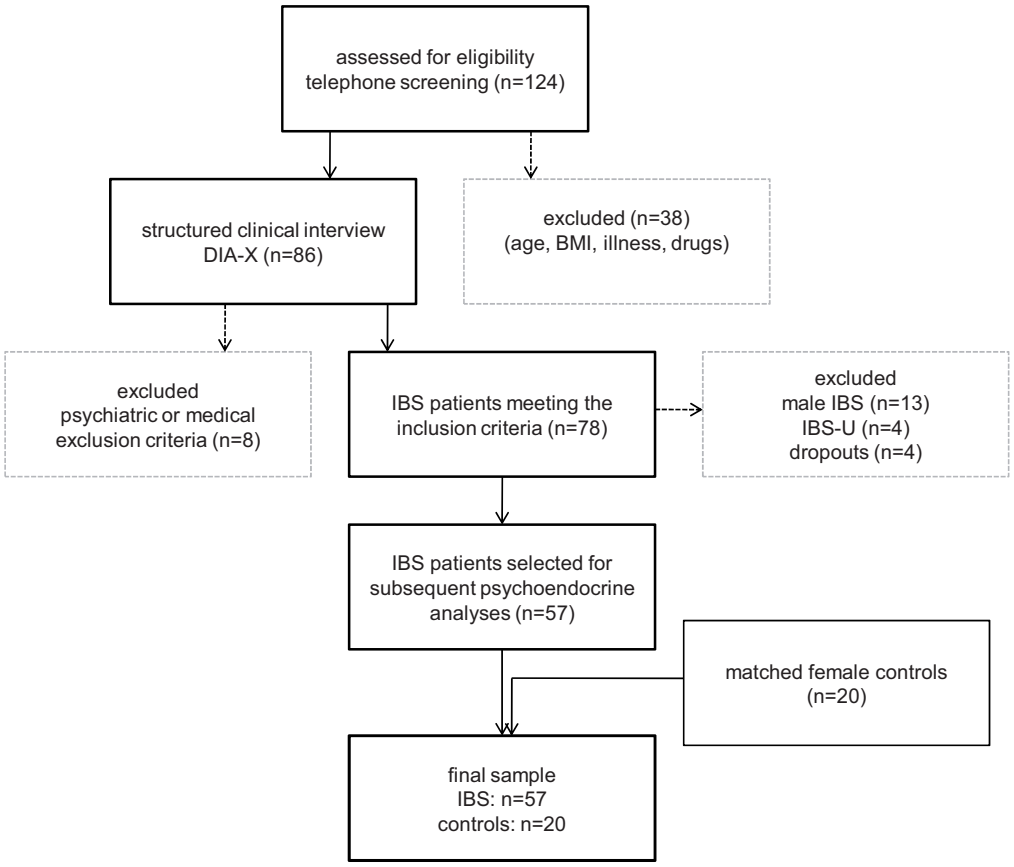

FIGURE 6: RECRUITMENT PROCESS OF THE STUDY

IBS diagnosis was verified using the IBS module (Rome III), and the co-existence of other gastrointestinal symptoms (e.g. reflux, nausea) was determined by the Gastro-Questionnaire (Leibbrand et al. 2002). Demographic and medical information including detailed gynecological history was documented for all participants. Subjects were informed about the course and aim of the study but were not given specific details of the experimental stress procedure. All participants gave written informed consent and were reimbursed for their time with CHF 200 after completion of the study.

7.2.2. Study Protocol

During the first visit, the structured diagnostic interview (Wittchen & Pfister, 1997) was conducted. Subjects received detailed information about the further course of the study and were acquainted with the handling of salivettes in order to collect saliva for morning and

diurnal cortisol profiles at home. A set of nine labeled salivettes and written instructions were handed out to the participants. Subjects were required to abstain from smoking, alcohol, caffeine and sports within 12 hours before both baseline saliva collection at home and the following study afternoon. Saliva samples for the assessment of free morning cortisol levels were measured at five time points: awakening, after 15, 30, 45, and 60 minutes. The diurnal course of the hormone was assessed by four saliva samples at 8:00, 11:00, 15:00, and 20:00 hours. The exact collection times were additionally recorded by written self-reports. Finally, participants were asked to send the saliva samples to our institute by regular mail the day after collection.

The study afternoon took part on a second day. Following a fast from 10:00 a.m., subjects reported to the lab of the Psychological Institute of Zurich at 12:30 p.m. For all women, the experimental day was scheduled for the late luteal phase (Kirschbaum et al. 1999), and to minimize circadian fluctuations of the HPA axis, it was conducted in the afternoon (Kudielka et al. 2003). At arrival, an intravenous catheter (Codan Medical AG, Baar, Switzerland) was inserted and kept patent with a lock. After an adaptation period of 30 minutes, subjects were asked to rate their stress level on a visual analogue scale (VAS 1) and the first saliva and blood samples (baseline) were obtained. Then, participants were introduced to the TSST (Kirschbaum et al. 1993, see below) and were subsequently told that they had five minutes to prepare. Afterwards, subjects rated again their perceived stress level (VAS 2), filled out a questionnaire assessing anticipatory stress appraisal (Gaab et al. 2005 & 2009, see below), and second saliva and blood samples were collected. Immediately thereafter, subjects were brought to the TSST room, where the stress task took place (10 minutes). After cessation of the stressor, participants gave their third stress rating (VAS 3) and further saliva and blood samples were drawn. To assess endocrine stress reactivity, further saliva and blood was obtained within one hour (+20, +30, +40, +60). During this time, subjects were allowed to read newspapers or magazines. At the end of the study afternoon, subjects were invited for a debriefing regarding the scope and methods of the TSST.

7.2.3. The Trier Social Stress Test (TSST)

The TSST is considered as a psychosocial stress paradigm that consists of performing an unscripted speech (5 minutes) and a mental arithmetic task (5 minutes) in front of an

audience. It has repeatedly been found that the TSST is able to induce endocrine and cardiovascular responses in 70 to 80% of subjects tested (Kirschbaum et al. 1993 & 1999). In order to introduce the participants to the TSST, they were brought to a room containing a panel of two observers and an ostentatious video camera. Subjects were told that a job interview would be simulated and that their performance would be videotaped for further analysis of their behavior. Subsequently, they were given five minutes to prepare their speech. After this anticipation period, participants were taken back to the TSST room, where they took part in the job interview followed by an unexpected and challenging arithmetic task.

7.2.4. Sampling Methods and Biochemical Analyses

Blood samples for measuring plasma ACTH were obtained via an indwelling catheter (Codan Medical AG, Baar, Switzerland) inserted about 30 minutes before obtaining the first sample. The blood samples were drawn into EDTA-coated tubes (Sarstedt, Sevelen, Switzerland) and immediately placed on ice until completion of the experiment. Subsequently, test tubes were centrifuged at 3600 rpm for 20 minutes at 4° C. Plasma was aliquoted and stored at -80° C until assayed. ACTH was measured using a chemiluminescence immunometric assay (DiaSorin, Saluggia, Italy). The lower detection limit was 2.0 pg/ml, intra-assay and inter-assay variabilities below 6.0 % and 14.0 %, respectively. Saliva for measuring cortisol was obtained by Salivette (Sarstedt, Sevelen, Switzerland) collection devices. The samples were stored at -20° C until biochemical analysis. Cortisol concentrations were measured by luminescence immunoassay (IBL, Hamburg, Germany) with a high sensitivity of 1.6pg/ml. Intra- and interassay variability were below 5% and 10%, respectively.

7.2.5. Assessment of psychometric data, (extra-) gastrointestinal symptoms and trauma

Additionally to the IBS module, the prevalence and intensity of gastrointestinal symptoms were assessed by the *Gastro-Questionnaire* (Leibbrand et al. 2002) containing a total of 27 items drawn from the Rome criteria. On the basis of the responses, 21 functional gastrointestinal disorders (FGID) can be categorized. Extra-gastrointestinal complaints were measured by the highly reliable *Screening for Somatoform Symptoms* (SOMS, Rief et al. 1997). A “somatic distress index” was determined by means of 53 items that assess organically unexplained physical symptoms on a five-point Likert scale.

During the study afternoon, subjective stress perception was repeatedly assessed by visual analogue scales (VAS). Immediately before the TSST, participants were required to fill out the 16-item transactional stress questionnaire *Primary Appraisal Secondary Appraisal* (PASA, Gaab et al. 2005). According to the transactional stress model by Lazarus & Folkman (1984), the PASA assesses relevant anticipatory cognitive processes during expectation of a stressful situation. A mean score for primary and secondary stress appraisal can be calculated. The difference between these two scales is labeled as the stress index.

Further testing was conducted using specific validated questionnaires: (1) Chronic stress was determined using a 57-item self-report instrument, the *Trier Inventory for the Assessment of Chronic Stress* (TICS, Schulz et al. 2004). Subjects were required to rate how often they had experienced the described stressful situations during the past year. (2) Interindividual stress susceptibility was assessed by the *Stress Reactivity Scale* (SRS, Schulz et al. 2005). The SRS measures the extent to which a person is disposed to exhibit immediate, intense and sustained emotional reactions in stressful situations. (3) The German translation of the *Perceived Stress Scale* (PSS, Cohen et al. 1983) was used to assess the degree to which everyday life situations during the preceding month were perceived as stressful. Items in the PSS are designed to determine how predictable, uncontrollable and overloading one's own life is considered to be. (4) The *Hospital Anxiety and Depression Scale* (HADS, Herrmann et al. 1995) was applied to detect state anxiety and depression. The HADS is accepted worldwide as a well validated and sensitive inventory. A sum score of ≥ 7 is regarded as a non-case. (5) Finally, childhood abuse and neglect experiences were assessed by the *Childhood Trauma Questionnaire* (CTQ, Bernstein & Fink 1998), a 28-item retrospective self-report measure. The CTQ consists of five subscales indicating emotional, physical and sexual abuse, and emotional and physical neglect. Cut-off scores are provided to classify abuse categorically.

7.2.6. Statistical Analyses

Data were analyzed using the SPSS statistical software package version 16.0 (SPSS, Chicago, Illinois, USA). All testing was two-tailed, with the significance level set at $p \leq 0.05$. Data were tested for normal distribution and homogeneity of variance using a Kolmogorov-Smirnov and Levene's test before statistical procedures were applied. Student's t-tests and one way ANOVAs were computed for comparison of the scale means of the questionnaires.

To test group and time effects for endocrine stress parameters (ACTH, cortisol), we performed general linear models with repeated measurements controlling for age, BMI and menstrual cycle. All reported results were corrected by the Greenhouse–Geisser procedure when the assumption of sphericity was violated. Post hoc LSD testing was performed. To assess associations between physiological parameters and psychological characteristics, bivariate (correlations) and multivariate methods (regression analyses) were used. For endocrine variables, areas under the response curve were additionally calculated with respect to increase (AUCi) using the trapezoidal method as an indicator for the physiological stress response (Pruessner et al. 2003). Unless otherwise indicated, all presented results are means and standard errors of means (SEM).

7.3. Results

7.3.1. Sample characteristics and psychometric results

A total sample of 77 women, 57 with IBS and 20 asymptomatic controls, was analyzed (FIGURE 6). As depicted in TABLE 8, the groups did not differ in sociodemographic characteristics, but IBS sufferers were more likely to report first-degree relatives with functional gastrointestinal disorders (FGID) and/or psychiatric diseases. On average, the patients had suffered for 6.6 (±5.4) years from IBS symptoms, had undergone 2.5 (±2.8) medical tests to rule out organic diseases, and had received the diagnosis 2.3 (±2.4) years ago.

According to the Rome III criteria, IBS patients were assigned as having IBS with diarrhea (IBS-D, n=22), IBS with constipation (IBS-C, n=14), or mixed IBS (IBS-M, n=21). Two thirds (59.6%, n=34) of the IBS group had no current Axis I comorbidity, while 5.3% (n=3) met criteria for generalized anxiety, 5.3% (n=5) for panic disorder, 7.1% (n=4) for social phobia, 5.3% (n=3) for specific phobia and 28.1% (n=16) were diagnosed with major depression or dysthymia. 15.8 % (n=9) met criteria for two or more current psychiatric comorbidities. The assessment of lifetime diagnosis revealed that 38.6% (n=22) had neverhad a psychiatric disorder, 36.8% (n=21) suffered from major depression or dysthymia, 8.8% (n=5) from one or more anxiety disorders and 15.8% (n=9) from mixed anxiety and depression. The IBS subtypes did not differ statistically with respect to the prevalence of concurrent psychiatric diagnosis (IBS-C: 28.6%, IBS-D: 45.5%, IBS-M: 42.9%). Subjects of

the control group had no current and no prior psychopathology. During the clinical interview, only one person reported sexual abuse. The CTQ highlighted that about 80% of participants reported none to low and 13.5% moderate experience of childhood abuse or neglect. 6.5% (n=5) showed severe emotional abuse/neglect and one person severe sexual and physical abuse. Patients and controls did not differ on CTQ subscales, except for emotional abuse (TABLE 8).

TABLE 8: SOCIODEMOGRAPHIC CHARACTERISTICS OF WOMEN WITH IBS AND CONTROLS (MEANS ± SEM OR % (N))

	IBS (n=57)	controls (n=20)
Age, years (range)	29.3 ± 0.98 (20-51)	29 ± 1.41 (23-43)
Body mass index, kg/m² (range)	21.01±0.28 (17.3-	21.34 ± 0.52 (18.3-
Married-partnered % (n)	75.4 (33)	70 (14)
Hormonal birth control % (n)	63.2 (36)	65 (13)
Family history of FGID % (n)	35.1** (20)	15 (3)
Family history of psychiatric disorder % (n)	35.1** (20)	5 (1)
CTQ emotional neglect	10.42 ± 0.55	9 ± 0.9
CTQ physical neglect	6.77 ± 0.3	5.95 ± 0.41
CTQ emotional abuse	8.8 ± 0.52*	6.85 ± 0.59
CTQ physical abuse	5.8 ± 0.31	5.34 ± 0.15
CTQ sexual abuse	5.67 ± 0.28	5.55 ± 0.3

n = valid cases, SEM = standard error of means, **p<0.01, *p<0.05

As expected, the IBS group reported more gastrointestinal, but also more extra-intestinal symptoms (SOMS) with considerable symptom distress. Furthermore, women with IBS revealed higher mean scores on overall psychometric measures including stress susceptibility (SRS), perceived stress (PSS), chronic stress (TICS), anxiety and depression (HADS). Group comparisons between controls and women with IBS were conducted stepwise: (a) for the total IBS sample (n=57), (b) after exclusion of current psychiatric comorbidity (n=34) and (c) after exclusion of prior (lifetime) comorbidity (n=22). Group differences between IBS and controls remained significant for all sum scores, except for the depression scale (HADS-D). Scale means (±SEM) and p-values are depicted in TABLE 9.

TABLE 9: PSYCHOMETRIC DATA, (EXTRA-) GASTROINTESTINAL SYMPTOMS (MEANS ± SEM)

	Controls	**IBS**		
	n=20	total sample n=57	(a) exclusion of current comorbidity	(b) exclusion of lifetime-comorbidity
			n=34	n=22
HADS-A	2.85±0.55	7.23±0.51**	6.32±0.58**	5.64±0.66*
HADS-D	2.15±0.56	3.8±0.45*	3.09±0.51	2.36±0.56
PSS	10.67±1.16	17.12±0.78**	15.26±0.79*	14.68±0.89*
SRS	55.5±1.97	64.54±1.21**	62.53±1.68**	61.27±1.7*
TICS	10.75±1.36	20.81±1.02**	18.52±1.03**	16.67±1.12*
Somatic distress	2.45±0.75	15.93±0.87**	14.01±1.1**	13.87±1.27**
GI symptoms (n)	0.2 ±.0.09	7.84±0.4**	7.19±0.41**	7.14±0.49**
Intensity of GI-	2.17±0.89	26.2±1.33**	23.48±1.53**	21.95±1.96**
FGID (n)	0	2.18±0.12**	2.06±0.15**	1.86±0.17**

n = valid cases, SEM = standard error of means, **p<0.01, *p<0.05

7.3.2. Morning and diurnal free salivary cortisol profiles

Considering the total sample, IBS patients and healthy controls showed a significant increase in free salivary cortisol within the first 30 minutes after awakening (ANOVA time effect: $F[1.98]=3.3$; $p<0.05$). However, no difference in the morning cortisol profile was found between the groups (ANOVA time x group: $F[1.99]=1.04$; $p=0.36$). Subsequently conducted analyses between controls and IBS patients without psychiatric comorbidity revealed that patients started off with significantly higher levels of cortisol at the time of awakening ($F(38)=2.41$; $p<0.03$; FIGURE 7). Moreover, controls showed a more pronounced cortisol increase (AUCi=22.85±5.2) than IBS patients (AUCi=12.8±4.1), although the difference was not significant.

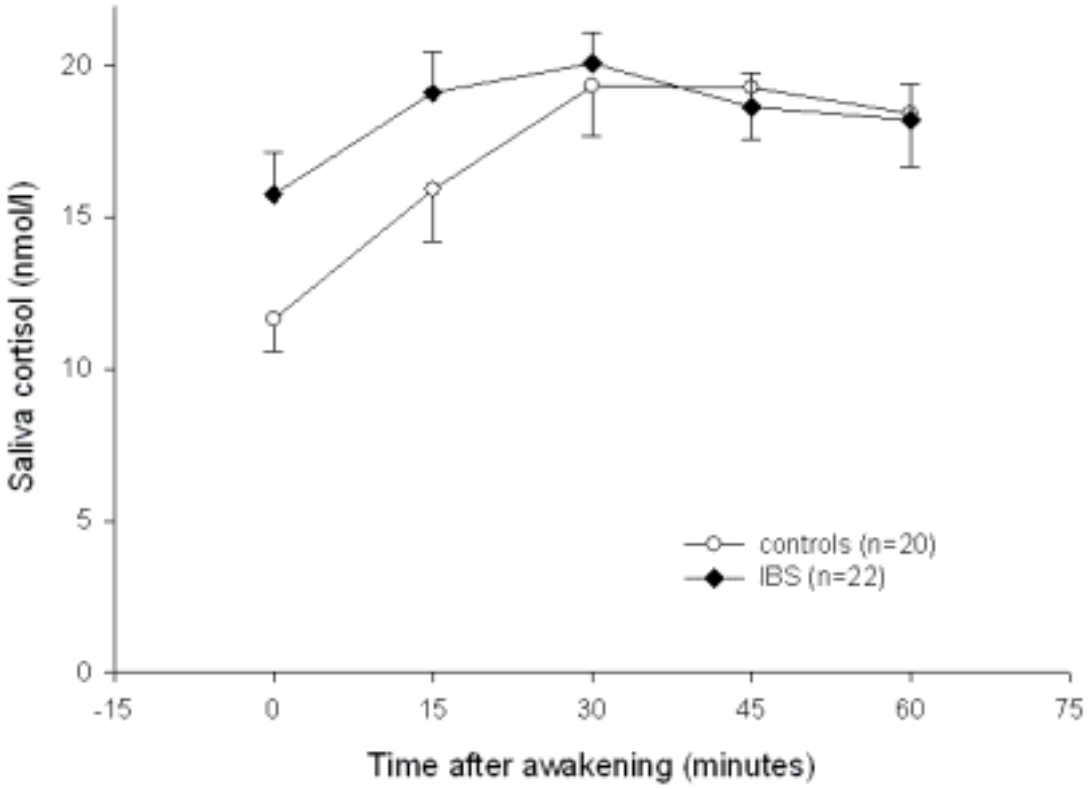

FIGURE 7: FREE SALIVARY CORTISOL MORNING PROFILE (MEANS ± SEM) IN WOMEN WITH IBS WITHOUT HISTORY OF PSYCHIATRIC COMORBIDITY (N=22) AND FEMALE CONTROLS (N=20).

Additionally, we explored the group differences in salivary cortisol increase after awakening between the IBS subtypes (IBS-C, IBS-D, IBS-M) and controls. ANOVA with repeated measures indicated a significant main effect of time ($F\ [4]=15.1$; $p<0.001$) and a trend towards a significant group x time effect ($F\ [6.73]=2.1$; $p=0.063$). ANOVA of AUCi values for cortisol awakening increase identified a significant difference ($F\ [3]=3.3$; $p<0.029$) between IBS-D and controls (FIGURE 8).

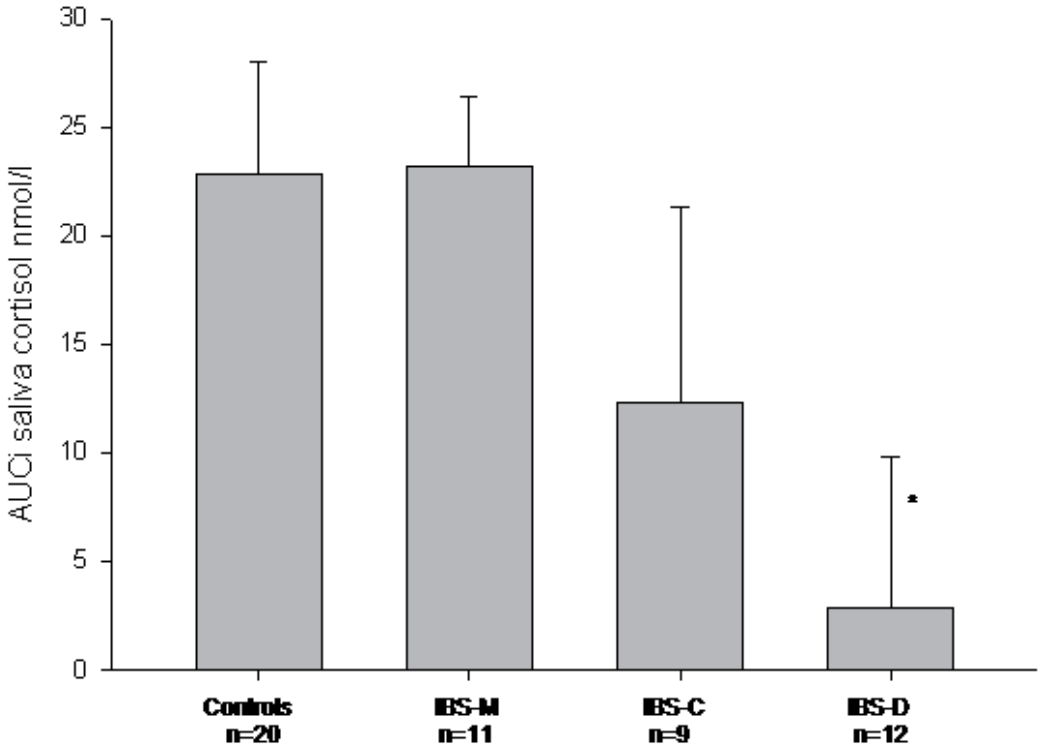

FIGURE 8: CORTISOL AWAKENING RESPONSE DEPICTED AS AREA UNDER THE RESPONSE CURVE WITH RESPECT TO THE INCREASE (AUCI) IN WOMEN WITH IBS WITHOUT PSYCHIATRIC COMORBIDITY AND CONTROLS (MEANS ± SEM). * P=0.024: IBS-D VERSUS CONTROLS.

No group differences were found for diurnal (8:00, 11:00, 15:00, 20:00 hours) cortisol profiles even after exclusion of current or prior psychiatric comorbidity or the consideration of IBS subtypes. All participants showed comparable diurnal decline in cortisol until they reached similar minimal levels in the evening.

7.3.3. Stress response to the TSST

In our study, the TSST effectively increased physiological (cortisol, ACTH) and psychological stress measures (PASA, VAS) in both women with IBS and controls (time effect; $p<0.01$).

7.3.3.1. Biological stress reaction

Our total sample of IBS patients and healthy controls exhibited significant increases in free salivary cortisol and plasma ACTH levels (ANOVA time effect: $F[2.39]= 6.25$; $p<0.001$ / $F[1.42]=16.15$; $p<0.001$) in response to the TSST, indicating a large, though comparable, activation of the HPA axis. As with psychometric data, stepwise analysis was performed. After exclusion of subjects with psychiatric comorbidity a significant time x group effect for cortisol was observed ($F[2.34]= 3.1$; $p=0.043$, see FIGURE 9) but not for ACTH ($F[1.8]= 0.24$; $p=0.76$). However, ACTH secretion in response to the TSST was slightly attenuated among IBS patients without psychiatric comorbidity compared to controls (FIGURE 10).

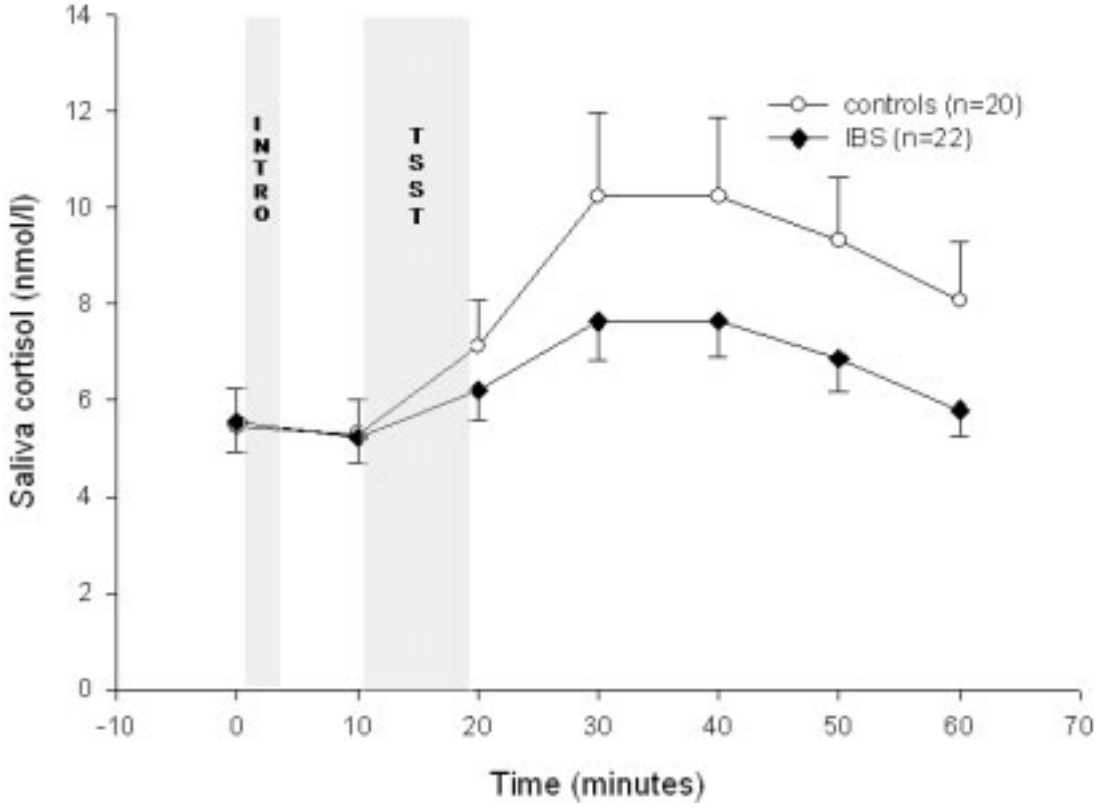

FIGURE 9: FREE SALIVARY CORTISOL LEVELS IN RESPONSE TO THE TSST (MEANS ± SEM) IN WOMEN WITH IBS WITHOUT CURRENT OR PRIOR PSYCHIATRIC COMORBIDITY (N=22) AND FEMALE CONTROLS (N=20).

Post hoc comparisons for cortisol highlighted a steeper increase in controls compared to women with IBS within the first 20 minutes after the introduction to the TSST (AUCi: $t[26.28]=2.02$, $p<0.05$). Subsequently, both groups remained at the maximal cortisol level for a further 10 minutes and then showed a parallel decline. Post hoc analyses for ACTH indicated a trend towards an attenuated maximal response to the TSST (+30 minutes) ($t[35]=1.83$; $p=0.075$) in IBS patients and documented significantly lower ACTH levels at the end of the recovery period (+60 minutes) ($t[34]= =2.17$; $p=0.037$) compared to healthy controls.

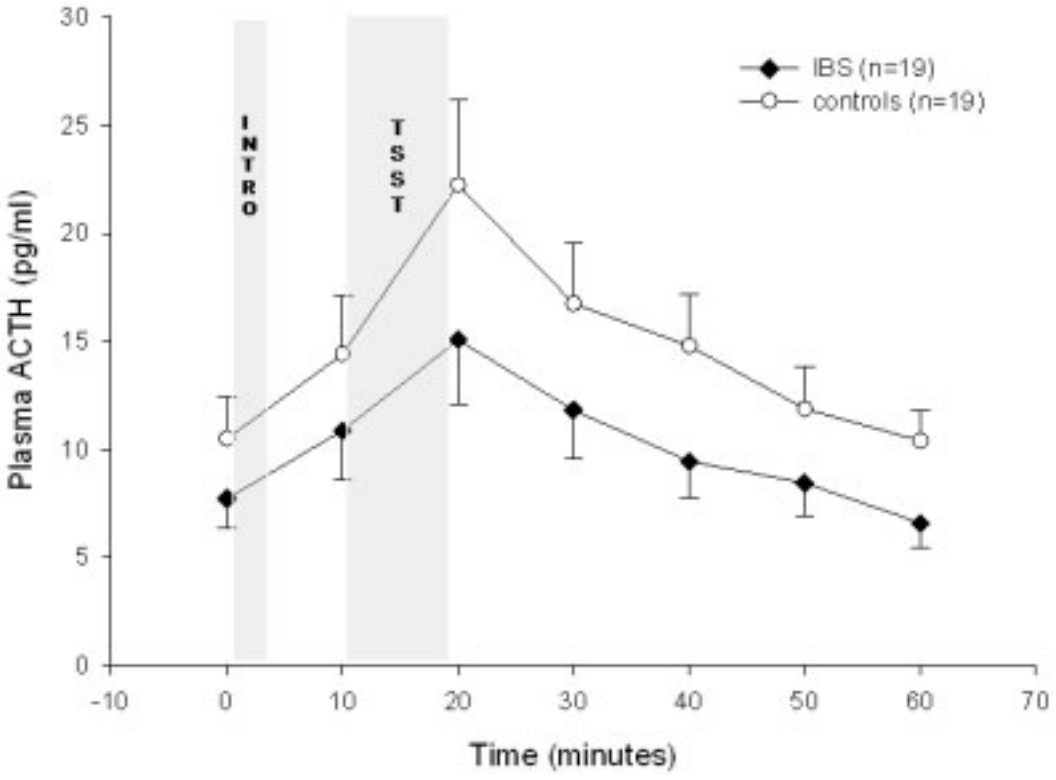

FIGURE 10: PLASMA ACTH LEVELS IN RESPONSE TO THE TSST (MEANS ± SEM) IN WOMEN WITH IBS WITHOUT CURRENT OR PRIOR PSYCHIATRIC COMORBIDITY (N=19) AND FEMALE CONTROLS (N=19).

We analyzed endocrine stress response with respect to the three IBS subtypes (IBS-C, IBS-D and IBS-M). Repeated measurement ANOVAS showed no group difference for cortisol or ACTH levels in response to the TSST ($F[7.19]=1.27$; $p=0.27$ / $F[4.27]=0.41$; $p=0.82$). This result remained stable after the exclusion of psychiatric comorbidity. Group comparisons of AUCi values for cortisol increase following the TSST revealed that IBS-C patients (without comorbidity) showed a blunted response compared to controls ($p<0.05$).

7.3.3.2. Anticipatory stress appraisal and psychological stress response

Women with IBS reported higher perceived stress levels in anticipation (VAS 2: $p<0.01$; PASA: $p<0.05$) and in response (VAS 3: $p<0.01$) to the TSST compared to the controls. No significant group difference was observed at baseline (VAS 1: p= n.s.). Following the exclusion of psychiatric comorbidity, this finding remained significant for the PASA ($p<0.05$) but not for VAS ratings (VAS 2: $p<0.07$, VAS 3: $p<0.09$). TABLE 10 summarizes the results and depicts mean values (±SEM) of anticipatory stress appraisal (PASA) and stress ratings at baseline (VAS 1), before (VAS 2) and after (VAS 3) the TSST.

TABLE 10: ANTICIPATORY STRESS APPRAISAL (PASA) BEFORE THE TSST AND SUBJECTIVE STRESS RATINGS AT BASELINE (VAS 1), BEFORE (VAS 2) AND AFTER (VAS 3) THE TSST, P-VALUES INDICATE DIFFERENCES BETWEEN IBS AND CONTROLS. (MEANS ± SEM).

	Controls (n=20)	IBS (n=57)	IBS-C (n=14)	IBS-D (n=21)	IBS-M (n=22)
PASA “primary appraisal”	2.5 (±0.22)*	3.1 (±0.13)	3.4 (±0.25)	2.9 (±0.24)	3.0 (±0.2)
PASA“secondary appraisal”	3.7 (±0.12) *	3.3 (±0.11)	3.1 (±0.22)	3.4 (±0.16)	3.2 (±0.2)
PASA “stress index”	-2.5 (±0.61) *	-0.4 (±0.42)	0.4 (±0.88)	-1.1 (±0.69)	-0.3 (±0.67)
VAS 1 (baseline)	1.37(±0.48)	2.1±(0.32)	2.34±(0.73)	1.3(±0.5)	2.76(±0.47)
VAS 2 (pre stress)	3.87(±0.61)**	5.8(±0.37)	6.03(±0.75)	5.74(±0.71)	5.74(±0.51)
VAS 3 (post stress)	3.12(±0.56)**	5.2(±0.38)	5.41(±0.8)	5.23(±0.71)	4.92(±0.52)

n = valid cases, SEM = standard error of means, **p<0.01, *p<0.05

7.4. Discussion

The present study set out to investigate basal and stimulated HPA axis activity and psychological stress reactivity in individuals with IBS while taking their predominant bowel habits and psychiatric comorbidity into consideration. An intact circadian fluctuation of basal HPA axis activity was observed in healthy controls as well as in IBS patients. Both groups showed a significant increase in free salivary morning cortisol levels within the first half hour after awakening followed by a steady decline, which reached a minimum in the evening. After the exclusion of current or prior psychiatric comorbidity, a significant group difference was detected, with IBS patients showing higher awakening cortisol levels than controls. However, post hoc analyses revealed that particularly women with IBS-D exhibited high cortisol levels at awakening, and subsequently, nearly no morning increase. Elevated morning cortisol in IBS patients compared to healthy individuals has previously been reported, although in these studies, participants were not assigned to IBS subtypes (Patacchioli et al. 2001), and nor were any differences between IBS subtypes and controls detected (Eriksson et al. 2008, Chang et al. 2009). Interestingly, 80% of these IBS samples consisted of IBS-D and IBS-A patients (Eriksson et al. 2008, Chang et al. 2009), whereas IBS-A was considered as an "alternator", which was not able to meet the diagnostic criteria for either IBS-C or IBS-D and included both diarrhea and constipation. Thus, it is possible that IBS-A patients mainly suffered from diarrhea at the time of data assessment. In conclusion, the present findings indicate that IBS-D patients without psychiatric comorbidity are characterized by basal HPA axis hyperactivity, which results in substantially elevated morning cortisol levels. This hypothesis is supported by results from animal studies suggesting an association between hyperactivity of CRH/CRH_1 signaling increased motility and diarrhea (Taché et al. 2005).

In response to the psychosocial stressor, the present findings indicate a reduced HPA axis reactivity in IBS patients without psychopathology compared to healthy controls. Prior to the TSST, the IBS group showed slightly lower ACTH levels, a less pronounced increase in response to the stressor, and significantly lower ACTH levels during recovery. An attenuated ACTH secretion is perhaps the consequence of chronically enhanced endogenous CRH release, which in turn results in a reduced number or sensitivity of pituitary CRH receptors. In addition, pure IBS patients without psychopathology showed blunted cortisol reactivity in response to the TSST. It is conceivable that attenuated ACTH levels are accompanied by

blunted cortisol secretion. However, the suppression was more pronounced for cortisol than for ACTH release. Therefore, we assume that additional mechanisms are involved in the hypoactivity of the adrenals, such as reduced sensitivity or number of glucocorticoid receptors. The timing of the cortisol and ACTH peaks, as well as the onset of negative feedback in response to the TSST, was similar in both groups, suggesting an intact HPA feedback mechanism in IBS patients. This assumption is supported by the observation of comparable cortisol suppression in controls and IBS patients following dexamethasone intake (Böhmelt et al. 2005, Dinan et al. 2006).

Our finding indicating a downregulated HPA axis reactivity is in line with Böhmelt et al. (2005), who documented lower cortisol and ACTH secretion following CRH challenge. However, other work groups have reported HPA axis hyperreactivity following pharmacological (Fukudo et al. 1998, Dinan et al. 2006) or combined psychological and visceral stress (Posserud et al. 2004). To some extent, the inconsistency in previous studies might be explained by differing methodology, such as the type of stressor. For instance, IBS patients probably estimate the relevance of rectal distention differently to healthy controls (Posserud et al. 2004, Dickhaus et al. 2003, Dorn et al. 2007). Only one study has investigated the HPA axis reactivity in IBS using a psychosocial stress test and found no difference between patients and controls in their physiological stress reactivity (Elsenbruch et al. 2006). However, several factors may have contributed to those findings. In contrast to our study, previous examinations did not distinguish between male and female IBS patients, failed to assess psychiatric comorbidity, or used a non-specific procedure, did not control for early trauma experience and diagnosed IBS according to classifications other than Rome III.

HPA axis dysregulation has been associated with early trauma and/or psychiatric disorders (Heitkemper et al. 2000, 2001 & 2008, Ehlert et al. 2001). Therefore, it is conceivable that IBS-specific HPA axis alterations are concealed by comorbid psychopathology. Nevertheless, most previous studies investigating HPA axis activity in IBS patients did not control for psychiatric comorbidity with appropriate methodology. While four work groups did not mention psychiatric conditions (Fukudo et al. 1998, Heitkemper et al. 1996, Patacchioli et al. 2001, Posserud et al. 2004), another four excluded psychopathology using non-specific procedures (Elsenbruch et al. 2001, 2004 & 2006, Dickhaus et al. 2003, Dinan et al. 2006, Eriksson et al. 2008). Only two work groups used a standardized diagnostic interview and

controlled for trauma experience (Böhmelt et al. 2005, Chang et al. 2009). In the present study, we assessed current and prior psychopathology as well as trauma with specific and well validated instruments (Wittchen & Pfister, 1997, Bernstein & Fink, 1998). Subsequently, stepwise analyses were conducted to determine the influence of these factors on the psychobiological stress response in IBS patients. Thus, the reduced HPA axis reactivity in IBS patients without psychopathology observed through this approach cannot be attributed to HPA axis dysregulation due to early trauma or psychopathology. Notably, HPA axis hypoactivity was associated with other stress-related conditions (Raison & Miller, 2003, Heim et al. 2008) and somatoform disorders including chronic fatigue syndrome (Van den Eede et al. 2007, Nater et al. 2008, Van Houdenhove et al. 2009), fibromyalgia (Crofford et al. 1994, Tanriverdi et al. 2007), and chronic pelvic pain (Ehlert et al. 1999, Heim et al. 1997 & 1999). Further studies are needed to explore whether FGID and other FSS show similar psychobiological alterations in terms of HPA axis activity.

The heterogeneity of IBS diagnostic criteria and IBS subtype assignment might also contribute to the inconclusive findings of the HPA axis activity in IBS patients (Esryd et al. 2007, Dorn et al. 2009). Previous reports provide evidence that the activation of the HPA axis either triggers or inhibits numerous gastrointestinal functions, including motility and gastrointestinal secretion (Fukudo, 2007). Thus, it is conceivable that the HPA axis regulation in IBS patients is associated with their predominant bowel habit. So far, data about HPA axis (re)activity in IBS subtypes are scarce. In addition to the above-discussed enhanced basal morning cortisol levels in IBS-D patients, we found that blunted HPA axis reactivity to the TSST was most pronounced in women with IBS-C. Elsenbruch et al. (Elsenbruch & Orr, 2001) have also reported subtype-specific cortisol reactivity, but in response to a standardized meal. Women with IBS-C exhibited lower postprandial cortisol levels compared to women with IBS-D. Nevertheless, the assumption that HPA axis hyper- or hypoactivity in IBS patients is associated with their predominant bowel habit remains to be clarified in further studies with larger sample sizes.

In contrast to the biological hyporeactivity in response to the TSST, we observed increased subjective stress perception in women with IBS compared to healthy controls. Enhanced emotional stress reaction in IBS patients following a psychological stress paradigm has been documented previously (Elsenbruch et al. 2001 & 2006, Dickhaus et al. 2003, Posserud et al.

2004). However, to our knowledge, no prior study has assessed anticipatory cognitive stress appraisal. Although we found higher pre- and post-stress ratings, the antecedent stress appraisal differentiated better between IBS patients and controls. Besides situation-specific stress measures, we assessed general ("trait") stress perception with several validated questionnaires (Cohen et al. 1983, Schulz et al. 2004 & 2005) and observed an increased disposition for general stress susceptibility in female IBS patients compared to control women. This result is in line with the assumption of reduced thresholds for stress coping in IBS patients (Fukudo, 2007). Given that cognitive stress appraisal has been shown to influence visceral perception (Dickhaus et al. 2003, Posserud et al. 2004), our finding of dispositional stress susceptibility in IBS may have important clinical implications and provides explanatory value for psychological mechanisms underlying cognitive-behavioral treatment interventions (Blanchard et al. 1993, Toner et al. 2000, Kearney et al. 2008).

We were able to identify differences in basal and stimulated HPA axis activity between IBS patients without psychopathology and controls. However, another 40% of the women in our IBS total sample met the criteria for one or more psychiatric disorders. Similar prevalence rates of anxiety and depression in IBS have been reported by previous studies (Masand et al. 1995, Hillilä et al. 2007). The influence of comorbid psychiatric diagnosis on HPA axis activity in IBS patients is poorly understood. One may assume that a comorbid depression leads to basal hypercortisolism and normal cortisol secretion following stress exposure, as it has been reported for subjects with isolated major depression (Heim et al. 2008). The current findings suggest that the interaction of IBS and psychiatric disorders is more complex and may be a result of a variety of endocrinological dysregulations rather than one specific HPA axis dysfunction. We observed similar basal and slightly but non-significantly increased stimulated ACTH levels in women with IBS and concurrent depression compared to controls (data not reported). The small group of IBS patients with comorbid anxiety exhibited a significantly stronger cortisol increase following the TSST as compared to controls and subjects with IBS without psychopathology. This result can possibly be explained by the fact that most women in the anxiety group met the criteria for social phobia, which has shown to be associated with enhanced cortisol response to psychosocial stress (Condren et al. 2002, Van West et al. 2008, Roelofs et al. 2009). In conclusion, we assume that in our

heterogeneous sample of psychiatric comorbidity, endocrine dysregulations canceled each other out.

Our study has several strengths, including the differentiated assessment of current or prior psychiatric comorbidity by using a structured clinical interview. Moreover, several major confounding variables were excluded (e.g. organic diseases, drugs, several psychiatric conditions) or controlled for (e.g. menstrual cycle, oral contraceptives, age, BMI, study time, bowel habit, food intake, trauma experience). The HPA axis activity was assessed through interval sampling, through two endocrine parameters (cortisol, ACTH) and under two different conditions (basal and stimulated). Finally, psychological stress was accurately assessed using several standardized instruments, allowing a differentiated conclusion about stress perception in IBS patients.

However, the results of the present study need to be interpreted in light of the following limitations. First, the findings document the psychobiological stress reaction of relatively young female IBS patients. Whether men or older subjects with IBS would show similar psychobiological stress patterns, still needs to be investigated. Second, we investigated the HPA axis reactivity to a psychosocial stressor, while a different reaction might be expected when using a visceral or pharmacological stressor. However, the application of a psychological stressor seems more equivalent to a stress experience in a subject's everyday life. Third, the current study classified patients according to the Rome III criteria, which have been shown to differ from the Rome II classification (Esryd et al. 2007). It is conceivable that some patients might fall into another subtype category when assigned according to Rome II or Rome III, respectively. However, Dorn and colleagues (Dorn et al. 2009) have reported a high overall agreement level (86.5%; κ 0.79) between these two classification guidelines. Fourth, our IBS sample showed a short disease history. Distinct response patterns might have been detected in chronic patients and in those experiencing greater pain. Fifth, the collection time of saliva samples for the basal HPA axis profile was controlled using self-report measures, and therefore compliance cannot be objectively verified. Finally, due to the small sample size, the validity of our analyses with respect to IBS subtypes should be viewed with caution and examinations in larger patient samples are needed.

To our knowledge, the present study is the first to investigate combined basal and stimulated HPA axis activity in IBS patients using a validated psychosocial stress paradigm and controlling for current and prior psychiatric comorbidity as well as predominant bowel habits. Moreover, this is the first study to assess psychological stress in individuals with IBS using several standardized situation-specific and general stress measures. The differences in the outcomes of the present study when compared to particular previous findings might be related to the characteristics of the study sample including psychopathology and methodology, such as type and intensity of the stressor. In summary, three main findings emerged from the current investigation: (1) Women with IBS without psychiatric comorbidity show blunted endocrine but exacerbated psychological stress response to a psychosocial stressor. (2) Dysregulated HPA axis activity is associated with the predominant bowel habit. (3) Enhanced stress susceptibility is a disposition of female IBS patients independent of comorbid psychopathology.

In recent years, the role of the HPA axis in IBS patients has gained in interest. Additionally, findings suggest that the HPA axis regulation is also associated with gut immune activity (Barbara et al. 2002, Chadwick et al. 2002, Dinan et al. 2006). Moreover, the development of promising chemical agents acting on CRH receptors has been promoted (Sagami et al. 2004, Martinez et al. 2006). Thus, a better understanding of the neuroendocrinological mechanisms in IBS patients is of substantial importance, and further studies in this area are needed.

8. General Discussion

Stress has been suggested as a central pathophysiological factor in FGID. Numerous studies have provided evidence for high psychosocial stress in individuals with FGID (chapters 3.6.3-3.6.6), and the influence of acute laboratory stress on bowel functions has been well established (chapter 3.6.2). However, there are two main gaps in the current knowledge about the association between stress and FGID. The operationalization of stress has often been vague and unidimensional, neglecting subjective appraisal. Moreover, the psychophysiological mechanisms linking stress and gastrointestinal symptoms are poorly understood. For this reason, we proposed (1) to describe the association between FGID and psychological stress based on a validated theoretical conceptualization, and (2) to explore HPA axis activity – an important mediator of the brain-gut interaction – in a sample of IBS patients.

8.1. Summary of the results of Study I and Study II

Below, a brief summary of the main findings of the two empirical studies (study I & II) will be given. Subsequently, these results will be discussed in terms of their clinical relevance and their limitations.

8.1.1. Psychological Stress and Self-Reported FGID

Adopting an internet-based survey, we assessed the association between psychological stress and self-reported gastrointestinal disorders in students. Nearly two thirds of the participants reported at least one FGID. This finding is in line with Norton et al. (1999), who investigated a similar population and reported FGID in about 50% of the students. This was the first study to assess the role of stress in FGID based on a validated multidimensional stress concept including chronic stress, inter-individual stress reactivity and coping strategies. Group comparisons between individuals with and without gastrointestinal symptoms revealed significant differences concerning all stress measures. In addition, we identified female sex, workload, work discontent, social overload, negative coping, and increased stress reactivity as main predictors for the occurrence of functional gastrointestinal symptoms. In conclusion, we found that self-reported functional gastrointestinal complaints are common in apparently

healthy students and that several stress measures (chronic stress, stress reactivity, coping ability) are strongly associated with the appearance of these symptoms.

8.1.2. Altered psychobiological stress responsiveness to psychosocial stress in women with irritable bowel syndrome

Women with IBS and matched controls were compared with respect to their diurnal and stimulated HPA axis activity. Patients were diagnosed according to the Rome III criteria and assigned to an IBS subtype (IBS-D, IBS-C or IBS-M). In all participants, psychiatric comorbidity was assessed using a validated clinical interview (DIA-X, Wittchen & Pfister, 1997). In the IBS sample, 40% met criteria for at least one current psychiatric disorder, whereas 61% reported prior psychopathology. All control women were free from any diagnosis.

The analyses of the total sample revealed no differences between IBS and controls in terms of HPA axis (re-)activity. Since we assumed that psychiatric comorbidity conceals a potential effect, subsequent calculations were conducted in "pure" IBS patients. We detected intact circadian rhythmicity of unstimulated salivary cortisol levels in both controls and women with IBS. Three main findings emerged from the examination of the HPA axis (re)activity. Firstly, compared to controls, IBS patients showed blunted endocrine, but exacerbated psychological stress response to the TSST. Secondly, an association between dysregulated HPA axis activity and IBS subtype was observed, since IBS-D and IBS-C patients differed from controls in their basal and stimulated cortisol levels. Thirdly, the IBS group reported enhanced general stress perception indicating increased dispositional stress susceptibility. In contrast to the biological data, the differences between IBS patients and controls in terms of psychological variables were independent of psychiatric comorbidity.

8.2. Integration of current findings

In the following sections, the main findings of the current thesis will be embedded in the theoretical background (chapter 2-4).

Given the fact of female preponderance in most FGID (Corazziari, 2004), it is not surprising that in our first study we identified female sex as a significant predictor for the number of functional gastrointestinal symptoms. However, to date, not much is known about gender

differences in psychosocial variables such as stress perception and coping (Chang et al. 2006a). Therefore, we conducted subsequent analyses and detected significantly higher scores for all stress scales in women compared to men with and without FGID (data not shown). Interestingly, previous studies reported gender differences in terms of visceral processing with female IBS patients, showing decreased pain thresholds and enhanced activation of limbic and paralimbic brain regions compared to their male counterparts (Ragnarsson et al. 1999, Naliboff et al. 2003, Mayer et al. 2005). The authors interpret their findings as gender-specific cerebral processing of aversive visceral stimuli. Taken together, these results may indicate that stress perception is a mediator variable for female preponderance in FGID.

The present finding of an association between gastrointestinal symptoms and work-related stress has been previously reported in Scandinavian employees (Krantz et al. 2005). Moreover, in Korean high school students, substantially higher prevalence of IBS was reported in individuals with high levels of study-related stress compared to those with low stress (Son et al. 2009). However, this association might not be specific for FGID, since several bodily complaints including sleep disturbances, headache, back pain and cardiovascular problems have been associated with problems at work (Hammar et al. 1994, Collins et al. 2005, Krantz et al. 2005). According to the bio-psycho-social model (chapter 3.8), we assume that work-related stress represents a chronic stressor that may trigger the onset or the maintenance of FGID in predisposed individuals.

Similarly, the observed relationship between gastrointestinal symptoms and the perception of interpersonal stress is in line with previous findings. A considerable lack of perceived interpersonal support and high interaction difficulties have been reported in patients with FGID (Herschbach et al. 1999, Lackner et al. 2005, Jones et al. 2006b). Taking into account that FGID have been associated with several insecure-avoidant personality traits (see chapter 2.5.3), including low assertiveness, high trait anxiety, hostility and social inhibition (Whitehead et al. 1980, Toner et al. 1992, Lackner et al. 2005, Farnam et al. 2008), we suggest that individuals with FGID exhibit lower emotional competence and higher interpersonal conflict avoidance. This hypothesis is supported by the finding of Porcelli et al. (1999). The authors reported high levels of alexithymia – which describes the paucity of

fantasy and the limited ability to identify and verbally express emotions – in individuals with IBS.

In our student sample, high levels of self-reported gastrointestinal symptoms were associated with the disposition to use negative coping strategies. Negative coping strategies (mostly illness related) in several groups of FGID patients have been documented previously (Xiong et al. 2004, Jones et al. 2006b, Seres et al. 2008). This result is not surprising given that the ability to cope with stressful situations has been suggested to be essential for individual health and well being (Folkman, 1997, De Kloet et al. 2005). Notably, cognitive schemata play a primary role in the individual coping process (Wilhelmsen, 2000). Interesting enough, negative schemata in the form of hypochondriac beliefs, disease phobia and bodily preoccupation have been observed in patients with IBS (Gomborone et al. 1995). In conclusion, increased stress perception and maladaptive coping behavior in subjects with FGID might be mediated by dysfunctional cognitive patterns, similar to the concepts of "automatic thoughts" or "irrational beliefs" described by Ellis (1962) and Beck (1976) in patients with depression and anxiety. This hypothesis might suggest a high prevalence of psychiatric disorders in FGID and indicates that cognitive therapies may be beneficial for at least a subgroup of patients.

To the best of our knowledge, no previous study has assessed inter-individual stress reactivity in FGID. In both empirical studies, we found a strong association between high general stress reactivity and functional gastrointestinal symptoms. These findings indicate that individuals with FGID are disposed to react in challenging situations with disadvantageous patterns characterized by an immediate, intense and long-lasting psychobiological stress response. According to McEwen's (1998) stress concept, the sustained activation of regulatory physiological processes results in overstraining or underactivity of the allostatic systems (allostatic load) and ultimately contributes to physical symptoms and disease. Thus, it is conceivable that high dispositional stress reactivity in combination with the occurrence of stressful life events or chronic ongoing stress triggers FGID in vulnerable individuals.

In the second empirical study, the focus was shifted to physiological stress measures. A major problem investigating the HPA axis activity is the amount of confounding variables including sex, age, drugs, trauma experience and comorbidity. Therefore, strict selection criteria were

defined for our empirical study II. The most important confounding factors might be psychiatric disorders, since they have been associated with HPA axis disturbances (Ehlert et al. 2001). In contrast to most previous studies, we assessed current and prior psychopathology adopting a structured clinical interview (DIA-X, Wittchen & Zaudig, 1997). In line with previous epidemiological findings, in the present sample, prevalence rates of 40% current and 60% lifetime anxiety and/or depression were found (Hillilä et al. 2007, Whitehead et al. 2007). Notably, differences in HPA axis activity between IBS patients and controls could only be detected after the exclusion of patients with a current and prior psychiatric diagnosis. This observation emphasizes that it is essential to consider psychiatric comorbidity in FGID research. However, we were not able to determine endocrine differences between IBS patients with different psychiatric diagnoses. We assume that concurrent psychopathology in IBS may result in a variety of endocrinological dysregulations (higher or lower HPA axis activity), which ultimately "cancel each other out". Nevertheless, this hypothesis is based on a small sample with substantial multi-comorbidity. Thus, further studies in this area are needed.

In line with previous findings, further analyses revealed intact diurnal HPA axis rhythmicity (Chang et al. 2009, Böhmelt et al. 2005) and increased awakening cortisol levels (Patacchioli et al. 2001, Eriksson et al. 2008, Chang et al. 2009) in "pure" IBS patients compared to controls. Post hoc analyses of our data revealed that particularly the subtype IBS-D showed high cortisol levels immediately after awakening, but not IBS-M and IBS-C patients. As yet, no study has assessed the association between IBS subtype and cortisol morning profile adopting comparable methodology. However, two previous studies that reported increased morning cortisol levels in IBS investigated mainly IBS-D and IBS-A (80%) patients (Eriksson et al. 2008, Chang et al. 2009). Since subjects with IBS-A suffer from both diarrhea and constipation, they were possibly diarrhea-predominant at the time of data assessment. Further evidence indicating an association between hypercortisolism and symptoms of diarrhea come from studies showing that the intracerebroventricular injection of CRH enhances colonic motility and decreases intestinal and colonic transit time, whereas the exogenous administration of a CRH antagonist abolishes this effect (Sagami et al. 2004, Taché et al. 2005, Fukudo, 2007, see chapter 3.6.2). Moreover, we observed nearly no morning increase in cortisol (ACR) in IBS-D patients. Wust et al. (2000) proposed that it may

be useful to distinguish between “responders” and “non-responders” (ACR below 2.5nmol/l), although there is no agreement about the amount of ACR that is associated with psychological well-being and health. Nevertheless, the present findings indicate an association between predominant bowel habit and basal HPA axis activity in women with IBS.

In line with Böhmelt et al. (2005), reduced HPA axis reactivity in response to the psychosocial stressor (TSST) was observed in IBS patients without psychopathology compared to healthy controls. Our IBS group showed slightly lower ACTH levels prior to the TSST, subsequently a less pronounced increase, and finally significantly lower ACTH levels during recovery. An attenuated ACTH secretion might be the consequence of chronically enhanced endogenous CRH release, which in turn results in a reduced number or sensitivity of pituitary CRH receptors. Furthermore, “pure” IBS patients showed significantly blunted cortisol secretion in response to the TSST. It is conceivable that attenuated ACTH levels are accompanied by blunted cortisol levels. However, we observed a more pronounced suppression for cortisol than for ACTH release. Therefore, additional inhibition mechanisms such as reduced sensitivity or number of glucocorticoid receptors have to be suggested. However, we assume intact HPA feedback mechanisms in IBS patients, since the timing of the cortisol and ACTH peaks, as well as the onset of negative feedback following the TSST, were similar in both groups. In line with this hypothesis, two studies reported comparable cortisol suppression in controls and IBS patients following dexamethasone intake (Böhmelt et al. 2005, Dinan et al. 2006). However, to date, glucocorticoid receptor number and sensitivity has not been studied in association with FGID.

Furthermore, since a history of early life events was reported to be a common characteristic in FGID, it has been suggested that altered HPA axis might be more a reflection of trauma experience rather than a specific marker for a given disorder (Heim et al. 2001). If this hypothesis is correct, the prevalence of early trauma may explain the divergent findings of previous studies, since only two of a dozen studies assessed this condition appropriately. Nevertheless, HPA axis dysregulation in the present empirical study II cannot be associated with PTSD or trauma experience, since PTSD was an exclusion criterion and trauma experience was low and not significantly different between patients and controls.

In conclusion, recent data suggest a dysregulated HPA axis under basal and stimulated conditions in IBS patients. However, future studies should take into account predominant bowel habit. Moreover, our data suggest that the assessment of lifetime history of psychopathology and trauma experience adopting an appropriate methodology is essential. Neglecting these confounding factors can be assumed to be associated with invalid results, since IBS- specific HPA axis alterations might be concealed or moderated by the psychiatric comorbidity.

Similar to the results of empirical study I, and in contrast to the biological data of study II, we observed psychological hyperresponsiveness to stress in women with IBS compared to healthy controls. Therefore, we assume that high dispositional stress reactivity is present in a major part of individuals with FGID. Enhanced psychological stress reactions in subjects with FGID following a laboratory stressor have been documented previously (Dickhaus et al. 2003, Wright et al. 2005, Elsenbruch et al. 2006). To draw a conclusion, there appears to be good evidence for increased situation-specific as well as general ("trait") psychological stress responsiveness in several FGID. However, females with FGID seem to be more disposed to develop high general stress susceptibility.

8.3. Summary of limitations

In the first empirical study, we made use of the advantages of web-based data collection including a fast and cost-effective access to a broad and homogeneous population, at the expense of diagnostic validity. The present sample consisted of young academic adults and is therefore not wholly representative of the general population in Switzerland. A major point of criticism of the empirical study I might be that FGID were assessed by a self-report measure. However, the Rome criteria provide high predictive values (Olden, 2002), and strong correlations between diagnosis from questionnaires and from physical examination have been reported (Talley et al. 1990). Nevertheless, we cannot rule out that a few cases that were classified as FGID might have suffered from an undiagnosed organic disease at the time of data collection. The failure to consider psychiatric conditions might be seen as a further weak point of the present online study. No specific questionnaires were applied to assess psychopathology, even though high associations between anxiety/depression and FGID have been reported previously in similar populations (Hazlett-Stevens et al. 2003, Sugaya &

Nomura, 2008). Issues such as self-selection bias and low response rate are additional methodology-specific limitations.

The second study was based on more restrictive selection criteria. However, the exclusion and control of numerous confounding factors took place at the expense of external validity. The current findings describe the psychobiological stress reactivity of young female IBS patients to a specific laboratory stressor (TSST). Whether these results can be generalized to men, older subjects or other FGID still needs to be investigated. Furthermore, the use of other stressors may reveal a different result, since the type of stress essentially modulates the psychobiological stress reaction (Kudielka et al. 2009). In study II, IBS was diagnosed according to the Rome III criteria. Therefore, caution is warranted when comparing the present findings with studies based on other classification criteria (Esryd et al. 2007). The diagnostic approach even differs between our first (Rome II) and our second (Rome III) empirical work, since the third version of the Rome criteria had been introduced (Drossman, 2006) at the same time as the data assessment of study I. However, Dorn and colleagues (2009) reported in a recent study high agreement between these two diagnostic guidelines.

We included both females with and without hormonal contraceptives, and since previous studies have indicated that hormonal birth control attenuates cortisol responsiveness (Kirschbaum et al. 1999), we decided to match controls and IBS patients in terms of this confounding factor. Moreover, the experiment day was scheduled for all participants in the late luteal phase. However, post hoc group comparison revealed no differences between women with hormonal contraceptives and those without.

In addition, our results have to be interpreted in the light of some methodological limitations: Firstly, cortisol was assessed by non-invasive saliva sampling, whereas ACTH measurement demands the collection of blood samples. As in some individuals the procedure of venepuncture causes substantial increase in ACTH and cortisol levels (Meeran et al. 1993), a rest period of 30 minutes was applied after the intravenous catheter had been inserted and before the first blood sample was drawn. Although the blood collection was standardized, there was a considerable interindividual variability in terms of blood flow velocity and accessibility/stability of the veins. Secondly, low glucose levels have been associated with an inhibition of glucocorticoid responsiveness (Kirschbaum et al. 1997, Gonzalez-Bono et al.

2002), and since participants were advised to fast for 4 hours before and 3 hours during the study, lower cortisol secretion might be expected. However, interindividual differences in glucose metabolism probably modulate this relationship. Thirdly, participants received detailed instructions about the saliva sampling at home, and the exact collection time was controlled using a self- report measure. Nonetheless, the compliance could not be objectively verified.

The optimal sample size to detect a large effect size of f^2=0.35 with a power ≥0.8 and α=5% for group differences in endocrine parameters between IBS patients and controls was calculated a priori with the statistical software G-Power (Buchner et al. 1997). However, our findings of an association between HPA (re)activity and predominant bowel habit were based on reduced sample sizes, since the subgroup distribution was not predictable. Therefore, the validity of IBS subtype- specific findings are limited and should be interpreted with caution.

Finally, both empirical studies were based on a cross-sectional design and therefore do not allow a causal interpretation of the present results. Thus, no conclusion can be drawn as to whether increased stress susceptibility and HPA alterations represent an etiological factor of FGID or epiphenomena of the disease.

8.4. Clinical implications and directions of future research

Although the findings regarding HPA axis activity in IBS are inconclusive, the development of promising chemical agents acting on CRH receptors is promoted (Sagami et al. 2004, Martinez et al. 2006). Thus, a better understanding of the neuroendocrinological mechanisms in individuals with FGID is essential and further studies in this area are needed.

Similar to the results of studies in other FSS, we observed HPA axis hypofunction in “pure” IBS patients (Van Houdenhove et al. 2009). This observation raises the exciting question of whether FSS and FGID represent a psychobiological entity. Hence, studies comparing different FFS and FGID with respect to their basal and stimulated HPA axis activity are needed. However, the present data suggest IBS subtype-specific alteration in the HPA axis activity. Therefore, we recommend that predominant bowel symptoms be taken into account in future studies.

The detection of IBS subtype-specific HPA axis alteration is a novel finding. We observed increased unstimulated morning cortisol levels in IBS-D patients and the extreme hyporeactivity to the TSST in women with IBS-C. As yet, only Elsenbruch et al. (2004) reported IBS subtype-specific differences in cortisol reactivity, although in response to a standardized meal. The emerging hypothesis that HPA axis hyper- or hypoactivity in IBS patients is associated with their predominant bowel habit remains to be verified in further studies with larger sample sizes.

It would be illuminating to investigate basal and stimulated HPA axis activity in FGID other than IBS adopting different types of stressors. Furthermore, the assessment of psychobiological stress responsiveness in a more natural setting would be desirable. Additionally, prospective surveys would help to verify the causality between stress and FGID. In this context, particularly the exploration of the etiological role of pre-, peri- or post-natal trauma experience is indicated, since neonatal maternal deprivation has been associated with alterations in gut transit time, epithelial barrier function and mucosal immunity in rodents (Barreau et al. 2004). In order to achieve a better understanding of the mechanisms responsible for a dysfunctional HPA axis activity in IBS and FGID, the investigation of glucocorticoid receptor numbers on peripheral immune cells and their sensitivity, respectively, is indicated.

Finally, an important issue for the future is the exploration of the neuroendocrine-immune interface. The reciprocal influence between enteric immunity and regulatory stress systems has been described previously (Barbara et al. 2002, Dinan et al. 2006, Mc Ewen, 2007). It is known from the literature that glucocorticoids inhibit immune activity (Ehlert et al. 2001), peripheral inflammation is able to trigger the HPA axis activity (Besedowsky & Del Rey 1996), and subtle alterations in immune activity have been postulated in IBS (Chapter 3.7.3).

In both empirical studies, we found higher psychological stress susceptibility including higher levels of chronic stress, negative stress appraisal and reduced coping ability in individuals with FGID. This result might inform clinical practice and indicates that psychotherapeutic interventions targeting stress management could be of great benefit for individuals with FGID reporting high stress levels. Given the fact that cognitive stress processing has been shown to influence visceral perception (Posserud et al. 2004, Dickhaus et

al. 2003), our finding of dispositional stress susceptibility in FGID may also provide explanatory insights into psychological mechanisms underlying the success of cognitive-behavioral treatment interventions (Toner et al. 2000, Moser, 2008). Assuming that such therapies may also normalize physiological disturbances, not only a decrease in psychosocial distress might be expected, but also concomitantly reduced functional gastrointestinal symptoms. However, this hypothesis remains to be tested.

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